

Autistic-like findings associated with a urea cycle disorder in a 4-year-old girl

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A 4-year-old girl presented at our clinic with autistic-like symptoms, aggressivity and occasional hyperactivity. She had no history of neurologic or physical symptoms. Her condition was diagnosed as pervasive developmental disorder not otherwise specified, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). She received pharmacologic (thioridazine), educational and speech therapy. During this process, a urea cycle disorder was also identified, namely, ornithine transcarbamylase deficiency and arginase deficiency, because of the high level of ammonia in the patient's bloodstream, the high level of organic acids in the 24-hour urine collection and the constant presence of slow multifocal epileptic discharges on the electroencephalograms. The patient's protein intake was restricted, and she was treated with sodium benzoate and arginine. After 1 year of treatment, the autistic-like findings and hyperactivity were no longer apparent.

Une fillette de 4 ans prise en charge à notre clinique présentait des symptômes rappelant ceux de l'autisme, de l'agressivité et, à l'occasion, de l'hyperactivité. Elle n'avait pas d'antécédents de symptômes neurologiques ou physiques. Le diagnostic de son état était celui d'un trouble profond non précisé du développement, selon les critères du *Diagnostic and Statistical Manual of Mental Disorders*, quatrième édition (DSM-IV). Elle recevait un traitement pharmacologique (thioridazine) et était suivie en pédagogie et en orthophonie. Au cours de ce processus, on décela aussi un trouble du cycle de l'urée, plus particulièrement une carence en ornithine transcarbamylase et une carence en arginase, étant donné le taux élevé d'ammoniaque dans le sang de la patiente, le taux élevé d'acides organiques dans l'urine par 24 heures et la présence constante, dans les électroencéphalogrammes, de décharges épileptiques multifocales lentes. On a limité l'apport en protéines de la patiente, qui a reçu du benzoate de sodium et de l'arginine. Après un an de traitement, on ne distinguait plus les signes rappelant les symptômes de l'autisme ni l'hyperactivité.

Introduction

The urea cycle is a metabolic cycle that involves the conversion and elimination of excess nitrogen formed by the degradation of the proteins used in nutrition. Excess nitrogen is transformed into urea by the liver. Several hereditary conditions can cause urea cycle disorders. The absence of a gene required for the production of the enzyme needed in the urea cycle causes the following genetic diseases that are classified as urea cycle disorders: ornithine transcarbamylase deficiency (OTC) (gene locus Xp21.1), citrullinemia (9q34), arginase deficiency (6q23), argininosuccinic aciduria (7cen-

q11.2), carbamyl phosphate synthetase deficiency (2q35) and *N*-acetylglutamate synthetase deficiency (17q21.3).¹ All of these are autosomal recessive disorders except for OTC, which is an X-linked recessive disorder.

The clinical manifestations of urea cycle defects are non-specific and overlap with each other because of the systemic and neurologic symptoms caused by hyperammonemia. They start in the first 24–72 months of life in 60% of cases. The initial symptoms are vomiting, lethargy and hypotonia. Progression is rapid and involves seizures and coma. Electroencephalograms (EEGs) often show suppression bursts, and cerebral edema is detected in brain imaging. Episodes of

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hyperammonemia occur during infancy and childhood, if the enzyme deficiency is less severe. Hyperactivity, behavioural abnormalities, and moderate or severe mental retardation are frequent signs.²

Case report

Our patient was a 4-year-old girl and the only child of her family. She was evaluated in our outpatient clinic because of her difficulty in relating with her peers and harming them, her lack of attention and appetite, her inability to form long sentences, her habit of inserting objects in her mouth and her occasional hyperactivity. The patient's parents are cousins with no known genetic illness and no history of mental disorder. The patient was born 10 days postmature by cesarean section. She weighed 4900 g and was 54 cm long at birth, and she was breast-fed by her mother for 1 month. Her neonatal period was totally normal. She sat up in her fifth month and walked in her fourteenth. Her first words were uttered in her eighth month, and she started speaking in 2-word sentences when she was 36 months old; however, at the age of 4 years she was unable to utter longer sentences. She had no history of febrile convulsion. She had an operation for an intestinal hernia in her tenth month. She was described as a restless baby, frequently waking from sleep and having colic during her first year. She had pneumonia repeatedly during her second to seventh months. Her intelligence was roughly estimated to be within the borderline limit. When she was 5 years old, her IQ was determined to be 72 using the Turkish version of the Stanford-Binet Intelligence Test for children,³ which proved our clinical observation. The results of neurologic examination and EEGs were normal. She underwent thioridazine treatment, 10 mg/d. Pedagogic consultation was also provided, and a kindergarten was recommended to the family.

Physical findings such as dragging of the right foot while walking were observed in the patient 6 months after her initial presentation. The pediatric outpatient clinic was consulted regarding this matter. The child had been removed from the kindergarten during that period because of her aggressive behaviour, and she exhibited a lack of attention, reduction in eye contact and negativism. She started talking about herself in the third person. In addition to these signs, she developed sleep disorders and stuttering, although she was able to form 3-word sentences. Her physical examination in the pediatric outpatient clinic revealed secondary minor microcephaly. Organomegaly was not detected. The results of chest and abdomen examinations were within normal limits. Nystagmus, optic atrophy and retinal degeneration were absent. Spastic-ataxic walking was observed in the lower extremities in the neurologic examination. Pes cavus and scoliosis were not present. Slow multifocal epileptic discharges were identified in the repeated EEGs. Cranial magnetic resonance images revealed cortical atrophy in the parieto-occipital mediosagittal sections and atrophy in the folia in the cerebellar vermis. Primary gross cerebocerebellar malformation findings were absent. Pathologic laboratory findings were as follows: aspartate aminotransferase (AST) 27 U/L

(reference range 16–60 U/L), alanine aminotransferase (ALT) 51 U/L (reference range 5–25 U/L) and creatine kinase was at a high level of 129 U/L (reference range 8–147 U/L). The ammonia level in the patient's bloodstream was also high: 144 μ mol/L (reference range 17–51 μ mol/L). Examination of the organic acids in the 24-hour urine collection revealed a moderate concentration of thymine and uracil, 1.32 mmol/L, and elevated orotic acid, 5.0 mg/24 h (reference range 1–1.5 mg/24 h). As a result of these examinations and assessments, a urea cycle disorder was diagnosed and, in particular, OTC and arginase deficiency. The protein intake of the patient was restricted to 0.75–1.0 g/kg per day, and sodium benzoate therapy, 1.5–1.75 mmol/kg per day, was initiated. Arginine, 50–150 mg/kg per day, was added to the treatment. Autistic findings and hyperactivity were no longer apparent after 1 year of medication, educational therapy, pedagogic consultation and speech therapy. The patient's stuttering continued with fluctuations. Her cooperation has improved. She has maintained good relationships with her peers.

Discussion

Our patient did not have seizures, although there was seizure activity of multifocal variable type constantly on the EEGs. Widespread cortical cerebral and cerebellar activity, loss of white matter due to ventricular enlargement and gliosis seen in advanced cases of OTC corresponded to our findings,⁴ and the high level of orotic acid in the patient's urine led us to the diagnosis of OTC. OTC is rare in girls and, when seen, it is asymptomatic or exhibits itself with excessive protein intake and migraine-like headaches. Pseudopsychotic episodes (such as delusions) have been reported. Minor developmental retardation, behavioural problems and neurologic dysfunctions are also observed.⁵ Such cases may also feature progressive tetraparesis, mental retardation and hyperactivity findings. Arginase deficiency is the rarest urea cycle disorder and is clinically different from the others. Mental retardation, microcephaly, spastic dysplasia or quadriplegia are observed in the first months or years of life. The pathogenesis of these symptoms is not known.²

Central nervous system functions are oversensitive to the metabolic changes that emerge during fetal or early postnatal life. Neurologic and cognitive damage depends on several factors including timing, the beginning of metabolic damage, its severity or duration, and the impact of therapeutic interventions. Spada et al⁶ described a 4-year-old boy who had normal development but bizarre behaviour, such as laughing and crying for no reason. Normal results were obtained in this case from general physical and neurologic examinations. This case was diagnosed as OTC when the patient was aged 8 years because of the absence of physical findings.⁶ Batshaw et al⁷ also reported a case diagnosed as OTC in a patient who had behavioural changes such as hitting her head, tearing hair and biting. Christopher et al⁸ defined typical findings of arginase deficiency in a 5-year-old boy but no psychiatric finding before or after that.

Behavioural problems and autistic-like findings similarly emerge with mental retardation in some other metabolic

disorders caused by innate metabolic damage. One of these is Wilson's disease. Another metabolic disease is phenylketonuria, which is similarly often accompanied by autistic findings. In Lesch-Nyhan syndrome, severe mental retardation in addition to choreoathetosis, spasticity and a major problem, self-mutilation, occur.⁹

The central nervous system can also be influenced in early intrauterine life in the case of chromosomal disorders. In Down's syndrome, autism and hyperactivity rarely accompany mental retardation. Many boys with fragile X syndrome develop autistic-like findings. Psychiatric problems and reduction in pain sensitivity may accompany hyperphagia in Prader-Willi syndrome.^{9,10} It has been reported that autism accompanies mental retardation and seizures in tuberous sclerosis. Mental retardation, autistic-like behaviours, stereotypical hand movements and seizures are also observed in Rett syndrome. The occurrence of autism and autistic-like findings simultaneously with certain genetic diseases¹¹ has led to the intensification of studies of the cause of autism. Whiteley and Shattock¹² discussed the opioid-excess theory in autism spectrum disorders. This theory suggests that autism is the result of a metabolic disorder whereby "peptides with opioid activity derived from dietary sources, in particular foods that contain gluten and casein, pass through an abnormally permeable intestinal membrane and enter the central nervous system ... to exert an effect on neurotransmission, as well as producing other physiologically-based symptoms" (p. 175).¹² Trifiletti and Packard¹³ emphasized that any organic condition that produces cortical dysfunction could present with psychiatric symptoms. At present, it is not possible to associate a specific cognitive and behavioural profile with a specific metabolic disease, but it is known that the genetic basis and consequently the fundamental biochemical defect are important in the pathogenesis.

Our patient presented at our clinic with only psychiatric findings rather than any physical or neurologic pathologic findings, and the diagnosis was reached when physical findings emerged during the follow-up visits. She has had multi-axial diagnoses. First, her condition was diagnosed as pervasive developmental disorder not otherwise specified (axis I disorder). She also received a diagnosis of borderline intelligence functioning (axis II disorder) and metabolic disorder placed in the group of general medical conditions (axis III disorder), according to the criteria of the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV).¹⁴ The existence of autistic-like findings among the psychiatric disorders observed in urea cycle disorders points to the variety of symptoms. This fact underlines the importance of keeping in mind the "metabolic disorder" that causes psychiatric findings such as behavioural problems, hyperactivity and autistic-like findings during infancy and early childhood and is accompanied by mild or severe mental retardation and

cognitive impairment. If the child psychiatrist encounters these patients at an early point in the course of illness, he or she will serve an important role in establishing a correct diagnosis. The earlier the metabolic damage is detected in urea cycle disorders, the earlier treatment starts and the lower the risks of morbidity and mortality.⁶

Competing interests: None declared.

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