Topical Review

Autism Spectrum Disorders and Inborn Errors of Metabolism: An Update

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ABSTRACT

BACKGROUND: Autism spectrum disorder is characterized by social communicative deficits with restricted interests occurring in about 1% of the population. Although its exact cause is not known, several factors have been implicated in its etiology, including inborn errors of metabolism. Although relatively uncommon, these disorders frequently occur in countries with high rates of consanguinity and are often associated with behavioral problems, such as hyperactivity and aggression. The aim of this review is to examine the association of autism with these conditions. METHOD: A computer-assisted search was performed to identify the most common inborn errors of metabolism associated with autism. RESULTS: The following disorders were identified: phenylketonuria, glucose-6-phosphatase deficiency, propionic acidemia, adenosine deaminase deficiency, Smith–Lemli–Opitz syndrome and mitochondrial disorders, and the recently described branched chain ketoacid dehydrogenase kinase deficiency. CONCLUSION: The risk of autistic features is increased in children with inborn errors of metabolism, especially in the presence of cognitive and behavioral deficits. We propose that affected children should be screened for autism.

Keywords: autism, metabolic disorders, autism spectrum disorders, inborn errors of metabolism

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Introduction

Autism spectrum disorder (ASD) is a behavioral syndrome characterized by social communication deficits with rigid restricted interests, occurring in about 1% of the population.1,2 Although ASD and autism are often used interchangeably, the former more correctly refers to a group of disorders of varying degrees of severity. At least 10% of patients with ASD suffer from comorbid disorders, such as tuberous sclerosis and fragile X syndrome.3

ASD can also occur with inborn errors of metabolism, sometimes referred to as inherited metabolic disorders, which occur in 1 in 800 live births.4 These conditions, which have become increasingly important because of the progress made in their diagnosis and management,5 occur when an enzyme or a transport protein deficiency causes a block in a metabolic pathway resulting either in a harmful accumulation of the substrate behind the block or in a deficiency of the product. They can be divided into acute and chronic categories. The former group usually begins in the first 2-3 years of life and may present in metabolic crisis (intoxication), whereas the latter may come to medical attention at any time and have a more insidious course. Metabolic disorders with intoxication often present with acute encephalopathy associated with acidosis, hyperammonemia, and/or hypoglycemia.5 Several behavioral and neuropsychiatric abnormalities can occur in children with metabolic disorders.6 These stem from the involvement of the central nervous system and include learning disability, social deficits, hyperactivity, aggression, catatonia, psychosis, and depression.7 Because most metabolic disorders are autosomal recessive,8 they are more common in countries with high rates of consanguinity, where they are associated with a significant degree of morbidity and mortality.9

Increased awareness of both autism and of inherited metabolic disorders has increased the focus on the comorbidity between them. Although, the exact rate of autism in patients with inherited metabolic disorders is not known, the rate of the latter in patients with autism is said to be around 2%. For example, in a study of 222 Greek children with autism, 2.7% suffered from a metabolic disorder.10 However, given that the correct diagnosis of an inborn error of metabolism requires both clinical and technological expertise, this figure is probably closer to 5%.11
There have been no recent reviews of the association of autism with metabolic disorders since the last review by Manzi and colleagues. Since then, several new reports have described the occurrence of autism in patients with inherited metabolic disorders. For example, a novel metabolic entity (branched chain ketoacid dehydrogenase kinase deficiency) was recently described in multiple consanguineous families with autism, epilepsy, and intellectual disability. The aim of this review is to describe the association between the two conditions with particular reference to publications since the review by Manzi et al.

Method

A computer-assisted PubMed search was performed with the keywords “autism,” “autism spectrum disorders,” “pervasive developmental disorders,” “metabolic diseases,” “metabolic disorders,” and “inborn errors of metabolism.” Through cross-references, reviews and book chapters were also examined. The following disorders were most commonly identified.

Aminoacidopathies

Phenylketonuria (PKU) is a common autosomal recessive disorder of amino acid metabolism occurring in about 1 in 10,000 people. It is caused by a dysfunction in the metabolism of phenylalanine resulting either from a deficiency of the enzyme phenylalanine hydroxylase or of its essential cofactor tetrahydrobiopterin. Because phenylalanine is not metabolized, it accumulates in the body and causes reduction of myelin and neuronal loss. If PKU is not treated immediately after birth, irreversible brain damage may occur, and, one of its features may include autism.

The exact prevalence rate of autism in PKU is not known. However, the association between the two disorders is well-documented in single case reports and case series. Chen and Hsaio described autistic features in an adolescent who was later diagnosed with classical PKU. Treatment with a low-phenylalanine diet started after the diagnosis of PKU did not decrease the autistic symptoms. The authors emphasized the need for excluding PKU as a cause of autism in those countries where neonatal screening is not done systematically. In a relatively recent Italian study, Balemli and colleagues examined the features of autism in a group of 97 patients with classical PKU. Sixty-two were diagnosed early based on neonatal screening and were receiving treatment. None in this group met the criteria of autism. In the remaining 35 patients, who were diagnosed late, two patients (5.7%) met the full criteria of autism. Patients in the former group were of normal intelligence, whereas those in the latter group were in the mentally disabled range.

Although the exact cause of autism in untreated PKU is not clear, it probably results from the accumulation of phenylalanine causing brain damage. Several other neuropsychological abnormalities have been described in persons with PKU, including those who have been treated. Some of these include executive function deficits and problems with attention and impulsivity. Once the diagnosis of autism in children with PKU is established, treatment should consist of incorporating educational and behavioral interventions focusing on the social and communication deficits.

Disorders of branched-chain amino acids

Branched chain amino acids (BCAAs, leucine, isoleucine, and valine) are essential amino acids required by the body. In a recent report, investigators examined three consanguineous families of Middle Eastern origin with autism, intellectual disability, and seizure disorder (or an abnormal electroencephalograph). They found that affected persons with the three disorders had low levels of BCAAs, which were corrected after the administration of the amino acids. The cause was the occurrence of mutations in the branched-chain ketoacid dehydrogenase kinase gene (BCKDH), which encodes a protein involved in inactivating the branched-chain ketoacid dehydrogenase complex, the deficiency of which causes maple syrup urine disease. Mice with this gene knocked out had low BCAA levels in plasma and in the brain and exhibited neurological impairments typical of autism. BCKDH-knockout mice fed a diet enriched in BCAAs showed neurological improvements. However, the clinical significance of this report is unclear. Even if plasma BCAAs are normalized, patients might be beyond the critical periods for developing social and language skills typical of autism.

Organic acidurias

Propionic acidemia

Propionic acidemia is a common form of organic aciduria resulting from the deficiency of propionyl-Coenzyme A carboxylase. It is characterized by frequent and potentially lethal episodes of metabolic acidosis often accompanied by hyperammonemia. The incidence of this disorder in countries such as Saudi Arabia is relatively high, with an estimated frequency of 1:2000-5000 live births partly resulting from tribal founder mutation. It is initially diagnosed by performing an acylcarnitine profile and analysis of urine organic acids. Further confirmation is done by enzyme assay or gene testing. Psychiatric symptoms such as visual hallucinations have been reported, as well as autism. Interestingly, recent reports have suggested that propionic acid administered by an intracerebroventricular injection or systemically may induce an animal model of autism. Therefore, in countries with high rates of recessive disorders, autism should be considered in the differential diagnosis whenever a patient with propionic acidemia presents with behavioral symptoms.

3-methylcrotonyl-CoA carboxylase deficiency

This is a disorder of leucine metabolism. Some reports have described the occurrence of mental retardation and developmental disorders in children with this enzyme deficiency at the time of birth and identified by neonatal screening. One report has mentioned the presence of autism in a child identified in a retrospective analysis of 35 patients. Another child was said to suffer from obsessive-compulsive disorder and was placed in a gifted program. However, details about the diagnosis were not given. It is difficult to say to what extent this deficiency contributed to the presence of autism.

Pyridoxine dependency epilepsy

Pyridoxine dependency epilepsy is a form of organic aciduria characterized by early-onset epileptic encephalopathy responsive to large dosages of pyridoxine. It is caused by antiquitin (α-aminoadipic-semialdehyde dehydrogenase) deficiency. In addition, most patients have intellectual disability despite good seizure control. Antiquitin is coded by the gene ALDH7A1. Presentations include late-onset of seizures and autism. In a large cohort with pyridoxine dependency epilepsy, Mills et al. reported that a single patient (F19) who had both seizures and autistic features responded to treatment with pyridoxine. The diagnosis is generally confirmed by measurement of α-aminoadipic semialdehyde and gene testing.

Purine and pyrimidine disorders

Adenosine deaminase (ADA) deficiency

Adenosine deaminase plays an important role in the regulation of the neurotransmitters such as dopamine and serotonin and also in the functioning of the immune system. Absence of the enzyme ADA leads to the accumulation of deoxyadenosine, which is toxic to the lymphocytes resulting in immunodeficiency. The disorder can be of early or late onset, with a range of clinical features depending on the level of deficiency of the enzyme. A few case reports have described autistic features in patients with reduced levels of ADA. Stubs and colleagues found that the level of ADA was decreased in children with autism compared with normal, intellectually disabled and children with cerebral palsy. In an Italian study, Bottini et al. compared 118 autistic children with 126 controls. The autistic group had increased levels of the variants of the enzyme that are associated with reduced activity. However, Hettinger et al. could not find evidence of disturbed enzyme activity in a study of 126 families in a North American sample. There is no evidence to suggest that treatment of ADA deficiency can lead to improvement of autistic features.
Adenylosuccinate lyase deficiency

Adenylosuccinate lyase deficiency is an autosomal recessive disorder of purine synthesis characterized by increased levels of succinylaminoimidazole carboxamide riboside and succinyladenosine. Clinical features include autistic symptoms, seizures, and mental retardation.\textsuperscript{40,41} The cause of autism in this syndrome is not known, but is probably mediated through the presence of mental retardation.

Dihydropyrimidine dehydrogenase and dihydroprymidinase deficiencies

These two enzymes in the pyrimidine metabolic pathway are required sequentially to catalyze the conversion of uracil/thymine to dihydrouracil/dihydrothymine followed by ß-ureidopropionate and ß-ketopropionyl-CoA carboxylase. The urine organic acid analysis and acylcarnitine profile may suggest the diagnosis; however confirmation requires biotinidase enzyme assay and/or gene testing. Besides a skin rash, the enzyme deficiency causes a neurological disease (poor hearing and vision, seizures, and developmental and behavioral disturbances).\textsuperscript{38} A single patient with partial biotinidase deficiency with autism has been reported.\textsuperscript{59}

Cerebral folate deficiency

Characterized by low cerebrospinal fluid folates (especially 5-methyltetrahydrofolate) and normal peripheral folate metabolism, cerebral folate deficiency is increasingly being recognized in various neurological disorders. It is associated with folate receptor autoimmunity and the deficiency of one of several enzymes involved in folate metabolism.\textsuperscript{56,57} Patients may exhibit autistic features in addition to psychomotor retardation, seizures, movement disorder, and visual and hearing impairment. If treated early, patients may show a favorable response to folic acid.\textsuperscript{42} Diagnosis may be challenging and requires the assay of cerebrospinal fluid neurotransmitters and specific enzymes.

Disorders of mitochondrial energy metabolism

Disorders of creatine metabolism

The hallmark of these disorders is the deficiency of creatine in the brain. Collectively called creatine deficiency syndrome, they include L-arginine:glycine amidotransferase deficiency, guanidinoacetate methyltransferase deficiency, and X-linked creatine transporter defect. Autism is seen in all of these disorders. Cerebral creatine deficiency by magnetic resonance spectroscopy of the brain is the characteristic feature of all of these disorders. Measurement of guanidinoacetate, creatine, and creatinine in body fluids (urine, serum, and cerebrospinal fluid) is also useful as a screening test. Enzymatic assay and/or gene testing are required for confirmation.\textsuperscript{53,54}

Mitochondrial disorders

Mitochondria are intracellular structures that play an important role in protein and lipid metabolism. They participate in the production of cell energy and modulate other functions such as signaling, cellular differentiation, and cellular death. Monoamine oxidase enzymes A and B, which have been implicated in a variety of psychiatric disorders, are localized in the outer mitochondrial membrane.\textsuperscript{55} Mitochondrial disorders have been reported predominantly with depression but also with other psychiatric disorders. In a review of the literature, Fattal and colleagues\textsuperscript{46,47} found 19 patients with mitochondrial disorders and associated psychiatric abnormalities such as bipolar disorder, anxiety disorders, and schizophrenia. For example, electron microscopic studies have revealed abnormalities in the size and density of mitochondria in the postmortem brains of patients with schizophrenia. Positron emission tomography studies have shown altered brain metabolism resulting from mitochondrial dysfunction in schizophrenia and bipolar disorder.

Altered mitochondrial gene expression has been reported in some psychiatric disorders using array-based technology. A few case reports have also described the occurrence of autism in mitochondrial disorders. In a study of 12 children with hypotonia, epilepsy, autism, and developmental delay, Fillano et al.\textsuperscript{58} found evidence of mitochondrial abnormalities in a significant number of children. These included abnormal appearance of mitochondrial organelles and mitochondrial DNA deletions. Ezuga et al.\textsuperscript{49} described a 12-year-old boy with autism, mental retardation, leg weakness, and dysmorphic features. A buccal swab electron transport chain analysis revealed a reduction in complex IV and complex 1 activities, whereas a molecular cytogenetic study showed a small deletion involving the 5q14.3 region. Because most of the reports describing autism in mitochondrial disorders were based on small numbers, they can only be regarded as preliminary.

Other disorders

Glucose 6-phosphate dehydrogenase (G6PD) deficiency

G6PD converts glucose-6-phosphate to ribose-5-phosphate, which is a precursor of molecules such as RNA and DNA. The enzyme deficiency increases the risk of the red blood cells to oxidative stress. It is the most common human enzyme defect, being present in more than 400 million people around the world. Symptoms include acute hemolytic anemia, chronic hemolytic anemia, and neonatal hyperbilirubinemia. G6PD deficiency is particularly common in people of African and Mediterranean origin, especially in areas endemic to malaria against which it provides some protection.\textsuperscript{59} Al-Salehi and Ghaziuddin\textsuperscript{42} described two boys with autism and G6PD deficiency from a case series in Saudi Arabia. Both patients had severe language delay with mental retardation, and one also had a seizure disorder. The authors postulated that the one factor leading to autism in patients with this enzyme deficiency might be the development of kernicterus resulting from hyperbilirubinemia. Thus, a subgroup of children with kernicterus may be vulnerable to developing autism, especially in developing countries, where a contributing factor is G6PD deficiency.

Smith–Lemli–Opitz syndrome

This is a recessive disorder in which the body does not metabolize cholesterol properly, leading to increased serum levels of 7-dehydrocholesterol. The symptoms range from isolated intellectual disability to severe physical and mental deficits incompatible with life. Some of the physical features include microcephaly, ptosis, short stature, and abnormalities of the second and third toes.\textsuperscript{52} Neurodevelopmental symptoms may consist of hyperactivity and autistic symptoms with stereotyped behaviors that may be specific to the syndrome. Among stereotyped behaviors of Smith–Lemli–Opitz patients, two may be relatively specific: a characteristic upper body movement (opisthotonic) and stereotypic stretching motion of the upper body accompanied by hand flicking.\textsuperscript{53} Treatment of the autistic features is symptomatic although some patients seem to respond to a supplementary diet of cholesterol.\textsuperscript{53}

Succinic semialdehyde dehydrogenase deficiency

Succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria) is caused by a defect in the catalytic pathway of the inhibitory neurotransmitter γ-aminobutyric acid. Urine organic acid analysis reveals the elevations of γ-hydroxybutyric acid. Clinically, the disorder is characterized by psychomotor retardation, hypotonia, ataxia, ASD, and seizures. Other behavioral manifestations (hyperkinetic behavior, aggression, self-injurious behaviors, hallucinations, and sleep disturbances) are seen in nearly half of all patients, more commonly in older individuals. Patients with this disorder are treated with vigabatrin, an anticonvulsant that irreversibly blocks γ-aminobutyric acid transaminase.\textsuperscript{54}

Sanfilippo syndrome (mucopolysaccharidosis type III)

The deficiencies of four enzymes involved in the degradation of heparan sulfate cause Sanfilippo syndrome, a lysosomal storage disease characterized by severe neurodegenerative course with minimal somatic
problems with maternal public health measures. 58


euthy, cyclic vomiting, early seizures, dysmorphic features. There is a general consensus that the earlier the diagnosis of autism, the better the long-term outcome. In addition, a timely diagnosis is also necessary for accessing the right kind of educational and psychological services and also for educating the parents about autism and its likely outcome.

Screening measures and rating scales for autism should be used, and complex cases should be referred to a specialist. Conversely, clinicians working in autism assessment centers should rule out comorbid metabolic disorders, especially in patients with mental retardation/intellectual disability, seizure disorder, and dysmorphic features and in those with a family history of these conditions. In consultation with an expert in metabolic disorders, screening should be done for serum amino acids, lactate, ammonia, acycarminite, urine mucopolysaccharides, and organic acids. An amino acid analysis, a urine organic acid screen, and an acycarminite profile are the most widely used screening tests for the evaluation of suspected metabolic disorders. These tests collectively have a high detection rate of many aminoacidopathies (e.g., phenylketonuria), organic acidurias (e.g., propionic academia), and urea cycle defects. Confirmation of the diagnosis usually requires an enzyme assay and/or gene testing. However, routine testing for metabolic disorders in all patients with autism is not indicated. 57 This partly because the yield of metabolic disorders in children with ASD is less than 5%. 11 At this stage, therefore, as recommended by the American College of Medical Genetics, selective metabolic screening/consultation should be considered only on the basis of clinical findings. 57 Possible clinical indications include a history of lethargy, cyclic vomiting, early seizures, dysmorphic features, intellectual disability, concerns about newborn screening, or birth outside the United States, suggesting problems with maternal public health measures. 58 Depending on the age of the child, dietary treatment for the metabolic disorder should be considered in addition to autism-specific interventions such as social skills training, speech therapy, and educational placement.

**Conclusion**

Autistic symptoms occur in a variety of inborn errors of metabolism. These are more likely to occur in certain countries, such as in the Middle East, where recessive conditions are common because of consanguinity. The association of autism with metabolic disorders underscores that autism can be the end result of a variety of insults and injuries. The severity of the autistic symptoms varies with the timing of the diagnosis and the subsequent treatment, as in the case of phenylketonuria. Screening for autism should be done when metabolic disorders occur with cognitive and behavioral problems. Treatment should address the symptoms resulting from both the inborn errors of metabolism and the autism spectrum disorder.

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