Psychomotor evaluation and non-invasive optical monitoring for comprehensive assessment of the benign external hydrocephalus syndrome

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Ph.D. DISSERTATION

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by

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A mio figlio Gabriele che mi ha dato la forza per scalare il picco piú ripido e raggiungere la vetta in questo lungo percorso…
che tu possa essere un sognatore e difendere sempre con coraggio quello in cui credi!

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GRAZIE...GRACIAS...THANK YOU...

The path traveled during these years of Ph.D. allowed me to broaden my educational and cultural horizons. This adventure represented for me not only a working challenge but also a personal growth. I can say I am a completely different person from the one I was before starting the PhD. I had the opportunity to improve my expertise in the clinical field as developmental disorders therapist and acquire new skills in the area of non-invasive optical technologies. The study was part of a European project (BitMap - Brain Injury and Trauma Monitoring using Advanced Photonics) that gave me the opportunity to travel and spread my research and know the leading experts in the field of optical technologies. Working in a reference hospital such as Vall d'Hebron, gave me also the chance of studying other pediatric diseases - that are not directly related to the objectives of the thesis and for this reason were not included - such as the traumatic brain injury (TBI), achondroplasia and craniosynostosis.

During this long path I met many people and I say a big "Thank you" to each one of them: starting from my supervisors who opened me the doors of the clinical research field and spent time to drive me making me learn and grow.

"Thanks" to my colleagues both at ICFO and Vall d'Hebron for the team work. Sometimes the work required us a big effort but together we could make it and many of you nowadays are an essential part of my life.

"Grazie" alla mia famiglia che mi è stata accanto in ogni momento e mi ha dato la forza di arrivare fino alla fine di questo percorso.

Especialmente, quiero decir “Gracias” a los niños y a sus familias por confiar y participar de forma activa en este proyecto. Sin vosotros este trabajo no hubiera sido posible.

LIST OF ABBREVIATIONS

ANS: autonomous nervous system

ASD: autism spectrum disorders

ASL: arterial spin labeled

BEH: benign external hydrocephalus

BESS: benign enlargement of subarachnoid spaces

BF: blood flow

BFI: blood flow index

CBF: cerebral blood flow

CBV: cerebral blood volume

CDIAP: Centre for Child Development and Early Intervention

CHD: congenital heart disease

CI: confidence interval

$CMRO_2$: cerebral metabolic rate of oxygen

CO_2: carbon dioxide

CPP: cerebral perfusion pressure

CSF: cerebrospinal fluid

CT: computer tomography

CW: continuous wave

DCS: diffuse correlation spectroscopy

DOS: diffuse optical spectroscopy

EI: Evans index

FD: frequency domain

FN: false negative

FP: false positive

GLH: general linear hypotheses

GLM: general linear model

H_2O: water

Hb: deoxy-hemoglobin

Hb-D: oxy- hemoglobin and deoxy-hemoglobin difference

HbO_2: oxy-hemoglobin

HC: head circumference

HI: head injury

ICP: intracranial pressure

ICREA: Institució Catalana de Recerca i Estudis Avançats

IPI: intracranial pressure index

LDF: laser Doppler flowmetry

LHR: likelihood ratio

LME: linear mixed effect

MLR: multiple logistic regression

MRI: magnetic resonance imaging

NHP: non-human primates

NIRS: near infrared spectroscopy

O_2: oxygen

OEF: oxygen extraction fraction

OFC: occipitofrontal circumference

OR: odds ratio

PI: pulsatility index

R: resistance

REM: rapid eye movement

RI: resistance index

RNN: reccurent neural network

SAH: subarachnoid hemorrhage

SDS: source detector separation

StO_2: tissue oxygen saturation

TBI: traumatic brain injury

TCD: transcranial Doppler

TD: time domain

THC: total hemoglobin concentration

TN: true negative

TOI: tissue oxygenation index

TP: true positive

TRS: time-resolved spectroscopy

VHIR: Vall d'Hebron Research Institute

VHUH: Vall d'Hebron University Hospital

WPPSI: Wechsler preschool and primary scale of intelligence

ΔP: difference inflow and outflow pressure

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ABSTRACT

The present thesis is the result of a collaboration between the Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain and ICFO - Insitut de Ciències Fotòniques, Barcelona, Spain.

The work is focused on the study of psychomotor and cerebral hemodynamics implications of the benign external hydrocephalus (BEH) syndrome in infants. The disease is related to an alteration of the cerebrospinal fluid dynamics leading to intracranial pressure (ICP) alterations. BEH is a rare syndrome that is object of debate since it is considered from the majority of clinicians as a benign pathology that resolves spontaneously when the child grows. However some children present difficulties in the gross motor, language and learning area when they are older. In parallel, ICP abnormalities leading to the appearance of pathological phenomena like the so-called B-waves that can potentially lead to severe sequelae if not treated are also presented. The thesis is developed on two related fronts: from one side investigating the psychomotor abilities of children affected by BEH and from the other, the application of non-invasive optical techniques in a sub-cohort requiring an ICP monitoring. The general objective of this work is to shine light on some controversial aspects of BEH such as the psychomotor and neurological problems leading to cerebral hemodynamics sequelae that are still not well known.

The psychomotor development of a cohort of children was assessed using standardized tools such as the Bayley scales (version III and IV) and the Peabody Developmental Motor scales (version 2). The psychomotor assessments revealed the presence of gross motor and language delay in some children that require attention. Non-invasive optical monitoring was

performed in some children simultaneously with the invasive monitoring which is commonly performed in clinical practice. Specifically, a hybrid near-infrared spectroscopy device based both on time-resolved spectroscopy (TRS) and diffuse correlation spectroscopy (DCS) has been built at ICFO (ST, MK and JF) and has been used in this study thus obtaining unique information about cerebral hemodynamics in children affected by BEH. Due to their noninvasiveness, these optical technologies represent an attractive method to be applied in the pediatric field. The optical monitoring has allowed collecting data about the tissue oxygen saturation (StO_2) and the cerebral blood flow (CBF). Analyzing the behavior of these parameters, I have found out significant variations of optical parameters during the ICP B-waves and I have visually detected oscillations of the blood flow index (BFI) similar to the ICP ones. The results are promising and give the hope that in future the invasive methods will be less needed and could be complemented by non-invasive techniques.

In conclusion, I tried to put an additional seed in clinical research about the study of a rare syndrome. The identification of the sequelae in terms of psychomotor development and possible implications of the cerebral hemodynamics can help to better understand BEH and adapt the treatment to each patient.

RESUMEN

La presente tesis es el resultado de una colaboración entre la unidad de investigación de Neurocirugía y Neurotraumatología (UNINN) del Hospital Universitario Vall d'Hebron (HUVH) y el grupo de óptica médica del Instituto de Ciencias Fotónicas (ICFO). Trabajar en esta tesis ha supuesto para mí la posibilidad de combinar mi experiencia en el campo clínico como terapeuta de trastornos del desarrollo y adquirir nuevas habilidades en el área de las tecnologías ópticas no invasivas. He estudiado el desarrollo psicomotor y las implicaciones en la hemodinámica cerebral en bebés afectados por el síndrome de hidrocefalia externa benigna (HEB), que está relacionado con una alteración de la dinámica del líquido cefalorraquídeo que provoca alteraciones de la presión intracraneal (PIC). La HEB es un síndrome raro que es objeto de debate, ya que se considera una patología benigna que se resuelve espontáneamente cuando el niño crece. Sin embargo, algún niño presenta dificultades residuales en el área de la motricidad gruesa, el lenguaje y el aprendizaje. En algunos de estos niños, anomalías de la PIC, que implican la aparición de fenómenos patológicos como las ondas B, pueden conllevar secuelas severas, si el niño no se trata. La tesis se centra, por un lado, en el estudio de las habilidades psicomotoras de estos niños y, por otro, en la aplicación de técnicas no invasivas en un grupo que requiere la monitorización de la PIC. El objetivo general de este trabajo ha sido profundizar en algún aspecto controvertido de la HEB como son los problemas psicomotores y neurológicos que aún no son bien conocidos. Se ha llevado a cabo la evaluación del desarrollo psicomotor de una cohorte de niños utilizando herramientas estandarizadas como las escalas de Bayley (versión III y IV) y las escalas motoras de desarrollo de Peabody (versión 2). La evaluación psicomotora ha revelado en un porcentaje de niños con HEB la presencia de un retraso en las habilidades grueso-motoras y en el lenguaje

que han requerido un estudio más detallado y tratamiento específico. En algunos niños se ha realizado una monitorización óptica no invasiva simultánea a la monitorización invasiva de la PIC. En concreto, mis compañeros del ICFO (ST, MK y JF) han desarrollado un dispositivo de *near-infrared spectroscopy* híbrido basado en la combinación de dos técnicas de óptica difusa, *time-resolved spectroscopy* (TRS) y *diffuse correlation spectroscopy* (DCS), que se ha utilizado en este estudio para obtener información única sobre la hemodinámica cerebral de los niños afectados por la HEB. Debido a su carácter no invasivo, las tecnologías ópticas representan un método atractivo para ser aplicado en el campo pediátrico. La monitorización óptica ha permitido recoger datos sobre la oxigenación cerebral (StO_2) y el flujo sanguíneo cerebral (CBF) de estos niños. Analizando el comportamiento de estos parámetros, he encontrado variaciones significativas durante las ondas B de la PIC y he detectado visualmente oscilaciones del índice de flujo sanguíneo similares a las de la PIC. Los resultados son prometedores y hacen esperar que en el futuro los métodos invasivos no serán tan necesarios y puedan ser complementados por técnicas no invasivas. En conclusión, he intentado poner una semilla adicional en la investigación clínica de un síndrome poco frecuente. La identificación de las séquelas en términos de desarrollo psicomotor y las posibles implicaciones de la hemodinámica cerebral puede ayudar en entender mejor la patología y definir la estrategia más adecuada para tratar cada paciente.

PREFACE

The thesis is presented as a collection of papers to obtain the academic degree of Doctor from the Universitat Autònoma de Barcelona. The work has been realized at the Department of Neurosurgery and Pediatric Neurosurgery Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus and Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain (UNINN, www.neurotrauma.com). In 2005, the UNINN has been recognized as "Quality Research group" by the Generalitat de Catalunya (Departament d'Universitats, Recerca i Societat de la Informació) with periodical renewal, the last in 2022 (2021 SGR 00810). The thesis is part of a collaboration with the Medical Optics group of ICFO - Insitut de Ciències Fotòniques, The Barcelona Institute of Science and Technology, Barcelona, Spain. The authors of the studies related to the present thesis declare no conflict of interest. The work has been supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 675332 (BitMap: Brain Injury and Trauma Monitoring using Advanced Photonics) and by the European Union's Horizon 2020 research and innovation programme grant agreement No 101017113 (TinyBrains) and No 101016087 (VASCOVID); Fondo de Investigación Sanitaria (Instituto de Salud Carlos III) grant PI18/00468; Fundació CELLEX Barcelona, Fundació Mir Puig, Agencia Estatal de Investigación (PHOTOMETABO, PID2019106481RBC31/10.13039/501100011033), the "Severo Ochoa" Programme for Centers of Excelence in R&D (CEX2019-000910-S), the Obra social "La Caixa" Foundation (LlumMedBcn), Generalitat de Catalunya (CERCA, AGAUR-2017-SGR-1380, RIS3CAT-001-P-001682 CECH), FEDER EC and LASERLAB EUROPE V (EC H2020 No 871124),

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INTRODUCTION

1 INTRODUCTION

William Kamkwamba, the boy who harnessed the wind creating currents of electricity and hope, tells us: "*After a few days of rain, the seedlings will push through the soil and unfold their tiny leaves. Two weeks later, if the rain is still good, we then carefully apply the first round of fertilizer, because each seedling requires love and attention like any living thing if it's going to grow up strong."* . This sentence appears fascinating since it perfectly describes all the needed elements for typical growth. The child is the center with his own abilities (seedling) but there are other elements influencing his growth. The environment (rain and fertilizer), which should give him/her what he/she need to develop his/her full potential and the love and attention he/she requires, someone who believes and motivates him/her. Unfortunately, not always all these elements are present; for example, unfavorable events during the prenatal period or the first days of life, or a deprived environment can affect the child's development during the first years of life. So, what happens if one or more of the mentioned elements fails? Most probably the child's development will deviate from the typical path. In such cases, the clinicians need to take into account all the elements involved; they need to know the child's limitations and possibilities and evaluate the environment to find the best tools for his/her development. They also need to have proper knowledge of the disease affecting the child and the possibilities and limitations related to its natural history.

These introductory lines are necessary since the thesis is focused on the study of the neurological sequelae of the benign external hydrocephalus (BEH) in terms of psychomotor development and cerebral hemodynamics. BEH is a syndrome affecting the child during the first years of life. The crucial point in the evaluation of these infants is that BEH pathophysiology is not completely described so there are not clear guidelines about its

management. Since the majority of the literature claims that it is a benign pathology that resolves spontaneously after the first years of life, clinicians are more prone to choose a conservative approach and to not treat these children. There is even a controversy about the name used to indicate the syndrome and about the fact it can be idiopathic or not. Looking into the literature many terms (e.g. external hydrocephalus, benign enlargement of the subarachnoid spaces, idiopathic macrocephaly, extraventricular obstructive hydrocephalus, benign external hydrocephalus, benign extra-axial fluid collections), have been used. In the present thesis, we use the term benign external hydrocephalus since we consider it is the most appropriate to describe this syndrome. We believe in fact, that BEH is initially characterized by the dilation of the subarachnoid spaces and once the fontanelles and sutures are closed, by ventricular enlargement.

BEH has been defined as macrocephaly or a rapidly increasing head circumference (HC), associated with enlarged subarachnoid spaces, especially overlying the frontotemporal lobes, and normal or moderately enlarged ventricles[1,2]. It is more common in boys than in girls and frequently associated with a family history of macrocephaly.

Another confounding factor is that BEH can be idiopathic or associated with genetic syndromes such as mucopolysaccharidoses, achondroplasia, Sotos syndrome, and glutaric aciduria type I[3]. Acquired disorders related to BEH can be complications of prematurity (premature exit from the neonatal ICU requiring ventilatory support), traumatic brain injury, and intraventricular hemorrhage[1]. We need to remark that when it is an associated condition of another primary disease, the clinical manifestations are conditioned by the primary pathology affecting the brain. For the aim of the present thesis, we excluded children presenting genetic or acquired disorders when we focused on the child's psychomotor assessment (article 1).

Instead, when we were interested in studying the pathophysiology of the syndrome, we included children with genetic disorders in the cohort since their condition was not influencing BEH expression from the cerebral hemodynamics perspective (article 2).

In the idiopathic form of BEH, the presence of psychomotor delay has been considered as a transient self-limiting condition, related to familiar macrocephaly and affecting just a small percentage of this population[4–6]. However, the association with permanent developmental delays and with an increased risk of subdural hematoma, have been described in some patients. At the short-term follow-up, hypertonia, hypotonia, motor problems, attention deficit, and hyperactivity have been reported[7–9]. At the long-term follow-up, gross motor and speech delays, reduced performance in attention tasks, learning problems in reading and mathematics, and psychiatric diseases have been diagnosed in almost 20% of BEH patients[10]. Despite these data, there are still few studies on the effects of BEH on the psychomotor development of these infants both at short and long-term.

The thesis supports the idea that BEH can be associated with a delay in the acquisition of developmental abilities due to its pathophysiology. Children affected by BEH in fact, present an alteration of the cerebrospinal fluid (CSF) dynamics which causes alterations in the intracranial pressure (ICP) that, persisting overtime, could lead to permanent developmental alterations. There are several theories about BEH etiology. The main one states that it is related to underdeveloped or a partial or complete block in the arachnoid granulations and, therefore, a problem in the CSF absorption together with a non-closed container how is the skull of infants[4,11]. An additional pathophysiological theory is that in some cases an elevated venous pressure may be the cause of an elevation in CSF pressure, which enlarges the skull relative to the brain size while the fontanelles and sutures are open, thus creating widened subarachnoid spaces[12]. Due to the reasons raised in the

previous lines, the general attitude in the management of the syndrome is conservative that means that these children are just followed with periodical revisions but they do not receive any treatment. However, we posit that the cerebral hemodynamics, oxygenation and metabolism are altered by this condition, especially in the presence of ICP alterations. This would call for an active management based on the ICP monitoring and, according to the results, on the placement of a ventriculoperitoneal shunt.

The present thesis aims to investigate the psychomotor development of children affected by BEH and cerebral hemodynamics implications. In fact, a part from the short and long term psychomotor delay described in literature, in some cases this syndrome can be associated with an alteration of the intracranial pressure (ICP). The ICP can be altered both quantitatively (i.e. mean ICP is higher than normal value) and qualitatively (i.e. the presence of pathological ICP waves). A pathological ICP could bring, if not treated, to severe neurological sequelae. In order to reach this general objective, from one side, the psychomotor assessment of the children through standardized developmental scales allowed us to better define their neurodevelopmental profile. On the other side, the application of non-invasive optical technologies revealed innovative information about cerebral hemodynamics.

Two main objectives were sought:

1. the detection of developmental delay and the identification of the most compromised areas through a longitudinal neurological and psychomotor assessment;
2. the collection of information about cerebral hemodynamics by looking at the ICP alterations through a non-invasive optical method.

Thanks to this kind of research, BEH syndrome could be better described; it is fundamental to define potential psychomotor and neurological sequelae

associated with this syndrome in order to identify children requiring treatment and act as soon as possible.

The main motivation of the thesis is related to the elements cited by William Kamkwamba[13]: knowing the child's possibilities and limitations, his/her environment to intervene as soon as possible and give him/her the instruments to learn during the function's appropriate critical period for cerebral development. Having a clearer understanding of the disease and intervene according to the child's needs, might improve the quality of life for him/her and the caregivers.

Another important element to take into account is the timing of the intervention. Brain development begins few weeks after conception and is thought to be complete by early adulthood. The basic structure of the brain first develops during the prenatal period and early childhood, and the formation and refinement of neural networks continue over life. Brain's functions do not develop at the same time nor do their developmental patterns follow the same time frame. Although basic sensation and perception systems are fully developed by the time children are two-four years old, other systems such as those involved in memory, decision making, and emotion continue to develop during childhood. The bases of many of these abilities, however, are constructed during the early years. Anatomical processes and experience are the first elements involved in normal brain development. However, experiences in the early years of childhood affect the development of the brain in a way dramatically higher than in older years. The brain, in fact, is much more sensitive to events experienced in the first few years of life than in later years. The plasticity of the brain allows much of the learning that occurs during this period. The sensitive period is effectively extended by specific experience[14]. When a pathological condition like BEH appears during the first years of life it is very important to detect it as soon as possible

and, for the reasons raised above, to intervene with the appropriate clinical and rehabilitation strategies.

1.1 BACKGROUND OF BENIGN EXTERNAL HYDROCEPHALUS

The benign external hydrocephalus (BEH) has been defined as an idiopathic condition in infants characterized by a large or rapidly increasing HC and radiologically confirmed by enlarged subarachnoid spaces at the frontal and temporoparietal level associated with normal ventricles or mild ventriculomegaly (Figure 1)[9]. The first definition was made by Dandy in 1914 who presented a classical paper reviewing the clinical presentation and experimental models on hydrocephalus[15]. Dandy later used the same term in 1946 to describe a 27-months-old boy with what would later come to be known as subdural hygroma[16]. The so-called 'benign enlargement of the subarachnoid spaces' is created for the first time in 1981 by the neurologist Laura Ment[1].

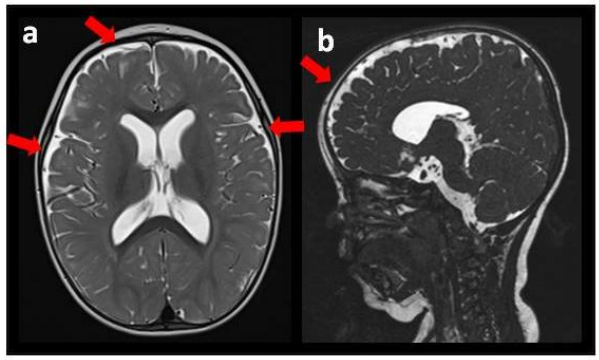

Figure 1. The magnetic resonance image (MRI) axial (a) and sagittal (b) T2-weighted images of a 25 month-old male are presented. The baby was born at 32 weeks of gestational age through a cesarean because of corioamniotis. After the birth he had cardiac and pulmonary complications. The neurological evaluation showed an increase in the head circumference. The image shows the typical enlargement of the subarachnoid spaces in the frontal and temporal regions (red arrows) in infants with benign external hydrocephalus, in this case associated with a moderate increase in ventricular size.

BEH affects the 0.5-0.8 per 1000 live and stillbirths, it is more frequent in boys than in girls and is frequently associated with complications of prematurity, such as bronchopulmonary dysplasia, mechanical ventilation and extracorporeal membrane oxygenation[1,17]. It can also be associated with a positive family history of macrocephaly[18,19]. BEH can be idiopathic or associated with some genetic syndromes such as mucopolysaccharidoses, achondroplasia, Sotos syndrome, and glutaric aciduria type I, among others[3].

1.1.1 Etiopathology and physiopathology

The Monroe-Kellie doctrine states that "*the cranium is a closed box with essentially non-compressible contents of approximately 80% brain tissue, 10% blood, and 10% cerebrospinal fluid. These percentages remain constant through intrinsic regulatory mechanisms, but an increase in anyone or more of the contents requires compensation and a decrease in the others."*[20]. Specifically, the CSF has an important role in the protection of the brain working as mechanical support, delivering nutrients and removing metabolites, and allowing the circulation of nutrients. It is produced mainly in the choroid plexus in the ventricles, exits into the basal cisterns, and goes into the subarachnoid spaces[3]. The CSF circulation and the creation of the main structure involved in its dynamics start during the prenatal period. At 8 weeks of gestation, the circulation of the CSF is already established, at 32 there is a decrease in the size of the subarachnoid spaces. Around 6-8 months of age the granulations (arachnoid villi), develop; they are small protrusions of the arachnoid mater (the thin second layer covering the brain) into the outer membrane of the dura mater (the thick outer layer). The granulations protrude into the dural venous sinuses of the brain and allow CSF to exit the subarachnoid space and enter the bloodstream. Around 2 years of age, the capacity of drainage can handle 2-4 times the production. Finally, around 3 years of age, the growth of the arachnoid villi leads to the formation of

Pacchionian bodies. A basic image of the main structures involved in CSF circulation is given in Figure 2.

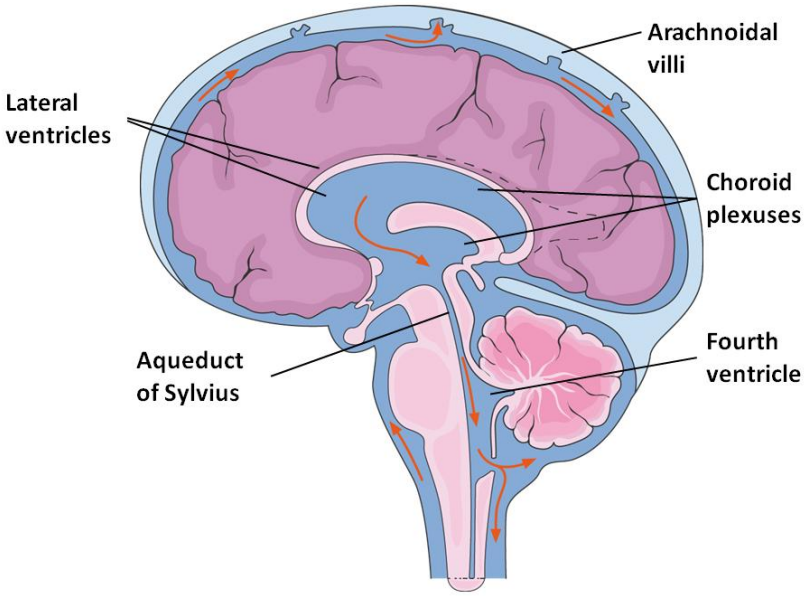

Figure 2. The red arrows show the cerebrospinal fluid (CSF)'s pathway. After its production, it passes from the lateral ventricles through the third and IV ventricle to the subarachnoid spaces. Then, it is reabsorbed into the dural sinus through the arachnoid villi. The illustration is inspired by SMART - Servier Medical Art (Anatomy and The Human Body | Nervous system | Brain | Cerebrospinal fluid).

The etiopathology of BEH has been related to the dilatation of the subarachnoid spaces in early stages preceding ventricular enlargement that occurs later when the fontanelles and sutures close, converting the infant's cranium to a closed and rigid container. For some authors, the increase in the size of the frontal subarachnoid spaces is the result of the gravitational force exerted by the developing brain contained inside a non-rigid cranium partially opened to the atmosphere[4,5]. The presumed pathophysiology of BEH

suggests that a partial or complete block in the arachnoid granulations and, therefore, in the CSF absorption is the main disturbance together with a non-closed container[4,11]. An additional pathophysiological theory is that in some cases an elevated venous pressure may be the cause of an elevation in CSF pressure, which enlarges the skull relative to the brain size while the fontanelles and sutures are open, thus creating widened subarachnoid spaces[12].

1.1.2 Clinical features and diagnosis

The diagnosis of BEH is usually made during the first year of life. The majority of the patients with suspected BEH are referred due to a head circumference (HC) that has exceeded the growth rate that can be anticipated by standard growth charts. These infants are generally healthy in appearance and do not show any signs of increased ICP. Neurologic examination is usually, but not always, normal. A clinical evaluation is performed to make the diagnosis according to the clinical features and radiological studies[21,22]. The pediatric neurosurgeon takes into account the presence of clinical symptoms, the family history, and the developmental trajectory of the child. The main clinical features are the presence of frontal bossing which means a prominent forehead and the presence of macrocephaly. It is described as a HC above the 97.5th percentile according to the study population nomogram. In the past, different criteria were used to define the macrocephaly: a HC greater than 95th percentile on the standard growth curve or circumference less than or at the 95th percentile, but which had crossed at least two percentile lines on the standard growth curves and radiographic evidence on CT of unusually prominent subarachnoid space with or without some degree of ventricular dilation present during the time of head growth[4]. Pettit suggested defining a child as macrocephalic when the initial occipitofrontal circumference (OFC) was greater than the 98th percentile or when periodic

HC measurements reveal an acceleration of head growth "crossing" the normal curve or head growth in the first two situations continues above but parallel to the 98th percentile.

However, in some infants, the macrocephaly is not present, but they have a rapidly increasing HC during the first year of life (at least crossing two percentiles) associated with enlarged subarachnoid spaces and with normal ventricular size (Evans' Index < 0.30) or mild ventriculomegaly (Evans' Index ≥ 0.30 and ≤0.35). The Evans' Index (EI) is calculated as the maximum width between the frontal horns of the lateral ventricles and the maximum transverse inner diameter of the skull at the same axial slice in the computerized tomography (CT) scan and magnetic resonance imaging (MRI) and in the same coronal slice in transfontanellar ultrasound (Figure 3)[21,22].

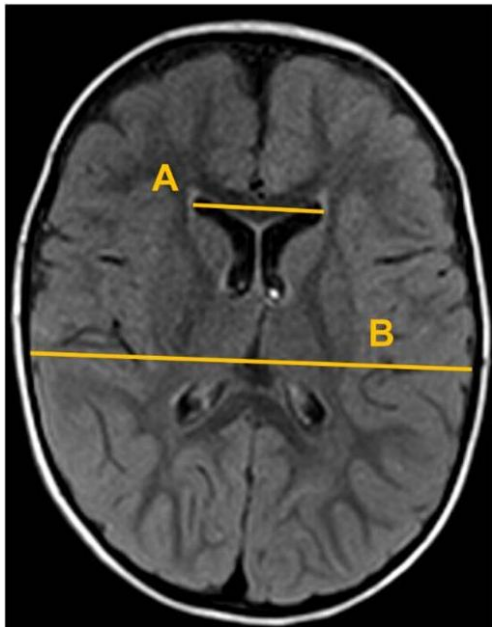

Figure 3. Example of Evans' Index calculation in a 33 months-old female presenting a rapid growth of the head circumference. The Evans' Index in this patient is 0.29 (A/B).

When performing the neuroimaging study other important information are obtained. The size of the extraventricular CSF compartments is measured along the frontal convexities at the coronal slices in transfontanellar ultrasound, CT, or MRI to calculate: the craniocortical width, the sinocortical width (the distance from the lateral wall of the superior sagittal sinus to the surface of the cerebral cortex), and the anterior part of the interhemispheric fissure. The upper limits of a normal craniocortical width range were defined by Zahl et al to be from 4 to 10 mm in infants <1 year of age, and from 3.3 to 5 mm in neonates[9]. The defined upper limit of the normal interhemispheric fissure width ranges from 6 to 8.5 mm, whereas a comparable spectrum for the sinocortical width is from 2 to 10 mm. Consequently, to establish the diagnosis of BEH at least one of three measurements of the frontal subarachnoid space has to be greater than 10 mm.

In order to have complete information, the parents should be asked about the presence of clinical symptoms that could be related to an increased ICP such as frequent headaches, frequent awakenings during the night, irritability, nausea, or vomiting. Another factor to take into account is familial history. Several families have members with external hydrocephalus and benign macrocephaly[4]. The HC of the parents should be also measured, to classify them as macrocephalic if they exceed the 97.5th percentile of the reference studies for the studied population. The graphic of the head circumference of a macrocephalic child is shown in Figure 4.

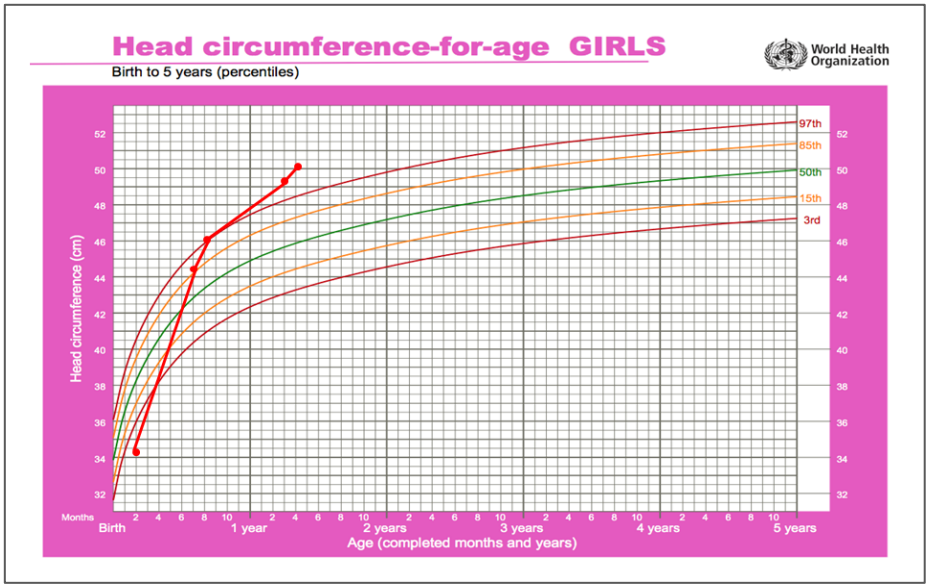

Figure 4. The graph has been created by the World Health Organization in 2009 and represents the standard growth of the head circumference (HC) in girls. It shows the percentile associated with the cm with respect to age. It is used in the common clinical practice to visually show the HC growth of children. The red curve has been created according to the HC measurement of a girl affected by BEH visited at our hospital at different age points. It shows an increase of HC starting from the first month of life and an HC above the 97th percentile. It means a deviation from the standard population curve that is one of the diagnostic criteria in BEH and drives clinicians to take into account a possible intervention.

Even though BEH is considered a benign pathology and the general attitude is a conservative management, short and long-term effects on psychomotor development have been described in literature. The association with permanent developmental delays and with an increased risk of subdural hematoma have also been found in some patients[23,24]. At the short-term follow-up, hypertonia, hypotonia, motor problems, attention deficit, and hyperactivity have been reported[3,8,10,25]. At the long-term follow-up, gross motor and speech delays, reduced performance in attention tasks, learning problems in reading and mathematics, and psychiatric diseases have been

diagnosed[2,9,26]. Several studies, including a total of 196 patients, have followed children with BEH for 2–5 years; of these, about 17% were described as having an abnormal psychomotor development at last follow-up[9]. In literature, there are still few studies on the effects of BEH on psychomotor development. In the next paragraph the debate about BEH prognosis will be presented.

1.1.2.1 Controversies about the "benignity" of BEH

BEH is generally considered a "benign", self-limiting condition related to familiar macrocephaly that does not require any intervention since it resolves spontaneously with age. However there is an open debate about the long-term resolution of the neuroradiological findings, the evolution of the macrocephaly and whether or not these children have a normal psychomotor development compared with their healthy peers (*see section 4.2 ARTICLE 1)*. Many authors have raised concerns about the "benignity" of BEH because although the majority of children do well in long-term, a considerable number may present psychomotor delays. Prassopoulos et al affirmed that BEH usually appears with macrocephaly or rapid head growth in infants and it is associated with minor neurological disturbances, such as mild gross motor delay or symmetrical hypotonia, but overall it has a good developmental prognosis[27]. Mild to moderate hypotonia has been reported in 30-45% of patients included in different studies[5,8]. Govaert et al reported that mild developmental delay or hypotonia may persist after the first years of life[28]. Halevy et al. supported the idea that external hydrocephalus is generally a benign phenomenon that is not necessarily associated with developmental difficulties or, it is just associated with transient delays due to the head weight or to the presence of hypotonia[5]. A reflection should be made on the presence of macrocephaly and hypotonia since they could cause delay in the acquisition of gross motor abilities such as sitting, crawling or walking. Because of this, some child may need to follow a rehabilitation program as

soon as the problem is identified. Moreover, BEH children may present residual deficits that interfere with intellectual development and hinder the child's acquisition during schooling. Although most BEH infants appeared normal around 2 years of age, it is not known whether they will have completely normal outcomes when older, due to a lack of long-term follow-up studies in large series of patients. The good prognosis of BEH patients was first questioned by Laura Ment who reported that in some cases BEH is associated with neurological dysfunction[1]. Pascual-Castroviejo et al described a wide profile of residual problems such as motor coordination difficulties, attention deficit, and/or hyperactivity, accompanied by discrete hypotonus in most of the patients[10]. Yew et al reported that 21% of their 99 external hydrocephalus patients aged 5 to 12 years showed developmental delay: specifically, 4% verbal, 20% gross motor, and 4% fine motor delay[29]. In the long-term follow-up, gross motor delay persisted in 5 patients, verbal delay in 2, and 6 children showed a language delay *ex novo*. Muenchberger et al detected the presence of gross motor delay at the first assessment and language delay at the follow-up; they also reported the presence of attention problems at the long-term follow-up[30]. Nickel and Gallenstein also demonstrated the presence of persistent or new verbal delay[31]. The review of Zahl et al[3] showed that although most of the papers reported children's development to be normal, a large number of them were affected by transient or long-term psychomotor delay[9]. In this study, 17% of 196 patients followed during 2–5 years, presented an abnormal psychomotor development at last follow-up. Moreover, Shen et al showed through magnetic resonance imaging that in children from 6 to 24 months the presence of benign enlargement of subarachnoid spaces (BESS) correlates with the risk of developing autism spectrum disorders (ASD). Infants who developed ASD had 20% greater extra-axial fluid than normal infants at 6-9 months, 33%

greater fluid at 12-15 months, and 22% at 18-24 months. These infants presented a significantly larger HC across all ages[33].

Another risk associated with BEH and described in literature is to present a subdural hematoma spontaneously or as a result of accidental injury[24]. This introduces another controversial aspect when evaluating a child with a subdural hematoma that leads to the suspicion that there has been a non-accidental trauma[24]. The differential diagnosis between BEH and non-accidental trauma is fundamental for the management of the child and the legal implications of the caregivers.

1.1.2.2. Alterations of the intracranial pressure (ICP)

We extensively show in our second paper that in some cases, BEH is characterized by abnormalities in CSF dynamics detectable as quantitative and qualitative alterations of ICP recordings. These alterations may induce changes in the cerebral oxygenation and blood flow thus causing neurological sequelae (*see section 4.2 ARTICLE 2)*. In order to detect CSF abnormalities the ICP mean value is not sufficient but the ICP time traces should be analyzed by an expert neurosurgeon. Specifically, of particular interest are the A- and B-waves. Regarding the ICP mean value, it is important to point out that the thresholds are different in children than in adults. Some authors suggested defining as pathological a mean ICP >10 mmHg for children younger than 5 years, or >5 mmHg for babies younger than 2 years[34].

As suggested by Tejada et al, ICP could be seen just like a number that should remain within certain limits but, going beyond, it can be analyzed by studying the presence of qualitative pathological phenomena such as the so-called A- and/or B-waves, first defined by Lundberg[35]. Specifically, the presence of A- or B-waves is considered to be indicative of reduced intracranial compliance and appears mainly during the REM (rapid eye movement) sleep when there is an increase in brain metabolism demand since

the CSF production is twice that of the day[36,37]. A- or plateau waves have been described as ICP elevations at least 20 mm Hg above the resting line, with abrupt onset and end, and lasting between 5 and 20 minutes. Lundberg defined the B-waves as short repeating elevations of ICP, occurring at a frequency of 0.5-2 ICP waves/minute, lasting at least 10 minutes[38]. Subsequently, the B-waves have been classified according to their amplitude in high (equal or above 10 mmHg) or low (below 10 mmHg) amplitude[35,38]. A graphical example for each type of wave is shown in Figure 5.

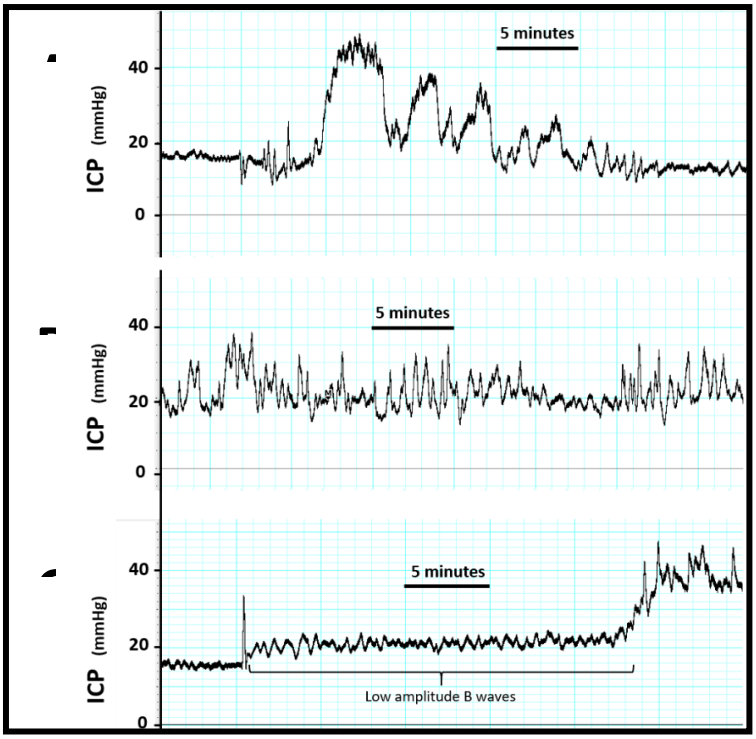

Figure 5. Representation of waves according to Lundberg description; A) shows the presence of several plateau waves, B) and C) show respectively high and low amplitude B-waves patterns. The figure has been freely created by the supervisor of the thesis (Dr Maria A Poca) in order to show in a didactic way the different type of

waves.

The first hypothesis to explain the origin of the B-waves (the most frequently found in BEH) etiology was that they are due to cerebral blood flow (CBF) fluctuations secondary to respiratory variations during abnormal breathing patterns; another hypothesis was that they are due to vasomotor waves of the regulating vessels in the cerebral circulation which are independent of respiration. The last hypothesis is that these vasomotor waves produce fluctuations in CBF and cerebral blood volume (CBV) reflected in ICP tracing, more prominently when intracranial compliance is low. We have a contribution in this debate that has been published and is part of the papers presented in this thesis (*see section 4.2 ARTICLE 2)*.[39]

1.1.3 Treatment

There is general agreement about the fact that the attitude at diagnosis of BEH should be conservative meaning that these children should just be followed up by the clinician without any intervention. Nevertheless, some children presents an elevated ICP and requires surgical treatment with the placement of a ventriculoperitoneal shunt[40]. In presence of clinical symptoms of increased ICP (such us recurrent headaches, irritability, or vomiting), ICP is invasively monitored. The ICP monitoring gives information about the mean ICP and the presence of pathological waves and it is necessary to support the decision-making for a surgical intervention[41]. In our study, the presence of mean ICP > 15 mmHg and/or the presence of A-waves (defined as ICP elevations at least 20 mmHg above the resting line, with abrupt onset and ending, and lasting between 5 and 20 min) and/or more than 20% of B-waves in the total duration of the nocturnal recording time were considered to be criteria for shunting following standard procedures of the hospital. The ICP monitoring findings are very important in the decision of shunt

implantation, providing a safe mean of investigating pediatric patients and valid information upon which to base the surgical management. The ICP monitoring leads in fact, to a more accurate patient selection and, therefore, avoids implanting unnecessary shunt[42].

In infants, clinicians can monitor indirect signs of potential increased ICP by measuring the HC and exploring the fontanelles, until the skull is closed. After this, increased ICP can be detected on fundoscopy when papilledema is present. However, these methods are not always so reliable, since ICP could be raised without papilledema[43]. The most effective way is to monitor ICP overnight[44]. Nowadays, in fact, the only way to verify maintained ICP increase or the presence of pathological ICP waves is the invasive monitoring, used, among others, in pediatric patients in cases of complex hydrocephalus, craniosynostosis, or shunt failure. As stated before, especially in BEH patients, when performing the ICP monitoring, the most appropriate way for deciding if a treatment is necessary is to look not just at the mean ICP but also at the qualitative alterations (mainly the B-waves) that could appear during sleep. The risks associated with the ICP monitoring are the ones of a procedure for which something is inserted into the brain, i.e. hemorrhage and infection. There is also a risk of the device's failure from surgical technique when placing it or the sensor being accidentally explanted by the patient[45].

1.1.3.1. ICP monitoring and shunting criteria

There is an open debate about the need for an ICP monitoring of these children. As previously mentioned, the general attitude is conservative. Generally, the surgical treatment is suggested based on clinical symptoms, HC, and radiological findings[41]. In a minority of cases, invasive ICP monitoring is performed and the decision-making for surgery is based on the

mean ICP calculation and visual detection of the A-waves or, more frequently, B-waves. The ICP monitoring has been used as diagnostic aid just when there is confusion about the associated signs and symptoms[42]. Generally, an intraparenchymal sensor was used to continuously record the ICP. However, the use of an epidural sensor reduces the risks of this diagnostic maneuver[46]. Preserving the dural covering intact not only reduces the rate of hemorrhagic complications but also minimizes the risk of infection. Furthermore, epidural pressure monitoring is a very useful method for patients requiring ICP monitoring for long periods, such as those with suspected normal pressure hydrocephalus, suspected shunt dysfunction, monitoring of ventriculostomy patency.

To evaluate the need for shunt's placement in children, a mean ICP of 10 mmHg has been considered the normal upper limit, a mean ICP between 10 and 15 mmHg has been defined as borderline and above 15 mmHg abnormal. Even though the analysis of the ICP recording may present some limitations and not be indicative of the need for surgery. For example, many patients present a borderline value. So, even if increases in ICP may play an important role in the pathophysiology, there is not a standard threshold. In pediatric patients, an elevated frequency of ICP elevations above 20 mmHg has been found, despite a borderline mean ICP between 10 and 15 mmHg[41]. Eide et al proposed to present the ICP curve as numbers of different levels and durations to standardize the data and compare between and within patients[41].

The ICP criteria for abnormal CSF dynamics used in our department were described in adults in 1991[47]. Generally, the presence of mean ICP > 15 mmHg and/or the presence of A-waves and/or more than 20% of B-waves in the nocturnal recording time are considered criteria for shunting. A- or plateau waves have been described as ICP elevations at least 20 mm Hg above the resting line, with abrupt onset and end, and lasting between 5 and

20 minutes. B-waves have been described as short repeating elevations of ICP, occurring at a frequency of 0.5-2 ICP waves/minute, lasting at least 10 minutes with high (equal or above 10 mmHg) or low (below 10 mmHg) amplitude[35,38].

1.2 NON-INVASIVE OPTICAL TECHNOLOGIES

During the past years, several non-invasive techniques have been developed to study cerebral hemodynamics. Among them, CT, MRI, transcranial Doppler (TCD), audiological or ophthalmological methods, are the most used. The disadvantages of these techniques are the elevated cost, the fact that they do not allow continuous measurement, and that they are operator-dependent[42,48–50]. A relatively new technique that has given a significant contribution in clinical research during the last years, is the family of techniques based on near-infrared (~650-950nm) diffuse light. They are attractive methods since they are safe, portable, and allow to measure real-time the oxygenation of the brain just placing soft probes on the forehead[51].
In the next section, near infrared spectroscopy (NIRS) technique will be presented. Generally, it uses near-infrared light - that penetrates biological tissue - to obtain non-invasively and real-time information on tissue oxygenation and metabolism[52,53].

1.2.1 Near-infrared spectroscopy techniques: continuous waves and time-resolved spectroscopy

Starting from the work of Jobsis in 1977, non-invasive near-infrared spectroscopy (NIRS) techniques has been initially used to study brain oxygenation, and then to investigate muscle oxidative metabolism in pathophysiology[54–57]. In the last years, NIRS has also been applied to the study of the functional activation of the human cerebral cortex[58].

NIRS is based on the premise that human tissues are relatively transparent to light in the so-called physiological window (650–950 nm). NIR light is either absorbed by chromophores or scattered in tissues and penetrates human tissues thanks to the scattering which is more probable than absorption. The high attenuation of NIR light in tissue is mainly due to hemoglobin (the oxygen transport red blood cell protein) located in small

vessels of the microcirculation (such as capillary, arteriolar, and venular beds), water and lipid (Figure 6). From the deoxy-hemoglobin and oxy-hemoglobin concentrations, the total hemoglobin concentration (THC) and tissue oxygen saturation (StO_2), which is a mixture of arterial and venous blood saturation, can be calculated.

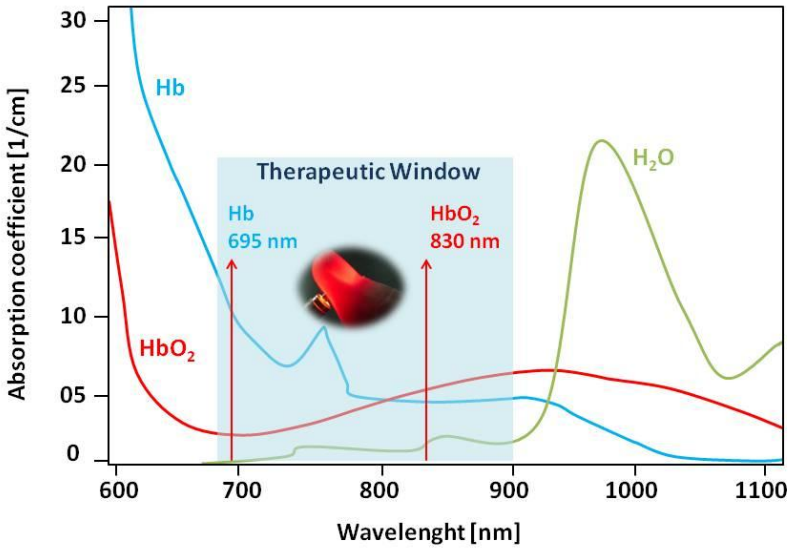

Figure 6. Shining infrared light on a finger cap, illuminate it thanks to the low absorption at the wavelengths in the therapeutic window. Absorption coefficients for deoxy-hemoglobin and oxy-hemoglobin (Hb and HbO_2) and water (H_2O), and wavelengths are shown. Figure re-drawn and inspired by *Gropman et al, Novel imaging technologies for genetic diagnoses in the inborn errors of metabolism, Journ Transl Genet Genom 2020, 4:429-45*.

NIRS is weakly sensitive to blood vessels >1 mm because they completely absorb the light. NIRS is a non-invasive and safe technique that utilizes a laser diode and/or light-emitting diode light sources in the physiological window and flexible fiber optics to carry the NIR light to and from tissues through a source and a detector placed on soft and usually, black

probes. A rule-of-thumb estimate indicates that the information revealed at a given source-detector pair is dominated by a depth of approximately one-half of the source-detector distance which requires a selection of the optimal source-detector distance according to the age of the subject (roughly separating newborns, young children and adult). The most used NIRS techniques are the so-called continuous wave (CW), the frequency-domain (FD), and the time-resolved spectroscopy (TRS) methods. The CW modality is based on constant tissue illumination and measures light attenuation through the head; the FD method illuminating the head with intensity-modulated light, measures both attenuation and phase delay of emerging light. Finally, the TRS technique illuminating the head with short pulses of light, detects the shape of the pulse after propagation through tissues.

The most commonly used CW-based NIRS instrumentation derives StO_2 estimation from multi-distance measurements[52]. The advantage of CW based systems is that they are low-cost and easy to transport, but only the FD and TRS techniques offer the possibility to absolutely characterize the optical properties of tissues and calculate absolute HbO_2 and Hb values[59,60]. TRS technique is able to adequately separate absorption effects from scattering effects and, therefore, measure absolute values more accurately and precisely. The possibility of measuring absolute values in a reliable manner represents an important advantage over existing clinical cerebral oximeters because it allows the comparison of concentration and oxygen saturation values among patients without any interventions.

1.2.2 The importance of monitoring the cerebral blood flow (CBF)

The NIRS modalities described in the previous section give information about the cerebral oxygenation[59,60]. New techniques that can monitor additional biomarkers like cerebral blood flow (CBF), have been proposed over the last years. In this section, the clinical relevance of CBF

and new non-invasive methods developed to study this parameter will be described.

The normal functioning of the brain requires ~20% of available oxygen making the regulation of BF and oxygen delivery critical for survival[61]. When talking about the regulation of the BF, two important features of the vessels need to be mentioned: compliance and resistance. The compliance refers to the fact that blood vessels are stretchable and it is calculated as the ratio between the change in volume and pressure. Thanks to its compliance, the tunica media of the vessel can modify its muscle tone in response to homeostatic changes and to induce vasoconstriction or vasodilation to keep blood pressure and flow within the normal ranges. Another important feature of the vessels is the resistance. It refers to the resistance to overcome in order to push the blood through the circulatory system and create flow. The resistance of large arteries and parenchymal arteries allows keeping the BF constant in a healthy subject[62]. The resistance is directly proportional to the viscosity and the length of the vessel and inversely proportional to its radius. So, narrow vessels have more resistance. Vascular resistance can change rapidly to alter regional and global CBF.

The term vascular homeostasis indicates the maintenance of the vascular function over time and includes the adaptation to environmental signals. It is based on intrinsic (i.e. autoregulation through metabolic or myogenic mechanisms) or extrinsic (activated by the autonomic nervous system) mechanisms. The intrinsic mechanisms are related to a metabolic response activated by tissue vasodilators like nitric oxide or by smooth muscle cells activity causing vasodilation in response to decreased pressure. The extrinsic mechanisms are mediated by the autonomic nervous system (ANS) or associated with the release of hormones by the endocrine system to maintain vascular homeostasis[63].

1.2.2.1 Cerebral autoregulation

In this paragraph, the mechanism of cerebral autoregulation will be briefly described. The potential sequelae caused by the impairment of this mechanism will also be presented.

The brain receive about 20% of cardiac output and oxygen consumption in a resting state thus being one of the most perfused organ of the body. Moreover, there is a lack of oxygen reserve in the brain and the skull (that is a rigid structure surrounding the brain) just allows minor changes in CSF and tissue. Because of this, the autoregulation that is the ability of the brain to maintain constant blood flow despite changes in perfusion pressure is a fundamental mechanism. Roy and Sherrington firstly described in 1890 the relation between blood flow and arterial pressure as being linear (i.e. the higher the arterial pressure, the greater is the amount of blood passing through the blood vessels and vice versa)[64]. In 1959, Niels Lassen suggested a wide range of mean arterial pressure in which despite of pressure changes, the CBF was constant[65]. In healthy adults, CBF was considered to be constant at 50 mL per 100g of brain tissue per minute, and the cerebral perfusion pressure (CPP) that is equal to the difference between the mean arterial pressure and the intracranial pressure, to be in the range of 60 to 150 mmHg[65]. Autoregulation was considered to be lost above and below this range. This concept has been graphically illustrated through the so called "Lassen curve". One of the key mechanisms involved is represented by the ability of changing the cerebrovascular resistance when an arterial blood pressure fluctuation occurs. According to recent literature, a small cerebral autoregulatory plateau region exists where CBF remain relatively constant in response to slower steady-state changes in mean arterial pressure (such as the infusion of a vasoactive drug), but CBF will not necessarily remain stable in all physiological/clinical conditions. Indeed, CBF will fluctuate in other conditions related to faster arterial pressure changes (such as exercise). It has

been described that the same patient can tolerate a large but slow change in arterial pressure without a significant change in CBF, and not afford a faster change in arterial pressure resulting in a reduction (or increase) of CBF. Moreover, it has been shown that the blood vessels of the brain are more effective at protecting the microcirculation against steady-state and transient increases, compared to decreases, in mean arterial pressure[66].

Usually, when autoregulation is exhausted, cerebral ischemia happens and the reduction in CBF is compensated by an increase in oxygen extraction from the blood[63]. When the decrease in perfusion exceeds the ability of increased oxygen extraction to meet metabolic demand, clinical signs of ischemia like dizziness, altered mental statuses, and eventually irreversible tissue damage infarction, appear.

This brief overview gives an idea about how subtle is the mechanism involved in the cerebral autoregulation and how crucial can be CBF monitoring to evaluate the brain health. CBF in fact, is an important biomarker in clinics for neuromonitoring since it allows among others, recognizing conditions like hypoxia and ischemia that can lead to severe impairment. The early identification of such impairment allows a fast intervention and the prevention of devastating sequelae.

In the next section, the main optical technique used to monitor CBF will be described.

1.2.3 Diffuse correlation spectroscopy (DCS)

The advance in techniques able to measure non-invasively, at cot side and continuously the microvascular CBF has a relevant importance in clinical research since they allow to obtain real-time information about the cerebral well-being and can be applied in a wide range of clinical scenarios [67]. Diffuse correlation spectroscopy (DCS) is an innovative, optical technique. It also uses near-infrared light, to obtain local, microvascular cerebral blood flow

(CBF), however, unlike NIRS, it relies on the coherence of the light source (i.e. a laser) and the statistics of the resultant diffuse speckles[68,69]. DCS gives real-time results and allows continuous monitoring during hours or days. During the same measurement, different regions can be explored and the tissue penetration is quite deep (~1 cm)[68].

DCS has been validated through a comparison with standard techniques like laser Doppler flowmetry (LDF) in rat brain and muscle tissues, transcranial Doppler ultrasound (TCD) in mouse tumors and infant and adult brain tissues, MRI in neonatal brain tissue, arterial-spin labeled MRI (ASL-MRI) in human muscle tissue during ischemia and in rat, neonatal and adult brain tissues, Xenon-CT in injured adult brain[67,70–73]. DCS has been applied to monitor subjects of a wide range of ages from preterm newborns to adults. Moreover, it has been applied in several clinical contexts such as brain study, cancer, and peripheral arterial disease[68]. DCS has also been used to measure the impaired cerebrovascular reactivity and autoregulation in ischemic stroke patients[74], the estimation of autoregulation and CBF in adult patients with traumatic brain injury and subarachnoid hemorrhage, the assessment of microvascular CBF, the cerebral metabolic rate of oxygen extraction ($CMRO_2$)[71,75] in prematurely born infants, and cerebrovascular reactivity, and postoperative changes after cardiac surgery in neonates and children born with severe congenital heart defects (CHD)[76]. Cerebrovascular reactivity in response to pharmacologically-induced vasodilation in healthy adults and patients suffering from carotid artery stenosis has also been studied. Another application is the study of the healthy hemodynamic responses to orthostatic challenges and variation with age[77].

In the present work, two optical techniques have been integrated into the same device: time-resolved spectroscopy (TRS) and diffuse correlation spectroscopy (DCS). As previously described, the first technique allows measuring deoxy-hemoglobin and oxy-hemoglobin (Hb, HbO_2),

concentration, total hemoglobin concentration (THC), and tissue/blood oxygen saturation (StO_2). The incorporation of traditional TRS and new DCS into the same instrumentation allows obtaining relevant information about cerebral hemodynamics and cerebral oxygen metabolism. This type of device is called "hybrid diffuse optical device". Hybrid instrumentation was first introduced for cerebral monitoring in rats in 2001[78] and the adult brain in 2004.

After describing the main features of the two optical techniques that have been applied to patients' monitoring for the studies included in the thesis, the application of optical techniques in clinics from their introduction will be presented. The devices used in clinics will be described presenting advantages and disadvantages and pointing out the role of more recent techniques. Specific importance will be given to the application of optical technologies in the pediatric field.

1.2.4 The application of optical techniques in clinics

As previously stated, the technologies currently used for measuring brain haemodynamics are not appropriate for pediatric monitoring since they are invasive or minimally invasive, not portable and do not provide continuous measurements. Nowadays, the most used cerebral oximeters are CW-NIRS devices and indeed, they have a version specific for the pediatric population but their availability is restricted to selected pediatric and neonatology units. Additionally, they are not robust and accurate enough to precisely monitor the infant's brain and pediatricians claim the need for a new technology[79].

1.2.4.1 Optical techniques for infant brain monitoring

It has been demonstrated the importance of monitoring brain oxygenation in several pathological conditions in infants[80,81]. It appears fundamental for example, in infants at risk of cerebral hypoxia such as the

pre-terms. As anticipated in *section 2.1*, the currently available oximeters estimate StO_2 from multi-distance measurement. They monitor the oxygenation but do not provide information about the oxygen supply that is necessary in specific pathological conditions[82]. Moreover, a high variability in StO_2 values derived by cerebral oximeters and low precision when replacing the probe, have been shown[83]. Inter-instrumentation variability has been demonstrated since in neonatal applications the cerebral oximeters displayed higher value than adults and, generally, measurements performed with different devices are not comparable. Another issue is that standard thresholds are not available. These findings make commercial oximeters not adequate for clinical monitoring and underline the need for standardization studies to improve both accuracy and precision of such devices.

Beyond the cerebral oximeters, studies applying other optical technologies exist. NIRS for example found widespread use in monitoring the infant brain, partly because of the convenient optical geometry of the infant's head. Another important motivation for the application of these methods with the pediatric population is related to the fact that they are completely non-invasive. Initially, NIRS studies focused on infants at risk of brain injury and subsequent neurodevelopmental abnormalities[84]. This technique has been used mainly as a research tool in premature infants and term infants with perinatal asphyxia and open-heart surgery. The majority of the studies focused on the changes in HbO_2 and Hb as measures of cerebral oxygenation, as well as changes in THC and/or the difference between HbO_2 and Hb (Hb-D)[85]. Later on, researchers realized the potential of NIRS as a monitor of functional brain activation during infancy. From here the development of a big portion of literature about fNIRS studies[86,87]. fNIRS is an interesting application that is beyond the scope of this thesis.

More advanced, i.e. complex and costly, optical techniques like TRS and DCS presented in the previous section, allow continuous and cot-side monitoring which results ideal for the pediatric population study. Their feasibility for non-invasive continuous bedside CBF and oxygenation monitoring in the pediatric population both in healthy and pathological conditions, was demonstrated[71,88]. TRS has been used to measure the changes in cerebral blood volume (CBV), tissue oxygen saturation (StO_2), and relative cerebral metabolic rate of oxygen ($rCMRO_2$) over the first year of normal brain development. In pathological conditions, the same parameters have been measured to determine the effect on cerebral hemodynamics of acute brain injury[89–91]. On the other hand, DCS has been validated for the assessment of cerebral blood flow (CBF) changes in infants' brain[75,92,93]. More recent studies[94–96], including the published paper presented in this thesis (*see section COMPENDIUM OF PUBLICATIONS)*, have proposed hybrid TRS and DCS devices in the cot-side monitoring of infants. The goal is to build a robust and accurate device that gives information on both oxygen saturation and blood flow and provides.

For the objectives of the present thesis, we were interested in the application of optical techniques in the neuromonitoring of infants affected by BEH. As anticipated in the introduction, even though the majority of the clinicians consider this condition as benign, there are cases in which cerebral hemodynamics could be compromised and an ICP monitoring is necessary. To avoid submitting the infant to an invasive procedure it could be great to have a non-invasive and reliable technique to study the cerebral well-being.

In the next section, the application of optical techniques in conditions of raised ICP will be presented.

1.2.5 Usefulness of optical techniques in conditions of increased ICP

1.2.5.1 ICP alterations and optical signal

The decision-making for surgery in a condition of raised ICP is based not only on the quantitative measurement of this parameter but also on the visual detection of pathological phenomena called B-waves[37,38]. As previously described, nowadays the gold-standard ICP monitoring is an invasive technique. Indeed, non-invasive methods to estimate ICP are needed to improve treatment of traumatic brain injury (TBI), hydrocephalus, stroke, and other diseases. Recent works in fact, have demonstrated that ICP affects DCS signals beyond reflecting slower changes in blood flow. Among others, our group demonstrated the feasibility of a method to estimate ICP from pulsatile, microvascular CBF data through a recurrent neural network in a population of six infants with BEH and six adults with traumatic brain injury[97]. Another group showed NIRS application to accurately estimate ICP changes over time using a non-human primate model[98]. The same group have developed a non-invasive method for quantifying ICP by measuring CBF through a DCS device. They have showed that recorded cardiac pulsation waveform in CBF undergoes morphological changes in response to ICP changes[99].

In our research, we were motivated to see whether there were cerebral hemodynamic changes associated with ICP B-waves that could be evaluated with non-invasive neuromonitoring. Such an advance is desirable, especially for the pediatric population and clearly in a syndrome such as BEH for which there is still confusion about its management. Given the fact that the prevailing approach among clinicians is conservative because the syndrome is considered to resolve spontaneously with age, it becomes fundamental to retrieve more information about cerebral hemodynamics than merely the ICP. Intracranial hypertension, in fact, could lead to permanent but potentially avoidable delays in these children.

In the next section the hypothesis and objectives of the thesis are presented.

HYPOTHESES AND OBJECTIVES

2

HYPOTHESES

The benign external hydrocephalus (BEH) is characterized by an alteration of the CSF dynamic which causes an increase in ICP values and the presence of pathological ICP waves, thus leading to cerebral oxygenation and blood flow impairment, and developmental delays.

The hypotheses tested during the studies included in the thesis were:

H1- BEH causes a developmental delay that can be early detected, allowing standardization of the clinical protocol applied to these infants.

H2- The cerebral hemodynamic changes appearing in presence of ICP alterations can be detected non-invasively through an optical device.

H3- The placement of a ventriculoperitoneal shunt will allow a clinical improvement in patients presenting an increase in ICP and the presence of pathological ICP waves (B-waves).

3

OBJECTIVES

The main objective of the thesis was to study the consequences of the BEH on psychomotor development and cerebral hemodynamics. The developmental abilities of the patients have been evaluated through the Third and Fourth Edition of the Bayley Scales of Infants and Toddlers Development (Bayley-III, Bayley-IV). The cerebral hemodynamics of children requiring invasive ICP monitoring have been studied through a non-invasive system based on optical techniques. Specific objectives were:

O1 (H1) - To assess the psychomotor development of children affected by BEH.

O2 (H2) - When invasive ICP monitoring is required, to study the cerebral oxygenation and cerebral blood flow through a non-invasive hybrid system, using time-resolved spectroscopy (TRS) and diffuse correlation spectroscopy (DCS) techniques. The application of optical techniques allows to:

- O2a- extend the number of children monitored with the TRS-DCS system and improve its suitability for the pediatric population.
- O2b- study the cerebral hemodynamic changes in pathological conditions.

O3 (H3) - In shunted patients, to observe if there is a change in the clinical symptoms and compare the psychomotor results obtained before shunt and six months after it using the Bayley scales.

COMPENDIUM OF PUBLICATIONS

4
COMPENDIUM OF PUBLICATIONS

4.1 SUMMARY OF THE METHODOLOGY

The papers of the present thesis include different cohorts of infants or children affected by BEH admitted to the Pediatric Neurosurgery Unit of the Vall d'Hebron University Hospital (VHUH). All of them received an initial psychomotor assessment (baseline) just after the diagnosis. A subgroup, candidate for the invasive ICP monitoring, received a simultaneous non-invasive optical monitoring. The inclusion criteria of the study related to the thesis and the details of each procedure are described in the following sections. Independently of the specific cohorts included in the two published papers, children have been evaluated for longer periods to follow their psychomotor evolution, especially those who have been treated surgically with the placement of a CSF shunt. These data will be used for future articles.

4.1.2 Criteria for the recruitment of patients

The criteria used by the neurosurgeon to diagnose BEH were: HC above the 97.5th percentile according to Spanish population nomogram, or a rapidly increasing HC during the first year of life (at least crossing two percentiles) and enlarged subarachnoid spaces, associated with normal ventricular size (Evans' Index < 0.30) or mild ventriculomegaly (Evans' Index ≥ 0.30 and ≤0.35). Patients are included in a specific database created in 2011 that includes patients treated in the Pediatric Neurosurgery Unit of the VHUH. They come from Catalunya and other Spanish autonomic regions since our institution is a tertiary neurosurgical center with a Neurosurgical Pediatric Unit that is one of the five reference centers for complex neurosurgical pathology in children in Spain: CSUR 46, (https://www.sanidad.gob.es/profesionales/CentrosDeReferencia/docs/ListaCSUR.pdf , last access 12/02/2023). The database is located in a server with

protected access; it is property of the UNINN. It contains the demographical and clinical data of the diagnosis and follow-up of the patients. The database has been filled by the responsible for the surgical treatment (Dr. Maria A Poca) and the responsible for the psychomotor evaluation (F. Maruccia) of the patients, respectively supervisor and candidate of the thesis. Dr. Maria A Poca is responsible for the security of the information contained in the database which respects all the needed requirements.

The first article (psychomotor assessment) is a cohort study realized to assess the psychomotor development in 51 consecutively recruited young children diagnosed with BEH at the VHUH, Barcelona, Spain, from May 2017 to February 2020. According to the inclusion criteria, a final cohort of 42 patients was included. After the diagnosis was made by the neurosurgeon according to the clinical features and the neuroimaging studies, the child's psychomotor development was evaluated by two trained evaluators (FM, LG), using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III)[100]. When any delay in language, cognitive, or motor skills milestones were detected, children were referred to a children's rehabilitation unit to enter programs for early psychomotor stimulation (Centre for Child Development and Early Intervention; CDIAP), and clinical and psychomotor follow-up was scheduled every six months.

The second article (non-invasive optical monitoring) includes 11 patients diagnosed with BEH according to the same criteria and procedures of the cohort involved in the previous study. However, in this second cohort a child with BEH-associated genetic syndromes (Dyrk 1A, achondroplasia) was not excluded. The all cohort was recruited from November 2017 to June 2020. The psychomotor development was evaluated by two trained evaluators (FM, LG) using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III). A child was evaluated through the

Wechsler Preschool and Primary Scale of Intelligence (WPPSI) because he was older than the age threshold established for Bayley III. When, according to the scales' threshold for the child's age, any delay in developmental milestones was detected, the child was referred to a CDIAP and a six months follow-up was performed. The indication of continuous ICP monitoring was established when the child presented persistent neurodevelopmental delay or clinical symptoms suggesting intracranial hypertension (irritability, frequent night awakenings, headache, vomiting) associated with macrocephaly (HC > 97.5th percentile) or rapidly increasing HC (defined as HC crossing at least two percentiles). Epidural ICP monitoring was performed for 72 hours in all patients and they were hospitalized for 3-4 days. In these 11 patients, a simultaneous ICP and optical monitoring was performed. The non-invasive optical device is described in section 4, paragraph 4.2 about "optical monitoring".

4.1.2.1 Neuroimaging studies

The size of the extraventricular CSF compartments was measured along the frontal convexities at the coronal slices in transfontanellar ultrasound or MRI to calculate: the craniocortical width, the sinocortical width (the distance from the lateral wall of the superior sagittal sinus to the surface of the cerebral cortex), and the anterior part of the interhemispheric fissure (Figure 7). In an extensive review of the literature, Zahl et al found that the upper limits of a normal craniocortical width range from 4 to 10 mm in infants <1 year of age, and from 3.3 to 5 mm in neonates[9]. The defined upper limit of the normal interhemispheric fissure width ranges from 6 to 8.5 mm, whereas a comparable spectrum for the sinocortical width is from 2 to 10 mm[9]. Prassopoulos and Cavouras showed that the extent of the subarachnoid spaces is not gender-dependent, either in children younger or older than 3 years[27]. Consequently, to establish the diagnosis of BEH we

required that at least one of three measurements of the frontal subarachnoid space was greater than 10 mm. Ventricular volume —in transfontanellar ultrasound, CT scan, or MRI— was estimated in all children using the (EI). Only patients with an Evans Index ≤ 0.35 were included.

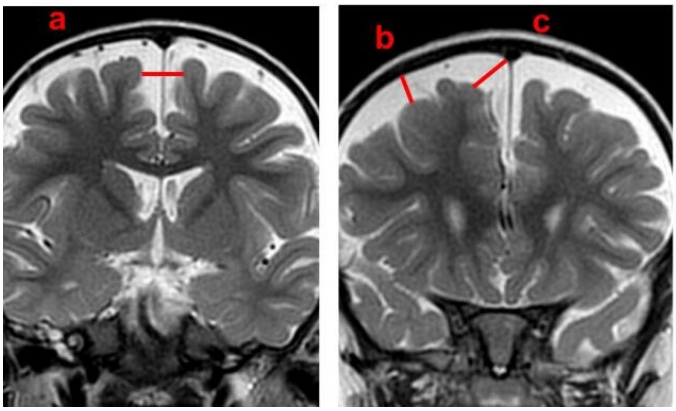

Figure 7. The figure shows the measurement of the extraventricular cerebrospinal fluid compartments in a Magnetic Resonance image of a 33-months-old girl affected by benign external hydrocephalus. The following measurements are shown: (a) interhemispheric fissure (12 mm), (b) craniocortical width (8.4 mm), and (c) sinocortical width (12.4 mm).

4.1.2 Psychomotor assessment: the Bayley-III scales

The third edition of the Bayley scale was published in 2006 and was designed to assess the developmental functioning of infants and toddlers from 16 days to 42 months 15 days of age, and the raw data was compared to a standardized norm of US children[100,101]. The Bayley-III scale has five distinct scales: Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior. In our study, we used the Cognitive, Language, and Motor scales since we were interested in the evaluation of the main developmental domains. In the Bayley-III scales, the examinee's chronological age (adjusted for prematurity if required) defines a starting point designated by a letter A through Q. This letter is used to determine the starting item for the

Cognitive, Language, and Motor scales. The Language scale consists of the receptive and expressive language subscales, and the motor scale has a fine and gross motor subscale. In the three selected scales, Bayley-III yields three composite scores reflecting infants' cognitive, language, and motor development. The composite language score combines expressive and receptive language, and the composite motor score includes both gross and fine motor scales that are converted to a composite standardized score with a mean of 100 and an SD of 15. To improve the sensitivity of Bayley-III, we also used the expressive and receptive language and fine and gross motor development subscales independently as they might identify differences in the language and the motor development, which might be hidden in composite scores. In the subscales, the standardized scores have a normative mean of 10 and an SD of 3.

Standardization sample: In Bayley-IIII, the standardization sample for the Cognitive, Language, and Motor scales included 1700 children aged 1 month to 42 months, divided into 17 separate age groups, with 100 individuals in each group[100]. Only children who were born at 36 to 42 weeks gestation and who were typically developing were included in the standardization sample.

4.1.2.1 Developmental delay criteria

We considered a delay when the children presented any delay in at least one of the five areas of the simple scales and/or in one of the three composite scales of the Bayley-III scales. Developmental delay was defined as a scaled score < 7 according to the simple scale[102]. A composite score < 85 was used for the composite scales as the best cut-off recommended by Johnson et al. for detecting neurodevelopmental delay[103]. We decided to take into consideration both the composite and simple scales to have a complete and detailed profile of the child's development. In Figure 8 we show the

graphic of an old girl obtained after the psychomotor evaluation with the Bayley III scales.

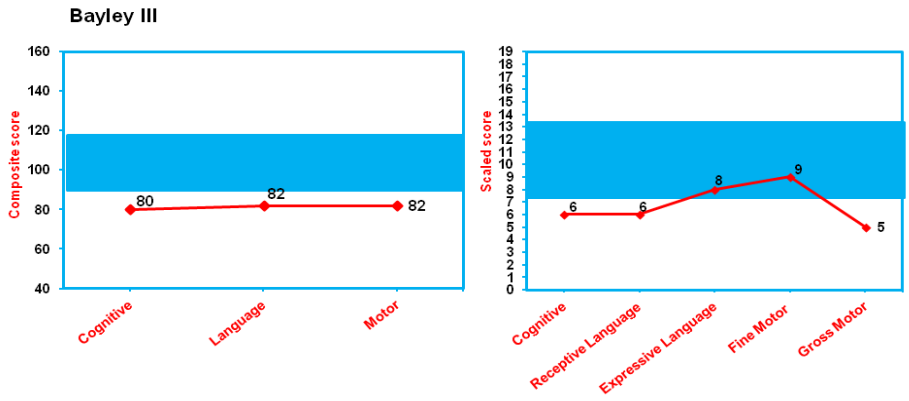

Figure 8. Plot of Bayley-III results of a 12-month-old girl referred to the pediatric neurosurgery unit for evaluation of macrocephaly with the rapid growth of the head circumference (HC). The girl's gestational age was 28/5 weeks, born in a eutocic delivery (weight = 1320 g, height = 37 cm and HC = 28.5 cm), with an Apgar score of 3-5-9. The results of the Bayley-III scales show a delayed development in all domains according to the composite score and in cognitive, receptive language, and gross motor areas according to the standard scores. In blue is indicated the normal range in a healthy population.

4.1.3 ICP and optical monitoring

4.1.3.1 Invasive epidural ICP monitoring

The ICP was measured through an epidural sensor (Neurodur-P®, Rehau AG+Co, Rehau, Germany) placed into the frontal left epidural space (a bur hall was always carried out in the pupilar line behind the hairline and in front of the coronal suture) and connected to a Raumedic monitor (MPR2 logO DATALOGGER, Rehau AG+Co, Rehau, Germany). ICP signal was sampled at 200 Hz and stored on a Windows 10 based computer using a computer-based data acquisition and analysis system (PowerLab 4SP

hardware and LabChart v8.1 software; ADInstruments, Ltd., Grove House, Hastings, UK). The child's movements or other artifacts were recorded in real-time by the parent of the child using an automated system. We have to remark that epidural ICP sensors are known to overestimate the absolute ICP values compared to parenchymal or ventricular ICP ones, at least in adults[46,104]. However, the qualitative information obtained from extradural recordings (presence and percentage of A- and B-waves) is completely parallel and valid[46]. In addition, in children, the dura is more easily detached from the internal table of the skull. This can reduce the differences in ICP values obtained in the epidural space compared to other intracranial compartments.

The ICP criteria for abnormal CSF dynamics used in our department were described in adults in 1991[47]. The presence of mean ICP > 15 mmHg and/or the presence of A-waves and/or more than 20% of B-waves in the nocturnal recording time were considered criteria for shunting. A- or plateau waves have been described as ICP elevations at least 20 mm Hg above the resting line, with abrupt onset and end, and lasting between 5 and 20 minutes[38]. We did not take into account A-waves for our analysis since just one patient showed them in the nocturnal ICP monitoring. B-waves have been described as short repeating elevations of ICP, occurring at a frequency of 0.5-2 ICP waves/minute, lasting at least 10 minutes with high (equal or above 10 mmHg) or low (below 10 mmHg) amplitude[35]. For the elaboration of the second paper, qualitative data were analyzed considering different ICP patterns:

a. Regular pattern (stable ICP recording without any pathological slow waves)
b. Low amplitude B-waves pattern (presence of a log section of B-waves with an amplitude < 10 mmHg)

c. High amplitude B-waves pattern (presence of a log section of B-waves with an amplitude ≥ 10 mmHg)
d. Artifacts.

An adjustable valve (Polaris Programmable Valve, Sophysa Ltd, Orsay, France) combined with an in-series gravity compensating accessory (Aesculap-Miethke ShuntAssistant 0/20 cm H_2O, Christoph Miethke GmbH & Co; Aesculap, Tuttlingen, Germany) or a single gravitational valve (Paedi-GAV valve; Christoph Miethke GMBH & Co; Aesculap, Tuttlingen, Germany) were used when indicated.

4.1.3.2 Optical monitoring

The non-invasive optical monitoring was performed by three researchers (FM, JF, ST) from ICFO and it took place simultaneously with the ICP monitoring during two consecutive nights. The probes were placed on the children forehead and wrapped with skin-compatible material. The measurement started after the child fell asleep and in agreement with the parents to create a situation as comfortable as possible. The measurement was performed during the night since at nighttime the ICP recording is more reliable in children[44] and there is the major appearance of B-waves, especially during the REM sleep[105,106]. Moreover, the child should move less so there is a reduction of movement artifacts that could affect the optical signal. The optical monitoring was performed with two different and complementary techniques: TRS and DCS combined in a single instrument. A detailed description of these two techniques is given in the chapter dedicated to non-invasive optical technologies.

The children's monitoring using the TRS technique allows calculating the concentration of deoxy-hemoglobin and oxy-hemoglobin (Hb, HbO_2)[23]. Afterward, total hemoglobin concentration (THC) and tissue oxygen saturation (StO_2) can be calculated. The DCS data provide information

related to blood flow index (BFI) which corresponds to the microvasculature's flow, i.e. the quantity of blood passing through an area during a certain time. This parameter is then converted into rCBF which gives the percentage of the change in BFI with respect to a baseline. TRS and DCS data were acquired at sampling rates respectively, of 1 sec and 2.5 sec.

The TRS setup has two pulsed laser sources at 690 nm and 830 nm (PicoQuant GmbH, Germany) and two hybrid photomultipliers (HPM-100-50, Becker&Hickl, GmbH, Germany); their signal is processed by 2 time-correlated single-photon counting cards (Becker&Hickl, GmbH, Germany). The DCS setup employs two continuous-wave laser sources (CrystaLaser, USA) at 785 nm, eight avalanche photodiodes (SPCM-AQ4C, Excelitas, USA) in detection, and a correlator (correlator.com, Germany). The two techniques were synchronized together via homemade Java software which also gives a signal for the synchronization with other medical devices via an analog I/O card. Sources and detectors' tips of both techniques were combined into two hand-made rubber-like soft black probes and shined light simultaneously. Initially, we used a source-detector separation (SDS) of 2.5 cm, and from subject 5, we used smaller probes more suitable for pediatric measurement with a SDS of 1.5 cm. The optical and the ICP measurements were synchronized using the LabChart software v7.0.3 (ADInstruments, New Zealand) and the data acquisition hardware PowerLab (ADInstruments, New Zealand).

The study algorithm and the measurement setup (ICP and optical monitoring) are shown in Figure 9.

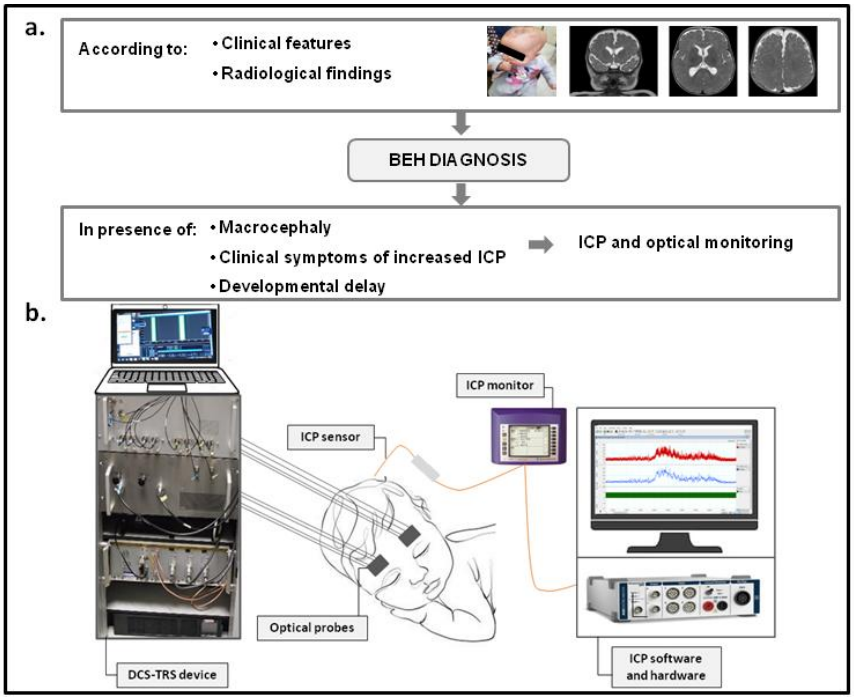

Figure 9. The image has been drawn to show both the general protocol followed during the study and the clinical and optical setup. In Figure 9a the study algorithm is shown. In Figure 9b the setup used for simultaneous intracranial pressure (ICP) and optical monitoring is presented. Two probes are placed on the child's forehead and connected to a hybrid optical device synchronized with the ICP software. The acquisition of ICP data is made through an invasive probe usually placed in the left epidural space. ICP data are shown through a monitor (that reveals the numerical values of ICP such as the mean) and a computer that presents the shape allowing to detect visually different patterns.

4.2 ARTICLE 1

Maruccia F, Gomáriz L, Rosas K, Durduran T, Sahuquillo J, Poca MA, *Neurodevelopmental profile in children with benign external hydrocephalus children. A pilot cohort study*, Child's Nervous System 37, 2799-2806 (May 2021).

DOI: 10.1007/s00381-021-05201-z, Impact factor: 1,327.

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4.2 ARTICLE 2

Maruccia F, Tagliabue S, Fischer JB, Kacprzak M, Perez-Hoyos S, Rosas K, Delgado Álvarez I, Sahuquillo J, Durduran T, Poca MA, *Transcranial optical monitoring for detecting intracranial pressure alterations in children with benign external hydrocephalus. A proof-of-concept study*, Neurophoton. 9(4), 045005(2022).
DOI: 10.1117/1.NPh.9.4.045005, Impact factor: 4,212.

Transcranial optical monitoring for detecting intracranial pressure alterations in children with benign external hydrocephalus: a proof-of-concept study

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Abstract

Significance: Benign external hydrocephalus (BEH) is considered a self-limiting pathology with a good prognosis. However, some children present a pathological intracranial pressure (ICP) characterized by quantitative and qualitative alterations (the so-called B-waves) that can lead to neurological sequelae.

Aim: Our purpose was to evaluate whether there were cerebral hemodynamic changes associated with ICP B-waves that could be evaluated with noninvasive neuromonitoring.

Approach: We recruited eleven patients (median age 16 months, range 7 to 55 months) with BEH and an unfavorable evolution requiring ICP monitoring. Bedside, nocturnal monitoring using near-infrared time-resolved and diffuse correlation spectroscopies synchronized to the clinical monitoring was performed.

Results: By focusing on the timing of different ICP patterns that were identified manually by clinicians, we detected significant tissue oxygen saturation (StO_2) changes ($p = 0.002$) and blood flow index (BFI) variability ($p = 0.005$) between regular and high-amplitude B-wave patterns. A blinded analysis looking for analogs of ICP patterns in BFI time traces achieved 90% sensitivity in identifying B-waves and 76% specificity in detecting the regular patterns.

Conclusions: We revealed the presence of StO_2 and BFI variations—detectable with optical techniques—during ICP B-waves in BEH children. Finally, the feasibility of detecting ICP B-waves in hemodynamic time traces obtained noninvasively was shown.

 [DOI: 10.1117/1.NPh.9.4.045005]

Keywords: benign enlargement of subarachnoid spaces; hydrocephalus; intracranial pressure monitoring; optical techniques; pathophysiology.

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1 Introduction

Benign external hydrocephalus (BEH) is a condition usually diagnosed during the first year of life in infants presenting with macrocephaly or a rapidly increasing head circumference (HC). Neuroradiological findings show enlarged subarachnoid spaces—specifically at the frontotemporal lobes— and normal or moderately enlarged ventricles.[1,2] BEH is commonly considered a self-limiting condition that does not require any treatment, but some children may present temporary or permanent psychomotor delays.[3–7] Fine, gross motor and attentional skills have been identified as the most compromised developmental areas in infants with BEH.[7–10] Additional complications, such as an increased risk of subdural hematoma and hypotonia, have also been reported.[4,11,12]

These findings complicate the management of BEH. In particular, there is still no consensus among clinicians about the effects of BEH on brain development and its optimal management. There is a general agreement that the attitude at diagnosis should be a wait and see approach, but there is also emerging evidence that some children require surgical treatment and the placement of a ventriculoperitoneal shunt.[13] When in doubt, intracranial pressure (ICP) monitoring is useful in deciding which patients are good candidates for shunting. This is motivated by the observation that some BEH children present abnormalities in cerebrospinal fluid (CSF) dynamics that can be observed as quantitative and qualitative abnormalities in ICP recordings. These alterations may induce changes in cerebral oxygenation and blood flow, which, in turn, may lead to neurodevelopmental delays.[5,14,15]

ICP abnormalities that are observed do not necessarily manifest themselves as alterations of the mean ICP value; therefore, in these patients, the mean ICP is not enough for detecting abnormalities of CSF dynamics.[16] There is more to ICP time traces. Of particular interest here are B-waves, which were first described by Lundberg as short repeating elevations of ICP, occurring at a frequency of 0.5 to 2 ICP cycles per minute and lasting at least 10 min[17] with high (equal or above 10 mmHg) or low (below 10 mmHg) amplitude.[16] The presence of B-waves is indicative of reduced intracranial compliance, and they appear mainly during the rapid eye movement (REM) sleep when there is an increase in cerebral blood flow (CBF) and brain metabolism.[18–21] The alteration of cerebral autoregulation or reactivity due to reduced intracranial compliance could be pathological in such a scenario.

This observation was the main motivation for our study. We posit that the detection of B-waves is relevant to evaluating these infants, but continuous ICP monitoring is rarely prescribed to these populations due to its invasiveness and safety considerations. Therefore, there is a niche need to evaluate whether noninvasive, bed/cot-side monitoring of surrogates of ICP alterations could be utilized to detect B-waves. In this study, our working hypothesis was that the ICP alterations present in BEH could be detected using noninvasive, hybrid near-infrared spectroscopies. In particular, we employed near-infrared time resolved spectroscopy (TRS) and diffuse correlation spectroscopy (DCS). In brief, both techniques utilize near-infrared light with TRS deriving the microvascular, cortical concentration of oxy- and deoxy-hemoglobin (HbO_2 and Hb)[22,23] and DCS obtaining an index proportional to microvascular, cortical CBF.[24,25] These techniques have been shown to be a good tool to study the cerebral hemodynamics noninvasively at bedside in healthy and pathological conditions both in adult and pediatric populations. Near-infrared spectroscopy (NIRS) has been applied to the study of infant brain in healthy and pathological conditions;[26–30] among others, it has been used to measure the changes in cerebral blood volume, cerebral tissue oxygenation (StO_2), and relative cerebral metabolic rate of oxygen.[31–33] DCS has been validated for the assessment of CBF changes in adult and infant brains.[34–37]

Our aim was to conduct a proof-of-concept study using optical neuromonitoring to study cerebral oxygenation and blood flow in BEH children presenting ICP alterations. We sought to identify and quantify hemodynamic changes associated with these ICP alterations and to evaluate whether these alterations could be detected by optical monitoring alone.

2 Materials and Methods

The clinical leg of the study was carried out at the Pediatric Neurosurgery Unit of the Vall d'Hebron University Hospital (VHUH), Barcelona, Spain. The study was approved by the VHUH Ethical Committee (PR-ATR-402/2017) and was carried out in accordance with the Code of Ethics of the World Medical Association (declaration of Helsinki).[38] The parents were asked for written informed consent before the inclusion. The study inclusion criteria were as follows: (1) children with a diagnosis of BEH and persistent neurodevelopment delay and/or clinical symptoms of increased ICP associated with macrocephaly or rapidly increasing HC during the first year of life and (2) a clinical indication for continuous ICP monitoring to establish a potential need for a CSF shunt.

2.1 *Clinical Protocol*

Most children with suspected BEH were referred to the Pediatric Neurosurgical Unit of the Neurosurgical Department at the VHUH by a pediatrician or a pediatric neurologist. A pediatric neurosurgeon conducted the first clinical evaluation, during which the clinical history of the child and the family was collected. BEH was defined as enlarged subarachnoid spaces in children with HC above the 97.5th percentile according to Spanish population, or rapidly increasing HC during the first year of life (at least crossing two percentiles of the normal values for the age), with normal ventricular size or mild ventriculomegaly. Moreover, the HC of the parents was measured, and they were classified as being macrocephalic according to the criteria described above for the children.[39]

In each patient, the size of the extraventricular CSF compartment was measured along the frontal convexities at the coronal slices in a transfontanellar ultrasound study or magnetic resonance imaging (MRI) to calculate the following measures: the craniocortical width, the sinocortical width, and the width of the anterior part of the interhemispheric fissure (Fig. 1). The diagnosis of BEH required that at least one of the three measurements was >10 mm independent of sex.[6,40] The ventricular volume—in transfontanellar ultrasound, computer

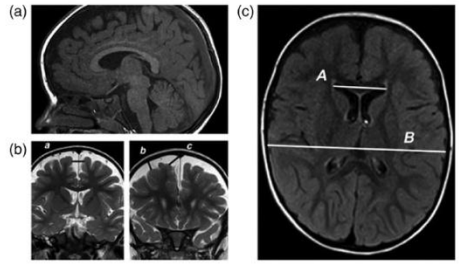

Fig. 1 Example of a 33-month-old female born in a eutocic delivery (gestational age: 35 weeks, weight = 2020 g, height 45 cm, and HC = 33 cm), with an Apgar score (that is a standard neonatal health assessment score) of 6-9-9 at 1, 5, and 10 min of delivery. She was referred to a pediatric neurosurgeon for evaluation of hypotonia and enlargement of subarachnoid spaces. MRI showed the characteristic findings of benign enlargement of subarachnoid spaces in the frontal lobes [(a) sagittal T1-weighted MRI and (b) coronal T2-weighted MRI images): *a*, size of the interhemispheric fissure (12 mm); *b*, craniocortical width (8.4 mm); and *c*, sinocortical width (12.4 mm). (c) (axial T1-weighted MRI), the Evans' Index (0.29) was calculated as the ratio between the maximum width of the frontal horns of the lateral ventricles ($A = 31$ mm) and the maximum transverse inner diameter of the skull at the same axial slice ($B = 105$ mm).

tomography (CT) scan, or MRI—was estimated using the Evans' index,[41,42] calculated as the maximum width between the frontal horns of the lateral ventricles and the maximum transverse inner diameter of the skull at the same axial slice in the CT scan/MRI, or in the same coronal slice in the transfontanellar ultrasound. We introduce Fig. 1 to illustrate typical findings and the procedure.

The psychomotor development was evaluated by two trained evaluators (F. M. and L. G.) in all children. The goal was to evaluate all children using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III).[43] Those who were above the age threshold for the Bayley III were evaluated with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV). The presence of clinical symptoms was evaluated by an expert neurosurgeon (M. A. P.). For ICP monitoring, institutional practices were followed. At VHUH, continuous ICP monitoring in BEH is indicated when the child presents a persistent neurodevelopmental delay and/or clinical symptoms suggesting intracranial hypertension (irritability, frequent night waking, headache, and vomiting) associated with macrocephaly or rapidly increasing HC during the first year of life. Epidural ICP monitoring is performed for at least 72 h.

2.2 *ICP Monitoring and Shunting Criteria*

The ICP was measured through an epidural sensor (Neurodur-P®, Raumedic AG, Germany) placed into the frontal left epidural space. The sensor was inserted through a burr hole following the pupilar line and in front of the coronal suture. The ICP sensor was connected to an ICP monitor (MPR2 logO DATALOGGER, Raumedic AG, Germany). The ICP signal was sampled at 200 Hz and stored on a personal computer using a computer-based data acquisition and analysis system (PowerLab 4SP hardware and LabChart v8.1 software; ADInstruments, Ltd., Grove House, Hastings, UK).

A comment about this type of sensor should be made since in the literature an overestimation of the absolute ICP values when using epidural ICP sensors with respect to the parenchymal or ventricular ones has been reported in adults.[44,45] In children, the epidural sensor is more reliable because dura mater is more easily detached from the internal table of the skull, thus reducing the differences in the absolute ICP values obtained in adults compared with other intracranial compartments. For the purposes of this study, the qualitative information obtained from the epidural sensors (frequency and amplitude of A- and B-waves) has been demonstrated to be equivalent to the quantitative data and valid.[44] The ICP criteria for identifying abnormal CSF dynamics were described elsewhere.[46] Here the presence of mean ICP > 15 mmHg and/or the presence of A-waves (defined as ICP elevations at least 20 mmHg above the resting line, with abrupt onset and ending, and lasting between 5 and 20 min)[17] and/or more than 20% of B-waves in the total duration of the nocturnal recording time were considered to be criteria for shunting following standard procedures of the hospital.

The ICP data were analyzed by an expert neurosurgeon (M. A. P.), and the different segments of the ICP recordings were categorized in one of the following profiles: (a) normal ICP profile, characterized by what we call a "regular pattern" (i.e., mean ICP < 15 mmHg with a stable recording and without any pathological waves), (b) low-amplitude B-waves pattern (presence of B-waves with an amplitude < 10 mmHg), (c) high-amplitude B-waves pattern (presence of B-waves with an amplitude ≥ 10 mmHg), and (d) measurement artifacts.

2.3 *Noninvasive Optical Monitoring*

The optical monitoring was performed with a hybrid platform using both TRS and DCS combined in a single instrument and probe, similar to those in references.[47–51] Briefly, TRS and DCS data were acquired at sampling rates of 1 and 2.5 Hz, respectively. The two techniques were synchronized together via a homemade software. The TRS hardware had two pulsed laser sources at 690 and 830 nm (PicoQuant GmbH, Germany) and two time-correlated single-photon counting cards (Becker&Hickl, GmbH, Germany). The DCS hardware had two continuous wave (CW) laser sources (CrystaLaser, USA) at 785 nm, eight avalanche photodiodes detectors (Excelitas, USA), and a hardware correlator (correlator.com, Germany). We employed two soft black probes, with fibers for the injection and detection of light being arranged by alternating

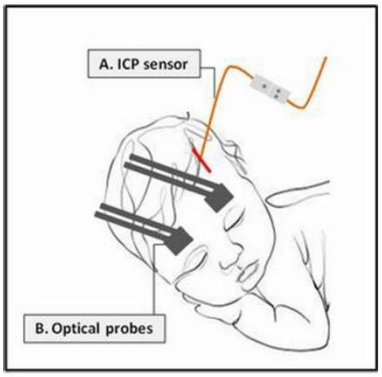

Fig. 2 An illustration of the nocturnal intracranial (ICP) and optical monitoring. The ICP sensor was located in the frontal left epidural space (A), and the optical probes were placed on the forehead (B).

DCS and TRS and shining light simultaneously. TRS employed multimode fibers for both injection [numerical aperture (NA) = 0.28] and detection, using bundles with a 5 mm of diameter (Fiberoptic Systems Inc., USA); instead, DCS light was conveyed by a multimode fiber (NA = 0.39) and collected by a bundle of four single-mode fibers (each with NA = 0.12, Fiberoptic Systems Inc., USA).

Initially, we used a source–detector separation (SDS) of 2.5 cm, but from subject five onward we used smaller probes that are more suitable for pediatric measurement with a SDS of 1.5 cm, which was previously validated.[25,31,34,52,53] We also employed a smaller fiber holder patch (probe). We used the same fibers by placing them closer. The probes were placed on the child's forehead just above the eyebrows to be able to monitor the frontal lobes and wrapped around the head with a skin compatible material (Fig. 2).

The synchronization between the optical and ICP measurements was realized through the LabChart software v7.0.3 (ADInstruments, New Zealand) and the data acquisition hardware PowerLab (ADInstruments, New Zealand). The ICP signal was sent from the monitor to the PowerLab, and the correlator sent a 10-Hz digital signal to PowerLab as a timing basis. The child's movements or other potential artifacts were recorded in real time by the researchers (F. M., J. F., and S. T.) by inserting a digital mark both in the optical and the ICP recordings. After the measurement, the TRS data were processed, and HbO_2 and Hb as well as total hemoglobin concentrations (THC) and StO_2 were calculated as time traces.[12] The DCS measurements also quantified the blood flow index (BFI) as being proportional to CBF as a time trace.[24]

2.4 *Nocturnal Monitoring*

Multimodal monitoring was carried out during night sleep, i.e., nocturnally, during two consecutive nights. The recording started after the child fell asleep as decided according to the parent's experience to create a situation as comfortable as possible. Nocturnal monitoring is associated with various benefits. For example, nocturnal ICP recordings were shown to be more reliable in children than day monitoring,[54] B-waves, which are of primary interest here, occur more frequently during the night, especially in REM sleep,[20,21] and ICP monitoring is prone to motion artifacts that are minimized during sleep.

2.5 *Statistical Methods*

Summary descriptive statistics were obtained for each variable. The median, minimum (min), and maximum (max) values were used for continuous variables, and percentages and frequencies were used to summarize the categorical variables. The statistical analysis was built on the general hypothesis that optical techniques are able to detect cerebral hemodynamic variations occurring during ICP B-waves. To verify this hypothesis, two different analyses, described in the next section, were performed.

Data are presented using time traces and tables. The statistical analyses were performed using R software v3.6.2 and the integrated development environment R Studio v1.2.5042 (RStudio, Inc., Boston, Massachusetts, USA);[55] the packages "lme4"[56] and "multicomp"[57] were used. The MATLAB software[58] (version R2018b, MathWorks, USA) was used for fitting the data and representing time traces.

2.5.1 *Changes of cerebral hemodynamics during ICP B-waves*

As a first step of our analysis, we hypothesized that the optical variables obtained noninvasively through a combined TRS-DCS platform can show significant changes in the presence of ICP alterations (specifically the B-waves). We also tested the hypothesis that the optical variables can show an increased variability (i.e., significant changes of the standard deviation) when B-waves occur. After the acquisition, the optical data measured during both nights from each subject were analyzed and were synchronized with the ICP recordings. We conducted a first analysis by building linear mixed effect (LME) models. The clinical and optical parameters, i.e., Hb, HbO_2, THC, StO_2, BFI, and ICP, were identified as outcome variables and the subject ID as a random effect. The presence or not of ICP waves and the different ICP patterns (regular, low-, and high-amplitude B-waves) were defined as fixed effects in two different models. A likelihood ratio (LHR) test was conducted to compare the built models to identify the best model, and residuals were checked. Specifically, the model defining the presence of B-waves and the one defining the pattern as fixed effect were separately compared with the null model. The Bayesian information criterion (BIC) was checked to confirm that we were choosing the model that better fits the data: the lower BIC represented the model better fitting the data. We opted not to test whether the combination of measured variables gave further improvements in identifying B-waves to avoid overusing the dataset. When a model including different types of ICP patterns (regular, low-, and high-amplitude B-waves) resulted in a statistically significant improvement as evaluated by the LHR analysis, a *post hoc* contrast analysis was performed through a general linear hypotheses (GLH) method. This test was designed to compare regular pattern and low-amplitude B-waves, regular pattern and high-amplitude B-waves, and low- and high-amplitude B-waves. An additional LHR analysis was performed by dividing the cohort into two subgroups according to the SDS used for the measurement.

2.5.2 *Effect of demographic and clinical variables on cerebral hemodynamics*

We also investigated the influence of demographic and clinical parameters of our cohort on the variation of the cerebral hemodynamics parameters obtained through noninvasive optical monitoring. Such parameters include psychomotor delay, presence of symptoms, prematurity, gender, and macrocephaly. Associations of the cerebral hemodynamics variables (THC, StO_2, and CBF) with the parameters were checked. We considered the mean values of THC, StO_2, and CBF during the regular period that is a period of inactivity (normal parameters) independently from the sleep stage. To do so, a linear regression model was built.

Additional variables that could somehow influence the studied parameters were also analyzed. In fact, we hypothesized that the widespread range of ages and gestational ages of the children could affect the behavior of the measured parameters. We studied whether the probe's distance from the brain could affect the optical signal. We assessed the influence of the HC because it is well known that extracerebral contamination increases as the upper layers get thicker. Finally, we tested the influence, as a fixed variable, of the probe type because two different probes with an SDS of 2.5 and 1.5 cm were utilized. Other additional variables

(age in months or gestational age or HC) were tested to see if they contributed to the LME model by adding them to the pattern fixed effects. The interactions between these variables and the identified pattern (low- and high-amplitude B-waves) were also tested. For all of the mentioned variables, we performed multiple comparisons through LHR to test the null hypothesis of no difference between the mean and standard deviation of the null model and the model with pattern, between the model with pattern and the models with the additional variables, and the interaction between these two models. The comparison was considered significant when the second model improved the previous. A schematic diagram of the analysis and the *R* script used to carry it out are reported in the Supplementary Material.

Statistical significance was considered when $p \leq 0.05$. For multiple comparisons through LHR in the analysis of additional variables, a Bonferroni correction was applied and a corrected type error of 0.01 was established. The symbol << was used when the p value was very low (i.e., more than 0.001 decimals).

2.5.3 *Visual detection of ICP patterns in BFI time traces*

The common practice for the evaluation of the ICP recording is the visual inspection of the time traces searching for B-waves. We observed a similarity between ICP and BFI time traces, so we hypothesized that an observer—blinded to the ICP data—can identify and distinguish the ICP patterns by looking at the BFI tracing of each subject. To verify the hypothesis, a blinded researcher (F. M.) carried out a visual detection of ICP patterns in BFI and marked regular and B-waves segments. We decided to not indicate the B-wave type (low and high amplitude) due to the relatively small sample size and excluded the periods with ICP artifacts from this analysis *a priori*.

We were interested in obtaining the sensitivity (i.e., our ability of recognizing the B-waves) and specificity (i.e., our ability of identifying the regular pattern) of our analysis. To calculate them, we compared the patterns identified by the blinded observer in BFI with the gold standard, which is the ICP patterns identified by the experienced neurosurgeon (M. A. P.). We defined the correctly identified B-waves as being true positive (TP) and the regular patterns as being true negative (TN), all from the noninvasive recording of BFI. Furthermore, regular patterns marked as B-waves were identified as being false positive (FP), and B-waves marked as regular patterns were a false negative (FN). The sensitivity was calculated as TP/(TP + FN), and the specificity was TN/(FP + TN).

3 Results

3.1 *Clinical and Psychomotor Assessment*

The recruitment lasted from November 2017 to June 2020 and included 12 children diagnosed with BEH that required continuous ICP monitoring. The data from one child were excluded because of poor optical signal quality. This subject was, in fact, awake, and the measurement was affected by movement artifacts. The final cohort included 11 children (5 girls) with a median age of 16 months (7 to 55 months).

The demographic and clinical data according to the inclusion criteria are summarized in Table 1. All children had a diagnosis of BEH. Macrocephaly was present in seven children (63.6%), and four (36.4%) presented a rapidly increasing HC during the first year of life. According to the age thresholds, the psychomotor development was evaluated in ten children using the Bayley-III scales[43] and in one child using the WPPSI-IV. In nine children (81.8%), a persistent neurodevelopmental delay was detected. All patients presented clinical symptoms of increased ICP. Hypotonia was present in eight (72.7%), irritability in two (18%), headache in two (18%), and night waking in two (18%) children. Additional parameters include prematurity (five children), a positive family history for macrocephaly (one child), and hydrocephalus (one child), with associated problems (six children). All children needed ICP monitoring to evaluate if the placement of a ventriculoperitoneal shunt was necessary.

Table 1 Demographic and clinical data of the BEH patients ($n = 11$).

Sex: boys/girls	6 (54.5%)/5 (45.4%)
Age in months (median, min, and max)	16 [7 to 55]
Gestational age	
Very preterm (28 to 31 week)	1 (9%)
Moderate preterm (32 to 33) week)	2 (18%)
Late preterm (34 to 37 week)	2 (18%)
Full term birth (38 to 42 week)	6 (54.5%)
HC	
Macrocephaly (HC > 97.5th)	7 (63.6%)
Rapidly increasing HC	4 (36.4%)
Positive family history	
Macrocephaly	1 (9%)
Hydrocephalus	1 (9%)
Associated problems	
Achondroplasia	2 (18%)
Genetic syndrome	2 (18%)
Subdural hematoma	1 (9%)
Chiari malformation type 1	1 (9%)
Persistent neurodevelopmental delay	9 (82%)
Cognitive area (Bayley-III)	2
Language area (Bayley-III)	5
Motor area (Bayley-III)	8
Language area (WPPSI-IV)	1
Planning (WPPSI-IV)	1
Clinical symptoms	
Hypotonia	8 (72.7%)
Irritability	2 (18%)
Headache	2 (18%)
Night waking	2 (18%)

Results are expressed as *N* (%). GA: gestational age; HC, head circumference; and WPPSI, Wechsler preschool and primary scale of intelligence.

3.2 *Epidural ICP Monitoring, Shunt Placement, and Follow-Up*

As planned, continuous ICP monitoring was carried out in all children. During the simultaneous noninvasive optical study and epidural ICP monitoring, the median ICP value was 18.5 mmHg (min: 13 mmHg and max: 26.1 mmHg). Of the total recording time, 114 periods of low-amplitude B-waves and 84 of high-amplitude B-waves were identified by the expert

neurosurgeon, giving a total of 198 ICP periods with B-waves. The median percentage of B-waves was 61% (min: 47 and max: 97) of the total duration of the recordings. Of these, low- and high-amplitude B-waves were divided approximately evenly (~50% to 50%). Only one patient presented plateau waves, which led us to discard plateau waves (A-waves) from the analysis. The ICP monitoring and clinical practice led to the placement of a ventriculoperitoneal shunt in all patients. A clinical and psychomotor follow-up was performed at 6 and 12 months after the surgery.

3.3 *Optical Monitoring*

The optical data acquired from the same hemisphere in which the epidural ICP sensor was implanted (frontal region of the left hemisphere) were used for the analysis because they showed a slightly better signal quality upon a qualitative evaluation. As planned, the optical measurement was performed during two consecutive nights (median time per night = 6 h, min: 2, and max: 7) per subject. DCS data were acquired for the whole cohort of 11 subjects. TRS data were acquired for nine subjects because of technical issues during the measurements of the remaining two subjects. From the initial 198 segments identified as B-waves, 32 were excluded because they comprised B-waves already started at the beginning and/or still ongoing at the end of the optical measurement. Furthermore, the so-called plateau waves were also identified, but because their appearance is quite rare in these children, they were not included in the analysis. Therefore, a total of 166 periods with B-waves and 60 regular segments that were detected in the ICP recordings were compared with the noninvasive optical data through an LHR analysis.

3.3.1 *Changes of cerebral hemodynamics during ICP B-waves*

The LHR analysis was applied to two models (one indicating the presence or not of B-waves and one including different patterns (regular, low-, and high-amplitude B-waves)). Both models were separately compared with the null one. ICP and StO_2 showed significant changes during B-waves ($p \ll 0.001$ and $p = 0.01$, respectively). Specifically, the presence of different patterns showed a significant increase of ICP and StO_2 with respect to the null model ($p \ll 0.001$ and $p = 0.001$, respectively). Moreover, the presence of B-waves revealed a significant increased variability of ICP and BFI with respect to the null model ($p \ll 0.001$ and $p = 0.003$, respectively). A significant variability of ICP and BFI was also detected during different patterns with respect to the null model ($p \ll 0.001$ and $p = 0.01$, respectively). The analysis was performed including the whole cohort (eleven subjects for ICP and BFI and nine subjects for StO_2 and THC). Detailed results are presented in Table 2. A further analysis was performed with a subcohort having both TRS and DCS measurements including nine subjects. There was no difference in significance between the two analyses. To confirm that we could use the subjects measured with different SDSs as a group, we also conducted the LHR analysis separately for the subjects measured with a long SDS ($n = 4$) and the ones measured with a short SDS ($n = 7$), thus finding no statistical difference between the two analyses. For the first group (long SDS), ICP and StO_2 showed significant changes during B-waves ($p \ll 0.001$ and $p = 0.003$, respectively). A significant change of THC during B-waves was also detected for this group ($p = 0.03$). The second group (short SDS) showed significant changes of ICP during B-waves ($p \ll 0.001$) and of ICP and StO_2 during different patterns ($p \ll 0.001$ and $p = 0.01$, respectively). Moreover, the presence of B-waves revealed a significantly increased variability of ICP and BFI with respect to the null model both in the first ($p \ll 0.001$ and $p = 0.04$, respectively) and second group ($p \ll 0.001$ and $p = 0.01$, respectively).

A *post hoc* analysis through GLH was applied to study which patterns were causing the significant changes reported in the previous analysis. Specifically, ICP showed a significant increase with respect to regular pattern during high-amplitude B-waves ($p \ll 0.001$) and low-amplitude B-waves ($p \ll 0.001$). Furthermore, high-amplitude B-waves showed a higher increase in ICP compared with low-amplitude B-waves ($p \ll 0.001$). StO_2 also showed a significant increase compared with the regular pattern during high-amplitude B-waves ($p < 0.001$), and they were also higher for high-amplitude compared with low-amplitude B-waves ($p = 0.01$).

Table 2 Optical variables characterization during different ICP patterns.

	Mean [min to max]			
Variable	Regular	High B waves	Low B waves	p value (LHR)
ICP ** (mmHg)	15.1 [8.7 to 27.4]	21.4 [4.8 to 36.7]	17.7 [9.7 to 28.5]	<<0.001
THC (μM)	7×10^4 [4.1×10^4 to 1.1×10^5]	7.2×10^4 [4.8×10^4 to 1×10^5]	6.9×10^4 [4×10^4 to 1×10^5]	0.1
StO_2* (%)	60.6 [49.7 to 76.1]	62.5 [51.1 to 73.6]	60.7 [51.5 to 74.5]	0.001
BFI (cm^2/s)	2.3×10^{-8} [8.4×10^{-9} to 8.2×10^{-8}]	2.3×10^{-8} [9.5×10^{-9} to 8.1×10^{-8}]	2.3×10^{-8} [9.9×10^{-9} to 6.7×10^{-8}]	0.8
Variable	Standard deviation [min to max]			p value (LHR)
ICP^^ (mmHg)	1.6 [0.4 to 6.8]	5 [1.3 to 13.2]	3.1 [0.7 to 8.2]	<<0.001
THC [μM]	5.2×10^3 [1.5×10^3 to 1.7×10^4]	4.7×10^3 [1.6×10^3 to 1.8×10^4]	4.1×10^3 [1.5×10^3 to 1×10^4]	0.2
StO_2 (%)	4.8 [2.07 to 9.2]	4.2 [2 to 7.7]	4.4 [2.2 to 9.5]	0.2
BFI^ (cm^2/s)	3.05×10^{-9} [3.4×10^{-10} to 2.5×10^{-8}]	3.6×10^{-9} [8.9×10^{-10} to 2.6×10^{-8}]	3.6×10^{-9} [4.8×10^{-10} to 2.6×10^{-8}]	0.01

Descriptive statistics of optical parameters during different ICP patterns is shown. The significance for each parameter at the LHR between the null model and the model including different patterns is also presented. Mean: *$p < 0.05$; **$p < 0.001$; standard deviation: ^$p < 0.05$; ^^$p < 0.001$. BFI, blood flow index; ICP, intracranial pressure; LHR, likelihood ratio; StO_2, tissue oxygen saturation; and THC, total hemoglobin concentration.

The same analysis was applied to study variability as described above. ICP presented a significant variability during both high-amplitude ($p \ll 0.001$) and low-amplitude ($p \ll 0.001$) B-waves with respect to the regular pattern. The ICP variability was also higher during high-amplitude B-waves with respect to the low-amplitude B-waves ($p \ll 0.001$). BFI showed higher variability also for both high-amplitude ($p = 0.01$) and low-amplitude B-waves ($p = 0.02$) but not between two types of B-waves.

3.3.2 *Effects of demographic and clinical variables on cerebral hemodynamics*

The demographic and clinical parameters did not show any significant effect on the measured variables. Specifically, THC, StO_2, and CBF were not associated with the presence of psychomotor delay, neither with the presence of symptoms nor with prematurity, gender, or macrocephaly ($p < 0.05$). Similarly, the analysis of the associations between the optical parameters and additional variables (such as age in months, GA, HC, and probe type) revealed no significant effect on the parameters measured through optics ($p < 0.05$).

3.3.3 *Visual detection of ICP patterns in BFI time traces*

As stated in the methods, for this analysis, we did not distinguished between high- or low-amplitude B-waves, and wherever the neurosurgeon identified a high-amplitude B-waves followed by a low-amplitude B-wave, for the sensitivity calculation, it was counted as a single B-wave. The total number of B-waves periods was initially 167, but the waves counted for the sensitivity analysis were, therefore, 87 and 60 regular segments in the ICP recordings. Figures 3 and 4 show some examples of the different patterns detected in the simultaneous invasive ICP and optical recordings. In Fig. 3, the pattern analysis done by the blind observer (F. M.) for three different subjects is shown. This figure illustrates different scenarios of the blinded analysis: when the patterns are correctly identified in BFI, when they are not identified, and when the patterns are caught correctly by the blind observer even though the distinction between regular

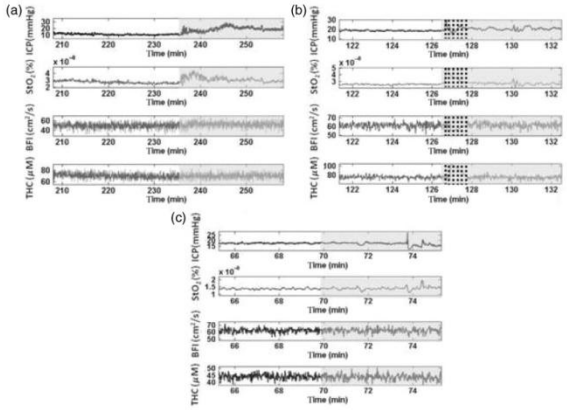

Fig. 3 (a)–(c) Three examples of data acquired through the simultaneous ICP and optical monitoring of three different subjects, respectively, 7-, 12- and 31-month-old, are shown. Regular pattern (white area) and B-waves (gray area) are marked in the measured variables. In subject (a), the B-waves were correctly distinguished from the regular pattern at the blind visual detection in BFI; in subject (b), they were not identified; and in patient (c), they were identified even though the difference from the regular pattern was subtle. Movement artifacts are represented through dashed lines. BFI, blood flow index; ICP, intracranial pressure; StO_2, tissue oxygen saturation; and THC, total hemoglobin concentration.

pattern and B-waves is subtle. In Fig. 4, we present an example of one night measurement with marked ICP abnormalities detected by the neurosurgeon and the BFI data analysis made by the blind observer. Figure 4(c) shows the identified or not identified patterns in BFI. All of the patterns were used to calculate the sensitivity and specificity. Finally, we identified 78 B-waves segments in BFI time traces over 87 and 43 regular segments in BFI over 60 in the ICP recordings. Considering all data, a sensitivity of 90% [confidence interval (CI) 95% 82 to 94] in the detection of B-wave pattern and a specificity of 76% (CI 95% 63 to 85) in the detection of regular patterns in the optical data were obtained.

4 Discussion

We used an innovative and noninvasive optical technique to monitor children affected by BEH during nocturnal, invasive ICP monitoring. In this study, we were able to detect quantitative changes in cerebral hemodynamic parameters obtained through optical techniques during the appearance of the so-called B-waves. Specifically, when the ICP recording revealed the presence of B-waves, we detected a significant increase in StO_2 ($p = 0.01$). We also detected a significant increase of standard deviation of BFI in the presence of B-waves ($p = 0.003$). Because the analysis of the ICP tracing is made by searching for B-waves manually by eye, we carried out an analogous analysis in the BFI data. We reported a good sensitivity (90%, CI 95% 82 to 94) and specificity (76%, CI 95% 63 to 85) to detect and distinguish B-waves. These findings overall motivate us to further study nocturnal optical monitoring as a means to characterize the presence and the potential deleterious effects of ICP waves in this population without the need for invasive ICP monitoring. This could complement the clinical practice and knowledge.

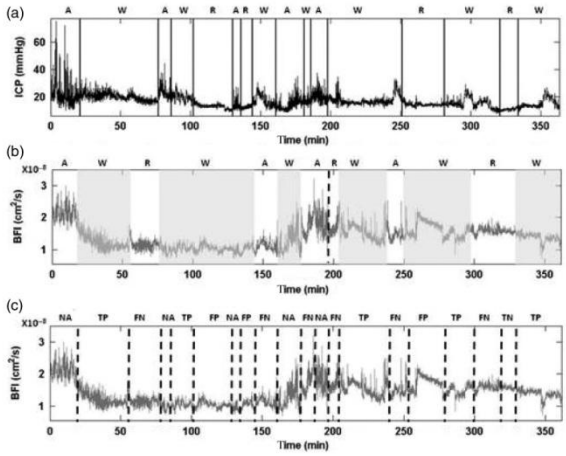

Fig. 4 Six-h and 3-min measurement of an 11-month-old child are shown. (a) The ICP analysis done by the neurosurgeon is shown. (b) The blinded visual detection and (c) the comparison to calculate sensitivity and specificity are presented. TP indicates B-waves correctly identified as B-waves, FP regular pattern identified as B-waves, TN regular pattern correctly identified as regular, and FN B-waves identified as regular pattern. In this example, six B-waves over seven and one regular pattern over four were correctly identified. In BFI, regular patterns/artifacts are represented as white areas and B-waves as gray areas. In (c), the outcome of the analysis is shown. It represents the correspondence between the patterns identified by (a) the neurosurgeon and by (b) the blinded researcher. A, artifact; BFI, blood flow index; FN, false negative; FP, false positive; ICP, intracranial pressure; NA, not applicable; R, regular; TN, true negative; TP, true positive; and W, waves.

In a previous study,[59] our group proved the feasibility of a method to estimate ICP from pulsatile, microvascular CBF data through a recurrent neural network in a population of six infants with BEH and six adults with traumatic brain injury. We found a high correlation ($R = 0.95$) and a mean difference of $+82\%$ in the Bland–Altman analysis between the invasive and the predicted ICP for the BEH cohort. For the adult cohort, a good correlation ($R = 0.96$) and a bias between the two methods of $+0.69\%$ were detected.

4.1 *Noninvasive Optical Techniques to Study Pathological Alterations in ICP*

The ICP monitoring reveals important information to address the management of children with BEH, but it is still an invasive technique. The risks associated with the insertion of a sensor into the cranium include hemorrhage and infection.[60] There is also a risk of device failure during insertion or the sensor being accidentally explanted by the patient.[60] In our series, none of the children presented any complications derived from the placement of the ICP sensor. However, the implementation of noninvasive techniques to study conditions of increased ICP in the pediatric population is desirable.

We looked at a noninvasive way to obtain information about cerebral hemodynamics in BEH children using optical techniques contemporary to the standard ICP monitoring. A deeper knowledge about the pathophysiology of this syndrome could open the path to a future in which

invasive techniques can be replaced by, or at least used in combination with, noninvasive methods in the pediatrics field. We used a noninvasive and cot-side device that combines TRS, for calculation of hemoglobin contents and oxygenation with newly developed DCS, for calculation of regional perfusion. The feasibility of such techniques for noninvasive continuous bedside CBF and oxygenation monitoring in the pediatric population was demonstrated.[33,34,61] As stated in the methods section, for ergonomic reasons, from subject 5, we decided to improve the optical setup by adapting it to the age (implying different anatomy and forehead dimensions than adults) of our population. In other words, we switched to a short SDS because it has been previously validated.[25,31,34,52,53] Moreover, in babies of this age, the skull thickness is quite small, allowing for good light penetration with no substantial difference between large and short SDSs.[56,57] We also proved that the probe type had no influence on the results by testing it as an additional variable to the pattern fixed effects and by performing the LHR analysis with two separate groups (subjects measured with long and short SDS). This could, in the future, be further analyzed by detailed simulations. The decision of switching from a long to a short SDS was also made considering the objective of the study. In fact, our main objective was to verify if the presence of ICP B-waves could cause changes (even small ones) in optical parameters revealing specific patterns without necessarily having a common amplitude. To reach this goal, a high signal-to-noise-ratio and precision were crucial. Therefore, we applied two techniques, i.e., TRS and DSC, with demonstrated high sensitivity to the brain.[23,62,63] On the one hand, TRS is considered the NIRS modality that allows for retrieving the optical properties (absorption and scattering) of the tissue and thus obtaining the absolute concentration of hemoglobin and tissue saturation. Moreover, depth sensitivity is reached due to the ability of detecting different time gates that represent the arrival time of the photons, thus allowing for differentiation between early (more sensitive to superficial layers) and late (more sensitive to deep layers) gates.[27] Depth sensitivity is reached due to the ability of detecting the arrival times of the photons. On the other hand, DCS has a higher sensitivity to the brain and less contamination from scalp and skull compared with CW-NIRS due to the strong differential in the number of moving scatterers (red blood cells) in the upper layers (scalp and skull) versus the lower layers (brain) because DCS is preferentially sensitive to the moving scatterers. Specifically, Selb et al.[63] demonstrated, through a Monte Carlo simulation on a head model, a relative brain-scalp sensitivity three times higher in DCS compared with that of CW-NIRS.

Previous studies have looked at the presence of slow oscillations, such as B-waves, in other signals obtained noninvasively. Spiegelberg et al.,[19] in their review, described the attempts of detecting measurable parameters that can show oscillations in the same frequency range of ICP B-waves, calling them "B-wave surrogates." The authors defined "B-wave surrogates as oscillations of signals associated with but different from ICP within the same frequency range as proper B-waves." The frequency of B-waves was originally defined as 0.5 to 2 cycles per minute and recently redefined with an extended range of 0.33 to 3 cycles per minute. In this frequency range, surrogates were found in transcranial Doppler (TCD) and NIRS signals. The oscillations detected in TCD coincide with fluctuations of the blood flow velocity that happen in phase with ICP changes and can also occur in healthy subjects. By applying a hybrid optical technique, we were able to detect changes of cerebral hemodynamic parameters occurring in the B-waves frequency range. In fact, we have acquired the TRS data at a sampling rate of 1 Hz and a DCS of 2.5 Hz, thus being able to catch signals in the range of 60 to 150 cycles per minute.

Fluctuations have also been identified as possible markers of shunt responsiveness in hydrocephalus patients. Droste et al.[64] referred to the presence of equivalents of B-waves (BWEs) in the TCD overnight monitoring of 10 healthy adults and in 11 patients with suspected normal pressure hydrocephalus (NPH). In the NPH subjects, these oscillations happened simultaneously with the ICP B-waves. The association of BWEs with B-waves in patients with NPH who were not improving after shunting has been demonstrated.[65,66] Moreover, rhythmic oscillations of ICP associated with fluctuations in the TCD signal have been detected during sleep, and their variations in accordance with the sleep stage have been demonstrated.[66] Specifically, there is an increase of BWEs during the REM phase. In our study, even though we performed a nocturnal monitoring and observed changes of the measured parameters in the presence of B-waves, we could not specify in which sleep stage they were occurring and we could not prove if their appearance was related to a specific sleep stage. The cited studies are in accordance with our

results because they confirmed the presence of CBF velocity oscillations in the major arteries (in case of TCD) or microvascular hemodynamics (in case of NIRS) during ICP changes and revealed the importance of characterizing the B-wave surrogates in healthy subjects and in patients not intended to undergo invasive ICP monitoring.

TCD is an accepted clinical modality, but it has limitations. In many subjects, it is not possible to find an appropriate "bone window" to use TCD.[67] TCD is also very sensitive to motion and probe placement and is often operator dependent.[68,69] On the other hand, DCS is not a direct surrogate of TCD because DCS measures local changes in microvascular blood flow. This is both an advantage and a complication. The ability to look at local changes could allow specific regions to be targeted to understand the potentially deleterious effects of ICP waves. The complication arises because, in the presence of abnormalities or due to the thick skull/scalp, DCS signals may not reflect the cortical signals, i.e., they can be contaminated by extra cerebral signals. These complications are not so prominent in pediatric populations due to the smaller scalp to brain distance and appropriate regions being selected based on radiology images. Our results indicate that DCS is usable in this population. The recent emergence of commercial DCS systems (HemoPhotonics S.L., Spain and ISS Inc., USA) and various research projects carrying them to medical device approvals stage funded by the European Commission and the National Institutes of Health demonstrate that, in the near future, DCS could provide simplified, relatively low-cost, noninvasive instrumentation that is not operator-dependent.

Slow oscillations during ICP B-waves were also found in NIRS parameters, suggesting that this technique may be used as a noninvasive marker of ICP slow waves. Several attempts of characterization were made in both healthy and pathological conditions. Weerakkody et al.[70] described a synchronization between slow ICP B-waves and Hb obtained through NIRS during controlled elevations of ICP (infusion test) performed in 19 patients with a history of CSF dynamic disorders. The mean frequency of slow waves was 1.32 (0.28) cycles per minute, with a range of 0.75 to 1.98 per minute. In this slow wave bandwidth, the presence of strong and regular slow waves of ICP coincided with waves of the same periodicity in Hb or HbO_2. They observed high coherence between NIRS variables and ICP (>0.7) in a frequency range consistent with the slow ICP waves described by Weerakkody et al.[70] Weerakkody et al.[71] described the changes in ICP and the mutual character of cyclic fluctuations in Hb and HbO_2 recorded through NIRS. They stated that slow ICP waves are accompanied by synchronous changes in Hb and HbO_2 in phase with each other. The authors proved that slow fluctuations in NIRS variables appear during ICP slow waves. These studies are based on CW NIRS systems with limitations such as the impossibility of calculating absolute HbO_2 and Hb values or their sensitiveness to motion artifacts with respect to time domain NIRS used in our work that are already known.

The presence of slow oscillations in Hb and HbO_2 has also been detected in pathological conditions, such as severe head injury and subarachnoid hemorrhage.[72] Cheng et al. detected oscillations of HbO_2 in a frequency range compatible with B-waves in nine patients with a Glasgow coma scale < 8. This implies that NIRS is able to detect such variations and could be used in situations of increased ICP. In contrast, we did not observe any significant changes in Hb or HbO_2, but we detected a significant increase of StO_2 during B waves ($p = 0.01$). Moreover, we proved an increased variability of BFI during B-waves ($p = 0.003$). Working with clinicians who were able to analyze the ICP by eye and distinguish between different patterns allowed us to study the effects of ICP patterns on the measured variables (THC, StO_2, and BFI), achieving innovative information. Specifically, StO_2 revealed a significant increase during high-amplitude B-waves with respect to the regular pattern ($p < 0.001$) and during low-amplitude compared with high-amplitude B-waves ($p = 0.01$); BFI showed a significant variability between regular pattern and high-amplitude B-waves ($p = 0.01$) and between regular pattern and low-amplitude B-waves ($p = 0.02$).

Attempts at identifying ICP variations noninvasively have also been made in the pediatric populations. Urlesberger et al.[73] observed cyclic fluctuations of Hb and HbO_2 in the frequency range of 3 to 6 cycles per minute in 58 healthy full-term infants. By looking at the amplitude of the fluctuations, they concluded that such fluctuations were in the normal ranges for parameters fluctuations in long-term NIRS tracings. Livera et al.[74] investigated the presence of oscillations in the NIRS signal in the frequency range from 3 to 5 cycles per minute in preterm infants reporting cyclic fluctuations in THC. In these studies, the origin of such fluctuations remains

unclear, and it is not related to a condition of pathological ICP. We were able to measure a population presenting ICP pathological B-waves and to characterize our signals during such oscillations.

The innovative approach in our contribution with respect to previous studies is given by the visual detection analysis performed by searching for analogs of ICP in BFI tracing. We obtained a good sensitivity (90%, CI 95% 82 to 94) in identifying analogs of ICP B-waves in BFI tracing. We were also able to detect regular ICP patterns, thus achieving a good specificity (76%, CI 95% 63 to 85). The visual analysis of noninvasive parameters variations in the presence of ICP B-waves could be studied in a larger cohort to confirm these findings and introduce optical techniques in addition to invasive monitoring. Such an advance is desirable, especially for the pediatric population and clearly in a syndrome such as BEH for which there is still confusion about its management. Given the fact that the prevailing approach among clinicians is conservative because the syndrome is considered to resolve spontaneously with age,[3,75] it becomes fundamental to retrieve more information about cerebral hemodynamics than merely the ICP. Intracranial hypertension, in fact, could lead to permanent but potentially avoidable delays in these children.[6,8,9] In our cohort, a pathological ICP and the need for a ventriculoperitoneal shunt was confirmed, thus supporting our hypothesis; we recorded a mean ICP of 18.5 mmHg (IQR 5.5, min: 13, and max: 26.1) and a median percentage of total B-waves of 61% (min: 47.3 and max: 96.6). The visual inspection revealed the presence of 114 ICP recording segments of low-amplitude B-waves, 84 of high-amplitude, and 3 plateau waves. All children included in the cohort were shunted.

Our results confirm that optical techniques can be used to monitor a pediatric cohort such as BEH children in a convenient way for the patients. First, they are safe and noninvasive, so there is no need for a surgical procedure. Second, the monitoring can be performed at bedside, continuously, and while the child is sleeping, thus not obliging him to not move during the daytime. The measurement can be adapted to the patient's needs in terms of protocol and materials. Moreover, using a hybrid TRS-DCS device in combination with the standard ICP monitoring, additional information about cerebral hemodynamics in a condition of increased ICP and in the presence of ICP B-waves could be obtained.

4.2 *Study Limitation*

The population is rather small, and all of the subjects have shown ICP waves with very few artifactual data that were noted to exclude the affected segment. In the future, a large and more heterogeneous population could be studied, including children with and without invasive ICP monitoring.

The sensitivity and specificity of the optical data to identify B-waves were assessed by a single observer who was deeply involved in the study but was blinded to the ICP traces. We did not evaluate interobserver variability, and we did not employ independent observers. This needs to be validated on a larger scale. Even though the visual analysis of optical data is complementary to the ICP recordings analysis and did not drive any clinical decision, it could provide additional information.

DCS is a relatively new technique, and artifacts that may present themselves as ICP waves cannot be fully ruled out. Our (and others') experience from NIRS suggests that powerful artifact identification and removal methods can be employed successfully, and as the field progresses, we expect to employ them.

Our methodology did not allow us to relate these findings to the developmental status of the children, and we did not include a long-term follow-up in this particular study. Although, some children will undergo such procedures.

5 Conclusions

We have demonstrated the feasibility of nocturnal optical monitoring in a BEH population using a hybrid near-infrared spectroscopic device. We collected innovative information about cerebral hemodynamic changes during ICP B-waves. Specifically, we found a significant increase of

StO_2 from regular to high-amplitude B-waves pattern and a significant variability of BFI during high-amplitude B-waves. In children, the visual detection of pathological patterns in ICP recording is considered relevant to drive the clinical management. We achieved good sensitivity and specificity in identifying B-waves and regular patterns in BFI time traces. To the best of our knowledge, this study is the first to assess the behavior of cerebral hemodynamic variables obtained noninvasively in a BEH cohort. The introduction of a noninvasive method could complement the gold standard ICP monitoring used in clinics and give additional and precious information about cerebral hemodynamics in this population.

Disclosures

Turgut Durduran and Jonas Fischer are inventors on relevant patents (*). ICFO has equity ownership in the spin-off company HemoPhotonics S.L. Potential financial conflicts of interest and the objectivity of research were monitored by ICFO's Knowledge and Technology Transfer Department. No financial conflicts of interest were identified. *Patent US8082015B2, "Optical measurement of tissue blood flow, hemodynamics and oxygenation." System and computer-implemented method for detecting and categorizing pathologies through an analysis of pulsatile blood flow;" European Patent EP18382664.3A (under examination); T. Durduran, Jonas B. Fischer, A. Ghouse, and U. M. Weigel; Priority date: 2018-09-14. Jonas Fischer was an employee of HemoPhotonics S.L. during part of this study. His role was defined by the BitMap project and was reviewed by the European Commission.

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Code, Data, and Material Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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GLOBAL SUMMARY OF THE RESULTS

5 GLOBAL SUMMARY OF THE RESULTS

5.1 PUBLISHED RESULTS

The first paper of the thesis is a pilot cohort study about the developmental status of infants and children diagnosed with BEH syndrome, published in *Child's Nervous System*. BEH is a condition characterized by macrocephaly or a rapidly increasing HC during the first years of life. Generally, it is considered a benign pathology, but in some patients, the presence of psychomotor delays has been detected. We aimed to assess the psychomotor abilities of young children through a standardized psychomotor test (Bayley-III) to detect the presence of delay and the most affected areas. We studied a cohort of 42 children affected by BEH, according to the following inclusion criteria: age from birth to 42 months of age (thresholds of the Bayley-III scales); HC above the 97.5th percentile according to Spanish population nomogram, or a rapidly increasing HC during the first year of life (at least crossing two percentiles); and enlarged subarachnoid spaces, associated with normal ventricular size (Evans' Index < 0.30) or mild ventriculomegaly (Evans' Index ≥ 0.30 and ≤0.35). The HC of the parents was measured, and they were classified as macrocephalic if they exceed the 97.5th percentile of the reference studies for the Spanish population. Moreover, a complete interview was administered to the parents to collect information about the child's birth, first developmental stages, presence of clinical symptoms, and family clinical history. Patients with known diseases such as genetic syndromes, premature infants who graduated from the neonatal ICU with pulmonary disorders that required either mechanical ventilation or extracorporeal membrane oxygenation, previous history of

meningitis, traumatic brain injury of any severity, intracranial hemorrhage, or other known causes of hydrocephalus, were excluded. The child's psychomotor development was evaluated and, when any delay was detected, he/she was referred to the Centre for Child Development and Early Intervention (CDIAP), and a follow-up was scheduled after six months.

At the first evaluation, we detected the presence of delay in at least one simple and/or composite scale in 18 (43%) of the children. We found statistically significant differences between our cohort and the healthy population in gross motor and composite motor scores. Moreover, a statistically significant difference was detected between children who were born at term and preterm in fine, gross motor and composite motor scores. We were able to conclude that these children need a strict follow-up to be able to intervene in the early phases of the development, when necessary. The paper also revealed the importance of standardizing the clinical protocol not just in terms of management of these children but also of the tools used for the psychomotor assessment.

The second paper of the thesis is a proof-of-concept study about non-invasive optical monitoring of children affected by BEH. It has been published in *Neurophotonics*. As described before, BEH has been considered a self-limiting pathology with a good prognosis until in some patients, the association with permanent developmental delays and with an increased risk of subdural hematoma was shown. The cerebral hemodynamic implications and the developmental problems related to BEH are not yet well known. We selected a series of 11 patients (median age 16 months, 7-55 months) with BEH and unfavorable evolution (neurodevelopment delay, clinical symptoms of increased intracranial pressure (ICP), and macrocephaly or a rapidly increasing in head circumference during the first year of life) in whom continuous ICP monitoring was indicated. Our purpose was to study non-

invasively cerebral hemodynamic parameters during ICP alterations such as the so-called B-waves. We performed a bedside monitoring via optical techniques, TRS and DCS, simultaneously to the invasive ICP monitoring used in the clinical protocol. We hypothesized that an alteration of the CSF dynamics is present and leads to quantitative and qualitative ICP alterations thus compromising cerebral oxygenation and CBF and leading overtime to developmental delays.

The ICP monitoring was pathological in all patients according to the clinical criteria applied. In fact, an increased mean ICP and the presence of low and high amplitude B-waves in more than 20% of the recording time were found. We have studied the changes of the optical parameters during the B-waves and we have detected a significant increase of StO_2 and a significant variability of BFI. We have also detected a similarity between ICP and BFI tracing so we have performed a blinded visual detection of ICP patterns in BFI data. We have achieved 90% sensitivity in identifying the B-waves and 76% specificity in detecting the regular ICP recording. We have demonstrated the feasibility of a non-invasive optical monitoring in BEH children. We have also proved the presence of cerebral hemodynamic parameters changes during the B-waves.

The application of non-invasive technologies is desirable especially for the pediatric population. The acquisition of new data about cerebral hemodynamics in BEH children is also a great advance which could lead in a future to a better understanding of this syndrome thus giving important hints for its management.

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optical monitoring for detecting intracranial pressure alterations in children with benign external hydrocephalus: a proof-of-concept study", *Neurophoton*. 9(4), 045005 (2022), doi: 10.1117/1.NPh.9.4.045005. The signed agreement has been attached to the Supplementary Material section.

5.2 UNPUBLISHED RESULTS

In this section, unpublished data related to the work done during these years are described. These results are still under analysis and will be published in future papers.

5.2.1 Psychomotor follow-up of BEH children

The cohort has been evaluated from May 2017 to July 2021 following a longitudinal prospective strategy. A total of 77 patients with a diagnosis of BEH have been recruited and their development has been evaluated. Initially the Bayley-III scales were used for the psychomotor assessment; starting from September 2020, we have introduced the Bayley-IV scales[108]. Out of 77 children, 17 were evaluated using this last version of the test. The Bayley-IV is very similar to the previous version of the scales. There are slight differences in terms of administration and scoring such as the flexible administration with series items and related items identified on the record form and supported via digital administration, motor response items in a separate motor response booklet, structured caregiver questions to support administration on relevant items, polytomous scoring approach (i.e., 2, 1, 0); content updates such as the updated item content based on research and user feedback; norms and clinical studies performed during 2017–2019 and updated reliability and validity studies; administration time that is a bit shorter then Bayley-III, i.e. 30 to 70 minutes (depending upon the age of child).

As described in the section Patients and methods (4.1 Criteria for the recruitment of patients), when, according to the thresholds of the Bayley scales for the child's age, any delay in developmental milestones was detected, the child was referred to a CDIAP and a six months follow-up was performed. To obtain consistent results from a clinical research perspective, fourteen patients were excluded for the following: five were older than 42

months and evaluated with other developmental scales, one was Arab and not Spanish speaking, three presented a genetic syndrome, two presented a spinal cord disease that could affect the results, two were born premature and presented severe complications during their stay in the neonatal ICU, and one had an EI>0.35. A total of 63 patients (44 boys and 19 girls, aged 6 to 41 months) were included even though for the clinical protocol a six months follow-up was scheduled for all children presenting a delay.

At the first evaluation, out of 63 children, 39 (62%) showed normal development and 24 (38%) presented a delay at least in one of the Bayley simple and/or composite scales. At the six months follow-up, of the 24 with some developmental delay, a total of 18 children was evaluated (two children were lost at the follow-up, one was already old to be evaluated with the Bayley scales and three follow-ups are still ongoing). Out of 18 patients, 10 (55.5%) showed good developmental abilities and 8 (44.4%) still presented a delay so a new follow-up was scheduled after six months. At the second follow-up, we lost a patient. Out of seven patients assessed, three (43%) presented a normal development. The remaining four (57%) children presenting a developmental delay are still under study.

We have to point out that at the baseline evaluation, six children of the 39 with normal development presented a score in the lower limit for the healthy population, so we decide to schedule a follow-up also for them and, after six months, they showed a delay that persisted at the second follow-up. The most affected area resulted to be the gross motor one at the baseline assessment since twelve children showed scores below the mean of the healthy population. At the six months assessment, the most compromised areas were the gross motor and the expressive language, affected in five children. At the twelve months follow-up, the gross motor and the expressive language areas were still compromised in seven children. Looking at these preliminary results, we can already affirm that it is crucial to perform a

psychomotor assessment in BEH patients to select the ones requiring rehabilitation and start an intervention program as soon as possible. Figure 10 presents the clinical algorithm used for studying children affected by BEH including the follow-up strategy and the results at the different assessments through the Bayley scales.

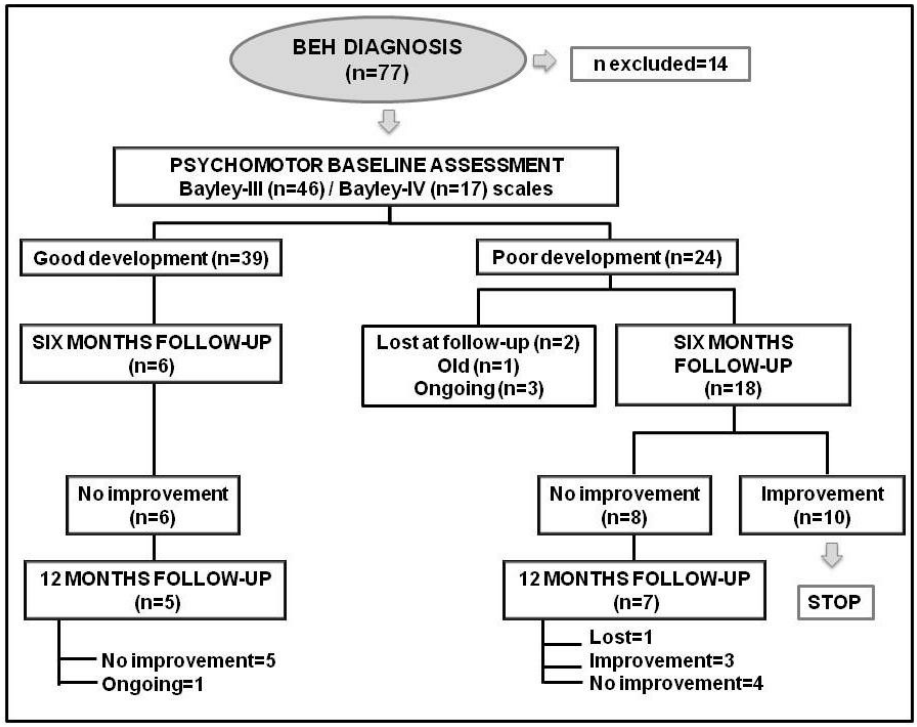

Figure 10. Psychomotor assessment of a cohort of children affected by benign external hydrocephalus (BEH) through the Bayley scales.

The longitudinal study of this cohort of patients goes beyond what has been published in Child's Nervous System (Article 1). This is the most extensive series of patients with BEH evaluated with the Bayley scales and

from its final analysis, we will be able to obtain more robust conclusions about the psychomotor development in children affected by this syndrome.

5.2.2 Shunted children

In this section, the psychomotor assessment and the optical monitoring of children requiring a ventriculoperitoneal shunt are described.

5.2.2.1 Psychomotor follow-up

As described in the previous section a total of 77 children have been recruited; out of them, nineteen received a ventriculoperitoneal shunt. A psychomotor evaluation has been performed six and twelve months after the surgery. For the analysis of this sub-cohort the presence of a genetic syndrome or complications related with prematurity were not considered as exclusion criteria. At the baseline evaluation (pre-shunt), 8 (42%) children presented a delay in at least one simple and/or composite scale of the Bayley-III scales and 11 (58%) showed normal development. The most affected area was the gross motor in which all children presented results lower than the healthy population. The expressive and receptive language and the cognitive area were affected in three children.

Six months after the surgery, a follow-up was performed in thirteen children. Six children did not receive the assessment because of the following reasons: three were old for the Bayley's age threshold and were evaluated with different developmental scales; three follow-ups are scheduled. Out of thirteen children, twelve (92%) presented a delayed development and one (8%) a normal development. The most affected area was the expressive language in which nine children showed a low performance, followed by the gross motor that resulted affected in six children. A twelve months follow-up has been performed in nine children. Four children did not receive the assessment: two were old for the Bayley's age thresholds and evaluated with others developmental scales, one received a diagnosis of a genetic syndrome

(Dyrk 1A) so was enrolled in a different protocol. Another patient was evaluated but he did not collaborate so the results were considered not reliable; three follow-ups are scheduled. Out of nine children, seven (78%) presented a developmental delay and two (22%) a normal development. The most affected area was still the language followed by the motor one.

We need to underline that for the seven children presenting a delay at the twelve months follow-up, BEH was associated with other factors that can affect the acquisition of the psychomotor milestones. Three of them were bilingual and four presented a syndrome. Specifically, one was affected by autism and the other three patients were affected by a genetic syndrome that was still investigated to have a final diagnosis.

In a simplistic analysis of these results, it could be deduced that the placement of a valve did not translate into a benefit for the psychomotor development of the children. However, it should be taken into account that children who required treatment were the most affected in terms of clinics. Many of them had symptoms of intracranial hypertension, which disappeared in all cases after the shunt placement. In the majority of them, BEH was just an epiphenomenon of a genetic process that affected the psychomotor development of the child, so the placement of a CSF shunt aimed to resolve the symptoms of intracranial hypertension or excessive growth of the skull, associated with the malformative/genetic syndrome of the child. Table 1 presents the diagnosis of children requiring the implantation of a CSF shunt and their performance at the psychomotor assessments.

PATIENT	DIAGNOSIS	PSYCHOMOTOR ASSESSMENT		
		Baseline	Follow-up (6 months)	Follow-up (12 months)
1	BEH	good		
2	BEH	good		
3	BEH, language delay	generalized delay	delay (EL)	delay (EL)
4*	BEH	good	delay (EL)	delay (EL)
5	BEH, Chiari malformation type I.	good	old	
6*	BEH	good	delay (EL)	delay (EL)
7*	BEH	generalized delay	delay (EL, RL)	delay (GM, EL)
8	BEH	delay (GM, EL)	delay (EL)	good
9	BEH	good	good	
10	BEH, subdural hematoma	delay (GM)	delay (GM)	good
11	BEH, Dyrk 1A	generalized delay	generalized delay	generalized delay
12	BEH, spinal arachnoid cyst, suspect ADHD	good	delay (GM)	not collaborating
13	BEH, genetic syndrome	general delay	generalized delay	generalized delay
14	BEH, autism	good	generalized delay	generalized delay

15	BEH	delay (GM)	delay (GM)	old
16	BEH, genetic syndrome	delay (GM)	generalized delay	generalized delay
17	BEH	good	scheduled	
18	BEH	good	old	
19	BEH	good	scheduled	

Table 1. The patients who received a ventriculoperitoneal shunt are included in this table. The diagnosis and the results at the psychomotor evaluation through the Bayley-III and IV scales are shown. * indicates bilingual children. **BEH**: Benign External Hydrocephalus; **EL**: Expressive Language; **RL**: Receptive Language; **GM**: Gross Motor; **ADHD**: Attention Deficit Hyperactivity Disorder.

GLOBAL SUMMARY OF THE DISCUSSION

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GLOBAL SUMMARY OF THE DISCUSSION

There is still an open debate about BEH benignity since it has been always considered as a condition that resolves spontaneously[4]. During the last years, some authors questioned this theory by showing the presence of short and long-term developmental delay in a percentage of children affected by BEH.

First studies focused on the most evident clinical features of this syndrome that are macrocephaly or rapid head growth and, even if they pointed out that it was leading to mild gross motor delay, they did not verify the presence of long-term delays.[109] The motor development of a child can be influenced by macrocephaly or hypotonia and, in some cases, it requires an intervention. Mild to moderate hypotonia has been reported in 30-45% of patients included in different studies [5,8] and some authors demonstrated that it persisted until the first year of life. [28] In our first study, we reported the presence of hypotonia in 14% (n=6) and macrocephaly in 76% (n=32) of our patients.

There is an increasing interest in studying the long-term sequelae of this syndrome since no study has been performed on a large scale. Generally, these children appear to have a good development in the first years of life, but starting from Laura Ment, some authors claimed the need to follow up them until school age[1,10]. Specifically, motor coordination difficulties, attention deficit and/or hyperactivity, and expressive language delay were described[30, 31, 110, 111]. Moreover, Shen et demonstrated a correlation between BESS and the risk of developing autism spectrum disorders (ASD)[33].

Our results are in accordance with the literature confirming that the

presence of delay in BEH children should not be underestimated. Out of 42 children included in our first paper, 18 (43%) presented a low performance in the gross motor area compared to their healthy peers. We consider very important to identify the presence of developmental difficulties, because when they are not detected and the child is not treated, then the development and quality of life of the child and his family are also affected. Zahl et al reported reduced quality of life in their BEH children (aged 8 to 18 years) due to developmental, social, cognitive problems since they need to struggle more at school than healthy children of their age[111]. In this study, out of 86 patients, 9.2% (n=13) showed delayed speech and 7.7% (n=11) of them were affected by motor impairment. Another interesting finding of our work is that some children had normal results at the baseline psychomotor evaluation and, nevertheless, pathological results appeared at the 6 months follow-up. This suggests that developmental deficits can be revealed later on when environmental requests increase. We believe in the importance of following up these children and intervene, when necessary.

When looking at the child's development, it is important to use the appropriate scale to test his/her abilities. The Bayley-III scales are a good tool to assess the child's development during the first years of life and it shows the difficulties he/she presents[30]. Even though, once the compromised area has been identified, it is fundamental to deeply study the delayed function by using tests created for that specific problem. We strongly believe that BEH children require attention to intervene and give them the right tools to learn during the function's critical period. Since the developmental profile of BEH children is not "clean" and some of them arrive at school age presenting not diagnosed delays, it is important to act during the first phases of the development. As remarked by Fischer et al. '*…children below the age of 3 years have more frequent contacts with health facilities, an important*

opportunity for identification and management of disabilities' and '*children at such a young age are more responsive to interventions*'[112].

The fact that a percentage of children present developmental problems and, in some of them, they are persisting over time when there is not an adequate treatment, goes against the classical criteria when evaluating these patients and questions the benignity of BEH.

In literature, BEH has been described as characterized at the neuroimaging by enlarged subarachnoid spaces with 'normal to slightly increased ventricular size'[4,5], but only few studies have quantified the ventricular size by using reliable, objective indexes. According to the literature, we defined ventricular dilation in presence of an Evans Index equal to or above 0.30[21,22]. In our first cohort, we found that 20 of the 42 children included (48%) showed an EI $\geq$ 0.30. This finding suggests that communicating and external hydrocephalus coexists in nearly half of these children, indicating that abnormalities in CSF dynamics are more relevant than suggested in previous studies. Most probably, BEH can present with different neuroradiological phenotypes; in fact, we believe that BEH is probably a continuum that has early dilatation of the subarachnoid spaces in early stages preceding ventricular enlargement that occurs later when the fontanelles and sutures close, converting the infant's cranium to a closed and rigid container. Other authors suggested that the increase in the size of the frontal subarachnoid spaces is simply the result of the gravitational force exerted by the developing brain contained inside a non-rigid cranium partially opened to the atmosphere[4,5]. This does not explain, however, the increase in the ventricular size in nearly 50% of the studied children. The most diffuse pathophysiological hypothesis is that in BEH may be present a partial or complete block or incompetence of the arachnoid granulations and,

therefore, an abnormality in the CSF absorption. We have also to remember that this happens in presence of a non-closed container in these children[11].

Some studies revealed that BEH children can present abnormalities in CSF dynamics, leading to quantitative and qualitative abnormalities in ICP recordings that can induce changes in cerebral oxygenation and blood flow, contributing to cause neurodevelopmental delays[7,12,113]. The ICP monitoring allows the detection of pathological phenomena[37,38] that are of central importance in the decision-making for surgical intervention in some children diagnosed with BEH. In our second study, during the simultaneous ICP and transcutaneous optical monitoring we detected a mean ICP of 18.5 mmHg (IQR 5.5, min: 13, max: 26.1), with a median percentage of B-waves of 60.6% (min: 47.3, max: 96.6). The ICP monitoring was abnormal in all children, being the presence of B-waves the most frequent finding. Specifically, in the complete series of eleven children, we found 114 ICP recording segments with low amplitude B-waves, 84 with high-amplitude B-waves, and 3 with the presence of plateau waves. We confirmed that different patterns of B-waves cause a significant increase in ICP ($<< 0.001$) and StO_2 ($p = 0.001$) respect to the null model. We could also observe a significant variability of ICP ($<< 0.001$) and BFI ($p = 0.01$) during different patterns respect to the null model.

In the past, other attempts of detecting non-invasively slow frequency oscillations have been done. Spiegelberg et al in their review described the *B-wave surrogates* defining them as *oscillations of signals associated with but different from ICP within the same frequency range as proper B-waves*[114]. The frequency of B waves was originally defined as 0.5 to 2 cycles per minute and recently redefined with an extended range of 0.33 to 3 cycles per minute. In this frequency range, surrogates were found in transcranial Doppler (TCD) and NIRS signals. The

oscillations detected in TCD coincide with fluctuations of the blood flow velocity that happens in phase with ICP changes and can occur also in healthy subjects. By applying a hybrid optical technique we were able to detect changes of cerebral hemodynamic parameters occurring in the B-waves frequency range. In fact, we have acquired the TRS data at sampling rate of 1 seconds and the DCS of 2.5 seconds.

Fluctuations have also been identified as possible markers of shunt responsiveness in hydrocephalus patients. Droste et al referred the presence of equivalents of B-waves (BWEs) simultaneous with B-waves in the TCD overnight monitoring of ten healthy adults and in eleven patients with suspected normal pressure hydrocephalus (NPH)[115]. The association of BWEs with B-waves in patients with NPH who were not improving after shunting, has been demonstrated[116,117]. Moreover, rhythmic oscillations of ICP associated with fluctuations in the TCD signal have been detected during sleep and their variations in accordance with the sleep stage, have been demonstrated[117]. Specifically, there is an increase of BWEs during the REM phase. In our study, even though we have performed a nocturnal monitoring and we have observed changes of the measured parameters in presence of B-waves, we could not specify in which sleep stage they were occurring and we could not prove if their appearance was related to a specific sleep stage. The cited studies are in accordance with our results since they confirmed the presence of oscillations during ICP changes and revealed the importance of characterizing the B-wave surrogates in healthy subjects and in patients not intended to undergo invasive ICP monitoring.

Weerakkody et al described a synchronization between slow ICP B-waves and Hb obtained through NIRS during controlled elevations of ICP (infusion test) performed in 19 patients with a history of CSF dynamic disorders[118, 119]. They observed high coherence between NIRS variables and ICP (> 0.7) in a frequency range consistent with the slow ICP waves

described by Lundberg et al. In another paper, they stated that slow ICP waves are accompanied by synchronous changes in Hb and HbO_2 in phase with each other. The authors proved that slow fluctuations in NIRS variables appear during ICP slow waves. Previous studies looked at the presence of slow oscillations in other signals obtained non-invasively.

The presence of slow oscillations in Hb and HbO_2 has also been detected in pathological conditions such as severe head injury (HI) and subarachnoid hemorrhage (SAH)[120]. This implies that NIRS is able to detect such variations and could be used in situations of increased ICP. In contrast, we did not observe any significant change in Hb and HbO_2 but we have detected a significant increase of StO_2 during B waves ($p = 0.01$). Moreover, we have proved an increased variability of BFI during B-waves ($p = 0.003$). The team-work with clinicians who were able to analyze the ICP by eye and distinguish between different patterns, allowed us to study the effects of ICP patterns on the measured variables (THC, StO_2 and BFI) achieving innovative information. Specifically, StO_2 revealed a significant increase during different patterns respect to the null model ($p=0.001$). BFI showed a significant variability during different patterns respect to the null model ($p= 0.01$). Specifically, StO_2 revealed a significant increase during high amplitude B-waves respect to the regular pattern ($p < 0.001$) and during low amplitude respect to high amplitude B-waves ($p=0.01$); BFI showed a significant variability between regular pattern and high amplitude B-waves ($p = 0.01$) and between regular pattern and low amplitude B-waves ($p = 0.02$).

Attempts of identifying noninvasively ICP variations have been made also in the pediatric population. Urlesberger et al observed cyclic fluctuations of Hb and HbO_2 in full term infants[121]. By looking at the amplitude of the fluctuations they concluded that such fluctuations were in the normal ranges for parameters fluctuations in long-term NIRS tracings. Livera et al [122] reported cyclic fluctuations in THC in preterm infants. In

these studies still the origin of such fluctuations remains unclear and it is not related to a condition of pathological ICP. We were able to measure a population presenting ICP pathological B-waves and to characterize our signals during such oscillations.

Our results confirm that optical techniques can be used to monitor a pediatric cohort like BEH children in a convenient way for the patients. First of all, they are safe and non-invasive so there is no need for surgical procedure, then the monitoring can be performed at bedside, continuously and while the child is sleeping thus not obliging him to not move during the daytime. The measurement can be adapted to the patient's needs in terms of protocol and materials. Moreover, by using a hybrid TRS-DCS device in combination with the standard ICP monitoring, additional information about cerebral hemodynamics in a condition of increased ICP and in presence of ICP B-waves, could be obtained.

In some patients diagnosed with BEH, the ICP waveform analysis has also been considered of central importance by recent literature[40]. We are also convinced that, in addition to recording absolute values, since the B-waves can be indicative of reduced intracranial compliance, the qualitative analysis of the ICP data is crucial. We found interesting results from the visual analysis of BFI data. We obtained a good sensitivity (90%, CI 95% 82-94) in identifying B-waves patterns. We were also able to detect regular patterns (specificity 76%, CI 95% 63-85). Our results suggest that optical techniques represent a valid tool since they allow to monitor patients at bedside, continuously and to obtain information about different variables involved in cerebral hemodynamics.

The importance of these findings is that the use of non-invasive methods like the one we proposed in the second study could be applied to patients with a BEH diagnosis to better understand the pathophysiology of the syndrome, look at the changes of the optical parameters over time and, in

future, drive the clinical decisions (such as the need of CSF shunt placement). Our results confirm that BEH is not a benign syndrome since we have detected an increased ICP and pathological B-waves causing changes in the cerebral oxygen saturation and blood flow. These findings could explain why some children can present developmental problems that are persisting over time if they are not treated. During the years, attempts of detecting non-invasively oscillations analogue to the ICP B-waves have been made.

The limitations of the research are presented in the next section.

6.1 LIMITATIONS

The work related to the papers included in the thesis presents some limitations that have been described for each study and will be also summarized in this section.

The cohort of children has been evaluated with the Bayley-III scales that are not validated for the assessment of the Spanish population.

The Bayley-III has been standardized on an American pediatric population, so differences in cross-cultural performance can exist. For this reason, a validation on a country-specific cohort of healthy children is needed. The lack of a standardized tool could lead to the loss of candidates for early intervention or treatment due to the underestimation of the developmental delay. The Bayley-III scales have been validated in a cohort of Spanish children affected by autism but not in a control group[123]. Moreover, to have complete information about long-term follow-up, we require the use of additional tests adequate for children > 42 months. This would allow us to evaluate children's development by studying each delayed area deeper and have a more complete idea about the child's developmental needs. This kind of research will allow us knowing the real number of BEH children presenting a long-term delay and their final diagnosis, thus characterizing their developmental profile and finding the right tools to help them.

The use of a relatively small cohort of patients.

We were able to include in our first paper 42 patients which is a good number for a rare syndrome. Even though to confirm some conclusions such as the association between uncomplicated prematurity and developmental delay in BEH, a larger number of patients should be included in future studies. A bigger cohort and follow-ups are also necessary to demonstrate that these

children do present long-term delays. Similarly we have recruited 11 patients for our second paper that is a small number but a good start point to study with new optical techniques children who need ICP monitoring.

Motion artifacts can affect the signal.

For our second study, we tried to contain the influence of the motion artifacts by performing the measurement during the night. It is well known that the ICP monitoring of children has to be performed during the night since there are fewer movement artifacts and the ICP pathological alterations appear during the REM sleep[105]. In addition, for the study performed for the second paper of this thesis, we were able to mark the child's movement on our software to be able to recognize artifacts and exclude them from the analysis, if necessary. The presence of the researcher during the entire monitoring time allows obtaining reliable results.

The sensitivity and specificity of the optical data to identify B-waves was assessed by a single observer deeply involved.

We did not evaluate inter-observer variability and we did not employ independent observers. This needs to be validated on a larger scale. Even though the visual analysis of optical data is complementary to the ICP recordings analysis and did not drive any clinical decision, it could provide additional information.

CONLCUSIONS

7

CONCLUSIONS

According to the established objectives and results of the papers, the following conclusions can be drawn:

Objective 1: To assess the psychomotor development of children affected by BEH.

Conclusions:

- A percentage (i.e. 43%) with BEH (idiopathic form) present a delay in at least one area of the Bayley-III scales and prematurity is a predictor of delay in these children. Children with BEH should be referred for a psychomotor assessment and followed until the school-age to exclude the presence/appearance of developmental delay.

Objective 2: When invasive ICP monitoring is required, to study the cerebral oxygenation and cerebral blood flow through a non-invasive hybrid system, using TRS and DCS techniques.

Conclusions:

- Continuous nightly monitoring realized through a hybrid (i.e. incorporating TRS and DCS techniques) optical system is feasible in children affected by BEH.

2a- To extend the number of children monitored with the TRS-DCS system and improve its suitability for the pediatric population.

Conclusions:

- Eleven children affected by BEH have been measured with optical techniques for the first time and new promising information about cerebral hemodynamics in this syndrome have been collected.

2b- To study the cerebral hemodynamic changes in pathological conditions.

Conclusions:

- In BEH children, cerebral hemodynamics can be compromised. Significant changes of ICP and StO_2 in presence of B-waves were detected. The main change in StO_2 was detected during high amplitude B-waves. The B-waves also caused a significant variability of ICP and BFI. The main change in BFI was reported during high amplitude B-waves.

- The blinded visual detection of analogues of ICP patterns in BFI tracing showed good results in identify and distinguish the B-waves.

Objective 3: In shunted patients, to observe if there is a change in the clinical symptoms and compare the psychomotor results obtained before and six months after the placement of the valve using the Bayley scales.

Conclusions:

- Preliminary results revealed that the shunt placement resolved the symptoms of intracranial hypertension even though it did not translate into an improvement of the psychomotor development.

FUTURE RESEARCH

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FUTURE RESEARCH

The studies included in the thesis have shown interesting results and created new research trajectories in BEH syndrome.

Looking at the psychomotor assessment, it appears clear t' work can be considered just a beginr n the direction of studying sl long-term developmental delays in these children. It can be very interesting to recruit a larger cohort of patients and perform a long-term follow-up. Moreover, coordination between different clinical centers to create standardized protocols could be fruitful.

The non-invasive measurement of BEH children should also move on to include more patients and confirm the usefulness of other cer hemodynamic parameters in a condition of pathological ICP. The study of a larger cohort will allow from one side to confirm the presence of cerebral hemodynamic parameters changes and from the other to objectively characterize the different patterns in BFI. Training about the identification of different patterns (regular and B-waves) in BFI could be done involving more people to be able to calculate the inter-observer agreement. A further step could be to distinguish between B-waves subtypes (high and low-amplitude).

Another important aspect in which we are still currently working is the observation of the changes in terms of developmental problems in children who received a ventriculoperitoneal shunt. The implantation, in fact leads to the normalization of the ICP. In these children we have performed a follow-up through the same non-invasive optical device six months after the surgery, revealing important changes of cerebral hemodynamic paran with respect to the pre-surgery optical monitoring. We are analyzing these data and, if our results will be confirmed, the treatment of some patients with the placement of a ventriculoperitoneal shunt should be incentivized.

9

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ANNEXES

10 ANNEXES

10.1 SUPPLEMENTARY MATERIAL

10.1.1 Document about the participation of the candidate in the published papers

The Ph.D. thesis "**Psychomotor evaluation and non-invasive optical monitoring for comprehensive assessment of the benign hydrocephalus syndrome**" has been presented as collection of papers. The partecipation of the candidate in each published article is described below.

1- Maruccia F, Gomáriz L, Rosas K, Durduran T, Sahuquillo J, Poca MA, *Neurodevelopmental profile in children with benign external hydrocephalus children. A pilot cohort study*, Child's Nervous System 37, 2799-2806 (May 2021), doi: 10.1007/s00381-021-05201-z.

The student took care of the patients' recruitment and realization of the psychomotor assessment. She was involved in the data interpretation and statistical analysis and wrote the drafts of the paper. The student actively participated to the manuscript review process under the supervision of the supervisors of the thesis.

2- Maruccia F, Tagliabue S, Fischer J, Perez-Hoyos S, Rosas K, Delgado Álvarez I, Sahuquillo J, Durduran T, Poca MA. *Transcranial optical monitoring for detecting intracranial pressure (ICP) alterations in children with benign external hydrocephalus. A proof-of-concept study.*

The candidate was responsible of the patients' optical measurement. She took care of the data analysis and of the drafting of the paper. She was involved in the discussion and revisions.

10.1.2 Additional documents

10.1.2.1 Etichal committee approval

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INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON

Sra. Mireia Navarro Sebstián, Secretaria del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

CERTIFICA

Que el Comité Ético de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de investigación está integrada, se reunió en sesión ordinaria nº 325 el pasado 26/01/2018 y evaluó el proyecto de investigación PR(ATR)402/2017, con fecha 01/11/2017, titulado "*Efectos en el desarrollo psicomotor de los niños afectos de secuelas neurológicas de una hemorragia de matriz germinal, de una dilatación benigna de los espacios subaracnoideos (hidrocefalia externa) o de un traumatismo craneoencefálico moderado o grave.*" que tiene como investigador principal a la Dra. Federica Maruccia de nuestro Centro.

Versión de documentos:

- Memoria proyecto (versión 2.0)
- Hoja de información y consentimiento informado para los padres del grupo control Versión 1.0 - 22/01/2018

El resultado de la evaluación fue el siguiente:

DICTAMEN FAVORABLE

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

Presidenta: Gallego Melcón, Soledad. Médico
Vicepresidente: Segarra Sarries, Joan. Abogado
Secretaria: Navarro Sebastián, Mireia. Química
Vocales: Armadans Gil, Lluís. Médico
Azpiroz Vidaur, Fernando. Médico
Balasso, Valentina. Médico
Cucurull Folguera, Esther. Médico Farmacóloga
De Torres Ramírez, Inés M. Médico
Fernández Liz, Eladio. Farmacéutico de Atención Primaria
Fuentes Camps, Inmaculada. Médico Farmacóloga
Gálvez Hernando, Gloria María. Diplomada Enfermería, Unidad de Atención al Paciente
Guardia Massó, Jaume. Médico
Joshi Jubert, Nayana. Médico
Martínez Muñoz, Montserrat. Diplomada Enfermería
Hortal Ibarra, Juan Carlos. Profesor de Universidad de Derecho
Iavecchia, María Luján. Médico Farmacólogo
Rodríguez Gallego, Alexis. Médico Farmacólogo
Sánchez Raya, Judith. Médico
Solé Orsola, Marta. Diplomada Enfermería
Suñé Martín, Pilar. Farmacéutica Hospital
Vargas Blasco, Víctor, Médico

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

Lo que firmo en Barcelona a 26 de enero de 2018

MIREIA NAVARRO SEBASTIAN

Firmado digitalmente por MIREIA NAVARRO SEBASTIAN
Nombre de reconocimiento (DN): c=ES, ou=Vegeu https://www.catcert.cat/verifyCAT (c)03, ou=Serveis Publics de Certificació CPISA-2, sn=NAVARRO SEBASTIAN, givenName=MIREIA, serialNumber=...381212267, cn=MIREIA NAVARRO SEBASTIAN
Fecha: 2018.01.31 13:52:47 +01'00'

Sra. Mireia Navarro

Secretaria del CEIm

10.1.2.2 Informed consent

Área Matemo-Infantil (AMI)
Unitat Assistencial: Neurocirurgia Pediàtrica
Unidad de Investigación de Neurotraumatología y Neurocirugía (UNINN)
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Informació al pacient per a un estudi sense cap procediment invasiu

Proyecto de investigación titulado: Efectos en el desarrollo psicomotor de los niños afectos de secuelas neurológicas de una hemorragia de matriz germinal, de una dilatación benigna de los espacios subaracnoideos (hidrocefalia externa) o de un traumatismo craneoencefálico moderado o grave.

Investigador principal: Federica Maruccia
Director: Dra Maria Antonia Poca
Servicio de Neurocirugía. Unidad de Neurocirugía Pediátrica, Hospital Universitari Vall d'Hebron (HUVH), Vall d'Hebron Institut de Recerca (VHIR). Barcelona
Promotor: Servicio Neurocirugía – Hospital Universitari Vall d'Hebron, ICFO - Institut de Cienciès Fotoniquès.

Definición de las patologías individuales que se incluyen en este estudio:
En este proyecto se incluye el estudio de las repercusiones en el desarrollo psicomotor de 3 patologías poco frecuentes que afectan a niños de diferentes edades, pero cuyas consecuencias neurológicas y psicomotoras todavía no están bien establecidas. Estas patologías son:

- *Hemorragia de la matriz germinal* (HMG): La HMG y la hidrocefalia post-hemorrágica son las complicaciones neuroquirúrgicas más frecuentes en los pacientes recién nacidos prematuros. La HMG conlleva consecuencias adversas en el desarrollo cerebral de los niños con esta afectación, cuya severidad se ha relacionado con la gravedad de la hemorragia. Entre las secuelas descritas se encuentra la parálisis cerebral, disfunciones cognitivas y en ocasiones afectación de la visión y crisis epilépticas.

- *Dilatación benigna de los espacios subaracnoideos (hidrocefalia externa):* La dilatación "benigna" de los espacios subaracnoideos (DBESA) constituye una de las causas de macrocefalia en los lactantes, considerada clásicamente como un proceso benigno y autolimitado. Sin embargo, en algunos casos el acumulo de LCR extraventricular es en realidad una hidrocefalia externa que produce un aumento de la presión intracraneal, que podría explicar que algunos de estos niños presenten un retraso en el desarrollo psicomotor y alteraciones neuropsicológicas a largo plazo.

- *Traumatismo craneoencefálico* (TCE) *moderado o grave*: Los TCEs son la causa más común de daño cerebral en la población entre 1 y 45 años de edad y suponen una serie de déficits cognitivos y motores que a menudo acompañan al paciente a lo largo de su vida. La magnitud y tipo de secuelas residuales que este puede ocasionar son muy variables entre personas, incluso habiendo sido sometidas al mismo tipo de traumatismo craneal. Sin embargo, las consecuencias pueden ser mucho mayores en los niños, dado que tienen lugar sobre un cerebral en desarrollo.

Objetivos:

Su hijo/a ha presentado una de estas 3 enfermedades anteriores:

- *Diagnóstico*:

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Le solicitamos su participación en este proyecto de investigación cuyo objetivo principal es profundizar en el conocimiento de factores neurológicos que puedan influir en el desarrollo psicomotor del niño/a y en sus secuelas finales.

Beneficios:

Es posible que de su participación en este estudio no se obtenga un beneficio directo. Sin embargo, la identificación de posibles factores relacionados con los efectos en el desarrollo psicomotor de las secuelas neurológicas en la HMG, DBESA o en los TCE, podría beneficiar en un futuro a otros pacientes que sufran estas patologías, contribuyendo a un mejor conocimiento y tratamiento de estas enfermedades.

Procedimientos del estudio:

Los niños que se encuentren afectos de las 3 patologías mencionadas serán tratados de forma estándar, siguiendo los protocolos clínicos más eficaces que en el momento actual recomienda la medicina basada en la evidencia. El protocolo de estudio rutinario de todos estos niños incluye la historia clínica habitual, con especial énfasis en el registro de prematuridad o de casos familiares, una valoración neurológica inicial y estudios de neuroimagen (ecografías transfontanelares, TC cerebral o RM craneal, según proceda). Estas exploraciones nos permiten descartar la presencia de lesiones patológicas y realizar mediciones de los espacios subaracnoideos y del sistema ventricular. En el caso de los neonatos o lactantes, también se procede a la medición del perímetro craneal (PC) del niño y de los padres y valoración de las curvas antropométricas sobre el crecimiento del PC, peso y talla del niño/a.

Los estudios específicos y adicionales que requiere el presente estudio son completamente no invasivos y no suponen ningún riesgo adicional para el niño. Estas exploraciones incluyen:

1- Valoración psicomotora. Escala de Desarrollo Bayley III

La Escala Bayley de desarrollo infantil–III (Bayley-III), es un instrumento validado para la población española que valora el desarrollo funcional de niños entre 1 y 42 meses. El principal objetivo es identificar niños con un déficit en el desarrollo y dar a conocer la información necesaria para desarrollar un plan de intervención. Para el desarrollo del estudio se utilizan tres escalas:

- *Escala Cognitiva*: incluye ítems que valoran desarrollo sensorio motor, exploración y manipulación, relación de objetos, formación de conceptos, memoria y otros aspectos cognitivos.
- *Escala de Lenguaje*: compuesta por comunicación receptiva (comportamientos preverbales, desarrollo del vocabulario, capacidad de identificar objetos e imágenes que son referidas, vocabulario relacionado con el desarrollo morfológico, algunos pronombres y preposiciones, plurales,) y expresiva (comunicación preverbal, como el balbuceo, gestos, referenciación conjunta y toma de turnos; desarrollo del vocabulario; y el desarrollo morfo-sintáctico).
- *Escala Motriz*. Esta escala está dividida en motricidad fina (prensión, integración perceptual motriz, planning motor, velocidad motriz) y gruesa (mide el movimiento de extremidades y torso, posición estática, movimiento dinámico, incluyendo locomoción y coordinación, balance, planning motriz).

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Las puntuaciones escalares oscilan entre 1-19, con una media de 10 y una derivación estándar (SD) de 3. El proceso de valoración se llevará a cabo en las consultas externas de Neurocirugía del HUVH de Barcelona (Módulos A ó C).

2- Estudio no invasivo de la oxigenación cerebral

Esta prueba permite medir la oxigenación cerebral en los lóbulos frontales con un sistema de monitorización óptica no invasivo, consistente en la colocación de "parches" colocados en la parte frontal o parietal del cráneo, que no producen ningún tipo de dolor ni efecto secundario sobre el paciente. El estudio de la oxigenación cerebral no invasiva utiliza una metodología híbrida DOS-DCS (espectroscopia óptica difusa-espectroscopia de correlación difusa). Hasta la fecha, la viabilidad de estos métodos híbridos y su potencial utilidad en la práctica clínica se ha demostrado en diversas patologías neurológicas y en la neuromonitorización neonatal. La instrumentación que se utilizará en este proyecto es portátil, barata, completamente no invasiva y rápida. Esta técnica ha sido ya implementada en el ámbito pediátrico (pacientes neonatales nacidos con defectos cardíacos congénitos graves y partos prematuros graves). Las mediciones no invasivas emplean luz difusa para investigar las propiedades del tejido. La fuente y los detectores están incrustados en una almohadilla de espuma y/o plástica que puede sujetarse a la cabeza del paciente. La sonda está cubierta con relleno negro aislando la luz láser y asegurando un buen contacto con el cráneo. Las mediciones se realizarán a nivel de la convexidad frontal del cerebro y, dependiendo de los pacientes, a nivel de la zona parietal, en dos segmentos de 4 horas (4 h. diurnas y 4 h. nocturnas), repetido en 2 ocasiones.

3- Estudio de biomarcadores (BMs) encefálicos en los niños a los que se les implante una derivación de LCR

A todos los niños que requieran una derivación de LCR incluidos en el estudio se les preservará una muestra de sangre venosa en el momento del estudio preoperatorio y una muestra de LCR para la determinación de BMs relacionados con distintos tipos de lesiones celulares. El LCR se obtiene de forma habitual cuando se inserta un catéter ventricular al colocar una válvula. La muestra de sangre puede obtenerse del laboratorio cuando se realice al niño el estudio preoperatorio rutinario, por lo que implica que deba realizársele ninguna punción venosa adicional.

Las lesiones cerebrales agudas comportan alteraciones funcionales o estructurales de las células gliales y de las neuronas que pueden estudiarse mediante BMs. Para este análisis se recogerá 1 muestra sanguínea de un volumen máximo de 1mL/kg, con EDTA, que se centrifugará y se preservará el plasma. Las muestras de LCR se obtendrán al realizar la punción ventricular durante la implantación de la válvula y se recogerán en un tubo con aprotinina. Todas las muestras obtenidas se centrifugarán, alicuotarán y congelarán a -80°C hasta el momento de su análisis (ELISA). Los resultados obtenidos en el LCR se compararán con los del plasma, con el fin de relacionar los niveles de los biomarcadores en ambos compartimentos sistémicos.

Protección de datos personales:

De acuerdo con la Ley 15/1999 de Protección de Datos de Carácter Personal, los datos personales que se obtengan serán los necesarios para cubrir los fines del estudio. En ninguno de los informes del estudio aparecerá su nombre, y su identidad

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no será revelada a persona alguna salvo para cumplir con los fines del estudio, y en el caso de urgencia médica o requerimiento legal. Cualquier información de carácter personal que pueda ser identificable será conservada por métodos informáticos en condiciones de seguridad por los investigadores (Dra. MA Poca), o por una institución designada por ella. El acceso a dicha información quedará restringido al personal del servicio de Neurocirugía – Neurotraumatología del Hospital Universitari Vall d'Hebrón, designado al efecto o a otro personal autorizado que estará obligado a mantener la confidencialidad de la información.

De acuerdo con la ley vigente, tiene usted derecho al acceso de sus datos personales; asimismo, y si está justificado, tiene derecho a su rectificación y cancelación. Si así lo desea, deberá solicitarlo al médico que le atiende en este estudio.

De acuerdo con la legislación vigente, tiene derecho a ser informado de los datos relevantes para su salud que se obtengan en el curso del estudio. Esta información se le comunicará si lo desea; en el caso de que prefiera no ser informado, su decisión se respetará.

Si necesita más información sobre este estudio puede contactar con el investigador director de este estudio, la Dra. Maria Antonia Poca del Servicio de Neurocirugía del Hospital Vall d'Hebron, Tel. +34 934893514 (Ext. 4590).

Su participación en el estudio es totalmente voluntaria, y si decide no participar recibirá todos los cuidados médicos que necesite y la relación con el equipo médico que le atiende no se verá afectada.

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CONSENTIMIENTO INFORMADO PARA EL FAMILIAR DEL PACIENTE

Efectos en el desarrollo psicomotor de los niños afectos de secuelas neurológicas de una hemorragia de matriz germinal, de una dilatación benigna de los espacios subaracnoideos (hidrocefalia externa) o de un traumatismo craneoencefálico moderado o grave.

Yo, *(nombre y apellidos)* _____
en calidad de padre/madre/tutor/ tutora (tachar el que no proceda), manifiesto que:

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el protocolo.
He recibido respuestas satisfactorias a mis preguntas.
He recibido suficiente información sobre el protocolo de estudio.
He hablado con *(nombre del médico o colaborador)*: _____

Comprendo que la participación es voluntaria.

Comprendo que puedo retirar la aceptación de participar:

1) Cuando quiera
2) Sin tener que dar explicaciones
3) Sin que esto repercuta en mis cuidados médicos o los de mi familiar.

Doy mi consentimiento para que los resultados obtenidos en las pruebas que se practiquen a mi hijo/hija *(nombre y apellidos)*

_____ sean usadas para llevar a cabo dicha investigación.

De acuerdo a todo lo anterior, doy mi conformidad para que mi hijo/a participe en dicho estudio.

_____	_____	_____
Fecha	Hora	Firma del representante
_____	_____	_____
Fecha	Hora	Firma del médico o colaborador

10.1.2.3 Permission for published papers

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Nov 05, 2022

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Licensed Content Publication	Child's Nervous System
Licensed Content Title	Neurodevelopmental profile in children with benign external hydrocephalus syndrome. A pilot cohort study
Licensed Content Author	Federica Maruccia et al
Licensed Content Date	May 10, 2021
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	full article/chapter
Will you be translating?	no
Circulation/distribution	1 - 29

Society of Photo-Optical Instrumentation Engineers (SPIE)

RE: Permission request

Renae Keep <renaek@spie.org>
Mon 11/21/2022 16:06
To: Federica Maruccia <Federica.Maruccia@icfo.eu>

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Frederica,
Thank you for your note. You are most welcome to share your *Neurophotonics* article as you have described.

We wish you the very best success and look forward to the opportunity to publish your work again in the future.

Thanks for advancing light-based research and technology for the betterment of the human condition.

Sincerely,
Renae

—

Renae Keep
Senior Editor, Journals
SPIE – the international society for optics and photonics
renaek@spie.org
+1 360 685 5582

SPIE.

From: Federica Maruccia <Federica.Maruccia@icfo.eu>
Sent: Saturday, November 19, 2022 12:11 AM
To: Renae Keep <renaek@spie.org>
Subject: Permission request

Caution: This is an external email and may be malicious. Please take care when clicking links or opening attachments.

Dear Renae,

I'm wrinting to ask a question in relation with our paper pubblished in Neurophotonics:

- **Transcranial optical monitoring for detecting intracranial pressure alterations in children with benign external hydrocephalus. A proof-of-concept study**, F. Maruccia, S. Tagliabue, JB Fischer, M. Kacprzak, S. Perez-Hoyos, K. Rosas, I. Delgado-Alvarez, J. Sahuquillo, T. Durduran, MA Poca, DOI:10.1117/1.NPh.9.4.045005.

I would like to ask you the permision to attach a pdf/word version of the paper to my PhD thesis. It will be presented as collection of papers both in printed and digital version at the Universitat Autonoma de Barcelona (UAB).

Best regards,

Federica

10.2 PUBLICATIONS

10.2.1 Presentations in congresses

10.2.1.1 Oral presentation 1

S. Tagliabue, M. Kacprzak, F. Maruccia, J. Scheel, L. Castro, M. R. Vilaboa, A. Rey-Perez, M. A. Poca, J. Sahuquillo, and T. Durduran, "The impact of hyperventilation therapy on cerebral blood flow and oxygenation in traumatic brain injured patients measured by diffuse optics," in *Biophotonics Congress: Biomedical Optics Congress 2018 (Microscopy/Translational/Brain/OTS)*, OSA Technical Digest (Optica Publishing Group, 2018), paper CW2B.4. https://opg.optica.org/abstract.cfm?URI=Translational-2018-CW2B.4

doi.org/10.1364/TRANSLATIONAL.2018.CW2B.4

10.2.1.2 Oral presentation 2

J. B. Fischer, A. Ghouse, S. Tagliabue, F. Maruccia, A. Rey-Perez, M. Báguena, P. Cano, R. Zucca, U. M. Weigel, J. Sahuquillo, M. A. Poca, and T. Durduran, "Non-invasive estimation of intracranial pressure by diffuse correlation spectroscopy," in *Biophotonics Congress: Biomedical Optics 2020 (Translational, Microscopy, OCT, OTS, BRAIN)*, OSA Technical Digest (Optica Publishing Group, 2020), paper BTh3C.4.
https://opg.optica.org/abstract.cfm?URI=BRAIN-2020-BTh3C.4

https://doi.org/10.1364/BRAIN.2020.BTh3C.4

10.2.1.3 Oral presentation 3

Jonas B. Fischer, Susanna Tagliabue, Federica Maruccia, Amelia Jiménez-Sánchez, Eashani Sathialingam, Wesley B. Baker, Aykut Eken, Ameer Ghouse, Anna Rey-Perez, Marcelino Báguena, Katiuska Rosas, Ofer Sadan, Prem A. Kandiah, Owen B. Samuels, Ramani Balu, Riccardo Zucca, Udo M. Weigel, David R. Busch, Erin M. Buckley, Arjun G. Yodh, Daniel J. Licht, W. Andrew Kofke, Maria A. Poca, Gemma Piella, Juan Sahuquillo, and Turgut Durduran, "Non-invasive estimation of intracranial pressure by fast correlation spectroscopy: a multi-center study", Proc. SPIE 11639, Optical Tomography and Spectroscopy of Tissue XIV, 1163912 (March 2021).

doi.org/10.1117/12.2577561

10.2.1.4 Oral presentation 4

Susanna Tagliabue, Claus Lindner, Ivette Chochrrón da Prat, Ángela Sánchez-Guerrero, Isabel Serra Mochales, Michal Kacprzak, Federica Maruccia, Udo M. Wiegel, Miriam de Nadal, Juan Sahuquillo, and Turgut Durduran "Cerebral hemodynamics and oxygen metabolism versus the bispectral index during propofol-induced anesthesia", Proc. SPIE PC11945, Clinical and Translational Neurophotonics 2022, PC1194503 (7 March 2022).

doi.org/10.1117/12.2608237

10.2.1.5 Oral presentation 5

S. Tagliabue, M. Kacprzak, A. Rey-Perez, J. Baena, M. R. Vilaboa, F. Maruccia, J. Fischer, M. A. Poca, J. Sahuquillo, and T. Durduran, "Quality control in hybrid diffuse optical neuro-monitoring when probing atypical or injured cerebral tissue," in *Biophotonics Congress: Biomedical Optics 2022 (Translational, Microscopy, OCT, OTS, BRAIN)*, Technical Digest Series (Optica Publishing Group, 2022), paper BTu2C.7.

https://opg.optica.org/abstract.cfm?URI=BRAIN-2022-BTu2C.7

doi.org/10.1364/BRAIN.2022.BTu2C.7