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RESEARCH ARTICLE

Development and Preliminary Validation of a Parkinsonism-Dystonia Scale for Infants and Young Children

Roser Pons, MD,[1*] Toni S. Pearson, MD,[2] Belen Perez-Dueñas, MD,[3] Angels Garcia-Cazorla, MD,[4] Manju A. Kurian, MD,[5,6] Zoi Dalivigka, MD,[7] Vasiliki Zouvelou, MD,[1] Chrysa Outsika, PT,[1] Eleftheria Kokkinou, MD,[1] Maria Sigatullina-Bondarenko, MD,[4] Alejandra Darling, MD,[4,8] Maria del Mar O'Callaghan, MD,[4,9] Robert Spaull, MD,[5] Dora B.D. Steel, MD,[5] Evdokia Salamou, MD,[1] Maria João Forjaz, PhD,[10,11] and Carmen Rodriguez-Blazquez, PhD[12]

ABSTRACT: Background: Parkinsonism in infancy is rare and is highly correlated with the presence of dystonia. Advances in treating and characterizing developmental and infantile degenerative parkinsonism have highlighted the need for a specialized assessment scale.
Objective: The aim of this study was to design and validate a scale that effectively assesses parkinsonism-dystonia in early life.
Methods: The Infantile Parkinsonism-Dystonia Rating Scale (IPDRS) was designed to capture the key clinical features of parkinsonism-dystonia in early life. It consists of 28 items across three subscales: Non-motor symptoms, Motor symptoms, and Dyskinesias. Thirty-two patients with hypokinetic movement disorder were scored following a standardized protocol. Filmed motor examinations were analyzed independently by three pediatric movement disorders specialists to evaluate interrater reliability. Twenty additional patients with primary neurotransmitter disorders were scored, and nine of them were evaluated at baseline and after treatment. Psychometric validation was conducted.
Results: A total of 52 patients were scored using the IPDRS. Mean age was 3.1 years (standard deviation [SD]: 2.0), and the mean IPDRS score was 40.8 (SD: 13.17). Internal consistency analysis demonstrated a Cronbach's α of 0.21 for Non-motor symptoms subscale, 0.84 for Motor symptoms subscale, and 0.95 for Dyskinesia subscale. Kappa indexes exceeded 0.70 in seven items. Correlation coefficients for dystonia items with the Barry-Albright-Dystonia Scale ranged from 0.46 to 0.64. After treatment, all IPDRS scores changed significantly, with an effect size of 2.42.
Conclusions: The IPDRS appears to be a reliable and valid tool for assessing parkinsonism in early life. Further validation studies with a larger sample size are needed to confirm these findings and complete the validation process. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: parkinsonism; hypokinesia; bradykinesias; dystonia; dopamine

[1]First Department of Pediatrics, Agia Sofia Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece; [2]Division of Neurology, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio, USA; [3]Pediatric Neurology Research Group, Vall d'Hebron Research Institute, Autonomous University of Barcelona, CIBERER, Spanish National Network for Research on Rare Diseases, Barcelona, Spain; [4]Neurometabolic Unit, Neurology Department, Institut de Recerca, MetabERN and CIBERER, Hospital Sant Joan de Déu, Barcelona, Spain; [5]Molecular Neurosciences, Developmental Neurosciences, Zayed Centre for Research into Rare Disease in Children, UCL Great Ormond Street Institute of Child Health, London, United Kingdom; [6]Department of Neurology, Great Ormond Street Hospital, London, United Kingdom; [7]Pediatric Rehabilitation Department, Pan & Aglaias Kyriakou Children's Hospital, Kallithea, Greece; [8]Movement Disorders Unit, Neurology Department, Hospital Sant Joan de Déu, Barcelona, Spain; [9]Genetics and Molecular Medicine Service, Hospital Sant Joan de Déu, Barcelona, Spain; [10]Red de Investigación en Cronicidad, Atención Primaria y Promoción de la Salud, Madrid, Spain; [11]Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain; [12]Centro Nacional de Epidemiología y Centro de Investigaciones Biomédicas en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Madrid, Spain

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*Correspondence to: Dr. Roser Pons, First Department of Pediatrics, Agia Sofia Children's Hospital, National and Kapodistrian University of Athens, Thivon and Levadias, 11527 Athens, Greece.
E-mail: roserpons@med.uoa.gr

Roser Pons and Toni S. Pearson contributed equally to this work.

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Parkinsonism represents a hypokinetic movement disorder characterized by the cardinal motor features observed in adult Parkinson's disease, which are due to degeneration of dopaminergic neurons in the substantia nigra.[1] According to the Movement Disorder Society (MDS), parkinsonism is defined by the presence of bradykinesia in combination with tremor, rigidity, or both.[2] Juvenile parkinsonism is defined as parkinsonism with onset before 21 years of age. Further subcategorization by age of onset has clinical utility given the differences in etiology in infants (birth to 2 years), childhood (>2 years), and adolescence (>12 years).[3,4]

Infantile and pediatric parkinsonism is rare, and its underlying pathophysiological mechanisms differ from those observed in adult-onset cases. It can emerge as a symptom of various genetic diseases and, in rare instances, as a result of acquired conditions. Parkinsonism in this age group encompasses a spectrum of variable manifestations and outcomes, where parkinsonism may be the predominant symptom or may present in combination with other neurological signs.[3,4] It is not only the underlying disease processes that differ between children and adults; in addition, the motor manifestations of parkinsonism differ in several respects, particularly in infants and young children: hypokinesia is commonly associated with hypotonia rather than rigidity, rest tremor is infrequent, and dystonia often coexists. Due to the frequent association with dystonia, parkinsonism in infancy is often referred to as infantile parkinsonism-dystonia.[5] In addition, postnatal brain development can result in the evolution of the phenotype over time or age-dependent phenotypic expression in some disorders, adding further complexity to the diagnosis.[3] These particularities pose challenges in both the recognition and the assessment of parkinsonism in early life.[1,3,4,6]

In recent years, there has been a notable surge in the diagnosis and understanding of monoamine neurotransmitter disorders associated with deficiency in the synthesis of dopamine.[7] Patients often manifest infantile parkinsonism together with developmental delay, axial hypotonia, dystonia, oculogyric crises (OGCs), and features of autonomic and endocrine dysfunction. In this group of disorders, parkinsonism is referred to as *developmental parkinsonism* because of the hypothesized nondegenerative disruption of dopaminergic connectivity during a critical period of neuromotor development in infancy and early childhood. Patients are treated with dopaminergic medications and show variable but persistent response to treatment.[4]

Recent advancements in next-generation sequencing technology have enabled the identification of a number of disorders emerging in early life that selectively involve the nigrostriatal pathway and result in a progressive degenerative course that mimics that of Parkinson's disease. These conditions are collectively termed *infantile degenerative parkinsonism*, with some of them demonstrating evidence of nigrostriatal degeneration on dopamine transporter scan.[3,4] In these patients, parkinsonism is often accompanied by various neurological manifestations, such as dystonia, myoclonus, OGCs, or dysautonomia. Response to dopaminergic drugs varies, with some patients experiencing an initial dramatic response followed by deterioration and motor fluctuations.[4]

The characterization of *developmental parkinsonism* and *infantile degenerative parkinsonism* as outlined earlier has spurred interest in the development of a tailored scale to assess parkinsonism and the highly prevalent dystonia in infants and young children. Such a scale needs to accommodate the unique characteristics of this hypokinetic movement disorder during early life and to permit the assessment of motor symptoms without requiring a child to follow instructions to perform specific voluntary movements, as is required by scales designed for adults, such as the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[8] We aimed to create a standardized method for evaluating disease severity, disease progression, and treatment response. This scale would have clinical value and, moreover, could support clinical research activities by facilitating the evaluation of novel treatments and fostering communication among researchers.

In this study, we have developed a rating scale specifically tailored for infants and young children with hypokinetic movement disorders. The objective of this study was to describe the development of a tool for quantifying the severity of parkinsonism and other associated features, monitoring disease progression, and evaluating treatment responses in clinical settings, as well as to perform pilot testing of the scale and conduct a preliminary analysis of its main psychometric attributes.

Subjects and Methods

Development of a Parkinsonism-Dystonia Rating Scale for Infants and Early Childhood

To design the scale, two of the authors (R.P. and T.S.P.) first selected the main clinical features of parkinsonism in infants and young children based on literature review[3,4,7] and clinical experience. Established and validated scales and assessment tools served as references, including the MDS-UPDRS,[8] Hypertonia Assessment Tool,[9] Hammersmith Infant Neurological Examination,[10] and Gross Motor Function Classification System.[11]

Recognizing the frequent presence of dystonia in *developmental* and *infantile degenerative parkinsonism*, it was deemed essential to incorporate this movement

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disorder as a key component of the scale. Consequently, the scale was designated as the "Infantile Parkinsonism-Dystonia Rating Scale" (IPDRS) (Supporting Information Data S1).

The IPDRS was constructed as a scale of 28 items grouped into three subscales: (1) Non-motor symptoms, (2) Motor symptoms, and (3) Dyskinesia. The scale incorporates a combination of clinician-reported outcome and observer-reported outcome elements. Instructions for raters on how to assess and score the three subscales are provided in Supporting Information Data S2.

1. *Non-motor symptoms subscale*: This subscale evaluates the presence and frequency of manifestations suggestive of autonomic dysfunction and emotional lability. It consists of five items addressing groups of autonomic dysfunction manifestations including: (1) sudomotor function and thermoregulation; (2) respiratory secretomotor function; (3) gastrointestinal motor function; (4) sleep; and (5) other symptoms, which include a miscellaneous group of manifestations such as myosis and ptosis, blood pressure or heart rhythm irregularities, among others. The sixth item of this subscale evaluates emotional lability.
2. *Motor symptoms subscale*: This subscale evaluates the presence of the cardinal features of parkinsonism, as defined by the MDS, including bradykinesia, tremor, and rigidity, as well as OGCs, dystonia, axial hypotonia, and motor development. It consists of 19 items, divided into two categories:
   Cardinal features of parkinsonism: nine items assessing bradykinesia (spontaneous movements across global, facial, lower limbs, and upper limbs, as well as voluntary movements of the upper limbs), tremor (distribution and severity), and rigidity (distribution and severity). Additional motor symptoms: 10 items evaluating OGCs (severity, duration, frequency), dystonia severity (facial, axial, upper limbs, and lower limbs), axial hypotonia (cervical and truncal), and motor development
3. *Dyskinesia subscale*: This subscale evaluates involuntary hyperkinetic movements, including chorea, athetosis, ballism, myoclonus, and hyperekplexia. It consists of three items: severity, duration, and distribution of the hyperkinetic movement disorder. Dystonia is not included because this movement disorder is assessed under the Motor symptom subscale. Stereotypies and tics are also excluded, because they are exceptionally reported in patients with infantile parkinsonism.

The Non-motor symptoms subscale and the OGCs from the Motor symptoms subscale are based on caregiver reports under clinician supervision. A set of structured questions to address these items is provided in the Instructions for Raters (Supporting Information Data S2).

Each item employs a five-level response format, where a score of 0 indicates the absence of a manifestation and a score of 4 represents its maximum severity (Supporting Information Data S1).

To evaluate the clarity, relevance, and intelligibility of the scale for the target population of users, we conducted focus group discussions with members of the European Reference Network for rare neurological disorders and the International Working Group on Neurotransmitter Related Disorders. In addition, a questionnaire was administered to several international experts in pediatric movement disorders to rate the scale's ability to capture relevant clinical features of dopamine deficiency in infants and young children, comprehensiveness, and clinical utility. The questionnaire and a summary of the expert responses are described in Supporting Information Data S3.

Assessment and Procedure

Thirty-two consecutive patients underwent assessment with the IPDRS during regular follow-up visits at the Pediatric Neurology Unit of the First Department of Pediatrics at Agia Sofia hospital from 2020 to 2024.

Inclusion criteria comprised patients of preschool age (<6 years) with evidence of slowness or paucity of voluntary and spontaneous movements. Patients older than 6 years and those demonstrating muscle weakness in the setting of neuromuscular disorders were excluded. Dystonia was scored using the Barry–Albright Dystonia (BAD) Scale,[12] and spasticity was scored using the Modified Tardieu scale (muscle reaction quality component).[13]

All patients were recorded on video following a standardized protocol that included several positions and tasks: lying supine and prone, sitting with or without support, and undergoing axial tone examination. Whenever feasible, more advanced motor tasks, including reaching, grasping, standing, or walking, were also recorded. In addition, when applicable, spontaneous play or object manipulation was filmed, either while the patient was in the caregiver's arms, sitting with or without support, or moving freely in the office.

The study was approved by the Ethics Committee of Agia Sofia hospital (AP 24067/19-10-16). All parents/legal guardians signed consent for video recording.

Using the videotaped material, three senior specialists in pediatric movement disorders (R.P., T.S.P., and B.P.-D.) analyzed the first 30 patients independently to assess interrater reliability. Nonmotor manifestations, OGCs, and rigidity were excluded from this analysis.

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Thirty-two patients from Agia Sofia hospital who fulfilled the earlier criteria were scored following the study protocol and included patients with the following conditions: 4 with mitochondrial disorders with basal ganglia lesions, 3 with developmental epileptic encephalopathy, 3 with primary neurotransmitter disorder, 2 with Aicardi-Goutières syndrome, 1 with acute necrotizing encephalitis, 1 with urea cycle disorder, 1 with Lesch-Nyhan disease, 1 with Canavan disease, and 16 with acquired ischemic lesions (9 neonatal hypoxic ischemic encephalopathy, 5 periventricular leukomalacia, 1 venous sinus thrombosis, and 1 Moyamoya disease).

Twenty additional patients outside the study protocol were also scored with the IPDRS and included:

- Eight patients with disorders of monoamine neurotransmitter synthesis, followed at Agia Sofia hospital (R.P.): These patients were retrospectively scored based on clinical notes and available video recordings. Three of these patients were scored multiple times during treatment titration:
  - One patient was scored at baseline and at 1, 6, and 15 months after initiation of levodopa (L-dopa)/decarboxylase inhibitor (DCI) treatment on 2.2, 4.8, and 10 mg/kg/day, respectively.
  - One patient was scored at baseline and at 1, 5, and 25 months after gene therapy.
  - One patient was scored at baseline and at 3 and 10 months after initiation of L-dopa/DCI treatment on 1.1 and 7.1 mg/kg/day, respectively.
- Six patients with disorders of monoamine neurotransmitter synthesis followed at the Department of Neurology in Great Ormond Street Hospital (London, UK): These patients underwent on-site scoring, as part of routine clinical assessment, by pediatric neurologists with expertise in movement disorders (M.A.K., R.S., and D.B.D.S.).
- Six patients with L-aromatic amino acid decarboxylase (AADC) deficiency treated with direct midbrain delivery of AAV2-AADC gene therapy in the Departments of Pediatrics and Neurology, Nationwide Children's Hospital (Columbus, OH, USA; T.S.P.). These patients were scored at baseline and 6 and 12 months after gene therapy. These patients were scored based on review of anonymized video recordings during neurological examination and gross motor function measure assessments.

Data Analysis

Descriptive statistics were applied to all variables: frequencies and percentages for categorical data, and means and standard deviations (SDs) for continuous data. The IPDRS total score did not follow a normal distribution. For the psychometric validation of the IPDRS, the following parameters were analyzed:

- Data quality and acceptability (the extent to which the scale can be used in an acceptable way)[14] were assessed through the percentage of missing data (criterion: ≤5%), fully computable data (criterion: ≥95%), floor and ceiling effects (criterion: <15%), skewness (criterion values, −1 to +1), and range of observed versus theoretical scores for items (criterion: coincident).[14]
- Reliability was analyzed through internal consistency (the extent to which all the items are measuring the same construct) and interrater reliability (the extent to which two raters agree in the scoring).[14]

TABLE 1 *Data quality, acceptability, and internal consistency of IPDRS*

	Non-motor symptoms subscale	Motor symptoms subscale	Dyskinesia subscale	IPDRS total
Data quality and acceptability				
Mean (SD)	7.90 (4.14)	31.62 (11.10)	1.62 (2.88)	40.8 (13.17)
Median	7.5	33.0	0	42.5
Observed range	0–18	2–54	0–9	4–74
Skewness	0.59	−0.74	1.50	−0.15
Floor effect, %	1.9	2.0	73.1	2.0
Ceiling effect, %	3.8	2.0	3.8	2.0
Reliability: internal consistency				
Cronbach's α	0.21	0.84	0.95	–
Corrected item-total correlation	−0.15 to 0.26	0.01–0.81	0.90–0.97	–
Interitem correlation coefficient	−0.26 to 0.35	−0.28 to 0.94	0.83–0.94	–
Item homogeneity index	0.05	0.22	0.90	–

Abbreviations: IPDRS, Infantile Parkinsonism-Dystonia Rating Scale; SD, standard deviation.

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- For internal consistency, Cronbach's α (criterion: α ≥ 0.70), item-total corrected correlation coefficients (criterion: >0.20), interitem correlation coefficient (criterion: 0.20–0.75), and item homogeneity index (criterion: ≥0.30) for each subscale were calculated.[15] Interrater reliability was assessed using the percentage of agreement and weighted kappa with quadratic weights index (criterion: ≥0.60) for items.[16]
- For convergent validity, a moderate Spearman's rank correlation coefficient (0.30–0.49) of the IPDRS items and subscales scores with BAD scale was hypothesized.[17] For known-groups validity, because of the diverse pathophysiology and clinical presentation among patients in relation to their conditions, significant differences in IPDRS by type of disease was hypothesized. Internal validity, that is, the association between subscales composing the scale, was calculated using Spearman's rank correlation coefficient, with coefficients between 0.30 and 0.70 deemed as satisfactory.[16]
- Nine children were assessed again at follow-up after treatment (the three patients from Agia Sofia Hospital on dopaminergic treatment and the six patients from Nationwide Children's Hospital after gene therapy). The Mann–Whitney test for comparing baseline and follow-up scores and effect size was calculated using Cohen's formula[18,19]: $(mean_{t2} - mean_{t1})/SD_{t1}$. A change in IPDRS scores was considered large if the ES was ≥0.80. Only the baseline IPDRS scores of these nine patients were used for psychometric analysis.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

IBM SPSS statistical software was used for calculations, and statistical significance was set at $P < 0.05$.

Results

A total of 52 patients were scored with the IPDRS; 55.8% were male patients, and the mean age was 3.1 years (SD: 2.0). The BAD scale showed a mean score of 11.7 (SD: 6.0), and the Tardieu scale had a median value of 1.8 (interquartile range: 1–2.25).

The mean total IPDRS score for all patients was 40.8 and the median 42.5 (SD: 13.17, range: 4–74). Missing data were minimal (only two missing data items in the Motor symptoms subscale), and floor and ceiling effects were absent (2.0% for both). Only the Dyskinesia subscale showed a floor effect (73.1%) (Table 1).

Regarding internal consistency, Cronbach's α was below the threshold only in Non-motor symptoms subscale (α: 0.21), whereas it was 0.84 for Motor symptoms and 0.95 for Dyskinesia subscales (Table 1). Corrected item-total correlation coefficients were lower than the standard criterion in most items in the Non-motor symptoms subscale and in six items in the Motor signs subscale. Interitem correlation coefficients were within the standard limits for Non-motor symptoms,

TABLE 2 *Interrater reliability of the IPDRS motor items*

	Rater 1 vs. 2		Rater 1 vs. 3	
	% agreement	Kappa index	% agreement	Kappa index
Body hypokinesia	95.19	0.75	95.93	0.79
Face hypokinesia (hypomimia)	95.00	0.66	93.13	0.55
Hypokinesia: spontaneous upper limb movements	95.56	0.71	92.72	0.62
Hypokinesia: voluntary upper limb movements	96.67	0.77	95.93	0.77
Hypokinesia: spontaneous lower limb movements	95.93	0.76	93.33	0.66
Tremor: distribution	96.67	0.65	93.33	0.45
Tremor: severity	98.33	0.65	98.33	0.79
Facial, ocular, and/or oromandibular dystonia	93.75	0.74	90.00	0.60
Cervical, laryngeal, and/or truncal dystonia	82.59	0.42	88.96	0.52
Dystonia of the upper limbs	93.97	0.39	94.37	0.38
Dystonia of the lower limbs	89.51	0.19	87.71	0.16
Head lag	95.91	0.82	97.63	0.89
Truncal hypotonia	94.18	0.68	95.04	0.72
Motor delay	96.67	0.80	97.50	0.74

Abbreviation: IPDRS, Infantile Parkinsonism-Dystonia Rating Scale.

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TABLE 3 *IPDRS total scores by type of deficiency (discriminative validity)*

	Total IPDRS	Non-motor symptoms subscale	Motor symptoms subscale	Dyskinesia subscale
Mixed neural disorders with bradykinesia-hypokinesia	39.23 (8.43)	5.53 (3.07)	31.70 (6.78)	0.60 (1.90)
Neurotransmitter patients: treated	28.50 (23.17)	8.33 (4.56)	17.50 (20.53)	2.17 (2.48)
Neurotransmitter patients: untreated	38.63 (13.58)	5.38 (2.39)	30.88 (11.62)	0.38 (1.06)
AADC deficiency patients before gene therapy	55.00 (13.13)	8.00 (4.50)	39.13 (13.37)	6.25 (3.01)
P[a]	0.013	0.152	0.068	<0.001

Means (SD) are displayed.
Abbreviations: IPDRS, Infantile Parkinsonism-Dystonia Rating Scale; AADC, L-aromatic amino acid decarboxylase; SD, standard deviation.
[a]Kruskal–Wallis test.

TABLE 4 *Convergent and internal validity of the IPDRS*

IPDRS Items	Barry-Albright scale	IPDRS Non-motor subscale	IPDRS Motor symptoms subscale
Non-motor subscale	**0.06**	–	**0.14**
Body hypokinesia	−0.12		
Face hypokinesia (hypomimia)	−0.25		
Hypokinesia: spontaneous upper limb movements	−0.06		
Hypokinesia: voluntary upper limb movements	−0.12		
Hypokinesia: spontaneous lower limb movements	−0.15		
Tremor: distribution	−0.11		
Tremor: severity	−0.10		
Rigidity: distribution	−0.11		
Rigidity: severity	−0.11		
Facial, ocular, and/or oromandibular dystonia	0.47[a]		
Cervical, laryngeal, and/or truncal dystonia	0.64[a]		
Dystonia of the upper limbs	0.46[a]		
Dystonia of the lower limbs	0.58[a]		
Head lag	0.01		
Truncal hypotonia	−0.35		
Motor delay	0.16		
Motor symptoms subscale	0.09	–	–
Dyskinesia: severity	−0.26		
Dyskinesia: duration	−0.26		
Dyskinesia: body parts	−0.27		
Dyskinesia subscale	**−0.25**	**0.15**	**0.24**
IPDRS total	**0.06**	–	–

Spearman's correlation coefficients.
Abbreviation: IPDRS, Infantile Parkinsonism-Dystonia Rating Scale.
[a]$P < 0.05$.

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TABLE 5 *Responsiveness of the IPDRS (N = 9)*[a]

	Baseline	First follow-up	Second follow-up	*P*[b]	Effect size
Non-motor subscale	7.50 (3.21)	3.67 (3.50)	2.00 (2.28)	0.016	1.71
Motor symptoms subscale	37.00 (15.00)	11.33 (4.32)	9.83 (3.87)	0.013	1.81
Dyskinesia subscale	6.50 (3.51)	10.50 (0.55)	10.33 (1.03)	0.004	1.09
IPDRS total	52.67 (13.23)	26.17 (7.60)	22.50 (5.36)	0.004	2.28

Means (SD) are displayed for scores.
Abbreviations: IPDRS, Infantile Parkinsonism-Dystonia Rating Scale; SD, standard deviation.
[a]Three patients with monoamine neurotransmitter disorders treated with dopaminergic medication and six patients with L-aromatic amino acid decarboxylase deficiency treated with gene therapy.
[b]Mann–Whitney test for baseline vs. second follow-up comparison.

and for the Motor and Dyskinesia subscales there were coefficients greater than 0.70. Item homogeneity index was below the threshold only for the Non-motor symptoms subscale (0.05).

Interrater reliability was analyzed with the first 30 patients, and results are displayed in Table 2, including the percentage agreement and Kappa index for each motor item assessed between raters. The items body hypokinesia, facial expression, voluntary upper limb movements, and motor delay demonstrated high agreement, with percentages ranging from 90.00% to 98.33%. Body hypokinesia, head lag, and motor delay showed substantial agreement with Kappa values greater than 0.75. Dystonia of the lower limbs and of the upper limbs had the lowest Kappa indices (as low as 0.16 and 0.19, respectively).

IPDRS scores did not differ by sex or age. Total score and Dyskinesia subscale values were significantly higher in patients with disorders of monoamine neurotransmitter synthesis (Table 3).

The correlation coefficients of the IPDRS total and Motor and Dyskinesia subscales with BAD scales are depicted in Table 4. Items on dystonia reached values from 0.46 to 0.64 with the BAD scale. Regarding internal validity, subscales correlated from 0.14 (Non-motor with Motor symptoms) to 0.24 (Motor symptoms with Dyskinesia) (Table 4).

Nine patients with monoamine neurotransmitter disorders were sequentially assessed before and after treatment. After treatment, all IPDRS scores showed significant changes (Table 5). The effect size for the total score was 2.28, with subscale effect sizes ranging from 1.09 to 1.81.

Discussion

We have developed the IPDRS, the first rating scale designed to measure the severity of parkinsonism-dystonia in infancy and early childhood. The IPDRS has been constructed based primarily on the clinical features of parkinsonism-dystonia in this age group[3,4,6] and on the structure of the MDS-UPDRS for Parkinson's disease.[8] These elements guided the development of its three subscales: (1) Non-Motor, reflecting autonomic and emotional symptoms; (2) Motor, capturing the cardinal features of parkinsonism along with dystonia and associated motor abnormalities; and (3) Dyskinesia, assessing hyperkinetic movements as part of the underlying condition or as a treatment effect. Preliminary results from this pilot study demonstrate that the psychometric properties of the scale are promising, with reliability and validity indicating its potential usefulness in clinical practice. The IPDRS can quantify the severity of parkinsonian and dystonic features in early life and can serve as a tool to establish baseline status and monitor response to treatment over time.

The Cardinal Features of Parkinsonism (Bradykinesia, Tremor, and Rigidity) in the IPDRS

Bradykinesia is a cardinal motor symptom of parkinsonism that refers to reduced velocity of movements. Recently, the concept of "bradykinesia complex" has been proposed that encompasses a range of features associated with bradykinesia and includes related abnormalities, such as hypokinesia (reduced movement amplitude), sequence effect (progressive reduction in speed and amplitude of movements during repetitive tasks), hesitations/halts, akinesia (absence of movement), and oligokinesia (reduction or lack of spontaneous/automatic movements).[20] Kinematic and neurophysiological studies in adult patients with monoamine neurotransmitter disorders have shown significantly reduced velocity, diminished movement amplitude, and irregular rhythm during repetitive finger-tapping tasks.[21] Assessing these features in infants and young children is challenging due to their early stage of neuromotor development. In addition, patients often have accompanying motor developmental delay and may be unable to follow instructions, further complicating the assessment process. A third challenge

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is that parkinsonism in early life is often associated with additional neurological manifestations that can also influence movement velocity and amplitude. Consequently, four of the five bradykinesia items in the IPDRS focused on the assessment of spontaneous movements (of the entire body, face, upper limbs, and lower limbs, respectively). Recognizing that infants may have developed the ability to reach and grasp, one item rating voluntary movements of the upper limbs was also incorporated into the assessment.

Bradykinesia is not exclusive to parkinsonism and can be seen in patients with dystonia[22] and with diseases primarily involving the corticospinal system and the cerebellum, as well as those with cognitive disturbances and psychiatric disorders.[23] As stated earlier in the Subjects and Methods section, the main inclusion criterion for our study was the presence of a hypokinetic movement disorder in the absence of muscle weakness attributable to a neuromuscular disorder, regardless of whether the patient met the criteria of parkinsonism according to the MDS. This enabled us to assess a wide array of different conditions ranging from mitochondrial disorders with basal ganglia lesions to acquired ischemic lesions in early life. Notably, all patients in our cohort exhibited varying degrees of dystonia, whereas only two patients exhibited prominent corticospinal tract dysfunction (scoring >3 on the Modified Tardieu Scale), which was identified as the main cause of their reduced motor activity.

The manifestation of tremor in infancy and early childhood parkinsonism diverges from that seen in adults with Parkinson's disease and varies depending on the underlying disease.[3,4,24,25] In infants with monoamine neurotransmitter disorders, tremor is observed in 75% of cases, although only around a quarter of them exhibit rest tremor.[3] Moreover, within this group of disorders, tremor can emerge in the first months of life as a paroxysmal or continuous rest and action coarse tremor with high amplitude and low frequency that involves the upper limbs and eventually generalizes. The tremor vanishes after 2–6 months either spontaneously or promptly with L-dopa treatment.[4] In this group of diseases, tremor can also be dystonic in nature (personal observations R.P.). Consequently, in the IPDRS, the presence, severity, and distribution of all types of tremor are included.

In *infantile degenerative parkinsonism*, rigidity is a predominant feature.[3,4] Conversely, in *developmental parkinsonism* related to monoamine neurotransmitter disorders, patients typically exhibit axial hypotonia, whereas appendicular tone varies widely, including hypotonia, hypertonia, fluctuating tone, rigidity, and even spasticity.[26] It is thought that the presence of dystonia could explain some of these tone abnormalities, because dystonia may cause hypertonia when it is present at rest (dystonic hypertonia), and also because dystonia fluctuates in presence and severity depending on factors such as body position, emotional state, or level of consciousness.[27] Assessment of axial tone has been incorporated into the IPDRS, given its clinical relevance in *developmental parkinsonism*. Some authors have proposed that this prevalent feature may represent the earliest expression of postural derangement in early life.[4]

Analysis of the IPDRS

The pilot testing demonstrates good data quality and acceptability. The only floor effect we observed was in the Dyskinesia subscale. Dyskinesias are commonly associated with patients with parkinsonism syndromes who are receiving dopaminergic treatment. Because only a minority of our study participants were receiving dopaminergic therapy, it is plausible that this contributed to the relative absence of dyskinesia in our cohort.

Internal consistency of the Motor symptoms subscale was generally adequate. For the Non-motor symptoms subscale, which evaluates features of autonomic dysfunction and emotional lability, internal consistency was lower. This was not unexpected because the Non-motor symptoms subscale contains a heterogeneous selection of symptoms, and patients with *developmental parkinsonism* as a result of neurotransmitter disorders typically exhibit a variable subset of these manifestations. For instance, although emotional lability is very characteristic of some neurotransmitter disorders such as AADC deficiency, it is not prevalent in others. In addition, because this subscale relies on caregiver reports with clinician assistance, variability in the questions and their interpretation by caregivers and clinicians may have contributed to the lower internal consistency. To address this, we developed a set of standardized questions, included in the "Instructions for Raters" (Supporting Information Data S2), to enhance consistency. These questions will be used in future studies with larger patient cohorts to further advance the validation of the scale.

Interrater reliability was demonstrated for most items of the scale, although it was relatively low for axial and limb dystonia. Notably, interrater reliability for all bradykinesia items demonstrated high agreement, which is noteworthy given the challenges in developing anchor descriptions for use in the young age group for which this scale was designed. In general, further clarification of the instructions and the future development of a teaching video may help to facilitate scoring and reduce inconsistency in rating for these items.

Regarding convergent validity, low correlation coefficients were observed between the BAD scale and the IPDRS. This outcome was anticipated, given the lack of scales specifically designed to evaluate hypokinetic movement disorders during early development, which

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would have been more suitable for assessing this clinimetric measure. Conversely, and also consistent with our expectations, dystonia exhibited strong correlation coefficients with the BAD scale.

Weak-to-moderate positive correlations were observed between the IPDRS subscales. This is likely attributable to the complex and heterogeneous nature of parkinsonism in early life. These findings underscore the necessity of reporting subscales separately, because each subscale captures distinct aspects of the condition, similar to the structure of the MDS-UPDRS, where different parts of the scale address specific elements of Parkinson's disease. This separation allows for a more comprehensive and accurate reflection of the complex nature of infantile parkinsonism-dystonia, providing better insight into the various manifestations and their progression.

Known-groups validity analysis demonstrated that the total IPDRS score, along with the Dyskinesia and Motor signs subscales, were significantly higher in patients with monoamine neurotransmitter disorders. These findings indicate that the IPDRS could be useful in clinical settings for effectively identifying and assessing individuals with such disorders. This finding is of particular interest because, in *developmental parkinsonism* caused by neurotransmitter disorders, dyskinesias induced by dopaminergic treatment occur early in the treatment course and are a reflection of response to treatment, whereas lower dyskinesia scores may reflect the eventual restoration of a more physiological dopamine state in these patients.[28,29] In contrast, in *infantile degenerative parkinsonism*, patients are more likely to exhibit patterns similar to Parkinson's disease, where high dyskinesia scores may represent disease progression and are viewed as a treatment complication.

Three patients with monoamine neurotransmitter disorders were scored retrospectively at baseline and during titration of dopaminergic treatment, and six patients with AADC deficiency were scored at baseline and 6 and 12 months after gene therapy. In all of these patients, clinical improvements were accurately reflected by the reduction in Motor and Non-motor subscale scores, as well as the total IPDRS score. These results are relevant for clinical practice because they suggest that the scale is useful to measure severity of parkinsonism and for monitoring the response to treatment over time.

The main limitation of this study is the inclusion of a highly heterogeneous set of pediatric conditions, with a small number of cases of developmental parkinsonism and no cases of *infantile degenerative parkinsonism*—an exceptionally rare condition with only a few identified genetic causes.[3,7] In addition, acquired causes of parkinsonism are exceedingly rare in early childhood.[4] These factors collectively posed a significant challenge in assembling a patient cohort for validating the IPDRS. However, through retrospective reviews and international collaborations, we were able to evaluate a total of 23 patients with disorders of monoamine neurotransmitter synthesis typically associated with *developmental parkinsonism*.

Another limitation is the lack of anchor descriptions for bradykinesia severity ratings from mild to severe. Although the UPDRS-MDS scale includes upper and lower limb repetitive tasks with well-defined anchors, these are not suitable for infants and young children due to developmental limitations. Even in children capable of performing these tasks, attention and cooperation may be inconsistent. However, interrater reliability for bradykinesia items remained high, with consistency percentages ranging from 93.33% to 96.67%, indicating that despite the absence of anchors, raters could reliably differentiate between mild and severe bradykinesia, thereby reducing the impact of this limitation.

Assessing movement disorders in very young patients is particularly complex due to age-dependent phenotypic variations influenced by ongoing brain development.[30] This variability is evident in monoamine neurotransmitter disorders linked to *developmental parkinsonism*, where tremor may manifest in an age-specific manner, potentially linked to the maturation of descending motor pathways and oscillatory thalamocortical activity.[24,25] Similarly, Segawa disease, caused by autosomal dominant GTP-cyclohydrolase deficiency,[31,32] demonstrates age-dependent phenotypic expression, with dystonia predominating in pediatric patients and parkinsonism features emerging later in life. Moreover, these patients can manifest diurnal variation of their motor symptoms, further complicating their assessment. The changes observed in the IPDRS scores of patients with neurotransmitter disorders rated longitudinally during treatment suggest that this scale could be a valuable tool for tracking the developmental progression of motor manifestations in these patients. In addition, our experience with the IPDRS in a diverse group of infants and young children with severe neurological disorders underscores its versatility and broader applicability as a rating scale. Although patients with cerebral palsy and significant spasticity typically undergo evaluation using validated spasticity scales and motor classification systems, the IPDRS appears particularly effective for assessing hypokinesia and dystonia in this age group. Further analysis with larger cohorts will be necessary to validate these observations.

In conclusion, our pilot study suggests that the IPDRS could be useful for assessing parkinsonism in children in clinical practice. The results of this pilot study should be confirmed in larger samples and with patients from other settings and origins using refined and improved instructions to raters and further optimizing the scale. Further analysis, such as exploratory and confirmatory factor analyses, and the use of analytical methods, such

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as those derived from item response theory (Rasch analysis), could contribute to refining and improving the scale. International collaboration is of the utmost importance to achieve this.

Author Roles: R.P. and T.S.P. contributed to the design of the study; R.P., T.S.P., B.P.-D., A.G.-C., M.A.K., Z.D., V.Z., C.O., E.K., M.S.-B., A.D., M.O., R.S., D.B.D.S., E.S., M.J.F., and C.R.-B. contributed to the execution of the study; R.P., T.S.P., M.J.F., and C.R.-B. analyzed the data; R.P., T.S.P., M.J.F., and C.R.-B. wrote the first draft of the manuscript; and all authors edited and approved of the final version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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