Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders

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The cause of autism remains largely unknown because it is likely multifactorial, arising from the interaction of biologic, genetic, and environmental factors. The specific role of metabolic abnormalities also is largely unknown, but current research may provide insight into the pathophysiologic underpinnings of autism, at least in some patients. We review a number of known neurometabolic disorders identified as having an autistic phenotype. We also discuss the possible involvement of mitochondrial disorders and dysfunction as well as a theory regarding an increased vulnerability to oxidative stress, by which various environmental toxins produce metabolic alterations that impair normal cellular function. Finally, we review various strategies for metabolic work-up and treatment. Accurate diagnosis of neurometabolic disorders and a broader understanding of underlying metabolic disturbance even in the absence of known disease have important implications both for individual patients and for research into the etiology of autism.

Introduction

Autism and related autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental disorders behaviorally defined by significant deficits in social interaction and communication and by the presence of restricted interests and repetitive behaviors. Despite intense research, the etiology of autism remains largely unknown but is likely multifactorial, including biologic, genetic, and environmental factors. The role of neurometabolic disorders or underlying metabolic dysfunction in producing an autism phenotype is not clear. Here we review recent research focused on a number of known neurometabolic disorders identified as having an autistic phenotype as well as theories related to other metabolic abnormalities thought to contribute to the development of autism. This is a particularly active area of autism research because a better understanding of these issues has implications both for discovery of the pathophysiologic underpinnings of the disorder and for the development of effective interventions.

Known Metabolic Disorders in Autism

Although it is clear that most of cases of autism are not associated with identifiable metabolic disorders, there are many neurometabolic disorders with an autistic phenotype. These include phenylketonuria (PKU), disorders of purine metabolism, biotinidase deficiency, disorders of cerebrospinal fluid (CSF) neurotransmitters such as deficiencies of folic acid, Smith-Lemli-Opitz syndrome (SLOS), and others. These are rare disorders that are typically inherited in an autosomal recessive fashion and generally present within the first 3 years of life. The early onset of these symptoms can coincide with the emergence of the behavioral abnormalities seen in autism. Interest in studying these rare cases is increasing, not only because proper diagnosis is important to a given patient but also because these cases may be able to provide clues to the underlying metabolic abnormalities in idiopathic autism.

Phenylketonuria

PKU results from decreased function of phenylalanine hydroxylase, the rate-limiting enzyme responsible for metabolizing phenylalanine to tyrosine [1]. Accumulation of phenylalanine results in mental retardation, seizures, altered brain development, and an autism phenotype. Early treatment of PKU by appropriate dietary restrictions has greatly reduced the prevalence of autism in affected children and may also improve the autistic phenotype in this population [2].

Disorders of purine metabolism

There are two disorders of purine metabolism associated with autism. The first, adenylosuccinase deficiency, is an autosomal recessive error of purine synthesis that results

in accumulation of aminoimidazole carboxamide riboside and succinyl adenosine in bodily fluids. Clinically, this disorder is characterized by developmental delay, seizures, agitation, and autistic features such as poor eye contact and repetitive behaviors [3]. Symptoms are thought to result from accumulation of succinyl purine in the brain, and no effective treatment is known. The second condition is adenosine deaminase (ADA) deficiency, an autosomal recessive immunodeficiency that results in severe combined immunodeficiency and has also been associated with an autism phenotype [4]. The role of the enzyme, ADA, is to convert deoxyadenosine, which is toxic to lymphocytes, to the nontoxic deoxyinosine. Mutations in the ADA gene on chromosome 20 reduce or eliminate the activity of ADA and allow the build-up of deoxyadenosine, which impairs normal immune function. The abnormal behaviors in these children appear proportional to the metabolic derangement and are hypothesized to be due to early neuronal injury caused by the defective enzyme [4]. Closer examination of this disorder may shed light on some of the neuroimmune abnormalities associated with autism.

Creatine deficiency

Another group of autosomal recessive disorders associated with an autism phenotype includes the creatine deficiencies, which produce a variety of clinical symptoms, including mental retardation, autism, speech delays, epilepsy, and extrapyramidal signs and symptoms [5••]. This subgroup includes a number of conditions, including arginine-glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, and disorders of creatine transport. The first two are systemic creatine deficiencies and appear to be responsive to oral supplementation, whereas patients with X-linked creatine transporter deficits are unresponsive to oral supplementation [6]. As with PKU, early treatment of these disorders results in improved long-term outcome, but it is not known whether early treatment also alters the autistic phenotype.

Biotinidase deficiency

Low biotin levels result in impaired neurologic function, developmental delay, and behavioral disturbances, some of which involve language and socialization [7]. There is at least one case report of a specific autism diagnosis in a case of biotinidase deficiency [8], but the prevalence of autism in this disorder is unknown. Hallmarks of biotinidase deficiency include visual and hearing deficits as well as severe motor impairments. Early treatment with the cofactor biotin may prevent the neurologic sequelae of this disease, as is evidenced by patients who are diagnosed by newborn screening and treated early.

Cerebral folate deficiency

Cerebral folate deficiency is considered a part of a larger, growing field of CSF neurotransmitter abnormalities and neurometabolic syndromes. CNS (central nervous system) folate deficiency (CFD) is one such condition associated with an autism phenotype. The hallmarks of this disorder in children include deceleration of head growth, psychomotor retardation, regression, cerebellar ataxia, dyskinesias, seizures, and low CSF 5-methyltetrahydrofolate (5-MTHF) levels [9]. In a recent case series, five of seven children who were capable of formal autism diagnostic testing met the diagnostic criteria for an ASD [10•]. These findings led the authors to conclude that children with autism, in the presence of other neurologic impairments such as regression, seizures, and dyskinesias may benefit from the analysis of CSF folate levels, specifically to diagnose this rare disorder in autistic children. It is possible that early treatment of this condition may also improve long-term neurologic outcome.

SSADH deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal recessive condition that results in mental retardation, seizures, hypotonia, language impairments, behavioral abnormalities, and possibly an autistic phenotype. Biochemically, SSADH is the enzyme responsible for converting γ-aminobutyric acid (GABA) to succinic acid. Deficiency of SSADH results in an accumulation of GABA and γ-hydroxybutyric acid (GHB), the latter of which is converted to 4-hydroxy butyrate, a highly volatile compound that is thought to be neurotoxic [11]. Although the pathophysiology of this rare condition is not well understood, its neurologic sequelae can be severe. Knerr et al. [12] recently reported on a case series demonstrating the variability in the behavioral phenotype associated with this condition. Although no specific ASD testing was done, two of seven patients (29%) received a diagnosis of pervasive developmental disorder, and a similar percentage had a diagnosis of obsessive compulsive disorder, whose symptoms can be likened to the repetitive behaviors and restricted interests seen in ASDs. Although the prevalence of autism in SSADH has not been clearly established, it is speculated that there is disruption in the metabolic pathway of SSADH resulting in significantly impaired behavior and language. A better understanding of this metabolic pathway may lead to interventions that could alter the course of the disease and perhaps even its phenotypic expression of autism.

Smith-Lemli-Opitz syndrome

SLOS is an autosomal recessive disorder characterized by prenatal and postnatal growth retardation, distinct facial features, microcephaly, mental retardation, and behavioral abnormalities including autism. SLOS is caused by a defect in cholesterol metabolism resulting from a deficiency of the enzyme 7-dehydrocholesterol (7DHC) reductase, which results in reduced levels of cholesterol and increased levels of 7DHC and its isomer, 8DHC. Previous studies have established that children with SLOS have a high incidence of autism, with rates ranging from 50% to 86% [13,14]. Although

blood cholesterol levels do not appear to be related to the severity of autistic symptoms, anecdotal data demonstrate that cholesterol supplementation may improve autistic behaviors in children with SLOS [15•]. Furthermore, the presence of hypocholesterolemia in a subgroup of autistic children without SLOS raises the possibility of an underlying cholesterol synthesis abnormality contributing to the autistic phenotype in idiopathic autism [15•].

Other disorders

Other rare neurometabolic disorders associated with an autistic phenotype include infantile ceroid lipofuscinosis, histidinemia, and urea cycle defects such as ornithine transcarbamylase deficiency, citrullinemia, argininosuccinic aciduria, carbamoyl phosphate synthetase deficiency, and Sanfilippo syndrome [5••]. It is likely that there are numerous other known and unknown neurometabolic disorders with a clinical phenotype of autism that remain unrecognized. Unfortunately, the actual prevalence of autism in known neurometabolic disorders remains unclear. This may be because practitioners frequently do not give an additional autism diagnosis in the presence of the neurometabolic disorder. However, this practice is not always helpful to families. The autism symptoms are sometimes the most disruptive of all the child's problems, and a diagnosis often provides needed behavioral services not otherwise available for children with neurometabolic disorders.

Mitochondrial Disorders and Autism

The role of mitochondrial disorders in autism has generated much discussion lately. Mitochondria are the "powerhouses" of eukaryotic cells, representing the central pathway for energy metabolism [16]. Many of the elements critical to mitochondrial function are coded for in the mitochondrial DNA (mtDNA), a small collection of genes separate from the nuclear DNA (nDNA) and housed in the mitochondria themselves. Unlike autosomal and sex-linked genetic disorders, diseases coded for by mtDNA mutations or deletions demonstrate a pattern of maternal inheritance in which there is heteroplasmy, a mixture of mutant and wild-type mtDNA within each cell [17]. Mitochondrial disease manifests itself when the number of abnormal mitochondria reaches a critical level in a phenomenon referred to as threshold expression [18].

Impaired mitochondrial function is frequently caused by an abnormality in the mitochondrial respiratory chain, the final common pathway for aerobic metabolism [16]. The respiratory chain consists of five enzyme complexes, each composed of different subunits that are encoded by nDNA or mtDNA. A mutation or a deletion/duplication in the mitochondrial genome can result in impairments in oxidative phosphorylation, producing a spectrum of syndromes, including Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP), and Leigh syndrome [19••]. Although all of the 13 polypeptides coded for by mtDNA are part of the respiratory chain, this system cannot function properly without at least 150 polypeptides that are encoded by nDNA [19••]. Thus, respiratory chain dysfunction can result from mutations in mtDNA or nDNA. Although each of these disorders has a relatively well-described clinical presentation, they all involve central nervous system dysfunction and patients will demonstrate some degree of behavioral disturbance, cognitive impairment, motor disturbance, and an increased risk of seizures.

The literature indicates that mitochondrial disorders are a rare cause of autism [20], and even identifying autistic children who merit further evaluation for mitochondrial disorders is difficult. However, there are a number of case reports and series implicating mitochondrial abnormalities in autism. In an analysis of five patients with A3243G mtDNA mutations and/or mtDNA depletion, three of the patients met the clinical criteria for autism, leading the authors to postulate that autistic features may be the expression of mitochondrial dysfunction in the developing brain [21]. Similarly, Filiano et al. [22] described mitochondrial dysfunction in children with a clinical constellation of hypotonia, epileptic seizures, autism, and developmental delay (HEADD). Although they found no point mutations associated with known mitochondrial disease, five of 12 patients harbored mtDNA deletions. Although no relationship could be established between the severity of neurologic disease and the extent of mitochondrial dysfunction, the study raised the possibility of a causal relationship between mitochondrial dysfunction and autism that has yet to be identified. In a case series by Tsao and Mendell [23], two children with autism demonstrated no abnormalities on genetic testing, but muscle biopsy showed deficiencies in several respiratory chain enzymes, including complexes I, II, and III and coenzyme Q. These case reports all raise important questions regarding the role of mitochondrial dysfunction in autism.

Unfortunately, case reports cannot speak to prevalence, and there has been little systematic evaluation of mitochondrial disorders in autism. However, a recent population-based study examining medical conditions in autism did find a disproportionately high prevalence of mitochondrial diseases in the autistic population. As part of a large epidemiologic study in Portugal, 120 children with autism underwent a broad metabolic work-up that included analyses of plasma amino acids, urine organic acids, oligosaccharides, mucopolysaccharides, purine and pyrimidines, creatine metabolites, and congenital glycosylation [24]. Of 69 children tested for lactic acid levels, 14 had elevations and underwent further investigation for mitochondrial disorders, with 11 undergoing muscle biopsies. Five were classified as having a definite mitochondrial respiratory chain disorder by muscle biopsy. Six remaining children were diagnosed as having possible or

probable disease, including five children with no discernable muscle pathology. It is notable that these children did not have any of the known mtDNA mutations and/or deletions associated with known mitochondrial disorders. Thus, these data invoke the concept of mitochondrial dysfunction rather than known disease in cases of autism.

Recently, the concept of mitochondrial dysfunction has drawn much more attention in both the science and lay communities due to a case report implicating mitochondrial dysfunction as a factor contributing to vaccine-related regression, a highly controversial topic. This case study described a previously healthy 19-month-old child who began showing signs of significant developmental regression and emergence of autistic features after receiving a set of five vaccinations [25••]. Laboratory tests revealed a persistent and mild elevation of lactic acid, increased aspartate aminotransferase, and elevated serum creatine kinase but no mtDNA or other genetic abnormalities. Muscle biopsy results were consistent with a mitochondrial disorder of oxidative phosphorylation with a marked reduction in the function of complexes I and III. After supplementation with levocarnitine, thiamine, and coenzyme Q for several years, the patient showed improvement in language function and sociability, but some mildly autistic behaviors persisted [25••].

Although the mechanism by which mitochondrial dysfunction occurs is not entirely clear, evidence points to an oxidative defect triggering a cascade of events in early brain development [26]. A similar pathogenesis has been proposed for the development of autism, with the hypothesis that an increased vulnerability to oxidative stress results in an impaired ability to detoxify free radicals in the environment. One theory is that abnormal mitochondrial function and deficient energy production may be precipitated by many different environmental toxins that contribute to dysfunction in multiple systems [27], including cognitive impairments, language deficits, and gastrointestinal disorders, all of which are features of autism. It is further posited that compared with classic mitochondrial disease, mitochondrial dysfunction may show less severe signs and symptoms and may not even show the classic mitochondrial pathology on muscle biopsy [22,26]. Clearly, further research is needed to determine the exact association between mitochondrial dysfunction and ASDs. However, mitochondrial dysfunction may be found to play an important role in elucidating the metabolic and genetic basis for the development of autism, at least in some patients.

Redox/Methylation Hypothesis

Beyond the associations with classic neurometabolic disorders, there is now a growing interest in exploring the underlying metabolic abnormalities in patients without discernable conditions or diseases. A leading theory implicates dysfunction in the pathways related to oxidative stress, which results from a complex interplay of genetic and environmental factors. This postulate is based on the idea that in genetically vulnerable individuals cellular damage could be initiated by environmental factors, resulting in neurologic deficits [28]. Toxins are known to impact cellular redox status directly or indirectly [29], and toxicologic involvement in neurologic diseases is well documented. Arsenic, lead, and mercury have been associated with a variety of neurologic deficits and disorders, including lower IQ [30], Alzheimer's disease [31], and Parkinson's disease [32].

The proposed metabolic abnormality underlying ASDs is outlined in the redox/methylation hypothesis, which states that there is an increased vulnerability to oxidative stress and a decreased capacity for methylation [33]. One mechanism by which this occurs is through an imbalance in the methionine cycle, resulting in decreased cysteine and glutathione, both of which are necessary for normal antioxidant activity. Methionine is activated by methionine adenosyltransferase to form S-adenosylmethionine (SAM) (Fig. 1). Methionine synthase is highly sensitive to oxidative stress [27], and toxins such as lead, mercury, and alcohol are known to inhibit the enzyme's activity [34], thereby reducing methylation capacity [35••]. Support for this theory comes from studies describing important gene–environment interactions. Data suggest that individuals with autism have a genetic predisposition to abnormal methionine metabolism; one study has demonstrated an association between autism and allelic variation in genes known to modulate the metabolic pathway of methionine [35••].

However, the metabolic abnormalities seen in autism are not easily explained by a single derangement in the redox pathway [33]. Like cysteine, glutathione has been identified as playing an important role in the antioxidant defense of the cell [36]. In a model suggested from multiple studies, it is postulated that there are disturbances in glutathione metabolism, resulting in a system in which redox homeostasis is impaired [35••,36]. These impairments in redox potential produce a system under chronic oxidative stress, resulting in metabolic alterations that can disrupt normal cellular function and eventually cause cell death [28].

Although this idea is relatively new, several studies in the literature support the hypothesis. Increased markers of oxidative stress, including 8-isoprostane [37] and malonyldialdehyde [38], have been reported in patients with autism. Abnormalities in platelet and endothelial function in autistic children also have been proposed because of findings of increased levels of isoprostane, prostaglandins, and thromboxane compared with controls [39]. Perhaps most compelling are the findings of James and colleagues [33], who conducted a study in which fasting blood samples were collected from 80 autistic patients and 73 controls. Measured metabolites included methionine, the ratio between SAM and S-adnenosylhomocysteine (SAH), cysteine, adenosine, and the ratio between reduced and oxidized glutathione. Relative to

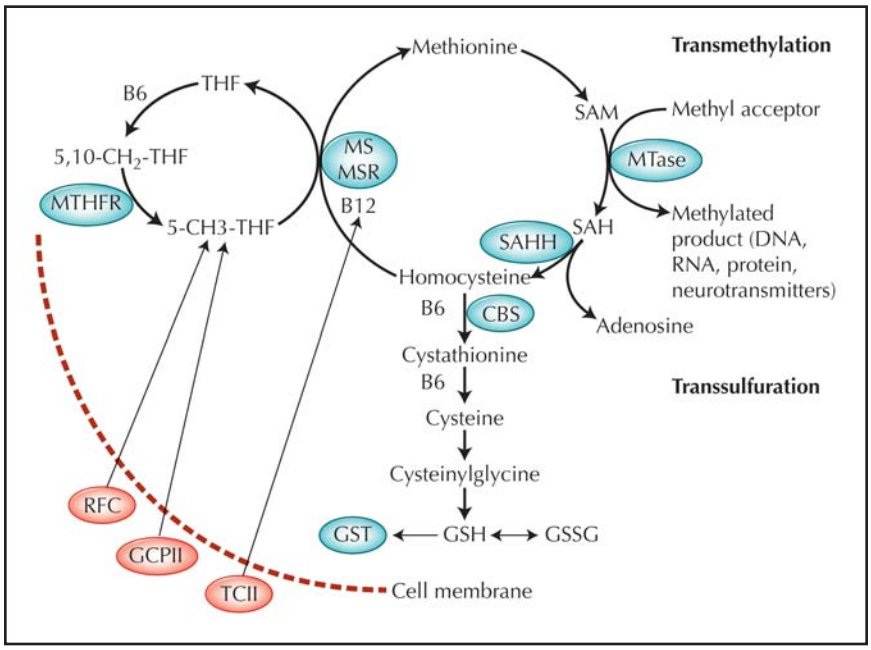

Figure 1. Basic schematic representation of transmethylation/transsulfuration pathways important for redox balance. CBS—cystathionine β-synthase; GCPII—glutamate carboxypepsidase II; GSH—reduced glutathione; GSSG—oxidized glutathione; GST—glutathione-S-transferase; MS—methionine synthase; MSR—methionine synthase reductase; MTase— methyltransferase; MTHFR—methylenetetrahydrofolate reductase; RFC—reduced folate carrier; SAH—S-adnenosylhomocysteine; SAHH—S-adnenosylhomocysteine hydrolase; SAM—S-adenosylmethionine; TCII—transport protein transcobalamin II; THF—tetrahydrofolate. (*From* James et al. [35••], with permission.)

control children, autistic children had decreased plasma levels of key oxidative proteins, including methionine and the ratio between SAM and SAH [33].

Further elucidation of this underlying metabolic disturbance may aid in improved mechanistic understanding of the pathophysiological underpinnings of autism. Additionally, an improved understanding has important treatment implications because interventions are available that may restore redox balance and perhaps even counteract oxidative injury. This was demonstrated in eight autistic patients, in whom interventions such as folinic acid, betaine, and injectable methylcobalamin were shown to normalize the metabolites reflecting oxidative injury [33]. Although clinical improvement in speech and cognition occurred in these patients, the data remain only anecdotal because improvements were not quantified. However, if further research supports both the underlying hypothesis and the efficacy of treatment, the findings could have a major impact on the field.

Diagnosis, Testing, and Treatment

Metabolic disorders that present with an ASD phenotype are probably very rare; however, exact estimates are not available because there are few population-based studies. Most studies in the literature use metabolic testing as one part of a larger genetics evaluation, and results regarding positive yields are routinely low. In a recent study, Schaefer and Lutz [40•] used a metabolic screen as first line along with a genetics history, physical examination, and audiogram. Their broad metabolic screen (serum amino acids, lactate, ammonia, acylcarnitine profile, urine mucopolysaccharides, and organic acids) yielded no abnormalities in 32 patients. In a similar study of 85 patients with ASDs who received a thorough medical work-up, no metabolic defects were found. Thus, the current literature suggests that routine metabolic screening in patients with an ASD carries a low yield.

The lack of large cohort studies screening unselected autistic children makes it impossible to estimate the true prevalence of metabolic disease in this population. It is still possible that a small percentage of the ASD population is affected by these disorders. Without a high index of suspicion, mild cases of metabolic disease may go undiagnosed or become masked by other comorbid conditions. Certainly, most children with autism do not see metabolic specialists, and some of the red flags for metabolic conditions could easily go unnoticed. Discovery of some of these disorders in even a small percentage of patients with autism could majorly benefit the individual patient and provide a better understanding of the underlying pathophysiology of autism in some cases.

Without better data, it remains important to tailor the diagnostic evaluation to the individual patient, and practitioners must rely heavily on clinical judgment in deciding which tests to order. The American Academy of Neurology Practice Parameters for autism recommend that the metabolic component of the work-up be reserved for patients with clinical indicators of a metabolic disorder, such as a history of lethargy, cyclic vomiting, early seizures, dysmorphisms, mental retardation, or regression [41]. Tests likely to diagnose the more common neurometabolic disorders include plasma amino acids, urine organic acids, plasma ammonia, lactate/pyruvate, and the acylcarnitine profile. Table 1 lists signs, symptoms, and medical comorbidities that may yield clues to disorders that could be used as red flags for further specific testing.

Proper diagnosis of these disorders can be crucial for families because many of these conditions have important implications for genetic counseling. Just as importantly, some of these conditions have effective treatments. For instance, patients with SLOS who began cholesterol supplementation before age 5 years had a reduced risk of an autism diagnosis compared with those who were not

Table 1. Recommended neurometabolic screening in patients with an autism phenotype

Signs and symptoms	Possible diagnoses	Metabolic tests to consider
Developmental delay, hypotonia, seizures, visual and hearing impairments	Biotinidase deficiency	Measurement of plasma biotinidase activity
MR, microcephaly, growth retardation, hypotonia	Smith-Lemli-Opitz syndrome	Serum 7-dehydrocholesterol level
Regression, seizures, dyskinesia, psychomotor retardation	CNS folate deficiency	CSF 5-MTHF level
Developmental delay, seizures, MR	ADA Creatine deficiency SSADH	Serum assay of ADA activity Blood and urinary concentration of creatine and guanidinoacetic acid Modified urinary organic acid screening for 4-hydroxybutyric acid [11]
MR, hyperactivity, aggression, regression, sleep disturbance	Sanfilippo syndrome	Urinary mucopolysaccharide electrophoresis; lysosomal storage enzyme testing for MPS III types A–D

ADA–adenosine deaminase; CNS—central nervous system; CSF—cerebrospinal fluid; MR—mental retardation; SSADH—succinic semialdehyde dehydrogenase; MPS III–mucopolysaccharidosis III; 5-MTHF—5-methyltetrahydrofolate.

treated (22% vs 88%) [15•]. For biotinidase deficiency, data suggest that early treatment with the cofactor biotin may prevent the neurologic sequelae of this disease, including vision and hearing impairments, and may also have some effects on language and socialization [7]. Likewise, in CFD, supplementation with oral folinic acid resulted in clinical improvement in motor, cognitive, and language skills but, interestingly, no improvements in autistic features were observed [10•].

The results of a metabolic work-up may be important even when a specific disorder is not detected or when testing reveals only a mild metabolic derangement. Abnormalities that are revealed could be important for understanding the underlying pathophysiology of autism and may even have treatment implications. One such example is gleaned from research on SLOS. Because of the high incidence of autism in this disorder, Tierney and colleagues [15•] investigated cholesterol abnormalities in children with idiopathic autism and described a subgroup of 19 of 100 children who had total cholesterol levels of less than 100 mg/dL, which was below the fifth percentile. This observation raised the possibility that hypocholesterolemia, in the absence of SLOS, may play a role in the etiology of ASDs [15•] and, further, that these patients might benefit from cholesterol supplementation.

Although still unproven, other potential treatments in autism are suggested by the mitochondrial dysfunction or the redox/oxidation hypothesis. Investigators have suggested that in the setting of impaired antioxidant activity, there may be a physiologic role for supplements such as vitamin E, glutathione, or methyl vitamin B_{12} [33]. Alternatively, children with underlying mitochondrial disorders and autism may benefit from coenzyme Q or carnitine. Unfortunately, none of these possibilities have been tested in any controlled manner, but some practitioners are routinely encouraging their use despite the lack of data.

Clearly, a better understanding of possible metabolic abnormalities in autism is needed. Research into basic metabolic mechanisms in ASDs could help elucidate important biologic defects that could lead to development of specific interventions and have a major impact on treatment strategies in the future, if only for some children with ASDs.

Conclusions

A number of known neurometabolic and mitochondrial disorders associated with an autism phenotype are described in this review. Although it is clear that most cases of autism are not associated with identifiable metabolic disorders, many neurometabolic disorders demonstrate an autism phenotype. Similarly, there are case reports of autism associated with mitochondrial disorders.

These associations are important from a clinical perspective. To date, the literature suggests that the presence of metabolic disorders in the ASD population is low. However, the exact prevalence remains unknown and there may be some patients whose diagnosis goes unrecognized. What is clear from the few studies using basic metabolic screens in autistic patients is that there is a low diagnostic yield of routine neurometabolic testing. To maximize this yield, clinicians must have a high index of suspicion and look beyond the behavioral phenotype of autism for various comorbid clinical findings, such as hypotonia, regression, epilepsy, and intellectual disability. In addition, there are some specific signs and symptoms that can be considered red flags alerting practitioners to pursue further diagnostic work-up (Table 1).

This review demonstrates the concept that metabolic dysfunction may be present in children with autism, even when no previously defined metabolic disorder is believed to exist. Thus, it is possible that underlying neurometabolic dysfunction, which may be mild and often

unrecognized, predisposes some children to the expression of an autism phenotype. Future investigations to improve our understanding of neurometabolic abnormalities in ASDs, such as disorders of cholesterol synthesis, mitochondrial dysfunction, and increased vulnerability to oxidative stress, could also potentially lead to effective treatments. Certainly, further research is needed to fully understand the complex interplay of these metabolic pathways and early brain development. Ultimately, these data will be important for elucidation of the metabolic pathophysiology underlying autism to promote clinician awareness, to determine appropriate practice parameters for work-up, and ultimately to design interventions effective in treating these frequently debilitating conditions.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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