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CASE REPORT

Autism Spectrum Disorder in a Child with Propionic Acidemia

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Abstract Autism is a neurodevelopmental disorder characterized by a combination of reciprocal social deficits, communication impairment, and rigid ritualistic interests. While autism does not have an identifying cause in most of the cases, it is associated with known medical conditions in at least 10% of cases. Although uncommon, cases of autism have also been reported in association with metabolic disorders. In this brief report, we describe the occurrence of autism in a 7-year-old girl with propionic acidemia (PA), a common form of organic aciduria resulting from the deficiency of propionyl-CoA carboxylase and characterized by frequent and potentially lethal episodes of metabolic acidosis often accompanied by hyperammonemia. It is particularly common in countries with high rates of consanguinity. Early diagnosis of autism in patients with metabolic disorders is important since autistic features are sometimes the most disruptive of all the child's problems. This facilitates providing the needed behavioral services not otherwise available for children with metabolic disorders.

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Abbreviations

PA	Propionic acidaemia
PPA	Propionic acid
ASD	Autism spectrum disorder

Introduction

Autism is a neurodevelopmental disorder characterized by a distinct combination of social and communication deficits with rigid restricted interests (Centers for Disease Control and Prevention 2007). It is classified as the main category in a group of disorders, called autism spectrum (or pervasive developmental) disorders (ASD), all of which are characterized by similar deficits (Schaefer and Lutz 2006). Although generally regarded as a disorder with strong genetic underpinnings, it is associated with known medical conditions in a subset of cases (Folstein and Rosen-Sheidley 2001; Pickler and Elias 2009). These medical conditions include chromosomal abnormalities, such as, fragile X syndrome (Clifford et al. 2007); neurological disorders, such as, tuberous sclerosis (Curatolo et al. 2010); and a range of inborn errors of metabolism. Among the latter, the most prominent include phenylketonuria, disorders of purine and pyramidine metabolism, glucose transport disorders, and mitochondrial disorders (Kayser 2008; Schaefer and Lutz 2006; Zecavati and Spence 2009). To our knowledge, autism has not been reported in association with propionic acidemia (PA), an autosomal recessive metabolic

disorder characterized by frequent and potentially lethal episodes of ketoacidosis and hyperammonemia. In this report, we describe a case of PA with autism.

Case Report

This Saudi girl, a product of uneventful pregnancy with normal birth growth parameters, was diagnosed with PA since birth based on tandem mass spectrometry and urine gas chromatography–mass spectrometry. *PCCA* gene sequencing revealed a homozygous G117D mutation. Family history was notable for parental consanguinity, but no history of neurodevelopmental disorders. At the age of 6 weeks, she presented with hyperammonemia (331 μmol/l) without metabolic acidosis. Subsequently, she had frequent episodes of metabolic acidosis, hyperammonemia (100–270 μmol/l) and recurrent pancreatitis (six attacks). She was treated with carnitine and sodium benzoate (250–400 mg/kg/day), which was changed later to carglumic acid (N-carbamylglutamate, 50 mg/kg/day) due to recurrent hyperammonemic episodes. Formal developmental assessment at the age of 8 years revealed that her cognitive and language skills coincided with the level of 21–24 months of age, while the gross and fine motor skills were at the level of 21–24 and 24 months of age, respectively. Her personal/social skills were at the level of 24–30 months of age. Nutritionally, she was on Propimex®-2 (66.5 g), polycose (80 g), whole milk (378 ml), and solid food providing total protein of 1.4 g/kg/day and natural protein of 0.68 g/kg/day. On physical exam, she was conscious with weight of 30 kg (90%), height of 124 cm (75%), and occipitofrontal circumference of 51 cm (2–50%). Chest, heart, and abdominal examination was unremarkable. Central nervous system examination revealed only mild hypotonia. Evaluation by electroencephalography and computed tomography of the brain did not reveal any abnormalities. The parents refused the brain MRI evaluation. Repeatedly, her propionylcarnitine was 106–114 (normal: <10 μmol/l) with a C3/C2 ratio of 4–5.89 (normal: 0–0.4). The free carnitine was 100–287 (normal: 6–72 μmol/l). *FMR1* gene testing revealed that she had normal CGG repeats of 22 and 29. Array-comparative genomic hybridization and *MECP2* gene sequencing were normal.

Psychiatric Evaluation

The patient was referred to the child psychiatrist because of behavioral problems consisting mainly of her difficulty in interacting with other children of her age, poor language skills, and resistance to follow commands. According to her parents, behavioral symptoms were noted before she was 3 years old and were initially attributed to her global intellectual disability. She used to spend several hours during the day watching cartoons on the DVD player and on the television. She would rewind the tape and watch her favorite scenes repeatedly, getting irritable and angry if stopped. At times, this would lead to severe temper tantrums, which would end only if her parents let her resume watching the cartoons again. She also liked spinning colored pens, holding them in a certain manner, and flicking them repeatedly. Other repetitive behaviors consisted of walking in circles; flapping her hands, especially when excited; switching lights on and off repeatedly; and occasionally smelling her mother's hair. Her imaginative play was minimal. With other children her of age, she would tend to isolate herself and not show any interest in joining them. Her conversation was limited to a few words, such as, bed-sheet or food items. However, she tended to repeat lines from her favorite cartoon shows, such as, *Mickey Mouse* and *Tom and Jerry*. She did not usually look at people when speaking to them nor would she point out to objects at a distance. Her facial expression, too, was limited. During the interview, she was well groomed and appeared her stated age. She was not aggressive or violent. However, she did not appear to be aware of personal boundaries; for example, she would occasionally stretch her hand across the desk and try to grab the pen from the examiner's hand without bothering to look at him. At times, she clapped her hands, and tried to reach behind her mother's head-cover to touch her (mother's) hair and smell it, while at other times, she would walk around in circles around the examiner's desk, flicking a pen, and screaming if stopped from doing so. When parents were interviewed about her behavior based on the Social Communication Questionnaire (SCQ) (Rutter et al. 2003), she received a score of 19, which is above the cutoff for autism.

Our patient in this report showed the typical triad of autistic symptoms – reciprocal social deficits, communication impairment, and restricted repetitive interests – from early childhood. Structured informant-based interviews for autism were conducted because of the lack of such instruments in Arabic. Therefore, based on the history and the clinical examination, and supplemented by scores on the rating scale, a diagnosis of autistic disorder as defined by the DSM IV (American Psychiatric Association 2000) was made by the child's psychiatrist.

Discussion

This case report describes the occurrence of autism in a child with propionic acidemia (PA). While a chance occurrence of the two syndromes cannot be ruled out, it is possible that PA may have played a role in the emergence

of autistic features in this patient because acute and chronic abnormalities of brain function are well-documented in PA (de Baulny et al. 2005; Schreiber et al. 2012). Alternatively, it is possible that the patient was already vulnerable to autism due to some other reason and that PA acted only as a trigger, a view consistent with the so-called two-hit hypothesis of the disorder (Ghaziuddin 2000). Noteworthy, urea cycle disorders, characterized by hyperammonemia, may present with confusion, bizarre behavior, and autistic-like symptoms (Gorker and Tuzun 2005; Sedel et al. 2007). It is possible that the recurrent bouts of hyperammonemia played a role in the development of the autistic symptoms in our patient. In the consensus conference about diagnosis and management of PA hosted in Washington, D.C. in January 2011, there was no reported association among the neurological sequalae of the disease between PA and autism (Schreiber et al. 2012; Sutton et al. 2012). This could be related to the fact that children with severe-profound intellectual disability may have impaired social interactions and the diagnosis of ASD might be challenging.

Recent reports have suggested that propionic acid (PPA) may be used to induce an animal model of autism (MacFabe et al. 2007, 2008). PPA, a short-chain fatty acid, is an intermediate of cellular metabolic pathways. As a weak acid, PPA exists in both aqueous and lipid soluble forms; it crosses the blood-brain barrier both passively and actively through specific monocarboxylate transporters (Thomas et al. 2010). Intracerebroventricular injection of PPA in adult rats produced behavioral, biochemical, electrophysiological, and neuropathological effects similar to those observed in autism (MacFabe et al. 2007, 2008; Shultz et al. 2009, 2008). Following intracerebroventricular infusions of PPA, there was an evidence of a relationship between changes in brain lipid profiles and the occurrence of autistic behaviors (Thomas et al. 2010). Collectively, the effects of PPA in rats included reversible repetitive dystonic behaviors, hyperactivity, turning behavior, retropulsion, caudate spiking, and the progressive development of limbic kindled seizures (MacFabe et al. 2007). Similarly, systemic administration of PPA has been shown to cause social deficits, anxiety-like and hypoactivity behavior in juvenile rats (Shams et al. 2009).

There is a strong correlation of gastrointestinal symptoms with autism severity in children with ASDs (Adams et al. 2011). Within the group of children with autism and gastrointestinal disturbances, unique impairments of carbohydrate digestion and transport, and mucosal dysbiosis were found (Williams et al. 2011). This underlies the hypothesis that there exists a relationship between increased production of enteric short chain fatty acids, including PPA from the altered carbohydrate fermentation and the long-term development of ASD-related behavioral changes (Ossenkopp et al. 2012).

Our patient's symptoms could not be explained on the basis of global intellectual disability alone. Compared to other intellectually disabled children, her symptoms had a unique and specific cluster marked by a distinct combination of reciprocal social deficits (as shown by her desire to be alone, difficulty in interacting with other children of the same cognitive level, inability to read the emotions and feelings of others, etc.), communication impairment (poor eye-contact and gesture, presence of echolalia, language delay etc.), and restricted range of interests/repetitive behaviors (watching the same cartoon shows, stereotyped body movements, sensory abnormalities such as touching hair, etc.) that strongly supported an additional diagnosis of autism. On a reliable and valid screening measure of autism, the Social and Communication Questionnaire (SCQ) (Rutter et al. 2003), she scored above the cutoff for that disorder. A semi-structured interview for autism, such as, the Autism Diagnostic Interview-Revised was not used because such instruments have not been translated into Arabic.

The association of PA with autism has both clinical and research implications. From a clinical standpoint, children with PA, especially in countries where its rates are high, should be routinely screened for autism because early diagnosis and intervention lead to a better outcome (Howlin et al. 2004). Conversely, children with autism should receive a thorough genetics evaluation using current technology (Folstein and Rosen-Sheidley 2001; Pickler and Elias 2009). Although screening for metabolic disorders is not recommended in all children with autism (Filipek et al. 1999), it may be necessary in selected patients, especially in countries with high rates of recessive disorders, such as Saudi Arabia. For example, affected children with PA are known to suffer from intellectual disability, and, it is possible that at least some of them suffer from autism. Pediatricians, community physicians, and medical geneticists should, therefore, be trained to suspect and screen for the presence of autism. Systematic studies should also be undertaken to examine the association of PA and autism in large samples.

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Synopsis

First report of Autism in propionic acidemia.

Competing Interests

None declared.

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Propionic acidaemia: OMIM 606054.

Propionyl-CoA carboxylase: EC 6.4.1.3.

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