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BRIEF REPORT

# Brief Report: Delayed Diagnosis of Treatable Inborn Errors of Metabolism in Children with Autism and Other Neurodevelopmental Disorders

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## Abstract

The objective of our study was to evaluate the frequency of treatable inborn errors of metabolism (IEM) in a clinical sample of Mexican children and adolescents with neurodevelopmental disorders (NDD). Amino acids and acylcarnitines in blood samples of 51 unrelated children and adolescents were analyzed by tandem mass spectrometry to detect treatable IEM of small molecules. One patient with isovaleric acidemia and autism spectrum disorder (ASD) and another with beta-ketothiolase deficiency and ASD/intellectual disability/attention-deficit/hyperactivity disorder (ADHD) were diagnosed, indicating an IEM frequency of 3.9% (1:26 subjects). The high frequency of treatable IEM indicates the need to perform a minimum metabolic screening as part of the diagnostic approach for patient with NDD, particularly when newborn screening programs are limited to a few disorders.

**Keywords** Autism spectrum disorders · Intellectual disabilities · Neurodevelopmental disorders · Inborn errors of metabolism · Metabolic screening

Neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD), intellectual developmental disorder/intellectual disability (IDD/ID), and attention-deficit/hyperactivity disorder (ADHD), are a group of medical conditions characterized by early emergence; a continuing course; abnormal neural circuit development; dysfunctions in cognition, learning, communication and behavior; and within cluster comorbidity (e.g., ASD/IDD, ASD/ADHD IDD/ADHD) (Bertelli et al. 2016). The IDD Mexico Study (Lazcano-Ponce et al. 2016) aimed to generate scientific evidence about IDD in Mexico, including the clinical and genomic characterization of these disorders, and as part of this characterization, the search for known treatable inborn errors of metabolism (IEM) in patients with IDD or/and ASD or/and ADHD was included (Ibarra-González et al. 2017).

IEMs are a complex group of monogenic disorders typically caused by partial or complete loss of function of a single enzyme, cofactor, or transport protein and are generally inherited as autosomal recessive or X-chromosomal traits. To date, more than 1000 IEMs have been described, and approximately 50% of them affect the central nervous system, causing mild to severe mental disability (Saudubray and

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Garcia-Cazorla 2018). IEM has been found in patients misdiagnosed with IDD, ASD and ADHD of unknown etiology (Simons et al. 2017; van Karnebeek et al. 2014). Early IEM diagnosis is vital because these diseases are often progressive, deteriorating and, sometimes, treatable, and its prompt identification in newborns facilitates timely interventions that significantly decrease morbidity, mortality, and disability (Caggana et al. 2013). Approximately 200 IEMs have a specific treatment that can prevent or ameliorate neurobiological damage and disability (van Karnebeek and Stockler 2012; Wasim et al. 2019). In high-income countries (HICs), nearly 60 treatable IEMs are routinely searched by applying newborn screening (NBS) (Urv and Parisi 2017), and the positive impact of NBS on children's public health has been profusely documented (Grosse et al. 2016). In low- and middle-income countries (LMICs), NBS programs usually include the detection of two to six diseases, such as phenylketonuria, congenital hypothyroidism, galactosemia, congenital adrenal hyperplasia, cystic fibrosis and glucose-6-phosphate dehydrogenase deficiency (Therrell et al. 2015), and only the first three of them are primarily related to NDD. In this work, we investigated the presence of treatable IEM in a group of Mexican children with NDD.

## Methods

### Participants

A total of 51 Mexican unrelated children and adolescents with ages ranging from 6 to 15 years (mean = 9.8 years) were included from June 2017 to July 2019 as participants of the IDD Mexico Study (Lazcano-Ponce et al. 2016); 78.4% were male, and most were attending public regular school (71%). Subjects were recruited at a public institution specialized in child psychiatry located in Mexico City; 33 out of 51 participants had ASD: alone (n = 7), or in comorbidity with ID (ASD/ID) (n = 11), with ADHD (ASD/ADHD) (n = 6) or with both (ASD/ID/ADHD) (n = 9); 11 out of 51 participants had IDD in the following manner: alone (n = 4) or in comorbidity with ADHD (n = 7); finally, ADHD alone was present in 7 participants.

### Psychiatric Diagnosis

The ASD diagnosis was given by child psychiatrists at the admission unit using the ICD-10 and confirmed with the Autism Diagnostic Interview Revised (ADI-R) (Rutter et al. 2003). Impairment of the cognitive functions for the IDD diagnosis was considered when an IQ below 70 was obtained from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler, 2005). Adaptive behavior was measured with the Vineland Adaptive Behavior Scale (VABS-II) (Sparrow et al. 2005). The clinical diagnosis of ADHD was confirmed with the Mini-kid (Mini International Neuropsychiatric Interview for Children and Adolescents) (Sheehan et al. 2000), and a dimensional diagnosis approach ("attentional problems") was obtained from the Child Behavior Checklist 6–18 Mexican version (Achenbach and Rescorla 2001). A functioning and disability assessment was carried out with the World Health Organization Disability Assessment Schedule (WHODAS 2.0) (Üstün et al. 2010) and with the UNICEF/Washington Group Child Functioning Module (Mactaggart et al. 2016). A medical (pre, peri- and postnatal) history, psychomotor development and a three-generation genealogy were obtained. Neurological and dysmorphological evaluations were also performed, and minor physical anomalies were evaluated through the modified version of the Waldrop scale (Green et al. 1998).

### Analytical Procedure and Detected IEM

From each patient, 4 drops of capillary blood were taken and deposited on 903 filter paper cards. Samples were dried for 3 h at room temperature and transferred to a specialized IEM laboratory. Eleven amino acids, free carnitine and 30 acylcarnitines were measured by tandem mass spectrometry with a commercial kit (NeoBase Nonderivatized MS/MS kit; PerkinElmer Waltham Massachusetts) according to the manufacturer´s instructions. Metabolites were quantified by reference to appropriate internal standards with MassLynx® software. Only treatable IEM of small molecules were included: 13 amino acid disorders, 19 organic acidemias and 11 fatty acid oxidation disorders. The detailed name and characteristics of the studied IEM were previously reported (Ibarra-González et al. 2017).

### IEM Diagnostic Confirmation Tests

All samples whose analytes were outside the known reference values were reprocessed and those that consistently demonstrated some abnormality were reported as suspicious to the public institution specialized in child psychiatry, for the immediate location of the patient and reference to the specialized IEM laboratory, where a blood mass spectrometry analysis was repeated and a urinary organic acid analysis was carried out by gas chromatography–mass spectrometry (GC/MS) on an Agilent 6890 N GC coupled to an MSD 5973 MS (5301 Stevens Creek Blvd, Santa Clara), as described by Sweetman (1991).

### Ethical Considerations

The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics, research, and biosecurity institutional committees. Once the parents

signed the informed consent form, the samples were collected. Children confirmed to have an IEM received specific medical care and genetic counseling at the specialized IEM laboratory.

## Results

A total of 51 samples from patients with NDD were analyzed. The patients' cognitive profile (WISC-IV score) showed a mean verbal comprehension of 66.61 (SD 22.54), a perceptual reasoning of 76.49 (SD 23.49), working memory of 65.80 (SD 16.39), processing speed (73.24 (SD 19.35) and full scale IQ of 65.16 (SD 21.86). Three patients showed abnormal blood acylcarnitine and amino acid results. Confirmatory studies were positive in two of the patients, both of whom had organic acidemias: one case of isovaleric acidemia (IVA, deficiency of the enzyme isovaleryl-CoA dehydrogenase, Mendelian Inheritance in Man MIM phenotype #243500, ICD10: E71.110) and another case with a beta-ketothiolase deficiency (BKT, Mendelian Inheritance in Man MIM phenotype # 203750; ICD10:71.118) (the characteristic abnormal metabolites found in blood and urine are shown in Table 1; see the urinary chromatograms in Fig. 1). The blood tests of the other suspicious case showed high levels of branched-chain amino acids (leucine, isoleucine and valine), but the urinary organic acid profile was normal, so the IEM was not confirmed.

The patient with IVA was an 11-year-old female with a clinical diagnosis of Asperger syndrome (AS) (F84.5) and a research diagnosis of ASD (Table 2). She was the first daughter of nonconsanguineous, apparently healthy parents, and her mother was 29 years old; the patient had an irrelevant family history, and her three-generation genealogy revealed no other similar cases. An uneventful pregnancy delivered by cesarean section at 39 weeks of gestation (due to premature rupture of membranes) without cervix dilatation was reported, with an Apgar score of 9–9, birth weight of 3600 g, and discharge from the hospital as a normal newborn. Newborn screening for congenital hypothyroidism and phenylketonuria was performed with negative results. In the first months of life, restlessness, irritability and difficulty in comforting her were observed. At 18 months, she stopped using verbal language. At 3 years old, she presented irritability alternated with somnolence and arrest of neurodevelopmental milestones with language delay; the presence repetitive play and difficulties in socialization; coincidentally, a selective eating behavior, with a rejection of rich protein foods and preference for vegetables and fruits, was observed. At the same age, she was diagnosed by her pediatrician as having probable AS and was referred to a psychiatric evaluation where she was given a diagnosis of AS. At the age of 6 years old, the patient presented an episode of vomiting, dehydration and abdominal pain, which was diagnosed as appendicitis and received surgical management. At the age of 11 years old, with a physical examination showing normal somatometry, no major physical anomalies, a high/steepled palate, and a large gap between the 1st and 2nd toes via the Waldrop scale, the IVA confirmation diagnosis was made (Table 1 and Fig. 1a). At this time, the patient's parameters of hematic biometry and blood chemistry were within normal limits, so she began nutritional treatment with a leucine-restricted diet supplemented with a leucine-free medical formula, carnitine 100 mg/kg/day and glycine 100 mg/day, with continued normalization of the biochemical parameters. After treatment, psychiatric improvements were observed mostly in the social communication and social interaction domains. Currently, the patient can share a smile, has good eye contact, and understands gestures. She has interest in peers and maintains social interaction (this interaction was previously brief and inappropriate). Regarding repetitive patterns of behavior, the patient sometimes exhibits repetitive behavior regarding a film but is more flexible in general. She is described as reserved and occasionally complains of being the subject of jokes that she does not fully understand. In addition, she is doing well in school, is in good physical

**Table 1** IEM detected in the studied Mexican patients with NDD and its abnormal metabolites found in blood and urine

| Patient | Acylcarnitines in blood | | | Organic acids in urine | IEM Diagnosis |
|---|---|---|---|---|---|
| | Metabolite | Concentration (μM) | Cut-off value (μM) | | |
| 1 | Isovalerylcarnitine (C5) | 3.35 | 0.36 | ↑3-hydroxy-isovaleric acid | Isovaleric acidemia |
| | C5/C0 ratio | 0.19 | 0.02 | ↑Isovalerylglycine | |
| | C5/C2 ratio | 0.35 | 0.04 | | |
| | C5/C3 ratio | 2.41 | 0.26 | | |
| 2 | 3-Hydroxy-isovalerylcarnitine + methylmalonylcarnitine (C5OH + C4DC) | 0.86 | 0.63 | ↑2-methyl-3-hydroxybutyric acid<br>↑3-hydroxybutyric acid<br>↑3-keto-3-methylvaleric acid | Beta-ketothiolase deficiency |

*C0* free carnitine, *C2* acetylcarnitine, *C3* propionylcarnitine

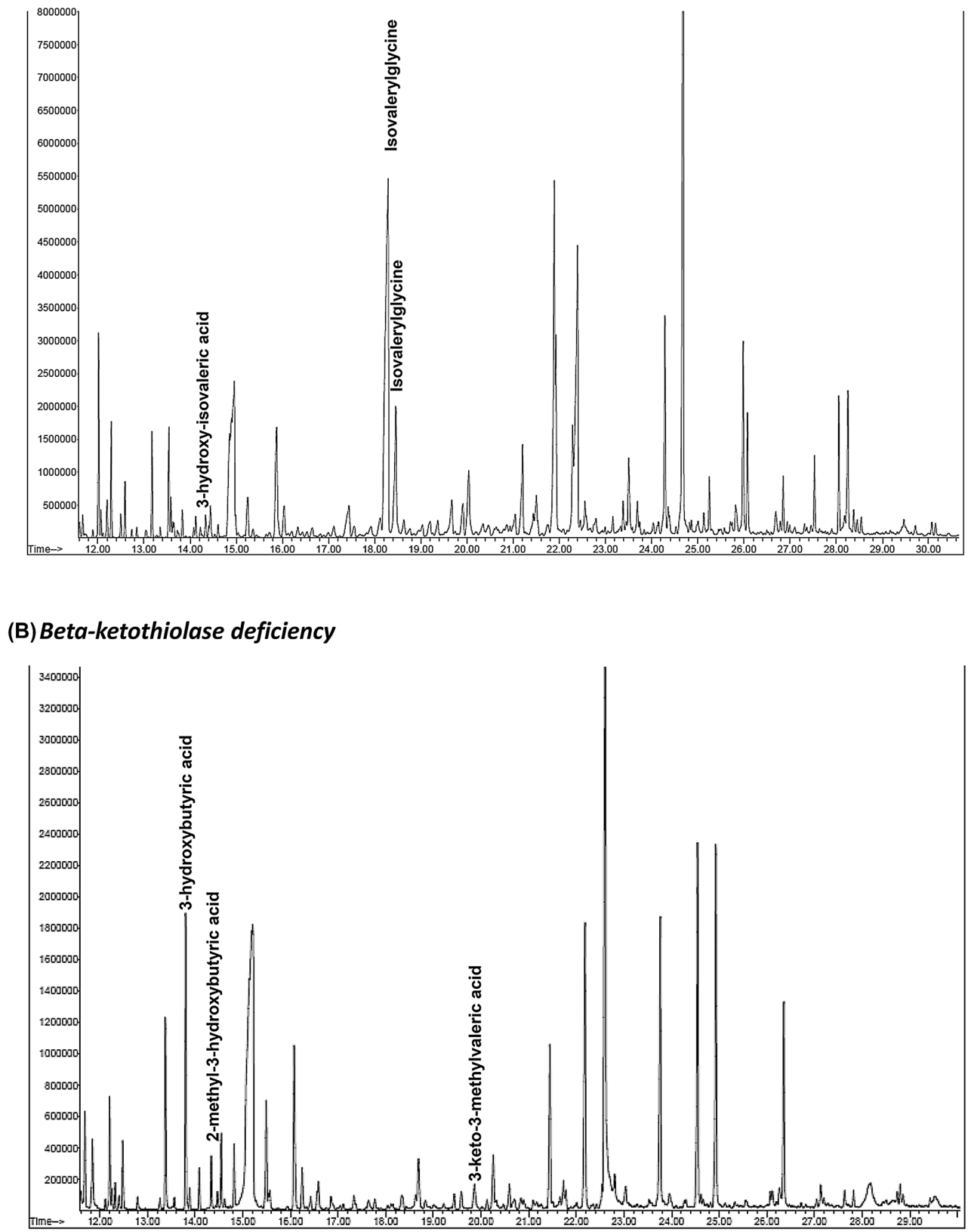


**Fig. 1** Urinary organic acid profile obtained by gas chromatography-mass spectrometry of the patients. **a** Isovaleric acidemia diagnostic chromatogram. **b** Beta-ketothiolase deficiency diagnostic chromatogram

**Table 2** Psychiatric evaluation results, sex and age of the two positive cases with IEM

| Variable | IVA | BKT |
|---|---|---|
| Age (years) | 11 | 6 |
| Sex | Female | Male |
| ICD-10 clinical diagnosis | F84.5 | F84.0 |
| Research diagnosis | ASD | IDD + ASD + ADHD |
| Autism Spectrum Disorders (ADI-R score) | | |
| Qualitative abnormalities in reciprocal social interaction | 27 | 23 |
| Qualitative impairments in communication and language | 19, Verbal | 11, Non-verbal |
| Restricted, repetitive, and stereotyped behaviors and interests | 5 | 9 |
| Abnormality of development evident at or before 36 months | 5 | 5 |
| Cognitive profile (WISC-IV score) | | |
| Verbal comprehension | 67 | 47 |
| Perceptual reasoning | 86 | 45 |
| Working memory | 71 | 50 |
| Processing speed | 97 | 50 |
| Full scale IQ | 74 | 40 |
| Adaptive behavior (VABS-II score) | | |
| Communication | 90 A | 63 L |
| Daily life skills | 78 Ml | 55 L |
| Socialization | 78 Ml | 55 L |
| Motor skills | – | 56 L |
| Composite adaptative behavior | 80 Ml | 55 L |
| ADHD (Minikid result) | Negative | Positive |
| Mental Health Problems (CBCL T score) | | |
| Attention problems (syndrome) | 50 N | 75 C |
| Attention deficit/hyperactivity problems (DSM) | 52 N | 62 N |
| Total competence | 46 N | 15 C |
| Activities | 60 N | 20 C |
| Social | 40 N | 23 C |
| School | 41 N | 33 B |
| Functioning and disability | | |
| General disability factor (WHODAS 2.0*) | Mild difficulty | Moderate difficulty |
| Disability index (CFM*) | Mild impairment | Mild impairment |

*IVA* Isovaleric academia case, *BKT* Beta-ketothiolase deficiency case, *ICD10* International Statistical Classification of Diseases and Related Health Problems 10th Revision, *ASD* autism spectrum disorders, *IDD* intellectual developmental disorders/intellectual disabilities, *ADHD* attention-deficit/Hyperactivity disorder, *ADI-R* autism diagnostic interview—revised, *WISC-IV* Wechsler Intelligence Scale for Children, Fourth Edition, *VABS-II* Vineland Adaptive Behavior Scales, Second Edition, *A* adequate, *Ml* moderately low, *L* low, *CBCL* child behavior checklist, *N* normal, *B* bordering, *C* clinical, *WHODAS 2.0* World Health Organization Disability Assessment Schedule, *CFM* UNICEF/Washington Group Child Functioning Module

*According to the International Classification of Functioning, Disability and Health, Children & Youth Version

health and has a good quality of life (i.e., social inclusion, self-determination, emotional well-being and personal development favoring her independence and autonomy).

The patient with BKT was a 6-year-old male with a clinical diagnosis of a pervasive developmental disorder (F84.0) and a research diagnosis of ASD/IDD/ADHD (Table 2). A first pregnancy in his 28-year-old mother, apparently healthy nonconsanguineous parents and a negative three-generation genealogy were reported. The patient was born at 38 weeks of gestation, with a birth weight of 3050 g. The pregnancy was uneventful with spontaneous vaginal delivery and an unknown Apgar because the newborn did not breathe and cry immediately at birth; he thus required reanimation maneuvers, without needing mechanic ventilation. He was hospitalized for 5 days because of poor thermic control and was discharged as a normal newborn. Newborn screening for 2 diseases was performed (congenital hypothyroidism and phenylketonuria) with negative results. The patient

showed a typical milestone developmental history until he was 2.5 years old, when insidious development was observed with loss of eye gaze and loss of language progression with socioemotional difficulties (irritability, poor eye contact, indifferent behavior) and regression of cognitive skills (fine motor, imitation and representational play development). Stereotypical movements of the hands were noticed. At 3 years old, he was referred to a psychiatric hospital, where a pervasive developmental disorder diagnosis was given (F84.0). At the age of 6 years old, his physical examination showed normal somatometry with no other major dysmorphic features, and his Waldrop scale revealed soft and pliable ears and mild clinodactyly. At the same age, the BKT diagnosis was confirmed (Table 1 and Fig. 1b), and the hematic biometry and blood chemistry were within normal limits; consequently, the patient began nutritional treatment with mildly restricted protein intake (1.5 g/kg/day), carnitine 100 mg/kg/day and avoidance of fasting, with slight improvement of the biochemical parameters; however, his diet compliance was poor. The psychiatric evaluation after treatment showed that difficulties in social communication and social interaction persist; the patient shows poor eye contact, sporadically looking for affect, and although now he understands and responds to gestures, he remains nonverbal. He tries to approach peers, but he only runs with them without understanding their games, and he engages in no imaginative play. He shows flapping of the hands, insistence on sameness (he repeated watches a favorite movie repetitively) and is hyperreactive to the texture of clothes. Regarding social inclusion, he is capable of tolerating new places, but if the location is crowded, he cries or has a tantrum. In addition, the patient is not socially included with peers; with a minimum of self-determination, he occasionally chooses his clothes. He must be assisted with hygiene but enjoys attending school.

## Discussion

The purpose of this study was to search for known treatable IEM in patients with NDD as part of the IDD Mexico Study (Lazcano-Ponce et al. 2016). Effectively, ASD was the most common of the NDD in this clinical sample, with ASD in comorbidity with IDD being the most frequent presentation. This finding agrees with the results from a systematic review carried out by McKenzie et al. (2016), suggesting that 40–60% of ASD patients have intellectual disabilities. In our study, the proportion of males to females was almost 4 to 1; although this male-to-female ratio is observed in most studies, a recent meta-analysis (Loomes et al. 2017) revealed a closer 3 to 1 ratio due to a diagnostic gender bias (girls being underdiagnosed), which may be the case, particularly in LMICs such as Mexico. Our results show that patients with NDD, such as ASD isolated or in comorbidity with IDD or/and ADHD, constitute a population at high risk of having a treatable IEM, since we found 2 patients, one with IVA and the other with BKT, representing a frequency of one case per 26 studied individuals (near 4%). The presence of IEM as a cause of NDD has been profusely documented by diverse authors, finding these diseases in 1–3% of nonconsanguineous IDD patients (van Karnebeek et al. 2014; Wasim et al. 2019). Therefore, conducting a minimal metabolic screening is justified, especially for those IEMs that can be treated, thus improving the clinical condition of patients (Asato et al. 2015).

An extensive review found that 85% of IVA patients diagnosed in the first 5 weeks of life had a normal neurocognitive outcome, in contrast to only 45% of patients who were late diagnosed (Schlune et al. 2018). Even when BKT deficiency is extraordinarily rare, with only 250 documented cases worldwide, the clinical onset in 82% of cases occurs at the age of 2 years, and developmental delay was reported in 19.6%. Consequently, this metabolic disorder is a suitable target for NBS (Grünert et al. 2020).

There is no consensus in the medical practice guidelines with respect to looking for IEM in children with psychiatric disorders (Simons et al. 2017) or ASD (Cohen et al. 2005). The American College of Medical Genetics (ACMG) 2013 revision guideline for the clinical genetic evaluation in identifying the etiology of ASD establishes that minimum metabolic screening is justified, especially in ASD patients with associated symptomatology, such as seizures, movement disorders, dystonia, parkinsonism, failure to thrive or neuroregression (Schaefer and Mendelsohn 2013). Clinical diagnosis of IEM is a complex issue, and a diagnostic delay is common due to diverse factors, such as the rarity of the diseases (IVA and BKT birth prevalence are 1 case per 326,629 newborns and less than 1 per 1,000,000 newborns, respectively) (Abdelkreem et al. 2019; Couce et al. 2017), the poor specificity of the symptoms, and lack of training in health and mental health professionals. Furthermore, the clinical phenotypes of these diseases are usually heterogeneous, and the onset of the symptoms depends on several factors, such as the genotype, environmental exposures (mainly nutritional) and degree of enzymatic activity; additionally, severe deficiencies produce acute clinical manifestations in the earliest days of life, but intermediate and mild deficiencies are accompanied by chronic, intermittent or subtle neurodevelopmental symptomatology with or without evident metabolic decompensations (Saudubray and Garcia-Cazorla 2018). The two patients found in this study had a chronic IEM presentation; both individuals presented subtle symptoms that were not considered metabolic disorders, which contributed to the delayed diagnosis despite the obvious NDD. Moreover, both patients were screened at birth for only two diseases (congenital hypothyroidism and phenylketonuria), so the natural history of IVA and BKT progressed, leading

to neurodevelopmental symptomatology, clinically diagnosed in the IVA case, and global neurodevelopmental arrest in the BKT case (Table 2). In both cases, the accurate metabolic diagnosis was established by studying blood drops in filter paper through tandem mass spectrometry and then confirmed in a urine sample by GC/MS (Table 1, Fig. 1).

In HICs, the early diagnosis of IEM potentially related to IDD through newborn screening has been implemented as a public health policy; currently, the number of detected disorders is growing fast (Pandor et al. 2004), and the outcome of the early detected individuals is better (Schlune et al. 2018; van Karnebeek and Stockler 2012) in comparison with our patients from LMICs. Furthermore, in HICs, new molecular techniques, such as next-generation sequencing, are being gradually incorporated into newborn screening programs, thus resulting in a larger increase in the number of detected IEMs (van Karnebeek et al. 2014), and NBS expansion must also consider other important issues, such as ethical, legal and social implications, as well as ethnicity (Goldenberg et al. 2019). Unfortunately, in LMICs, due to various factors such as budget restrictions and other epidemiological priorities, deploying expanded newborn screening programs seems to be a distant prospect (Urv and Parisi 2017), despite growing evidence of the benefits of early diagnosis and preventive management (Grosse et al. 2016). Meanwhile, in LMICs, other feasible public health alternatives, such as minimum metabolic screening tests in the diagnostic approach of all patients with NDD or with arrest of neurological milestones, could be implemented. Based on our results, health personnel who are involved in the care of patients with NDD must have information and training to request and perform metabolic screening tests to discard monogenic metabolic disorders as soon as possible. Even further, the precise determination of the etiology of the disease is critical to implement the proper clinical care and treatment of IEM patients, as well as to provide accurate information and genetic counseling to the affected family.

One limitation of this study is that the MSMS panel used as the first screening methodology only allowed the detection of amino acid diseases, organic acidemias and fatty acid oxidation disorders. The other IEMs of large molecules (such as lysosomal disorders) that could be the cause of NDD symptomatology (Wolfenden et al. 2017) were not included; otherwise, the number of cases with other IEMs may be even greater.

## Conclusion

In the diagnostic approach of all patients with NDD, the presence of a treatable IEM must be considered due to the high frequency of these diseases in this high-risk population. Metabolic screening, including amino acid and acylcarnitine determination by MS/MS, should be performed as soon as possible as part of their initial medical approach. This is especially important in LMICs in which newborn screening programs are limited to few disorders.

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