Autism spectrum disorder as the isolated presentation of hyperprolinemia type 1

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome, diagnosed solely on the basis of the triad of persistent social and language deficits and stereotypic behaviors. Currently a genetic cause can be identified in 5% to 20% of children with ASD. Autism have been reported in association with inborn errors of metabolism (IEM) with a rate higher than that found in the general population. We describe the occurrence of autism in a 4-year-old boy with hyperprolinemia. Hyperprolinemia is present in two inherited metabolic disorders, caused by defects in the proline catabolism – hyperprolinemia types I and II. Type I hyperprolinemia (HPI) results from deficiency of proline oxidase (POX), a mitochondrial enzyme expressed in kidney, liver and brain, which is encoded by the proline dehydrogenase (PRODH) gene, which is located in the 22q11 chromosomal region. Hyperprolinemia type II (HPII) is caused by a deficiency of Δ-1-pyrroline-5-carboxylate (P5C) dehydrogenase (P5CDh). The P5CDh gene (ALDH4A1) is located on chromosome 1 (1p36.13). Early diagnosis of metabolic disorders in autistic patients is important since some of them are amenable to treatment.

Case Report

A 4-year-old boy, first child of nonconsanguineous parents with no family history, was born at term with birth weight of 3500 g. He said his first words and started walking alone at 1 year.

The patient was referred to the child psychiatrist at 4 years because of behavioral problems such as repetitive and stereotyped movements, poor eye contact, isolation from other children. A diagnosis of ASD was made.

On admission in our hospital his body weight, height and head circumference were within normal range. Physical examination was unremarkable except for mild dysmorphic facial features – an elongated face and dysplastic ears. The psychological assessment showed a mild mental retardation (IQ = 70).

The patient was diagnosed with hyperprolinemia based on tandem mass spectrometry and urine gas chromatography–mass spectrometry. His values of proline ranged from 530 to 610 µmol/l (normal range 0 – 440 µmol/l). Urine organic acid profile was normal.

Discussion

Autism have been reported in association with inborn errors of metabolism (IEM) with a rate higher than that found in the general population. In these patients autistic behavior is usually accompanied by clinical signs characteristic for IEM such as epilepsy, ataxia, lethargy, cyclic vomiting, and intellectual disability. Rarely patients with IEM presented only autism, without any other findings, as in the our case.

There are several mechanisms by which high proline concentrations could affect brain functioning and cause neuropsychiatric disorders. High proline levels induce oxidative stress, alter glutamatergic transmission by potentiating excitatory transmission at hippocampal synapses and mediate processes such as apoptosis in selected neurons.

We report a child with neuropsychiatric disorders consisting of autistic behavior and mild mental retardation, presenting high proline plasma levels. Performed DNA analysis confirmed diagnosis hyperprolinemia types I.

In HPI, blood proline is usually fivefold–tenfold higher than the normal range of 0 – 440 μmol/L (as in our case). In HPII, blood proline usually exceeding 1500 μmol/L.

Conclusion

Although screening for metabolic disorders is not recommended in all children with autism, selective metabolic testing should be done in the presence of suggestive clinical findings for IEM. Hyperprolinemia is not always a benign condition. In some patients, early diagnosis of the metabolic disorders and proper therapeutic interventions may significantly improve the cognitive and behavioral outcome.
References:


The authors declare that they have no conflict of interest.