

**Neurocognitive Impairment
in Inherited Metabolic Disorders**

Marta Gil-González

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Neurocognitive Impairment *in* **Inherited Metabolic Disorders**

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PhD Thesis
Doctoral Program in Neuroscience

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Neurocognitive Impairment *in* Inherited Metabolic Disorders

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Tutored by **Dr. Jordi Ortiz de Pablo**

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Abstract

Brain development is a highly energy-dependent process in which metabolism plays a crucial role in neurogenesis, synaptic plasticity, myelination, and circuit maturation. Disruptions to metabolic balance during critical developmental stages can lead to lasting changes in brain structure and function, contributing to neurocognitive impairment. Inherited metabolic disorders (IMDs) are a diverse group of rare diseases in which specific metabolic defects directly interfere with neurodevelopment. However, their neurocognitive profiles are often not well-characterized.

This doctoral thesis explores neurocognitive impairments in children and adolescents with treatable IMDs, due to intoxication and energy defects. The central hypothesis posits that IMDs with distinct biochemical mechanisms share common neurodevelopmental vulnerabilities.

A multicenter cross-sectional cohort study was conducted, integrating comprehensive neuropsychological assessments with advanced brain volumetric analyses and high-resolution lipidomic profiling. The neuropsychological findings revealed convergent cognitive profiles across IMD subtypes, with mean intellectual functioning one standard deviation below population norms and consistent impairments in executive functioning, attention, fine motor skills, and social cognition. Nearly half of the cohort exhibited traits resembling ADHD and ASD, supporting the inclusion of IMDs within a broader neurodevelopmental spectrum.

Lipidomic analyses identified a distinct metabolic signature characterized by altered glycerolipid, glycerophospholipid, and sphingolipid profiles, associated with poorer neuropsychological outcomes and reduced adaptive functioning. Brain volumetric analyses revealed atypical cortical and subcortical expansion, with cerebellar vulnerability emerging as a sensitive biomarker of neurocognitive impairment. An observational pre–post study demonstrated that personalized-dose methylphenidate improved attentional control and adaptive functioning without detectable structural changes in the brain.

Overall, this thesis supports an integrated transdiagnostic model in which metabolic dysregulation drives shared neurodevelopmental pathways, leading to common cognitive phenotypes across different IMDs. These findings emphasize the need for early and systematic neuropsychological assessments, biomarker identification, and multidisciplinary, targeted interventions to improve long-term outcomes and quality of life for individuals with IMDs.

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Abbreviations

ABAS-II: Adaptive Behavior Assessment System, Second Edition	IMD: Inherited Metabolic Disorder
ABCD: Adolescent Brain Cognitive Development	IQ: Intelligence Quotient
ADHD: Attention-Deficit/Hyperactivity Disorder	ISI-HRT CPT: Inter-stimulus interval HRT, CPT-3
AEDs: Antiepileptic Drugs	K-CPT-2: Kids Continuous Performance Test, Second Edition
ANCOVA: Analysis of Covariance	LC-MS/MS: Liquid Chromatography–Tandem Mass Spectrometry
ANTS: Advanced Normalization Tools	LO: Late-Onset
AR-NEPSY: Affect Recognition, NEPSY-II	LPC: Lysophosphatidylcholine
ASD: Autism Spectrum Disorder	LPE: Lysophosphatidylethanolamine
ATP: Adenosine Triphosphate	LT: Liver Transplantation
B- SENA: Behavioural Problems, SENA	MCAD: Medium-Chain Acyl-CoA Dehydrogenase Deficiency
BASC: Behaviour Assessment Scale for Children	MCTs: Monocarboxylate Transporters
BCAA: Branched-Chain Amino Acids	MeSH: Medical Subject Headings
BD: Block Design, Wechsler Scales	mPFC: Medial Prefrontal Cortex
BLOCK-HRT CPT: Bloch Change HRT, CPT-3	MPH: Methylphenitade
BR- BRIEF: Behavioural Regulation, BRIEF	MRI: Magnetic Resonance Imaging
BRIEF: Behavior Rating Inventory of Executive Function	MSUD: Maple Syrup Urine Disease
BSID-II: Bayley Scales of Infant and Toddler Development, Second Edition	NAT: Noradrenaline Transporter
C ABAS-II: Conceptual Domain, ABAS-II	NBS: Newborn Screening
C Wechsler: Coding, Wechsler Scales	NDDs: Neurodevelopmental Disorders
C-CPT: Comissions, CPT-3	NEPSY-II: Developmental Neuropsychological Assessment, Second Edition
CDH: Ceramide Dihexoside	NGS: Next-Generation Sequencing
CE: Cholesteryl Esters	NMDA: N-Methyl-D-Aspartate
CELF-5: Clinical Evaluation of Language Fundamentals, Fifth Edition	NPCs: Neural Progenitor Cells
Cer: Ceramides	NVI: Nonverbal Index, Wechsler Scales
CHOL: Cholesterol Free	OA: Organic Acidurias
CONS HRT: Hit Reaction Time Consistency, CPT-3	O-CPT: Omissions, CPT-3
CPI: Cognitive Proficiency Index, Wechsler Scales	OTCD: ornithine transcarbamylase deficiency
CPT-3: Conners' Continuous Performance Test, Third Edition	P ABAS-II: Practical Domain, ABAS-II
CR-BRIEF: Cognitive Regulation, BRIEF	PCA: Principal Component Analysis
CSF: Cerebrospinal Fluid	PET: Positron Emission Tomography
DAG: Diacylglycerols	PKU: Phenylketonuria
DAT: Dopamine Transporter	PLS-DA: Partial Least Squares Discriminant Analysis
DHCer: Dihydroceramides	PPT: Purdue Pegboard Test
DHSM: Dihydrosphingomyelin	PRI: Perceptual Reasoning Index, Wechsler Scales
DLPFC: Dorsolateral Prefrontal Cortex	PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
DSM: Diagnostic and Statistical Manual of Mental Disorders	PR-SENA: Personal Resources, SENA
DsB: Digit Span Backward, Wechsler Scales	PSI: Processing Speed Index, Wechsler Scales
DsF: Digit Span Forward, Wechsler Scales	ROCF: Rey–Osterrieth Complex Figure
DTI: Diffusion Tensor Imaging	ROS: Reactive Oxygen Species
E-SENA: Emotional Problems, SENA	S ABAS-II: Social Domain, ABAS-II
EF-SENA: Executive Functions, SENA	SD: Standard Deviation
ER-BRIEF: Emotional Regulation, BRIEF	SS: Standard Scores
EO: Early-Onset	SS Wechsler: Symbol Search, Wechsler Scales
fMRI: Functional Magnetic Resonance Imaging	SENA: System for the Evaluation of Children and Adolescents
fNIRS: Functional Near-Infrared Spectroscopy	SM: Sphingomyelin
FDR: False Discovery Rate	S1P: Sphingosine-1-Phosphate
FRI: Fluid Reasoning Index, Wechsler Scales	TAG: Triacylglycerols
G-SENA: General Problems, SENA	TCA: Tricarboxylic Acid Cycle
G-BRIEF: General Functioning, BRIEF	TIV: Total Intracranial Volume
GA-1: Glutaric Aciduria Type I	ToM: Theory of Mind
GAI: General Ability Index, Wechsler Scales	UCD: Urea Cycle Disorders
GAB: General Adaptive Behaviour, ABAS-II	UPLC-HRMS: Ultra-Performance Liquid Chromatography Coupled to High-Resolution Mass Spectrometry
GM: Gray Matter	V: Vocabulary, Wechsler Scales
GMV: Gray Matter Volume	VABS-3: Vineland Adaptive Behavior Scales, Third Edition
GLUT: Glucose Transporter	VAR-HRT: variability in HRT, CPT-3
GLUT1DS: GLUT1 Deficiency Syndrome	VCI: Verbal Comprehension Index, Wechsler Scales
GSD: Glycogen Storage Diseases	VSI: Visual Spatial Index, Wechsler Scales
HexCer: Hexosylceramides	vmPFC: Ventromedial Prefrontal Cortex
HM: Healthy Model	WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition
HRT-CPT: Hit Reaction Time, CPT-3	WISC-V: Wechsler Intelligence Scale for Children, Fifth Edition
ICD: International Classification of Diseases	WMI: Working Memory Index, Wechsler Scales
ICIMD: International Classification of Inherited Metabolic Disorders	WM: White Matter
ID: Intellectual Disability	WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition
IFG: Inferior Frontal Gyrus	

Chapter I

The role of metabolism in brain health and disease

1. Introduction

1.1. Metabolism in brain development

Metabolism involves a series of complex biochemical reactions in cells, enabling them to produce and use energy for proper functioning. Cellular metabolism consists of two main processes: anabolism, which builds essential molecules, and catabolism, which breaks down complex molecules to release energy and provide components for anabolic reactions (*Figure 1*). These processes are organized into various metabolic pathways, depending on the type of metabolic substrate involved.

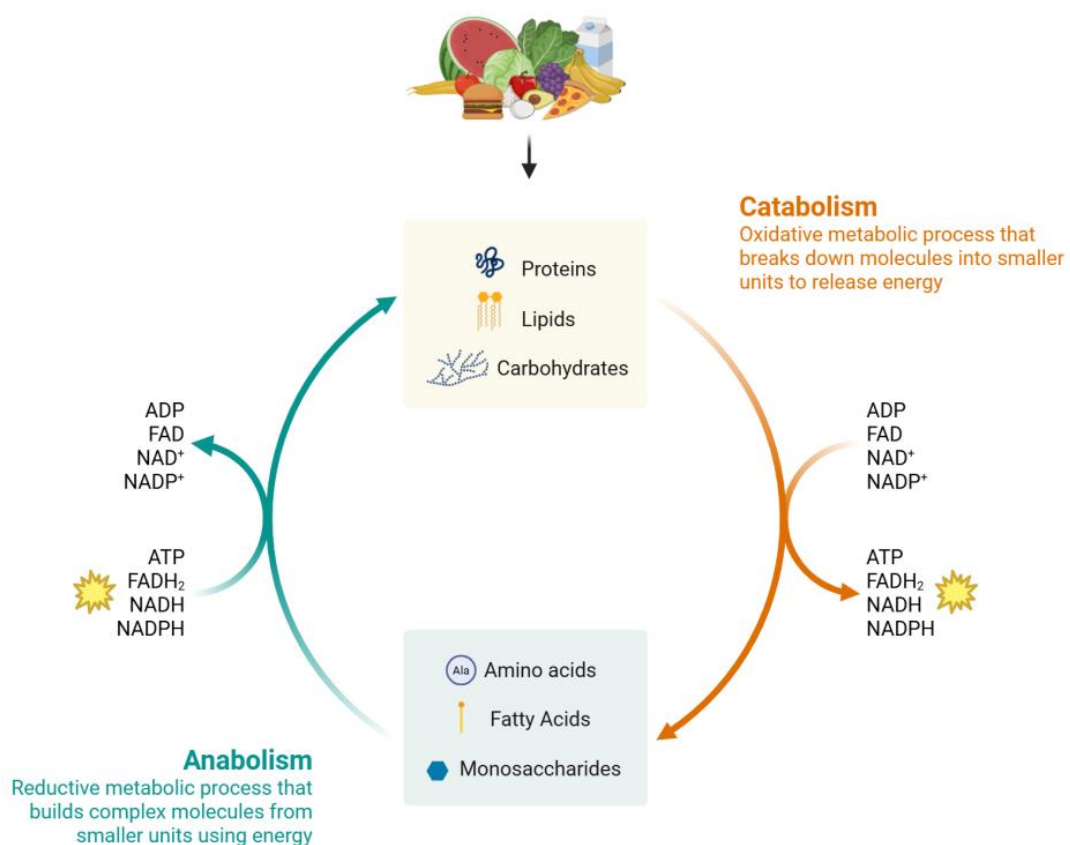


Figure 1. Metabolic processes from food intake to catabolism and anabolism. Catabolism (orange) degrades proteins, lipids, and carbohydrates into simple units (amino acids, fatty acids, and monosaccharides), releasing energy as ATP and reduced coenzymes (NADH, FADH₂). Anabolism (green) uses this energy to synthesize macromolecules required for growth, repair, and cellular maintenance.

The metabolic capacities of different tissues in the body are not uniform; they can vary in their ability to use substrates such as glucose, lactate, or fatty acids. The brain, which accounts for only about 2% of total body weight, consumes nearly 25% of the body's energy when at rest and does it ten times faster than the rest of tissues (Kotchetkov et al., 2023). In children, the brain demands even more energy for growth and plasticity, reaching up to 44% of the body's metabolic rate (Oyarzabal et al., 2021).

1.1.1. From neurogenesis to pruning

The human brain develops significantly from the third gestational week to early adulthood, with neural progenitor cells (NPCs) generating neurons that shape the volume, structure, and network of the cerebral cortex (Espinós et al., 2022; Uytun, 2018; Taverna et al., 2014), differentiating into neurons and glia, and migrating to build complex brain structures, establishing neural circuits, and engaging in crucial cell-to-cell signalling. Figure 2 shows a timeline of brain development, adapted from Uytun, 2018.

Originating from the dorsal neural tube of the embryo, neural crest cells migrate and differentiate into various cell types, controlled by complex genetic interactions between signaling systems, transcription factors, and epigenetic factors (Bhattacharya et al., 2021). Changes in the number of copies of a coding gene can lead to increased or decreased expression levels, which may impact various processes during development, resulting in clinical phenotypes and neurodevelopmental disorders (Espinós et al., 2022).

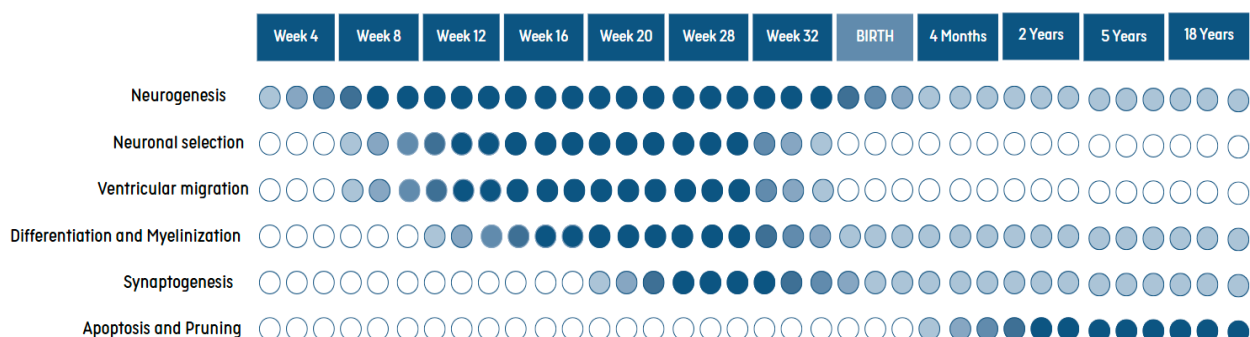


Figure 2. Timeline of brain development, adapted from Uytun, MC. In Prefrontal Cortex, Starcevic and Filipovic, 2018.

After neurogenesis and differentiation, neurons in the neocortex are spatial and functional specialized into six layers, with dendritic and axonal branching formation of synapses, cell death and pruning of synapses, glial proliferations and differentiation (Espinós et al., 2022; Uytun, 2018). The prefrontal cortex is one of the last regions of the brain to mature due to the complexity of the dendritic trees and its intensive interconnections with other regions.

Epigenetic refers to changes in gene expression without modifying the underlying DNA sequence. It regulates neuronal lineage, differentiation, and connectivity, significantly impacting the structure and function of synapses (Lossi et al., 2024).

Various epigenetic mechanisms, including DNA methylation, histone modifications, and chromatin structure, influence gene expression in radial glial cells during neurogenesis. During the transition from fetal development to young adulthood, the methylome undergoes significant rearrangement, which is closely linked to synaptogenesis (Lossi et al., 2024; Espinós et al., 2022).

For instance, DNA methylation regulates the differentiation of oligodendrocytes and Schwann cells during development and repair. It controls mRNA transcription by enabling transcription factors to bind to DNA, which is then translated into proteins in the cytoplasm. Although DNA methylation is a stable epigenetic modification, it can be dynamically altered in response to various environmental factors, including diet, stress, toxins, and early-life experiences (Lossi et al., 2024; Espinós et al., 2022; Iwata & Vanderhaeghen, 2021).

Histone methylation and acetylation also guide the differentiation of NPCs into various neural cell types, including neurons and glial cells. Positive environmental factors, such as cognitive stimulation and physical activity, can promote histone modifications associated with synaptic plasticity and learning. Conversely, exposure to toxins can adversely affect histone acetylation (Lossi et al., 2024).

In conclusion, epigenetic changes can result in alterations to gene expression and protein levels, emphasizing the link between genetic variations and brain development. Research has identified key critical periods in brain development when essential nutrients are particularly important to plasticity and affect neural connectivity. For example, at birth, a temporary change in the role of

GABA from inhibitory to excitatory has been associated with autism spectrum disorders. The networks established during these critical periods are mainly irreversible; however, compensatory connectivity patterns can still emerge. Therefore, the optimal window of success for intervention to best support brain development is in late fetal and early postnatal life. Lack of essential nutrients during these times can lead to long-lasting dysfunction ([Dehorter & Del Pino, 2020](#)).

Metabolism is closely linked to signal transduction, gene regulation and cellular function, highlighting the critical role of energy homeostasis in brain development.

The availability and distribution of ions and metabolites that create the electrochemical gradient is essential in determining the energy states of cells. Glucose is the main cellular energy resource in the brain. The metabolism of glucose comprises the gluconeogenesis (anabolic pathway) and glycolysis (catabolic pathways). Gluconeogenesis consists in glucose production from non-carbohydrate precursors such as lactate, oxaloacetate, and glycerol, predominantly in peripheral tissues such as the renal cortex or liver. However, brain astrocytes are also capable of storing glycogen. In contrast, within the cytoplasm glycolysis converts glucose to pyruvate, an ATP precursor, which can be converted into lactate. Cytoplasmic pyruvate can also enter mitochondria to feed the tricarboxylic acid (TCA) cycle, which generates the fuels for OXPHOS to generate ATP (*Figure 3*). Glycolysis generate less ATP but faster, and is often used in highly proliferative cells, such as neural stem and progenitor cells. On the other side, mitochondrial OXPHOS produce ATP more efficiently so it's used in energy-demanding differentiated cells, such as neurons. During delamination and differentiation of NPCs, there is a key bioenergetic transition from a highly glycolytic state during migration shifting to OXPHOS enzyme expressions and reducing aerobic glycolysis. Disruption in these metabolic transitions may affect embryonic development ([Kotchetkov et al., 2023](#); [Brunetti et al., 2021](#); [Iwata & Vanderhaeghen, 2021](#); [Bhattacharya et al., 2021](#)).

In summary, proper metabolic regulation is crucial for the specification, migration, and differentiation of neural cells. Metabolism is a central signaling hub that interacts with various signal transduction pathways and influences the epigenome and proteome, thereby regulating important cellular functions and behaviors. Disruptions in metabolism can result in significant neurodevelopmental disturbances ([Bhattacharya et al., 2021](#); [Iwata & Vanderhaeghen, 2021](#)).

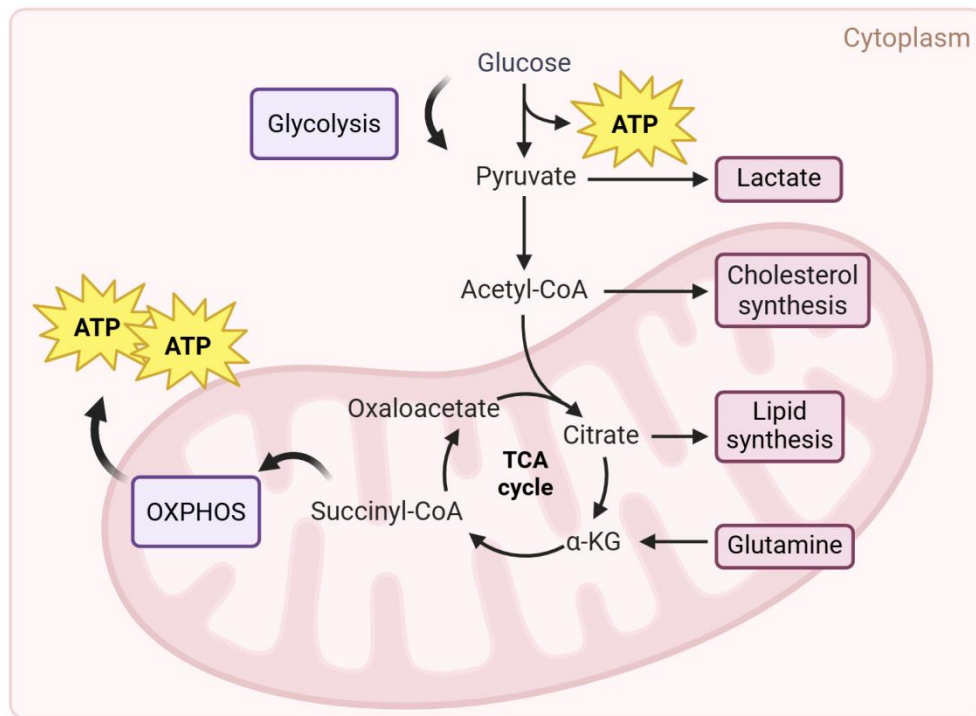


Figure 3. Glucose metabolic pathways for ATP generation via glycolysis and mitochondrial oxidative phosphorylation (OXPHOS). Glucose is metabolized in the cytoplasm through glycolysis, producing rapid ATP and pyruvate. Pyruvate is converted to acetyl-CoA and enters the mitochondria to fuel the tricarboxylic acid (TCA) cycle, generating intermediates such as citrate, oxaloacetate, α -ketoglutarate, and succinyl-CoA. In parallel, OXPHOS produces additional ATP more efficiently, supporting essential cellular functions.

Following neurogenesis, the generation of astrocytes and oligodendrocytes continues during the early postnatal period. Deep-layer cortical pyramidal neurons are produced at the expense of upper-layer neurons and glial cells, which may impact cortical networks. Epigenetic factors, such as social deprivation, can alter the maturation and myelination of oligodendrocytes in the prefrontal cortex. Additionally, the activation of astrocytes and microglia also contributes to plasticity within the neocortex (Dehorter & Del Pino, 2020).

Between 24 to 72 months postnatally, there is a significant increase in the number of neurons across all areas of the cortex. In infants, pyramidal neurons in the frontal lobe take longer to mature and exhibit less complex dendritic structures when compared to regions like the primary sensorimotor cortices. Synaptic density in the prefrontal cortex peaks around 3.5 years, registering a 50% increase

over adult levels, while white matter continues to grow, reaching its pinnacle in mid-adolescence (Uytun, 2018).

During postnatal period, neurons significantly decrease in the neocortex in a programmed pruning, reconfiguring the neural network, especially higher-order functions such as social behaviour and motor learning. For instance, GABAergic inhibitory interneurons mediate the competition between electrical activity through calcium-dependent phosphatase and phosphatase tensin homolog protein, and controls plasticity. Dysregulation in glutamatergic neurons can lead to altered motor learning and autism-like behaviours as well. Failure to stabilize neural circuits and reducing plasticity as the brain development underlies the physiopathology of a range of neurodevelopmental disorders (Dehorter & Del Pino, 2020).

As previously noted, proper brain development requires tightly regulated metabolic homeostasis, and disrupted energy supply during critical developmental periods may irreversibly impact brain maturation. Neurons consume significant energy to maintain their excitability, but the brain consists of various cell types, each playing a unique role in regulating brain function and metabolism. A synergistic interaction among vascular endothelial cells, pericytes, astrocytes, and neurons is essential for maintaining brain metabolism. These cell types work together in a complex neurovascular unit network, which regulates energy import and utilization. For instance, glucose transport into the brain is primarily facilitated by glucose transporters (GLUT-1 and GLUT-3). GLUT-1 is predominantly expressed by endothelial cells and, to a lesser extent, by astrocytes, while GLUT-3 is responsible for glucose uptake in neurons. GLUT-1 is the primary carrier for importing glucose from blood circulation into the brain. Additionally, alternative energy sources such as lactate, pyruvate, and ketone bodies are transported by monocarboxylate transporters (MCTs), primarily found in neurons and astrocytes. Ketone bodies provide acetoacetyl-CoA and acetyl-CoA for the synthesis of lipids, fatty acids and cholesterol. They are metabolized from medium and short fatty acids and transported into the brain through specific transporters such as MCT1, for being later oxidized into acetyl-CoA and enter into the TCA cycle to generate the fuel. Oligodendrocytes rely on lactate for myelin production and as astrocytes, they supply lactate to the axon through MCT1 transporters (Kotchikov et al., 2023; Oyarzabal et al., 2021).

Fuel molecules like ATP and lactate are crucial for signalling that promotes synaptic plasticity. Electrically active axons depend on glycolysis and lactate from oligodendrocytes, which provide myelin insulation (Trevisiol et al., 2017). In demyelinated axons, ATP consumption significantly increases due to the redistribution of ion channels (Alizadeh et al., 2015; Salzer, 2015). A decrease in mitochondrial ATP production leads to free radical generation, causing lipid peroxidation and damaging cellular membranes (Garcia-Cazorla et al., 2018).

This section has primarily focused on mechanisms of energy metabolism, as they are the most extensively studied and best understood in relation to neurodevelopment. However, the metabolism of amino acids, lipids, purines, pyrimidines, neurotransmitters, and other biochemical families also plays a significant role in brain development and function. At present, our knowledge of these pathways is more limited, and a comprehensive discussion of all these mechanisms would be overly extensive and beyond the scope of this thesis.

In summary, metabolism plays a key role during brain development and functioning, contributing as well to neurodevelopmental disorders, although the complex underlying mechanisms are yet to be clarified (Kotchetkov et al., 2023; Oyarzabal et al., 2021). *Table 1* summarizes the key metabolic factors that influence brain development.

Table 1. Key metabolic influences on brain development

Mechanism/Pathway	Developmental Role	Example/Outcome	References
Glycolysis/OXPHOS shift	Drives neuronal maturation and complexity	Accelerated by mitochondrial activity	Garone et al., 2024 Iwata et al., 2023 Andrews & Pearson, 2023 Iwata & Vanderhaeghen, 2021
Nutrient availability	Regulates progenitor proliferation/differentiation	Methionine restriction impairs neurogenesis	Pennington & Andrews, 2025 He et al., 2025; Xing et al., 2024
Mitochondrial dynamics	Supports astrocyte maturation, cortical organization	Fission enables astrocyte branching	Pennington & Andrews, 2025 Rajan & Fame, 2024 Iwata & Vanderhaeghen, 2021
Metabolite-driven epigenetics	Modifies gene expression, cell fate	Acetyl-CoA, SAM for histone/DNA mods	Pennington & Andrews, 2025 Iwata & Vanderhaeghen, 2021 Zhou et al., 2019
Lipid/amino acid metabolism	Supports neural stem cell proliferation	Glutaminolysis, fatty acid synthesis	Andrews & Pearson, 2023 Namba et al., 2020 Knobloch et al., 2012
Cooperative metabolism	Astrocyte-neuron metabolic support	Lactate shuttling	Pennington & Andrews, 2025 Rajan & Fame, 2024

1.2. *Neurodevelopmental disorders*

Neurodevelopmental disorders (NDDs) encompass a variety of conditions that disrupt the development of the nervous system and continue to affect individuals into adulthood. The prevalence of NDDs among the school-age population ranges from 5% to 15%. These disorders typically arise from a combination of genetic and environmental factors, which can lead to atypical brain structures and connectivity. The multifactorial etiology of these disorders contributes to a diverse range of symptoms and frequent comorbidities. Many NDDs manifest as complex syndromes, resulting in varying degrees of cognitive, emotional, social, or behavioral impairments that can significantly impact an individual's daily life. Furthermore, these deficiencies may also serve as risk factors for developing additional mental health disorders in the future (Michelini et al., 2024).

The term "neurodevelopmental disorders" has gained significant importance through international classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), which employ a categorical approach. In their most recent editions, these systems aim for a more flexible classification that accommodates a broader spectrum of severity across each disorder. Both the DSM-5-TR and ICD-11 classify these conditions within a neurodevelopmental cluster. While these classifications serve as valuable tools for clinicians, the prevalent co-occurrence and overlap among neurodevelopmental disorders, coupled with the heterogeneity observed within disorders in the clinical practice, often extend beyond the clearly defined diagnostic criteria outlined in these reference manuals.

As we improve our understanding of brain mechanisms in the developing brain, we move towards a more integrative and dynamic approach of symptoms embedded in a common set of physiopathology and biological processes. Consequently, multidisciplinary care is essential to address each patient individually with a tailored and holistic approach.

Michelini et al. (2024) recently proposed a transdiagnostic dimensional framework to encompass the neurodiversity inherent in neurodevelopmental disorders and other psychiatric conditions (*Figure*

4). This framework emphasizes the significance of symptom severity and heterogeneity, shifting the focus toward individual strengths and weaknesses rather than adhering strictly to categorical diagnoses.

This perspective is supported by various lines of research that link several genes to broader neurodevelopmental and biological processes. For instance, approximately 80% of the phenotypic correlation between autism spectrum disorder (ASD), attention deficit and hyperactivity disorder (ADHD), and other NDDs can be attributed to shared genetic influences (Michelini et al., 2024).

Many NDDs show abnormal uptake of energy substrates, such as glucose and lactate, due to altered transporter expression. As a result, genetic mutations associated with NDDs could disrupt the neurovascular cellular machinery, leading to metabolic imbalances in the brain. Metabolic dysregulation can be both a cause and consequence of NDDs, suggesting shared mechanisms (Kotchetkov et al., 2023; Oyarzabal et al., 2021).

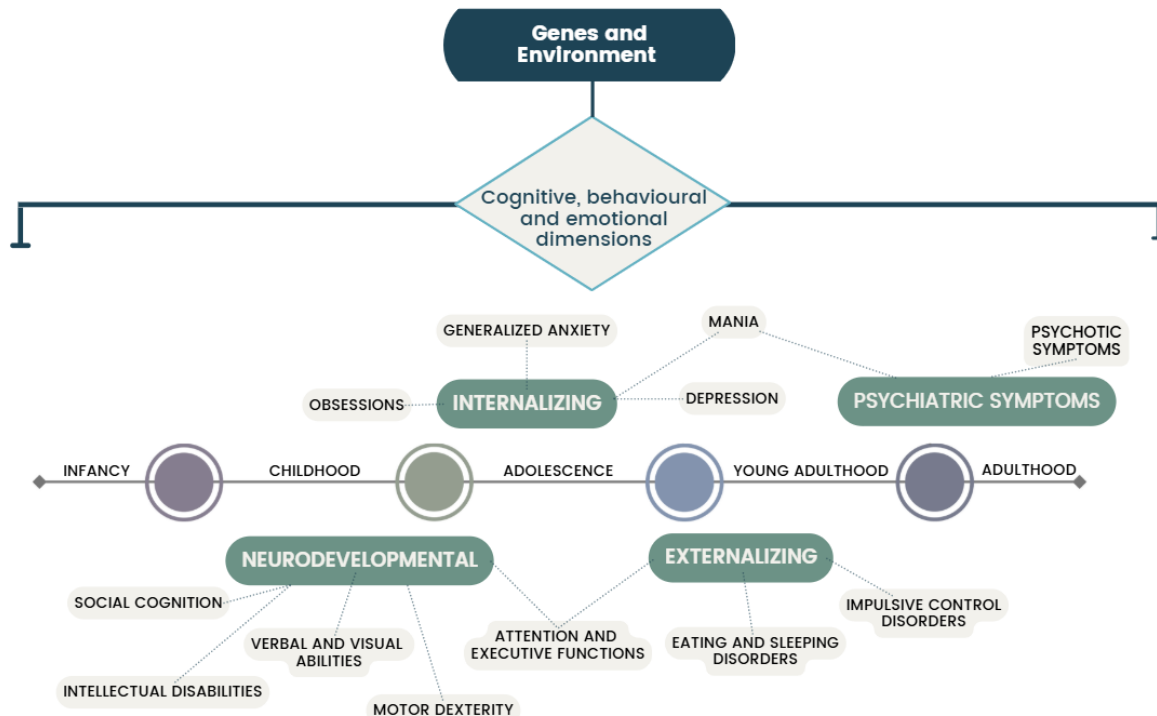


Figure 4. Transdiagnostic framework of neurodevelopmental spectrum alongside dimensions, adapted from Michelini et al. (2024).

Regarding cognitive impairment, deficits in executive functioning are observed across most neurodevelopmental disorders, with quantitative differences. Attention and social cognition deficiencies generally follow a consistent developmental trajectory throughout life, but motor hyperactivity tends to decrease during adolescence, and it is often replaced by internalizing symptoms. Additionally, brain structural and functional features in frontal and striatal-thalamic regions, and abnormalities in the default mode and dorsal attention networks may serve as a unifying feature across the spectrum of neurodevelopmental disorders ([Michelini et al., 2024](#)).

Metabolic dysfunctions can be either the primary cause of NDDs, such as inherited metabolic disorders, or they can contribute secondarily to the underlying pathophysiology of these conditions. It is crucial to explore the link between metabolism and neurodevelopmental disorders to determine whether these metabolic issues could serve as therapeutic targets for effective management.

2. Inherited Metabolic Disorders (IMDs)

2.1. Definition

In the first section of this chapter, we have mentioned how metabolism involves thousands of enzymes, cofactors, receptors and transporters, which are essential for brain development. When metabolic processes are disrupted, it can result in deficiencies that affect both the growth and overall functioning of the brain.

Inherited Metabolic Disorders (IMDs) encompass a large and heterogeneous group of rare genetic diseases that alter the functioning of different metabolic pathways by the accumulation or deficiency of a particular compound, or a diversion of the substrate to an alternative pathway.

IMDs can involve different carbohydrates, lipids and proteins. However, they do not only affect metabolites and organelles, but also involve many different molecules, several cellular compartments, and the continuous remodelling of membranes ([Morava et al. 2015](#)).

Even though each disorder alone is rare, as a group are frequent and present an estimated overall prevalence of 1:800-1:1000 individuals (Baglioni et al., 2024; Van de Burgt et al., 2023; Kiess et al., 2020; Ferreira & Karnebeek, 2019).

IMDs are, in most cases, autosomal recessive disorders. A small percentage of cases are autosomal dominant or X-linked. IMDs reduce the function of single genes and can alter the structural genome (Baglioni et al., 2024; Ferreira et al., 2021).

2.2. Classification

In 2015, Morava and colleagues pointed out the challenges of the emerging novel disorders by the shift towards genetic-based diagnosis. In this concept re-definition, if the impairment of specific enzymes or biochemical pathways is intrinsic to the pathomechanism, the disorder could be labelled as an IMD. This definition expanded the scope of metabolic disorders and emphasized the need for a new classification system that included all previously identified disorders and facilitated the addition of new ones.

The International Classification of Inherited Metabolic Disorders (ICIMD) (Ferreira et al., 2021) classifies more than 1.450 disorders into 24 categories (*Table 2*). This classification is based on the clinical or biochemical phenotype associated with specific genes that define particular "monogenic" conditions. Genetically defined diseases are classified according to their associated metabolic pathways, which typically share common pathogenic mechanisms. As a result, these diseases often present similar clinical features and can be identified using the same biochemical diagnostic methods (Ferreira et al., 2021). The constantly updated IMD base already includes more than 1.800 diseases (<http://www.iembase.org/>).

In recent years, there has been a shift towards a pathophysiological-based clinical approach that integrates the specific functions of neuronal cell compartments with their metabolic characteristics (García-Cazorla & Saudubray, 2018). In-depth and accurate descriptions of each disease are important for enhancing our understanding of metabolic disorders. As with neurodevelopmental

disorders, patients with IMD often exhibit complex, overlapping characteristics that do not fit neatly into defined categories. Therefore, a more integrative approach is critical for unravelling the mechanisms and phenotypes in IMDs.

Table 2. ICIMD classification of IMD categories, adapted from Ferreira et al., 2021.

<i>Intermediary metabolism: Nutrients</i>	1) Disorders of amino acid metabolism 2) Disorders of peptide and amine metabolism 3) Disorders of carbohydrate metabolism 4) Disorders of fatty acid and ketone body metabolism
<i>Intermediary metabolism: Energy</i>	5) Disorders of energy substrate metabolism 6) Mitochondrial DNA-related disorders 7) Nuclear-encoded disorders of oxidative phosphorylation 8) Disorders of mitochondrial cofactor biosynthesis 9) Disorders of mitochondrial DNA maintenance and replication 10) Disorders of mitochondrial gene expression 11) Other disorders of mitochondrial function 12) Disorders of metabolite repair/proofreading
<i>Miscellaneous</i>	13) Miscellaneous disorders of intermediary metabolism
<i>Lipid transport metabolism</i>	14) Disorders of lipid metabolism 15) Disorders of lipoprotein metabolism
<i>Heterocyclic complex metabolism</i>	16) Disorders of nucleobase, nucleotide and nucleic acid metabolism 17) Disorders of tetrapyrrole metabolism
<i>Complex molecules and organelle metabolism</i>	18) Congenital disorders of glycosylation 19) Disorders of organelle biogenesis, dynamics and interactions 20) Disorders of complex molecule degradation
<i>Cofactors and minerals metabolism</i>	21) Disorders of vitamin and cofactor metabolism 22) Disorders of trace elements and metals
<i>Cellular metabolic signalling</i>	23) Neurotransmitter disorders 24) Endocrine metabolic disorders

To this end, Saudubray et al. (2019) proposed a simplified classification based on clinical and pathophysiological considerations to improve the diagnosis and treatment of patients with IMDs. This classification associates symptoms, pathophysiology and therapeutic management. It is based on the size of the molecules and their involvement in energy metabolism, classified into three broad categories: small molecules disorders, complex molecules disorders and energy-related defects (Figure 5). An illustrated connection between the ICIMD and the simplified classification can be found in Supplementary Figure 1.

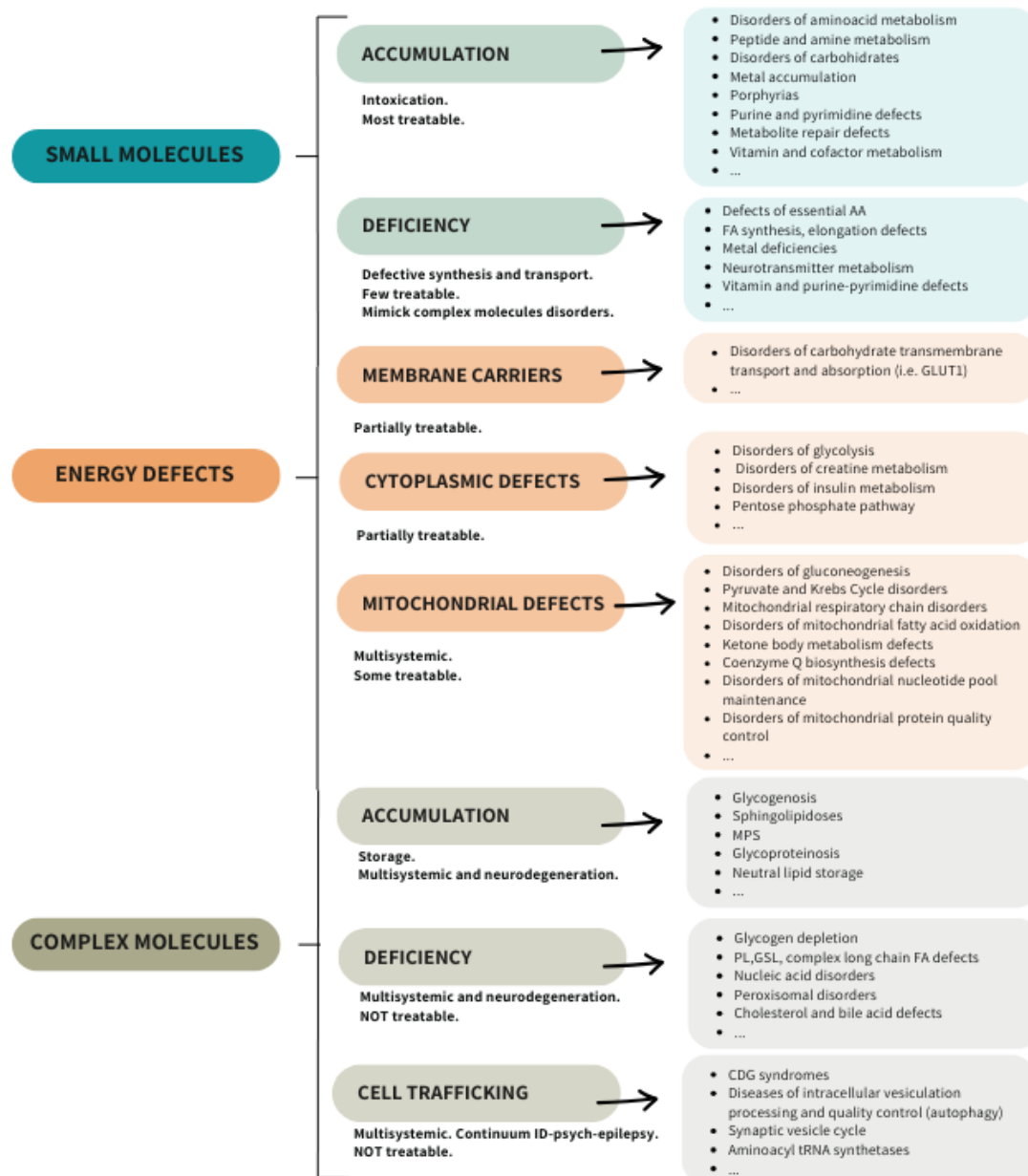


Figure 5. Simplified classification of inherited metabolic disorders (IMD), adapted from Saudurbay et al. (2019).

2.2.1. Small molecules disorders

Accumulation of small molecules or *Intoxication IMD* are caused by the abnormal accumulation of proximal compounds that lead to acute, intermittent, chronic, or even progressive intoxication. This condition can potentially be reversed once the toxin accumulation is removed, making most of these disorders treatable with special diets and cofactors. Since these disorders

typically do not interfere with the embryo or fetal development, they often present after a symptom-free period, followed by clinical signs of intoxication triggered by fasting, catabolism, fever, intercurrent illnesses and excessive food intake (Saudubray et al. 2019; Garcia-Cazorla & Saudubray, 2018).

This group includes disorders related to amino acid metabolism, urea cycle disorders, organic acidurias, carbohydrate intoxications, metal accumulation, porphyrias, purine and pyrimidine metabolism defects, and metabolite repair defects. Most of these disorders can be detected through newborn screening and have identifiable biomarkers. Diagnosis often depends on testing plasma, urine, and cerebrospinal fluid.

In the brain, these intoxicating molecules can act like amino acid neurotransmitters (Kölker, 2018) or stimulate biological pathways associated with impaired autophagy and neural growth factors. As a result, synaptic plasticity and excitability are often compromised.

Deficiency of small molecules disorders are characterized by defects in the synthesis of a distal compound or the transport of an essential molecule derived from the diet through the intestinal epithelium, blood-brain barrier, and cytoplasmic or organelle membranes. Some of them are treatable by supplying the deficient compound (Saudubray et al. 2019).

These small molecules play a vital role in brain formation by contributing to signaling, guiding the cytoskeleton, facilitating synapse formation, and enabling experience-dependent synapse remodeling. Therefore, this group of IMDs causes significant neurodevelopmental disruptions in the embryo, impacting crucial functions such as neuronal precursor proliferation, migration, pruning, and dendritic development. These IMDs are associated with severe global encephalopathy, resulting in chronic impairment of nearly all neurological functions. Patients often exhibit severe psychomotor delays, microcephaly, hypomyelination, movement disorders, and epilepsy (Saudubray et al. 2019; Garcia-Cazorla & Saudubray, 2018).

IMDs of carrier defects affect the transport of essential compounds and can lead to neurological syndromes. Likewise, non-essential compounds can be synthesized through various pathways within the cell, and these IMDs are usually linked to enzyme defects. Conditions such as

metal deficiencies, neurotransmitter transport defects, certain vitamin-related disorders, and some purine-pyrimidine defects also fall within this category ([Garcia-Cazorla & Saudubray, 2018](#)).

2.2.2. Complex molecules disorders

This group includes progressive neurological diseases caused by the accumulation or deficiency of complex molecules that are poorly water-soluble or diffusible. The involvement of various organelles, such as mitochondria, lysosomes, peroxisomes, the endoplasmic reticulum, the Golgi apparatus, lipid droplets, and synaptic vesicles, is often associated with systemic manifestations. Most diseases do not have well-identified biomarkers; therefore, their diagnosis relies on molecular techniques such as next-generation sequencing and whole-exome sequencing ([Saudubray et al. 2019](#)).

The complex molecules affected may include glycogen, sphingolipids, phospholipids, cholesterol, bile acids, glycosaminoglycans, oligosaccharides, glycolipids, and nucleic acids. Recent discoveries have identified defects in systems involved in intracellular vesiculation, trafficking, processing of complex molecules, and quality control processes, such as protein folding and autophagy, that also fall into this category.

The neurological manifestations are diverse and complex, with a predominance of motor symptoms (such as spastic paraparesis, ataxia and movement disorders). They are often progressive and may be associated with extra-neurological signs.

The *storage of accumulated proximal compounds* is associated with catabolic defects, such as those found in classical lysosome disorders. Similar to intoxication-related IMDs, some of these conditions may be potentially reversible if the accumulation is addressed ([Garcia-Cazorla & Saudubray, 2018](#)).

Deficiencies in complex molecules represent an expanding category of IMDs, including classic organelle disorders (defects in lysosomes and peroxisomes), carbohydrate-deficient glycoprotein syndromes, and various synthesis defects. The synthesis or remodeling of these

complex molecules can interfere with embryonic neurodevelopment, resulting in more severe outcomes. The symptoms associated with these disorders are permanent and progressive and do not depend on other concurrent health events.

These conditions share characteristics with a broader group of disorders related to cellular processing, trafficking, and quality control, which also involve protein metabolism (intracellular vesiculation, trafficking, repair, synaptic vesicle). They are at the crossroads between traditional IMDs and genetic diseases, including classical organelle disorders and diverse cell biology mechanisms (Garcia-Cazorla & Saudubray, 2018).

2.2.3. Energy-related defects

This group of IMDs is characterized by deficiencies in energy production or utilization within a variety of tissues, including the liver, myocardium, muscle, and brain. These disorders can be categorized into three main types according to the simplified classification: membrane carriers defects, cytoplasmic defects and mitochondrial defects (Saudubray et al., 2019).

Membrane Carriers include disorders related to the transmembrane transport and absorption of carbohydrates, such as GLUT1 deficiency. *Cytoplasmic Energy Defects* encompass disorders affecting glycolysis, glycogen metabolism, gluconeogenesis, hyperinsulinism, creatine metabolism, and the pentose phosphate pathway. *Mitochondrial Defects* include pyruvate disorders, defects in the Krebs cycle, mitochondrial respiratory chain disorders, defects in mitochondrial transporters of molecules, coenzyme Q biosynthesis defects, fatty acid oxidation, and ketone bodies metabolism defects.

These conditions are partially treatable, and diagnosis can be addressed by functional tests that measure glucose, lactate, ketones, and other energy-related molecules in blood, urine, and cerebrospinal fluid. Confirmation of the diagnosis usually requires enzymatic and genetic analyses.

These disorders can present as severe neonatal encephalopathies accompanied by lactic acidosis, often along with multisystem symptoms. Patients may experience acute neurological episodes during times of high energy demand, chronic motor signs (such as movement disorders,

ataxia, and peripheral neuropathy), myoclonic epilepsy, atypical absences, and various neurosensory impairments (García-Cazorla & Saudubray, 2018).

2.3. *Diagnosis and treatment*

The implementation of newborn screening (NBS) programs in different countries has become an essential tool for the early diagnosis and treatment of IMDs (Kiess et al., 2020). These neonates, once detected, require a disease confirmation throughout clinical, biochemical and, in some cases, genetic analysis.

However, the panels used in NBS can vary significantly in their sensitivity to detect different disorders and their availability may also differ across countries and regions (Castiñeras et al., 2019). Furthermore, some IMDs may not present symptoms until the adolescence or adulthood, often without any warning signs during childhood (Van de Burgt et al., 2023).

In many cases, the presence of specific biochemical changes in blood tests, such as hyperammonemia, hypoglycemia, and hyperlactatemia, is crucial for an IMD diagnosis.

Next-generation sequencing (NGS) is a technology that determines the order of nucleotides in targeted regions of the genome. NGS can produce large amounts of data rapidly, enabling whole-genome profiling and facilitating the discovery of novel genes and variants associated with diseases, particularly those found in non-coding regions. Consequently, NGS has greatly enhanced the diagnostic capabilities and aids in categorizing IMDs into biochemical groups, such as defects in synthesis, transport, remodeling, catabolism and trafficking (García-Cazorla & Saudubray, 2018). Parallel with NGS techniques, other rapidly evolving diagnostic techniques include proteomics, lipidomics, and glycomics (Morava et al. 2015).

The number of treatable IMDs continues to increase, along with an improved care for the already treatable conditions (Ferreira & Karnebeek, 2019). Treatments for IMDs include nutritional therapy, which involves supplementation and dietary interventions, enzyme replacement therapy, organ transplants, and, in some cases, gene therapies (Kiess et al., 2020).

Many IMDs are complex multisystem disorders that require collaboration among various professional specialties to ensure a comprehensive and optimal care. Consequently, a

multidisciplinary unit is essential for addressing the complexity of these disorders (Morava et al. 2015).

Timely identification of IMDs helps prevent metabolic decompensation that cause brain damage and allows for the rapid implementation of specific treatments to improve clinical outcomes. Hence, a delayed recognition of these metabolic conditions can result in irreversible damage to the central nervous system (Baglioni et al., 2024).

2.4. Clinical presentations

As our understanding of disease mechanisms in the developing brain evolves, we are transitioning from a historical reliance on adult approaches, which often focus on stable brain functioning, to a "spectrum-continuum of symptoms" embedded in a common set of biological processes. Regardless of size, metabolites may play different roles during development (García-Cazorla & Saudubray, 2018).

Different factors can influence the prominence of specific symptoms, including the particular defect, the age of the patient, and the individual's unique features. Additionally, symptoms in the developing brain can overlap, even when they arise from different biochemical pathways. Three major clinical presentations can be outlined in IMD: early encephalopathies, the synaptopathy spectrum, and the complex motor spectrum, see *Table 3* (Ferreira & Karnebeek, 2019; García-Cazorla & Saudubray, 2018).

Many children affected by IMDs may also exhibit early-onset psychiatric symptoms. Sometimes, it can be challenging to differentiate between a primary psychiatric disorder and one that arises as a consequence of a metabolic disorder in adolescents or young adults. Therefore, mental health professionals must recognize the possible metabolic conditions underlying psychiatric presentations. Early detection is essential, as most treatments are more effective during the psychiatric phase of the IMD before irreversible neurological damage occurs.

Table 3. Clinical presentations in IMDs, adapted from García-Cazorla and Saudubray, (2018).

	BRAIN FUNCTIONS AFFECTED	CLINICAL SIGNS	DISEASES
Early complex encephalopathies	Neuronal precursor proliferation, migration, synapse and dendrite formation, astrocyte development, pruning, cytoskeleton guidance, signalling and synapse remodelling.	First few months of life. Psychomotor functions, head size, excitability and behaviour.	Small molecules and complex molecules defects.
Synaptopathy spectrum	Synaptic communication. Biogenesis and transport of synaptic vesicles. Quality control, autophagy.	Epilepsy, intellectual disability, movement disorders, behaviour and autism-like symptoms. Multisystemic symptoms. Spastic paraparesis, axonal neuropathy, cortical malformations. Neurodegeneration.	SSADH (GABA defect) Synaptic vesicle defects Parkinsonism-related diseases.
Motor spectrum	Brain structures related to movement and muscle tone.	More frequent in younger patients. Dyskinetic movements, pyramidal signs, hypotonia, ataxia, spastic paraparesis.	Disorders of synthesis, remodelling, trafficking, processing and quality control of complex molecules.

Updated systematic reviews of the psychiatric symptoms in IMD (Baglioni et al., 2024; Van de Burgt et al., 2023), described a series of useful *red flags* in the psychiatric field to suspect an underlying IMD, such as atypical psychotic symptoms (visual hallucinations, confusion, acute onset, treatment resistance, unusual side effects of psychotropic drugs), atypical depressions with psychotic symptoms, strong or progressive cognitive decline, motor symptoms (tremor, involuntary movements or spasms), intellectual disability, gastrointestinal and abdominal symptoms (vomiting, diarrhoea, acute abdominal pain), exercise intolerance (unusual muscle cramps, fatigue or tenderness, nausea or vomiting after exercise, rapid loss of breath or insufficient heart rate during exercise) or vertical supranuclear gaze palsy.

In summary, metabolism is essential for brain development. Disruptions in metabolic processes, such as those seen in inherited metabolic disorders, can lead to deficiencies that adversely affect both brain growth and overall function. These disruptions may give rise to a range of neurodevelopmental disorders. Gaining insight into this relationship enhances our understanding of how the body's biochemical processes shape cognitive functions and mental health.

3. Rationale and significance of the study

Despite advances in early diagnosis and treatment have improved survival and reduced severe neurological outcomes, many individuals with IMDs continue to experience mild but persistent neurocognitive difficulties that negatively affect academic performance, daily functioning, and quality of life. These impairments are often under-recognized in clinical practice.

Currently, there is a significant gap in the existing literature on the neurodevelopmental consequences of metabolic dysregulation. IMDs have traditionally been studied as distinct entities based on their biochemical pathways; however, there is limited understanding of whether different metabolic mechanisms share neurodevelopmental vulnerabilities. Higher-order cognitive domains, such as attention and executive functions, as well as their underlying neurobiological mechanisms, have been insufficiently explored.

From a methodological perspective, there is a lack of integrative studies combining standardized neuropsychological assessment with objective biomarkers, such as neuroimaging and lipidomic profiles, that could clarify shared pathogenic pathways across disorders. This integrated approach surpasses conventional clinical descriptions and provides potential biomarkers that may improve risk stratification and prognostic accuracy in this population.

This doctoral thesis is justified by the need for a transdiagnostic and multidisciplinary approach to characterize neurocognitive impairment in intoxication and energy-related IMDs. From a broader healthcare perspective, this research has the potential to address the chronic, lifelong challenges posed by IMDs, which create significant burdens for individuals, families, and health systems. By identifying metabolic, neuroanatomical, and cognitive biomarkers associated with poorer functional outcomes, this thesis contributes to the development of more individualized and multidisciplinary care strategies. Early identification of neurocognitive risks and timely interventions may improve long-term outcomes, foster functional autonomy, and enhance the quality of life for children and adolescents with IMDs.

4. Hypotheses and Objectives

This doctoral thesis is grounded in the general hypothesis that disruption of metabolic homeostasis during critical periods of brain development constitutes a shared pathogenic mechanism underlying convergent neurocognitive phenotypes across distinct IMDs. Within this framework, the following specific hypotheses are proposed:

- a) Beyond the well-documented motor disturbances associated with IMDs, both intoxication and energy-related IMDs are associated with impairments in higher-order cognitive domains, particularly executive functions and attention.
- b) Intoxication and energy-related IMDs share common brain volumetric biomarkers of neurocognitive impairment, with a predominant involvement of fronto-parietal regions related to the attentional and executive dysfunction.
- c) Intoxication and energy-related IMDs share lipidomic biomarkers associated with neurocognitive impairment, particularly involving sphingolipid pathways, as reported in other NDDs.
- d) Treatment with methylphenidate at personalized doses leads to improvements in attentional deficits in individuals with IMDs.

To test these hypotheses, the primary objective of this thesis is to provide a comprehensive characterization of neurocognitive impairment in intoxication and energy-related IMDs, thereby contributing to a deeper understanding of the underlying mechanisms involved. Small-molecule deficiencies and complex-molecule IMDs are excluded from this study, as these conditions generally present with severe and progressive neurodegenerative phenotypes, with limited therapeutic options, and fall beyond the scope of this research. The specific objectives of this doctoral research are:

- 1) To synthesize the current state of the art through an updated systematic review of the literature, focusing on the neuropsychological domains affected in intoxication and energy-related IMDs.
- 2) To conduct a comprehensive and standardized neuropsychological assessment of a cohort of intoxication and energy-related IMDs to determine specific and shared profiles.

- 3) To investigate lipidomics and advanced brain volumetric techniques to uncover potential biomarkers linked to the neurocognitive impairment in intoxication and energy-related IMDs.
- 4) To evaluate the effectiveness of methylphenidate in improving attentional deficits within the IMD population.

Overall, this research aims to advance the understanding of metabolic disorders and their impact on brain development and cognitive functioning. Identifying characteristic neuropsychological profiles and associated biomarkers could significantly enhance the development of more accurate targeted therapeutic strategies, ultimately improving clinical outcomes and health-related quality of life for individuals with IMDs and their families.

5. Research structure

This doctoral thesis comprises seven chapters design to address the hypotheses and objectives outlined above. While each chapter can be read independently and may be suitable for publication, all chapters are interconnected and collectively contribute to our understanding of neurocognitive impairment in IMDs.

In **Chapter I**, the introduction emphasized the critical role of metabolism in brain development and function, as well as how IMDs can disrupt these processes. Building on this framework, the primary hypotheses and objectives are outlined, and will be explored in the following chapters.

Chapter II addresses the first specific objective through an updated systematic review of the literature to establish the current state of knowledge in the field, and compare our upcoming research with existing studies. Given the limited number of studies on neurocognitive functioning in IMDs, this review also represents a valuable contribution to the field.

The second and third specific objectives of this thesis are addressed through a cross-sectional multicenter cohort study of children with intoxication and energy-related IMDs. **Chapter III** presents a comprehensive neuropsychological assessment to identify shared patterns of impairment

across IMDs. To further understand the mechanisms underlying these neurocognitive impairments, **Chapter IV** investigates potential brain volumetric biomarkers using advanced neuroimaging techniques, while **Chapter V** explores untargeted lipidomic profiles associated with neurocognitive dysfunction through high-resolution mass spectrometry.

To address the final objective, **Chapter VI** evaluates whether treatment with personalised doses of methylphenidate can effectively improve attentional deficits and modulate brain structure, through an observational pre-post cohort study.

The final chapter, **Chapter VII**, synthesizes and discusses the key findings of the thesis. This discussion integrates and contextualizes the results in relation to the hypotheses and proposes a comprehensive transdiagnostic model of neurocognitive impairment in IMDs. By collectively analyzing the findings, this chapter emphasizes the clinical relevance and provides recommendations for standardized neuropsychological assessments in IMDs. These recommendations are intended to serve as a practical resource for both clinicians and researchers, promoting consistency and reliability across both settings. Furthermore, this chapter outlines limitations of this study and, identifies directions for future research, and concludes with references and data annexes, reinforcing the commitment to transparency and ethical research practices.

Chapter II

Neurocognitive impairment in IMDs:

A Systematic Review

This article has been published in the Journal of Inherited Metabolic Disorders:

Gil-González M, Arias C, Saudubray JM, Colomé-Roura R, García-Cazorla Á. Neurocognitive Impairment in Inherited Metabolic Disorders due to Intoxication and Energy Defects: A Systematic Review. J Inherit Metab Dis. 2025 Sep;48(5):e70084. doi: 10.1002/jimd.70084. PMID: 40864165; PMCID: PMC12382599.

1. Introduction

As discussed in Chapter I, *inherited metabolic disorders (IMDs)* disrupt metabolic pathways, significantly affecting brain development and function. These disruptions increase the risk of a wide range of neurodevelopmental and psychiatric disorders ([Horvath et al., 2020](#)).

Among them, phenylketonuria (PKU) and other well-studied IMDs have become models for understanding cognitive dysfunction caused by abnormal brain chemistry and neuronal damage ([Aitkenhead et al., 2021](#); [Jahja et al., 2017](#)). However, beyond these classic disorders, the number of recognized IMDs has rapidly increased in recent years. Although IMDs are estimated to account for up to 5% of non-specific intellectual disabilities ([Sklirou & Lichter-Konecki, 2018](#)), this figure requires constant revision as new diseases are identified. With advancements in medical care, long-term survival rates for individuals with IMDs have improved significantly, underscoring the importance of health-related quality of life as an important area of research ([Bösch et al., 2020](#); [Brown et al., 2017](#)).

However, the current body of literature on neurocognitive functioning in IMDs is notably sparse, leaving significant gaps in our understanding of how these conditions impact cognitive processes and brain function.

This systematic review provides a comprehensive synthesis of evidence on cognitive and behavioural impairments associated with intoxication and energy-related IMDs. Predicting cognitive trajectories in these patients can support the development of early detection strategies and therapeutic interventions, ultimately helping to prevent learning disabilities and neuropsychiatric disorders. These efforts can significantly improve the quality of life for individuals with IMDs and their families.

2. Methods

2.1. Inclusion and exclusion criteria

To ensure accuracy, this systematic review focuses on specific subgroups of the International Classification of Inherited Metabolic Disorders (ICIMD) (Ferreira et al., 2021) related to the broad categories of "Intoxication IMDs" and "Energy-related IMDs" of the simplified classification (Saudubray et al., 2019).

The inclusion criteria encompassed all prospective and retrospective studies, as well as case reports, that utilized standardized cognitive measures, such as developmental scales and neuropsychological tests. Due to the limited number of cognitive studies available for this population, we included all research published up to August 2024 involving children and adult samples.

We excluded review reports and studies with animal models or non-standardized cognitive measures. Additionally, complex molecule disorders and small molecule deficiencies were not included, as they fall outside the scope of this research. PKU was also excluded because its neuropsychological outcomes have already been extensively documented.

2.2. Search strategy

The systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines established in 2020 (Rethlefsen et al., 2021).

A comprehensive search was conducted in the Pubmed database for articles reporting neurocognitive impairment in patients with intoxication and energy-related IMD. PubMed, including MEDLINE, was searched for its broad biomedical coverage and precise MeSH indexing for rare disorders. Other databases yielded very few additional relevant studies. The search was complemented by manual screening of reference lists to identify further eligible articles.

Up to 617 IMDs, 421 energy-related IMDs and 196 intoxication IMDs, were searched using the terms "*cognition*" AND "*each specific IMD*".

2.3. Selection of publications

After searching the Pubmed database, a total of 416 records were identified. Abstracts and full texts were evaluated by one reviewer and verified by another, with any disagreements addressed through discussion. Following an initial screening of the titles and abstracts, 31 review studies were excluded from the analysis. From the remaining 385 records, a full-text evaluation for eligibility was conducted, resulting in the removal of 222 studies due to the lack of standardized neuropsychological measures or the use of animal models. Ultimately, 163 records were included in this review (*Figure 1*).

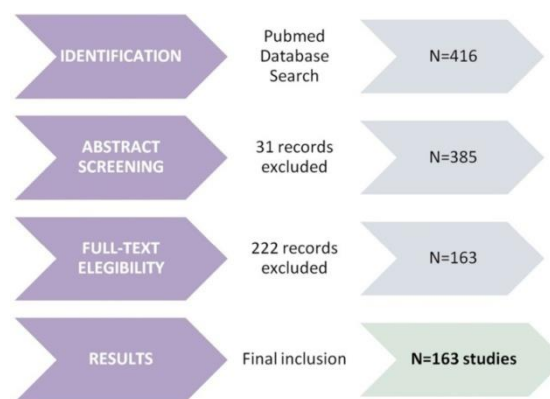


Figure 1. Flow diagram summarizing the different steps of the review based on the PRISMA 2020 statement.

In cases where a study addressed more than one IMD, the analysis was separated for each disorder. Consequently, we identified 166 articles focusing on intoxication IMDs (83%) and 34 articles on energy-related IMDs (17%).

2.4. Data analysis

The variables reviewed in all studies included the year of publication, sample size, sample age, and the classification of each IMD. To assess intellectual disability (ID), the percentage of individuals with ID was included when available, along with the reported severity levels (moderate to severe ID, mild to borderline ID, and average intellectual quotient or IQ).

The cognitive domains recorded were executive functions, attention, processing speed, language, speech, visual performance, fine motor dexterity, memory, behavioural and emotional regulation, and social cognition. When available, performance in any cognitive domain was measured on a categorical scale of "impaired" or "preserved." Only studies that described performance in each function were included in the analysis of cognitive domains.

Prior to the statistical analysis, we performed a normality test to the quantitative variables, using the Kolmogorov-Smirnov test. A significant p-value ($p < 0.05$) indicated that the variables studied did not follow a normal distribution. Therefore, we used non-parametric tests: Mann-Whitney U test for categorical variables with two categories and the Kruskal-Wallis test for those with three or more groups. Fisher's exact test was used for variables with fewer than five cases in any category. For qualitative variables, we applied the Pearson's Chi-square test.

All statistical tests were conducted with a confidence level of 95% and were considered significant at $p < 0.05$. The IBM SPSS statistical software 29.0 was used to perform all analyses.

3. Results

A total of 163 studies about neurocognitive impairment in IMDs, published between 1981 and 2024, were reviewed (*Supplementary Table 1*).

3.1. Year of publication

Most of the studies (74%) were published from 2010 onwards (*Figure 2*). The year with most publications was 2020 ($n=21$). Regarding the different cognitive domains, we found that speech was reported less impaired in recent years ($p=0.004$; Chi-square test).

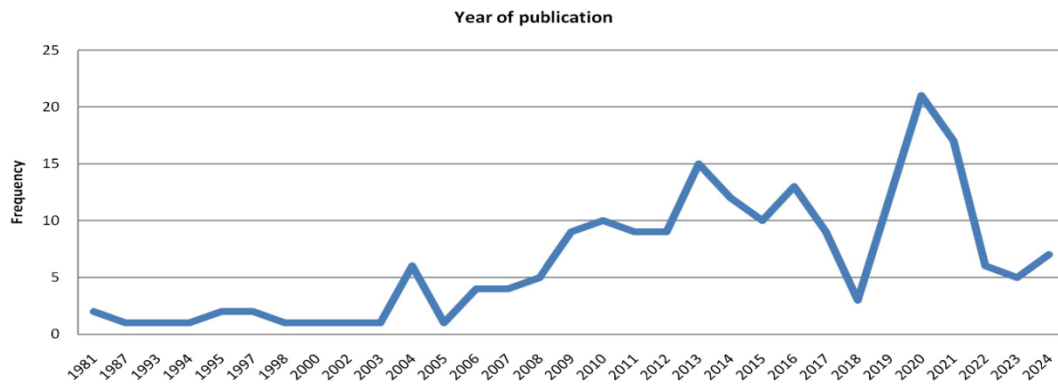


Figure 2. Number of reports published each year from 1981 to 2024.

3.2. Age of the samples

Most of the studies reviewed were focused on pediatric samples. Children accounted for 60.5% of the studies, whereas only 11% of the studies used an adult sample. About 28.5% of all studies used both children and adults participants. In order to clear this confusing variable, studies with mixed children and adult samples were excluded from the statistical analysis, and only studies with children (84.6%) or adults (15.4%) were considered.

Among studies on intoxication IMDs, 86% were on children and 14% were on adults. Energy-related IMDs studies also were more frequent on children (79.3%) than adult samples (20.7%). Among energy-related IMDs, we found that cytoplasmic defects had a higher percentage of studies with adults (37.5%) than mitochondrial defects (20%) and cell membrane disorders (9.1%).

Regarding the cognitive impairment related to the age of the sample, no significant differences between children and adults were found on the Pearson Chi-Square test regarding severe/moderate ID, mild/borderline ID, average IQ, executive functions, attention, processing speed, visual performance, motor dexterity, memory, behavioural and emotional regulation, and social cognition. However, the studies reviewed reported significantly more language and speech problems on children than adults ($p=0.007$, Chi Square test; $p=0.042$, Fisher's exact test).

3.3. Sample size and most reported IMDs

Taking into account all the studies reviewed, the number of subjects added up to 4.313 patients with IMDs; more than 1.717 children and 527 adults. We found that the mean number of subjects per article was 21.57 (SD=40.97). Studies with intoxication IMD had a mean number of 24.54 subjects per study (SD=44.21), whereas studies with energy-related IMDs had a mean of 7.03 subjects per study (SD=9.47).

Considering the simplified classification, intoxication IMDs were the most reported in the literature (83%), whereas energy-related IMDs represented only 17% of all studies. Accordingly, amino acid metabolism disorders encompassed 58% of the evidence, being urea cycle disorders and organic acidurias the most frequently studied among them (26.5% and 13%, respectively). Disorders of carbohydrate metabolism were the second most reported category (20%), being disorders of galactose metabolism (12%) the most studied diseases within this category. Among energy-related IMD, cell membrane carriers (41.2%) were the most frequently studied, followed by mitochondrial defects (32.3%) and cytoplasmic defects (26.5%).

Considering each disease alone, the most reported in the literature was galactose-1-phosphate uridylyltransferase deficiency (11.5%), followed by ornithine transcarbamylase deficiency (8%), GLUT1 deficiency (7%) and glutaryl-CoA dehydrogenase deficiency (6%).

3.4. Neurocognitive impairment

3.4.1. IMDs global cognitive functioning

Regarding neurocognitive outcomes, the most commonly studied impairment was intellectual disability (ID), encompassing 88% of the evidence. However, about 66.5% of the studies reported mild/borderline ID (n=177) and 53.4% an average IQ (n=94). Only 32.2% of the records reported severe or moderate ID (n=57) (*Figure 3*).

The mean percentage of ID reported in the studies was 49.44 (SD=39.15). Higher percentages of ID were related to more language and social cognition impairment ($p=0.001$ and $p=0.022$, respectively; Mann-Whitney U test). However, no other cognitive domains were related to the percentage of ID.

Considering all the studies reviewed, the domains most frequently reported as impaired were fine motor dexterity (80.9%), behavioural and emotional regulation (80%), executive functions (73.3%), attention (72.4%) and social cognition (65.6%). On the opposite, the less reported as being impaired was processing speed (36.4%).

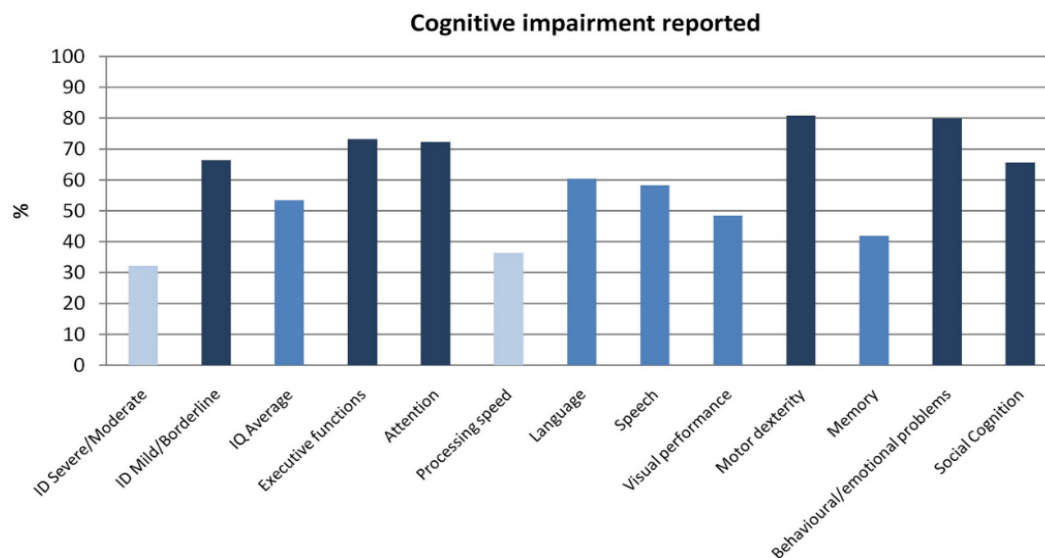


Figure 3. Percentage of studies reporting impairment of each cognitive domain.

3.4.2. Intoxication and Energy-related IMD

When the data were analyzed according to each IMD type, we found that intoxication IMDs presented a significantly higher percentage of studies than energy-related IMDs with average IQ (57.3%, $p=0.029$; Chi square test). Although there was also a difference in mild/borderline ID percentages, it was not statistically significant ($p=0.107$, Chi-square). Accordingly, energy-related IMDs had a higher percentage of cases with severe-moderate ID (51.5%) than intoxication IMDs (27.8%), being the differences statistically significant ($p=0.008$; Chi-square test).

The percentage of ID was higher among energy-related IMD (mean 60.95, SD=42.46) than intoxication IMDs (mean 46.91, SD=38.08). When the variable energy-related IMDs were decomposed, the mean percentage of ID among cytoplasmic defects (mean 80.38, SD=27.89; $p=0.025$, Kruskal-Wallis test) was significantly higher than cell membrane carriers (mean 68.35, SD=40.41) and mitochondrial defects (mean 35.80, SD=45.94). In cytoplasmic defects severe-moderate ID (66.7%) was more common than in cell membrane carriers (57.1%) and mitochondrial defects (30%), being the differences statistically significant ($p=0.017$; Chi-square test). Likewise, average IQ was more frequently reported among mitochondrial defects (60%) than cell membrane carriers (35.7%) and cytoplasmic defects (11.1%), with significant differences as well ($p=0.026$; Chi-square test). No differences were found regarding mild/borderline ID.

Disorders of energy substrate metabolism, disorders of peptide and amine metabolism, neurotransmitter disorders and disorders of mitochondrial gene expression were the most common showing severe-moderate ID ($p=0.001$, Chi-square test). For mild/borderline ID, the most frequent categories were nuclear-encoded disorders of oxidative phosphorylation, disorders of mitochondrial DNA maintenance and replication, disorders of amino acid metabolism and disorders of carbohydrate metabolism ($p=0.049$; Chi-square test). Lastly, the categories with higher percentages of average IQ were disorders of tetrapyrrole metabolism and disorders of fatty acid and ketone body metabolism ($p=0.019$; Chi-square test). No differences were found for other cognitive domains among the more specific categories.

Both types of IMDs showed a similar pattern of impairment in specific cognitive domains (*Figure 4*). After applying the Chi-Squared test, with a 95% of confidence, no statistically significant differences were found. However, qualitatively, intoxication IMDs showed more frequently attentional and language deficits, while energy-related IMDs had more frequently visuospatial deficits, specifically cell membrane carriers ($p=0.024$; Chi-square test).

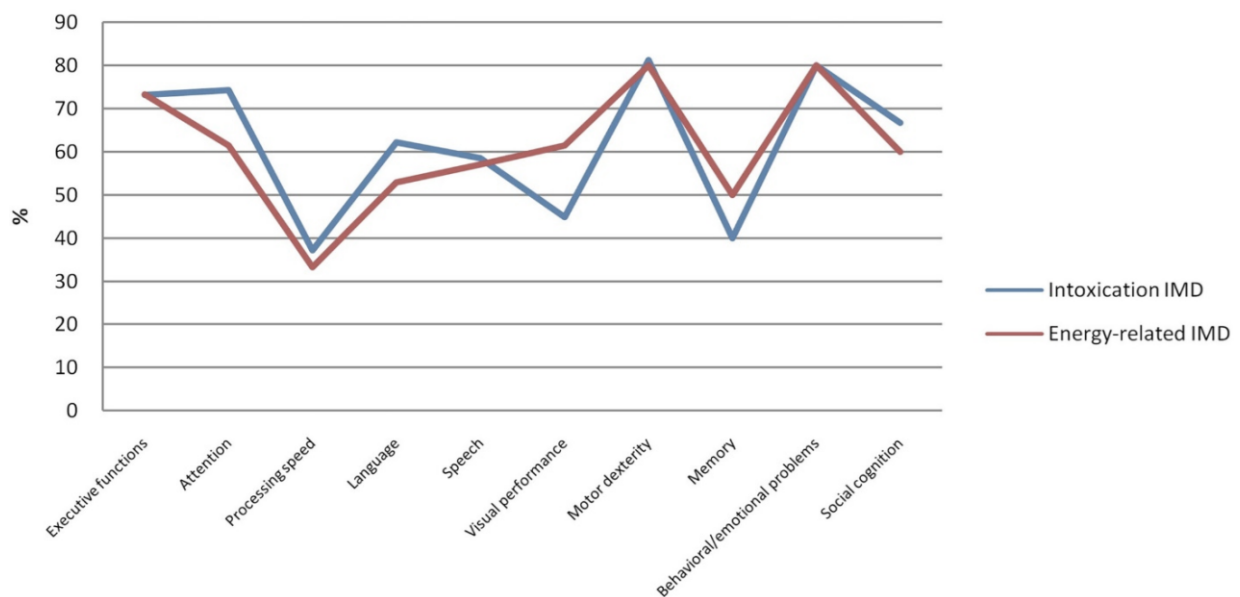


Figure 4. Percentage of studies reporting impairment on each cognitive function among Intoxication and Energy-related IMDs.

3.4.3. Neurocognitive impairment in particular disorders

Due to the significant diversity and complexity of the diseases involved, conducting statistical analysis on larger groups was not feasible. However, qualitative descriptions can still be drawn from the data, highlighting patterns of impairment associated with each specific IMD. *Figure 5* and *Figure 6*, serving as a visual resource, offer a guided summary of the cognitive impairments reported for each group and specific disease. As previously mentioned, many IMDs exhibit similar patterns of impairment, with motor dexterity, executive functions, and attention being the most frequently reported issues. However, some groups of IMDs lack detailed descriptions of cognitive functioning. For instance, biotin metabolism disorders have mainly been associated with motor dexterity and visuospatial deficits. Disorders related to pyruvate carboxylase deficiency have shown a greater prevalence of language disorders. In contrast, disorders such as those related to heme synthesis and porphyrias have primarily been characterized by psychiatric symptoms, along with difficulties in behavioural and emotional regulation.

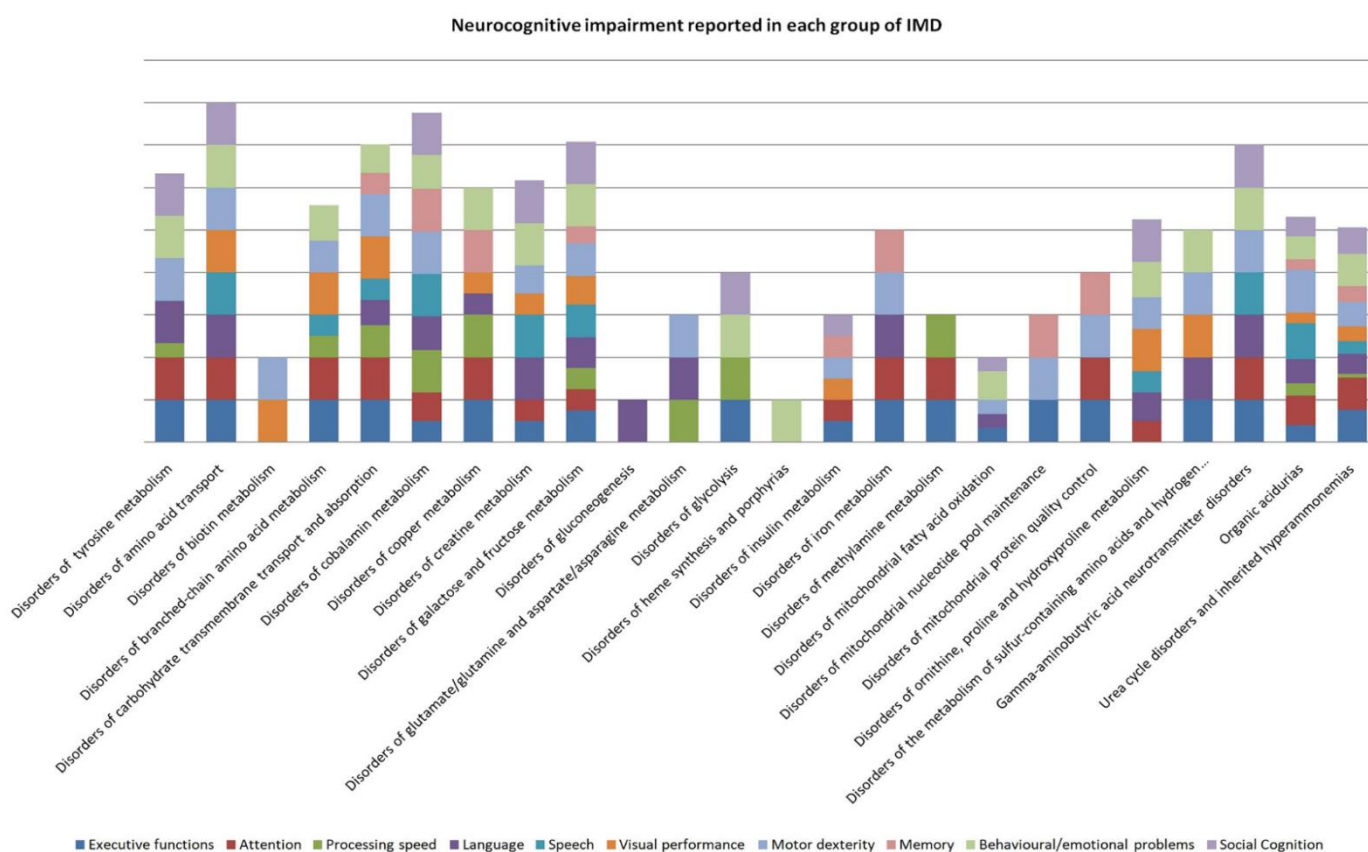


Figure 5. A visual guide illustrating the specific neurocognitive impairments associated with each group of IMDs.

3.5. Risk of bias

Due to the heterogeneity of study designs and case reports, it was not possible to employ standardised tools for the thorough assessment of quality or the evaluation of potential bias within the included studies.

Specific domains reported as impaired for each IMD

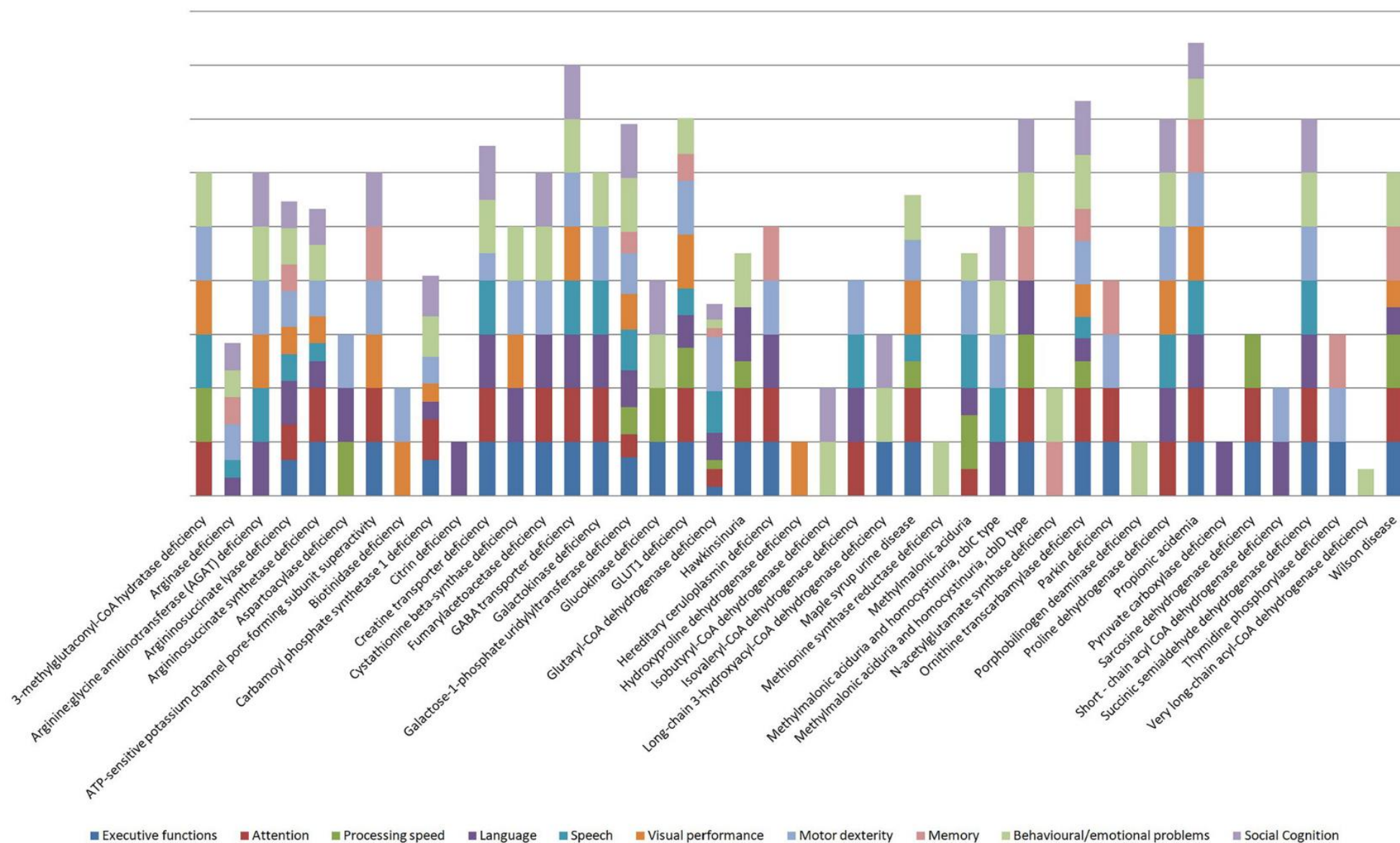


Figure 6. A visual guide illustrating the specific neurocognitive impairments associated with each specific IMD.

4. Discussion

To the best of our knowledge, this review summarizes most of the evidence available about cognitive and behavioural functioning in a large number of IMDs.

Over the past decade, there have been an increasing number of studies focused on the neurocognitive outcomes of IMDs. Previously, the core of the research was based on genetic, metabolic and neurological studies, since most survivors presented moderate to severe developmental disabilities (Waisbren & Gropman, 2016). Recently, areas such as executive functions and social cognition have gained increased attention in the literature on IMDs. While much work still needs to be done, the scientific community is becoming more aware of the neuropsychological impairments associated with these rare diseases, enhancing research in this field.

In recent years, the frequency of studies highlighting speech difficulties has declined, partially pointing towards positive effects of early detection and improved treatments and dietary interventions.

Among the records reviewed, the vast majority focused on intoxication IMDs. The most commonly reported conditions included urea cycle disorders, organic acidurias, and galactose metabolism disorders. Among energy-related IMDs, cell membrane carriers, such as GLUT1 deficiency, were the most frequently studied.

Overall, the specific disorders that received the most research attention were galactosemia, ornithine transcarbamylase (OTC) deficiency, GLUT1 deficiency, and glutaric aciduria type I (GA-1). Given that IMDs are rare diseases, the average number of subjects in studies was relatively small. For intoxication IMDs, the mean was 24 subjects, while for energy-related IMDs, it dropped significantly to 7 subjects per study. This disparity may result from the limited availability and variability of patient samples, as well as a high percentage of severe encephalopathies in pediatric energy-related disorders, which makes unfeasible the study of detailed neuropsychological profiles. Finally, these limitations force studies to concentrate on specific diseases or individual case reports and underscore the inherent challenges of researching rare diseases and complicate efforts to draw comprehensive conclusions.

Systematic reviews that focus on specific IMDs also face similar limitations, such as heterogeneous or small sample sizes, lack of control groups, and incomplete neuropsychological evaluations. Furthermore, the absence of standardised protocols in psychometric assessments across different centres complicates comparative analysis and makes it difficult to draw clear conclusions (Baglioni et al., 2024; Van de Burgt et al., 2023; Waisbren et al., 2019).

4.1. Intellectual disability (ID)

More than half of the subjects exhibited average IQ levels. Among those studies reporting on ID, a significant majority identified cases of mild ID or borderline IQ, whereas severe to moderate ID was the least represented in the literature.

Intoxication IMDs presented an overall better cognitive functioning than energy-related IMDs, with a significantly higher number of subjects with average IQ and mild ID. Accordingly, energy-related IMDs had more subjects with moderate to severe ID, especially among cytoplasmic defects such as creatine disorders. Mitochondrial beta-oxidation defects such as MCAD had the best cognitive outcome among energy-related IMDs.

A wide range of genetic and epigenetic factors are involved in the heterogeneity of global cognitive functioning (Lossi et al., 2024). Following the implementation of newborn screening and improved detection methods, some IMDs can now be identified at an earlier stage. This advancement has helped prevent many life-threatening symptoms and severe neurological damage. Consequently, there is an increasing number of asymptomatic patients and individuals exhibiting milder phenotypes when diagnosed before symptoms appear (Waisbren et al., 2019; Ferreira et al., 2019; Lai et al., 2016).

Disorders related to energy substrate metabolism, such as defects in creatine, are associated with more severe outcomes and in particular creatine transporter deficiency, since creatine supplementation and other dietetic strategies may not affect brain creatine concentrations or cognitive

outcomes (Li & Xu, 2023; Shi et al., 2021). Therefore, new treatment strategies are still needed to prevent this population's most severe cognitive impairments.

It is important to note that measuring severe to moderate ID using psychometric standardized tests can also be challenging. Developmental tests may struggle to differentiate among lower ability levels accurately due to the *floor effect*. As a result, some studies excluded may have used qualitative measures for individuals with more severe ID, potentially leading to their underrepresentation in the literature.

This review found that a higher percentage of ID is associated with increased language and social cognition. It is known that vocabulary levels and language development are essential in bolstering overall cognitive functioning.

On the other hand, the complex processes involved in social cognition engage advanced cognitive skills. Understanding social functioning is essential to conceptualizing intellectual disabilities, as it constitutes one of the primary components of overall adaptive functioning, alongside traditional IQ measures. Furthermore, it is important to note that autism spectrum disorder frequently co-occurs with intellectual disabilities; in fact, over 40% of genetic syndromes associated with ID tend to score relatively poorly on established social-cognitive assessments.

Additionally, performance on social-cognitive tasks in individuals with ID is related to difficulties in executive function and language. This connection underscores the challenge of separating social-cognitive abilities from language and general cognitive difficulties central to ID when using traditional assessment methods. The nature of these difficulties and the degree to which they emerge varies greatly among different disorders.

While most studies reported average or milder phenotypes, neurocognitive impairment can still be present in patients with higher overall cognitive abilities.

The neuropsychological domains most commonly reported as impaired in the literature include fine motor dexterity, behavioural and emotional regulation, executive functions, attention, and social cognition. In contrast, processing speed, aside from severe ID as previously mentioned, is less frequently documented.

4.2. Motor dexterity impairment

Motor disturbances are the most commonly observed impairments in individuals with IMDs. Since motor disorders may negatively impact many psychometric tests, lower scores often do not accurately reflect the individual's cognitive abilities. The interaction between motor difficulties and cognitive testing emphasises the need for a careful assessment approach to provide a more comprehensive understanding of the individual's capabilities.

Among intoxication IMDs, organic acidurias such as glutaric aciduria type I typically show acute-onset dystonia and dyskinesia. Following an acute encephalopathic crisis, these children may suffer from motor and language impairment, and severe dystonia can affect their long-term outcomes. Neuroimaging findings in this population often include frontotemporal atrophy, delayed myelination patterns, subdural hygromas, ventriculomegaly, and acute striatal necrosis of the basal ganglia. These factors contribute to movement disorders and motor delays (Reddy et al., 2018; Gropman, 2012).

Among energy-related IMDs, GLUT1 deficiency syndrome is commonly associated with dysarthria and various movement disorders (Kim et al., 2019; Sharma et al., 2017). Movement disorders in this condition have been associated to pyramidal, extrapyramidal and cerebellar systems (Wang et al., 2005), and epilepsy is also common among this population. Early intervention in GLUT-1 deficiency syndrome has been associated with improved motor outcomes and better control of epileptic seizures. However, the connection to cognitive outcomes still requires further research. Mild improvements in processing speed have been reported, and research shows that beginning treatment at an earlier stage may lead to more favourable cognitive IQ scores (Kolic et al., 2021; De Giorgis et al., 2019; Alter et al., 2015; Ramm-Petersen et al., 2014).

4.3. Executive functions and attentional deficits

Executive functions are often reported to be affected in intoxication and energy-related IMDs. Research on this topic has used advanced neuroimaging techniques, including diffusion tensor imaging (DTI), magnetic resonance spectroscopy, functional MRI (fMRI), functional near-infrared spectroscopy (fNIRS), or positron emission tomography (PET) (Gropman & Anderson, 2020). These

impairments are likely the most important consequences affecting individuals with neurodevelopmental disorders, influencing their ability to plan, focus, and regulate their behaviour effectively. The impact of these impairments extends beyond cognitive challenges, profoundly affecting individuals' overall functioning and quality of life.

Intoxication IMDs have been particularly associated with attentional deficits and dysexecutive functioning. In a review of 678 patients with urea cycle disorders, OTCD patients showed a higher dorsolateral prefrontal cortex (dlPFC) activity, suggesting a pattern of prefrontal inefficiency, and decreased white matter integrity in the frontal lobe, cingulum, and supplemental motor (Waisbren & Gropman, 2016). These findings correlated with an altered cognitive profile in working memory, executive functioning and attention. Similarly, in a twin case study with OTCD, the hemodynamics of the prefrontal cortex with fNIRS during an N-back working memory task showed a higher hemodynamic variation in a sibling with OTCD, especially in the left prefrontal cortex, during a higher working memory demand and a reduced interhemispheric functional connectivity as the task load increased (Anderson et al., 2020). These findings correlated with inefficient autoregulation and executive functioning in OTCD.

A study with children with MSUD found that almost all patients had attentional and executive dysfunction (Bouchereau et al., 2017). They speculated that the chronic accumulation of BCAA could provoke white matter abnormalities with consequent executive dysfunction. Also, amino acid depletion leads to neurotransmitter deficits like dopamine, crucial in the prefrontal circuit and executive functions.

4.4. Behavioural and emotional dysregulation

This is often associated with the psychiatric symptoms related to intoxication and energy-related IMDs. During episodes of acute decompensation, individuals may experience a range of psychiatric symptoms, including mental confusion, delirium, anxiety, aggression and agitation, bizarre behaviour, delusions and psychosis. These manifestations have been observed in conditions such as porphyrias, homocystinurias, or urea cycle disorders, among others. In cases of subacute or chronic psychiatric manifestations, mood and anxiety disorders are often seen as clinical manifestations related to the underlying disease and treatment management. In contrast, symptoms like

schizophrenic-spectrum disorders, catatonia, eating disorders, and aggressive and self-harm behaviours can indicate specific features of different IMDs (Baglioni et al., 2024; Van de Burgt et al., 2023; Mochel & Sedel., 2016).

Approximately 6% of cases of secondary psychosis are associated with neurometabolic disorders. However, the prevalence of IMDs within the mental health population is often underestimated, as psychiatric symptoms may overshadow neurological signs for years before becoming evident (Baglioni et al., 2024; Van de Burgt et al., 2023). Understanding the underlying causes of these psychiatric manifestations is essential for effective patient management. Since simple dietary modifications can lead to improvements in treatment outcomes, IMDs should be considered a potentially treatable cause of acute psychosis (Duarte et al., 2017; Colafrancesco et al., 2015).

Furthermore, clinicians should be alert to the possibility of an IMD if patients with intellectual disabilities and epilepsy show resistance to antipsychotic medications or experience adverse side effects that complicate their treatment (Herrera et al., 2017). A family history of consanguinity, signs of multisystem involvement, and unexplained infant deaths can all provide significant clues pointing towards the diagnosis of IMDs (Sklirou & Lichter-Konecki, 2018).

Therefore, systematic assessments for metabolic disorders should be conducted when atypical signs are observed in the psychiatric population. This approach can facilitate earlier diagnosis and treatment, ultimately enhancing the quality of mental health care (Van de Burgt et al., 2023; Echeverri et al., 2018; Herrera et al., 2017).

4.5. Social cognition deficits

Social behaviour have gained interest in the literature of IMDs in recent years. Even though the prevalence of IMDs in non-syndromic autism spectrum disorder (ASD) might be similar to the general population, the incidence is higher in countries with elevated consanguinity rates (Glinton & Elsea, 2019; Campistol et al., 2016).

In a series of 179 patients diagnosed with ASD, 3.3% had an IMD and the disorders identified in these patients included undiagnosed phenylketonuria (PKU), homocystinuria, Sanfilippo syndrome,

and 3-methylcrotonyl-CoA carboxylase deficiency (Çakar & Yilmazbas, 2021). Other organic acidurias, such as propionic academia, have also been associated with ASD (Shchelochkov et al., 2024), as well as cerebral creatine deficiency, succinic semialdehyde dehydrogenase deficiency, glycogen storage disease type IXa, pyrimidine metabolism disorders, and hypobetalipoproteinemia (İnci et al., 2021). PKU remains a significant health concern in patients from countries that lack newborn screening programs, especially among those who immigrated as refugees (İnci et al., 2021).

Although the association between ASD and IMDs has not been extensively documented in the literature, an underlying IMD could potentially be a treatable cause of ASD symptoms. While metabolic screenings in the ASD population may not seem cost-effective (Campistol et al., 2016), it is essential to gather a thorough personal and family medical history of the patient. Additionally, metabolic and genetic studies should be conducted when atypical findings are present, such as epilepsy, intellectual disabilities, dysmorphic features, motor disturbances, and other neurological or psychiatric disorders (Çakar & Yilmazbas, 2021; Žigman et al., 2021). However, further research is necessary to enhance our understanding of the association between ASD and IMDs, as well as how these conditions may interact and inform treatment opportunities.

4.6. Differences between intoxication and energy-related IMDs

In our review, we found similar cognitive and behavioural patterns between intoxication and energy-related IMDs despite differences in global intelligence. No significant differences were observed in any cognitive functions; however, slight tendencies were noted. Specifically, language skills were slightly more impaired in cases of intoxication IMDs, particularly in disorders related to carbohydrate metabolism, such as galactosemia.

In patients with galactosemia, a study found more extensive connectivity in brain regions responsible for language production deficits, particularly in frontal and motor regions, and a weaker connectivity in superior temporal regions (Timmers et al., 2015). Also, higher baseline blood flow was shown in the inferior frontal gyrus, superior temporal regions, insula and supplementary motor area. These changes within the language network could be associated with impairment in syntactic and speech-motor planning in patients with galactosaemia. Similarly, risk factors associated with language impairment were described in classical galactosaemia with a history of sound speech disorders

(Potter et al., 2008). Participants with typical cognitive development showed more often expressive language disorders, while those with borderline-low cognitive development had both receptive and expressive language disorders. They concluded that children with galactosaemia and speech disorders have a 4-6 times greater risk of developing language impairment than patients with speech disorders of unknown origin.

Among energy-related IMDs, visuoperception was the only domain that showed a significant impairment in patients with cell membrane carrier defects. In a retrospective study with 25 patients with GLUT1 deficiency syndrome, difficulties in visuospatial and visuomotor skills were particularly pronounced among this population (De Giorgis et al., 2019). However, they suggested that these deficits could be influenced by prominent extrapyramidal symptoms, including movement disorders.

4.7. Age-related manifestations

A wide range of IMDs usually presents in the newborn period or childhood. As children transition into the school environment, a cognitively challenging environment, these disabilities can exacerbate and lead to increasingly dysfunctional outcomes.

As a result, much of the existing research on neurocognitive impairment has primarily focused on pediatric populations. Interestingly, while both types of IMDs are reported more frequently in children compared to adults, those related to intoxication show a notably higher concentration of studies involving children. In contrast, IMDs associated with energy deficiency tends to have a greater proportion of research on adults, highlighting a significant difference in how these disorders manifest and are studied across different age groups.

Cytoplasmic defects like creatine metabolism disorders were the most described in adults, particularly in males due to the X-linked character of creatine transporter deficiency. Female patients with creatine deficiency tend to have a more attenuated phenotype or be completely asymptomatic, which allows a more detailed evaluation in adulthood (Sklirou & Lichter-Konecki, 2018).

Urea cycle disorders (UCD) were the intoxication IMD more represented on adult samples, primarily asymptomatic OTCD. However, studies on children or both children and adult series were

more frequent among these disorders. It is important to note that PKU probably represents much of the literature about adult intoxication type IMD and was not included in this review.

When examining neurocognitive outcomes related to age, both children and adults displayed a similar pattern of dysfunction. However, language and speech disorders were found more frequently in children than in adults. Given that language and speech are cognitive functions that develop during infancy and childhood, it is not surprising that a substantial proportion of the literature concentrates on these developmental stages, highlighting the impact of cognitive disruptions during this period.

Currently, the emergence of new genetic and metabolic treatments offers potential, but their efficacy and long-term impact on cognitive outcomes require further exploration through longitudinal studies and clinical trials. The available treatments can prevent neurocognitive impairment by avoiding most metabolic decompensations that cause additional neurological damage and stabilizing premorbid functioning. The new interventions have shown a notable effect on motor disorders. For instance, in a review with 270 patients with GLUT1 deficiency syndrome, ketogenic diet improved epilepsy for 83% of the sample within days or weeks, and movement disorders improved by 82% within months. However, cognition only improved in 59% of the patients and remained stable for 40% (Schwantje et al., 2020).

The direct effect of treatments on specific cognitive deficits remains uncertain, revealing a need for systematic neuropsychological assessments and interventions in this population (Jain-Ghai et al., 2020; Waisbren et al., 2019; Crowe et al., 2018).

Although the evidence points towards a large variability in cognitive functioning among IMD, we progress towards a vision of IMD as a continuous spectrum of symptoms in which the particular defect and the individual idiosyncrasy determine the predominance of one symptom over another (Michelini et al., 2024; Saudubray et al., 2019). Providing an overview of the clinical manifestations reported in the literature can help identify a spectrum of neuropsychological deficits and ultimately guide the individual neuropsychological assessments and interventions to improve IMD's quality of life.

4.8. Limitations and Future Directions

The main limitation of this review is the scarcity of evidence on neurocognitive impairment. It is important to remark that IMDs often cause severe encephalopathies, and some patients are not suitable for detailed neuropsychological assessments. Consequently, the current body of literature may fall short of fully representing IMD's wide-ranging complexity and diversity. This gap underscores the need for more comprehensive research to understand better the neurocognitive consequences associated with these conditions.

Moreover, the significant variability in the methodologies employed across the studies presents a complex challenge to drawing broad conclusions. Each study often utilizes different standardized measures, and the sizes of the samples vary considerably, further complicating the reliability of the results. The symptoms associated with each IMD also exhibit considerable heterogeneity, adding another layer of difficulty to generalization. These intricate factors underscore the need to interpret the data carefully. Additionally, it emphasizes the necessity of shifting the way cognitive functions are recorded and analyzed in the literature to more accurate representations and a deeper understanding of cognitive processes.

The classification of IMD and cognitive-behavioural disorders may have changed over time as our understanding of these conditions has evolved. As a result, many studies utilize different classifications, which complicates the review process in terms of searching, organizing, and synthesizing the data.

Additionally, many studies fail to clarify key clinical features relevant to neurocognitive outcomes. Important aspects to consider in future studies include the age at onset of symptoms, the frequency of metabolic crises, neuroimaging and biochemical analysis associated with each disease-specific profile. As a consequence, the findings should only guide future research and help personalize assessments based on the patient's history and daily functioning.

Further comprehensive, multicenter, and longitudinal neuropsychological studies are needed to understand better the underlying mechanisms of cognitive-behavioural impairment in this population. However, international protocols for neuropsychological assessment and treatment are

needed to standardize methodology, facilitate the comparison of studies, and establish guidelines for evidence-based interventions addressing the frequent neurocognitive impairments associated with IMD.

By conducting thorough and systematic evaluations, we can facilitate the early detection of cognitive strengths and weaknesses, allowing for timely personalised interventions. This proactive approach can help prevent negative impacts on academic performance and daily functioning, enhancing the quality of life for individuals with IMDs and their families.

4.9. Conclusions

This systematic review summarizes the existing literature on neurocognitive functioning in a wide range of inherited metabolic disorders. Various neurocognitive impairments, including intellectual disabilities, motor disturbances, executive dysfunction, attention deficits, behavioural and emotional deregulation, as well as deficits in social cognition, are frequently reported among individuals with these disorders. These impairments significantly affect both the daily functioning and quality of life for patients and their families.

A similar pattern of neurocognitive impairment was observed between intoxication and energy-related IMDs. However, slight differences, such as in language and visuoperception, were noted. Overall, intoxication IMDs demonstrated better global cognitive performance, with higher IQ scores.

Despite the recent increase in cognitive studies, there is still a significant need for more research to establish guidelines for early detection and treatment, to enhance the neuropsychological outcomes of IMDs. This discussion includes important risk factors and indicators that can aid in early differential diagnosis.

Key Findings

- IMDs share a pattern of motor disturbances and neuropsychological deficits in executive functions, attention, social cognition and behavioural regulation, affecting daily life.
- Intoxication IMDs generally show better cognitive outcomes than energy-related IMDs.
- Early detection and treatment improve motor and cognitive outcomes, but effects may vary.
- Research is limited by small, heterogeneous samples and inconsistent, non-standardized assessments.
- Standardized and longitudinal neuropsychological studies are needed for early detection and personalized interventions.

Chapter III

Neuropsychological Characterization:

A multicenter cohort study

1. Introduction

In recent decades, there has been a shift in paradigm from reactive to proactive management of IMDs, particularly concerning cognitive outcomes. The implementation of newborn screening (NBS), next-generation sequencing (NGS), and early dietary or molecular interventions have allowed for earlier diagnosis and treatment, often preventing irreversible brain damage. Longitudinal studies consistently demonstrate that individuals treated early exhibit significantly better cognitive outcomes than those diagnosed later, as a result of preventing metabolic crises (Mutze et al., 2020; Kiess et al., 2020; Castiñeras et al., 2019).

NGS and genome-first approaches have further revolutionised diagnostic strategies. The "BabyDetect" study (Boemer et al., 2025) found that approximately 42% of treated metabolic conditions would have been missed by conventional biochemical screening alone. By integrating genomic sequencing with metabolic profiling, not only diagnostic accuracy improves but also enables pre-symptomatic interventions that preserve neurocognitive function. However, as mentioned in previous chapters, the presence of a pathogenic genotype does not always predict the phenotype, which may be influenced by environmental and polygenic modifiers as well (García-Cazorla & Saudubray, 2018; Morava et al. 2015).

Dietary management remains a foundation of therapy in many IMDs. The restriction of specific substrates combined with tailored supplementation can significantly improve metabolic stability and support brain development, especially when initiated early. While these interventions can often be burdensome for patients and families, they are powerful tools for improving neurological outcomes (Kiess et al., 2020). However, there is a need for future clinical trials to incorporate comprehensive measures of neuropsychological and adaptive functioning to assess the effectiveness of emerging therapies more accurately (Cannon Homaei et al, 2022).

Since most IMDs affecting the nervous system leading to significant neurodevelopmental disruptions, many individuals display a wide range of cognitive and behavioural impairments.

Neurodevelopmental disorders (NDDs) associated with IMDs can span a broad spectrum of symptoms and severity, from learning difficulties to intellectual disability, and include neuropsychiatric symptoms and motor disturbances (García-Cazorla & Saudubray, 2018).

Although these patients might not fully meet the criteria for established NDDs such as ASD or ADHD, they often exhibit a dimensional range of overlapping symptoms, highlighting the necessity for holistic neuropsychological assessments and individualised support (Michelini et al., 2024; Cannon Homaei et al, 2022).

As discussed in Chapter II, several cognitive domains are consistently impaired across treatable IMDs, including fine motor dexterity, behavioral and emotional regulation, executive functioning, attention, and social cognition (Gil-González et al. 2025). These findings suggest that despite the variability of symptoms, intoxication and energy-related IMDs may share underlying patterns of impairment, even though they arise from distinct pathophysiological mechanisms. This perspective broadens our understanding of how IMDs affects brain function, highlighting the need to recognize subtle neurocognitive deficits beyond global intelligence measures.

This Chapter aims to characterise the neuropsychological outcomes of pediatric patients with intoxication and energy-related IMDs, using broad and standardised neuropsychological assessments. We hypothesise that, despite different underlying pathophysiological mechanisms, both groups could demonstrate similar patterns of cognitive dysfunction. We also aim to investigate how other clinical variables, including age, gender, onset, or other medical conditions, may contribute to neurocognitive impairment in IMDs.

2. Methods

2.1. Participants

The study included participants aged 6 to 17 with a confirmed diagnosis of intoxication or energy-related IMD, established through genetic and biochemical testing. All participants exhibited either mild phenotypes or were asymptomatic ($IQ > 55$), with good adherence to treatments and controlled metabolic decompensations (≤ 1 /year). Exclusion criteria included a history of significant head trauma, the presence of other neurological disorders unrelated to the IMD, and patients treated with methylphenidate or other psychostimulant medication, as it may influence cognitive performance.

Patients were recruited from several reference hospitals in Spain: 37 from Hospital Sant Joan de Déu in Barcelona (52.9%), 18 from the Hospital Materno-Infantil in Las Palmas de Gran Canaria (25.7%) and 15 from Hospital 12 de Octubre in Madrid (21.4%). The final sample included 70 participants, 40 with intoxication IMD (57.1%) and 30 with energy-related IMD (42.9%). Descriptive statistics were used to summarize demographic and clinical features of the cohort (*Table 1*).

2.2. Neuropsychological assessment

A comprehensive two-hour neuropsychological assessment was conducted to evaluate multiple cognitive, behavioral, and adaptive domains, with tasks tailored to the patient's age. Specific psychometric tests and scales are detailed in *Table 2*.

The evaluation covered global cognitive functioning, language abilities (vocabulary, verbal fluency, oral comprehension, morphosyntax, phonological errors), visuoconstructive skills, attention (focused/vigilance, sustained attention), executive functions (inhibitory control, working memory, cognitive flexibility, planning, phonemic fluency, and processing speed) and social cognition (affect recognition, theory of mind). Additionally, fine motor coordination was assessed through an assembly task measuring dexterity.

Table 1. Demographic and clinical characteristics of the cohort.

Patient	Age	Gender	Hospital	IMD type	IMD Category	IMD	Gene #OMIM	Onset	Diet	Special needs	Medical history observations
1	17y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		
2	7y 2m	M	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	School accommodations	
3	16y 4m	M	Barcelona	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		
4	6y 1m	M	Barcelona	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Early onset	No		
5	7y	M	Barcelona	Intoxication	Amino acid metabolism	Propionic acidemia	PCCA #232000	Early onset	Low protein	School accommodations	LT
6	8y 8m	M	Canarias	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Late onset	Low protein	Speech therapy	
7	8y 6m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	School accommodations Speech therapy Psychology	Epilepsy, AEDs
8	17y 9m	F	Canarias	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Late onset	Low fat		
9	12y 2m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	School accommodations	
10	6y 11m	M	Barcelona	Intoxication	Amino acid metabolism	Arginase deficiency	ARG1 #608313	Early onset	Low protein	Speech therapy Psychology	LT
11	12y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		LT
12	6y 10m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Carnitine palmitoyltransferase 2 deficiency	CPT2 #600650	Early onset	Low fat	School accommodations Speech therapy Psychology School reinforcement Physical therapy	
13	9y 9m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	Speech therapy Psychology School reinforcement	Epilepsy
14	10y 10m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	School accommodations School reinforcement	
15	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	School accommodations School reinforcement	
16	16y 3m	M	Barcelona	Intoxication	Amino acid metabolism	Argininosuccinate lyase deficiency	ASL #608310	Late onset	No		
17	12y 4m	F	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	School accommodations Speech therapy	

										School reinforcement Physical therapy	
18	9y 4m	F	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	School accommodations Speech therapy Psychology School reinforcement	
19	8y 4m	F	Barcelona	Intoxication	Amino acid metabolism	Tyrosinemia type 2	TAT #613018	Early onset	Low protein	School accommodations	
20	17y	M	Barcelona	Intoxication	Vitamin and cofactor	Biotinidase deficiency	BTD #609019	Early onset	No	School accommodations	
21	13y 7m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		
22	8y 8m	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		
23	14y 7m	M	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		
24	7y 9m	M	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein		
25	6y 1m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
26	10y 9m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
27	15y 4m	F	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		
28	7y 5m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 6	PYGL #613741	Late onset	Low Glycemic Index		
29	6y 1m	M	Canarias	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat		
30	15y 1m	M	Canarias	Intoxication	Amino acid metabolism	Cystathionine beta-synthase deficiency	CTH #607657	Late onset	Low protein		
31	14y 1m	F	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		
32	9y	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Early onset	Low protein	School accommodations School reinforcement	LT
33	16y 6m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No	Speech therapy School reinforcement	
34	6y 10m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
35	13y 11m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	School accommodations Psychology School reinforcement	
36	10y 5m	M	Canarias	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Late onset	No	School accommodations Speech therapy Psychology School reinforcement	Epilepsy, AEDs

										Physical therapy
37	12y 1m	M	Barcelona	Intoxication	Vitamin and cofactor	5,10-methylenetetrahydrofolate reductase deficiency	MTHFR #607093	Late onset	No	School accommodations School reinforcement
38	11y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic	School accommodations School reinforcement Physical therapy
39	8y 7m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	
40	10y 11m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	
41	8y 5m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School accommodations Speech therapy School reinforcement Physical therapy
42	8y 9m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Carnitine palmitoyltransferase 2 deficiency	CPT2 #600650	Early onset	Low fat	
43	16y 11m	M	Barcelona	Intoxication	Carbohydrate metabolism	Galactose-1-phosphate uridylyltransferase deficiency	GALT #606999	Early onset	Low galactose	School accommodations Speech therapy
44	15y	M	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	
45	14y 6m	F	Canarias	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Late onset	No	
46	6y 10m	F	Barcelona	Intoxication	Amino acid metabolism	3-metil crotonil glicinuria	MCCC2 #609014	Early onset	No	
47	6y 3m	M	Madrid	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat	School accommodations Speech therapy
48	8y 6m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School accommodations
49	10y 11m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Late onset	Low fat	
50	8y 4m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	
51	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Late onset	Low fat	School accommodations School reinforcement
52	13y 1m	F	Madrid	Energy-related	mtDNA	Mitochondrial tRNA-Leu 1 deficiency	MT-TL1 #590050	Early onset	No	School accommodations
53	12y 10m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School reinforcement Epilepsy
54	11y 9m	F	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic	
55	9y 11m	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	School accommodations School reinforcement

56	9y	F	Barcelona	Intoxication	Amino acid metabolism	Arginase deficiency	ARG1 #608313	Late onset	Low protein	School accommodations Speech therapy Psychology School reinforcement Physical therapy	LT
57	7y 3m	F	Madrid	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Early onset	Low protein		
58	13y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		
59	10y 8m	M	Barcelona	Intoxication	Amino acid metabolism	Propionic acidemia	PCCB #232050	Late onset	Low protein	School accommodations School reinforcement	LT
60	10y 9m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School accommodations School reinforcement	
61	13y 10m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		
62	9y 5m	M	Barcelona	Intoxication	Amino acid metabolism	Maple syrup urine disease	DBT #248610	Early onset	Low protein		
63	13y 1m	F	Canarias	Energy-related	Fatty acid and ketone bodies	Carnitine-acylcarnitine translocase deficiency	SLC25A20 #613698	Early onset	Low fat	Psychology School reinforcement	LT
64	14y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		
65	9y 9m	F	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		
66	17y 7m	M	Barcelona	Energy-related	mtDNA	Mitochondrial tRNA-Leu 1 deficiency	MT-TL1 #590050	Late onset	No		Epilepsy, AEDs
67	8y 1m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Early onset	Low Glycemic Index		
68	9y 6m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	School accommodations Speech therapy	
69	10y	M	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	Speech therapy Physical therapy	
70	13y 2m	F	Canarias	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein	School accommodations	

AEDs= antiepileptic drugs
LT= liver transplant

Behavioral and emotional regulation were explored through caregiver questionnaires addressing internalizing (such as depression, anxiety, somatic complaints, obsessive-compulsive behaviors, and posttraumatic symptoms) and externalizing behaviours (hyperactivity-impulsivity, attention issues, aggressive behavior, defiant behavior, anger control problems, and antisocial behavior), as well as overall executive functioning (emotional, behavioural and cognitive regulation). Finally, adaptive behavior was evaluated, providing insight into each individual's cognitive, social, and practical skills necessary for daily functioning.

The psychometric tests and the ABAS-II were scored using Standard Scores (SS), with an average score of 100 and a standard deviation of 15. Scores below 80 were classified as impaired. The behavioral questionnaires SENA (except for PR-SENA) and BRIEF, used an inverse standard score system, and scores above 120 were considered impaired.

2.3. Statistical analysis

The study examined various descriptive variables, including age, gender, type of disease and specific categories from the International Classification of Inherited Metabolic Disorders (ICIMD) (Ferreira et al., 2021). It also examined the age at disease onset, defining early-onset as 0-11 months and late-onset as over 1 year.

Additional factors considered were the presence of special needs (such as speech therapy, school accommodations, psychological support, and physical therapy), school year (primary school, secondary school, or high school), ADHD and ASD criteria according to the DSM-5-TR, and other medical conditions (such as epilepsy, use of antiepileptic drugs, and liver transplant).

Before performing statistical analyses, we conducted a normality test on the quantitative variables using the Kolmogorov-Smirnov test, and the variables did not follow a normal distribution. Consequently, we used non-parametric tests: the Mann-Whitney U test for categorical variables with two categories and the Kruskal-Wallis test for those with three or more groups. Fisher's exact test was applied to variables with fewer than five cases. For qualitative variables, we used Pearson's Chi-square test.

Table 2. Summary of the cognitive domains and tests included in the neuropsychological evaluation.

Cognitive Function	Specific Domains	6 – 16:11 years	17-17:11 years
Global Cognitive Performance	-Intelligence Quotient (IQ)	-WISC-V - Verbal Comprehension Index (VCI) - Visual-Spatial Index (VSI) - Fluid Reasoning Index (FRI) - Working Memory Index (WMI) - Processing Speed Index (PSI) - General Ability Index (GAI) - Cognitive Proficiency Index (CPI) - Nonverbal Index (NVI).	-WAIS-IV - Verbal Comprehension Index (VCI) - Perceptual Reasoning Index (PRI) - Working Memory Index (WMI) - Processing Speed Index (PSI)
Language	- Vocabulary	-Vocabulary (V) WISC-V	-Vocabulary (V) WAIS-IV
	- Verbal Fluency	-Semantic Word Generation (NEPSY-II)	-Animals Test
	- Oral comprehension	-Qualitative notes	-Qualitative notes
	- Morphosyntax	-Qualitative notes	-Qualitative notes
	- Phonological errors	-Qualitative notes	-Qualitative notes
Visual-Spatial Skills	-Visual organization and constructional praxis	-Block Design (BD) WISC-V -Rey-Osterrieth Complex Figure (ROCF)	-Block Design (BD) WAIS-IV -Rey-Osterrieth Complex Figure (ROCF)
Attention	-Focused attention / Vigilance	-Digit Span Forward (DsF) WISC-V -K-CPT-2 (6-7y) or CPT-3 (≥8y) - Omissions O-CPT - Commissions C-CPT - Hit reaction time HRT-CPT - Consistency CONS HRT-CPT - Variability VAR HRT-CPT - Inter-stimulus interval HRT ISI CPT	Digit Span Forward (DsF) WAIS-IV -CPT-3 - Omissions O-CPT - Commissions C-CPT - Hit reaction time HRT-CPT - Consistency CONS HRT-CPT - Variability VAR HRT-CPT - Inter-stimulus interval HRT ISI-CPT
	-Sustained attention	- Block change HRT BLOCK-CPT	- Block change HRT BLOCK-CPT
Executive Functions	-Inhibitory control / Impulsivity	-K-CPT-2 or CPT-3 - Commissions C-CPT - Hit reaction time HRT-CPT - Perseverations PERS-CPT -Inhibition NEPSY-II	-CPT-3 - Commissions C-CPT - Hit reaction time HRT-CPT - Perseverations PERS-CPT -Stroop Test
	- Working Memory	-Digit Span Backwards (DsB) WISC-V	-Digit Span Backwards (DsB) WAIS-IV
	-Cognitive flexibility	-Inhibition NEPSY-II	-Stroop Test
	-Phonemic Fluency	-Phonemic Fluency NEPSY-II	-FAS test
	-Planning	-Plan-ROCF	-Plan-ROCF
	-Processing Speed	-Time-ROCF -Coding (C) WISC-V -Symbol Search (SS) WISC-V	-Time-ROCF -Coding (C) WAIS-IV -Symbol Search (SS) WAIS-IV
Social Cognition	-Affect Recognition	-AR NEPSY-II	-AR NEPSY-II (16:11)
	-Theory of mind	-ToM NEPSY-II	-ToM NEPSY –II (16:11)
Motor Skills	-Fine motor dexterity	Purdue Pegboard Test (PPT)	Purdue Pegboard Test (PPT)
Behavior and Emotional Regulation	-Internalizing symptoms	-Emotional problems (E)-SENA -Emotional Regulation (ER) BRIEF -Personal Resources (PR) SENA	-Emotional problems (E)-SENA -Emotional Regulation (ER) BRIEF -Personal Resources (PR) SENA
	-Externalizing symptoms	-Behavioral problems (B) SENA -General problems (G)-SENA -Executive functions (EF)-SENA -Behavioral Regulation (BR)-BRIEF -Cognitive Regulation (CR)-BRIEF -General functioning (G)-BRIEF	-Behavioral problems (B) SENA -General problems (G)-SENA -Executive functions (EF)-SENA -Behavioral Regulation (BR)-BRIEF -Cognitive Regulation (CR)-BRIEF -General functioning (G)-BRIEF
Adaptive Behavior	-Global adaptive behavior	-GAB ABAS-II	-GAB ABAS-II
	-Cognitive/Academic settings	-C ABAS-II	-C ABAS-II
	-Social settings	-S ABAS-II	-S ABAS-II
	-Practical settings	-P ABAS-II	-P ABAS-II

WISC=Wechsler intelligence scale for children, WAIS= Wechsler adults intelligence scale, NEPSY= Developmental Neuropsychological Assessment, CPT= Conners' Continuous Performance Test, SENA= Sistema de Evaluación de Niños y Adolescentes (children and adolescent evaluation system), BRIEF= Behavior rating inventory of executive function, ABAS= Adaptive behaviour assessment system.

All statistical tests were carried out with a confidence level of 95% and considered significant at $p < 0.05$. The analyses were performed using IBM SPSS statistical software version 29.0.

2.4. Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. The potential risks and benefits were explained to the participants and their families. Participation was voluntary, and participants could withdraw from the study at any time without any consequences to their medical care. The study was approved by the Research Ethics Committee of Hospital Sant Joan de Déu, and written informed consent was obtained from the parents or legal guardians of all participants, with assent collected from children over the age of 12.

3. Results

The cohort was composed of 70 patients, 40 with intoxication IMD (57.1%) and 30 with energy-related IMD (42.9%), with a mean age of 10.95 ± 3.32 (*Table 1*).

3.1. Overall neurocognitive performance

Firstly, the study examined the cognitive abilities of the entire cohort, which had a mean IQ of 85.84 (SD=15.68). Notably, lower scores were recorded in the WMI, with a mean score of 84.80 (SD=16.57), and in the CPI, with a mean score of 83.64 (SD=17.08). These scores suggest that attentional processes are interfering with overall cognitive performance.

Regarding specific cognitive functions, the lowest scores, falling below the average range, were observed in fine motor dexterity, as measured by the PPT, with a mean score of 78.79 (SD=18.68). Overall, the cohort exhibited slower and more variable reaction times, along with a high rate of omission errors. These findings suggest deficits in processing speed and focused attention: O-CPT (M=82.22, SD=23.37), HRT-CPT (M=80.84, SD=19.50), CONS HRT-CPT (M=79.72, SD=25.57), VAR HRT-CPT (M=82.78, SD=20.90), PERS-CPT (M=82.88, SD=23.61), HRT ISI-CPT (M=83.03, SD=22.38). Additionally, the sample had low scores in social cognition, with a mean score of 83.67 (SD=13.42) on the ToM-Nepsy.

When evaluating behavioural and emotional regulation through questionnaires, the cohort performed poorly on the C-ABAS (M=83.53, SD=18.48) and the CR-BRIEF (M=117.17, SD=21.76). These results indicate deficits in cognitive executive functioning, potentially leading to a negative impact on learning abilities. *Figure 1* illustrates the mean standard scores (SS) of the entire cohort across each neuropsychological test.

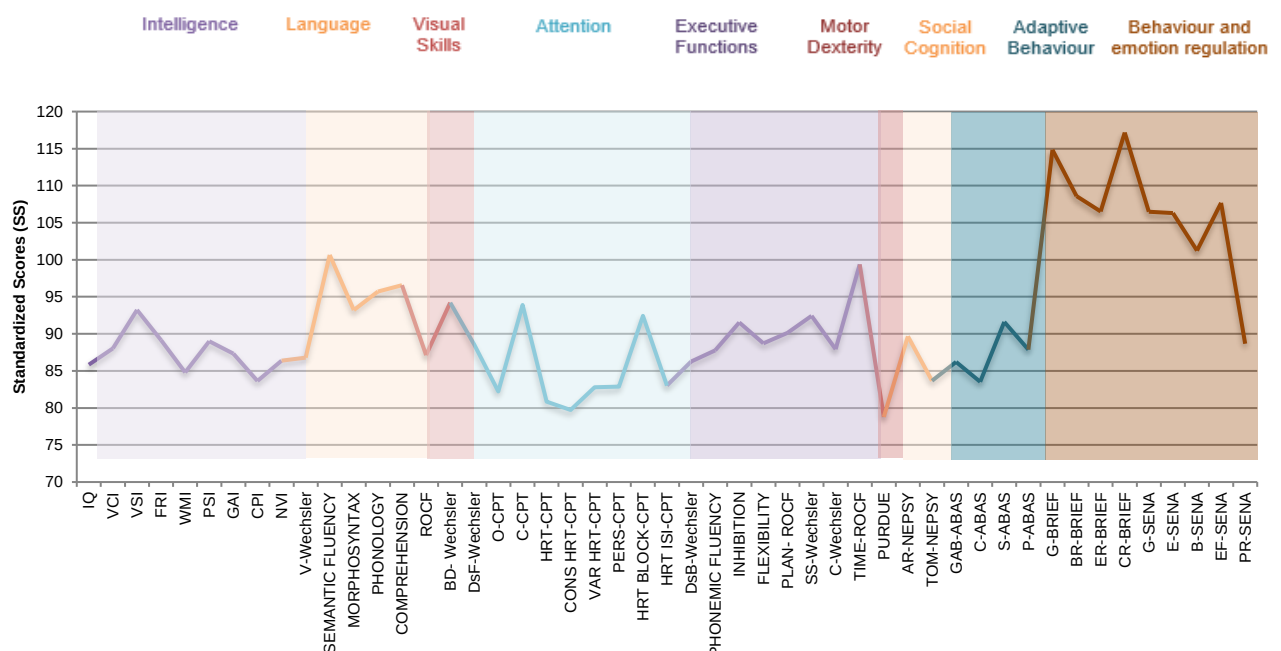


Figure 1. Mean standardized scores obtained across all neuropsychological domains in the entire cohort.

Nearly half of the participants in the cohort met the criteria for ADHD (45.7%) or exhibited traits of ASD (47.1%). This finding emphasizes the need for specialized therapies or accommodations to the IMD population. In our sample, the most common forms of support provided included school accommodations (40%), school reinforcement (28.6%), speech therapy (21.4%), psychological support (12.9%), and physical therapy (10%).

3.1.1. Differences between intoxication and energy-related IMDs

A similar pattern of impairment was observed between intoxication and energy-related IMDs (*Figure 2*). However, energy-related IMDs had lower scores than intoxication IMDs in focused attention, with almost significant differences in VAR HRT-CPT ($p=0.052$, Mann-Whitney U). On the other hand, intoxication IMDs showed lower scores in language, specifically in morphosyntax ($p=0.028$, Mann-Whitney U).

Comparing more specific categories of IMDs from the ICIMD, vitamin and cofactor disorders had lower global cognitive performance (GAI, $p=0.021$, Kruskal-Wallis), as well as lower scores in vocabulary (V-Wechsler, $p=0.027$, Kruskal-Wallis) and affect recognition (AR-NEPSY, $p=0.049$, Kruskal-Wallis). Overall, the category with a better cognitive outcome was fatty acid and ketone bodies disorders ($p=0.042$, Kruskal-Wallis).

With 95% confidence, no other significant differences were found between intoxication and energy-related IMDs, or any of their specific categories, concerning neurocognitive performance, ADHD criteria ($p=0.729$, Chi-square), or ASD symptoms ($p=0.945$, Chi-square). Furthermore, the Pearson Chi-square test revealed no significant differences between intoxication and energy-related IMDs in special needs, including speech therapy ($p=0.153$), school accommodations ($p=0.622$), psychology ($p=0.536$), school reinforcement ($p=0.445$), or physical therapy ($p=1.000$).

Due to the heterogeneity of the sample, it was not possible to analyse disorder-specific neuropsychological profiles. Instead, *Table 3* and *Table 4* provide a qualitative description of the affected cognitive domains for each patient, clustered by specific disorders of intoxication and energy-related IMDs.

Table 3. Description of the neuropsychological domains impaired across the intoxication IMD sample, clustered by specific diseases.

IMDs	IMD GROUP	AGE	SEX	ONSET	IQ	Language	Attention	Executive Functions	Visuo-Motor	Social Cognition	Behaviour Regulation
Biotinidase deficiency	Biotin metabolism	17y	M	EO	135				X	X	
Maple syrup urine disease	Branched-chain amino acid metabolism	9y 5m	M	EO	73		X	X		X	X
Wilson disease	Copper metabolism	13y 7m	M	LO	82	X	X	X	X	X	X
Wilson disease	Copper metabolism	15y 4m	F	LO	72	X	X		X	X	X
Wilson disease	Copper metabolism	16y 6m	M	LO	82		X		X		
Wilson disease	Copper metabolism	13y 10m	M	LO	76		X	X			X
5,10-methylenetetrahydrofolate reductase deficiency	Folate metabolism	12y 1m	M	LO	92		X			X	
Hereditary fructose intolerance	Fructose metabolism	16y 4m	M	LO	78		X	X	X	X	X
Hereditary fructose intolerance	Fructose metabolism	14y 7m	M	LO	94	X				X	X
Hereditary fructose intolerance	Fructose metabolism	14y 1m	F	LO	69	X	X	X	X	X	X
Hereditary fructose intolerance	Fructose metabolism	9y 9m	F	LO	77		X		X		
Galactose-1-phosphate uridylyltransferase deficiency	Galactose metabolism	16y 11m	M	EO	95		X	X	X		
3-metil crotonil glicinuria	Organic Aciduria	6y 10m	F	EO	70	X			X	X	
Cystathionine beta-synthase deficiency	Organic Aciduria	15y 1m	M	LO	108				X	X	X
Glutaryl-CoA dehydrogenase deficiency	Organic Aciduria	8y 8m	M	LO	97		X				
Glutaryl-CoA dehydrogenase deficiency	Organic Aciduria	12y 4m	F	EO	116		X				X
Glutaryl-CoA dehydrogenase deficiency	Organic Aciduria	9y 4m	F	EO	93		X				
Glutaryl-CoA dehydrogenase deficiency	Organic Aciduria	15y	M	EO	64		X		X	X	
Glutaryl-CoA dehydrogenase deficiency	Organic Aciduria	10y	M	EO	103			X			
Propionic acidemia	Organic Aciduria	7y	M	EO	105			X			
Propionic acidemia	Organic Aciduria	10y 8m	M	LO	66	X	X		X	X	X
Pyridoxine-dependent epilepsy	Pyridoxine metabolism	8y 6m	F	EO	60	X	X	X	X	X	X
Pyridoxine-dependent epilepsy	Pyridoxine metabolism	9y 9m	F	EO	69		X	X	X	X	X
Pyridoxine-dependent epilepsy	Pyridoxine metabolism	7y 9m	M	EO	97			X			
Tyrosinemia type 1	Tyrosine metabolism	7y 2m	M	LO	75			X			X
Tyrosinemia type 1	Tyrosine metabolism	9y	F	EO	73			X	X	X	
Tyrosinemia type 1	Tyrosine metabolism	9y 11m	F	LO	85		X	X	X		
Tyrosinemia type 2	Tyrosine metabolism	8y 4m	F	EO	110			X	X	X	X
Arginase deficiency	Urea Cycle Disorder	6y 11m	M	EO	71			X	X	X	
Arginase deficiency	Urea Cycle Disorder	9y	F	LO	88		X		X	X	X
Argininosuccinate lyase deficiency	Urea Cycle Disorder	16y 3m	M	LO	93		X		X		X
Argininosuccinate synthetase deficiency	Urea Cycle Disorder	6y 1m	M	EO	88		X		X		
Argininosuccinate synthetase deficiency	Urea Cycle Disorder	10y 5m	M	LO	87			X			X
Argininosuccinate synthetase deficiency	Urea Cycle Disorder	14y 6m	F	LO	77		X	X	X	X	
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	17y	F	LO	100			X			
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	12y	F	LO	94		X	X			X
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	8y 8m	F	LO	81		X				
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	7y 3m	F	EO	86		X	X	X	X	
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	14y	F	LO	81	X	X	X	X	X	
Ornithine transcarbamylase deficiency	Urea Cycle Disorder	13y 2m	F	LO	72			X	X	X	X

Table 4. Description of the neuropsychological domains impaired across the energy-related IMD sample, clustered by specific diseases.

IMD	IMD group	Age	Sex	Onset	IQ	Language	Attention	Executive Functions	Visuo-Motor	Social Cognition	Behaviour Regulation
Carnitine palmitoyltransferase 2 deficiency	Carnitine metabolism	6y 10m	F	EO	105					X	
Carnitine palmitoyltransferase 2 deficiency	Carnitine metabolism	8y 9m	F	EO	100		X	X			
Carnitine-acylcarnitine translocase deficiency	Carnitine metabolism	13y 1m	F	EO	75	X	X	X	X	X	X
GLUT1 deficiency	GLUT1	8y 5m	M	LO	69	X	X	X	X	X	X
GLUT1 deficiency	GLUT1	8y 6m	F	LO	61	X	X	X	X	X	
GLUT1 deficiency	GLUT1	12y 10m	F	LO	89	X	X			X	X
GLUT1 deficiency	GLUT1	13y 3m	M	LO	84		X	X		X	
GLUT1 deficiency	GLUT1	10y 9m	M	LO	102	X			X		
Glycogen storage disease type 3	Glycogen storage	11y 3m	M	EO	66			X			X
Glycogen storage disease type 3	Glycogen storage	11y 9m	F	EO	106		X	X			X
Glycogen storage disease type 6	Glycogen storage	7y 5m	M	LO	92	X			X		X
Glycogen storage disease type 9	Glycogen storage	12y 2m	M	LO	92		X		X	X	
Glycogen storage disease type 9	Glycogen storage	10y 10m	M	LO	110		X		X	X	
Glycogen storage disease type 9	Glycogen storage	13y 11m	M	LO	93		X	X	X	X	X
Glycogen storage disease type 9	Glycogen storage	10y 11m	M	LO	73				X		
Glycogen storage disease type 9	Glycogen storage	8y 1m	M	EO	91		X	X		X	
Long-chain ketoacyl-CoA thiolase	Mitochondrial fatty acid oxidation	17y 9m	F	LO	83		X	X			
Long-chain ketoacyl-CoA thiolase	Mitochondrial fatty acid oxidation	6y 1m	M	EO	96			X			
Long-chain ketoacyl-CoA thiolase	Mitochondrial fatty acid oxidation	6y 3m	M	EO	108						X
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	8y 9m	M	EO	73		X				X
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	6y 1m	F	EO	79	X	X		X	X	X
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	10y 9m	F	EO	101		X				
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	6y 10m	M	EO	75	X	X	X		X	X
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	8y 7m	F	EO	62	X	X	X	X	X	X
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	10y 11m	F	LO	55	X	X	X	X	X	
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	8y 4m	M	EO	91		X	X		X	
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	8y 9m	M	LO	103		X				
Medium-chain acyl-CoA dehydrogenase	Mitochondrial fatty acid oxidation	9y 6m	F	EO	93		X	X			
Mitochondrial tRNA-Leu 1 deficiency	mtDNA	13y 1m	F	EO	60	X	X	X	X	X	
Mitochondrial tRNA-Leu 1 deficiency	mtDNA	17y 7m	M	LO	88		X	X			

3.2. Neurocognitive performance based on the age of the sample

In the entire cohort, older patients demonstrated significantly worse performance in executive functions, motor dexterity, and behavioural and emotional regulation, as indicated by the Spearman correlation: PPT ($p=0.024$), Plan-ROCF ($p=0.000$), Time-ROCF ($p=0.000$), BR-BRIEF ($p=0.046$), E-SENA ($p=0.079$) and EF-SENA ($p=0.074$). In contrast, the youngest patients exhibited the lowest attentional scores: O-CPT ($p=0.006$), HRT-CPT ($p=0.045$), CONS HRT-CPT ($p=0.053$), and PERS-CPT ($p=0.021$).

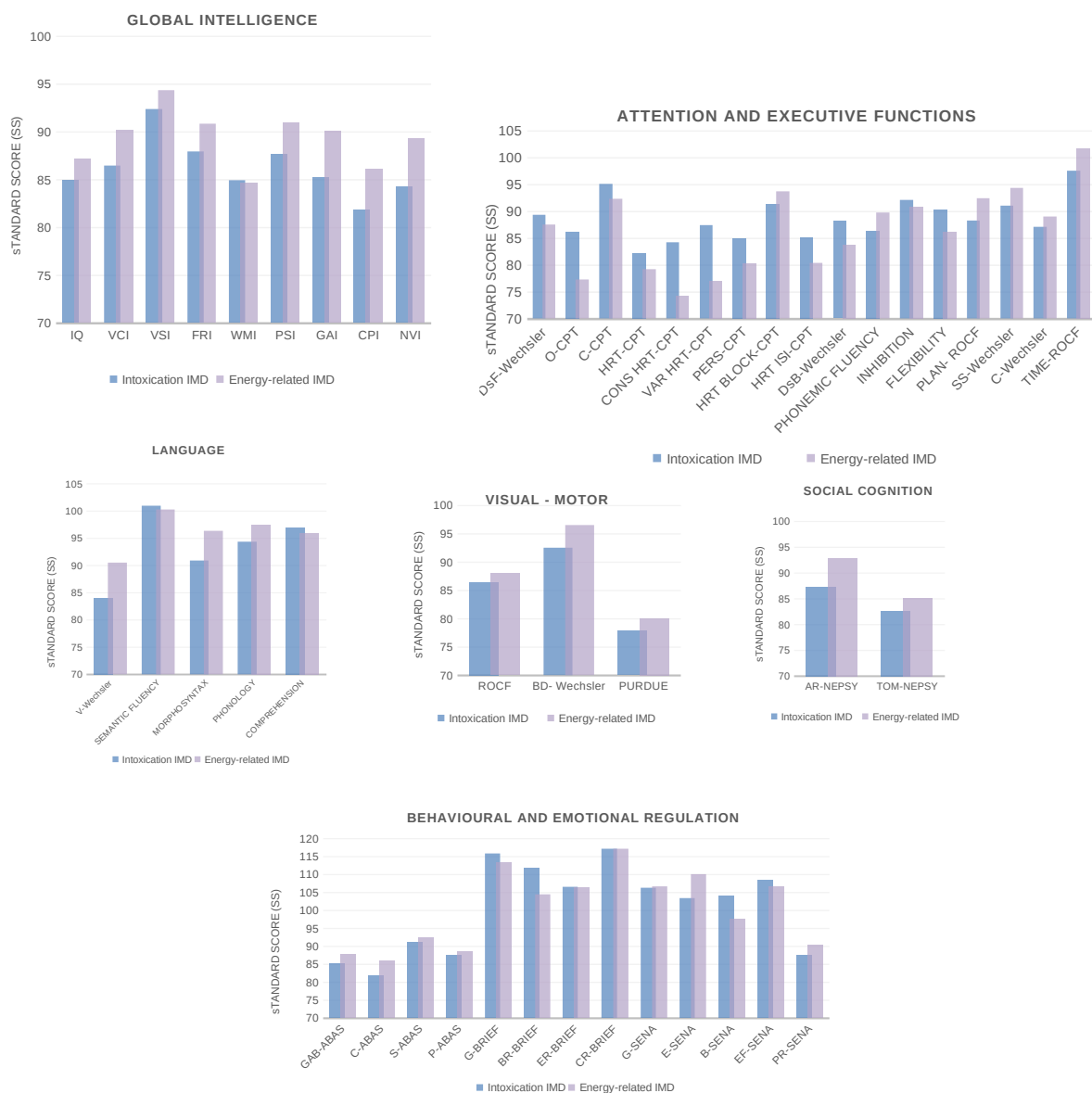


Figure 2. Comparison of mean standardized scores between patients with intoxication and energy-related IMD, across all neuropsychological domains.

Most of our patients (70%) were in primary school, 24.3% in secondary school, and only a few reached high school (5.7%). When we grouped the ages of the sample according to their school year, we observed a consistent pattern through the Kruskal-Wallis test. Children in primary school had lower scores in attention and executive functions on several measures: O-CPT ($p=0.002$), HRT-CPT ($p=0.003$), CONS HRT-CPT ($p=0.001$), VAR HRT-CPT ($p=0.009$), PERS-CPT ($p=0.000$), HRT ISI-CPT ($p=0.016$), DsB-Wechsler ($p=0.057$), inhibition ($p=0.042$), and flexibility ($p=0.050$). In contrast, secondary and high school adolescents scored lower in visual planning (Plan-ROCF, $p=0.008$) and the time of visuoconstruction (Time-ROCF, $p=0.004$). As a result, 55.1% of primary school students met the criteria for ADHD, while none of the high school students did ($p=0.031$, Chi-square test). Although older students showed more frequently symptoms of ASD, the differences were not statistically significant ($p=0.227$, Chi-square test).

3.2.1. Differences between intoxication and energy-related IMDs

In the sample with intoxication IMDs, a similar pattern emerged. Older patients exhibited more significant difficulties with planning tasks, as shown by Plan-ROCF ($p=0.009$) and Time-ROCF ($p=0.030$). In contrast, the youngest children displayed poorer attention and inhibition, as evidenced by O-CPT ($p=0.013$), HRT-CPT ($p=0.021$), CONS HRT-CPT ($p=0.044$), PERS-CPT ($p=0.004$), and inhibition ($p=0.035$). Furthermore, their performance was lower in cognitive adaptive behaviour (C-ABAS) with a $p=0.041$, suggesting a negative impact on their school abilities.

In energy-related IMDs, older patients exhibited poorer motor dexterity and slower processing speed, as indicated by PPT ($p=0.037$), Time-ROCF ($p=0.022$), C-Wechsler ($p=0.068$), and PSI ($p=0.086$). Furthermore, older patients demonstrated worse executive functioning, behaviour, and emotional regulation: G-BRIEF ($p=0.002$), BR-BRIEF ($p=0.063$), ER-BRIEF ($p=0.004$), CR-BRIEF ($p=0.007$), G-SENA ($p=0.015$), E-SENA ($p=0.007$), and EF-SENA ($p=0.004$). These deficits appear to impact daily functional abilities, as suggested by the P-ABAS score ($p=0.080$).

3.3. Neurocognitive performance based on the onset of IMD

In our cohort, 47.1% of the patients exhibited early-onset (EO) of symptoms between birth and 12 months of age. In contrast, 52.9% had a late-onset (LO) of symptoms, beginning after one year of life.

Overall, patients with a LO of symptoms demonstrated significantly lower scores in processing speed and executive functioning, as indicated through the Mann-Whitney U test: PSI ($p=0.033$), Plan-ROCF ($p=0.002$), Time-ROCF ($p=0.045$), C-Wechsler ($p=0.027$) and EF-SENA ($p=0.033$). Additionally, nearly significant differences were also found in fluid reasoning and motor dexterity: FRI ($p=0.055$) and PPT ($p=0.057$).

3.3.1. Differences between intoxication and energy-related IMDs

Although patients with intoxication IMDs had a higher incidence of LO (57.5%) compared to those with energy-related IMDs (46.7%), this difference was not statistically significant ($p=0.369$; Chi-square). The most common categories of IMDs with LO symptoms were disorders related to trace elements and metals (100%) and carbohydrate metabolism disorders (77.8%). In contrast, the categories with EO symptoms were fatty acid and ketone body disorders (80%) and vitamin and cofactor disorders (80%). The differences between these categories were statistically significant ($p=0.005$, Chi-square).

In our analysis of the cognitive differences between EO and LO within each type of IMD, we found that individuals with LO energy-related IMDs exhibited significantly worse scores in logical reasoning, processing speed, motor dexterity, and executive functioning, through the Man-Whitney U test: FRI ($p=0.007$), PSI ($p=0.004$), CPI ($p=0.019$), NVI ($p=0.017$), phonemic fluency ($p=0.010$), SS-Wechsler (0.002), C-Wechsler (0.012), Time-ROCF (0.024), PPT ($p=0.006$), EF-SENA ($p=0.037$). Additionally, although not statistically significant, LO patients with energy-related IMDs showed lower scores in social cognition: AR-Nepsy ($p=0.064$) and ToM-Nepsy ($p=0.068$). For intoxication IMDs, the

only significant difference noted was in planning, where LO patients had lower scores in Plan-ROCF ($p=0.017$).

Upon examining more specific categories of IMDs, we found that patients with carbohydrate metabolism disorders who exhibited EO of symptoms performed worse in visuoconstruction tasks (as measured by the ROCF and the Plan-ROCF; $p=0.022$ and $p=0.033$, respectively, using the Kruskal-Wallis test) and in affect recognition (as measured by the AR-NEPSY; $p=0.028$, Kruskal-Wallis), compared to other categories of IMDs. No significant differences were observed among late-onset IMDs among the specific categories evaluated.

Additionally, no other significant differences were found between age at disease onset of and gender ($p=0.358$; Chi-square), ADHD criteria ($p=0.602$; Chi-square), or ASD symptoms ($p=0.455$; Chi-square).

3.4. Neurocognitive performance based on the sex of the sample

Our cohort had a nearly equal sex distribution, with 54.3% of the patients being male and 45.7% being female.

Both males and females performed similarly in the neuropsychological tests, and no statistically significant differences were found. However, females exhibited slightly poorer sustained attention in the HRT BLOCK-CPT ($p=0.075$, Mann-Whitney U) and lower executive function in the BRIEF ($p=0.074$, Mann-Whitney U). However, there were no significant differences between males and females concerning ADHD criteria ($p=0.858$, Chi-square) or ASD symptoms ($p=0.602$, Chi-square).

3.4.1. Differences between intoxication and energy-related IMDs

When examining gender differences in cognitive performance within each specific type of IMDs, we found no statistically significant differences in intoxication IMDs between male and female performance. However, a trend was observed where females met the ADHD criteria more often (63.2%) than males (33.3%), approaching the statistical significance ($p=0.059$, Chi-square). Additionally, we found that females with vitamin and cofactor disorders performed worse in language tasks than those in other categories of IMDs; specifically, they had lower scores in morphosyntax ($p=0.018$, Kruskal-Wallis) and phonemic fluency ($p=0.036$, Kruskal-Wallis).

Among individuals with energy-related IMDs, males showed a greater impact of attentional processes on cognitive proficiency compared to females ($p=0.031$; Mann-Whitney U test). As a result, a higher percentage of males (58.8%) met the criteria for ADHD compared to females (23.1%), with this difference being statistically significant in the Chi-square test ($p=0.050$).

No gender differences were observed in ASD symptoms among intoxication IMDs ($p=0.516$, Chi-square) or energy-related IMDs ($p=0.961$, Chi-square).

3.5. Neurocognitive performance related to other medical history

Patients who have undergone liver transplantation (10%) showed no differences in cognitive impairment compared to those who have not had a transplant.

However, patients with epilepsy (7.1%) exhibited significantly worse cognitive outcomes than those without epilepsy in global intelligence, language, attention, social cognition, executive functions, behaviour, and emotion regulation, through the Mann-Whitney U test: IQ ($p=0.046$), VCI ($p=0.031$), FRI ($p=0.021$), GAI ($p=0.005$), NVI ($p=0.018$), V-Wechsler ($p=0.017$), semantic and phonemic fluency ($p=0.014$ and $p=0.032$), ROCF ($p=0.050$), O-CPT ($p=0.020$), HRT-CPT ($p=0.017$), CONS HRT-CPT ($p=0.012$), VAR HRT-CPT ($p=0.005$), HRT ISI-CPT ($p=0.008$), ToM-Nepsy ($p=0.014$), G-BRIEF ($p=0.009$), BR-BRIEF ($p=0.005$), ER-BRIEF ($p=0.018$) and EF-SENA ($p=0.049$). Additionally, all patients with epilepsy met the criteria for ADHD ($p=0.017$; Fisher's exact test).

3.5.1. Differences between intoxication and energy-related IMDs

There were no significant differences in epilepsy ($p=0.893$, Chi-square), antiepileptic drugs ($p=0.733$, Chi-square), or liver transplant ($p=0.107$, Chi-square) between intoxication and energy-related IMDs. Additionally, no statistical differences were found among the more specific categories of IMDs. This may indicate that these medical conditions were uniformly distributed across the sample and did not bias the results.

4. Discussion

An exhaustive neuropsychological assessment was performed to characterize the neurocognitive impairment in a multicentric cohort of patients with intoxication and energy-related IMDs. Despite the inherent limitations of research on rare diseases, important conclusions can be drawn.

4.1. Lower global cognitive functioning

In the general population, the mean intelligence quotient (IQ) is estimated to be 100, with a standard deviation (SD) of 15. In our cohort of individuals with IMD, we observed that while the standard deviation remained comparable ($SD=15.68$), the mean IQ fall in the low-average range, at 85.84.

Considering that our study cohort primarily included individuals with asymptomatic or mild phenotypes, these findings suggest that even those with less severe clinical presentations are at higher risk of developing low intellectual functioning. Such neurocognitive deficits can profoundly impact daily life, affecting personal relationships, family dynamics, academic performance, and overall quality of life.

Several studies involving large cohorts with specific IMD have reported similar findings regarding global intelligence. For instance, an evaluation of 107 individuals with glutaric aciduria type 1 (GA-1)

found a significantly reduced mean IQ of 87 compared to normative population data (Märtner et al., 2021).

Further supporting the persistence of these cognitive deficits, Hermans et al. (2024) assessed individuals with classic galactosemia and found a mean IQ of 82.7 (SD = 10.8) in children, which declined further to a mean IQ of 76.5 (SD = 10.5) in adults. These findings suggest that, despite early dietary management, patients may increasingly distance themselves from their chronological age population over time. Expanding the scope, Warner-Levy et al. (2024) recently investigated the prevalence and severity of intellectual disability (ID) across a large, multi-ethnic cohort of adults with various IMDs (n = 357). They reported an overall ID prevalence of 15.7%, with the majority presenting with mild ID (64.8%), followed by severe ID (20.9%) and moderate ID (13.6%), while profound ID was rare (0.7%). Notably, most ID cases were already prominent during childhood (317/357). These studies highlight the significant risk of persistent or progressive cognitive impairment across a range of metabolic disorders, emphasising the importance of long-term neuropsychological monitoring.

4.2. *Specific neurocognitive domains impaired*

In our cohort, the most affected cognitive domains were fine motor dexterity, focused attention, processing speed, executive functions, and social cognition. Consequently, there was a high prevalence of overlapping characteristics with ADHD (46%) and ASD (47%), with no differences between intoxication and energy-related IMDs.

In the literature, aside from intellectual disabilities, the most commonly reported neuropsychological domains include fine motor dexterity, behavioral and emotional regulation, executive functions, attention, and social cognition. In contrast, processing speed is the least frequently addressed, as well as severe intellectual disability (Gil-González et al., 2025). Thus, our findings are consistent and extend the existing evidence by providing further support for a distinctive neurodevelopmental pattern associated with IMD.

These deficits, particularly those affecting executive functions such as working memory, planning, and organizational skills, are crucial for academic performance and everyday functioning in school-aged children. As a result, a significant proportion of the cohort received educational and therapeutic interventions, reflecting a recognized need for tailored accommodations in this population.

When comparing intoxication and energy-related IMDs, we observed broadly similar neurodevelopmental trajectories. However, subtle differences emerged. Individuals with energy-related IMDs exhibited slightly more pronounced impairments in focused attention. Attention is a basic cognitive function that requires significant energy from the brain, as it depends on the coordinated activity of large-scale neural networks. High-demand areas of the brain, such as the prefrontal and parietal cortex, need substantial amounts of ATP to maintain rapid synaptic transmission and network oscillations. These processes are essential for focused attention, vigilance, and managing cognitive fatigue.

On the other hand, patients with intoxication IMDs, especially females with vitamin and cofactor disorders, exhibited more significant language deficits in morphosyntax and phonemic fluency. These deficits may be influenced by early neurotoxic injury that occurs before dietary interventions are implemented or to metabolic decompensation during critical periods of language development. Usually, expressive language development tends to be more affected than comprehension in IMDs. For instance, it is estimated that 40% to 85% of children with classical galactosemia will develop speech disorders, compared to just 4% of young school-aged children without IMDs. The roots of these language deficits still require more research. However, the cerebellum may play a role in these deficits, suggesting a complex interplay between motor development and language skills ([Peter et al., 2022](#); [Timmers et al., 2011](#)).

When examining more specific categories, disorders related to the metabolism of fatty acids and ketone bodies showed better cognitive outcomes in our cohort. Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD) was the most prevalent among these disorders. MCAD typically leads to episodic energy crises that are triggered by fasting or catabolic stress, rather than causing persistent metabolic disruption. Early detection through NBS has facilitated timely interventions, which help minimize neuronal injury caused by hypoglycemia. When properly managed, the brain's strong preference for using glucose over fatty acids for energy further reduces the negative impact of

defective fatty acid oxidation. Therefore, brain structure and functioning could be preserved when recurrent metabolic decompensations are avoided through early identification and treatment. These factors may explain the preserved neurodevelopmental trajectories observed in MCAD, particularly since all subjects in our cohort were diagnosed in the neonatal period, indicating early onset. However, other environmental factors associated with the overall medical condition, such as hospitalisations or adherence to treatments, may still impact daily living skills in this population (Joy et al., 2009, Waisbren et al., 2008).

In our cohort, patients with epilepsy (7%) were equally distributed among intoxication and energy-related IMDs. In all cases, epilepsy became a significant risk factor for higher widespread neurocognitive impairment affecting intelligence, language, attention, executive functions, social cognition and behaviour regulation. Additionally, all of them met the diagnostic criteria for ADHD, according to DSM-5-TR. These findings underscore the importance of controlling for comorbidities when assessing neurocognitive risk in IMD populations (Cannon Homaei et al, 2022).

Although different genes and pathophysiological mechanisms are involved in both intoxication and energy-related IMDs, our findings suggest a possible convergence in neurocognitive functioning that were not better explained by sex, age at disease onset or other medical conditions such as liver transplant or epilepsy. This overlap might indicate that there may be common neurodevelopmental vulnerabilities contributing to the cognitive dysfunction associated with IMDs, which warrants further exploration into shared mechanisms and potential targeted interventions. However, it is essential to recognise the significant variability that exists both between and within IMDs subgroups, making it important to approach conclusions with caution and always individualize the clinical interventions. Future research should aim to investigate biomarkers that could predict neurodevelopmental trajectories, and explore targeted interventions to mitigate cognitive outcomes.

4.3. Age-related cognitive functioning

In our pediatric cohort, developmental trajectories of cognitive and behavioral functions varied notably with age. Younger children demonstrated greater difficulties in basic focused attention, with 55.1% of primary school-aged patients meeting diagnostic criteria for ADHD. As age increased, there was a progressive decline in executive functions, fine motor dexterity, and emotional and behavioral regulation. These findings align with previous evidence indicating that neuropsychiatric manifestations, including ADHD symptoms, are prominent in many IMDs. Such associations are thought to arise from shared neurochemical pathways that interfere with the synthesis, transport, metabolism, or receptor functions of monoaminergic neurotransmitters, mechanisms considered central to the pathophysiology and treatment of ADHD ([Cannon Homaei et al., 2022](#)).

In typical brain development, highly metabolic areas, such as the prefrontal cortex, mature gradually. This process includes synaptic pruning, white matter myelination, and the establishment of long-range connectivity, which continues into the third decade of life ([Mills et al., 2021](#); [Tamnes & Luna, 2020](#)). Therefore, IMD can disrupt the integration of different brain regions that are necessary for higher-order cognitive processes. Early damage to the brain may lead to maladaptive neural reorganization or reduced neural plasticity, limiting the brain's ability to meet developmental demands ([Friedrichs-Maeder et al., 2017](#); [Cao et al., 2017](#)).

Over time, the cumulative effects of recurrent metabolic crises, chronic low-grade toxicity, or inadequate delivery of essential substrates (as seen in disorders like urea cycle defects, mitochondrial diseases or organic acidemias) particularly impact executive networks. While younger children may initially demonstrate relatively preserved cognitive skills, deficits in more complex executive functions, such as planning, inhibition, cognitive flexibility or emotional regulation, become increasingly evident during adolescence, when these functions typically mature. Consequently, this may lead to a widening gap between expected and actual cognitive abilities over time. This gap often contributes to academic difficulties, social impairments, and psychiatric comorbidities during adolescence and early adulthood. As a result, during adolescence, this population faces a higher risk of academic underachievement and subsequent school dropout. Only those with improved cognitive outcomes are likely to reach post-compulsory educational levels.

Distinct neurodevelopmental trajectories were observed in our cohort of patients between those with intoxication and energy-related IMDs. Like the entire cohort, adolescents with energy-related IMDs exhibited significant deficits in fine motor coordination, processing speed, executive functions, and emotional and behavioural regulation. These deficiencies had a notable impact on their practical adaptive behaviour, requiring greater support for daily living skills.

In contrast, younger children with intoxication IMDs demonstrated deficits in attention and inhibition, as well as more pronounced issues with cognitive adaptive behaviour. These difficulties are likely to interfere with early learning processes and resemble characteristics commonly associated with ADHD. Over time, older children in this group showed progressive impairments in visual planning.

These findings highlight the cumulative burden of metabolic dysfunction on neurodevelopment. Clinicians should proactively screen children with IMDs for NDDs early in their lives. An integrated, cross-diagnostic approach could enhance timely treatment that improves learning skills, self-control, and adherence to challenging therapies, such as strict dietary regimens. Therefore, close collaboration among paediatricians, psychologists, and caregivers is crucial to avoid misdiagnosis and improve patient outcomes ([Cannon Homaei et al., 2022](#)).

4.4. Onset-related cognitive functioning

Even though newborn screening (NBS) and next-generation sequencing (NGS) have improved early diagnosis and treatment in many treatable IMDs, our cohort revealed that 53% of the patients were diagnosed after one year of life.

Late diagnosis is a significant risk factor for neurological outcomes, as reported in the literature. In our cohort, patients with late-onset conditions exhibited poorer fine motor dexterity, processing speed, fluid reasoning, and executive function compared to children diagnosed with early-onset conditions during the neonatal period. The specific disorders with the highest incidence of late-

onset were Wilson disease and disorders related to carbohydrate metabolism. This highlights the urgent need to improve early detection in this population to prevent adverse neurocognitive outcomes. In contrast, disorders related to fatty acids and ketone bodies, as well as vitamin and cofactor deficiencies, were more frequently diagnosed at an early onset.

Similarly, energy-related IMDs with late-onset were significantly more affected compared to those with early onset. Late-onset patients exhibited worse logical reasoning, processing speed, motor dexterity, and executive functions, with a tendency towards lower social cognition. Among intoxication IMDs, participants with late-onset disease showed poorer visual planning. No differences were identified in specific categories among late-onset patients. However, early-onset carbohydrate metabolism disorders demonstrated worse visual construction and affect recognition.

These findings highlight the complex relationship between disease progression and critical periods of brain development, during which cognitive vulnerabilities can emerge. This emphasises that neuropsychological deficits may persist even in individuals displaying mild phenotypes despite an early diagnosis. Such insights reveal that the impact of IMDs can extend beyond severe manifestations, affecting cognitive functioning in subtler forms.

4.5. Sex-related cognitive functioning

Regarding sex differences, our results revealed no significant differences in overall cognitive performance between males (54%) and females (46%) across the cohort.

However, females with intoxication IMDs presented lower scores in attention and executive functions, with 63% of females meeting ADHD diagnostic criteria according to DSM-5-TR, compared to 33% of males. Among vitamin and cofactor-related disorders, females also exhibited more significant deficits in language abilities, especially in morphosyntactic skills and phonemic fluency.

In X-linked disorders, males are typically more severely affected than females. Considering that this study is based on patients with mild or asymptomatic phenotypes, males with X-linked

disorders may not be well represented in the cohort. However, the results imply that even asymptomatic females, who may appear unaffected, can still exhibit ADHD symptoms.

On the other hand, an opposite pattern was observed in energy-related IMDs. Males demonstrated poorer cognitive performance, especially in attention tasks with a significant higher prevalence of ADHD diagnoses (58%) than females (23%). Males with energy-related IMD may be more vulnerable to disruptions in their attentional networks.

These findings indicate that global neurodevelopmental trajectories may be similar for both genders. However, the underlying vulnerabilities related to attention and executive functions may differ slightly based on metabolic causalities. Further research involving larger sample sizes is necessary to explore the neurobiological susceptibilities and psychosocial mechanisms that influence coping and compensatory strategies related to these patterns.

4.6. *Limitations and Future Directions*

This study has some limitations that should be acknowledge when interpreting the findings. As is common in research on rare diseases, the sample size was limited, which may have affected the statistical power and generalizability of the results. Additionally, the cohort displayed significant heterogeneity in terms of specific diseases. The simplified classification employed in this study, while practical, may not capture certain mechanisms related to disease-specific neuropsychological impairments. Consequently, these results should be interpreted cautiously and may advise the development of individualised assessments and intervention strategies.

Our findings highlight the importance of incorporating early neuropsychological assessments and ongoing monitoring into clinical practice, regardless of the specific IMD. This population is at a higher risk for neurocognitive impairment, so access to individualized educational plans and therapeutic interventions should be prioritized.

Moreover, future studies should further investigate the long-term cognitive trajectories of patients with IMDs into adulthood, the neurobiological causes of cognitive decline, and the effectiveness of targeted cognitive rehabilitation programs. There is also a need to explore potential biomarkers through advanced neuroimaging and metabolomics studies to gain a better understanding of the brain and the metabolic mechanisms underlying neuropsychological outcomes.

4.7. Conclusions

This study presents a detailed neuropsychological profile of children and adolescents with inherited metabolic disorders, revealing significant cognitive, behavioural, and emotional challenges even in those with mild or asymptomatic cases. While the overall intellectual functioning of the participants fell within the low-average range, notable deficits were observed in areas such as attention, processing speed, executive functioning, social cognition, and fine motor skills. These impairments were consistently observed across both intoxication and energy-related IMDs. However, there were subtle differences between these subtypes and variations related to other clinical factors influencing neurodevelopmental trajectories, such as epilepsy, sex, age, and the age at disease onset.

By conceptualising the diversity and complexity of IMDs as a dimensional spectrum of neurodevelopmental disorders rather than relying on categorical classifications, we approach the reality of the clinical practice. However, this perspective underscores the necessity of tailoring assessments and interventions to the unique needs of each individual.

Key Findings

- Even mild or asymptomatic individuals with IMDs are at risk of persistent neuropsychological deficits.
- The most affected cognitive domains were fine motor dexterity, attention, executive functions and social cognition.
- IMDs present overlapping symptoms with other neurodevelopmental disorders, like ASD or ADHD.
- Late-onset and epilepsy are risk factor for poorer neurocognitive outcomes in IMDs
- IMDs should have systematic neuropsychological assessments tailored to each individual's needs.

Chapter IV

Volumetric biomarkers of neurocognitive impairment:

A multicenter cohort study

1. Introduction

Diagnosing and treating *Inherited Metabolic Disorders (IMDs)* present significant challenges due to the wide variability in phenotypes and the complex genetic backgrounds associated with these conditions ([Chantada-Vázquez et al., 2022](#)). These challenges underscore the need for integrated approaches that combine novel multidisciplinary techniques to enhance our understanding of disease mechanisms and aid in identifying non-invasive and clinically actionable biomarkers.

In recent years, advancements in neuroimaging, particularly volumetric magnetic resonance imaging (MRI), have provided important insights into the structural brain changes associated with IMDs. Volumetric analysis allows for precise measurement of regional brain volumes and effectively detects subtle neuroanatomical changes that may not be visible with conventional imaging techniques. Thus far, this method has shown disease-specific patterns of volume abnormalities, offering insights into disease progression, severity, and the underlying physiopathology ([Alfonsi et al., 2022](#)). However, studies are scarce and have focused mainly on specific IMDs, so further research is needed to assess the consistency of these findings.

Widespread abnormalities in both grey and white matter have been observed in individuals with various IMDs, often correlating with cognitive and neuropsychiatric impairments ([Rahimi, 2024](#); [Alfonsi et al., 2022](#); [Shribman et al., 2022](#); [Gropman & Anderson, 2020](#); [Song, 2020](#)).

Most studies utilizing advanced MRI techniques have focused on intoxication IMDs. For instance, patients with Wilson disease often show significant reductions in grey and white matter volume in subcortical regions, including the basal ganglia, thalamus, cerebellum, insula, left precentral gyrus, and orbitofrontal cortex. These changes in subcortical areas correlate with the severity of neurological symptoms ([Rahimi, 2024](#); [Shribman et al., 2022](#); [Song, 2020](#)). Similarly, in glutaric aciduria type I (GA-1), bilateral and symmetrical hyperintensities have been noted in the putamen, caudate, globus pallidus, and cerebral peduncles ([Gropman & Anderson, 2020](#)).

In energy-related IMDs, most abnormalities in brain structure are hallmarks of disrupted energy metabolism during critical periods of neurodevelopment. In mitochondrial disorders, such as pyruvate dehydrogenase deficiency, neuroimaging reveals abnormalities in deep grey matter structures and widespread white matter ([Gropman & Anderson, 2020](#)).

Evidence suggests that neurodevelopmental disruptions in brain structures may persist over time, even with early treatment. For instance, recent research on early-treated adult patients with phenylketonuria (PKU) have shown a reduction in global white matter volume and a decrease in several subcortical grey matter structures, particularly in the pallidum and brainstem. This highlights the significance of volumetric MRI in assessing the long-term effects of metabolic imbalances on the brain ([Pardo et al., 2024](#)).

Together, these findings underscore neuroanatomical alterations across distinct IMDs. Subcortical structures, white matter tracts, and the cerebellum seem to be repeatedly implicated, with regional volume loss correlating with clinical outcomes. High-resolution volumetric MRI enables the detection of microstructural changes with functional significance, offering a non-invasive modality for longitudinal assessment. These imaging markers may represent a powerful tool in clinical trials and individualized treatment planning, where tracking subtle structural changes can inform decisions regarding therapeutic timing, efficacy, and safety.

In this Chapter, we aim to provide an in-depth volumetric analysis of brain structure in a cohort of children with intoxication and energy-related IMDs, and correlate the findings with exhaustive and standardized neuropsychological assessments. Our objective is to identify potential volumetric biomarkers of neurocognitive impairment and clinical severity. By characterizing the neuroanatomical substrates of cognitive dysfunction in these disorders, we aim to advance the development of diagnostic tools, improve patient treatment and monitoring, and contribute to the growing field of precision medicine in inherited metabolic diseases.

2. Methods

2.1. Participants

The study included participants aged 6 to 17 with a confirmed diagnosis of intoxication or energy-related IMD, established through genetic and biochemical testing. All participants exhibited either mild phenotypes or were asymptomatic (IQ>55), with good adherence to metabolic treatments and controlled decompensations (≤ 1 /year). Exclusion criteria included a history of significant head trauma, the presence of other neurological disorders unrelated to the IMD, and patients treated with methylphenidate.

Patients were recruited from several reference hospitals in Spain: 26 from Hospital Sant Joan de Déu in Barcelona (72.2%), 6 from Hospital 12 de Octubre in Madrid (16.6%), and 4 from the Hospital Materno-Infantil in Las Palmas de Gran Canaria (11.1%). The final sample included 36 participants, 20 with intoxication IMDs (55.5%) and 16 with energy-related IMDs (44.4%). *Table 1* shows a detailed description of the sociodemographic and clinical features of the sample.

2.2. MRI Acquisition

MRI scans were performed for a volumetric brain analysis. An expert paediatric neuroradiologist reviewed all images to exclude the presence of signs of acute injury (i.e. infarction or edema). Quality control measures included visual inspection of each scan for artifacts and segmentation errors.

Non-standardized MRI protocols were employed to process T1-weighted structural MRI data acquired across multiple centres. Images were obtained using 3D gradient-echo-based sequences, but acquisition parameters varied between sites and within centres. Voxel sizes ranged from $0.4 \times 0.4 \times 2.0 \text{ mm}^3$ to $1 \times 1 \times 1 \text{ mm}^3$, number of slices 150–300, TR range: 7.3–14 ms, TE range: 3.4–5.8. To ensure consistency, our volumetric analysis pipeline was designed to provide robust measurements independently of acquisition protocol or scanner-specific settings.

Table 1. Sociodemographic and clinical features of the cohort.

Patient	Age	Gender	Hospital	IMD type	IMD Category	IMD	Gene #OMIM	Onset	Diet	Special needs	Medical history observations
1	17y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		
2	7y 2m	M	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	School accommodations	
3	16y 4m	M	Barcelona	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		
4	7y	M	Barcelona	Intoxication	Amino acid metabolism	Propionic acidemia	PCCA #232000	Early onset	Low protein	School accommodations	LT
5	8y 8m	M	Canarias	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Late onset	Low protein	Speech therapy	
6	8y 6m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	School accommodations Speech therapy Psychology	Epilepsy, AEDs
7	12y 2m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	School accommodations	
8	12y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		LT
9	9y 9m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	Speech therapy Psychology School reinforcement	Epilepsy
10	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	School accommodations School reinforcement	
11	16y 3m	M	Barcelona	Intoxication	Amino acid metabolism	Argininosuccinate lyase deficiency	ASL #608310	Late onset	No		
12	12y 4m	F	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	School accommodations Speech therapy School reinforcement Physical therapy	
13	9y 4m	F	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	School accommodations Speech therapy Psychology School reinforcement	
14	8y 8m	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		
15	7y 9m	M	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein		
16	6y 1m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
17	7y 5m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 6	PYGL #613741	Late onset	Low Glycemic Index		
18	16y 6m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No	Speech therapy School reinforcement	
19	6y 10m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
20	13y 11m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	School accommodations Psychology School reinforcement	
21	12y 1m	M	Barcelona	Intoxication	Vitamin and cofactor	5,10-methylenetetrahydrofolate reductase deficiency	MTHFR #607093	Late onset	No	School accommodations School reinforcement	
22	11y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic	School accommodations School reinforcement Physical therapy	
23	8y 7m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		
24	10y 11m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index		
25	15y	M	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein		
26	6y 3m	M	Madrid	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat	School accommodations Speech therapy	
27	8y 6m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School accommodations	
28	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Late onset	Low fat	School accommodations School reinforcement	

29	12y 10m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School reinforcement	Epilepsy
30	11y 9m	F	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic		
31	9y 11m	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	School accommodations School reinforcement	
32	9y	F	Barcelona	Intoxication	Amino acid metabolism	Arginase deficiency	ARG1 #608313	Late onset	Low protein	School accommodations Speech therapy Psychology School reinforcement Physical therapy	LT
33	13y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		
34	10y 9m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	School accommodations School reinforcement	
35	9y 5m	M	Barcelona	Intoxication	Amino acid metabolism	Maple syrup urine disease	DBT #248610	Early onset	Low protein		
36	17y 7m	M	Barcelona	Energy-related	mtDNA	Mitochondrial tRNA-Leu 1 deficiency	MT-TL1 #590050	Late onset	No		Epilepsy, AEDs

AEDs= antiepileptic drugs
LT= liver transplant

2.3. Image processing and brain tissue segmentation

Structural magnetic resonance imaging data were processed according to the following steps. First, a template was created using the Advanced Normalization Tools (ANTs) template construction utility, utilizing high-resolution MRI scans from healthy individuals (ages 9-10) in the Adolescent Brain Cognitive Development Study (ABCD) database (Casey et al., 2018). Tissue and atlas segmentation of this representative brain were performed with the Computational Anatomy Toolbox (CAT12) for SPM (Gaser et al., 2024), incorporating Neuromorphometrics Inc. parcellated brain regions (<http://www.neuromorphometrics.com/>) for gray-matter anatomical labels, and the high-resolution SUIT cerebellar parcellation (Diedrichsen et al., 2009). This approach divided brain volumes into 170 regions. Elastic registration, implemented through ANTs software, was then employed to map reference labels onto individual subject spaces, enabling precise volume extraction for each segmented region. To account for brain size variations across participants and age, the volumes of each segmented region were normalized considering the participant's total intracranial volume (TIV), which included total gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes.

Volumes of cortical and subcortical brain structures were obtained for each patient and then compared with the healthy model (HM) matched by age.

2.4. Neuropsychological data

Complete neurocognitive data was obtained from the reference neuropsychological assessments, available in Chapter III.

The assessment included global intelligence (Full-Scale IQ, Wechsler), expressive language (Verbal Comprehension Index, Wechsler), visuospatial performance (Visuospatial Index, Wechsler), focused attention (Digit Span Forward and CPT-3), sustained attention (CPT-3), working memory (Digit Span Backward), processing speed (Processing Speed Index, Wechsler), inhibition and cognitive flexibility (Inhibition subtest, NEPSY-II), social cognition (Affect Recognition and Theory of Mind, NEPSY-II), fine motor dexterity (Purdue Pegboard Test), and adaptive behaviour (ABAS-II).

2.5. Statistical analysis

Comparisons between IMD patients and age-matched healthy model were conducted using independent t-test and covariance (ANCOVA) analysis, adjusting for TIV, age, sex, age at disease onset (early-onset 0-12 months and late-onset >12 months) and sub-group of IMD diseases. Post-hoc pairwise comparisons were conducted using Tukey's HSD test to identify which specific groups differed significantly after the overall ANCOVA effect. Additionally, associations between brain volumetric measures and neuropsychological results were evaluated using Pearson correlation. This approach enabled us to evaluate the associations between brain volume and cognitive outcomes, controlling for the influence of age-related factors.

All statistical tests were carried out with a confidence level of 95% and considered significant at $p < 0.05$. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) correction according to the Benjamini–Hochberg method. Besides, Cohen's d was used to estimate the effect size for pairwise comparisons of normally distributed data. For non-normally distributed data, the rank-biserial correlation (r) was calculated. The analyses were performed using IBM SPSS statistical software version 29.0.

2.6. Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. The potential risks and benefits were explained to the participants and their families. Participation was voluntary, and participants could withdraw from the study at any time without any consequences to their medical care. The study was approved by the Research Ethics Committee of Hospital Sant Joan de Déu, and written informed consent was obtained from the parents or legal guardians of all participants, with assent collected from children over the age of 12.

3. Results

3.1. Volumetric differences between patients and controls

In comparison to the HM, patients in our cohort demonstrated increased volume in several fronto-parietal areas (*Figure 1*). Specifically, this included extremely marked volume differences in certain regions, all showing $p < 0.001$ and a very large effect size with Cohen's $d > 2.0$ in an independent sample t-test. The most pronounced differences were a 75% volume increase in the left triangular part of the inferior frontal gyrus, a 71% increase in the left anterior orbital gyrus, a 54% increase in the right medial frontal cortex, a 54% increase in the left putamen and a 51% of the left angular gyrus. Additionally, we observed a 31% reduction in cerebrospinal fluid (CSF).

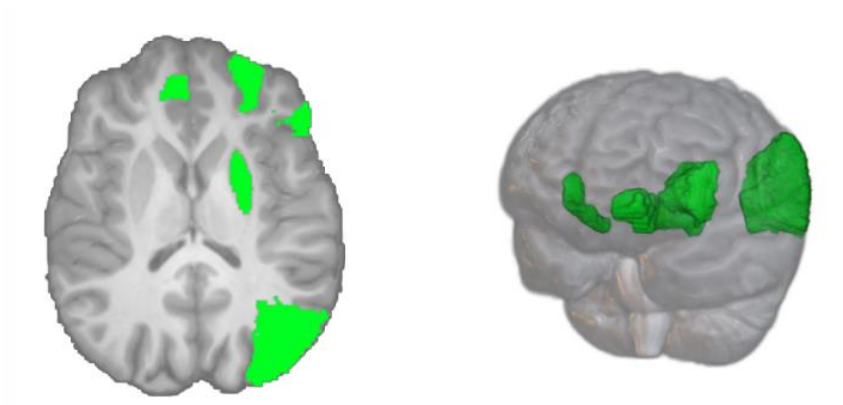


Figure 1. Increased volumes, particularly in left fronto-parietal regions (highlighted in green), in our cohort compared to an age-matched healthy model.

In our cohort, we observed a similar pattern of impairment in both intoxication IMDs and energy-related IMDs when compared to the HM (*Table 2*). Both subgroups of IMDs demonstrated an increased volume in the frontal, parietal and subcortical areas, resulting in a decreased volume in the ventricular system. However, intoxication IMDs also showed a reduction in cerebellar and entorhinal areas compared to the healthy model.

Table 2. Significant volumetric differences between the healthy model and each subgroup of IMD, all showing adjusted $p < 0.001$ and a very large effect size with Cohen's $d > 2.0$.

Main Brain Area	Brain Region	Difference
Intoxication IMDs		
Frontal	Left_Anterior_Orbital_Gyrus	72.40
Frontal	Left_Triangular_Part_of_the_Inferior_Frontal_Gyrus	71.34
Parietal	Left_Angular_Gyrus	54.29
Frontal	Right_Medial_Frontal_Cortex	51.82
Basal ganglia	Left_Putamen	47.69
Frontal	Left_Lateral_Orbital_Gyrus	44.03
Occipital	Right_Middle_Occipital_Gyrus	44.02
Cerebellum	Right_VIIla_2201	-26.50
Limbic System	Right_Entorhinal_Area	-27.03
Limbic System	Left_Entorhinal_Area	-29.17
Cerebellum	Right_X_2212	-31.14
Energy-related IMDs		
Frontal	Left_Triangular_Part_of_the_Inferior_Frontal_Gyrus	80.00
Limbic System	Left_Subcallosal_Area	69.72
Frontal	Left_Anterior_Orbital_Gyrus	69.27
Basal Ganglia	Left_Putamen	62.47
Frontal	Right_Medial_Frontal_Cortex	56.85
Limbic System	Right_Subcallosal_Area	49.12
Parietal	Left_Angular_Gyrus	47.06
Frontal	Left_Frontal_Pole	45.38
Frontal	Right_Lateral_Orbital_Gyrus	45.24
Frontal	Right_Anterior_Orbital_Gyrus	44.29
Parietal	Left_Supramarginal_Gyrus	43.03
Ventricular System	CSF_Right	-36.93
Ventricular System	CSF	-38.82
Ventricular System	CSF_Left	-40.57

We conducted an ANCOVA test to analyse the volume differences between patients and healthy controls, considering factors such as age at MRI acquisition, sex, and age at disease onset. Overall, sex and age did not significantly affect the volumetric differences between the two groups. However, significant differences in volume were noted concerning age at disease onset. In our cohort, we found significant differences in the volumes of the left Crus II ($p=0.029$) and right Crus II ($p=0.024$) in the cerebellum, as well as in the right amygdala ($p=0.041$) and the right temporal pole ($p=0.045$). Patients with early-onset disease exhibited decreased volumes in these temporo-cerebellar areas compared to those with late-onset disease.

3.2. Volumetric differences between intoxication and energy-related IMDs

When comparing intoxication and energy-related IMDs, different volumetric signatures emerge after adjusting brain volumes with the HM (*Figure 2*).

In our cohort, intoxication IMDs had a reduction in the volume of several fronto-temporal brain regions, including the left amygdala ($p=0.008$), left entorhinal area ($p=0.028$), left temporal pole ($p=0.029$), right temporal pole ($p=0.029$), left precentral medial gyrus ($p=0.026$), and right precentral medial gyrus ($p=0.020$). In contrast, energy-related IMDs showed an increase in the volume of the right putamen ($p=0.020$).

The cerebellum appears to be a distinct biomarker among our cohort of individuals with IMDs. While those with energy-related IMDs exhibited increased cerebellar volumes, individuals with intoxication IMDs showed reduced volumes in several cerebellar nuclei. The most significant differences were observed in the following regions: left Crus II ($p=0.034$), left V ($p=0.034$), left VI ($p=0.002$), left VIIa ($p=0.001$), left VIIb ($p=0.015$), left VIIIb ($p=0.005$), right Crus II ($p=0.028$), right IX ($p=0.037$), right V ($p=0.015$), right VI ($p=0.032$), right VIIb ($p=0.011$), right VIIa ($p=0.002$), right VIIIb ($p=0.001$), and the vermis IX ($p=0.044$).

Additionally, both types of IMDs exhibited a reduction in the CSF compared to the HM, with the difference being significantly pronounced among energy-related IMDs ($p = 0.003$). Notably, no statistically significant differences were found in extraxial CSF or the overall ventricles volumes. However, the intoxication IMDs group showed an enlargement of the lateral ventricles ($p=0.034$), compared to energy-related IMDs and the HM.

We conducted a further analysis of this pattern by examining specific disease categories from the ICIMD, while acknowledging that the limited sample size may affect the statistical outcomes. For this post-hoc analysis, we included only groups with more than four patients: organic acidurias (OA), urea cycle disorders (UCD), GLUT1 deficiency syndrome (GLUT1DS), fatty acid and ketone body disorders, and glycogen storage diseases (GSD).



Figure 2. Differences in cortical and subcortical gray matter volumes between intoxication and energy-related IMDs. Red indicates volume reduction in intoxication IMDs, whereas green indicates volume increase in energy-related IMDs.

While the volumetric atrophy observed in intoxication IMDs was common across the different disease categories, it was particularly pronounced in the OA group. Compared to the other categories, OA exhibited significantly decreased volumes in several temporal, subcortical and cerebellar regions: the left pallidum ($p=0.019$), the right pallidum ($p=0.016$), the right putamen ($p=0.004$), the right entorhinal cortex ($p=0.006$), the left entorhinal cortex ($p=0.015$), the left amygdala ($p=0.014$), the right amygdala ($p=0.036$), the left temporal pole ($p=0.014$), the right temporal pole ($p=0.031$), and the cerebellum ($p=0.008$). Additionally, OA showed an increase in CSF volume ($p = 0.045$) and ventricular volume ($p = 0.001$). Notably, GLUT1DS demonstrated an increased cerebellar volume compared to other IMD groups ($p=0.026$).

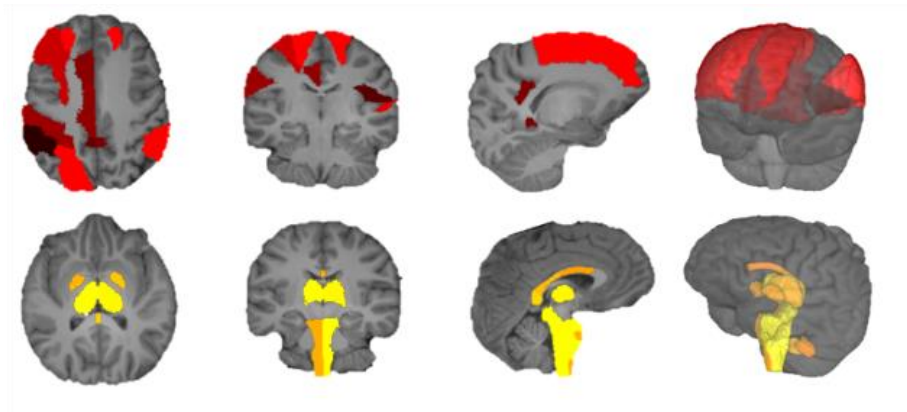
3.3. Correlation between volumetry and neuropsychological assessment

3.3.1. Volumetric biomarkers of cognitive impairment in IMDs

We examined the association between regional brain volumes and neuropsychological performance, in the overall cohort of IMDs.

Considering the volume differences mentioned above between all patients and controls, only the increased volume in the right medial frontal cortex was related to worse social cognition and motor dexterity. Overall, social cognition (*Figure 3a*) and motor dexterity (*Figure 3b*) demonstrated the strongest correlation with brain volume.

3a) Social cognition



3b) Fine motor dexterity

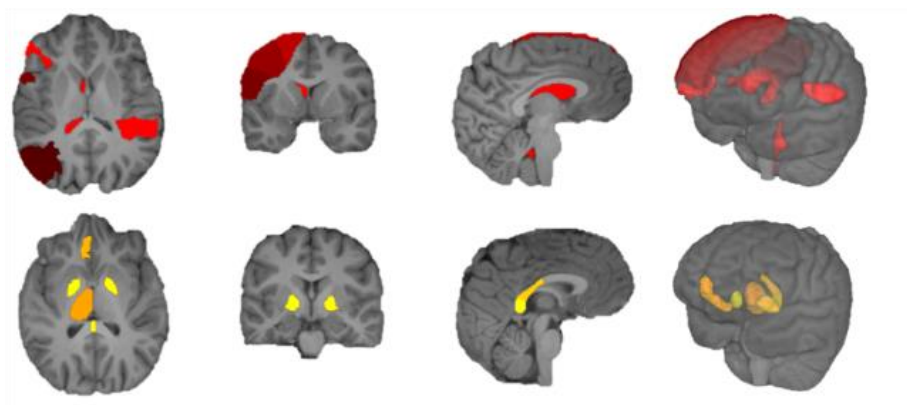


Figure 3. Brain regions correlated with social cognition (3a) and motor dexterity (3b) in the full IMD cohort. Red regions indicate negative correlations, meaning that higher regional volumes are associated with lower performance in the corresponding domain. Yellow regions indicate positive correlations, where lower regional volumes are associated with lower performance.

Specifically, decreased volumes in the corpus callosum ($r=0.50$, $p=0.003$), white matter ($r=0.47$, $p=0.006$), brainstem ($r=0.45$, $p=0.010$), and basal ganglia ($r=0.48$, $p=0.005$) were associated to poorer social cognition, as well as higher volumes of the cingulate cortex ($r=-0.41$, $p=0.020$) and parietal lobe ($r=-0.42$, $p=0.016$), particularly the right supramarginal gyrus ($r=-0.53$, $p=0.002$).

In our cohort, fine motor dexterity impairment was associated with reduced volume of the basal ganglia ($r=0.46$, $p=0.010$) and increased volume of the right angular gyrus ($r=-0.41$, $p=0.022$) and

frontal areas, such as the right middle frontal gyrus ($r=-0.43$, $p=0.016$), the right superior frontal gyrus ($r=-0.43$, $p=0.015$) and the right opercular part of the inferior frontal gyrus ($r=-0.46$, $p=0.009$).

Besides fine motor dexterity impairments, increased volume of the right angular gyrus was significantly correlated to poorer executive functions such as focused attention ($r=-0.45$, $p=0.008$), flexibility ($r=-0.47$, $p=0.013$) and processing speed ($r=-0.50$, $p=0.002$).

These findings suggest that fronto-parietal hypertrophy and subcortical atrophy is associated with impaired integration of higher-order cognitive functions in our cohort of IMDs.

3.3.2. Volumetric biomarkers in intoxication and energy-related IMD

Volumetric analyses conducted within the intoxication IMDs and energy-related IMDs subgroups revealed region-specific associations with cognitive performance (*Table 3*).

In intoxication IMDs, social cognition impairment was associated with decreased volumes of the corpus callosum, basal ganglia, brainstem, and cingulate, as well as increased volumes in the right inferior frontal gyrus and right parietal regions. Decreased volumes in the left inferior frontal gyrus and subcallosal areas correlated with poorer fine motor dexterity, visuospatial performance, and executive functions such as inhibition and cognitive flexibility. Additionally, larger ventricular volumes were linked to poorer motor dexterity. Impairments in focused attention were associated with increased volumes in the right medial and orbital frontal cortex, the right angular gyrus, as well as reductions in cerebellar volume.

These findings suggest that a pattern of fronto-parietal hypertrophy and subcortical-cerebellar atrophy among the intoxication IMD cohort, correlated to specific cognitive deficits, especially social cognition, executive functions and fine motor dexterity.

In energy-related IMDs, larger volumes of the limbic system (cingulate cortex, parahippocampal gyrus, amygdala, and entorhinal cortex) were associated with poorer outcomes in global IQ, working memory, social cognition, and visuospatial abilities.

In subcortical regions, a decrease in overall basal ganglia volume was related to poorer social cognition and working memory, particularly the accumbens volumes. Notably, reduced volumes of the putamen were associated with worse adaptive behaviour, highlighting the basal ganglia's role as a biomarker for daily functionality in individuals with energy-related IMDs.

Within the cerebellum, larger volumes in Crus I–II, lobules VIIb–VIIIb, IX, V, and vermis VIIIb–X correlated with poorer social cognition, visuospatial performance, and executive functions such as cognitive flexibility, inhibition, and focused attention.

In the frontal cortex, increased volume exhibited negative associations with fine motor dexterity, social cognition, and executive functions like working memory and flexibility. Similarly, parietal regions, including the left supramarginal and right angular gyrus, were negatively correlated with cognitive flexibility and processing speed. Furthermore, the right fusiform gyrus was linked to poorer social cognition in our cohort, while larger volumes in the temporal lobe and insula correlated with diminished fine motor dexterity.

In contrast, reduced volumes of white matter and the brainstem were positively associated with poorer motor dexterity, social cognition, and working memory performance.

Overall, the findings suggest that reduced volumes in white matter and the basal ganglia, along with widespread cortico-cerebellar hypertrophy, can serve as volumetric predictors of poorer neurocognitive functioning in individuals with energy-related IMDs.

Table 3. Correlation between regional brain volumes and cognitive performance across multiple domains in intoxication IMDs and energy-related IMDs.

Main Brain Area	Brain Region	Cognitive Domain	Correlation (r)	P-value
Intoxication IMDs				
Frontal Cortex	Frontal Pole - Right	<i>Focused Attention</i>	−0.50	0.039
	Right Lateral Orbital Gyrus	<i>Focused Attention</i>	−0.48	0.045
	Right Medial Frontal Cortex	<i>Focused Attention</i>	−0.51	0.033
	Inferior Frontal Gyrus – Opercular, Right	<i>Social Cognition</i>	−0.67	0.004
	Inferior Frontal Gyrus – Triangular, Left	<i>Flexibility</i>	0.76	0.002
		<i>Inhibition</i>	0.60	0.022
		<i>Visuospatial</i>	0.55	0.020
		<i>Motor Dexterity</i>	0.52	0.045
		<i>Inhibition</i>	0.65	0.010
		<i>Flexibility</i>	0.66	0.013
	Subcallosal Area- Right	<i>Motor Dexterity</i>	0.55	0.031
	Subcallosal Area - Left	<i>Motor Dexterity</i>	0.60	0.016
		<i>Visuospatial</i>	0.49	0.043
Parietal Cortex	Angular Gyrus - Right	<i>Focused Attention</i>	−0.54	0.023
	Supramarginal Gyrus - Right	<i>Social Cognition</i>	−0.56	0.022
	Parietal Operculum - Right	<i>Social Cognition</i>	−0.69	0.002
Basal Ganglia	Accumbens- Right	<i>Social Cognition</i>	0.59	0.014
Brainstem	Brainstem	<i>Social Cognition</i>	0.54	0.031
Corpus Callosum	Corpus Callosum	<i>Social Cognition</i>	0.68	0.004
Cingulate Cortex	Cingulate Cortex Posterior	<i>Social Cognition</i>	0.59	0.014
Cerebellum	Crus II - Right	<i>Focused Attention</i>	0.51	0.035
	VIIb - Right	<i>Focused Attention</i>	0.51	0.033
	Vermis X	<i>Focused Attention</i>	0.54	0.024
Ventricular System	Lateral Ventricles	<i>Motor Dexterity</i>	−0.52	0.046
Energy-related IMDs				
Limbic System	Amygdala – Left	Global IQ	−0.53	0.039
		Visuospatial	−0.54	0.034
	Amygdala – Right	Visuospatial	−0.58	0.022
		Visuospatial	−0.55	0.030
	Entorhinal – Left	Visuospatial	−0.63	0.011
		Visuospatial	−0.63	0.011
	Entorhinal – Right	Visuospatial	−0.63	0.011
		Visuospatial	−0.63	0.011
	Parahippocampal Gyrus – Left	Global IQ	−0.59	0.018
		Working Memory	−0.54	0.035
	Parahippocampal Gyrus – Right	Global IQ	−0.71	0.002
		Social Cognition	−0.53	0.038
		Working Memory	−0.62	0.012
		Visuospatial	−0.61	0.014
		Visuospatial	−0.61	0.014
		Social Cognition	−0.53	0.041
Basal Ganglia	Basal Ganglia	Social Cognition	0.62	0.013
		Working Memory	0.74	0.001
	Putamen – Left	Inhibition	0.55	0.032
		Adaptive Behaviour	0.66	0.010
	Putamen – Right	Adaptive Behaviour	0.61	0.019
	Accumbens – Left	Working Memory	0.59	0.020
Cerebellum	Accumbens – Right	Working Memory	0.61	0.012
	Crus I – Left	Social Cognition	−0.51	0.048
	Crus II – Left	Flexibility	−0.58	0.034
	Crus II – Right	Flexibility	−0.70	0.006
	VIIb – Left	Flexibility	−0.68	0.010
	VIIb – Right	Flexibility	−0.67	0.012
	VIIIa – Left	Flexibility	−0.65	0.014
	VIIIa – Right	Flexibility	−0.59	0.031

	VIIIb – Left	Visuospatial	−0.57	0.024
	V – Left	Focused Attention	−0.58	0.023
	V – Right	Focused Attention	−0.56	0.027
	Vermis VIIIb	Flexibility	−0.60	0.029
	Vermis X	Inhibition	−0.54	0.037
		Adaptive Behaviour	−0.53	0.047
Frontal Cortex	Frontal Lobe	Motor Dexterity	−0.68	0.005
	Frontal Pole – Left	Flexibility	−0.57	0.037
	Middle Frontal Gyrus – Left	Working Memory	−0.62	0.013
	Middle Frontal Gyrus – Right	Social Cognition	−0.54	0.034
	Inferior Frontal Gyrus – Orbital, Right	Working Memory	−0.68	0.004
	Inferior Frontal Gyrus – Triangular, Right	Social Cognition	−0.54	0.037
		Working Memory	−0.73	0.001
Parietal Cortex	Supramarginal Gyrus – Left	Flexibility	−0.78	0.001
	Angular Gyrus – Right	Flexibility	−0.58	0.034
		Processing Speed	−0.60	0.016
Temporal Cortex	Temporal Lobe	Motor Dexterity	−0.53	0.041
	Fusiform Gyrus – Right	Social Cognition	−0.66	0.006
Insula	Insula	Motor Dexterity	−0.57	0.026
Brainstem	Brainstem	Working Memory	0.54	0.037
White Matter	White Matter	Social Cognition	0.64	0.009
		Motor Dexterity	0.57	0.026
	White Matter – Right	Working Memory	0.53	0.041

3.3.3. Age at disease onset as a cerebellar volume modifier

We examined the impact of age at disease onset on the association between brain volume and neuropsychological outcomes.

Our findings revealed significant differences between early-onset (EO) and late-onset (LO) patients, particularly in the frontal regions and cerebellum, which were associated with lower overall cognitive functioning in both groups (all showing correlations of $r \pm 0.60$ -0.93, and $p < 0.05$). Patients with EO exhibited increased frontal volumes and decreased cerebellar volumes, while LO patients displayed reduced frontal volumes and increased cerebellar volumes in relation to neurocognitive functioning.

Although intoxication and energy-related IMDS were similarly represented in both onset groups, the EO pattern was more pronounced in cases of organic acidurias. In contrast, the alterations observed in the LO group were predominantly associated with energy metabolism pathways, particularly those involving GLUT1 and glycogen metabolism.

4. Discussion

This study provides novel insights into the microstructural brain correlates of neurocognitive dysfunction in IMDs due to intoxication and energy metabolism defects. By comparing patients to a healthy model and analysing volumetric differences both between IMD subtypes and in relation to neuropsychological outcomes, several key findings emerge.

Broadly, our findings point to a fronto-parietal hypertrophy pattern across the cohort, but with clear phenotype-specific signatures that differentiate intoxication IMDs from energy-related IMDs. These patterns offer relevant pathophysiological insights into the neural basis of cognitive dysfunction in IMDs.

4.1. *Shared volumetric patterns across IMDs*

Despite most of our cohort displaying normal MRI results, we observed an increased microstructural volume in fronto-parietal and subcortical regions, including the left triangular part of the inferior frontal gyrus (IFG), the left orbital gyrus, the right medial frontal cortex, the left putamen and the left angular gyrus, compared to age-matched healthy models. Additionally, a 32% reduction in cerebrospinal fluid (CSF) volume might reflect compensatory intracranial dynamics due to relative expansion in adjacent structures. This shared volumetric expansion among the intoxication and energy-related IMDs needs to be further explored in larger cohorts. However, it highlights common disruption in the early brain development, possibly reflecting either altered neurogenesis differentiation, myelination, synaptogenesis or pruning due to the underlying metabolic stress (Bhattacharya et al., 2021; Iwata & Vanderhaeghen, 2021; Dehorter & Del Pino, 2020; Uytun, 2018).

The differences in brain volume between patients with IMDs and healthy controls are both anatomically and functionally significant. Specifically, individuals with poorer social skills exhibit larger volumes in the parietal region, particularly in the right supramarginal gyrus, along with reduced volumes in subcortical structures such as white matter, the corpus callosum, the brainstem, and the basal ganglia. Additionally, patients with impairments in fine motor skills show decreased volumes in the basal ganglia, while having larger volumes in the right frontal and parietal areas, especially the right angular gyrus, which is also associated with poorer executive functions.

Our findings align with existing literature indicating that the fronto-striatal and fronto-cerebellar circuits, particularly those involving the basal ganglia and brainstem, are crucial for emotional regulation, social inference, and behavioural adaptation. This supports the idea that social cognition relies on a distributed network connectivity rather than isolated regions of the cortex (Van Overwalle et al., 2020). In neurodevelopmental disorders, reduced white matter is correlated with symptoms of ASD (Sato & Uono, 2019).

The prefrontal cortex, including the dorsolateral, orbitofrontal, and anterior cingulate circuits, play a key role in executive functioning and emotional regulation. Their interaction with the basal ganglia via reciprocal fronto-striatal circuits underpins much of the cognitive modulation affected in IMD (Batista & Mattos, 2018). Similarly, social cognition likely recruits a fronto-temporo-limbic network, including the medial prefrontal cortex (mPFC), precuneus, temporal poles, and the IFG, all regions found to be structurally affected in our cohort (Starcevic & Filipovic, 2018).

In our cohort, the age at disease onset emerged as a key modifier of volumetric patterns, with early-onset IMDs associated with decreased volume in right temporo-cerebellar regions, including the bilateral Crus II of the cerebellum, the right amygdala, and the right temporal pole. The differences in cerebellar volume between early-onset (decreased) and late-onset (increased) patients were associated with a general impairment in neurocognitive function in both groups equally. However, in early-onset patients, those with organic acidurias exhibited the most significant cerebellar atrophy. Conversely, in late-onset patients, individuals with energy defects, such as GLUT1 deficiency syndrome or glycogen storage diseases, showed more pronounced cerebellar hypertrophy.

These findings highlight that even in patients with early diagnosis and treatment, microstructural brain damage and related neurocognitive outcomes may occur. A recent study examining adults with phenylketonuria emphasises the ongoing neurodevelopmental vulnerabilities associated with metabolic toxicity, even in individuals who received early treatment. They also reported reduced volumes in white matter and subcortical structures (Pardo et al., 2024).

Therefore, it is crucial to conduct systematic neuropsychological assessments and ongoing follow-up care for patients with IMDs, even if they have been treated early or appear clinically asymptomatic. This approach will help identify any subtle cognitive or behavioural changes that may

arise over time, ensuring timely interventions and support to optimise patient functioning and quality of life.

4.2. *Distinct volumetric biomarkers in intoxication and energy-related IMDs*

The specific volumetric patterns between intoxication and energy-related IMDs highlight distinct microstructural vulnerabilities.

4.2.1. *Intoxication IMDs*

The intoxication IMD cohort presented a marked atrophy in multiple limbic–temporal regions (amygdala, entorhinal cortex, temporal pole) and primary motor areas, accompanied by reduced cerebellar volumes across Crus II, lobules V–VIIIb, and vermis IX. Enlargement of the lateral ventricles in this group suggests parenchymal loss, which may reflect either chronic or repeated episodes of metabolic decompensation and the chronic accumulation of neurotoxic metabolites, even in patients with clinically mild or asymptomatic phenotypes.

This pattern of impairment, although widespread among intoxication IMDs, was especially pronounced in organic acidurias, particularly in glutaric acidurias.

Neurocognitive impairment associated to specific brain volumes

In our cohort with intoxication IMDs, a distinct pattern of fronto-parietal hypertrophy and subcortical-cerebellar atrophy correlated to specific deficits in social cognition, executive functions (focused attention, flexibility, inhibition) and fine motor dexterity. On the other hand, we found that decreased volumes in the left IFG and subcallosal areas were associated with poorer fine motor dexterity, visuospatial performance, and executive functions, such as inhibition and cognitive flexibility. Additionally, larger ventricular volumes were linked to reduced motor dexterity.

The cerebellum is structurally and functionally connected to the superior temporal cortex and has been consistently linked to executive functions, including working memory, cognitive flexibility, and processing speed (Bègue et al., 2024; Palesi et al., 2017). In addition to executive control, Crus II also plays a role in social prediction and mentalizing processes (Van Overwalle et al., 2020). Alongside the

right amygdala and the right temporal pole, which are both central to socio-emotional processing and integration, this network may contribute to the social cognition impairments in intoxication IMDs.

4.2.2. Energy-related IMDs

Energy-related IMDs exhibited a predominant hypertrophic pattern, particularly in the right putamen and cerebellar regions. The reduction in CSF volume, in the absence of overt ventricular enlargement, may indicate a developmental volumetric imbalance or a process of neuroinflammation.

This pattern of impairment, although generalized among energy-related IMDs, was particularly pronounced in GLUT1DS.

Neurocognitive impairment associated to specific brain volumes

Energy-related IMDs who had a poorer performance in cognitive functions exhibited widespread cortico-cerebellar hypertrophy, particularly in the limbic system, fronto-parietal, and cerebellar regions, as well as reduced volumes in white matter and basal ganglia. Particularly, the most significant correlations were found with social cognition, executive functions and fine motor dexterity.

This pattern points to a developmental hypertrophic signature with subcortical vulnerability, possibly reflecting chronic energy imbalance and disrupted network maturation.

Notably, our cohort of patients with energy-related IMDs exhibited increased bilateral putaminal volumes compared with age-matched healthy controls. Interestingly, this volumetric enlargement was specifically associated with better adaptive behaviour.

Consistent with prior neuroimaging studies, putaminal hypertrophy has been described in various neurological and neuropsychiatric conditions and is considered a potential compensatory neuroplastic mechanism supporting cognitive and motor functions (Luo et al., 2019). In children, volumetric changes in subcortical structures must be interpreted in the context of a highly plastic, developing brain. In our sample, the increased putaminal volume observed in mild and asymptomatic children may reflect an early adaptive process mitigating the neurocognitive impact typically associated with subcortical vulnerability in metabolic disorders. Similar patterns have been reported in pediatric

epilepsy, where putaminal hypertrophy has been interpreted as a compensatory response to seizure activity, reflecting the putamen's central role in networks supporting motor control and cognition (MacEachern et al., 2020). Nonetheless, structural hypertrophy does not always imply functional improvement, and these findings should be interpreted cautiously and validated through longitudinal studies to clarify their developmental trajectory and functional significance.

4.3. *The cerebellum as a key neurodevelopment biomarker*

Our findings reveal a differential cerebellar signature across metabolic subtypes, with cerebellar atrophy in intoxication IMDs and hypertrophy in energy-related IMDs. This differential pattern underscores the cerebellum's sensitivity to metabolic disruptions and its potential role as a neurocognitive biomarker of metabolic physiopathology.

Acute or intermittent metabolic crises characteristic of intoxication IMDs likely induce structural injury and atrophy within subcortical–cerebellar systems, followed by secondary cortical reorganization. In contrast, chronic energetic deficiency in energy-related IMDs may interfere with developmental processes such as synaptic pruning and long-range network maturation, resulting in hypertrophy of cortical association areas and the cerebellum, accompanied by subcortical disconnection. These observations align with known metabolic vulnerabilities of the brain, wherein cerebellar structures and associated white matter tracts exhibit high susceptibility to both energy depletion and toxic metabolite accumulation.

During neurodevelopment, the cerebellum transitions from a set of local processing hubs into a network-integrated structure through myelination and the establishment of long-range cortico-cerebellar connections. Damage during this period, when cerebellar-cortical connectivity is still immature, can impair fine motor coordination and higher order cognitive functions due to connectional diaschisis and limited compensatory capacity (Beuriat et al., 2022). Structural neuroimaging across neurodevelopmental disorders has consistently identified alterations in cerebellar gray matter volume (GMV). Increased GMV has been reported in the left cerebellum and basal ganglia in ADHD (Li et al., 2022; Albajara et al., 2020), while ASD studies reveal abnormalities in cerebellar–cortical and subcortical circuits, including volumetric increases in the hippocampus, ventricles, and amygdala (Li et al., 2023; Richards et al., 2020). Moreover, disrupted cerebellar connectivity with the ventromedial

prefrontal cortex (vmPFC) and other nodes of the social brain has been linked to deficits in empathy, social cognition, and theory of mind (Van Overwalle, 2020; Sato & Uono, 2019).

Beyond categorical neurodevelopmental diagnoses, cerebellar volumetry correlates closely with cognitive performance. Distinct cerebellar subregions, including Crus I/II and lobules VI and X, have been associated with working memory, cognitive flexibility, and processing speed (Bègue et al., 2024). These functional territories align with major cortico-cerebellar communication loops, namely the cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways, which support not only motor control but also visuospatial processing, attention and executive functions (Brissenden, 2018; Palesi et al., 2017).

Mechanistically, the cerebellum's metabolic vulnerability is strongly linked to its excitatory–inhibitory dynamics. Following metabolic insults, neuroinflammatory cascades lead to excessive production of reactive oxygen species (ROS), mitochondrial dysfunction, and calcium overload through NMDA receptor overactivation, ultimately triggering apoptotic pathways and structural atrophy (Revuelta et al., 2020). In the cerebellum, oxygen–glucose deprivation induces depolarization of Purkinje cells, the principal GABAergic output neurons, resulting in glutamate overflow and excitotoxic damage (Revuelta et al., 2020; Tamada et al., 2020). This excitatory–inhibitory imbalance triggered by perinatal brain damage compromises Purkinje cell integrity and myelination, particularly in cerebellar and brainstem tracts in IMD patients (Blaser, 2016).

The glutamatergic imbalance has also been implicated in the physiopathology of other neurodevelopmental disorders. In ASD, reduced Purkinje cells diminish inhibitory control, leading to cerebellar hyperexcitability and abnormal functional hyperconnectivity with sensorimotor cortices (Rudolph et al., 2023; Trimarco et al., 2021). These alterations may alter cerebello-thalamo-cortical loops, disrupting motor coordination, sensory integration, social communication, and executive functions, thereby positioning the cerebellum as an integral component of the limbic system, disrupted in neurodevelopmental disorders (Rudolph et al., 2023).

Taken together, these findings support a developmental vulnerability model in which the cerebellum, owing to its early maturation, high metabolic demand, and extensive long-range connectivity, acts as a central hub susceptible to systemic metabolic stressors. Early metabolic

imbalance can propagate across cortico-cerebellar networks, producing long-lasting effects on cognitive, social-emotional and sensorimotor domains. Thus, the cerebellum should be regarded not merely as a motor coordinator but as a dynamic, integrative structure whose metabolic and neurofunctional integrity is pivotal to transdiagnostic neurodevelopment and cognitive outcomes in IMDs. Future interventions aimed at preserving or restoring the integrity of the cerebellum could be beneficial in reducing neuropsychological outcomes in IMDs.

These findings have significant clinical implications for the diagnosis, monitoring, and treatment of inherited metabolic disorders. The identification of volumetric changes in the cerebellum, basal ganglia, and white matter as potential biomarkers provides a structural basis for the early detection of neurocognitive vulnerabilities, even in early-treated patients with normal conventional MRI results.

Recognizing distinct patterns associated with intoxication and energy-related IMDs can help guide personalized therapeutic strategies. These strategies may include targeted neuroprotective interventions and neuropsychological rehabilitation.

Furthermore, the protective role of early diagnosis emphasizes the importance of prompt metabolic screening and the initiation of treatment to prevent or reduce long-term cognitive, socio-emotional, and motor impairments. Incorporating advanced neuroimaging and neuropsychological assessments into routine follow-up protocols could facilitate the monitoring of disease progression, assess the effectiveness of interventions, and ultimately enhance patient outcomes through timely and personalized care.

4.4. *Limitations and future directions*

This study presents some limitations that should be considered when interpreting the results. The relatively small sample size and the diversity of IMDs may limit the generalization of the findings. Future research should involve larger longitudinal cohorts to monitor brain volumetry and cognitive outcomes throughout disease progression and investigate the effects of targeted interventions on structural and functional brain networks, in both intoxication and energy-related IMDs.

While advanced volumetric MRI provided valuable insights into rare diseases, standardized protocols are needed to facilitate the comparison between studies. Future studies are warranted to validate these findings and elucidate the mechanisms underlying structural-functional relationships in metabolic disorders.

4.5. Conclusions

In summary, this study supports the utility of volumetric MRI as a potential biomarker in IMDs, providing valuable insight into the neurobiological underpinnings of cognitive deficits in IMDs. In our cohort, the cerebellum emerges as a key structure for disease stratification, distinguishing intoxication from energy-related IMDs, while fronto-parietal hypertrophy and subcortical atrophy correlate with cognitive dysfunction across domains, particularly in social cognition, executive functions and fine motor dexterity. Such microstructural patterns could complement biochemical and genetic diagnosis, support disease monitoring, and help identify patients at risk of cognitive dysfunction.

Overall, these findings indicate that early and targeted neuroprotective interventions addressing specific vulnerabilities in brain regions could help preserve cognitive and functional abilities in individuals with IMDs. Furthermore, the correlation between hypertrophy and poorer performance suggests that increased volume should not be interpreted as a marker of preserved function in IMDs, but rather as a sign of maladaptive or inefficient neural processing.

Key Findings

- Advanced volumetric MRI revealed widespread microstructural brain abnormalities in mild and asymptomatic IMDs, despite largely normal conventional MRI findings.
- Distinct neuroanatomical signatures differentiated IMD subtypes, with intoxication IMDs showing limbic–temporal and cerebellar atrophy and energy-related IMDs demonstrating predominant cortico-cerebellar and putaminal hypertrophy.
- A shared pattern of fronto-parietal hypertrophy combined with subcortical vulnerability was associated with deficits in social cognition, executive functioning, and fine motor skills across IMDs.
- Differential cerebellar volumetric patterns, with hypertrophy in energy-related IMDs and atrophy in intoxication IMDs, related to cognitive impairment, highlight the cerebellum as a distinct neurocognitive biomarker.
- Age at disease onset modulated brain structure, with late-onset IMDs linked to cerebellar hypertrophy associated with neurocognitive impairment.

Chapter V

Lipidomic biomarkers of neurocognitive impairment:

A multicentre cohort study

1. Introduction

Over the past two decades, omic-based technologies have transformed our ability to investigate human diseases, with metabolomics playing a crucial role in clarifying the biochemical landscape of *Inherited Metabolic Disorders (IMDs)*. Unlike targeted methods, untargeted metabolomics can simultaneously profile thousands of metabolites across multiple pathways. This approach enables a comprehensive characterization of metabolic networks, the discovery of novel disease biomarkers, and the development of personalized medicine strategies (Ismail et al., 2019; Glinton & Elsea, 2019; Mussap et al., 2018). Untargeted metabolomics has already been applied to at least 100 distinct IMDs, including methylmalonic acidemia and propionic acidemia, as well as to over 1,400 known genetic conditions. However, it remains underutilized in routine clinical practice, partly due to challenges in data interpretation, standardization, and validation across diverse independent cohorts. Furthermore, research employing untargeted metabolomics are relatively scarce and often involve small cohorts. As a result, novel biomarkers require further validation before they can be implemented in clinical settings (Wurth et al., 2024; Kvasnička et al., 2023).

Lipidomics is the qualitative and quantitative study of lipid species and their metabolic pathways, and it has emerged as an important approach for understanding disorders that involve the nervous system. Lipids are the second most abundant cellular component, after water, and the human brain has the highest lipid content of any organ, accounting for over 50% of its dry weight. Complex lipid structures, such as myelin and cell membranes, are essential for synaptic signalling, vesicle trafficking, mitochondrial energy production, and inflammation processes (Bernal-Vega et al., 2023; Esvap & Ulgen, 2023; Yu et al., 2020; El-Ansary et al., 2020).

While brain organization and function undergo significant changes during development, the specific changes in lipid concentrations during these processes remain poorly understood. A range of genetic and environmental factors, such as gene mutations, age, sex, diet, and medications, can influence the lipidome (Kvasnička et al., 2023; Yu et al., 2020).

Disruptions in lipid metabolism are increasingly recognized as central to the pathophysiology of diverse neurodevelopmental and neurodegenerative disorders, including autism spectrum disorder

(ASD), attention deficit hyperactivity disorder (ADHD), Parkinson's disease, and Alzheimer's disease (Yan et al., 2025; Mei et al., 2023; El-Ansary et al., 2020).

Research on ASD has identified changes in sphingolipids, proposing elevated levels of ceramides and sphingosine-1-phosphate (S1P) as potential diagnostic biomarkers (Li et al., 2024; Esvap & Ulgen, 2023; El Ansary et al., 2020; Wu et al., 2017). Similarly, ADHD symptoms have been associated with reduced levels of circulating sphingomyelins and ceramides, suggesting a compromise in neuronal membrane composition and neurotransmitter signalling (Bernal-Vega et al., 2023; Brunkhorst-Kanaan et al., 2021). In neurodegenerative diseases, dysregulation of sphingolipids contributes to neuroinflammation, oxidative stress, and progressive neuronal loss, with specific patterns linked to disease stage and severity (Mei et al., 2023; Blot et al., 2021). These findings emphasize the crucial role of lipid metabolism in the pathophysiology of several neurological and psychiatric disorders. They also demonstrate that lipidomic studies have the potential to reveal shared altered pathways across various neuropsychiatric conditions and predict clinical phenotypes (Modesti et al., 2025).

Lipids are particularly vulnerable to metabolic dysfunction in IMDs due to their essential roles in cellular structure and energy production. However, current lipid analyses in clinical settings do not provide a comprehensive lipidomic profile, leaving much valuable information unexplored (Zandi-Lang et al., 2023). Lipidomic analyses conducted across various IMDs have uncovered consistent disruptions in mitochondrial lipid homeostasis, suggesting that lipid dysregulation is a common mechanism contributing to neuroenergetic failure and neuroinflammation. In the brain, lipids are particularly vulnerable to oxidative stress, leading to rapid peroxidation and may affect cellular signalling (El-Ansary et al., 2020).

Complex lipids are synthesized from small molecules such as glucose and acetyl-CoA, which are key molecules involved in thousand of chemical reactions in intermediary metabolism. That could explain the important consequences of intoxication and energy related disorders in lipid metabolism. In addition to that, lipids such as cholesterol, ubiquinone, dolichol, glycerophospholipids, long and very long chain fatty acids, plasmalogens and sphingolipids are important components of the brain (Figure 1).

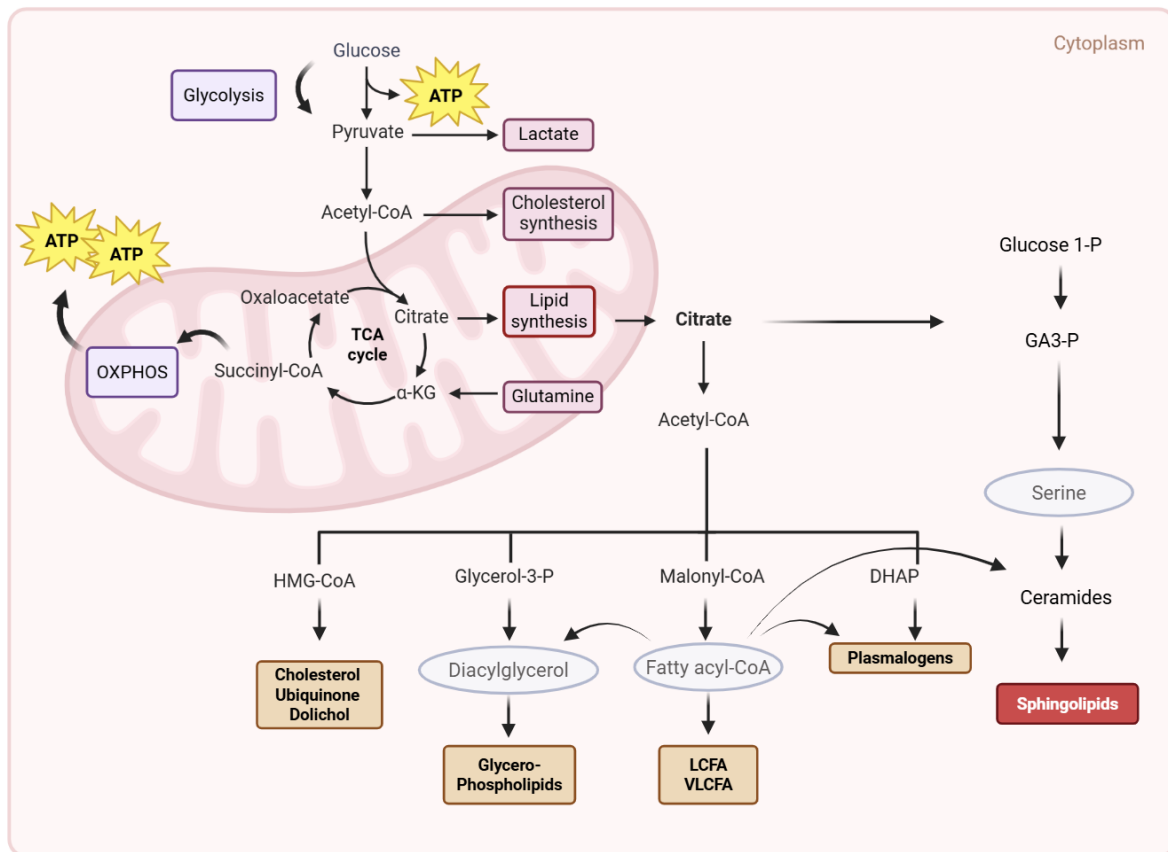


Figure 1. Schematic representation of metabolic connections between small molecules and lipid synthesis in the brain. Pyruvate derived from glycolysis is converted into acetyl-CoA, which can be transformed into citrate and exported to the cytoplasm. Cytosolic citrate supports the synthesis of cholesterol, ubiquinone, dolichol, glycerophospholipids, fatty acids (long-chain and very long-chain), and plasmalogens. Citrate also participates in serine metabolism and contributes to sphingolipid biosynthetic pathways essential for normal brain function.

In energy-related IMDs, impaired β -oxidation and mitochondrial dysfunction can alter lipid profiles. Recent studies have revealed characteristic alterations in these disorders, including elevated levels of medium- and long-chain acylcarnitines, imbalances in phosphatidylcholines and lysophospholipids, and disrupted ceramide-sphingomyelin ratios. These changes reflect not only defective energy production but also secondary inflammatory responses ([Zandi-Lang et al., 2023](#); [Tucci, 2022](#)).

Upon activation of phospholipases (e.g. PLA2), results in the release of arachidonic acid from phospholipids, which is subsequently metabolized into bioactive lipid mediators, including pro-inflammatory eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and anti-inflammatory or

pro-resolving molecules such as lipoxins and resolvins (Farooqui & Farooqui, 2024; O'Donnell et al., 2018). The balance between these metabolites is critical for regulating neuroinflammatory responses.

Ceramides, a central sphingolipid, are generated either by hydrolysis of sphingomyelin (a membrane phospholipid) or via de novo synthesis. Ceramides act as bioactive signaling molecules that modulate cell death, cytokine production, and immune cell function. Elevated ceramide levels are associated with the induction of pro-inflammatory pathways, including activation of transcription factors (e.g., NF- κ B), promotion of cytokine release, and assembly of membrane microdomains (lipid rafts) that facilitate immune receptor signalling (Gomez-Larrauri et al., 2025; Thakkar et al., 2025; Albeituni & Stiban, 2019; Cai et al., 2016; Iwabuchi et al., 2015; Maceyka & Spiegel, 2014). Ceramide-rich platforms can interact with phospholipid-derived mediators, amplifying or modulating inflammatory signaling.

In intoxication, IMDs, untargeted lipidomic analyses have shown increases in glycerophospholipids, such as lysophosphatidylethanolamine (LPE) and lysophosphatidylcholine (LPC), as well as elevated triglycerides (TAG) in patients with phenylketonuria (PKU), independent of phenylalanine levels (Van der Weerd et al., 2024). Similarly, in glycogen storage disease type Ia (GSD-Ia), significant increases in ceramides, LPC, TAG, diacylglycerols (DAG), and cholesterol esters (CE) have been observed. Ceramides, in particular, appear to play a pivotal role as mediators of endoplasmic reticulum stress, apoptosis, and insulin resistance, underscoring their importance in systemic metabolic stress and liver pathology (Rossi et al., 2024).

Overall, the evidence emphasizes that lipid alterations in IMDs extend beyond secondary metabolic effects, reflecting fundamental disruptions in cellular homeostasis, mitochondrial function, and inflammatory signalling. By providing a broad understanding of these changes, untargeted lipidomics offers unprecedented opportunities to identify potential biomarkers for early diagnosis, monitor disease progression, and uncover shared pathogenic pathways across different IMDs. This insight paves the way for precision medicine approaches and the development of novel therapies (Modesti et al., 2025; Wurth et al., 2024; Ismail et al., 2019).

As discussed in previous Chapters, the spectrum of neuropsychological impairment associated with IMDs include deficits in fine motor skills, attention, executive functions, social

cognition, and behaviour regulation (Gil-González et al., 2025). However, the underlying mechanisms of neurocognitive dysfunction in IMDs remain unclear. Since lipid-related pathways have been identified as significant contributors to neuropsychiatric disorders, lipidomic analysis could provide valuable insights into potential biomarkers for neurocognitive impairment in individuals with IMDs.

Through an untargeted lipidomic approach, this multicenter study aims to explore potential biomarkers of neurocognitive impairment in a cohort of children and adolescents with intoxication and energy-related IMDs. Identifying novel lipidomic biomarkers associated with the pathophysiology of these metabolic disorders can improve our understanding of the neurobiological factors underlying brain damage and neuropsychological outcomes in IMDs. Ultimately, this research seeks to establish a foundation for integrating lipidomics and neuropsychological assessments into clinical practice, to facilitate early diagnosis, disease monitoring, and personalized interventions for individuals with IMDs.

2. Methods

2.1. *Participants*

The study included participants from the cohort in Chapter III, aged 6 to 17 with a confirmed diagnosis of intoxication or energy-related IMD established through genetic and biochemical testing. All participants exhibited either mild phenotypes or were asymptomatic (IQ>55), with good adherence to metabolic treatments and controlled decompensations (≤ 1 /year). Exclusion criteria included a history of significant head trauma, the presence of other neurological disorders unrelated to the IMD, and patients treated with methylphenidate.

Patients were recruited from several reference hospitals in Spain: 32 from Hospital Sant Joan de Déu in Barcelona (49.3%), 18 from the Hospital Materno-Infantil in Las Palmas de Gran Canaria (27.7%) and 15 from the Hospital 12 de Octubre in Madrid (23%). The final sample included 65 participants (Table 1), 37 with intoxication IMD (57%) and 28 with energy-related IMD (43%).

2.2. *Biological samples acquisition*

Blood samples were collected from participants (n=65) after an overnight fast, when possible, and were processed to obtain serum (n=63) or plasma (n=16). The control group consisted of serum and plasma samples from age-equivalent healthy patients stored in the Hospital Sant Joan de Déu biobank (n=15).

Metabolites were extracted from plasma samples using a methanol-based protein precipitation method. Samples were then analyzed using ultra-performance liquid chromatography coupled to high-resolution mass spectrometry (UPLC-HRMS). The UPLC system (Waters Acquity) was coupled to a Q-Exactive Orbitrap mass spectrometer (Thermo Fisher Scientific) operating in both positive and negative ion modes.

Data acquisition involved full MS scans with a resolution of 70,000, followed by data-dependent MS/MS scans for structural elucidation of metabolites. Data processing and peak alignment were performed using Compound Discoverer (Thermo Fisher Scientific) and MetaboAnalyst for downstream statistical analysis.

2.3. Lipidomic data processing

Lipid extraction was conducted using a modified Bligh and Dyer method. Extracted lipids were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a QTRAP 6500+ system (Sciex). The LC separation was performed on a C18 column, and the MS analysis included multiple reaction monitoring to quantify lipid species across different classes, including phospholipids, sphingolipids, and neutral lipids (*Table 2*).

Data were processed using LipidView (Sciex) software, and lipid species were identified and quantified based on retention time, mass-to-charge ratio (m/z), and characteristic fragmentation patterns.

Table 1. Demographic and clinical description of the cohort.

Patient	Age	Gender	Hospital	IMD type	IMD Category	IMD	Gene #OMIM	Onset	Diet	Medical history	Biological sample
1	17y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		Seum Plasma
2	7y 2m	M	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein		Seum
3	16y 4m	M	Barcelona	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		Seum
4	6y 1m	M	Barcelona	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Early onset	No		Seum Plasma
5	7y	M	Barcelona	Intoxication	Amino acid metabolism	Propionic acidemia	PCCA #232000	Early onset	Low protein	LT	Seum Plasma
6	8y 8m	M	Canarias	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Late onset	Low protein		Seum
7	8y 6m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	Epilepsy, AEDs	Seum
8	17y 9m	F	Canarias	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Late onset	Low fat		Seum
9	12y 2m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index		Seum
10	12y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein	LT	Seum
11	6y 10m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Carnitine palmitoyltransferase 2 deficiency	CPT2 #600650	Early onset	Low fat		Seum
12	9y 9m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	Epilepsy	Seum
13	10y 10m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index		Seum
14	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
15	16y 3m	M	Barcelona	Intoxication	Amino acid metabolism	Argininosuccinate lyase deficiency	ASL #608310	Late onset	No		Seum Plasma
16	12y 4m	F	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein		Seum Plasma
17	9y 4m	F	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein		Seum
18	8y 4m	F	Barcelona	Intoxication	Amino acid metabolism	Tyrosinemia type 2	TAT #613018	Early onset	Low protein		Seum Plasma
19	17y	M	Barcelona	Intoxication	Vitamin and cofactor	Biotinidase deficiency	BTD #609019	Early onset	No		Seum
20	13y 7m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		Seum
21	8y 8m	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		Seum
22	14y 7m	M	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		Seum
23	7y 9m	M	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein		Seum
24	6y 1m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
25	10y 9m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
26	15y 4m	F	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		Seum
27	7y 5m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 6	PYGL #613741	Late onset	Low Glycemic Index		Seum
28	6y 1m	M	Canarias	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat		Seum
29	15y 1m	M	Canarias	Intoxication	Amino acid metabolism	Cystathionine beta-synthase deficiency	CTH #607657	Late onset	Low protein		Seum
30	14y 1m	F	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		Seum
31	9y	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Early onset	Low protein	LT	Seum
32	16y 6m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		Seum
33	6y 10m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
34	13y 11m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index		Seum
35	10y 5m	M	Canarias	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Late onset	No	Epilepsy, AEDs	Seum
36	12y 1m	M	Barcelona	Intoxication	Vitamin and cofactor	5,10-methylenetetrahydrofolate reductase deficiency	MTHFR #607093	Late onset	No		Seum Plasma
37	11y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic		Seum
38	8y 7m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
39	10y 11m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index		Seum
40	8y 5m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		Seum

											Plasma
41	8y 9m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Carnitine palmitoyltransferase 2 deficiency	CPT2 #600650	Early onset	Low fat		Seum
42	15y	M	Barcelona	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein		Seum Plasma
43	14y 6m	F	Canarias	Intoxication	Amino acid metabolism	Argininosuccinate synthetase deficiency	ASS1 #603470	Late onset	No		Seum
44	6y 10m	F	Barcelona	Intoxication	Amino acid metabolism	3-metil crotonil glicinuria	MCCC2 #609014	Early onset	No		Seum
45	6y 3m	M	Madrid	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat		Seum
46	8y 6m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		Seum Plasma
47	10y 11m	F	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Late onset	Low fat		Seum Plasma
48	8y 4m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum Plasma
49	8y 9m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Late onset	Low fat		Seum Plasma
50	13y 1m	F	Madrid	Energy-related	mtDNA	Mitochondrial tRNA-Leu 1 deficiency	MT-TL1 #590050	Early onset	No		Seum
51	12y 10m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	Epilepsy	Seum Plasma
52	11y 9m	F	Barcelona	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 3	AGL #610860	Early onset	Ketogenic		Seum
53	9y 11m	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein		Seum
54	7y 3m	F	Madrid	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Early onset	Low protein		Seum
55	13y 3m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		Seum
56	10y 8m	M	Barcelona	Intoxication	Amino acid metabolism	Propionic acidemia	PCCB #232050	Late onset	Low protein	LT	Seum
57	10y 9m	M	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic		Seum Plasma
58	13y 10m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No		Seum
59	13y 1m	F	Canarias	Energy-related	Fatty acid and ketone bodies	Carnitine-acylcarnitine translocase deficiency	SLC25A20 #613698	Early onset	Low fat	LT	Seum
60	14y	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		Seum Plasma
61	9y 9m	F	Canarias	Intoxication	Carbohydrate metabolism	Hereditary fructose intolerance	ALDOB #612724	Late onset	Low fructose		Seum
62	8y 1m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Early onset	Low Glycemic Index		Seum
63	9y 6m	F	Madrid	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat		Seum
64	10y	M	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein		Seum
65	13y 2m	F	Canarias	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein		Seum

AEDs= antiepileptic drugs

LT= liver transplant

Table 2. Lipid classes included in the lipidomic analysis.

LIPID CLASS	LIPID SUBCLASS	LIPID SPECIES
Glycerophospholipids (GP)	Phosphatidylcholines (PC)	38
	Lyso-phosphatidylcoline (LPC)	12
	Phosphatidylethanolamines (PE)	8
	Lyso-phosphatidylethanolamines (LPE)	4
Glycerolipids (GL)	Diacylglycerols (DAG)	20
	Triacylglycerols (TAG)	59
Sterol Lipids (ST)	Cholesterol – Free (CHOL)	1
	Cholesteryl ester (CE)	26
Sphingolipids (SP)	Sphingosine	1
	Sphinganine	1
	Sphingosine-1-phosphate (S1P)	1
	Sphinganine-1-phosphate	1
	Ceramides (Cer)	10
	Dihydroceramides (DHCer)	6
	Sphingomyelin (SM)	14
	Dihydrosphingomyelin (DHSM)	7
	Hexosylceramide (HexCer)	4
	Ceramide dihexoside (CDH)	7

2.4. Neuropsychological assessment

The complete neuropsychological assessment data is available in the referenced study (Chapter III). This study included measures of global intelligence (Full-Scale IQ, Wechsler), expressive language (Verbal Comprehension Index, Wechsler), visual performance (Visuospatial Index, Wechsler), focused attention (Digit Span Forward – Wechsler and CPT-3), sustained attention (CPT-3), working memory (Working Memory Index- Wechsler), processing speed (Processing Speed Index, Wechsler), inhibition and cognitive flexibility (Inhibition- NEPSY-II), social cognition (Affect Recognition and Theory of Mind, NEPSY-II), fine motor dexterity (Purdue Pegboard Test), adaptive behaviour (ABAS-II) and internalizing/externalizing problems (BRIEF and SENA).

2.5. Statistical analysis

For lipidomic data, multivariate statistical analyses, including principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA), were conducted to identify metabolic patterns distinguishing IMD patients from controls. Univariate analyses with correction for multiple comparisons (e.g., Benjamini-Hochberg FDR procedure) were performed to identify significantly altered metabolites and lipids.

Lipidomic differences were analysed within the overall sample of IMDs and within each specific type of IMD, using the simplified classification by Saudubray et al. (2019). We also considered the more detailed categories and groups of diseases from the ICIMD (Ferreira et al., 2021). Additionally, our analysis accounted for the potential impact of various dietary types on the lipidome.

In order to examine the relationship between neuropsychological data with the lipidomic profiles, this study employed linear regression models, adjusting for potential confounders such as age, sex or disease. All statistical tests were carried out with a confidence level of 95% and considered significant at $p < 0.05$. The analyses were performed using IBM SPSS statistical software version 29.0.

2.6. Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. The potential risks and benefits were explained to the participants and their families. Participation was voluntary, and participants could withdraw from the study at any time without any consequences to their medical care. The study was approved by the Research Ethics Committee of Hospital Sant Joan de Déu, and written informed consent was obtained from the parents or legal guardians of all participants, with assent collected from children over the age of 12.

3. Results

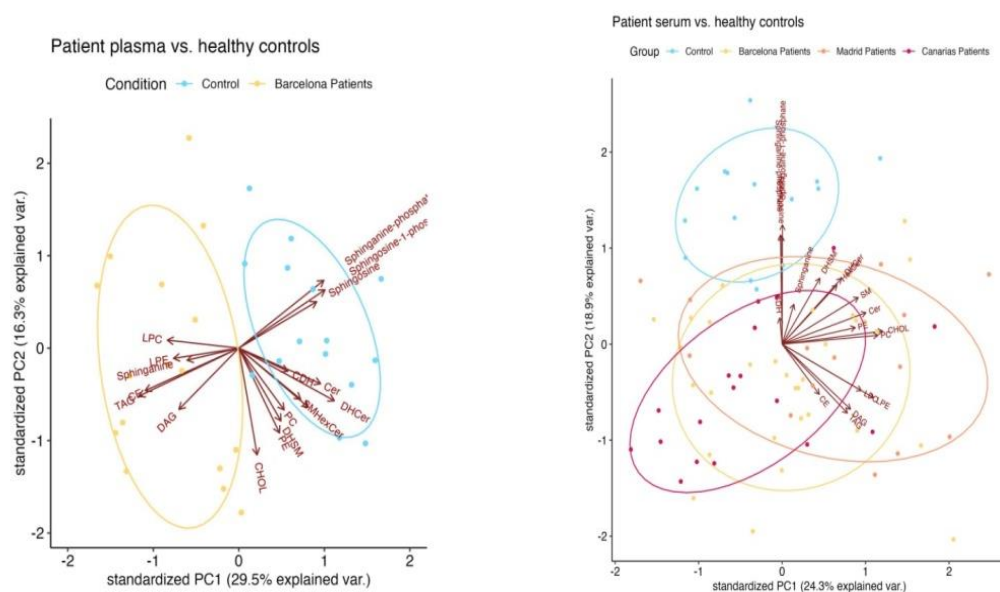
3.1. Overall lipidomic profile

Global lipidomic profiling of serum and plasma samples revealed significant differences in lipid composition between IMD-patients and healthy controls. Notably, no major differences were observed when comparing both samples types, obtaining similar differences in both, and therefore all analysis have been continued on serum samples only (*Figure 2*).

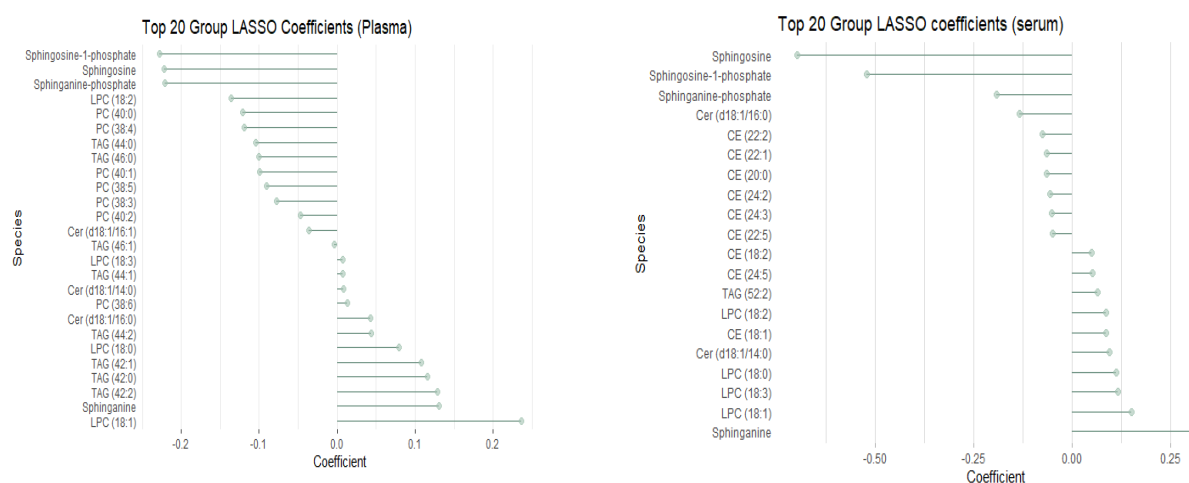
Comparison between IMD-patients and controls revealed that the former showed elevated serum levels of cholesteryl esters (CE), glycerophospholipids, and glycerolipids, including

lysophosphatidylcholines (LPC), lysophosphatidylethanolamines (LPE), diacylglycerols (DAG) and triacylglycerols (TAG). In contrast, there were reduced concentrations of sphinganine-phosphate, sphingosine, and sphingosine-1-phosphate (S1P) when compared to healthy controls.

1a) Principal component analysis (PCA) of plasma and serum lipid species illustrating the separation between patients with IMDs and healthy controls, based on global lipidomic profiles.



1b) LASSO coefficients showing the most relevant lipid species in plasma and serum contributing to discrimination between patients and controls.



1c) Differences in serum lipid species between patients and controls, mapped across metabolic pathways.

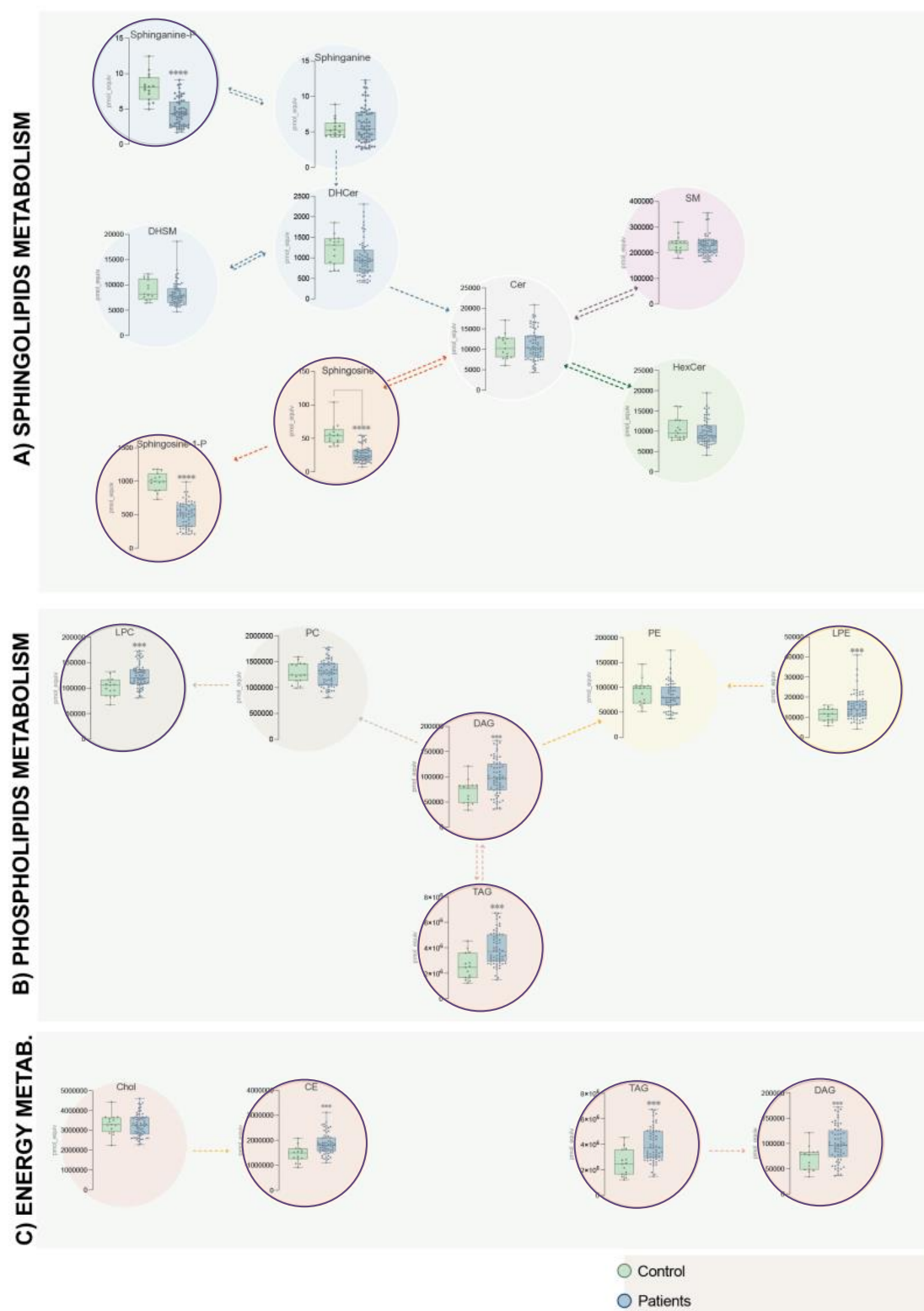


Figure 2. Distinct lipidomic profiles in serum and plasma samples from patients and controls. **(a)** Principal component analysis (PCA) showing the global lipidomic profiles and group separation. **(b)** LASSO coefficients identifying the lipid species contributing most to the discrimination between patients and controls. **(c)** Differences in serum lipid species between patients and controls, mapped across metabolic pathways; statistically significant species are marked with an asterisk (*) and highlighted.

For a more precise characterization, we subdivided the different diseases into 1) amino acids, 2) carbohydrate, 3) fatty acids and ketone bodies and 4) vitamins or cofactors metabolism.

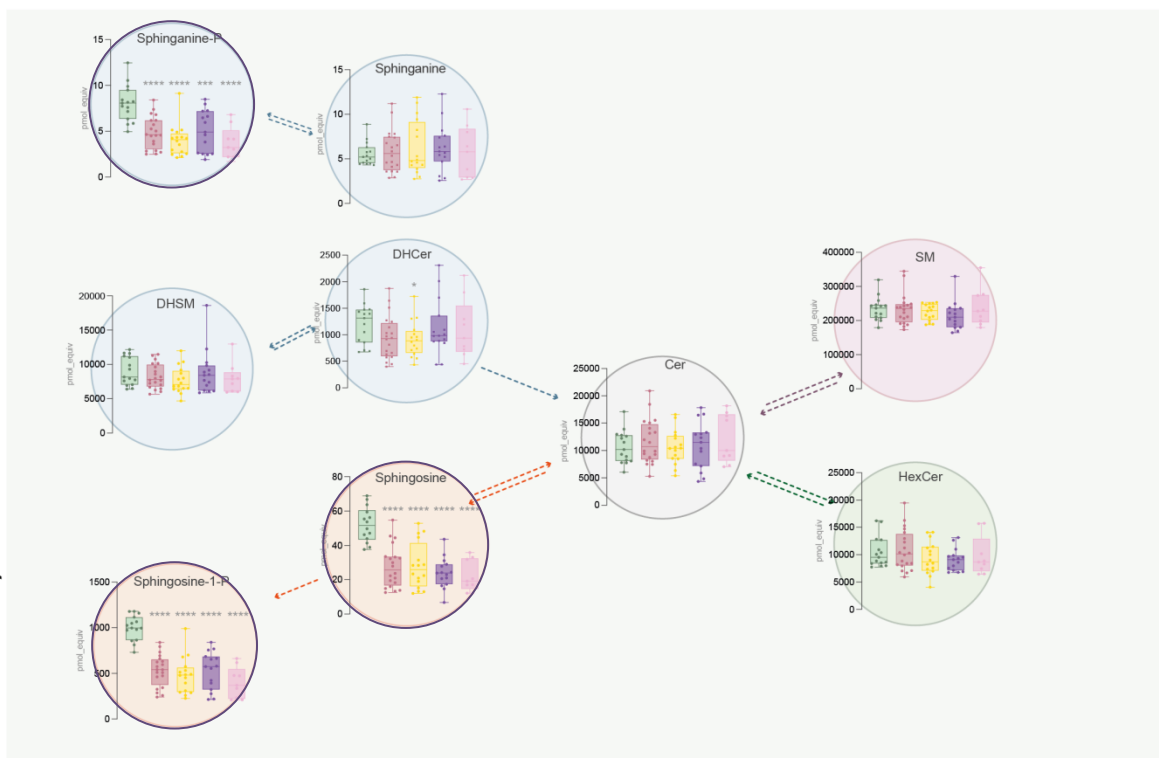
The analysis of lipids classes, comparing specific groups of diseases to age and sex-matched controls revealed, in general terms, a common profile across IMDs. Despite some differences observed among individuals within each specific category, all IMDs presented a similar profile of reduced sphingolipids (specifically sphingosine, S1P and sphinganine-P) and increased glycerolipids (TAG and DAG) and glycerophospholipids, specially their lyso-form (LPC and LPE) (*Figure 3*).

3.2. Influence of the diet on the lipidome

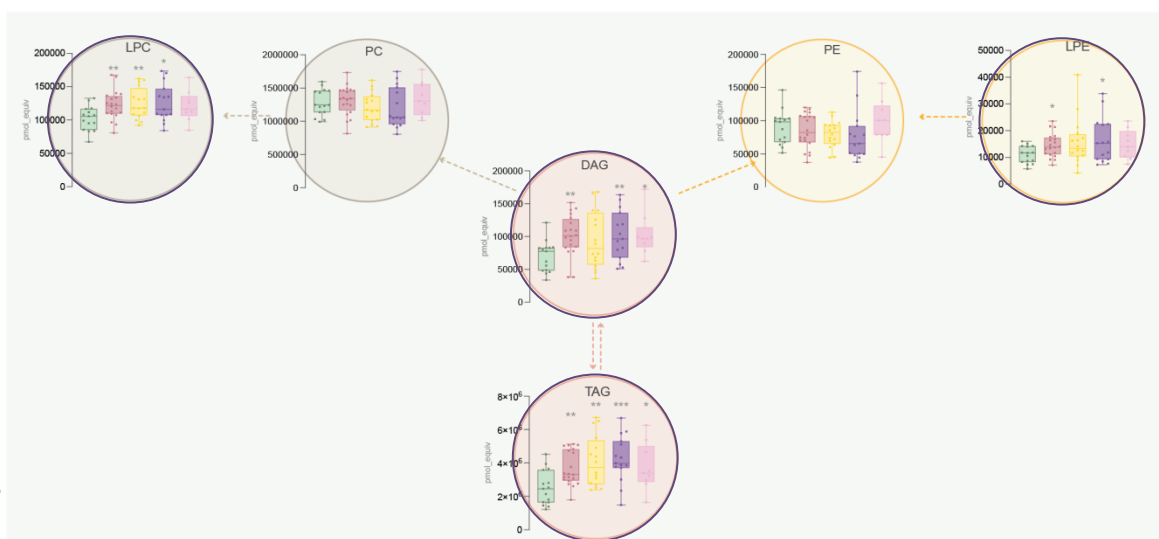
Lipidomic profiles can be profoundly affected by different dietary scenarios, specially in peripheral tissues as plasma or serum. As further discussed, dietary management is one of the most frequent therapeutic tools in the management of inborn errors of metabolism. Yet, according to the presented data, the different types of diets did not appear to significantly influence the IMD lipidome, as they did not alter the differences observed between patients and controls (*Figure 4*). For example, if we consider the concentration of sphingolipids in patients receiving two types of “opposite diets” (such as ketogenic diet opposed to low fat or low protein diets), we observe that all patients show reduced concentrations compared to the controls.

While the proper analysis to diminish the dietary effect should include a set of patients without dietary restrictions and differences, this is not clinically feasible. Our analysis does not rule out this effect, but sets its impact as a limited condition.

A) SPHINGOLIPIDS METABOLISM



B) PHOSPHOLIPIDS METABOLISM



C) ENERGY METAB.

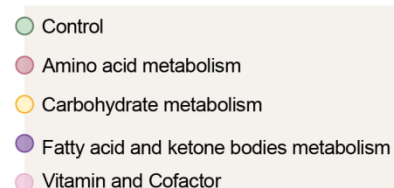
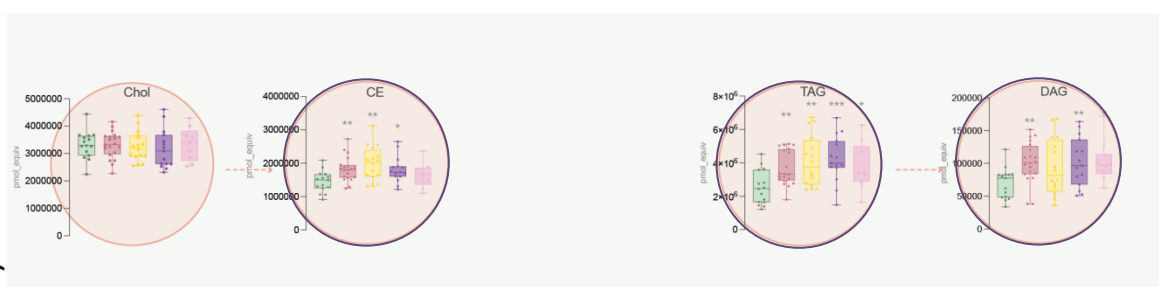


Figure 3. Distinct lipidomic profiles in serum between individuals from specific IMDs categories and healthy controls, mapped across metabolic pathways. Statistically significant species are marked with an asterisk (*) and highlighted.

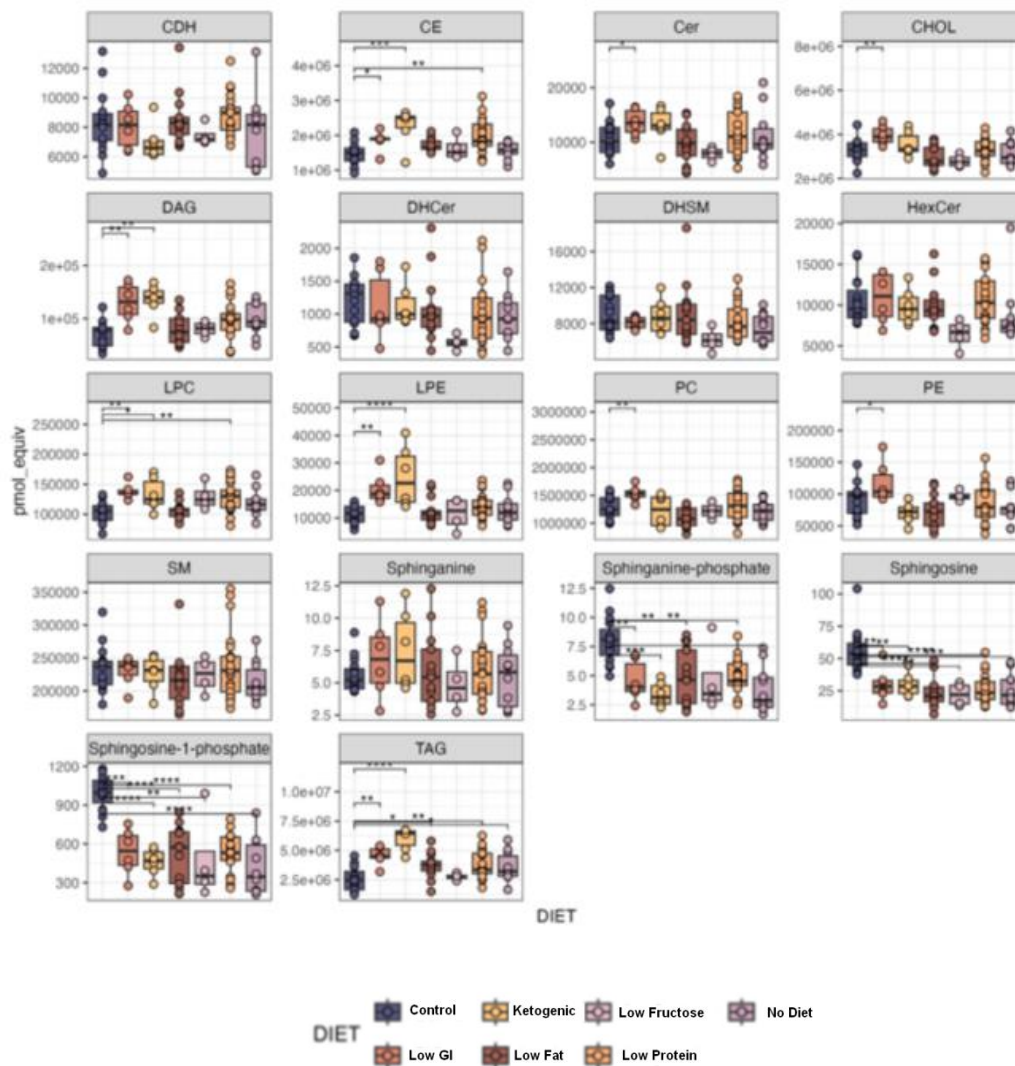


Figure 4. Analysis of serum lipid species across specific dietary types (low glycemic index, ketogenic diet, low fat, low fructose, low protein), patients with no specific diets and healthy control.

3.3. Associations between lipidome and neurocognitive domains

In our cohort of patients with IMDs, several lipid species were significantly associated with neuropsychological impairments (Table 3). While serum samples showed mild to moderate correlations with cognitive functioning, plasma samples exhibited higher correlations.

Table 3. Summary of the significant correlations between serum and plasma lipid subclasses and specific cognitive domains.

Cognitive Domain	Lipid Class	Subclass	Sample	Cohort	Correlation (r)	P-values
Global Intelligence	Glycerolipids	TAG	Plasma	Entire cohort	-0.77	0.027
Attention	Glycerolipids	TAG	Serum	Entire cohort	-0.32	0.038
			Plasma	Entire cohort	-0.83	0.015
Processing Speed	Glycerolipids	TAG	Plasma	Entire cohort	-0.74	0.046
Inhibition	Glycerophospholipids	LPE	Serum	Entire cohort	-0.35	0.022
Cognitive Flexibility	Glycerolipids	TAG	Plasma	Entire cohort	-0.71	0.050
Language	Sphingolipids	Sphingosine	Serum	Energy-related IMD	-0.51	0.007
		S1P		Energy-related IMD	-0.57	0.002
		Sphinganine-phosphate		Energy-related IMD	-0.45	0.021
Visuospatial Skills	Glycerophospholipids	LPE	Serum	Entire cohort	-0.35	0.025
	Glycerolipids	DAG	Serum	Entire cohort	-0.39	0.011
Social Cognition	Glycerophospholipids	LPC	Serum	Entire cohort	-0.36	0.018
	Glycerophospholipids	LPE	Serum	Entire cohort	-0.54	<0.001
				Intoxication IMD	-0.47	0.006
	Glycerolipids	DAG	Serum	Entire cohort	-0.50	<0.001
				Intoxication IMD	-0.52	0.002
	Glycerolipids	TAG	Serum	Entire cohort	-0.51	<0.001
				Intoxication IMD	-0.55	<0.001
	Sphingolipids	Sphingosine	Serum	Entire cohort	-0.40	0.007
				Energy-related IMD	-0.53	0.005
				Entire cohort	-0.40	0.008
				Energy-related IMD	-0.39	0.050
Fine Motor Dexterity	Glycerophospholipids	LPE	Serum	Entire cohort	-0.35	0.024
				Intoxication IMD	-0.44	0.013
Adaptive Behavior	Glycerophospholipids	LPC	Serum	Entire cohort	-0.33	0.034
	Glycerophospholipids	LPE	Serum	Entire cohort	-0.35	0.024
	Glycerolipids	TAG	Serum	Entire cohort	-0.40	0.009
				Intoxication IMD	-0.43	0.015
			Plasma	Entire cohort	-0.76	0.037

Overall, higher concentrations of triacylglycerols (TAG) and diacylglycerols (DAG) in serum and plasma were consistently associated with poorer cognitive outcomes across multiple domains, including IQ, attention, executive functions such as processing speed and cognitive flexibility, visuospatial abilities, social cognition, and adaptive behaviour.

Among glycerophospholipids, elevated levels of lyso-phosphatidylcholine (LPC) and lyso-phosphatidylethanolamine (LPE) in serum were associated with poorer fine motor dexterity, social cognition, inhibition, visuospatial skills and adaptive behaviour.

While correlations between cognitive domains and glycerolipids and glycerophospholipids were observed in the entire cohort, they were particularly pronounced in patients with intoxication IMDs.

Interestingly, the lower levels of sphingolipids found in the cohort of IMD were not associated with poorer neuropsychological outcomes. In our cohort, higher levels of sphingosine, sphingosine-1-

phosphate (S1P), and sphinganine-phosphate in serum were linked to social cognition deficits. Although these correlations were observed across the entire cohort, they were more pronounced among individuals with energy-related IMDs.

Notably, a distinct pattern emerged when examining the association between sphingolipid levels and language performance. In the energy-related IMD group, higher concentrations of S1P, sphingosine, and sphinganine-phosphate were significantly correlated with poorer language skills. Conversely, although not statistically significant, an opposite trend was noted in intoxication IMDs, where patients with lower concentrations of these sphingolipids tended to perform worse on language tasks (Figure 5).

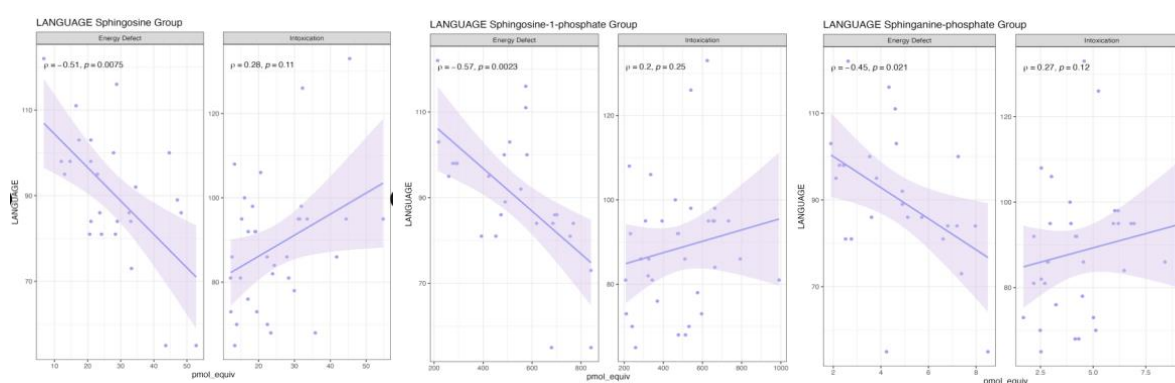


Figure 5. Serum sphingolipids concentrations associated to language performance in intoxication and energy-related IMD.

4. Discussion

This multicentre study integrates the neuropsychological outcomes in children with intoxication and energy-related IMDs and untargeted lipidomics, to explore potential biomarkers. Our findings revealed a distinct lipidomic pattern between individuals with IMDs and age- and sex-matched healthy controls, regardless of the specific disease or distinct dietary treatment. Such lack of disease-association in the lipidome strengthens the one with the neuropsychological outcomes, also seen in previous Chapters, suggesting that lipid metabolism dysregulation may play a role in the neurobiological basis of cognitive and behavioural impairments in individuals with IMDs.

4.1. Glycerophospholipids and glycerolipids biomarkers

The elevated levels of glycerolipids (DAG and TAG) and glycerophospholipids (specially LPE and LPC) identified in our cohort are consistent with previous studies that report shared disturbances in lipid metabolism among patients with IMDs, despite their distinct enzymatic defects (Van der Weerd et al., 2024; Zandi-Lang et al., 2023; Tucci, 2022).

On one hand, glycerophospholipids constitute 50–60% of cellular membranes and are essential for maintaining the stability, fluidity, and signalling capabilities of the membrane bilayer. Both LPC and LPE are crucial bioactive lipids derived from cell membrane phospholipids, acting as signalling molecules. Specifically, LPC is a potent pro-inflammatory lipid that promotes oxidative stress, while LPE has been associated with altered synaptic transmission and impaired axonal maintenance (Bernal-Vega et al., 2023). On top of that, both lipid classes hold crucial as membrane components, suggesting a potential alteration in lipid membrane dynamics, which will compromise neurotransmitter vesicle trafficking or synaptic plasticity (Lamari et al., 2025; Modesti et al., 2025; Rossi et al., 2024; Mei et al., 2023; Tucci, 2022; Ismail et al., 2019). Similar increases in LPC concentration have been previously described in other neurodevelopmental conditions such as ASD and ADHD (Esvap & Ulgen, 2023; El-Ansary et al., 2020).

On the other hand, we have described an elevation in the concentration of DAG and TAG in our IMD cohort. It has to be considered that DAG metabolism is intertwined with the metabolism of all the aforementioned routes: it participates on ceramides and phospholipids metabolism, reinforcing the previous message, and along with TAG and CE participates in energy metabolism directly. The alteration in all DAG, TAG and CE likely reflects impaired mitochondrial fatty acids β -oxidation, directly affecting energy homeostasis (Van der Weerd et al., 2024; Zandi-Lang et al., 2023).

Besides specific alterations in IMDs, a major finding of this research is the consistent link between specific lipidome patterns and neuropsychological outcomes. Specifically, higher levels of TAG and DAG were associated with poorer performance in various domains, including general intelligence, attention, executive functions, and social cognition. Similarly, increased concentrations of LPE were linked to deficits in visuospatial skills, inhibition, social cognition, and motor functions. On its side, elevated levels of LPC were correlated with poorer social cognition. Importantly, this specific

lipidomic profile was related to a decreased reported adaptive behaviour. While the pattern was consistent across the cohort, the correlations were especially pronounced in the subgroup of patients with intoxication IMDs. These parallelisms suggest that similar lipid-driven mechanisms may underlie cognitive and behavioural impairments across genetically distinct neurodevelopmental disorders, including IMDs (Modesti et al., 2025).

It needs to be brought into consideration that specific metabolic alterations can directly impact lipidic homeostasis. Likewise, alteration in other metabolic routes could affect lipids balance, underlying in the described profiles. To minimize this effect, we have classified all the included diseases into categories from the ICIMD, therefore buffering the effect of specific pathways disruption and focusing on more metabolic alterations.

Dietary restrictions can significantly influence lipidomic profiles. Such was the case of the study by Van der Weerd et al., 2024, in which they describe that individuals with phenylketonuria (PKU) show significant increases in serum LPE, LPC, and phosphatidylinositol (PI), independent of phenylalanine levels. Interestingly, they found that elevated TAG levels were associated with higher carbohydrate intake, and therefore concluded that chronic dietary restriction and changes in fatty acid availability could alter the balance of phospholipids and the composition of cell membranes in these patients (Van der Weerd et al., 2024). Opposite to these findings, in our cohort, general dietary treatments did not appear to affect the lipidome, suggesting that lipid alterations are relatively stable, particularly under well-controlled therapeutic regimens (Rossi et al., 2024). However, the specific effects of dietary composition and supplementation on the lipidome could not be examined in detail. Further research is therefore required to elucidate the mechanisms underlying these observations.

4.2. Sphingolipids biomarkers

Sphingolipids constitute approximately one-third of the total brain lipids and are essential for maintaining myelin integrity, facilitating synaptic transmission, and promoting communication between neurons and glial cells (Esvap & Ulgen, 2023; Blot et al., 2021). Imbalances between ceramides and S1P can lead to neuroinflammation, apoptosis, and impaired synaptic signaling (Li et al., 2024; Mei et al., 2023; Tucci, 2022). The patterns identified in our study highlight the vulnerability of sphingolipid

metabolism in IMDs, showing remarkably lower levels of serum sphingosine and its metabolite sphingosine-1-phosphate (S1P), along with decreased concentration of sphinganine-phosphate (Figure 6).

As previously reported for glycerophospholipids, specific sphingolipid classes and alterations correlated with specific neuropsychological domains. Interestingly, while patients presented overall decreased levels of sphingosine (and related metabolites), higher concentrations were associated to deficits in social cognition, a correlation that was especially pronounced among individuals with energy-related IMDs. Likewise, language impairment was found in energy-related IMDs with higher concentrations of S1P, sphingosine, and sphinganine-phosphate; but in intoxication IMDs with lower concentrations of these sphingolipids. This opposing pattern may reflect differences in compensatory or maladaptive responses involving sphingolipid metabolism, particularly in relation to energy metabolism or increased carbohydrate intake in individuals with intoxication IMDs. Nevertheless, further research is required to clarify how sphingolipid dysfunction may influence language-related neural networks.

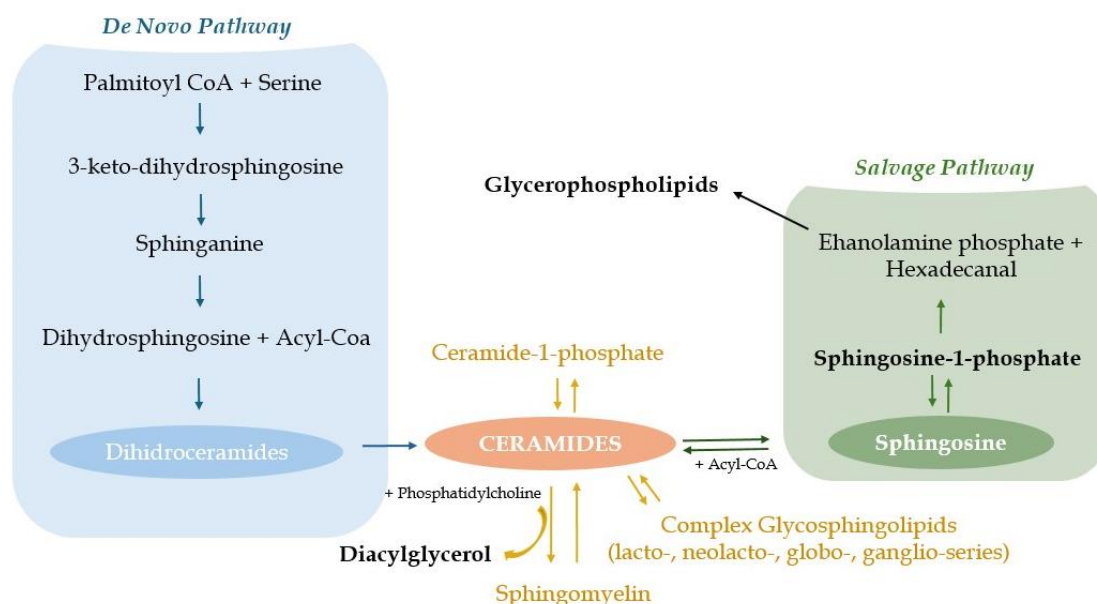


Figure 6. Overview of sphingolipid metabolic pathways and their interconnection with glycerolipid and glycerophospholipid metabolism. The most relevant lipid species identified in this study are highlighted in bold. The *de novo* pathway (blue block) leads to the formation of dihydroceramides from palmitoyl-CoA and serine, which are subsequently converted into ceramides (orange). The salvage pathway (green block) mediates the breakdown of ceramides into sphingosine and sphingosine-1-phosphate, thereby linking sphingolipid metabolism to glycerophospholipid pathways. Glycerolipids act as metabolic intermediates connecting multiple processes across these pathways.

Our findings are consistent with previous studies that associate higher sphingolipid levels with neurocognitive deficits in other neurodevelopmental disorders. Several studies have highlighted sphingolipid metabolism as a central component of ASD. Although approximately 5% of ASD cases are linked to IMDs, the consistent abnormalities in mitochondrial function, oxidative stress, and lipid metabolism suggest a broader biochemical convergence in the pathophysiology of ASD (Glinton & Elsea, 2019). Increased levels of S1P in ASD-specific brain models align with empirical findings of elevated S1P in both serum and cerebrospinal fluid (Yan et al., 2025; Li et al., 2024; Esvap & Ulgen, 2023; Wu et al., 2017). Lipidomic analyses have further revealed that altered levels of sphingomyelin, deoxycarnitine, and related metabolites are positively associated with ASD risk, suggesting that disruptions in sphingomyelin metabolism may affect neuronal membrane composition and lipid signalling, which are associated with neuroinflammation (Yan et al., 2025; Li et al., 2024). Furthermore, other studies have shown that perturbations in sphingolipids and cholesterol alter excitatory/inhibitory neurotransmission and glutamate receptor trafficking, providing a mechanistic link between lipid metabolism and neuronal excitotoxicity (El-Ansary et al., 2020).

In individuals with ADHD, reductions in serum sphingomyelins and ceramide have been identified as potential peripheral biomarkers (Henríquez-Henríquez et al., 2015). These deficiencies suggest decreased dihydroceramide desaturase activity or altered ceramide conversion, which may compromise neuronal membrane integrity and myelin-associated signalling. Moreover, elevated plasma levels of S1P and sphinganine-1-phosphate in individuals with ADHD, along with increased levels of endocannabinoids, indicate a compensatory activation of sphingolipid and endocannabinoid pathways that are associated with dopaminergic and glutamatergic transmission (Brunkhorst-Kanaan et al., 2021). These studies align with Modesti et al. (2025), who proposed that lipid-related pathways constitute core mechanisms in psychiatric and neurodevelopmental disorders. Abnormal signalling of ceramide and S1P can disrupt dopaminergic tone, alter glutamate balance, and affect GABAergic inhibition, all of which are neurotransmitter systems central to ADHD symptoms (Bernal-Vega et al., 2023).

Collectively, these findings suggest that disrupted sphingolipid metabolism may be related with alterations in neurotransmitter signalling and membrane excitability, potentially serving as a common biochemical pathway for the neuropsychological deficits observed in some

neurodevelopmental disorders, including IMDs. A possible biochemical continuum across various neuropsychiatric conditions has already been proposed ([Bernal-Vega et al., 2023](#); [Blot et al., 2021](#); [Brunkhorst-Kanaan et al., 2021](#)).

4.3. Limitations and future directions

This study explores promising opportunities for discovering neurocognitive biomarkers and advancing precision medicine in IMDs. Despite the promising findings, several limitations should be acknowledged.

While untargeted approaches are comprehensive, they require standardization across analytical platforms to ensure reproducibility and comparability across different cohorts ([Glinton & Elsea, 2019](#)). Therefore, the current use of untargeted lipidomics is limited and most studies focus on isolated disorders or small samples ([Wurth et al., 2024](#)). Although the sample size in our study is relatively large for a cohort of rare diseases, it limits statistical power and the ability to generalize the results to all metabolic disorders. Future studies should use targeted validation in independent cohorts to confirm the diagnostic and prognostic value of the identified biomarkers.

Additionally, it remains unclear whether peripheral lipid profiles accurately reflect lipid metabolism in the central nervous system, despite previous studies reporting significant correlations between serum and cerebrospinal fluid for sphingolipids ([Mussap et al., 2018](#); [Henríquez-Henríquez et al., 2015](#)). It is also important to consider that the influence of medications, subclinical metabolic fluctuations, and dietary adherence could not be fully excluded. Future research that integrates CSF analysis, neuroimaging, and data on the gut-brain axis could provide insights into the relationship between systemic lipid changes and brain function.

Identifying common lipid alterations across different IMDs provides valuable insights into the shared mechanisms behind neurodevelopmental disruptions. As our understanding advances, we are moving toward recognizing these disorders as part of a dynamic spectrum that may exhibit overlapping symptoms. Finding reliable biomarkers of neuropsychological functioning could provide clinicians and researchers with tools to identify risk factors for neurocognitive impairment and to

develop targeted neuroprotective lipid therapies. Additionally, this approach allows monitoring disease progression and evaluating treatment effectiveness, even in patients treated early.

This study emphasises the importance of systematic neuropsychological assessment, as recognising deficits, even in mild or asymptomatic cases, can help clinicians provide more comprehensive and personalised care, thereby significantly improving patients' quality of life.

In this regard, addressing IMDs through an integrative framework that combines biomarker identification with detailed neuropsychological characterization is particularly promising for advancing both research and clinical practice. This approach enables a better understanding of phenotypic heterogeneity and developmental trajectories associated with these disorders, as well as the establishment of more precise relationships between metabolic alterations, brain function, and cognitive-behavioral profiles. Moreover, it supports the development of earlier, personalized, and more effective intervention strategies that align with the complexity of neurodevelopment and the specific alterations each metabolic disorder induces in the developing brain.

4.4. Conclusions

This multicenter study identified potential lipidomic biomarkers shared across children and adolescents with different IMDs, using an untargeted approach. We identified a consistent lipid profile characterized by elevated levels of glycerolipids and glycerophospholipids, along with reduced sphingolipid concentrations. These alterations were associated with specific neuropsychological domains and adaptive functioning, particularly social cognition and executive functions.

These findings suggest that lipid dysregulation may be a common mechanism contributing to cognitive and behavioural impairments in IMDs, potentially sharing neurobiological pathways within a spectrum of neurodevelopmental disorders. Overall, the results emphasize the potential of lipidomics as a valuable tool for deepening our understanding of the biological basis of neuropsychological outcomes in IMDs. Further longitudinal studies are needed to clarify the underlying mechanisms.

Key Findings

- Children with IMDs showed a shared lipidomic signature distinct from controls, independent of disease subtype or dietary treatment.
- IMDs were characterized by increased glycerolipids (DAG, TAG) and glycerophospholipids (LPC, LPE) alongside reduced sphingolipids.
- Higher TAG and DAG levels were associated with poorer global cognition, attention, executive functions, and social cognition.
- Elevated LPE and LPC concentrations correlated with deficits in visuospatial abilities, inhibition, motor skills, and social cognition.
- Elevated sphingolipid concentrations were associated with language and social cognition impairments, particularly across energy-related IMDs.

Chapter VI

Methylphenidate use in Inherited Metabolic Disorders:

An observational cohort study

1. Introduction

Inherited Metabolic Disorders (IMDs) are complex, multisystem conditions that require collaboration among specialities to provide a comprehensive care (Morava et al., 2015). Due to a significant heterogeneity among metabolic disorders, there is an emergent shift towards a precision medicine approach that aims to provide targeted personalized treatments tailored to each patient's specific disorder and individual needs.

Currently, treatments available for IMDs include a range of options for effectively managing each condition. These treatments include nutritional therapy, which may involve significant dietary changes and targeted supplementation; enzyme replacement therapy that replenishes missing or deficient enzymes to support metabolic processes; organ transplants to replace malfunctioning organs and restore normal metabolic function; and novel gene therapies, that hold the potential to address the root causes of these disorders by correcting genetic anomalies at the molecular level. While these interventions can often be burdensome for patients and families, they are powerful tools for improving clinical outcomes (Kiess et al., 2020; Breilyn & Wasserstein, 2020).

Longitudinal studies consistently demonstrate that individuals treated early exhibit significantly better cognitive outcomes than those diagnosed later, as a result of preventing metabolic crises and chronic brain damage (Mutze et al., 2020; Kiess et al., 2020; Castiñeras et al., 2019). Although clinical improvement is evident in most patients after treatment, studies describing the long-term neuropsychological outcomes of therapies are scarce, and more research is required (Gil-González et al., 2025).

As discussed in previous Chapters, individuals with IMDs have an increased risk of neurocognitive impairment, which can persist even with early detection and treatment (Pardo et al., 2024). While they may not fully meet the criteria for established neurodevelopmental disorders (NDDs) like autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD), they could exhibit overlapping features. A dimensional range of symptoms highlights the necessity for

comprehensive neuropsychological assessments and personalized therapies (Michelini et al., 2024; Homaei et al., 2022).

Despite the frequent impairments in attention and executive functions observed in IMDs, studies exploring targeted pharmacological treatments for these symptoms are limited. Psychostimulant medications, such as methylphenidate (MPH), have been shown to effectively improve attention, executive control, and behavioural regulation in various NDDs and are currently considered the gold standard medication for treating ADHD.

Over the past few decades, neuroimaging and electrophysiological studies have revealed how MPH modulates large-scale brain networks involved in attention, motivation, and motor control, primarily in the ADHD population. Acute and chronic administration of MPH have been shown to normalise brain connectivity by reducing excessive activity within the default mode network, and improving both functional segregation (specialisation of brain regions) and functional integration of distributed networks (Silberstein et al., 2016; Silk et al., 2016). Mechanistically, these effects could arise from dopaminergic and noradrenergic modulation of frontostriatal circuits, which enhances communication related to cognitive tasks while suppressing irrelevant neural activity, minimising distractibility (Gorka et al., 2020; Yoo et al., 2017; Rubia et al., 2009).

Within limbic and reward circuits, MPH may normalise hyperconnectivity between mesolimbic regions (including the nucleus accumbens, amygdala, and ventral tegmental area) and cortical areas involved in emotion and decision-making (Pape et al., 2021). Therefore, MPH not only regulates cognitive control but also stabilises affective processing networks, often dysregulated in NDDs. Similarly, MPH may enhance connectivity in the premotor and cerebellar regions of patients with brain injuries, improving as well cortico-striatal network efficiency related to motor timing and action selection (Dorer et al., 2018).

While most functional changes induced by MPH occur without immediate brain structural alterations, longitudinal studies indicate that stimulant treatment may influence the trajectory of brain maturation. MPH may promote the normalisation of delayed network maturation in ADHD, aligning functional connectivity with typical developmental trajectories and contributing to cognitive and behavioural improvements (Zimmer, 2017; Bos et al., 2017). Furthermore, chronic MPH

administration may enhance trophic and metabolic support for frontostriatal pathways, thereby indirectly contributing to volumetric normalisation (Pereira-Sánchez et al., 2020).

However, the effects of MPH have been poorly studied in individuals with IMDs. IMDs often involve shared neurochemical mechanisms that disrupt the synthesis, transport, metabolism, or receptor functions of monoamine neurotransmitters. Consequently, ADHD medications could also ameliorate these symptoms in IMDs (Homaei et al., 2022; Barone et al., 2019). In clinical settings, the relatively common use of MPH in IMDs points towards some improvements in attention and executive functions (Barroso et al., 2020; Couce et al., 2015).

This study aims to investigate whether pharmacological treatment with MPH can effectively modulate brain function and enhance attention and executive functions in individuals with intoxication and energy-related IMDs, similar to the improvements observed in other NDDs. We employ a naturalistic observational design, selected from a larger cohort (Chapter III), to analyse these potential benefits, using personalised doses of MPH tailored to each individual's needs, on neuropsychological performance and brain volumetry. By further exploring these effects, our study aims to provide deeper insights into personalised therapies that promote neuropsychological outcomes in patients with IMDs.

2. Methods

2.1. Participants

We conducted an observational study of MPH use in a cohort of patients from Chapter III. *Table 1* provides a detailed description of the sociodemographic and clinical features of the sample before and after MPH treatment.

The study included participants aged 6 to 17 who had a confirmed diagnosis of intoxication or energy-related IMD, established through genetic and biochemical testing. All participants demonstrated good adherence to metabolic treatments and had controlled decompensations (≤ 1 per year). This study only included patients meeting the diagnostic criteria for ADHD according to the DSM-5-TR, who were clinically eligible for treatment with MPH. The clinical decision was based on the

severity of symptoms, functional interference in different settings, and previous non-pharmacological interventions.

Patients were recruited from several reference hospitals in Spain: 7 from Hospital Sant Joan de Déu in Barcelona, 6 from Hospital 12 de Octubre in Madrid, and 5 from Hospital Materno-Infantil in Las Palmas de Gran Canaria. After treatment began, two patients withdrew due to gastrointestinal issues, and five patients voluntarily dropped out of the study. The final sample included 11 participants: 7 intoxication IMD and 4 energy-related IMD.

2.2. Neuropsychological assessment

The neuropsychological assessment was tailored to each individual's age and included standardised measures of attention, executive functions, behavioural and emotional regulation, as well as adaptive behaviour (*Table 2*). The pre-treatment assessment, available in Chapter III, was compared to the assessment conducted after at least 9 months of uninterrupted MPH treatment.

Psychometric tests were scored using Standard Scores (SS), with a mean of 100 and a standard deviation of 15. Scores below 80 were classified as impaired, except for SENA and BRIEF, which used an inverse standard score system, with scores above 120 considered impaired.

Table 1. Sociodemographic and clinical characteristics of the cohort before and after MPH use.

Patient	Age Pre-MPH	Age Post-MPH	Gender	Hospital	IMD type	IMD Category	IMD	Gene #OMIM	Onset	Diet	MPH dose (mg)	MPH time (m)
1	7y 2m	8y 10m	M	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	10	9m
2	8y 6m	10y 7m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	36	22m
3	9y 9m	11y 10m	F	Madrid	Intoxication	Vitamin and cofactor	Pyridoxine-dependent epilepsy	ALDH7A1 #107323	Early onset	Low protein	10	16m
4	8y 9m	11y 5m	M	Barcelona	Energy-related	Fatty acid and ketone bodies	Medium-chain acyl-CoA dehydrogenase	ACADM #607008	Early onset	Low fat	20	22m
5	9y 4m	11y 6m	F	Madrid	Intoxication	Amino acid metabolism	Glutaryl-CoA dehydrogenase deficiency	GCDH #608801	Early onset	Low protein	20	21m
6	8y 8m	11y 6m	F	Barcelona	Intoxication	Amino acid metabolism	Ornithine transcarbamylase deficiency	OTC #300461	Late onset	Low protein	15	31m
7	16y 6m	18y 2m	M	Canarias	Intoxication	Trace elements and metals	Wilson disease	ATP7B #606882	Late onset	No	10	12m
8	10y 11m	13y 1m	M	Madrid	Energy-related	Carbohydrate metabolism	Glycogen storage disease type 9	PHKA2 #300798	Late onset	Low Glycemic Index	15	19m
9	6y 3m	8y 6m	M	Madrid	Energy-related	Fatty acid and ketone bodies	Long-chain ketoacyl-CoA thiolase	HADHB #143450	Early onset	Low fat	15	11m
10	8y 6m	11y 7m	F	Barcelona	Energy-related	Carbohydrate metabolism	GLUT1 deficiency	SLC2A1 #138140	Late onset	Ketogenic	20	9m
11	9y 11m	11y 7m	F	Canarias	Intoxication	Amino acid metabolism	Tyrosinemia type 1	FAH #613871	Late onset	Low protein	36	12m

Table 2. Standardized neuropsychological assessment pre-post MPH.

Cognitive Function	Specific Domains	6 – 16:11 years	17-17:11 years
Attention	<i>-Focused attention / Vigilance</i>	-Digit Span Forward (DsF) WISC-V -K-CPT-2 (6-7y) or CPT-3 (≥8y) - Omissions O-CPT - Commissions C-CPT - Hit reaction time HRT-CPT - Consistency CONS HRT-CPT - Variability VAR HRT-CPT - Inter-stimulus interval HRT ISI CPT	Digit Span Forward (DsF) WAIS-IV -CPT-3 - Omissions O-CPT - Commissions C-CPT - Hit reaction time HRT-CPT - Consistency CONS HRT-CPT - Variability VAR HRT-CPT - Inter-stimulus interval HRT ISI-CPT
		- Block change HRT BLOCK-CPT	- Block change HRT BLOCK-CPT
Executive Functions	<i>-Sustained attention</i>		
	<i>-Inhibitory control / Impulsivity</i>	-K-CPT-2 or CPT-3 - Commissions C-CPT - Hit reaction time HRT-CPT - Perseverations PERS-CPT -Inhibition NEPSY-II	-CPT-3 - Commissions C-CPT - Hit reaction time HRT-CPT - Perseverations PERS-CPT -Stroop Test
	<i>- Working Memory</i>	-Digit Span Backwards (DsB) WISC-V	-Digit Span Backwards (DsB) WAIS-IV
	<i>-Cognitive flexibility</i>	-Inhibition NEPSY-II	-Stroop Test
	<i>-Phonemic Fluency</i>	-Phonemic Fluency NEPSY-II	-FAS test
	<i>-Planning</i>	-Plan-ROCF	-Plan-ROCF
	<i>-Processing Speed</i>	-Time-ROCF -Coding (C) WISC-V -Symbol Search (SS) WISC-V	-Time-ROCF -Coding (C) WAIS-IV -Symbol Search (SS) WAIS-IV
Behavior and Emotional Regulation	<i>-Internalizing symptoms</i>	-Emotional problems (E)-SENA -Emotional Regulation (ER) BRIEF -Personal Resources (PR) SENA	-Emotional problems (E)-SENA -Emotional Regulation (ER) BRIEF -Personal Resources (PR) SENA
	<i>-Externalizing symptoms</i>	-Behavioral problems (B) SENA -General problems (G)-SENA -Executive functions (EF)-SENA -Behavioral Regulation (BR)-BRIEF -Cognitive Regulation (CR)-BRIEF -General functioning (G)-BRIEF	-Behavioral problems (B) SENA -General problems (G)-SENA -Executive functions (EF)-SENA -Behavioral Regulation (BR)-BRIEF -Cognitive Regulation (CR)-BRIEF -General functioning (G)-BRIEF
Adaptive Behavior	<i>-Global adaptive behavior</i>	-GAB ABAS-II	-GAB ABAS-II
	<i>-Cognitive/Academic settings</i>	-C ABAS-II	-C ABAS-II
	<i>-Social settings</i>	-S ABAS-II	-S ABAS-II
	<i>-Practical settings</i>	-P ABAS-II	-P ABAS-II

2.3. Volumetric analysis

Magnetic resonance imaging (MRI) scans were performed in our cohort to assess volumetric brain changes after at least 9 months of methylphenidate treatment. These scans were compared to previous volumetric analyses. Detailed information about MRI acquisition, image processing, and brain tissue segmentation, are available in Chapter IV.

Non-standardized MRI protocols were used to process T1-weighted structural MRI data collected across multiple centres. To ensure consistency in the analysis, our volumetric analysis pipeline was designed to provide reliable measurements regardless of acquisition protocols or scanner-specific settings.

Volumes of cortical and subcortical brain structures were obtained for each patient and compared to an age-matched template created using the Advanced Normalization Tools (ANTs) template construction utility. This template was developed utilizing high-resolution MRI scans from healthy individuals aged 9 to 10 in the Adolescent Brain Cognitive Development Study (ABCD) database ([Casey et al., 2018](#)).

2.4. Methylphenidate treatment

The medication used for all patients was immediate-release methylphenidate hydrochloride (MPH), which non-competitively blocks the reuptake of dopamine and noradrenaline into the terminal by inhibiting their transporters (DAT and NAT). This action increases the levels of dopamine and noradrenaline in the synaptic cleft (*Figure 1*).

Patients started at 5 mg per day, with progressive increases in dose and frequency (5-10 mg per week) until the optimal personalised dose was reached. Due to the clinical significance of dietary treatments and frequent gastrointestinal issues in IMDs, it was crucial to avoid any side effects of MPH on dietary intake. Drug monitoring was conducted by the referring physician for each patient.

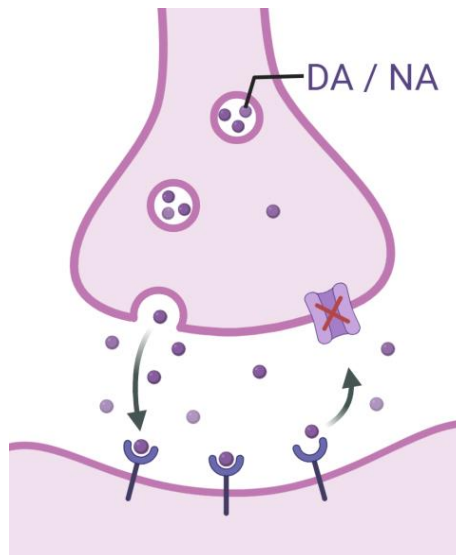


Figure 1. Methylphenidate action mechanism. MPH increases dopamine (DA) and noradrenaline (NA) levels by blocking their reuptake through the dopamine transporter (DAT) and noradrenaline transporter (NAT) in presynaptic neurons.

All patients were treated for a minimum duration of 9 months before undergoing repeated neuropsychological assessments and MRI scans. Treatment with positive outcomes continued after the post-treatment assessments were completed.

2.5. Statistical analysis

The study examined various descriptive variables, including age, gender, type of disease (intoxication or energy-related IMD) (Saudubray et al., 2019), and specific categories from the ICIMD (Ferreira et al., 2021). It also examined the age at disease onset, defining early-onset as 0-11 months and late-onset as over 1 year. Additional factors considered were the presence of special needs (such as speech therapy, school accommodations, psychological support, and physical therapy), school year (primary school, secondary school, or high school). Additionally, total treatment time and final dosis of methylphenidate was analysed. These variables were correlated with the neuropsychological performance before and after methylphenidate treatment.

Before performing statistical analyses, we conducted a normality test on the quantitative variables using the Shapiro-Wilk test. A significant p-value ($p < 0.05$) indicated that the studied variables did not follow a normal distribution. Consequently, we used non-parametric tests: Wilcoxon test or McNemar Chi-square test for binary data.

For the volumetric change analysis, comparisons between IMD patients and age-matched healthy model were conducted using independent t-test and covariance (ANCOVA) analysis, adjusting for TIV, age, sex, age at disease onset (early-onset 0-12 months and late-onset >12 months) and sub-group of IMD diseases. Post-hoc pairwise comparisons were conducted using Tukey's HSD test to identify which specific groups differed significantly after the overall ANCOVA effect. Additionally, associations between brain volumetric measures and neuropsychological results were evaluated using Pearson correlation. This approach enabled us to evaluate the associations between brain volume and cognitive outcomes before and after treatment with methylphenidate. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) correction according to the Benjamin–Hochberg method. Besides, Cohen's d was used to estimate the effect size for pairwise comparisons of normally distributed data. For non-normally distributed data, the rank-biserial correlation (r) was calculated.

All statistical tests were carried out with a confidence level of 95% and considered significant at $p < 0.05$, and IBM SPSS statistical software version 29.0 was used.

2.6. Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. The potential risks and benefits were explained to the participants and their families. Participation was voluntary, and participants could withdraw from the study at any time without any consequences to their medical care. The study was approved by the Research Ethics Committee of Hospital Sant Joan de Déu, and written informed consent was obtained from the parents or legal guardians of all participants, with assent collected from children over the age of 12.

3. Results

3.1. Neuropsychological changes post-methylphenidate

The mean age at the second neuropsychological assessment was 11 years and 8 months (SD=2.54). The patients had been receiving treatment with methylphenidate (MPH) for at least 9 months, with an average duration of 16.73 months (SD=6.93). The mean final dose was 18.82 mg (SD=9.34). Descriptive data comparing variables before and after MPH treatment are presented in *Table 3*.

Table 3. Descriptive variables of the cohort before and after MPH treatment.

	Mean / N	Deviation / %
Age at 1st Neuropsychological Study	9,47	2,66
Age at 2nd Neuropsychological Study	11,70	2,54
Final dose of MPH	18,82	9,34
Total time with MPH	16,73	6,93
ASD symptoms	3	27,3%
School accommodations		
PRE	7	63,6%
POST	10	90,9%
Speech therapy		
PRE	5	45,5%
POST	4	36,4%
School reinforcement		
PRE	5	45,5%
POST	5	45,5%
Psychological therapy		
PRE	2	18,2%
POST	3	27,3%

The comparative analysis of the neuropsychological assessments conducted before and after treatment found positive effects of methylphenidate (*Figure 2*). Significant improvements were noted in attention, specifically in the HRT ISI-CPT ($p=0.037$), indicating a positive change in participants' ability to maintain vigilance and focus their attention effectively.

In addition, there was an improvement in personal resources, as reflected in the PR-SENA scores ($p=0.045$), suggesting a better self-regulation and coping.

Furthermore, the analysis revealed nearly significant differences in adaptive behaviour, emphasizing functional transfer across cognitive and practical skills. Both the P-ABAS ($p=0.068$) and C-ABAS ($p=0.068$) showed a trend towards the potential benefits of methylphenidate in daily functioning.



Figure 2. Neuropsychological performance in attention, executive functions, behaviour and emotion regulation, and adaptive behaviour, before and after methylphenidate (MPH) treatment.

3.2. Brain volumetric changes post-methylphenidate

We conducted a volumetric analysis to compare brain volumes before and after MPH treatment, controlling for age-matched healthy controls and accounting for time.

We analysed the mean volumetric differences observed before and after MPH treatment within the patient and healthy cohorts to control for the impact of time. Both differences were correlated with the intercept coefficient, with a significance threshold set at $p < 0.05$ to indicate significant changes between the patients and controls after adjusting for age and time pre- and post-MPH.

The patients maintained the same differences compared to the healthy controls as reported in Chapter IV. After MPH treatment, the differences between patients and controls were more pronounced in increased frontal and temporal areas, and reduced basal ganglia, white matter, cerebellum, and limbic system (*Table 4*). Although the differences were statistically significant, they did not survive the false discovery rate (FDR) correction, indicating they failed to meet the significance criteria after multiple-comparison adjustment. Brain volume related to neuropsychological impairment follow the same pattern reported before MPH (Chapter IV), and no significant changes related to neurocognitive impairment were found before and after MPH treatment.

Table 4. Brain volume differences between patients and controls pre-post MPH.

Brain Area	Brain Region	Coef_Intercept	P_value
Frontal	Left_Superior_Frontal_Gyrus	0,004	0,017
	Right_Superior_Frontal_Gyrus	0,003	0,044
	Right_Triangular_Part_of_the_Inferior_Frontal_Gyrus	0,001	0,022
Temporal	Left_Temporal_Pole	0,002	0,010
Limbic	Limbic_System	-0,001	0,033
Cerebellum	Left_CrusII_2111	-0,002	0,037
	Right_CrusII_2111	-0,003	0,019
White matter	Brain_Stem	-0,003	0,010
	Corpus_callosum	-0,000	0,021
Basal Ganglia	Basal_Ganglia	-0,005	0,042

4. Discussion

This study provides longitudinal evidence of the use of methylphenidate (MPH) for specific ADHD symptoms in individuals with intoxication and energy-related IMDs. Consistent with our hypotheses, MPH treatment was associated with measurable improvements in attentional performance and adaptive functioning. In contrast, volumetric analysis did not reveal detectable changes in brain volume after treatment. Taken together, these findings highlight the potential of MPH as a targeted symptomatic intervention for executive and attentional difficulties in IMDs, despite the stable underlying neuroanatomical abnormalities.

4.1. Neuropsychological improvements after methylphenidate

Our cohort showed a significant improvement in hit reaction times during inter-stimulus intervals (HRT-ISI), indicating enhanced vigilance and focused attention, after at least 9 months of continuous MPH treatment. Attention was assessed using the Conners' Continuous Performance Test (CPT), a standardised measure that requires respondents to press the appropriate key for any letter except "X." This test has proven effective for clinically screening ADHD and evaluating responses to MPH, particularly the reaction time variability (Levy et al., 2018; Huang-Pollock et al., 2012). Such variability is linked to occasional slow reaction times, which reflect lapses in attention and difficulties in attention regulation. Evidence also suggests that amphetamines can enhance vigilance in healthy adults (MacQueen et al., 2018). Additionally, combining behavioural therapies (e.g., reinforcement) with lower doses of MPH can help normalise vigilance in children with ADHD (Bubnik et al., 2015).

In our cohort, the mean dose was 18 mg. Although patients with IMDs may require lower doses to minimise intake side effects, this population could also benefit from MPH to enhance vigilance, similar to findings in ADHD.

These findings are consistent with the established pharmacological effects of MPH on prefrontal and striatal circuits, which improve vigilance, cognitive control, and the suppression of irrelevant stimuli (Gorka et al., 2020; Yoo et al., 2017; Rubia et al., 2009). This research extends these effects to individuals with IMDs, supporting the clinical observation that attentional deficits in IMDs may share underlying neurochemical vulnerabilities with other neurodevelopmental disorders.

In addition to improvements in attention, MPH was associated with enhancements in personal resources, indicating better self-regulation and adaptive coping strategies. The observed trend towards improved adaptive behaviour suggests that MPH may have positive effects on everyday functioning, even in the absence of widespread neurocognitive changes. This aligns with prior research showing that improvements in executive function can lead to gradual functional gains, particularly in populations with complex medical conditions (Michelini et al., 2024). IMDs are particularly vulnerable due to the interplay of metabolic dysregulation, chronic medical and nutritional burdens, and ongoing neurodevelopmental risks. Thus, improving autonomy and daily functionality could significantly enhance the quality of life for both patients and their families.

Neurodevelopment in IMDs often occurs under conditions of compromised cellular energetics. Processes such as neurogenesis, neuronal migration, synaptic organisation, and glial maturation all require adequate energy production. When metabolic pathways are disrupted, early insults can lead to selective vulnerabilities in neuronal and glial populations (Gropman, 2020). Damage may be widespread but disproportionately affect regions that share metabolic and neurotransmitter systems, including frontoparietal and cerebellar circuits responsible for executive functioning and behavioural regulation. This developmental vulnerability may explain the persistent executive dysfunction observed in IMDs, even with optimal metabolic management.

Although evidence supporting stimulant treatment in IMDs is scarce, it is growing. In classical phenylketonuria (PKU), a well-characterised IMD, the use of stimulants reached 26% in one cohort, compared to 2–8% in the general ADHD population, with all treated individuals reporting clinical benefits without adverse effects on phenylalanine levels (Arnold et al., 2004). Subsequent analyses further confirmed the safety and potential effectiveness of stimulants in PKU (Ashe et al., 2019; Antshel & Waisbren, 2003). Our findings extend these observations to a broader range of IMDs,

indicating that MPH can be both effective and well-tolerated in complex metabolic conditions when used under clinical supervision.

However, metabolic insufficiency can also contribute to psychiatric symptoms that are not entirely addressed by stimulant treatment alone (Phakey et al., 2020). The complex nature of neuropsychiatric symptoms in IMDs underscores the need for multimodal pharmacological and psychological interventions.

4.2. Brain volumetric stability following methylphenidate

In contrast to the cognitive and behavioural improvements observed, our volumetric analyses did not reveal significant structural changes following MPH treatment. Some regions, such as the fronto-subcortical and cerebellar areas, exhibited changes; however, these differences did not remain significant after correcting for multiple comparisons and should be interpreted with caution. This may be due to the small sample size, highlighting the need for further research with larger longitudinal cohorts.

Our findings contrast with some ADHD studies that suggest that chronic stimulant exposure may normalise delayed neurodevelopmental trajectories (Bos et al., 2017; Zimmer, 2017). However, even within the ADHD research, evidence for structural changes is mixed. Zimmer (2017) reported that after 1 year of stimulant treatment, no significant differences in white matter microstructure were observed, indicating that MPH does not induce significant anatomical changes. Instead, it is possible that functional reorganisation, particularly within the frontostriatal, frontoparietal, and cerebellar circuits, may occur independently of any detectable structural remodelling (Bos et al., 2017).

The lack of structural changes may point to fundamental differences in the mechanisms underlying brain abnormalities in IMDs. While volumetric anomalies in ADHD are thought to reflect delayed developmental trajectories, the structural differences related to IMDs typically result from early metabolic insults, neuroinflammation, energy deficiency, and toxic metabolite accumulation.

These processes could lead to stable alterations in brain architecture that catecholaminergic agents do not easily modify.

Persistent alterations in the frontoparietal and subcortical areas, as well as the cerebellum, have been previously documented in this cohort (see Chapter IV) and may indicate early developmental disruptions rather than delayed maturation. These cortico-cerebellar networks are crucial for attention and executive functions. Although volumetric anomalies remain, MPH may enhance functional connectivity within this system. This is supported by ADHD research showing that MPH improves the efficiency and integration of frontoparietal circuits (Yoo et al., 2017; Wu et al., 2017), even in the absence of structural changes. In our cohort, stimulant benefits in IMDs are likely functional rather than structural, mediated by transient neuromodulatory effects rather than long-term anatomical remodelling. Moreover, the variability in IMDs' pathophysiology may lead to differences in brain vulnerability across individuals, thereby limiting the potential for uniform treatment-related structural changes. MPH may partially compensate for these deficits by increasing extracellular catecholamine levels, thereby enhancing network communication despite persistent structural vulnerabilities.

Research on ADHD consistently shows that 20–30% of patients are poor responders to MPH. Neuroimaging studies suggest that structural biomarkers may help predict treatment response. For example, Chang et al. (2021) found that smaller left putamen volumes and larger precuneus volumes at baseline were associated with poor responses to MPH. These brain regions are involved in cognitive control, reward processing, and self-referential networks, all of which are commonly affected in IMDs. More research involving larger and longitudinal samples is necessary to identify volumetric predictors of MPH benefit in the IMD population.

4.3. Clinical implications

This study underscores several clinically significant findings. The use of MPH appears safe and beneficial for individuals with attentional deficits associated with IMDs, advocating for its application as a targeted symptomatic treatment within a demographic that is often underrepresented in psychopharmacological research. Notably, these benefits persist even in the presence of structural brain abnormalities, indicating that functional modulation is both feasible and clinically meaningful

despite anatomical features. Continued treatment appears to contribute to improvements in adaptive behaviour, with cognitive enhancements potentially leading to better overall autonomy and daily functioning.

However, important considerations must be taken into account when treating the IMD population. In our original cohort, two patients withdrew from the study after the initiation of MPH treatment due to gastrointestinal side effects, although no clinically relevant adverse effects were observed in the remainder sample. Careful monitoring of methylphenidate use in individuals with IMDs is essential, as appetite suppression may increase the risk of metabolic decompensation, particularly in intoxication IMDs. Therefore, it is recommended to initiate treatment with subtherapeutic doses and titrate gradually, allowing careful monitoring of appetite and minimizing the risk of adverse effects.

These findings reinforce the importance of routine neuropsychological assessments in individuals with IMDs and support the integration of stimulant therapy within multimodal precision-medicine approaches.

4.4. *Limitations and Future directions*

Several limitations should be considered. First, the small sample size poses an inherent constraint due to the rarity of IMDs, limiting statistical power and generalizability. Although the findings are clinically significant, larger cohorts are needed to confirm these patterns.

Second, the sample consists of heterogeneous IMDs, each with distinct altered metabolic pathways. While this diversity reflects the reality of clinical settings, it may cover distinctive patterns of response related to specific disorders.

Third, the study's observational design lacks a placebo control and blinding, which may introduce expectancy effects into caregiver-reported measures. Therefore, randomized clinical trials are recommended.

Fourth, volumetric measures may not adequately capture functional neural changes associated with cognitive improvement. Future studies that incorporate resting-state or task-based functional MRI (fMRI) may be more sensitive in detecting these functional changes.

Further longitudinal studies of IMD using standardised neuropsychological measures are needed to describe better the effects of MPH on cognitive impairment and quality of life.

4.5. Conclusions

Methylphenidate treatment in children and adolescents with intoxication and energy-related IMDs resulted in significant improvements in attentional performance and personal self-regulatory resources, which enhanced adaptive behaviour. These benefits occurred in the absence of structural brain changes, suggesting that MPH exerts functional neuromodulatory effects that support cognitive performance despite persistent metabolic-related volumetric abnormalities. Our findings underscore the potential of personalised pharmacological interventions within precision-medicine frameworks for IMDs and highlight the importance of continued research into targeted treatments for neuropsychological impairments in this population.

Key Findings

- Methylphenidate significantly improved vigilance in individuals with intoxication and energy-related IMDs.
- Treatment was associated with better self-regulation and adaptive daily functioning.
- No significant brain volumetric changes were observed following methylphenidate treatment.
- Methylphenidate is a promising targeted symptomatic treatment for attentional deficits in IMDs when carefully monitored for intake-related side effects.

Chapter VII

Discussion and Conclusions:

*Towards An Integrated Transdiagnostic Model of
Neurocognitive Impairment in IMDs*

1. Discussion

This thesis provides a comprehensive characterization of neurocognitive performance, brain volumetry, and lipidomic profiles in patients with intoxication and energy-related *Inherited Metabolic Disorders (IMDs)*. By integrating these findings, we confirmed our hypothesis about a set of common neurodevelopmental vulnerabilities that extend beyond the biochemical and phenotypic diversity of IMDs, and align closely with patterns previously observed in specific metabolic and neurodevelopmental disorders. This research enhances our understanding of neuropsychological functioning and collectively supports a model suggesting that metabolic dysregulation, whether caused by energetic failure or toxic accumulation, affects neurodevelopment through shared underlying mechanisms.

1.1. Towards an Integrated Transdiagnostic Model

Collectively, our findings converge on a multidimensional transdiagnostic model of neurocognitive impairment, in which metabolic dysfunction initiates a cascade of neurodevelopmental disturbances that interact with altered neurochemistry, brain volumetry, to ultimately produce the spectrum of neuropsychological symptoms observed in IMDs. *Figure 1* illustrates the Integrative Transdiagnostic Model proposed in this thesis, which adds value to the existing frameworks of neurodevelopmental vulnerabilities (Michelini et al., 2024; Brown et al., 2017).

As described in previous Chapters, IMDs genetically disrupt specific metabolic pathways that lead to biochemical stress during critical periods of neurodevelopmental, including neurogenesis, synaptogenesis, myelination, and glial maturation. The altered energy homeostasis can profoundly affect lipid membrane dynamics, compromising neurotransmitter vesicle trafficking and synaptic plasticity (Lamari et al., 2025; Modesti et al., 2025; Rossi et al., 2024; Mei et al., 2023; Tucci, 2022; Ismail et al., 2019).

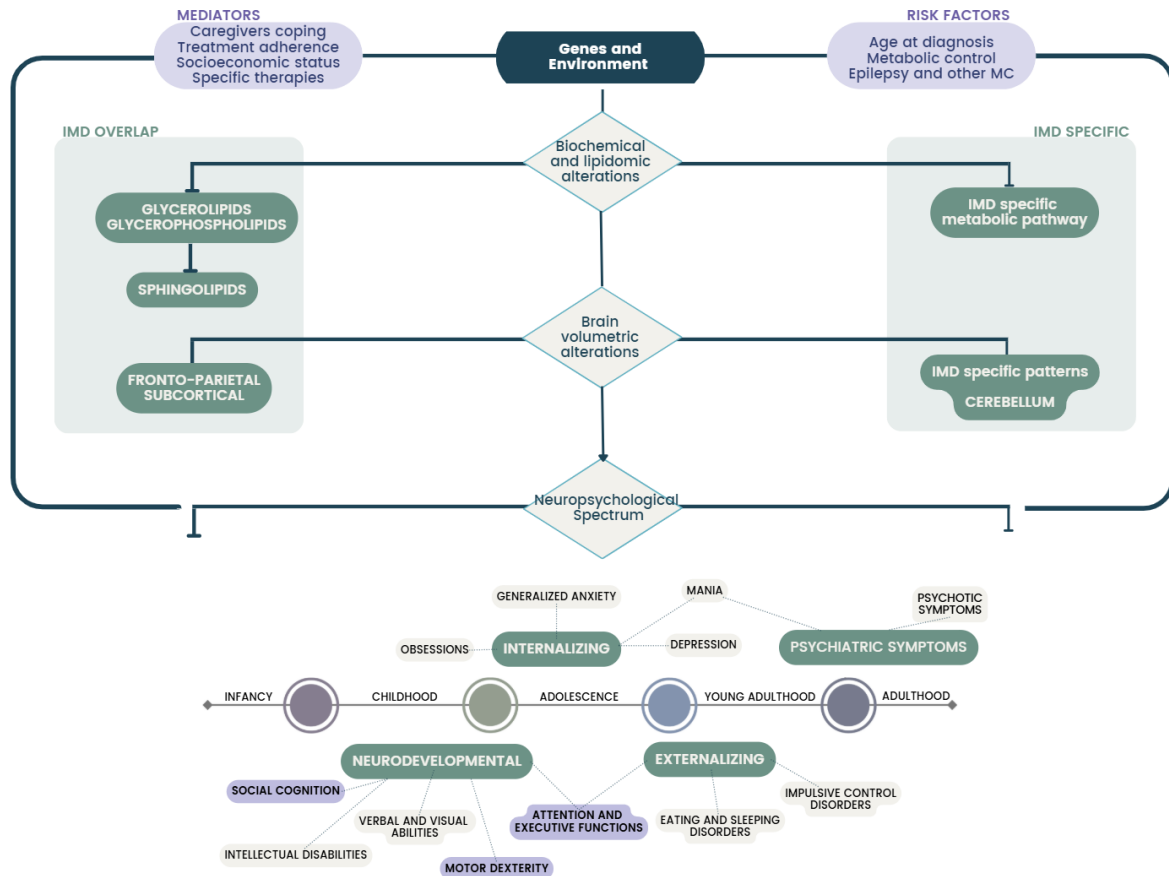


Figure 1. Integrated Transdiagnostic Model of Neurocognitive Impairment in IMDs. The figure illustrates how genetic and environmental factors, together with biochemical alterations (including glycerophospholipids, glycerolipids and sphingolipids) and brain volumetric changes (frontoparietal, subcortical, and cerebellar regions), contribute to a continuum of neuropsychological outcomes across the lifespan. This spectrum ranges from neurodevelopmental difficulties, and internalizing symptoms (e.g., anxiety, obsessions, and depression) to externalizing behaviors. In adulthood, these alterations may evolve into broader psychiatric disorders.

Our findings revealed a distinct lipidomic pattern between individuals with IMDs and age- and sex-matched healthy controls, regardless of the specific disease or distinct dietary treatment. Our cohort presented elevated serum and plasma concentrations of glycerolipids and glycerophospholipids (TAG, DAG, LPC, and LPE), associated with poorer intelligence, attentional deficits, executive dysfunction, and impaired social cognition. This profile had a direct impact on the daily functioning of patients, leading to a decrease adaptive behaviour, especially among patients with intoxication IMDs. LPC is a potent pro-inflammatory lipid that promotes oxidative stress, whereas LPE has been linked to altered synaptic transmission and impaired axonal maintenance (Bernal-Vega et al., 2023). The accumulation of TAG may reflect compensatory responses to mitochondrial dysfunction, although these responses can themselves be neurotoxic (Yu et al., 2020).

Sphingolipids, constituting approximately one-third of total brain lipids, are essential for maintaining myelin integrity, supporting synaptic transmission, and enabling neuron–glia communication (Esvap & Ulgen, 2023; Blot et al., 2021). Our cohort of IMDs presented lower serum concentrations of sphingolipids, particularly sphingosine, sphingosine-1-phosphate, and sphinganine-phosphate. However, higher concentrations were associated to a poorer social cognition and language impairment, particularly among energy-related IMDs.

Disrupted ceramide–S1P balance can induce neuroinflammation, apoptosis, and impaired synaptic signalling (Li et al., 2024; Mei et al., 2023; Tucci, 2022). Additionally, perturbations in sphingolipids and cholesterol have been shown to alter excitatory–inhibitory neurotransmission and glutamate receptor trafficking, providing a mechanistic link between lipid metabolism and neuronal excitotoxicity (El-Ansary et al., 2020). Abnormal ceramide and S1P signalling can further disrupt dopaminergic tone, glutamatergic balance, and GABAergic inhibition, neurotransmitter systems centrally implicated in neuropsychological impairment (Bernal-Vega et al., 2023). Previous studies have associated higher sphingolipid levels with neurocognitive deficits in other neurodevelopmental disorders (Yan et al., 2025; Li et al., 2024; Esvap & Ulgen, 2023; Wu et al., 2017).

Lipidomic alterations may interfere the maturation of cortico-cerebellar circuits during a critical period when specific brain regions are transitioning from a set of local processing hubs into a fully integrated network (Beuriat et al., 2022). Even though brain damage may be widespread, it can disproportionately affect regions that share metabolic and neurotransmitter systems, including frontoparietal and cerebellar circuits responsible for executive functioning and behavioural regulation.

Brain volumetric analyses in our cohort revealed microstructural alterations that not only align with the existing literature on metabolic disorders but also uncover broader neurobiological patterns related to neuropsychological functioning. We found an increased microstructural volume in frontoparietal and subcortical regions. Specifically, there was notable enlargement of the left triangular part of the inferior frontal gyrus (IFG), the left orbital gyrus, the right medial frontal cortex, the left putamen, and the left angular gyrus, when compared to age-matched healthy individuals. Additionally, there was a 32% reduction in cerebrospinal fluid (CSF) volume, suggesting compensatory intracranial dynamics caused by the relative expansion of adjacent structures.

These findings suggest atypical cortical expansion potentially linked to neuroinflammation or energy-mediated dysregulation affecting synaptic maturation and pruning (Bhattacharya et al., 2021; Iwata & Vanderhaeghen, 2021; Dehorter & Del Pino, 2020; Uytun, 2018).

In intoxication IMDs, we found that fronto-parietal hypertrophy and subcortical-cerebellar atrophy were associated with specific deficits in fine motor dexterity, social cognition and executive functions, including focused attention, cognitive flexibility, and inhibition. Additionally, decreased volumes in the left IFG and subcallosal areas correlated with poorer outcomes in fine motor skills, visuospatial performance, and executive functions. Moreover, larger ventricular volumes were associated with reduced motor dexterity.

In contrast, energy-related IMDs exhibited widespread hypertrophy, especially in the limbic system, fronto-parietal regions, and cerebellar areas, along with reduced volumes in white matter and the basal ganglia. These patterns correlated with greater deficits in social cognition, executive functions, and fine motor skills.

The cerebellum was identified as a sensitive biomarker of neurocognitive impairment in our cohort. We found that cerebellar atrophy in intoxication IMDs and hypertrophy in energy-related IMDs were associated with poorer neuropsychological outcomes. This cerebellum vulnerability has also been described in other neurodevelopmental disorders. In ADHD, increased grey matter volume has been noted in the left cerebellum and basal ganglia (Li et al., 2022; Albajara et al., 2020), and studies with ASD have identified abnormalities in cortico-cerebellar and subcortical circuits (Li et al., 2023; Richards et al., 2020).

The cerebellum's metabolic vulnerability is closely linked to the dynamics of excitatory and inhibitory signals. Neuroinflammatory processes lead to excessive production of reactive oxygen species (ROS), mitochondrial dysfunction, and calcium overload, driven by the overactivation of NMDA receptors (Revuelta et al., 2020). During oxygen–glucose deprivation, the depolarization of Purkinje cells, the primary GABAergic output neurons, leads to glutamate overflow and excitotoxic damage (Revuelta et al., 2020; Tamada et al., 2020). This imbalance between excitatory and inhibitory signals, particularly during the perinatal period, activates apoptotic pathways and

compromises the integrity and myelination of Purkinje cells, ultimately leading to atrophy in individuals with IMDs (Revuelta et al., 2020; Blaser, 2016).

The association between specific lipid species and brain volumes with a spectrum of neuropsychological symptoms further reinforces the idea that these potential biomarkers serve as crucial and measurable links between metabolic dysfunction and disruptions in neural networks.

This thesis aligns with existing research on neurocognitive outcomes in IMDs (Gil-González et al., 2025; Warner-Levy et al., 2024) and emphasizes that even mild or asymptomatic IMDs can result in significant neuropsychological impairments. Similar volumetric and lipidomic findings have also been reported in other genetically distinct neurodevelopmental disorders (Modesti et al. 2025; Yan et al., 2025; Li et al., 2024; Esvap & Ulgen, 2023; Li et al., 2023; Rudolph et al., 2023; Trimarco et al., 2021; Li et al., 2022; Richards et al., 2020; Albajara et al., 2020; El-Ansary et al., 2020; Wu et al., 2017). In our cohort, 46% of IMDs had ADHD symptoms, and 47% ASD symptoms. The high prevalence of ADHD- and ASD-like traits reinforces the notion that IMDs can express phenotypes typically attributed to idiopathic neurodevelopmental disorders. A spectrum of symptoms across various neuropsychiatric conditions has already been proposed (Michelini et al., 2024; Bernal-Vega et al., 2023; Blot et al., 2021; Brunkhorst-Kanaan et al., 2021), and our findings align with this broader framework.

In our cohort, the average intellectual functioning was measured at an IQ of 85, which is one standard deviation below the general population. The neuropsychological results revealed a pattern of shared vulnerabilities, particularly affecting fine motor dexterity, executive functions, attention, and social cognition. Notably, these neuropsychological domains were more strongly linked to lipidomic and brain volumetric patterns, as higher cognitive functions depend on metabolically demanding and densely myelinated circuits that are especially susceptible in IMDs.

Although no differences were noted in the neurocognitive profiles between intoxication and energy-related IMDs, the heterogeneity among these population requires systematic and individualized neuropsychological assessments to accurately identify and address each individual's needs.

The observational study conducted after treatment with methylphenidate (MPH) adds an important longitudinal dimension to our findings. After a prolonged period of treatment, participants demonstrated significant improvements in vigilance and personal resourcefulness, which reflects better attentional control and adaptive coping skills. These benefits occurred even in the absence of detectable microstructural changes in the brain. This suggests that MPH may modulate functional processes via dopaminergic and noradrenergic signalling within frontostriatal and frontoparietal networks, rather than structural remodelling.

This integrative transdiagnostic model enhances our understanding of the overlapping symptoms in biochemically diverse IMDs and other neurodevelopmental disorders, such as ASD or ADHD. Although evidence points towards a large variability in cognitive functioning among individuals, we progress towards a vision of IMD as a continuous spectrum of symptoms in which the particular defect and the individual idiosyncrasy influence the predominance of one symptom over another (Michelini et al., 2024; Saudubray et al., 2019).

1.2. Clinical implications

The thesis findings emphasizes the importance of neuropsychological functioning in diagnosing, managing, and providing long-term care for individuals with IMDs. By establishing recurrent neuropsychological assessments and identifying potential biomarkers of impairment, we can significantly enhance diagnostic accuracy and tailor interventions that improve the patients' clinical outcomes and quality of life.

Despite advancements in early diagnosis and treatment, our study found that 53% of patients were diagnosed after their first year of life. Consistent with previous research, a late diagnosis is a significant risk factor for poorer neurocognitive outcomes and a key modifier of volumetric patterns.

Our findings indicate that individuals who are diagnosed and treated early, even those with less severe clinical presentations, face a higher risk of microstructural brain damage and

neurocognitive impairments. These impairments can have significant consequences for their daily lives, affecting interpersonal relationships, academic performance, and overall family well-being.

Cognitive vulnerabilities can worsen over time, resulting in greater deficits in executive functions, motor coordination, and emotional regulation as children enter more challenging academic environments. This can further widen the gap between these children and their peers (Gil-González et al., 2025). Consequently, individuals with IMDs face a heightened risk of academic underachievement and an increased likelihood of dropping out of school.

Given the overlapping symptoms between metabolic and psychiatric conditions, it is important to conduct metabolic and genetic studies when psychiatric symptoms co-occur with atypical features. These features may include epilepsy, intellectual disability, dysmorphic traits, gastrointestinal and motor disturbances. Additionally, clinicians should be suspicious when psychiatric patients exhibit resistance to antipsychotic medications or experience adverse side effects that complicate their treatment. A family history of consanguinity, signs of multisystem involvement, and unexplained infant deaths can all provide significant clues that may indicate the presence of an IMD (Van de Burgt et al., 2023).

Neuropsychological assessments aid in tailoring cognitive and behavioural interventions and targeted clinical strategies. Although treatments for IMDs have improved over the last few decades, their impact on higher-order cognitive domains remains limited. Our findings emphasize the potential of methylphenidate (MPH) as a potential targeted intervention for attentional deficits in IMDs. However, since MPH can lead to loss of appetite, the IMD population requires careful and personalized dose adjustments to mitigate these secondary effects on dietary management. Further longitudinal studies are necessary to evaluate the efficacy of MPH in this population.

Treatments can significantly impact the social and emotional quality of life for both patients and their families, decreasing their health-related quality of life (Bosch et al., 2004). A study by Zeltner et al. (2017) identified significant burdens in children and adolescents, including dietary restrictions, emotional challenges, cognitive issues, fatigue, and social stigma. Similarly, Brown et al. (2017) found that how parents cope with stress influences their children's internalizing symptoms, while the family's management strategies are associated with children's externalizing behaviours and social skills.

Additionally, environmental factors related to the overall medical condition, such as hospitalizations and adherence to treatment, can affect daily living skills in this population (Joy et al., 2009; Waisbren et al., 2008). Early identification of these psychosocial factors could improve family support and health-related quality of life. As neurocognitive impairment increases, health-related quality of life tends to decline (Konomura et al., 2024; Siegert et al., 2022). Therefore, early and ongoing neuropsychological assessments are essential for identifying individuals and families who require support.

Together, evidence strongly supports including a neuropsychologist in metabolic units as part of a multidisciplinary team in clinical and research settings.

1.3. Neuropsychological assessment recommendations

Despite an increasing awareness of neuropsychological impairments in IMDs, there is currently no standardized neuropsychological protocol for assessing children or adults. Phenylketonuria (PKU) is one of the few IMDs for which formal European guidelines have been established. These guidelines recommend assessments on an as-needed basis during childhood, with systematic evaluations at ages 12 and 18. This approach underscores the importance of tailoring assessment timing to each patient's specific risk factors, such as metabolic instability, academic difficulties, and concerns expressed by caregivers, professionals, or the patients themselves (Ashe et al., 2019).

These risk indicators highlight the need for ongoing follow-up, as subtle changes in cognitive, emotional, or behavioural functioning may indicate metabolic dysregulation before biochemical abnormalities or medical complications arise. Based on our findings, we recommend conducting a neuropsychological assessment at the time of diagnosis and systematic follow-ups, even in early treated or asymptomatic patients. By conducting comprehensive, repeated evaluations, we can facilitate early identification of cognitive strengths and weaknesses, enabling timely, personalized interventions. This proactive approach aims to prevent adverse impacts on academic performance and daily functioning, ultimately enhancing the health-related quality of life for individuals with IMDs and their families.

Nevertheless, standardized tests can have significant limitations. For instance, floor effects can reduce sensitivity in individuals with lower cognitive ability, and motor impairments may affect performance in several time-limited psychometric tests. This emphasizes the need for an experienced neuropsychologist to carefully select and interpret the psychometric tools to reflect an individual's capabilities accurately.

Neuropsychological assessments should go beyond evaluating overall cognitive function to include areas that are particularly sensitive to metabolic instability. A comprehensive neuropsychological evaluation must include a clinical history, the administration of standardised psychometric tests, and the use of structured behavioural and adaptive scales (Waisbren et al., 2016). Given the complex relationships among metabolic dysfunction, psychosocial challenges, and behavioural manifestations, these assessments should include insights from both patients and caregivers. This approach will help capture functional impairments and track changes over time (Shapiro et al., 2016). Conducting systematic neuropsychological assessments throughout development enables early identification of deficits and timely intervention.

1.3.1. Clinical History

A comprehensive clinical history is crucial for selecting appropriate neuropsychological measures. Clinicians should assess potential behavioural or emotional issues, social adjustment, academic performance, caregiver concerns, and quality of life. A brief psychiatric history is essential, as even mild symptoms of depression or anxiety can negatively impact cognitive performance, particularly attention and processing speed (Ashe et al., 2019).

Additionally, factors that may interfere with neurocognitive outcomes must be considered, including age at disease onset, metabolic control and treatment adherence. In this thesis, epilepsy emerged as a significant risk factor associated with widespread neurocognitive impairments, affecting areas such as intelligence, language, attention, executive functions, social cognition, and behavioural regulation. These findings highlight the importance of accounting for comorbidities when assessing neurocognitive risk in populations with IMDs (Cannon Homaei et al., 2022).

1.3.2. Neuropsychological battery

Given the cognitive vulnerabilities associated with IMDs, it is important to conduct a thorough examination of all cognitive domains. When time is limited, clinicians should focus on the domains most sensitive to metabolic disturbances: intelligence, attention, executive functions, motor dexterity, and social cognition (Boy et al., 2023; Ashe et al., 2019).

Developmental milestones in infants aged 1 to 2 years can be assessed using the Bayley Scales of Infant and Toddler Development (BSID-II) or the Vineland Adaptive Behaviour Scales (VABS-3). For preschool children aged 3 to 5 years, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) is recommended. For individuals aged six and older, a recommended neuropsychological assessment for all cognitive domains, tailored to the patient's age, is presented in *Table 1*.

For individuals with moderate to severe cognitive impairment, adaptive behaviour interviews with caregivers, such as the VABS-3, are crucial for obtaining a meaningful assessment of daily functioning and for avoiding floor effects observed in other psychometric tests. Regular adaptive, psychosocial and quality-of-life assessments are essential in long-term management (Boy et al., 2023). Validated behavioural measures such as the ABAS-II and BRIEF have demonstrated reliability in IMD populations and can effectively describe daily functioning (Waisbren et al., 2016).

Our findings highlight the urgent need for standardized, reliable, and valid neuropsychological guidelines to establish a systematic approach for IMDs. The recommendations outlined aim to create a consistent and clinically valuable resource for neuropsychological assessments in individuals with IMDs. This framework is designed to improve diagnostic accuracy, enable earlier and more targeted interventions, and ultimately enhance the long-term outcomes for patients and their families.

By integrating medical history, psychiatric background, and neuropsychological data, clinicians can design individualized intervention plans tailored to the specific needs of patients with IMDs (Ashe et al., 2019; Shapiro et al., 2016).

Furthermore, these neuropsychological recommendations extend beyond clinical settings and can also enhance the quality of research. Relying solely on general measures of intelligence and

qualitative assessments does not adequately capture the complexity of IMDs. Therefore, comprehensive neuropsychological assessments are essential in research environments as well.

Table 1. Recommended comprehensive neuropsychological assessment for individuals with IMDs.

Cognitive Function	Specific Domains	6 – 16:11 years	+17 years
Global Cognitive Performance	-Intelligence Quotient (IQ)	-WISC-V	-WAIS-IV
Language	- Vocabulary - Verbal Fluency - Morphosyntax - Oral comprehension	-Vocabulary (V) WISC-V -Semantic Word Generation (NEPSY-II) -CELF-5 -CELF-5	-Vocabulary (V) WAIS-IV -Animals Test -CELF-5 (≤21 years) -CELF-5 (≤21 years)
Visual-Spatial Skills	-Visual organization and constructional praxis	-Block Design (BD) WISC-V -Rey-Osterrieth Complex Figure (ROCF) -Beery Visual-motor Integration (VMI)	-Block Design (BD) WAIS-IV -Rey-Osterrieth Complex Figure (ROCF) - Beery Visual-motor Integration (VMI)
Attention	- Focused attention - Vigilance - Sustained attention	-Digit Span Forward (DsF) WISC-V -K-CPT-2 (6-7) or CPT-3 (≥8)	Digit Span Forward (DsF) WAIS-IV -CPT-3
Executive Functions	-Inhibitory control / Impulsivity	-K-CPT-2 or CPT-3 -Inhibition NEPSY-II -Five Digits Test	-CPT-3 -Stroop Test -Five Digits Test
	- Working Memory	-Digit Span Backwards (DsB) WISC-V	-Digit Span Backwards (DsB) WAIS-IV
	-Cognitive flexibility	-Inhibition NEPSY-II -Five Digits Test	-Stroop Test -Five Digits Test
	-Phonemic Fluency	-Phonemic Fluency NEPSY-II	-FAS test
	-Planning	-Plan-ROCF	-Plan-ROCF
	-Processing Speed	-Time-ROCF -Coding (C) WISC-V -Symbol Search (SS) WISC-V	-Time-ROCF -Coding (C) WAIS-IV -Symbol Search (SS) WAIS-IV
Social Cognition	-Affect Recognition	-Affect Recognition NEPSY-II	-Read the Mind in the Eyes Test (RMET)
	-Theory of mind	-ToM NEPSY-II -ADOS-2/ADI-R	-Faux Pas test / Happé Strange Stories -ADOS-2/ADI-R
Motor Skills	-Fine motor dexterity	Purdue Pegboard Test (PPT)	Purdue Pegboard Test (PPT)
Behavioural and psychiatric screening	-Internalizing and externalizing symptoms	-SENA/BASC-3 -BRIEF-2	-SENA/BASC-3 -BRIEF-2
Adaptive Behavior	-Adaptive behaviour and psychosocial adjustment	- ABAS-II - VABS-3	- ABAS-II -VABS-3

WISC=Wechsler intelligence scale for children, WAIS= Wechsler adults intelligence scale, NEPSY= Developmental Neuropsychological Assessment, CELF= Clinical Evaluation of Language Fundamentals, VMI= visual-motor integration, CPT= Conners' Continuous Performance Test, ToM= Theory of Mind, ADOS= Autism Diagnostic Observation Schedule, ADI=Autism Diagnostic Interview, SENA= Sistema de Evaluación de Niños y Adolescentes (children and adolescent evaluation system), BASC= Behaviour Assessment System for Children, BRIEF= Behavior rating inventory of executive function,, ABAS= Adaptive behaviour assessment system, VABS= Vineland Adaptive Behavior Scale,

1.4. Limitations and Future Directions

Even though this work makes an important contribution to the field of IMDs, it has several limitations that should be acknowledged when interpreting the findings.

Data comparability

The lack of research specifically focused on neurocognitive impairment in IMDs, combined with significant variations in study methodologies, limits our ability to compare our results. Additionally, changes in the classification of IMDs and cognitive-behavioural disorders over time make it more challenging to synthesise the existing evidence. The heterogeneous diagnostic systems and the simplified classification used in this study, although clinically useful, may overlook disease-specific mechanisms. Therefore, the findings of this study must be interpreted with caution.

Sample size and heterogeneity

In studies of rare diseases, sample sizes are often small (a mean of 7-24 subjects). Although our cohort of 70 participants is relatively large for IMD research, the heterogeneity of IMD included reduces statistical power and limit the generalizability of our findings. Disease-specific neuropsychological, volumetric and lipidomic patterns could not be analysed in detail, so further studies with larger samples are needed to replicate our findings in specific IMDs.

Study design

Our cohort's cross-sectional and observational designs lacked randomized, placebo-controlled trials, which limits our ability to make causal inferences and may introduce bias. Additionally, the lack of available standardized protocols for advanced volumetric and lipidomic analyses hinder reproducibility.

Moreover, peripheral biochemical measurements, such as serum lipidomics, may not adequately reflect processes occurring in the central nervous system. The reliance on dietary management for treating IMDs further complicates the assessment of confusing variables in these disorders.

Additionally, factors such as dietary adherence, supplements and medications, and subclinical metabolic fluctuations could not be precisely measured.

This study categorized age at disease onset as early-onset (≤ 1 year) or late-onset (> 1 year). However, the late-onset group could not be further subdivided due to the small sample size. In our cohort, only 8 of 70 patients had disease onset between 6 and 12 years, and only 1 patient had onset after 12 years. Larger studies are needed to determine whether age at disease onset influences neurodevelopment during critical periods, such as 6 and 12 years.

Future Directions

These limitations highlight the need for future research to develop more comprehensive and standardized methods for understanding neurocognitive outcomes in IMDs. It is essential to conduct larger, multicenter, and longitudinal studies to clarify disease trajectories, validate emerging biomarkers, and investigate the structural and functional mechanisms linking metabolic disturbances to neurocognitive impairment. Future research should also evaluate the long-term effects of treatments, such as methylphenidate, using consistent neuropsychological measures in this population.

Integrating analyses of structural and functional advanced neuroimaging, cerebrospinal fluid lipidomics, gut-brain axis data, and targeted metabolomics may help reveal the metabolic factors contributing to neuropsychological dysfunction.

There is also a need for standardized international protocols for neuropsychological assessment and intervention to strengthen the evidence base and enhance reproducibility across studies.

Finally, incorporating early and systematic neuropsychological assessment into routine clinical care remains critical for identifying at-risk individuals, guiding personalized interventions and supports, and ultimately improving neurodevelopmental outcomes across the diverse spectrum of IMDs.

1.5. Conclusions

This thesis provides a comprehensive characterization of neurocognitive impairment in intoxication and energy-related IMDs. Specific objectives were followed to contrast the initial hypotheses:

Objective 1: To synthesize the current state of the art through an updated systematic review of the literature, focusing on the neuropsychological domains affected in intoxication and energy-related IMDs.

IMDs are characterized by a shared pattern of motor disturbances and neuropsychological deficits, including impairments in executive functions, attention, social cognition, and behavioural regulation, all of which impact daily life. Intoxication IMDs generally show better cognitive outcomes than energy-related IMDs. Early detection and treatment can improve motor and cognitive outcomes, although the effects are variable. Overall, current evidence is limited by small, heterogeneous samples and the use of inconsistent, non-standardized assessments.

Objective 2: To conduct a comprehensive and standardized neuropsychological assessment of a cohort of intoxication and energy-related IMDs to determine specific and shared profiles.

Even individuals with mild or asymptomatic IMDs are at risk of persistent neuropsychological deficits. The most affected cognitive domains include fine motor dexterity, attention, executive functions, and social cognition. IMDs often present symptoms overlapping with other neurodevelopmental disorders, such as ASD or ADHD. Late-onset disease and epilepsy are associated with poorer neurocognitive outcomes.

Our first hypothesis is supported by objectives 1 and 2, as both intoxication and energy-related IMDs are associated with impairments in higher-order cognitive domains, particularly executive functions and attention.

Objective 3: To investigate lipidomics and advanced brain volumetric techniques to uncover potential biomarkers linked to the neurocognitive impairment in intoxication and energy-related IMDs.

Advanced volumetric MRI revealed widespread microstructural brain abnormalities in mild and asymptomatic IMDs, despite largely normal findings on conventional MRI. Distinct neuroanatomical signatures differentiated IMD subtypes: intoxication IMDs showed limbic-temporal and cerebellar atrophy, whereas energy-related IMDs exhibited predominant cortico-cerebellar and putaminal hypertrophy. A shared pattern of fronto-parietal hypertrophy combined with subcortical vulnerability

was associated with deficits in social cognition, executive functioning, and fine motor skills across IMDs. Differential cerebellar volumetric patterns, hypertrophy in energy-related IMDs and atrophy in intoxication IMDs, were linked to cognitive impairment, highlighting the cerebellum as a potential neurocognitive biomarker. Age at disease onset modulated brain structure, with late-onset IMDs associated with cerebellar hypertrophy and corresponding neurocognitive deficits.

Children with IMDs also exhibited a shared lipidomic signature distinct from healthy controls, independent of disease subtype or dietary treatment. IMDs were characterized by increased glycerolipids (DAG, TAG) and glycerophospholipids (LPC, LPE), alongside reduced sphingolipids. Elevated TAG and DAG levels correlated with poorer global cognition, attention, executive functions, and social cognition, while higher LPE and LPC concentrations were associated with deficits in visuospatial abilities, inhibition, motor skills, and social cognition. Increased sphingolipid levels were linked to language and social cognition impairments, particularly in energy-related IMDs.

Our second and third hypotheses are supported by objective 3, as both intoxication and energy-related IMDs share common brain volumetric and lipidomic biomarkers of neurocognitive impairment, with a predominant involvement of fronto-parietal regions linked to attentional and executive dysfunction, as well as alterations in sphingolipid pathways.

Objective 4: To evaluate the effectiveness of methylphenidate in improving attentional deficits within the IMD population.

Methylphenidate significantly improved vigilance in individuals with both intoxication and energy-related IMDs. Treatment was also associated with enhanced self-regulation and adaptive daily functioning. No significant changes in brain volumetry were observed following treatment. These findings suggest that methylphenidate is a promising targeted symptomatic therapy for attentional deficits in IMDs, provided that intake-related side effects are carefully monitored.

Finally, our fourth hypothesis is supported by objective 4, as treatment with methylphenidate at personalized doses led to improvements in attention (vigilance) in individuals with IMDs.

This thesis emphasizes the clinical importance of early and systematic neuropsychological assessments, highlights the potential value of emerging biomarkers, and underscores the relevance of tailored interventions for specific cognitive deficits. Larger, longitudinal, and standardized studies are needed to better characterize disease trajectories and treatment efficacy.

Despite significant biochemical and phenotypic diversity, IMDs share a set of neurodevelopmental vulnerabilities. This work proposes an Integrative Transdiagnostic Model that offers a framework for future research and contributes to a growing recognition of IMDs as complex neurodevelopmental disorders rather than isolated biochemical conditions. This perspective calls for coordinated, multidisciplinary, and lifelong support to improve affected individuals' quality of life.

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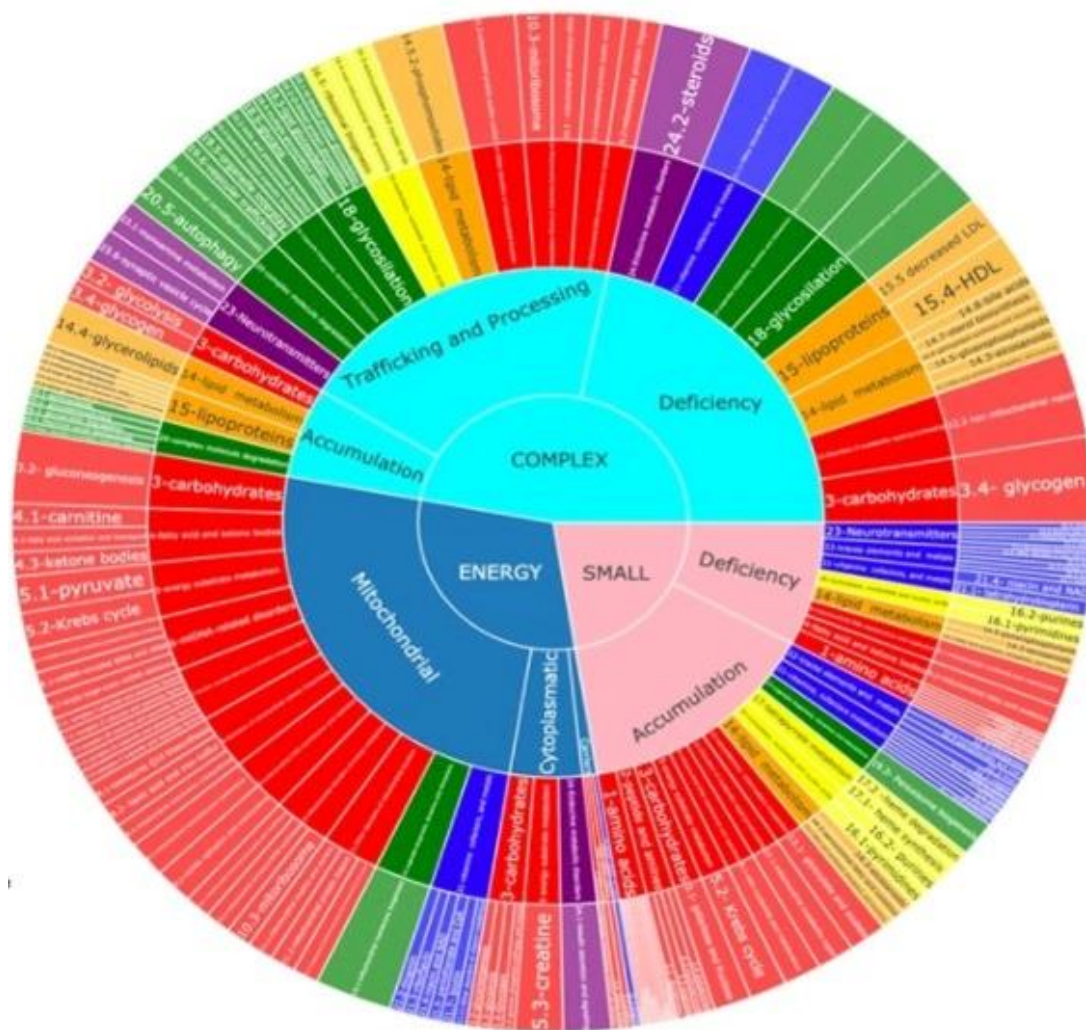
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Annex

Supplementary Figure 1. Association between de ICIMD and the simplified classification.



Supplementary Table 1. References reviewed for each specific IMD

Inherited Metabolic Disorder			Reference	N	Age of the sample	Severe ID	Mild ID	Average IQ	Executive Functions	Attention	Processing Speed	Language	Speech	Visual Skills	Motor dexterity	Memory	Behaviour	Social Cognition
Intoxication IMD																		
Small molecules accumulation																		
Children Disorders of amino acid metabolism	Urea cycle disorders and inherited hyperammonemias	Arginase deficiency	Garg et al., 2020	3	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A
			Kido et al., 2021	8	Children and adults	N/A	N/A	N/A	0	0	0	0	0	0	0	0	0	0
			Krivitzky et al., 2009	3	Children	0	1	1	N/A	N/A	N/A	1	1	N/A	N/A	N/A	N/A	N/A
			Pontoizeau et al., 2020	1	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Yokoi et al., 2021	1	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Waisbren et al., 2016	17	Children and adults	0	1	1	0	0	0	0	0	0	1	1	1	1
		Argininosuccinate lyase deficiency	Ah Mew et al., 2012	28	Children	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Kido et al., 2021	14	Children and adults	N/A	N/A	N/A	0	0	0	0	0	0	0	0	1	1
			Kim et al., 2013	6	Children	0	1	1	N/A	N/A	N/A	1	1	N/A	1	N/A	N/A	N/A
			Krivitzky et al., 2009	17	Children	0	1	1	1	1	N/A	1	1	N/A	N/A	N/A	N/A	N/A
			Pontoizeau et al., 2020	7	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Waisbren et al., 2016	71	Children and adults	0	1	1	1	1	0	1	0	1	1	1	0	0
			Serrano et al., 2010	2	Children	0	1	0	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	1	N/A
		Argininosuccinate synthetase deficiency	Liu et al., 2021	5	Children	1	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Ah Mew et al., 2012	37	Children	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Kido et al., 2021	43	Children and adults	N/A	N/A	N/A	1	1	0	0	0	0	0	0	0	1

Carbamoyl phosphate synthetase 1 deficiency																	
Citric deficiency																	
Mitochondrial ornithine transporter deficiency																	
N-acetylglutamate synthase deficiency																	
Ornithine transcarbamylase deficiency																	

			Buerger et al., 2019	300	Children and adults	0	0	1	1	1	N/A	N/A	N/A	1	N/A	1	N/A	N/A
			Crowe et al., 2018	4	Children	1	1	0	1	1	N/A	N/A	N/A	N/A	N/A	1	1	N/A
			Gropman et al., 2011	19	Children and adults	0	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Anderson et al., 2019	17	Children and adults	0	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Anderson et al., 2020	1	Children	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Gropman et al., 2012	19	Children and adults	0	0	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Gyato et al., 2003	19	Adults	0	0	1	1	1	N/A	0	0	1	1	0	N/A	N/A
			Kido et al., 2021	117	Children and adults	N/A	N/A	N/A	1	1	0	0	0	0	0	0	1	1
			Kim et al., 2013	8	Children	0	1	1	1	1	N/A	1	1	N/A	1	N/A	N/A	N/A
			Krivitzky et al., 2009	43	Children	1	1	1	1	1	N/A	1	1	N/A	N/A	N/A	1	1
			Nicolaides et al., 2002	28	Children	1	0	1	1	1	N/A	1	N/A	N/A	N/A	N/A	1	N/A
			Pontoizeau et al., 2020	5	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Sprouse et al., 2014	45	Children and adults	0	0	1	1	1	N/A	0	N/A	0	1	N/A	N/A	N/A
			Waisbren et al., 2016	320	Children and adults	0	1	1	1	1	1	0	0	1	1	1	1	1
			Sen et al., 2024	302	Adults	N/A	N/A	N/A	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
	Miscellaneous	Jain-Ghai et al., 2020	9	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
		Jamolkowski et al., 2015	52	Children	0	1	0	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
Organic acidurias	3-methylglutaconyl-CoA hydratase deficiency	Eriguchi et al., 2006	1	Adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Mercimek-Mahmutoglu et al., 2011	2	Children	0	1	0	0	1	1	0	1	1	1	0	1	0	0
	Glutaryl-CoA dehydrogenase deficiency	Bekiesinska-Figatowska et al., 2021	1	Children	0	0	4	1	1	0	1	0	0	1	1	0	0	0

			Märtner et al., 2021	72	Children	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A
			Beauchamp et al., 2009	4	Children	0	1	1	0	0	0	0	1	0	1	0	0	0
			Boneh et al., 2008	4	Children	0	1	1	0	0	0	1	1	0	1	0	0	0
			Boy et al., 2015	30	Children and adults	0	0	1	0	0	1	0	0	0	1	0	0	0
			Brown et al., 2014	6	Children	0	1	1	0	0	0	0	1	0	1	0	1	1
			Kyllerman et al., 1994	7	Children	1	1	0	0	1	0	0	1	0	1	0	0	0
			Tsai et al., 2017	11	Children and adults	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A
			Strauss et al., 2020	10	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Paria et al., 2022	24	Children	0	1	1	N/A	N/A	N/A	1	1	N/A	1	N/A	N/A	1
			Bjarnia et al., 2008	10	Children	0	1	1	N/A	N/A	N/A	1	1	N/A	1	N/A	N/A	N/A
			Kyllerman et al., 2004	28	Children	1	1	1	N/A	N/A	N/A	N/A	1	N/A	1	N/A	N/A	N/A
			Isobutyryl-CoA dehydrogenase deficiency	Eleftheriadou et al., 2021	1	Children	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
		Isovaleryl-CoA dehydrogenase deficiency	Mütze et al., 2020	91	Children	0	0	1	N/A	N/A	N/A	N/A	1	N/A	1	N/A	N/A	N/A
			Nizon et al., 2013	18	Children	0	1	1	N/A	1	N/A	1	1	N/A	1	N/A	N/A	N/A
			Couce et al., 2016	16	Children and adults	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A
			Grünert et al., 2012	13	Children and adults	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A
		Propionic acidemia	Jain-Ghai et al., 2020	1	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0
			Nizon et al., 2013	24	Children	1	1	1	N/A	1	N/A	1	1	N/A	1	1	1	N/A
			North et al., 1995	6	Children	1	0	0	1	1	N/A	1	N/A	1	1	N/A	1	N/A
			Longo et al., 2017	3	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A

			Grünert et al., 2013	55	Children	1	1	1	1	1	N/A	N/A	N/A	N/A	1	N/A	1	1
			De la Batie et al., 2017	19	Children and adults	1	1	0	1	1	N/A	N/A	N/A	N/A	1	N/A	N/A	1
		Miscellaneous	Jain-Ghai et al., 2015	100	Children	0	1	0	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	1	1
	Disorders of the metabolism of sulfur-containing amino acids and hydrogen sulfide	Cystathionine beta-synthase deficiency	Almuqbil et al., 2019	25	Children and adults	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
			El Bashir et al., 2014	28	Children and adults	0	1	1	1	N/A	0	1	N/A	1	1	N/A	1	N/A
	Disorders of ornithine, proline and hydroxyproline metabolism	Hydroxyproline dehydrogenase deficiency	Kim et al., 1997	1	Children	0	0	1	0	0	0	0	0	1	0	N/A	0	N/A
		Proline dehydrogenase deficiency	Di Rosa et al., 2008	4	Children	1	1	0	N/A	N/A	N/A	N/A	N/A	1	N/A	1	1	1
			Di Rosa et al., 2014	10	Children and adults	1	1	0	N/A	1	N/A	1	N/A	1	N/A	1	1	1
			Duarte et al., 2017	1	Children	0	1	0	N/A	N/A	N/A	N/A	1	1	N/A	N/A	1	N/A
			Raux et al., 2006	8	Children	1	1	0	N/A	N/A	N/A	1	N/A	N/A	1	N/A	1	1
			Evers et al., 2015	64	Children and adults	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
	Disorders of lysine, hydroxylysine, and tryptophan metabolism	Saccharopinuria	Norioka et al., 2021	1	Children and adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of histidine metabolism	Histidine ammonia-lyase deficiency	Levy et al., 2004	31	Children and adults	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of glutamate/glutamine and aspartate/asparagine metabolism	Aspartoacylase deficiency	Sarret et al., 2015	1	Children	0	1	0	0	0	1	1	N/A	0	1	N/A	0	0
	Disorders of branched-chain amino acid metabolism	Maple syrup urine disease	Jain-Ghai et al., 2020	3	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0
			Bouchereau et al., 2017	21	Children	0	1	1	1	1	1	0	0	1	0	0	1	0
			Hoffmann et al., 2006	15	Children	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Strauss et al., 2020	82	Children and adults	1	1	1	N/A	N/A	N/A	N/A	N/A	1	N/A	1	N/A	N/A
			Muelly et al., 2013	35	Children and adults	0	1	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A

			Shelmer et al., 2010	14	Children and adults	0	1	1	1	1	N/A	N/A	N/A	N/A	1	N/A	1	N/A
			Walsh and Scott, 2010	1	Children	0	1	0	1	1	0	0	1	1	1	0	1	N/A
			Chin et al., 2015	1	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Couce et al., 2015	14	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of amino acid transport	GABA transporter deficiency	Johannessen et al., 2017	24	Children	0	1	0	1	1	N/A	1	1	1	1	N/A	1	1
			Breuilard et al., 2019	19	Children	0	1	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Trivisano et al., 2023	5	Children	1	1	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
			Caputo et al., 2023	2	Children and adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of tyrosine metabolism	Fumarylacetoacetase deficiency	Bendadi et al., 2014	10	Children and adults	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Couce et al., 2019	52	Children and adults	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			De Laet et al., 2011	10	Children	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			García et al., 2017	12	Children and adults	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Thimm et al., 2011	9	Children	0	1	1	N/A	N/A	N/A	1	N/A	N/A	1	N/A	N/A	N/A
			Van Ginkel et al., 2016	19	Children and adults	0	1	1	1	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A	1
			Van Vliet et al., 2019	31	Children and adults	N/A	N/A	N/A	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	1
			Zeybek et al., 2014	20	Children	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Van Vliet et al., 2022	33	Children	0	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
			Pohorecka et al., 2024	12	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
		Hawkinsinuria	Blundell et al., 2018	11	Children and adults	N/A	N/A	N/A	N/A	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A
			Barroso et al., 2020	2	Children	0	1	0	1	1	0	1	0	0	N/A	N/A	1	N/A

			Tyrosine aminotransferase deficiency	Gokay et al., 2016	1	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Galactokinase deficiency	Rubio-Gozalbo et al., 2020	47	Children	0	1	0	1	1	N/A	1	1	N/A	1	N/A	1
				Antshel et al., 2004	25	Children	0	1	0	1	0	0	1	N/A	1	N/A	1	1
				Doyle et al., 2010	28	Children and adults	0	1	0	1	0	0	0	0	0	N/A	0	N/A
				Gubbels et al., 2011	18	Adults	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
				Hoffmann et al., 2011	32	Children and adults	0	1	1	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A
				Iakovou et al., 2019	2	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				Kaufman et al., 1995	45	Children and adults	0	1	1	0	0	0	0	0	0	1	0	N/A
				Komer et al., 2019	22	Children and adults	0	1	0	N/A	1	1	N/A	N/A	1	0	0	N/A
				Lewis et al., 2012	4	Children	0	1	1	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A
				Lewis et al., 2013	1	Children	0	1	0	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A
				Lynch et al., 2014	10	Children	0	0	1	N/A	N/A	N/A	0	N/A	0	1	1	1
				Manis et al., 1997	35	Children	0	0	1	N/A	N/A	N/A	1	N/A	1	1	N/A	N/A
				Rubio-Agusti et al., 2013	47	Adults	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	1	N/A	1	N/A
				Ozgun et al., 2019	46	Children	N/A	N/A	N/A	N/A	N/A	N/A	1	1	N/A	1	N/A	N/A
				Potter et al., 2008	33	Children	0	1	1	N/A	N/A	N/A	1	1	N/A	N/A	N/A	N/A
				Ryan et al., 2013	54	Children	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
				Schadewaldt et al., 2010	23	Children and adults	0	1	1	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A
				Shield et al., 2000	34	Children	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				Welsink-Karssies et al., 2020	48	Children and adults	0	1	0	1	1	1	1	N/A	1	N/A	N/A	1

			Mazzini et al., 2024	21	Children	N/A	N/A	N/A	1	1	1	1	1	N/A	N/A	N/A	N/A	N/A
			Hermans et al., 2023	61	Children and adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	1	1
			Wasbren et al., 2021	44	Children	0	0	1	N/A	N/A	N/A	0	1	N/A	0	N/A	N/A	N/A
			Hermans et al., 2024	23	Children and adults	0	1	1	1	N/A	1	N/A	N/A	1	N/A	N/A	1	1
			Hermans et al., 2024	10	Adults	0	1	0	0	0	0	N/A	N/A	1	N/A	N/A	N/A	N/A
Disorders of peptide and amine metabolism	Disorders of polyamine metabolism	Spermine synthase deficiency	Alencastro et al., 2007	3	Children and adults	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Kesler et al., 2009	2	Children and adults	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Disorders of tetrapyrrole metabolism	Disorders of methylanine metabolism	Sarcosine dehydrogenase deficiency	Benarrosh et al., 2012	1	Adults	1	0	0	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of heme synthesis and porphyrias	Porphobilinogen deaminase deficiency	Grabowski and Yeragani, 1987	1	Adults	0	0	1	0	0	0	0	N/A	0	N/A	N/A	1	N/A
	Disorders of iron metabolism	Hereditary ceruloplasmin deficiency	Skidmore et al., 2007	1	Adults	0	0	1	1	1	N/A	1	N/A	N/A	1	1	N/A	N/A
			Shang et al., 2006	1	Adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Disorders of trace elements and metals	Disorders of copper metabolism	Wilson disease	Sloan et al., 2020	1	Adults	N/A	N/A	N/A	1	1	1	1	N/A	1	N/A	N/A	1	N/A
			Lesniak et al., 2022	30	Adults	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
			Camarata et al., 2021	62	Adults	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
			Shribman et al., 2022	40	Children and adults	N/A	N/A	N/A	1	1	1	0	0	0	N/A	1	1	0
			Rangarajan et al., 2022	10	Adults	N/A	N/A	N/A	1	1	1	N/A	N/A	N/A	N/A	1	N/A	N/A
	Disorders of biotin metabolism	Biotinidase deficiency	Ramaekers et al., 1993	1	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	1	1	N/A	N/A	N/A
Disorders of vitamin and cofactor metabolism	Disorders of cobalamin metabolism	Methylmalonic aciduria	Nizon et al., 2013	38	Children	1	1	1	N/A	1	N/A	1	1	N/A	1	N/A	1	N/A
			O'Shea et al., 2012	43	Children and adults	0	0	1	0	0	1	0	N/A	0	N/A	N/A	0	N/A
			Matos et al., 2013	2	Children	N/A	N/A	N/A	N/A	N/A	N/A	1	1	N/A	1	N/A	1	1
			Whitaker et al., 2017	6	Children	0	1	0	N/A	N/A	N/A	1	N/A	0	N/A	N/A	N/A	N/A

			De las Heras et al., 2020	1	Children	N/A	N/A	N/A	1	1	1	1	N/A	0	N/A	1	1	1	
			Parini et al., 2013	1	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Sun et al., 2022	42	Children	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Scalais et al., 2023	4	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		5,10-methylenetetrahydrofolate reductase deficiency	Tallur et al., 2005	2	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Disorders of folate metabolism	Methionine synthase reductase deficiency	Huang et al., 2024	1	Adults	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	
Neurotransmitter disorders	Gamma-aminobutyric acid neurotransmitter disorders	Succinic semialdehyde dehydrogenase deficiency	Philippe et al., 2004	2	Adults	1	1	0	N/A	N/A	N/A	1	N/A	N/A	1	N/A	1	N/A	
			Latzer et al., 2024	62	Children	1	1	0	N/A	N/A	N/A	1	1	N/A	1	N/A	1	1	
			Keller et al., 2021	16	Children	1	0	0	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	1	
			Philippe et al., 2004	2	Children and adults	1	0	0	N/A	N/A	N/A	1	1	N/A	N/A	N/A	1	1	
			Energy-related IMD																
Cell membrane carriers																			
Disorders of carbohydrate metabolism	Disorders of carbohydrate transmembrane transport and absorption	GLUT1 deficiency	Tornese et al., 2020	1	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
			Tzadok et al., 2014	8	Children	0	1	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	
			Alter et al., 2014	12	Children and adults	0	1	0	N/A	N/A	N/A	1	N/A	1	1	N/A	N/A	N/A	
			Byrne et al., 2011	2	Children	0	1	0	1	1	1	1	N/A	1	1	N/A	N/A	N/A	
			De Giorgis et al., 2019	25	Children and adults	1	1	1	1	1	1	0	N/A	1	1	N/A	N/A	N/A	
			Gumus et al., 2015	6	Children	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	
			Ito et al., 2011	6	Children	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	
			Koy et al., 2011	1	Children	0	0	1	N/A	N/A	N/A	N/A	1	1	1	N/A	N/A	N/A	
			Ragona et al., 2014	1	Children	0	1	0	1	1	0	N/A	N/A	1	1	1	N/A	N/A	

				Ramm-Petersen et al., 2014	6	Children and adults	1	1	0	1	1	1	1	N/A	1	1	0	N/A	N/A	
				Veggiotti et al., 2010	3	Adults	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	
				Scoppola et al., 2021	1	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	
				Barthold et al., 2023	8	Children	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
				Kolic et al., 2021	1	Children	0	0	1	N/A	N/A	N/A	0	0	N/A	1	N/A	0	0	
Cytoplasmic defects																				
Disorders of carbohydrate metabolism	Disorders of glycolysis	Glucokinase deficiency	Maiorana et al., 2021	3	Children	0	1	0	1	N/A	1	N/A	N/A	N/A	N/A	N/A	1	1		
Disorders of energy substrate metabolism	Disorders of creatine metabolism	Arginine:glycine amidinotransferase (AGAT) deficiency	Battini et al., 2017	4	Children	1	1	0	0	0	0	1	1	1	N/A	N/A	N/A	N/A		
			Edvardson et al., 2010	2	Adults	1	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
			Nouioua et al., 2013	2	Children	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
			Stockler-Ipsiroglu et al., 2015	16	Children and adults	1	1	0	N/A	N/A	N/A	1	N/A	N/A	1	N/A	1	1		
		Creatine transporter deficiency	Thurm et al., 2016	1	Children	1	0	0	N/A	N/A	N/A	1	1	N/A	1	N/A	1	1		
			Chilosi et al., 2012	5	Children	1	1	0	1	1	N/A	1	1	0	0	N/A	1	1		
Endocrine metabolic disorders	Disorders of insulin metabolism	ATP-sensitive potassium channel pore-forming subunit superactivity	Bowman et al., 2019	8	Adults	0	1	0	1	1	0	0	N/A	1	1	1	N/A	1		
		Primary congenital insulin deficiency	Bowman et al., 2019	4	Adults	0	0	1	0	0	0	0	N/A	0	0	0	N/A	0		
Mitochondrial defects																				
Disorders of carbohydrate metabolism	Disorders of gluconeogenesis	Pyruvate carboxylase deficiency	Baal et al., 1981	1	Children	0	0	1	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A		
Disorders of fatty acid and ketone body metabolism	Disorders of mitochondrial fatty acid oxidation	Medium-chain acyl-CoA dehydrogenase deficiency	Joy et al., 2009	38	Children	0	0	1	0	0	0	0	N/A	0	0	0	N/A	N/A		
			Wilcken et al., 2007	38	Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
		Short - chain acyl CoA dehydrogenase deficiency	Waisbren et al., 2008	14	Children	1	0	0	N/A	N/A	N/A	1	N/A	N/A	1	N/A	N/A	N/A		
		Very long-chain acyl-CoA dehydrogenase deficiency	Brown et al., 2014	8	Children	0	0	1	0	0	0	0	0	0	0	0	1	0		
Cox et al., 1998	1		Children	0	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0			

		Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	Strandqvist et al., 2015	8	Children	1	1	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
Disorders of mitochondrial DNA maintenance and replication	Disorders of mitochondrial nucleotide pool maintenance	Thymidine phosphorylase deficiency	Carod-Artal et al., 2007	1	Adults	0	1	0	1	0	0	0	0	0	1	1	N/A	N/A
Disorders of mitochondrial gene expression	Disorders of mitochondrial transcript processing and modification	2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency	Stepien et al., 2018	1	Children and adults	1	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nuclear-encoded disorders of oxidative phosphorylation	Disorders of complex IV subunits and assembly factors	Cytochrome c oxidase assembly factor 7 deficiency	Lyons et al., 2016	1	Children	0	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Other disorders of mitochondrial function	Disorders of mitochondrial protein quality control	Parkin deficiency	Benbunan et al., 2004	2	Adults	N/A	N/A	N/A	1	1	0	0	N/A	N/A	1	1	N/A	N/A

0=Preserved;
1=Altered; N/A=Not
Available