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Autism in patients with propionic acidemia

Peter Witters [a], Eric Debbold [b], Kea Crivelly [b], Kristel Vande Kerckhove [a], Karen Corthouts [a], Brett Debbold [b], Hans Andersson [b], Lena Vannieuwenborg [c], Sam Geuens [c], Matthias Baumgartner [d], Tamas Kozicz [b,e], Lisa Settles [f], Eva Morava [a,b,*]

[a] Department of Pediatrics, Metabolic Center, University Hospitals Leuven, Leuven, Belgium
[b] Hayward Genetics Center, Tulane University School of Medicine, New Orleans, LA, USA
[c] Department of Psychology, Metabolic Center, University Hospitals Leuven, Leuven, Belgium
[d] Division of Metabolism, Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland
[e] Donders Institute for Brain, Neuroscience, Radboudumc, Nijmegen, The Netherlands
[f] Department of Psychiatry, Tulane University School of Medicine, New Orleans, LA, USA

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ABSTRACT

Certain inborn errors of metabolism have been suggested to increase the risk of autistic behavior. In an animal model, propionic acid ingestion triggered abnormal behavior resembling autism. So far only a few cases were reported with propionic acidemia and autistic features. From a series of twelve consecutively diagnosed cases with propionic acidemia, we report on eight patients with autistic features.

The patients were followed 2–4 times a year and underwent regular clinical, dietary and laboratory investigations. Psychological evaluation was performed every second to fourth year.

All patients were compliant with the standard diet and carnitine supplementation. None of the patients had frequent metabolic decompensations. From the metabolic factors known to impact neuropsychological outcome we detected chronically decreased valine levels and altered valine to leucine ratios in five out of the eight patients. Recurrent lactic acid elevations were present in six out of the eight patients. Five of the eight patients were diagnosed with Autism Spectrum Disorder, four of them had pathogenic variants in *PCCB*. Disorder according to DSM-IV and/or DSM-5 criteria. One of the patients diagnosed with propionic acidemia by newborn screening had the most significant behavioral features and another was diagnosed with Autism Spectrum Disorder prior to propionic acidemia.

We hypothesize that chronic suboptimal intracellular metabolic balance may be responsible for the increased risk for autistic features in propionic acidemia. We propose that patients diagnosed with propionic acidemia should be screened for Autism Spectrum Disorder.

1. Introduction

Propionic acidemia (PA) is a severe organic acidemia, characterized by acute episodes of metabolic acidosis, ketosis, lactic acidemia, hyperammonemia, lethargy, basal ganglia involvement, and seizures. Even well treated patients might develop growth delay, developmental and speech delay. Long term outcome is often characterized by intellectual disability [1,2]. Recurrent episodes of pancreatitis, muscle weakness and metabolic cardiomyopathy occur in a high percentage of cases, especially in those with insufficient therapeutic compliance [3]. Even the most adequately treated patients might develop neurologic symptoms including psychomotor retardation, speech delay, dystonia and even ischemic strokes of the basal ganglia [2]. Behavioral changes are relatively common in adolescent patients with PA, though Autism Spectrum Disorder (ASD) has been only reported in a single patient.

ASD is a complex neurodevelopmental disorder, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior. Several inborn errors of metabolism have been described as increasing a patient's risk for ASD, including lysosomal storage diseases, disorders of the creatine synthesis, disorders of purine and pyrimidine metabolism or dysfunction of the urea cycle, but autistic features are not frequently reported in organic acidemias [5,8,9,10,11]. With the growing frequency of patients being diagnosed with ASD, sometimes it is difficult exclude a coincidental diagnosis of autism in certain metabolic conditions from comorbidity, especially in case of intellectual disability. The incidence of metabolic disorders in autistic patients is not known, but is estimated as high as 5%, while in the general population cumulative occurrence of inborn errors of metabolism is closer to 1 in 800[5]. In recent guidelines for the

* Corresponding author at: Hayward Genetics Center, Tulane University School of Medicine, New Orleans, LA, USA; Department of Pediatrics, Metabolic Center, University Hospitals Leuven, Leuven, Belgium.
E-mail address: emoravakozicz@tulane.edu (E. Morava).

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treatment of propionic acidemia, evaluation and monitoring for autism is not yet included [2].

Interestingly, studies evaluating the effects of elevated propionic acid in rats have suggested a possible connection with autism [6,7]. Propionic acid administered systemically or by intracebro-ventricular injection to adult rats produced a rapid induction of repetitive movements, hyperactive activity, and seizure activity along with neuro-pathological and biochemical similarities to human ASD [6]. The mechanisms by which elevated levels of propionic acid affect the CNS are unknown, but possible candidates include interference with cellular metabolism, increased inflammatory cytokines and the reduction of intercellular gap-junctional communication.

Here we report on eight patients with autistic features and propionic acidemia from a case series of twelve consecutively diagnosed propionic acidemia patients. Biochemical and clinical information was collected and evaluated whether a risk factor for autism could be found.

2. Methods

2.1. Patient selection

A total of eight patients with propionic acidemia (PA) were evaluated in detail in this study. The inclusion criteria were the biochemical diagnosis of propionic acidemia confirmed in fibroblasts, in two centers, between 1995 and 2015. Twelve patients were diagnosed during the twenty years period. Four patients were excluded from the data analysis due to the unavailability of sufficient detailed clinical/metabolic and behavioral data. The patients' age range was between 3 and 20 years, with a median age of 7.5 years. Patients 6 and 7 are fraternal twins, patients 4 and 9 and Patient 10 and 11 were brothers. Seven patients were male, and one was female (Table 1). With regards to therapy, all of the patients followed a strict protein-restricted diet, with a maximum daily intake of 0.8–1 g/kg/day of natural protein and high caloric intake (110–138 cal/kg/day). All patients received carnitine (50–100 mg/kg/day) and biotin (10 mg/day) supplements. All but one patient received amino acid based metabolic formula, free of the precursor amino acids (Met, Val, ILe, Thr) additional to protein-free metabolic formula with extra sources of calories through carbohydrates and fats.

2.2. Prognostic factors

Prognostic factors known to play a role in PA patients' long-term outcome were retrospectively evaluated in our cohort. We included clinical, neurologic, and neuropsychiatric features, disease history and disease severity, anomalies on brain imaging, developmental features, behavioral problems, the presence of autistic features or the diagnosis of Autism Spectrum Disorder, and metabolic laboratory values in

Table 1
Clinical and genetic information in eight patients with features of the autistic spectrum, out of a twelve patients' cohort diagnosed with propionic acidemia (four patients; Patient 9–12 were not included in the analysis due to insufficient detail on neurodevelopmental and biochemical data).

Patient	Sex	Age (years)	Diagnosis	[e]Metabolic crises/year	Motor delay	Intellectual disability	Speech development	CNS involvement	Basal ganglia involvement	Organ involvement	[g]Pathogenic variants (cDNA and protein)
1.	M	3[c]	NBS	2	Mild	N/A	Absent	Hypotonia[f]	Infantile	None	*PCCB* c.1209 + 3A> G/p.V356E403del c.1209 + 3A> G/p.V356E403del
2.	M	4	NBS	2–3	Severe	Moderate	Absent	Hypotonia[f]	Neonatal	None	*PCCB* c.562G>A/p.G188AR c.562G>A/p.G188R
3.[b]	M	4	NBS	0	Moderate[h]	Moderate	Absent	None	None	None	*PCCB* c.638C>T/p.P228L c.638C>T/p.P228L
4.[a]	M	7	3 years	0	None	None	Delayed	None	None	None	*PCCB* c.683delC/p.P228L c.683delC/p.P228L
5.	M	8	7 days	2–3	Moderate	Moderate	Delayed	None[d]	None	None	*PCCA* c.1891C>G/p.G631R c.1891C>G/p.G631R
6.[a]	M	11	2.5 months	1–2	Mild	Moderate	Delayed	Abnormal gait[d]	None	None	*PCCB* c.1218_1231del14ins12 p.G407Rfs*14 and [h]c.479A>G p.D160G
7.[a]	M	11	NBS	2–3	Mild	Mild	Delayed	Abnormal gait	None	Arrhythmia	*PCCB* c.1218_1231del14ins12 p.G407Rfs*14 and [h]c.479A>G p.D160G
8.[a]	F	21	3 months	1	Moderate	Moderate	Delayed	Spasticity[d]	None	Pancreatitis	N/A
Patients with insufficient data for analysis											
9.	M	9	5 years	0	None	None	Normal	None	None	None	*PCCB* c.683delC/p.P228L c.683delC/p.P228L
10.	M	7	5 days	1–2	None	None	Delayed	None	None	None	*PCCB* c.1210G>A p.E404K c.1210G>A p.E404K
11.	M	3[c]	3 years	NA	None	None	Normal	None	None	Pancreatitis	*PCCB* c.1210G>A p.E404K c.1210G>A p.E404K
12.	F	4[c]	10 days	2–4	Severe	N/A	Absent	Hypotonia	None	Pancreatitis	*PCCA* c.923dupT/p.L308fs c.923dupT/p.L308fs

NBS denotes newborn screening test positive for Propionic academia.
Patients 6 and 7 are fraternal twins, patients 4 and 9 and Patient 10 and 11 were brothers.
[a] Diagnosis of autism (ASD) according to DSM-IV (Lord et al., Autism Diagnostic Observation Schedule (ADOS-2), 2nd Ed. 2000).
[b] Diagnosis of autism (ASD) according to DSM-5 criteria (Sparrow, Cicchetti, Balla, Vineland Adaptive Behavior Scales-2nd Ed. 2005).
[c] Patient deceased.
[d] Propionic acidemia related early coma episode.
[e] Number of metabolic disarrangements in the first 4 years of life.
[f] Central hypotonia.
[g] Previously described mutations in all but one patient (Kraus et al., J Inherit Metab Dis (2012) 35:51–63; Perez et al., Mol Genet Metab 2003,78: 59; Lamhownwah et al., Genomics. 1990, 8:249).
[h] So far unreported, predicted pathogenic variant.