Received: 21 May 2021 | Revised: 30 June 2021 | Accepted: 7 July 2021

DOI: 10.1002/jimd.12416

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Assessment of intellectual impairment, health-related quality of life, and behavioral phenotype in patients with neurotransmitter related disorders: Data from the iNTD registry

Mareike Keller[1] | Heiko Brennenstuhl[1] | Oya Kuseyri Hübschmann[1] | Filippo Manti[2] | Natalia Alexandra Julia Palacios[3] | Jennifer Friedman[4] | Yılmaz Yıldız[5] | Jeanette Aimee Koht[6] | Suet-Na Wong[7] | Dimitrios I. Zafeiriou[8] | Eduardo López-Laso[9] | Roser Pons[10] | Jan Kulhánek[11] | Kathrin Jeltsch[1] | Jesus Serrano-Lomelin[12] | Sven F. Garbade[1,13] | Thomas Opladen[1] | Helly Goez[14] | International Working Group on Neurotransmitter related Disorders (iNTD) | Alberto Burlina[15] | Elisenda Cortès-Saladelafont[3,16] | Joaquín Alejandro Fernández Ramos[9] | Angeles García-Cazorla[3] | Georg F. Hoffmann[1] | Stacey Tay Kiat Hong[17] | Tomáš Honzík[11] | Ivana Kavecan[18] | Manju A. Kurian[19] | Vincenzo Leuzzi[2] | Thomas Lücke[20] | Francesca Manzoni[15] | Mario Mastrangelo[2] | Saadet Mercimek-Andrews[21,22] | Pablo Mir[23] | Mari Oppebøen[24] | Toni S. Pearson[25] | H. Serap Sivri[5] | Dora Steel[19] | Galina Stevanović[26] | Cheuk-Wing Fung[7]

[1]Division of Child Neurology and Metabolic Medicine, University Children's Hospital Heidelberg, Heidelberg, Germany

[2]Department of Human Neuroscience, Unit of Child Neurology and Psychiatry, Università degli Studi di Roma La Sapienza, Rome, Italy

[3]Inborn errors of metabolism Unit, Department of Neurology, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Barcelona, Spain

[4]UCSD Departments of Neuroscience and Pediatrics; Rady Children's Hospital Division of Neurology, Rady Children's Institute for Genomic Medicine, San Diego, California, USA

[5]Hacettepe University, Faculty of Medicine, Department of Pediatrics, Section of Pediatric Metabolism, Ankara, Turkey

[6]Department of Neurology, Oslo University Hospital, Oslo, Norway

[7]Department of Pediatrics and Adolescent Medicine, The Hong Kong Children's Hospital, Hong Kong, Hong Kong

[8]First Department of Pediatrics Aristotle University of Thessaloniki, Thessaloniki, Greece

[9]Pediatric Neurology Unit, Department of Pediatrics, University Hospital Reina Sofía, IMIBIC and CIBERER, Córdoba, Spain

[10]First Department of Pediatrics of the University of Athens, Aghia Sofia Hospital, Athens, Greece

[11]Department of Pediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

Mareike Keller, Heiko Brennenstuhl, Thomas Opladen, and Helly Goez contributed equally to this study.

[12]Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada

[13]Dietmar-Hopp Metabolic Center, University Children's Hospital Heidelberg, Heidelberg, Germany

[14]Department of Pediatrics, University of Alberta, Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada

[15]U.O.C. Malattie Metaboliche Ereditarie, Dipartimento della Salute della Donna e del Bambino, Azienda Ospedaliera Universitaria di Padova – Campus Biomedico Pietro d'Abano, Padova, Italy

[16]Inborn Errors of Metabolism and Child Neurology Unit, Department of Pediatrics, Hospital Germans Trias i Pujol, Badalona and Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

[17]KTP-National University Children's Medical Institute, National University Health System, Singapore, Singapore

[18]Faculty of Medicine, University of Novi Sad, Institute for Children and Youth Health Care of Vojvodina, Novi Sad, Serbia

[19]Developmental Neurosciences, UCL Great Ormond Street-Institute of Child Health and Department of Neurology, Great Ormond Street Hospital, London, UK

[20]University Children's Hospital, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

[21]Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada

[22]Department of Medical Genetics, University of Alberta, Women and Children's Health Research Institute, Stollery Children's Hospital, Edmonton, Alberta, Canada

[23]Unidad de Trastornos del Movimiento Servicio de Neurología y Neurofisiología Clínica Unidad de Gestión Clínica de Neurociencias Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Sevilla, Spain

[24]Children's Department Division of Child Neurology Oslo University Hospital Rikshospitalet, Oslo, Norway

[25]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA

[26]Clinic of Neurology and Psychiatry for Children and Youth, School of Medicine, University of Belgrade, Belgrade, Serbia

Correspondence
Mareike Keller, Department of General Pediatrics, Division of Neuropediatrics and Metabolic Medicine, University Children's Hospital Heidelberg, 69120 Heidelberg, Germany.
Email: mareike.keller@med.uni-heidelberg.de

Funding information
Dietmar Hopp Stiftung (DE); Medical Faculty of the University of Heidelberg

Communicating Editor: Avihu Boneh

Abstract

Inherited disorders of neurotransmitter metabolism are a group of rare diseases, which are caused by impaired synthesis, transport, or degradation of neurotransmitters or cofactors and result in various degrees of delayed or impaired psychomotor development. To assess the effect of neurotransmitter deficiencies on intelligence, quality of life, and behavior, the data of 148 patients in the registry of the International Working Group on Neurotransmitter Related Disorders (iNTD) was evaluated using results from standardized age-adjusted tests and questionnaires. Patients with a primary disorder of monoamine metabolism had lower IQ scores (mean IQ 58, range 40-100) within the range of cognitive impairment (<70) compared to patients with a BH_4 deficiency (mean IQ 84, range 40-129). Short attention span and distractibility were most frequently mentioned by parents, while patients reported most frequently anxiety and distractibility when asked for behavioral traits. In individuals with succinic semialdehyde dehydrogenase deficiency, self-stimulatory behaviors were commonly reported by parents, whereas in patients with dopamine transporter deficiency, DNAJC12 deficiency, and monoamine oxidase A deficiency, self-injurious or mutilating behaviors have commonly been observed. Phobic fears were increased in patients with 6-pyruvoyltetrahydropterin synthase deficiency, while individuals with sepiapterin reductase deficiency frequently experienced communication and sleep difficulties. Patients with BH_4 deficiencies achieved significantly higher quality of life as compared to other groups. This analysis of the iNTD registry data highlights: (a) difference in IQ and subdomains of quality of life between BH_4 deficiencies and primary neurotransmitter-related disorders and (b) previously underreported behavioral traits.

KEYWORDS

behavioral phenotype, cognitive impairment, iNTD, intelligence, neurotransmitter deficiencies, quality of life

1 | INTRODUCTION

Neurotransmitter deficiencies (NTDs) are a group of rare inherited metabolic diseases. The group consists of disorders directly affecting the synthesis, transport or degradation of monoamine neurotransmitters, and disorders affecting cofactor metabolism. Neurotransmitter metabolites include biogenic amines (catecholamines norepinephrine, epinephrine, and dopamine and serotonin) and amino acids (glycine, glutamate and γ-aminobutyric acid [GABA]). Tetrahydrobiopterin (BH_4) is an essential cofactor for enzymes involved in biogenic amine synthesis. A lack of BH_4 can, therefore, mimic the clinical and biochemical profile of monoamine NTDs.[1-3] Approximately 1500 cases of NTDs are reported in the literature; the prevalence of individual diseases is difficult to estimate.[4] NTDs can either present with an acute onset epileptic encephalopathy after birth and/or chronic metabolic disturbances resulting in a wide variety of clinical symptoms, including motor dysfunction, hypotonia, and developmental delay. Since the clinical phenotype overlaps with more frequently occurring neurological entities, inherited NTDs are underrecognized and often misdiagnosed.[1,3]

Neuropsychological symptoms have been described in all NTDs, however, a global structured analysis of data on cognitive aspects, neurobehavioral attributes, or quality of life (QoL) and also the differences between subgroups on patients with NTDs is missing so far.[5] We, therefore, gathered and statistically analyzed data from patients registered to the patient registry of the International Working Group on Neurotransmitter Related Disorders (iNTD; www.intd-registy.org).[4] Our main goal was to improve our understanding of NTDs by covering the following objectives: (a) assessing IQ outcomes in individuals with NTDs; (b) identifying behavioral traits and problems associated with NTDs; and (c) exploring potential differences in QoL in the domains of physical well-being, psychological health, social relationships, and environment. The results from this research will help clinicians to include NTDs in their differential diagnosis, enable the development of targeted psychosocial support programs and inform future research.

2 | MATERIALS AND METHODS

2.1 | Database characteristics

The iNTD is a worldwide consortium of clinicians, laboratory, and basic scientists.[4] The iNTD patient registry is an important cornerstone within the network activities. Currently, 42 health-care providers from 26 countries contribute patients to the registry. The database query for this study was completed on 1 August 2020. Patients missing a definitive diagnosis of a neurotransmitter-related disease and infants with a birth weight less than 1500 g were excluded from the analyses. After applying the selection criteria, n = 148 individuals remained for whom information on at least one quality: IQ, QoL, or behavior was available. If measurement results at multiple time points for individual patients were stored in the registry database, only the most recent ones were evaluated. Detailed characteristics of the subanalysis datasets are discussed in the following sections. Table 1 provides an overview of the distribution of patients and their diagnoses.

2.2 | IQ analysis

Each center had the freedom to choose a standardized test to perform IQ assessments. All tests were age-adjusted and included: The Wechsler Preschool and Primary Scale for Intelligence (WPPSI-III), Wechsler Intelligence Scale for Children (WISC-IV), and the Wechsler Adult Intelligence Scale (WAIS-IV). Individuals with scores below 70 were interpreted as intellectually disabled according to the standard definition of the tests. Scores between 85 and 114 are considered as average range.[6] Individuals that were evaluated with the Denver II Score, the Bayley Scales of Infant and Toddler Development (BDSI)-II and -III, and Griffiths Developmental Scale were excluded from the analysis.

2.3 | Behavior and emotional problems

Behavior and emotional traits were assessed using a self-report (for patients above the age of 13 years) or a parental report form. Thirty-three items were selected from the symptom list of the Mannheimer Eltern Interview by Esser et al[7] and covered four main categories: (a) neurotic and emotional disorders, (b) anti-social and delinquent behavior, (c) hyperkinetic syndrome, and (d) additional specific disorders. The items covered the features of extraversive, introversive, autistic, attention deficit hyperactivity disorder (ADHD), and psychosomatic spectra behaviors (aggressiveness, anorexia, anxiety, complaining of pain, compulsive behavior, difficulties falling asleep, distractibility, encopresis, enuresis, hyperactivity, impulsiveness, lying, mood swings, mutism, overeating, phobias, pica, problems communicating wishes, problems understanding other people's feelings, being sad or unhappy, self-endangering behavior, self-mutilation, self-stimulation, inappropriate sexual behavior, short attention, being shy or timid, social withdrawal, stealing, substance abuse, temper tantrums, tics, waking up at night, and yelling).

TABLE 1 Groups, diseases, and number of patients included in this study

Group	Affected enzyme (OMIM disease code)	(n = 148, percent of total)	Age at diagnosis (in months), range	IQ analysis Professional assessment (n = 39)	Behavior analysis (n = 128)		PedsQL (n = 38)		WHOQoL (n = 29)
					Parental reports (n = 86)	Patient reports (n = 42)	Parental reports (n = 15)	Patient reports (n = 23)	Patient reports (n = 26)
BH_4 deficiencies	arGTPCH (#233910)	6 (4%)	50.7, 6.9-167.9	2 (5%)	2 (2%)	2 (5%)	1 (7%)	1 (4%)	2 (8%)
	adGTPCH (#233910)	24 (16%)	173.8, 27.6-623.6	5 (13%)	3 (3%)	15 (36%)	6 (40%)	10 (43%)	8 (31%)
	PTPS (#261640)	32 (21%)	23.2, 0.1-395.7	14 (36%)	19 (22%)	10 (24%)	4 (27%)	3 (13%)	7 (27%)
	DHPR (#261630)	13 (9%)	9.6, 0.4-23.7	3 (8%)	8 (9%)	4 (10%)	—	—	—
	SR (#612716)	11 (7%)	120.8, 6.9-311.8	2 (5%)	7 (8%)	2 (5%)	—	1 (4%)	4 (15%)
Primary disorders of monoamine metabolism - defects in biosynthesis and catabolism	AADC (#608643)	25 (17%)	61.5, 4.6-383.7	8 (21%)	18 (21%)	7 (17%)	2 (13%)	2 (9%)	3 (12%)
	TH (#605407)	13 (9%)	63, 4.4-203.9	2 (5%)	7 (8%)	1 (2%)	2 (13%)	6 (26%)	1 (4%)
	MAOA (309850)	4 (3%)	174.9, 6.4-431.7	1 (3%)	4 (5%)	—	—	—	1 (4%)
Chaperon deficiency	DNAJC12 (#617384)	2 (1%)	143.9, 119.9-167.9	—	2 (2%)	—	—	—	—
Dopamine transporter deficiency	DAT (#613135)	1 (1%)	8.9, 8.9-8.9	—	1 (1%)	—	—	—	—
Other amino acid metabolism disorders	SSADH (#271980)	16 (11%)	55.7, 0.5-191.9	2 (5%)	14 (16%)	1 (2%)	—	—	—
	NKH (#605899)	1 (1%)	3.9, 3.9-3.9	—	1 (1%)	—	—	—	—

Abbreviations: AADC, aromatic L-amino acid decarboxylase; adGTPCH, autosomal dominant GTP cyclohydrolase I; arGTPCH, autosomal recessive GTP cyclohydrolase I; DAT, dopamine transporter; DHPR, dihydropteridine reductase; MAOA, monoamine oxidase A; NKH, nonketotic hyperglycinemia; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; SSADH, succinic semialdehyde dehydrogenase; TH, tyrosine hydroxylase.

2.4 | Health-related QoL

QoL was measured using the Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0) for patients between the age of 2 and 18 years,[8,9] and the World Health Organization Quality of Life Project assessment tool WHOQoL-BREF (Skevington et al[10]) for patients age 18 and older. Both tests measure QoL as a multidimensional construct. The PedsQL consists of 23 items on a five-step Likert-scale and measures functioning and adaption in physical, emotional, social, and academic domains over the last month. The subscales can be grouped into the dimensions of physical health (8 items) and psychosocial health (15 items). The PedsQL is available as a self-report (used for age ≥18 years) and parent proxy report forms (used for ages from 8 to 18 years). The WHOQoL-BREF is a short form of the original WHOQoL-100.[11] It consists of 26 items on a five-step Likert-scale and measures QoL over the following dimensions: physical well-being, psychological health, social relationships, and environment over the 4 weeks preceding the completion of the questionnaire.

2.5 | Statistical analysis

Descriptive statistics for IQ (mean and standard deviation [SD]) are reported for BH_4 deficiencies and primary NTDs. Analysis of variance (ANOVA) was used to estimate differences in a continuous variable (IQ and WHOQoL-BREF score) among NTD groups. ANOVA post hoc comparisons were computed using Tukey HSD contrasts. Two groups were compared with *t* test with Welch correction when the response variable was continuous. A classification and regression tree (CART) analysis was used to perform supervised clustering of IQ values across all diagnoses.[12] This method uses a binary algorithm that divides patients over all diagnosis groups according to differences in IQ. The term binary refers to the fact that two groups at a time can arise from a subdivision. Count data from frequency tables were analyzed with log-linear models, and likelihood ratio test was used to assess statistical significance. Deviation between observed and expected frequency were interpreted by means of Pearson residuals. Resulting *P* values are reported as $*P \leq .05$, $**P \leq .01$, $***P \leq .001$.

3 | RESULTS

3.1 | Overall dataset metrics

The study sample consists of a total of n = 148 patients from the iNTD patient registry, in whom information about the IQ, QoL, or behavioral and emotional traits was entered. An overview of the diseases included in the data set of this study and the abbreviations used for them throughout the manuscript can be found in Table 1. We divided disorders according to their biochemical background or the main pathophysiological principle in five groups. The group of BH_4 deficiencies included ar/adGTPCH, PTPS, DHPR, and SR deficiency and the group of primary disorders of monoamine metabolism included AADC, tyrosine hydroxylase (TH), and MAOA deficiency. The remaining diseases are distributed into the groups of chaperone deficiencies (DNAJC12 deficiency), transportopathies (DAT deficiency), and amino acid disorders (nonketotic hyperglycinemia [NKH] and succinic semialdehyde dehydrogenase [SSADH] deficiency, see Table 1). Patients included in this study were primarily from Germany (n = 30), Italy (n = 24), Spain (n = 20), the United States (n = 13), and Turkey (n = 12). A world map with the distribution of patients included in the analysis can be found in Figure 1.

3.2 | General IQ analysis clustering of IQ data (CART analysis)

Data on the intellectual performance of 39 patients were available. A total of n = 26 (67%) individuals were diagnosed with a BH_4 deficiency, whereas n = 11 (28%) patients were diagnosed with a primary monoamine NTD, and one patient suffered from SSADH deficiency (3%) (Table 2). The IQ recorded at the last visit (mean age 16.5 years, range 3-42 years) was determined using WISC-IV IQ tests (n = 16), WISC-V tests (n = 2), WAIS-IV IQ tests (n = 14), and WPPSI-III IQ tests (n = 7). Sex was equally distributed (51.3% [n = 20] female, 48.7% [n = 19] male). With regard to sex, no significant difference in total IQ score ($P = .51$) between male (mean 73, SD ± 27, range 33-129) and female (66, SD ± 33, range 32-129) individuals was detected.

The mean overall IQ was 70 and showed a wide dispersion across all disease groups (SD ± 29, range 32-129). There was no statistically significant difference in IQ score when performing ANOVA comparison over individual diseases. It was found that a higher age at diagnosis was associated with a slight trend toward higher IQ scores. However, when looking at the individual disorders, it is striking that a trend toward higher IQs at later diagnosis time points is only observable for AADC and TH deficiency, as well as for adGTPCH deficiency. Individuals with PTPS deficiency revealed a trend toward lower IQ scores at later age of diagnosis, whereas a large variability of IQ values was observed in the group of early diagnosed PTPS patients (Figure 2A,C). Across all diseases, a longer

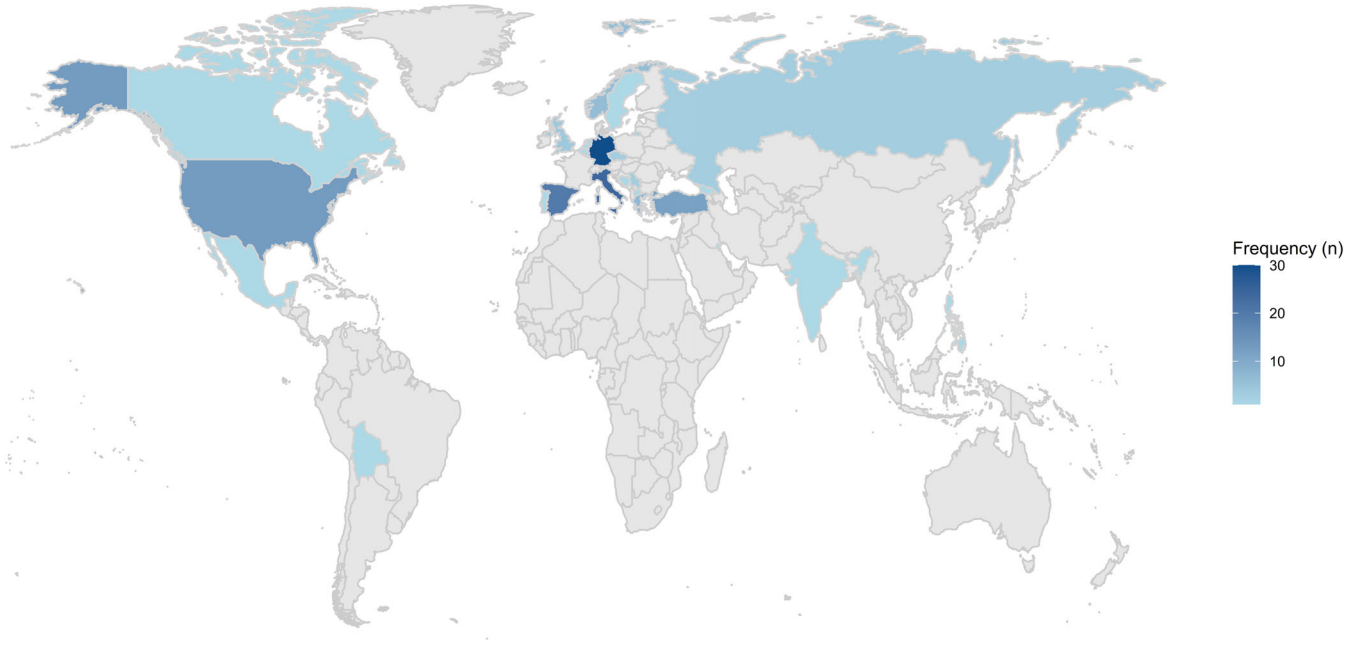

FIGURE 1 Distribution pattern of patients with neurotransmitter related disease in this study. Number of identified affected individuals per country in this study, frequency is coded as a continuous variable in blue scales. The majority of patients originated from European countries

TABLE 2 IQ over disease groups and individual diseases

Group	Affected enzyme (n)	Mean IQ (±SD, range)
BH_4 deficiencies	arGTPCH (n = 2)	93 (±25, 75-110)
	adGTPCH (n = 5)	99 (±31, 48-129)
	PTPS (n = 14)	65 (±30, 32-124)
	DHPR (n = 3)	81 (±45, 40-129)
	SR (n = 2)	79 (±9, 72-85)
Primary disorders of monoamine metabolism	AADC (n = 8)	63 (±21, 40-100)
	TH (n = 2)	42 (±2, 40-43)
	MAOA (n = 1)	54 (NA)
Other amino acid metabolism disorders	SSADH (n = 2)	42 (±13, 32-51)

Abbreviations: AADC, aromatic L-amino acid decarboxylase deficiency; adGTPCH, autosomal dominant GTP cyclohydrolase I deficiency; arGTPCH, autosomal recessive GTP cyclohydrolase I deficiency; DHPR, dihydropteridine reductase deficiency; MAOA, monoamine oxidase A deficiency; PTPS, 6-pyruvoyltetrahydropterin synthase deficiency; SSADH, succinic semialdehyde dehydrogenase deficiency; SR, sepiapterin reductase deficiency; TH, tyrosine hydroxylase deficiency.

diagnostic delay was associated with a trend toward lower IQ scores, however, the length of diagnostic delay did not significantly affect the IQ score in our cohort ($P = .78$). Again, when looking at the individual diseases, this trend predominantly applied to individuals with AADC and arGTPCH deficiency. In contrast, a slight positive correlation between diagnostic delay and IQ was shown for PTPS deficiency, although in this case the diagnostic delay reached negative values due to possible identification of patients in newborn screening (Figure 2B,D).

A decision tree model was used to explore the IQ data and find disease groups that differ considering IQ. We detected a first order binary separation of IQ values (Figure 3) distinguishing primary monoamine NTDs and BH_4 deficiencies. The mean full IQ score was lower in the group of primary monoamine NTDs (n = 11; mean IQ 58, SD ± 20, range 40-100) compared to the group of BH_4 deficiencies (n = 7; mean IQ 84, SD ± 29, range 40-129), with the exception of PTPS deficiency (n = 14; mean IQ 65, SD ± 30, range 32-124). Patients with adGTPCH deficiency (n = 5) had an overall clinically very mild course with predominantly motor involvement and a mean IQ of 99 (SD ± 30, range 48-129). To prevent any distortion of the data toward higher IQ scores in the group of BH_4 deficiencies, we decided to exclude patients with adGTPCH deficiency from the CART analysis.

3.3 | Behavior

In total, data from n = 129 behavioral questionnaires were analyzed, of which n = 87 were completed by parents and n = 42 by patients themselves. The disease distribution of the participants can be found in Table 1.

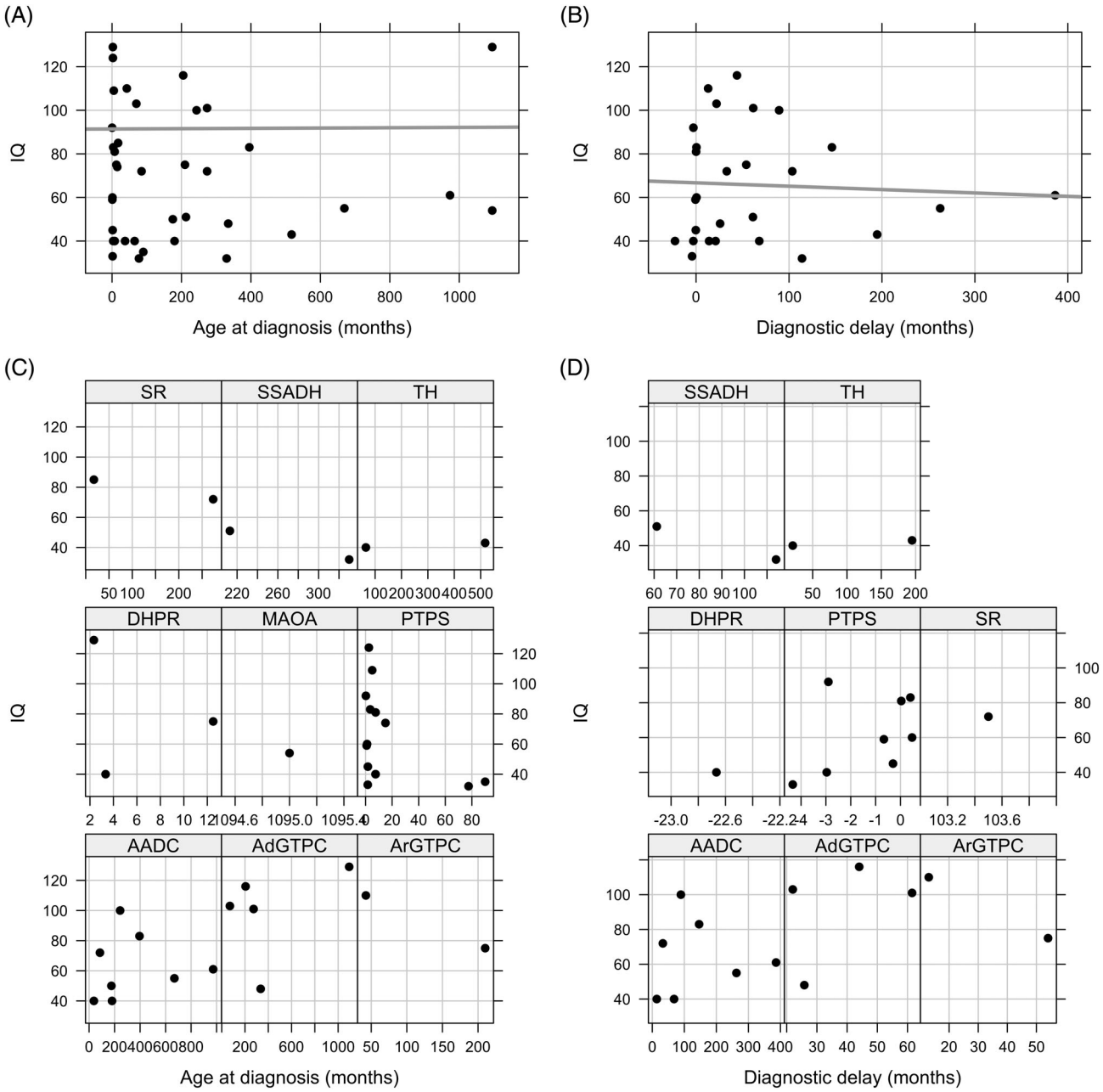

FIGURE 2 Influence of age at diagnosis and diagnostic delay on IQ. Summary of age at diagnosis (in months) (A) and diagnostic delay (in months) (B) on IQ for all diseases displayed individually in (C) and (D) respectively

The specified behaviors were analyzed independently of their occurrence time as a symptom report. The behavioral trait most frequently mentioned by parents when reporting on their children across all disease groups was short attention (63.86%), followed by distractibility (59.52%). In the patient self-reports, anxiety was mentioned as the most common emotional problem (46.34%). Distractibility was likewise the second most frequently stated (40.0%). None of the patients reported pica, substance abuse, exaggerated sexual behavior, or stealing as typical behaviors in their self-report. The behavior documented by parents and self-reports are shown in Figure 4A,B.

To obtain a more fine-grained representation of the data in relation to the underlying disease of the individual patients, we performed a contingency table analysis. Thus, we found that in parent reports, self-stimulatory behavior was observed with higher frequency in patients with SSADH deficiency and nonketotic hyperglycinemia (SSADH 9/17; NKH 2/2; likelihood ratio test $P < .01$). In the patient groups with DAT, DNAJC12, and MAOA deficiency we observed an increase in self-injurious or

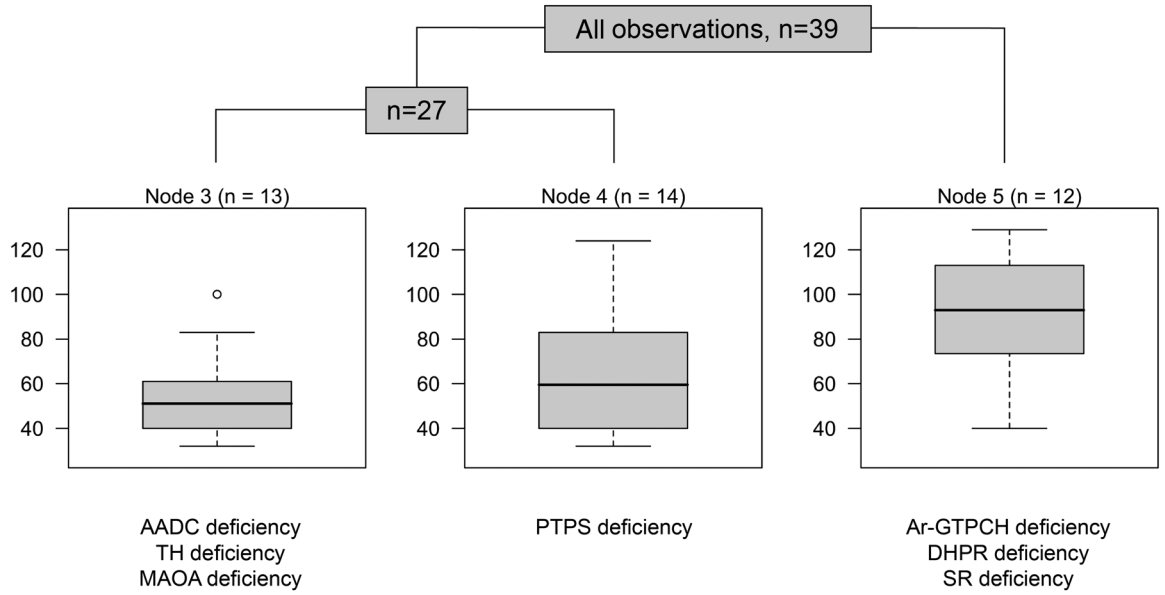

FIGURE 3 CART analysis with response IQ and predictor disease. Unsupervised machine learning approach to cluster disease groups by IQ. Boxplots show lower and upper quartile with median marked as a horizontal line and whiskers showing the 1.5 times deviation of the upper and lower quantiles. Outliers are depicted as dots. Group 1 contains only primary NTDs, whereas group 3 non-PTPS-BH_4 deficiencies. Group 2 contains exclusively patients with PTPS deficiency and shows a heterogeneous distribution pattern of IQ values

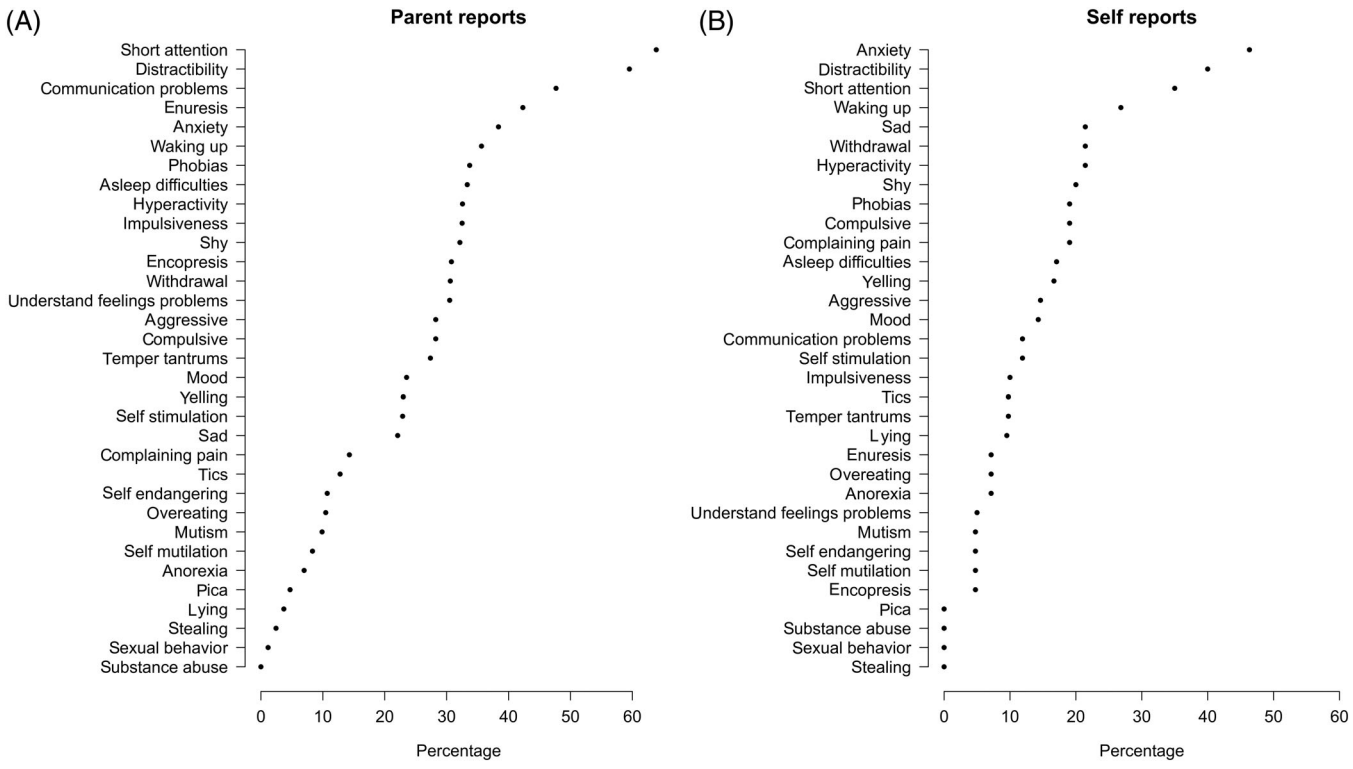

FIGURE 4 Behavioral traits in parental reports and patient self-reports. Percentage distribution of behavioral traits in parental reports (A) and patient self-reports (B) in neurotransmitter-related disorders as listed in Table 1

mutilating behaviors (DAT 1/1; DNAJC12 1/2; MAOA 2/4; likelihood ratio test $P < .01$). In patients with an arGTPCH or DAT deficiency we observed difficulties with food intake (arGTPCH 1/1; DAT 1/1; likelihood ratio test $P = .03$). Although statistical relevance of these results was detectable in the overall group comparison,

TABLE 3 WHOQOL-BREF results on four domains of BH_4 deficiencies and disorders of monoamine metabolism

Domain	Group	n	Mean WHOQOL-BREF score	SD	Range	*P* value
Psychological	BH_4	21	75.20	±12.44	45-91.67	.03*
	Primary monoamine NTD	4	60.42	±8.67	50-70.83	
Social relationships	BH_4	20	73.12	±21.65	0-100	.04*
	Primary NTD	4	40.62	±47.19	0-87.50	
Environment	BH_4	21	79.59	±13.22	46.88-100	.01*
	Primary NTD	4	60.16	±14.29	40.62-75.00	
Physical health	BH_4	21	72.90	±12.29	46.43-89.29	.06 (n.s.)
	Primary NTD	4	59.67	±11.61	46.43-70.83	

Note: The significance of * is $p < 0.5$.

the very small number of patients must be considered when interpreting these results. In self-report analysis, patients with PTPS deficiency reported phobic fears with high frequency (6/11; likelihood ratio test $P < .05$). Patients with SR deficiency frequently suffered from communication problems (2/3; likelihood ratio test $P < .01$) and problems with the initiation of sleep (3/3; likelihood ratio test $P < .05$).

3.4 | Quality of life

Data about QoL were available for n = 23 patients and n = 15 parents completing the PedsQL and n = 26 patients completing the WHOQoL-BREF questionnaire. For some subcategories of the PedsQL, incomplete answer sheets were available from the participants, so that we refrained from forming sum scores during the evaluation. Due to inherent differences in theoretical concepts, we did separate analyses for the two instruments.

Patients' assessment of their own QoL differs from that of their parents. Results from the PedsQL questionnaire showed that patients rated their QoL an average of 10 points higher compared to parental rating. Further analyses according to disease subgroups or an overarching biochemical clustering did not yield statistically significant differences.

Analysis of the WHOQoL-BREF revealed significant differences in QoL in the three domains psychological well-being, social relationships, and environment between patients with a BH_4 deficiency and those suffering from a primary NTD. In all three domains, patients with a BH_4 deficiency reported significantly higher QoL. Only in the domain of physical health, no significant difference between the two patient groups was found. Table 3 presents the WHOQoL-BREF results on the four subdomains broken down by primary NTDs and BH_4 deficiencies.

4 | DISCUSSION

Our analysis of 148 patients of the iNTD registry explores neurotransmitter-related disorders through the dimensions of intelligence, behavioral phenotype, and QoL. Such analyses on large cohorts are particularly important in rare diseases to better understand the various aspects of these diseases, recognize them timely, and improve patient-care approaches.

4.1 | Intellectual functioning

Neurotransmitters, in particular dopamine and serotonin, are significantly involved in tasks attributed to cognitive function and neurodevelopment. These include verbal and operational skills, working memory, and logical thinking, beyond the link between neurotransmitters and intelligence in general.[13-16] To date, only few studies on the cognitive abilities of patients with neurotransmitter diseases have been published, most of which are based on the analysis of singular diseases and rather small case series.[17-20] By analyzing the comprehensive iNTD registry data set, we were able to review a larger cohort of patients with a variety of underlying diseases.

In alignment with previous studies, it was shown that the variability of intelligence within specific groups of conditions and individual diseases was high.[21,22] While the attempt to group diseases according to their biochemical background did not add further clarity to the picture, using the CART algorithm helped in revealing patterns that showed a difference in the mean values between a group of predominantly primary monoamine NTDs and BH_4 deficiencies. Patients with primary monoamine NTDs, which included TH, MAOA, and AADC deficiency showed lower IQ values when compared to patients with BH_4 metabolism defects when excluding adGPTCH and with the exception of PTPS deficiency. In the latter group,

patients revealed a rather heterogeneous IQ value distribution ranging from 32 to 124. The pathophysiologic causes for this range are certainly multifactorial. The following mechanisms may contribute to the variance: For some BH_4 disorders, newborn screening allows early diagnosis. In addition, residual enzyme activity, well studied for ad- and arGTPCH deficiency, also plays a relevant role as well as the underlying mutation.[1]

Neurotransmitters play an important role in early brain development, where they control the generation of neurons, their migration as well as the formation of complex brain structures that enable higher cognitive functions.[23-25] Mild disease progression potentially determines that diseases are not diagnosed until later in life. In our study population, both age at diagnosis and diagnostic delay had a rather small impact on intellectual outcome in relation to the full IQ across all diseases (Figure 2). Nevertheless, a negative correlation of age at diagnosis to IQ was found for some diseases, primarily observable for individuals with PTPS deficiency. This effect might partially be attributed to a delay in treatment initiation, although low IQ values were also observed in PTPS patients diagnosed early in life. Considering the overall heterogeneity in the IQ distribution in individual diseases, a clear correlation between intellectual outcome and a sufficient, timely control symptom as one might expect could not be demonstrated. A simple correlation of IQ with the age at diagnosis or the diagnostic delay of patients with neurotransmitter diseases is difficult because multiple factors might have an impact on IQ: the severity of the phenotypic traits, differences in the availability of early diagnosis through, for example, newborn screening programs, and the availability of drugs that have a lasting impact on the course of the disease.

4.2 | Behavior

The studied group showed a heterogeneous profile of behavioral patterns. Some behaviors occurred with greater probability in certain disease groups, so that the assumption can be made that specific biochemical changes in the individual neurotransmitter systems are associated with distinct behavioral abnormalities. Short attention span and anxiety were the most commonly reported behavioral problems by parents and patients, respectively, in all neurotransmitter subgroups. It is unclear whether this behavioral change can be attributed specifically to neurotransmitter dysfunction or to some other secondary mechanism. The general role of neurotransmitters in executive function and correlations with some diagnostic criteria of ADHD, such as increased impulsivity or decreased attention, and the neurobiology of anxiety in children have been explored.[26] For ADHD, an underlying dopamine hypofunctional state has been suggested.[27] However, since we found the behavioral abnormality also in other neurotransmitter disorders, a dopamine deficiency is probably not the sole underlying cause. This is confirmed by the fact that the short attention span is independent of L-dopa substitution. Other studies also showed little or no effect of L-dopa supplementation on ADHD symptoms such as short attention.[28] L-dopa treatment has also been reported to improve cognitive inflexibility in patients with mild forms of Parkinson's disease. However, since in the study by Cools et al at the same time, impulsivity was also increased in relation to riskier decision-making, at least an effect of the treatment itself would also have to be discussed.[29] Families and patients in the present sample placed short attention span and anxiety as troublesome behavioral characteristics. To address these symptoms, personalized and patient- or family-centered psychotherapeutic approaches may be worthwhile for patients with NTDs.

According to parental reports, self-stimulatory behaviors were seen in 9/17 children with SSADH deficiency. In previous reports,[30-33] these behaviors were not reported in association with SSADH deficiency. Whether this behavior is associated with significant cognitive delay, impulse control, or hyperkinetic behavior needs to be explored.

Self-injurious behaviors found in our study in patients with DAT, DNAJC12, and MAOA deficiencies were previously reported for these diseases within the spectrum of aggression. The DNAJC12 deficiency has been associated with behavioral and neurological phenotypes including a spectrum ranging from mild autistic features or hyperactivity to severe intellectual disability, dystonia, and parkinsonism.[34,35] Bortolato et al expended on the phenotypic description of MAOA deficiency, Brunner syndrome, and report on a range from autism to aggression.[36] Self-mutilation though is described as a unique entity within the range of extreme aggression and reported in conditions such as Lesch-Nyhan syndrome, creatine deficiency, Rett disorder, and some are grouped under the term "pediatric psychocutaneous disorders."[37-40] However, interestingly in our study, mutilating behaviors were found in patients with DAT, DNAJC12, and MAOA deficiencies. Looking into associations of self-mutilating behavior and mental condition, Simeon et al were able to show that it was significantly correlated with impulsivity, chronic anger, and somatic anxiety.[41] The authors suggested that it supported their hypothesis of an underlying serotonergic dysfunction. Self-mutilation is also reported in association with dysregulation of pain perception.[42] Whether dopaminergic involvement affecting pain perception through the reward system contributes to this behavior remains to be elucidated.

Another intriguing finding in our study was that patients with arGTPCH deficiency or DAT deficiency

demonstrated limited food intake. A dopamine transporter dysregulation was described in association with disorders affecting insulin levels and signaling such as diabetes and anorexia.[43] Disturbed neopterin and biopterin concentrations were associated with dysregulation of food intake, including loss of appetite in patients with diabetes and perhaps an enzymatic defect in GTPCH leading to low concentrations of neopterin could explain this previously unreported behavioral feature.[44]

Phobic fears were increased in self-reports of patients with PTPS deficiency. This is also not specified in previously reported data although aggression and psychiatric disorders were generally mentioned.[20,45,46] In alignment with literature, patients with SR deficiency in our study, frequently experienced communication and sleep difficulties.[47-49]

4.3 | Quality of life

Comparison of the parent and self-reports using the PedsQL showed that patients rated their QoL on average 10 points higher than their parents did in the overall view of all results. This observation coincides with descriptions of a divergent perception of QoL by children with other neurodevelopmental and neurological conditions with physical impairments and their parents, and can be found in particular for areas of subjective experience.[50-54] Our analysis of the WHOQoL-BREF revealed significant differences in QoL between individuals with BH_4 deficiencies compared to those with primary NTDs in the three domains of psychological well-being, social relationships, and environment, where patients with a BH_4 deficiency reported on significantly higher QoL. We believe that this finding may be associated with our reported difference in IQ between these two groups; with an overall higher IQ in the BH_4 deficiency group as compared to primary NTDs. This also aligns with literature reporting on higher IQ being associated with higher QoL in individuals with intellectual disability.[55-57]

As related to traits affecting QoL within the domains of psychological well-being, social relationship, social support, and environment, our findings also align with previous reports in other neurodevelopmental conditions with intellectual disability. There is evidence in the literature of a positive correlation of peer support, emotional function, social abilities, and environmental living factors including socioeconomic status and QoL.[58-61] In the physical health domain of the QoL analysis, there were no significant differences between the abovementioned patient groups. Interestingly, the literature is also polarized in associations between burden of disease (in other neurological and neurodevelopmental conditions) and QoL. Irazabel et al showed that the behavioral problems in a context of mental disorders, intellectual disability, disability in personal care, and the copresence of intellectual disability and mental disorder significantly account for family burden.[62] Similarly, in children with epilepsy, seizure frequency as well as their severity negatively impacted QoL as compared to children with other non-neurological chronic conditions such as asthma or diabetes.[63,64] On the other hand, studies on subjective well-being of individuals with cerebral palsy showed that satisfaction in life was not decreased in this patient population that clearly suffers from physical disability in a variable range,[65,66] and that the postoperative improvement of IQ and QoL in children who underwent corpus callosotomy for refractory seizures in the context of Lennox-Gastaut syndrome was not related to postoperative seizures control per se.[67]

4.4 | Limitations of this study

Although, this study describes the assessment of intellectual impairment, health-related QoL, and behavioral phenotype in the largest cohort of neurotransmitter patients to date, one of the main limitations of this study is the relatively small number of patients for (individual) subgroup analyses, which makes data allocation and disease-specific analyses difficult. While the IQ survey is based on internationally standardized tests, the iNTD registry does not specify which ones are to be used for data collection. Each center has the option to use a test that is most suitable for them, slightly affecting the comparability of the results. To overcome this challenge, we have only interpreted data from patients for whom standardized IQ tests were filled out, which significantly reduced the amount of data points. Furthermore, for some individuals, longitudinal data were available, which further decreased overall disease-specific data availability, since only the latest test performed was evaluated. The assessment of intellectual abilities is extremely complex, because especially higher mental functions (executive functions, adaptive skills, and emotional profiles) are not covered in the iNTD registry. This is important because it is these functions that are significantly influenced by neurotransmitters (especially though the dopaminergic axis). For patients with Parkinson's disease, early initiation of therapy with L-dopa resulted in higher cognitive flexibility in the long term, while at the same time a negative effect on reverse learning was recorded.[68] In contrast, a negative effect on short-term verbal memory was described for dopamine agonists.[69] Severe disease courses with massive impairment of cognitive function are frequently reported for some NTD groups. As a result,

certain diseases might be underrepresented in this analysis, as there are no suitable test options for IQ, behavior, or QoL. Some of the behavioral abnormalities described in our cohort have been observed in a very small number of patients. This consistently presents a challenge to researchers working with rare and ultrarare disorders. We have therefore attempted to interpret the results with the greatest possible caution, taking this limitation into account.

5 | CONCLUSION

This study is the first to analyze IQ, behavioral patterns, and QoL data from a large cross-disease cohort of pediatric and adult patients with NTDs. We describe previously unreported behavioral phenotypes that will contribute to a better assessment of patients and better psychological treatment approaches. Extending the phenotype will encourage clinicians to include neurotransmitter defects in their differential diagnoses and permit earlier treatment in some patients. The IQ results align with recognized patterns as related to disease severity. The QoL results align with the literature from other neurological and neurodevelopmental conditions. NTDs are complex neurological conditions. A better understanding of the problems as perceived by families and patients promotes patient-centered care in which physician-patient-family discussions determine the goals of management and care.

ACKNOWLEDGMENTS

We thank the patients and their parents for participation in the iNTD patient registry. We also thank the Women and Children's Health Research Institute (Canada) to facilitate statistical services. Heiko Brennenstuhl received financial support from the physician scientist program of the Medical Faculty of the University of Heidelberg. This study was in parts funded by the Dietmar Hopp Foundation, St. Leon-Rot, Germany.

CONFLICT OF INTEREST

Thomas Opladen received research support and teaching honorarium from PTC Therapeutics. Heiko Brennenstuhl and Oya Kuseyri Hübschmann received teaching honorarium from PTC Therapeutics. Mareike Keller, Filippo Manti, Natalia Alexandra Julia Palacios, Jennifer Friedman, Yılmaz Yıldız, Jeanette Aimee Koht, Suet-Na Wong, Dimitrios I Zafeiriou, Eduardo López-Laso, Roser Pons, Jan Kulhánek, Kathrin Jeltsch, Jesus Serrano-Lomelin, Sven F. Garbade, Helly Goez, Alberto Burlina, Elisenda Cortès-Saladelafont, Joaquín Alejandro Fernández Ramos, Angeles García-Cazorla, Georg F. Hoffmann, Stacey Tay Kiat Hong, Tomáš Honzík, Ivana Kavecan, Manju A. Kurian, Vincenzo Leuzzi, Thomas Lücke, Francesca Manzoni, Mario Mastrangelo, Saadet Mercimek-Andrews, Pablo Mir, Mari Oppebøen, Toni S. Pearson, H. Serap Sivri, Dora Steel, Galina Stevanović, and Cheuk-Wing Fung declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mareike Keller, Heiko Brennenstuhl, Helly Goez, and Thomas Opladen designed the study and wrote the initial draft of the manuscript. Mareike Keller, Sven F. Garbade, and Jesus Serrano-Lomelin performed the statistical analyses. All authors examined patients and/or collected data. All authors revised the manuscript and approved the submission.

COMPLIANCE WITH ETHICAL STANDARDS

The present study has been approved by the local ethic committee and all iNTD partners (Ethics Committee of the Medical Faculty, University of Heidelberg, Germany under the document identifiers S-533/2015 and S-471/2014) and the HREB Ethics Board, University of Alberta (pro00064513).

ORCID

Heiko Brennenstuhl https://orcid.org/0000-0002-6909-0003

REFERENCES

1. Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T. Inherited disorders of neurotransmitters: classification and practical approaches for diagnosis and treatment. *Neuropediatrics*. 2019;50:2-14.
2. Kurian MA, Gissen P, Smith M, Heales S Jr, Clayton PT. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. *Lancet Neurol*. 2011;10:721-733.
3. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders—clinical advances and future perspectives. *Nat Rev Neurol*. 2015;11:567-584.
4. Opladen T, Cortes-Saladelafont E, Mastrangelo M, et al. The International Working Group on Neurotransmitter related Disorders (iNTD): a worldwide research project focused on primary and secondary neurotransmitter disorders. *Mol Genet Metab Rep*. 2016;9:61-66.
5. Opladen T, Lopez-Laso E, Cortes-Saladelafont E, et al. Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies. *Orphanet J Rare Dis*. 2020;15:126.
6. Schalock RL, Luckasson R, Tassé MJ. *Intellectual Disability: Definition, Diagnosis, Classification, and Systems of Supports*. 12th ed. Washington, DC: American Association on Intellectual and Developmental Disabilities; 2021.
7. Esser G, Blanz B, Geisel B, Laucht M. Mannheimer Elterninterview. Strukturiertes Interview zur Erfassung von kinderpsychiatrischen Auffälligkeiten; 1989.

8. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001; 39:800-812.
9. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care*. 1999;37: 126-139.
10. Skevington SM, Lotfy M, O'Connell KA, Group W. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res*. 2004;13:299-310.
11. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med*. 1998;28:551-558.
12. Breiman L, Friedman J, Stone CJ, Olshen RA. *Classification and Regression Trees (Wadsworth Statistics/Probability)*. Boca Raton: Taylor & Francis; 1984.
13. Kaminski JA, Schlagenhauf F, Rapp M, et al. Epigenetic variance in dopamine D2 receptor: a marker of IQ malleability? *Transl Psychiatry*. 2018;8:169.
14. Marsman A, Mandl RCW, Klomp DWJ, et al. Intelligence and brain efficiency: investigating the association between working memory performance, glutamate, and GABA. *Front Psych*. 2017;8:154.
15. Previc FH. Dopamine and the origins of human intelligence. *Brain Cogn*. 1999;41:299-350.
16. Tseng PY, Lee IH, Chen KC, et al. The correlation between mid-brain serotonin transporter availability and intelligence quotient in healthy volunteers. *Eur Psychiatry*. 2015;30:193-197.
17. Leuzzi V, Carducci CA, Carducci CL, et al. Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency. *Clin Genet*. 2010;77:249-257.
18. Leuzzi V, Mastrangelo M, Polizzi A, et al. Report of two never treated adult sisters with aromatic L-amino acid decarboxylase deficiency: a portrait of the natural history of the disease or an expanding phenotype? *JIMD Rep*. 2015;15:39-45.
19. Lopez-Laso E, Sanchez-Raya A, Moriana JA, et al. Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease. *J Neurol*. 2011;258:2155-2162.
20. Manti F, Nardecchia F, Banderali G, et al. Long-term clinical outcome of 6-pyruvoyl-tetrahydropterin synthase-deficient patients. *Mol Genet Metab*. 2020;131:155-162.
21. Liu KM, Liu TT, Lee NC, Cheng LY, Hsiao KJ, Niu DM. Long-term follow-up of Taiwanese Chinese patients treated early for 6-pyruvoyl-tetrahydropterin synthase deficiency. *Arch Neurol*. 2008;65:387-392.
22. Ye J, Yang Y, Yu W, et al. Demographics, diagnosis and treatment of 256 patients with tetrahydrobiopterin deficiency in mainland China: results of a retrospective, multicentre study. *J Inherit Metab Dis*. 2013;36:893-901.
23. Luhmann HJ, Fukuda A, Kilb W. Control of cortical neuronal migration by glutamate and GABA. *Front Cell Neurosci*. 2015; 9:4.
24. Manent JB, Represa A. Neurotransmitters and brain maturation: early paracrine actions of GABA and glutamate modulate neuronal migration. *Neuroscientist*. 2007;13:268-279.
25. Ruediger T, Bolz J. Neurotransmitters and the development of neuronal circuits. *Adv Exp Med Biol*. 2007;621:104-115.
26. Wehry AM, Beesdo-Baum K, Hennelly MM, Connolly SD, Strawn JR. Assessment and treatment of anxiety disorders in children and adolescents. *Curr Psychiatry Rep*. 2015;17:52.
27. Iversen SD, Iversen LL. Dopamine: 50 years in perspective. *Trends Neurosci*. 2007;30:188-193.
28. England SJ, Picchietti DL, Couvadelli BV, et al. L-Dopa improves restless legs syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. *Sleep Med*. 2011;12:471-477.
29. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41:1431-1441.
30. Knerr I, Gibson KM, Jakobs C, Pearl PL. Neuropsychiatric morbidity in adolescent and adult succinic semialdehyde dehydrogenase deficiency patients. *CNS Spectr*. 2008;13:598-605.
31. Lapalme-Remis S, Lewis EC, De Meulemeester C, et al. Natural history of succinic semialdehyde dehydrogenase deficiency through adulthood. *Neurology*. 2015;85:861-865.
32. Pearl PL, Gibson KM, Acosta MT, et al. Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. *Neurology*. 2003;60:1413-1417.
33. Pearl PL, Wiwattanadittakul N, Roullet JB, Gibson KM. Succinic semialdehyde dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews (R)*. Seattle, WA; University of Washington; 1993.
34. Anikster Y, Haack TB, Vilboux T, et al. Biallelic mutations in DNAJC12 cause hyperphenylalaninemia, dystonia, and intellectual disability. *Am J Hum Genet*. 2017;100:257-266.
35. Blau N, Martinez A, Hoffmann GF, Thony B. DNAJC12 deficiency: a new strategy in the diagnosis of hyperphenylalaninemias. *Mol Genet Metab*. 2018;123:1-5.
36. Bortolato M, Floris G, Shih JC. From aggression to autism: new perspectives on the behavioral sequelae of monoamine oxidase deficiency. *J Neural Transm (Vienna)*. 2018;125:1589-1599.
37. Al Hawsawi K, Pope E. Pediatric psychocutaneous disorders: a review of primary psychiatric disorders with dermatologic manifestations. *Am J Clin Dermatol*. 2011;12:247-257.
38. Cauwels RG, Martens LC. Self-mutilation behaviour in Lesch-Nyhan syndrome. *J Oral Pathol Med*. 2005;34:573-575.
39. Iwata BA, Pace GM, Willis KD, Gamache TB, Hyman SL. Operant studies of self-injurious hand biting in the Rett syndrome. *Am J Med Genet Suppl*. 1986;1:157-166.
40. Mercimek-Andrews S, Salomons GS. Creatine deficiency syndromes. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews(R)*. Seattle, WA; University of Washington; 1993.
41. Simeon D, Stanley B, Frances A, Mann JJ, Winchel R, Stanley M. Self-mutilation in personality disorders: psychological and biological correlates. *Am J Psychiatry*. 1992;149: 221-226.
42. Haavik J, Blau N, Thony B. Mutations in human monoamine-related neurotransmitter pathway genes. *Hum Mutat*. 2008;29: 891-902.
43. Barbarich NC, Kaye WH, Jimerson D. Neurotransmitter and imaging studies in anorexia nervosa: new targets for treatment. *Curr Drug Targets CNS Neurol Disord*. 2003;2:61-72.
44. Gurcu S, Girgin G, Yorulmaz G, Kilicarslan B, Efe B, Baydar T. Neopterin and biopterin levels and tryptophan degradation in patients with diabetes. *Sci Rep*. 2020;10:17025.

45. Roze E, Vidailhet M, Blau N, et al. Long-term follow-up and adult outcome of 6-pyruvoyl-tetrahydropterin synthase deficiency. *Mov Disord*. 2006;21:263-266.
46. Wang L, Yu WM, He C, et al. Long-term outcome and neuroradiological findings of 31 patients with 6-pyruvoyltetrahydropterin synthase deficiency. *J Inherit Metab Dis*. 2006;29:127-134.
47. Friedman J. Sepiapterin reductase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews(R)*. Seattle, WA; University of Washington; 1993.
48. Friedman J, Hyland K, Blau N, MacCollin M. Dopa-responsive hypersomnia and mixed movement disorder due to sepiapterin reductase deficiency. *Neurology*. 2006;67:2032-2035.
49. Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. *Ann Neurol*. 2012;71:520-530.
50. Lim Y, Velozo C, Bendixen RM. The level of agreement between child self-reports and parent proxy-reports of health-related quality of life in boys with Duchenne muscular dystrophy. *Qual Life Res*. 2014;23:1945-1952.
51. Longo E, Badia M, Begona Orgaz M, Gomez-Vela M. Comparing parent and child reports of health-related quality of life and their relationship with leisure participation in children and adolescents with Cerebral Palsy. *Res Dev Disabil*. 2017;71:214-222.
52. Murray CB, Holmbeck GN, Ros AM, Flores DM, Mir SA, Varni JW. A longitudinal examination of health-related quality of life in children and adolescents with spina bifida. *J Pediatr Psychol*. 2015;40:419-430.
53. Olafsdottir LB, Egilson ST, Arnadottir U, Hardonk SC. Child and parent perspectives of life quality of children with physical impairments compared with non-disabled peers. *Scand J Occup Ther*. 2019;26:496-504.
54. White-Koning M, Grandjean H, Colver A, Arnaud C. Parent and professional reports of the quality of life of children with cerebral palsy and associated intellectual impairment. *Dev Med Child Neurol*. 2008;50:618-624.
55. Ali A, Ambler G, Strydom A, et al. The relationship between happiness and intelligent quotient: the contribution of socio-economic and clinical factors. *Psychol Med*. 2013;43:1303-1312.
56. Chaplin R, Barley M, Cooper SJ, et al. The impact of intellectual functioning on symptoms and service use in schizophrenia. *J Intellect Disabil Res*. 2006;50:288-294.
57. Hallin AL, Stjernqvist K. Adolescents born extremely preterm: behavioral outcomes and quality of life. *Scand J Psychol*. 2011;52:251-256.
58. Fayed N, Davis AM, Streiner DL, et al. Children's perspective of quality of life in epilepsy. *Neurology*. 2015;84:1830-1837.
59. Hrabok M, Sherman EM, Bello-Espinosa L, Hader W. Memory and health-related quality of life in severe pediatric epilepsy. *Pediatrics*. 2013;131:e525-e532.
60. Nota L, Ferrari L, Soresi S, Wehmeyer M. Self-determination, social abilities and the quality of life of people with intellectual disability. *J Intellect Disabil Res*. 2007;51:850-865.
61. Szumski G, Firkowska-Mankiewicz A, Lebuda I, Karwowski M. Predictors of success and quality of life in people with borderline intelligence: the special school label, personal and social resources. *J Appl Res Intellect Disabil*. 2018;31:1021-1031.
62. Irazabal M, Marsa F, Garcia M, et al. Family burden related to clinical and functional variables of people with intellectual disability with and without a mental disorder. *Res Dev Disabil*. 2012;33:796-803.
63. Austin JK, Smith MS, Risinger MW, McNelis AM. Childhood epilepsy and asthma: comparison of quality of life. *Epilepsia*. 1994;35:608-615.
64. Hoare P, Mann H, Dunn S. Parental perception of the quality of life among children with epilepsy or diabetes with a new assessment questionnaire. *Qual Life Res*. 2000;9:637-644.
65. Hergenroder H, Blank R. Subjective well-being and satisfaction with life in adults with spastic cerebral palsy: a pilot study of a randomized sample. *Dev Med Child Neurol*. 2009;51:389-396.
66. White-Koning M, Arnaud C, Dickinson HO, et al. Determinants of child-parent agreement in quality-of-life reports: a European study of children with cerebral palsy. *Pediatrics*. 2007;120:e804-e814.
67. Liang S, Zhang S, Hu X, et al. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. *Eur J Paediatr Neurol*. 2014;18:670-676.
68. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Spectrum of addictions in Parkinson's disease: from dopamine dysregulation syndrome to impulse control disorders. *J Neurol*. 2010;257:S276-S283.
69. Brusa L, Pavino V, Massimetti MC, Bove R, Iani C, Stanzione P. The effect of dopamine agonists on cognitive functions in non-demented early-mild Parkinson's disease patients. *Funct Neurol*. 2013;28:13-17.

How to cite this article: Keller M, Brennenstuhl H, Kuseyri Hübschmann O, et al. Assessment of intellectual impairment, health-related quality of life, and behavioral phenotype in patients with neurotransmitter related disorders: Data from the iNTD registry. *J Inherit Metab Dis*. 2021;44(6):1489-1502. https://doi.org/10.1002/jimd.12416