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ORIGINAL ARTICLE

Autism spectrum disorders in propionic acidemia patients

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Abstract Propionic acidemia is the result of a deficiency in propionyl-CoA carboxylase activity. Chronic neurologic and cognitive complications frequently occur, but the psychiatric evolution of the disorder is not well documented. We conducted a pedopsychiatric evaluation of 19 children, adolescents and young adults, aged between 2 and 25 years, using ADI-R, CARS-T, as well as ADOS when autism spectrum disorder was suspected. Previous psychometric examinations were also taken into consideration. Thirteen patients had an IQ < 80. Two patients presented with autism and two additional patients with other autism spectrum disorders. Five patients did not fulfill diagnostic criteria for autism spectrum disorder but showed difficulties indicative of a broader autism phenotype (BAP). Four other patients had severe anxiety manifestations related to their disease. Two patients presented with acute psychotic episodes. The number of decompensations in the first 3 years of life was lower in patients with autism spectrum disorder or related symptoms. These patients were also older when they were assessed (median age of 15 years old versus 11 years old). There was no significant correlation between 3-hydroxypropionate levels during the first 6 years of life and autism spectrum disorder diagnosis. In conclusion, autism spectrum disorder is frequent in patients with propionic acidemia. These patients should undergo in-depth psychiatric evaluation and be screened for autism spectrum disorder. Further studies are needed to understand the underlying mechanisms.

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Introduction

Propionic acidemia (PA) is an inborn error of the catabolism of branched-chain amino acids in which the activity of propionyl-Co A carboxylase (PCC; EC 6.4.1.3) is deficient in the liver and other tissues (Nuria Carrillo-Carrasco and Venditti 1993). PCC is responsible for the conversion of propionyl-CoA into D-methylmalonyl-CoA, which is then transformed into succinyl-CoA, thus providing tricarboxylicacid cycle (TCA) intermediates. The latter are required for the synthesis of NADH, a major substrate of the mitochondrial respiratory chain (RC).

PCC deficiency leads to the accumulation in the mitochondria of propionyl-CoA and its metabolic by-products, notably methylcitrate, 3-hydroxypropionate (3-OHP), tiglylglycine, and propionylglycine. PA usually presents as acute metabolic distress at birth with coma associated with dehydration when the enzymatic deficiency is complete, or later in life with recurrent ketoacidotic episodes, psychomotor retardation, and chronic vomiting when the deficiency is partial (Nuria Carrillo-Carrasco and Venditti 1993; Baumgartner et al 2014).

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Specific changes in the levels of urinary and plasma metabolites are the hallmark of the classical forms of the disease including ketoacidosis, hyperlactatemia, hyperamoniemia, and cytopenia in variable proportions. In urine, specific organic acids are nearly pathognomonic. Enzymatic and genetic analyses confirm the diagnosis.

As propionate is produced by the catabolism of branched-chain amino acids, fatty acids with a carbon odd-chain, and the intestinal flora, the treatment is based on a strict low-protein diet associated with sufficient caloric intake, carnitine, and antibiotics. It aims to reduce the accumulation of toxic compounds.

Despite remarkable therapeutic improvements over the last 20 years, the overall outcome of patients with PA remains unsatisfactory. Recent reports highlight long-term complications, such as neurological disorders by degeneration of the basal ganglia, acute neurological symptoms (Nizon et al 2013; Haas et al 1995; Nyhan et al 1999), cardiomyopathy and prolonged QT syndrome (Romano et al 2010), myopathy, chronic digestive symptoms such as chronic vomiting and anorexia, and pancreatitis (Pena et al 2012). A study of 24 patients with PA found 37% of patients to have abnormal neurological examination, 61% displayed abnormal cognitive tests at the age of 3 years, and 56% had basal ganglia lesions (Nizon et al 2013).

As for psychiatric complications, dementia was described in a young adult (Sethi et al 1989), while atypical acute psychotic episodes were reported in two adolescents from our group (Dejean de la Bâtie et al 2014) and recurrent visual hallucinations in two children (Shuaib et al 2012). In a retrospective study of 55 cases, parents reported psychological problems in half of the patients, notably difficulty in interaction with their peers (four times more than their healthy relatives) (Grünert et al 2013). Finally, autism spectrum disorder (ASD) has been described in a 7-year-old girl (Al-Owain et al 2012) and recently in five patients (Witters et al 2016). In the latter study, three patients had autistic features without a formal ASD diagnosis.

Psychiatric symptoms are well known in inherited metabolic diseases such as ornithine transcarbamylase deficiency, homocystinuria, Wilson's disease, creatine deficiency, porphyrias etc. (Walterfang et al 2013), and compared to the general population, prevalence of ASD is higher in patients with various inborn errors of metabolism (Ververi et al 2012; Spilioti et al 2013; Ghaziuddin and Al-Owain 2013).

Interestingly, several studies showed that the administration of propionic acid in rats induced reversible autistic-like behaviors (MacFabe et al 2007; MacFabe et al 2011; MacFabe 2013). Biochemical and neuropathological studies of these rats' brains showed inflammation, elevated oxidative stress markers, and CREB factor activation (MacFabe et al 2007; MacFabe et al 2011; El-Ansary et al 2012).

ASD comprise a set of heterogeneous neurodevelopmental symptoms, characterized by early-onset difficulties in social interaction, in communication, and restricted, repetitive behaviors and interests (American Psychiatric Association and American Psychiatric Association 2013, Lai et al 2014). In ICD-10, a diagnosis of autism requires significant alteration of communication and social interaction, and restricted, repetitive interests and behaviors, with an onset prior to age 3. Patients who do not reach a sufficient number of symptoms in one of these three dimensions, or with later onset, may be diagnosed with another pervasive developmental disorder (other PDD), or pervasive developmental disorder, non-otherwise specified (PDD-NOS) (WHO 1993). DSM-5 recently modified the criteria for ASD, notably by merging two main features: persistent deficits in communication and social interaction, which are labeled social communication disorders; in addition, severity specifiers were introduced (American Psychiatric Association and American Psychiatric Association 2013).

In order to better delineate the long-term developmental and psychiatric outcome of patients with PA, and to outline evaluations and early care that might benefit these patients, we screened a cohort of 19 patients for ASD in relation to clinical, biochemical, and genetic parameters.

Patients and methods

Setting and patients

The Reference Center of Inherited Metabolic Diseases at Necker-Enfants Malades Hospital (Paris, France) diagnoses and ensures the follow-up of patients with PA. The Child Psychiatry department of the hospital is involved in the management of patients warranting a pedopsychiatric evaluation and/or treatment.

Of 27 alive patients with PA that were listed in the reference center, we included 22, who were aged between 2 and 25 years old. Eligibility criteria were: an enzymatic and/or molecular diagnosis of PA, age between 2 and up to 25 years, and follow-up at Necker-Enfants Malades hospital. Children and parents accepted this evaluation as part of their regular follow-up. This work was approved by our institutional Ethics Committee.

Specific organic acids included urinary 3-OHP, propionylglycine, tiglylglycine, and methylcitrate, measured by gas chromatography-mass spectrometry using standard protocols. PA positive diagnosis was achieved by measuring propionyl-CoA carboxylase activity in skin fibroblasts and/or by sequencing *PCCB* and *PCCA* genes.

Acute decompensation was defined as the association of acute clinical symptoms and at least one of the following results for plasma biochemical examination: pH < 7.30,

bicarbonate <18 mM, ammonemia >70 mM. The accumulation of 3-OHP in urine was measured at each decompensation and at each visit. The number of acute decompensations and the mean value of urinary 3-OHP outside of acute decompensations were analyzed as possible markers of metabolic balance during the first 6 years of life (which are the most crucial for neurodevelopment).

Psychiatric and developmental assessments

Meetings with patients were planned both individually (unaccompanied patients) and in the presence of one or both parents. Diagnosis of ASD included rating of the Autism Diagnostic Interview (ADI-R) (Lord et al 1994) and Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al 2012) which are standard diagnostic tools for ASD. ADI-R is a structured interview in which parents are asked questions about present and past symptomatology (between 4 and 5 years old). For patients with suspected ASD (one or more positive items of ADI-R and/or clinical features of ASD), the ADOS-2 was conducted and videotaped by LO who received official training, in order to validate the diagnosis of ASD.

Previous psychometric, neuropsychological, speech, and motor coordination evaluations were collected and analyzed. Patients with a total intellectual quotient below 80 on the Wechsler scales are hereafter described as having an intellectual disability (ID).

Therapeutic management

Patients were treated according to a standardized protocol associating a strict low-protein diet with a sufficient caloric intake that was adapted to the tolerance of the individual; this was combined with L-carnitine and with antibiotics to limit propionate production by the gut flora.

Statistical analysis

Descriptive statistics such as percentages, range (minimum–maximum: min-max), median with 25th and 75th percentiles (P25-P75), mean with standard deviation (SD) were used to summarize patient characteristics. Due to non-normal distributions, comparisons were based on non-parametric tests. The relations between ASD or ASD + BAP phenotype, ID and sex, age of PA diagnosis, cardiomyopathy, and affected gene were analyzed using Mann-Whitney or Fisher's exact tests. Statistical analyses were performed with STATA statistical software (release 13.0; Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Among 22 eligible patients, 19 (eight females and eleven males) were included in this study between January and September 2015. At inclusion, the mean (SD) age was 13.4 (6.1) years. Nine patients had a neonatal-onset PA (47.4%) and ten (52.6%) were diagnosed after the first month of life.

The medians (P25-P75) of number of acute decompensations during the first 3 years, and between 3 and 6 years were 2 (1–4) and 1 (0–1) with maximum values of 8 and 3 decompensations, respectively. The median values of urinary 3-OHP in these age groups were 40 (20–88) mmol/L and 46 (22–69) mmol/L, respectively. Seven patients (36.8%) had a cardiomyopathy. *PCCA* and *PCCB* genes were analyzed in 17 patients. Six had deleterious *PCCA* mutations and 11 had deleterious *PCCB* mutations (Table 1).

Neurodevelopmental and psychiatric description of the patients

Table 1 shows the results of the psychometric evaluations. The ADI-R algorithm was rated for 16 patients. For one child aged 26 months ADI-R could not be rated because his developmental age was less than 24 months, for a second child the available time with the parent was insufficient to complete the interview, and for a third child no parent could answer questions regarding symptoms between age 4 and 5. These three patients were clinically examined by a senior expert in ASD (LO) and did not have any ASD symptoms. The ADOS was offered when a diagnosis of ASD was suspected; eight patients underwent the ADOS evaluation.

ASD patients

Four patients had the symptoms required for a diagnosis of ASD, with convergent results of ADI-R and ADOS: two presented with typical autism, and two with other ASD. Their ages ranged between 13 and 20 years. Social communication was the most impaired dimension, although all presented with RRB to some extent (particularly intolerance to change and sensory hypersensitivity). All four had associated ID (mild to moderate) and anxiety symptoms. ASD severity was light to moderate. No patient had tantrums or self-harming behaviors.

Onset of symptoms was prior to 3 years of age in all ASD cases, and parents described the first year of life as normal for social interactions, with a progressive onset of abnormalities during the following years. Two patients had a neonatal diagnosis of PA and in two patients with later diagnosis, the onset of social communication disorders occurred prior to PA diagnosis. Notably, three out of these four patients were born in 2000 or before, which corresponds to a transition year in the

Table 1 Characteristics of cohort patients and results of autism diagnosis scales

No.	Age at inclusion	Sex	Age at diagnosis	Affected gene	Number of acute decompensations		Mean urinary 3-OHP outside acute decompensations (mmol/mol of creatine)		Cardiomyopathy	Intellectual disability (IQ < 80)	ADI-R†	ADOS-2 total score	ASD diagnosis
					(0–3 years old)	(3–6 years old)	(0–3 years old)	(3–6 years old)					
1	2	M	>1 month	*PCCB*	NR	NR	NR	NR	No	No	NA	NR	No
2	4	F	>1 month	*PCCA*	1	NR	1	NR	No	No	None	NR	No
3	6	F	>1 month	*PCCB*	3	1	136	90	No	Yes	SI, C	NA	No
4	7	M	>1 month	*PCCB*	4	1	20	22	No	Yes	None	NR	No
5	10	M	>1 month	*PCCB*	0	0	NA	46	No	No	None	NR	No
6	10	F	Neonatal	*PCCA*	3	3	20	20	Yes	No	SI, C	1	BAP
7	12	M	Neonatal	*NA*	7	2	110	127	No	Yes	NA	NR	No
8	13	M	>1 month	*PCCB*	0	1	32	49	No	Yes	SI, C, R	12	ASD (autism)
9	14	M	Neonatal	*PCCB*	4	0	94	11	Yes	No	R	3	No
10	14	F	>1 month	*PCCB*	0	1	NA	13	No	No	None	NR	BAP
11	15	M	Neonatal	*NA*	2	0	30	33	No	Yes	NA	NR	No
12	15	F	Neonatal	*PCCA*	3	1	66	99	No	Yes	SI, C	17	ASD
13	15	F	>1 month	*PCCB*	2	0	5	18	Yes	Yes	None	NR	BAP
14	15	M	>1 month	*PCCA*	1	0	21	66	No	Yes	SI, C, R	15	ASD (autism)
15	15	F	Neonatal	*PCCB*	6	3	56	129	Yes	Yes	None	NR	No
16	20	M	Neonatal	*PCCB*	1	1	88	53	Yes	Yes	C	14	ASD
17	21	M	Neonatal	*PCCA*	8	1	49	44	Yes	Yes	None	NR	No
18	22	F	Neonatal	*PCCB*	1	3	40	25	Yes	Yes	SI, C	3	BAP
19	25	M	>1 month	*PCCA*	1	0	NA	69	No	Yes	SI	4	BAP

† ADI-R results are expressed as dimensions for which the threshold was reached (C, communication; SI, reciprocal social interactions; R, restricted repetitive interests and behavior)

Abbreviations *3-OHP* 3-hydroxypropionate, *ASD* autism spectrum disorder, *BAP* broader autism phenotype, *F* female, *M* male, *NA* data not available, *No* number of patient, *NR* not relevant

management of organic acidurias and other inherited metabolic disorders in our center. This suggests that suboptimal metabolic management of the disorder may have taken place (see Discussion). One of these patients presented with three atypical acute psychotic episodes as an adolescent and young adult (patient 16 in Table 1, described as patient B in a previous paper (Dejean de la Bâtie et al 2014)). Two other patients had possible auditory hallucinations with an onset of these symptoms during adolescence.

BAP patients

Seven other patients did not have enough recorded symptoms to warrant diagnosis of ASD, and did not meet the ADI-R and/or ADOS-2 thresholds for ASD, but presented with a milder degree of social communication difficulties and/or resistance to change, sensory abnormalities and/or RRBs. Four of these patients had ID (patients 3, 13, 18, and 19). Three did not have ID but presented with developmental dyspraxia and/or executive disorders (patients 6, 9, and 10).

Five of these patients met the diagnostic threshold for some of the dimensions of the ADI-R algorithm (patients 3, 6, 9, 18, and 19). The latter (patients 18 and 19) met the criteria for pervasive developmental disorder, non otherwise specified, but not for ASD, when undergoing the ADOS. One patient scored positively on two dimensions of the ADI-R algorithm, and seemed to present with ASD as a younger child, but underwent orthotopic liver transplantation since then and

development of social communication subsequently improved, resulting in sub-threshold scores for the ADOS (patient 6). Two patients (patient 3 and patient 9) were classified as having autism related symptoms, without an ASD diagnosis. Patient 3 was a girl with moderate ID, which seemed to account for a large number of the items scoring positive on the ADI-R algorithm. Upon psychiatric examination at age 6, her social communication had improved considerably (she was receiving appropriate care) and it was not possible to have her undergo the ADOS (for unrelated travel constraints). Patient 9 was a boy with sensory abnormalities and repetitive behavior but good social communication skills and the diagnostic threshold for ASD was not met for the ADOS-2. Two other patients had sub-threshold scores for all dimensions of ADI-R and presented with severe social anxiety, resistance to change, and feeding difficulties (patients 10 and 13).

Five patients with social communication difficulties or severe social anxiety, and intolerance to change had a broader autism phenotype (BAP): patients 6, 10, 13, 18, and 19.

Other symptoms

Three patients with no autism-related symptoms presented attention deficit symptoms and two of these had significant chronic anxiety symptoms. A majority of patients had clinical sensory hypersensitivity (13). Fourteen patients seemed to present with either developmental dyspraxia or fine motor disorder, which have to be assessed with standardized procedures. ID was observed in 13 patients (total IQ < 80): six had mild ID (IQ between 50 and 80), seven had moderate to severe ID (IQ < 50). Only two patients had a strictly normal development with no significant mental or developmental disorders. They both had a late-onset form of PA.

Relations between ASD phenotypes, ID and clinical, biochemical, and molecular variables

No significant relation between ASD, or ASD + BAP, with sex, age at PA diagnosis, urinary 3-OHP levels, or *PCCA*/*PCCB* mutations was found. The number of decompensations in the first 3 years of life was linked to the ASD + BAP phenotype ($p = 0.031$), and fewer acute decompensations were documented in patients with ASD or related symptoms (median of 4 decompensations in patients without ASD or BAP, and median of 1 decompensation in patients with ASD or BAP). This phenotype was also associated with the age at inclusion ($p = 0.039$): those with ASD or related symptoms were older (median age of 15 years in ASD + BAP patients versus 11 years in other patients). Similarly, a relation between ID and age at inclusion ($p = 0.017$) was identified (ID patients were older: median age of 15 years in ID patients versus 10 years in non ID patients).

Higher 3-OHP levels between 3 and 6 years were observed in ID patients: the median level of 3-OHP was 53 mmol/mol of creatinine in ID patients versus 16.5 mmol/mol of creatinine in non ID patients ($p = 0.024$).

Both genes *PCCB* (11/17) and *PCCA* (6/17) were involved in ASD and BAP phenotypes. Among patients with ASD, two had PCCB mutation and two had PCCA mutation; among patients with BAP, three had PCCB mutation and two had PCCA mutation. Among those who had no autism symptoms, six had PCCB and two had PCCA mutation.

Discussion

This is the first series of PA patients with systematic ASD assessment. The first descriptions of psychiatric symptoms among PA patients reported visual hallucinations and psychotic decompensations (Shuaib et al 2012, Dejean de la Bâtie et al 2014), as well as ASD (Al-Owain et al 2012; Witters et al 2016). The latter study reported on five PA patients with ASD as well as three other patients with autistic features without a formal ASD diagnosis.

In our series of 19 children and young adults with PA, the vast majority presented with neurodevelopmental and/or psychopathological disorders. Four presented with ASD (21.1%), and five other patients seemed to present autism-related symptoms, which we described as a BAP. Thus, 47.4% of patients presented autism-related features, a very high rate compared to the general population which is currently around 1% (Lai et al 2014). In contrast to ASD cohorts where the sex ratio is 4 males/1 female in ASD and 2/1 in syndromic ASD patients (Lai et al 2014), and the series of Witters et al (2016) (7 males/1 female), no significant association between sex and presence of ASD or ASD + BAP was identified in our study.

All patients with ASD in our cohort had associated ID, but three patients with a BAP did not. A total of 68% of patients had sensory hypersensitivity and 74% seemed to have developmental dyspraxia or fine motor disorder, thus warranting further investigation.

The high prevalence of ASD and BAP in this population is likely to result from complex intricate mechanisms. Neuropathological factors related to the accumulation of toxic metabolites seem to play a part in these developmental disorders, which appear progressively in the first years of life. As in the study of Nizon et al (2013), which included the majority of our patients, the number of acute decompensations and their severity did not influence the prognosis in terms of ID, but a statistical association between the number of acute decompensations and the presence of autistic features was found in the current study. Interestingly, in this cohort, the number of acute decompensations in the first 3 years of life showed a moderately significant negative association with autism-related symptoms, which indicates that there is no evident simple

causation mechanism leading to ASD in PA (discussed below).

As in Nizon et al (2013), the biochemical profile (urinary 3-OHP) and long term neurologic outcome in PA (ID) were related (which is not surprising as most of our patients were studied in their cohort), but this parameter was not significantly associated with psychiatric outcome in the present study. Accordingly, as in the series published by Witters et al (2016), metabolic imbalance did not seem to be prognostic for ASD either.

Despite the fact that no genotype phenotype analysis was possible in our cohort, no association was found between ASD nor BAP and genotype, contrarily to Witters et al (2016) who found a pathogenic variant in PCCB in all patients diagnosed with autism.

Contrary to ID, which is more frequent in neonatal onset PA, no association was identified between ASD diagnosis and age of PA diagnosis. Thus, ID and ASD seem to be distinct disorders in PA patients, probably resulting from different factors.

In this cohort, patients with ASD or BAP were older than patients without autism-related symptoms, which could indicate that those older patients did not benefit from later therapeutic progress which enabled better development in the younger patients.

Neonatal-onset PA results from more severely reduced PCC enzyme activity but is diagnosed and treated earlier, whereas less severe forms tend to be diagnosed later with a possibly longer untreated chronic intoxication. This presumably accounts for the comparable number of ASD in both populations in this study and for the presence of typical autism in two late-onset PA patients. Of note, the parents of the late-onset patients described possibly ASD-related symptoms several months to years before the diagnosis of PA. This could account for the greater severity of autistic symptoms in those patients, compared to patients who were diagnosed and treated earlier. In addition, for both these patients with typical autism, parents described some degree of social communication improvement once treatment for PA was implemented. This suggests that adequate metabolic management might help to partly antagonize the development of ASD in PA patients, although prospective monitoring would be necessary to confirm this hypothesis.

Additionally, growing up with PA impacts numerous bio-psycho-social aspects of experience. These patients very often have pronounced fatigability, disease-related anxiety, and low self-confidence. Their everyday life is constrained by the need for a strict diet and often tube feeding, which impacts family functioning, parent-child interactions (as does prolonged anorexia), and social integration in a peer group. A majority of them have sensory abnormalities and fine motor difficulties which may impair the development of body representation and even capacities of "mental rotation", or "decentration", which are necessary for the acquisition of a "theory of mind" (Berthoz 2004; Xavier and Bottineau 2012; Xavier et al 2013).

All of these parameters could likely interact with other individual risk and protective factors.

Further studies are needed to investigate the mechanisms leading to ASD in PA patients. Our study was monocentric and involved only 19 patients, most of whom were already adolescents or young adults. Longitudinal prospective studies with psychiatric evaluation and screening for ASD would help to identify which early signs should be monitored in the first years of life as they would require early interventions in order to optimize neurodevelopmental outcome.

Better characterization of PA patients' development, including brain imaging and neuropsychological testing, is likely necessary for a better understanding of these disorders. Finally, assessment of patients with other classical organic acidurias for autism-related disorders is recommended.

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Compliance with ethical standards

Conflict of interest C. D. de la Bâtie, V. Barbier, C. Roda, A. Brassier, J.-B. Arnoux, V. Valayannopoulos, A.-S. Guemann, C. Pontoizeau, S. Gobin, F. Habarou, F. Lacaille, J.-P. Bonnefont, P. Canouï, C. Ottolenghi, P. De Lonlay, and L. Ouss declare that they have no conflict of interest.

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