Epilepsy & Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder

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ARTICLE INFO

Article history:
Revised 25 August 2014
Accepted 27 August 2014
Available online xxxx

Keywords:
Autism
Epilepsy
Mitochondrial dysfunction
Mitochondrial disease
Cerebral folate deficiency
Metabolic disorders
Comorbidities

ABSTRACT

Autism spectrum disorder (ASD) affects a significant number of individuals in the United States, with the prevalence continuing to grow. A significant proportion of individuals with ASD have comorbid medical conditions such as epilepsy. In fact, treatment-resistant epilepsy appears to have a higher prevalence in children with ASD than in children without ASD, suggesting that current antiepileptic treatments may be suboptimal in controlling seizures in many individuals with ASD. Many individuals with ASD also appear to have underlying metabolic conditions. Metabolic conditions such as mitochondrial disease and dysfunction and abnormalities in cerebral folate metabolism may affect a substantial number of children with ASD, while other metabolic conditions that have been associated with ASD such as disorders of creatine, cholesterol, pyridoxine, biotin, carnitine, γ-aminobutyric acid, purine, pyrimidine, and amino acid metabolism and urea cycle disorders have also been associated with ASD without the prevalence clearly known. Interestingly, all of these metabolic conditions have been associated with epilepsy in children with ASD. The identification and treatment of these disorders could improve the underlying metabolic derangements and potentially improve behavior and seizure frequency and/or severity in these individuals. This paper provides an overview of these metabolic disorders in the context of ASD and discusses their characteristics, diagnostic testing, and treatment with concentration on mitochondrial disorders. To this end, this paper aims to help optimize the diagnosis and treatment of children with ASD and epilepsy.

This article is part of a Special Issue entitled "Autism and Epilepsy".

1. Introduction

Autism spectrum disorders (ASDs) are a group of behaviorally defined neurodevelopmental disorders with lifelong consequences. They are defined by impairments in communication and social interaction along with restrictive and repetitive behaviors [1]. Autism spectrum disorder is now estimated to affect 1 out of 68 individuals in the United States, with approximately four times more males than females being affected [2]. Although ASD is behaviorally defined, children with ASD also have many co-occurring medical conditions such as gastrointestinal abnormalities [3], seizures and epilepsy [4], attention deficits [5], anxiety [6], and allergies [7], just to name a few.

One of the most significant comorbidities associated with ASD that causes significant disability is epilepsy. A number of studies suggest that epilepsy affects a high proportion of individuals with ASD. Indeed, the reported prevalence of epilepsy in ASD ranges from 5% to 38%, which is clearly higher than the 1%–2% prevalence in the general childhood population [8–12]. In addition, the prevalence of treatment-resistant epilepsy is believed to be higher in children with ASD than in the general childhood population [13]. Interestingly, recent reviews note shared cognitive symptoms in epilepsy and ASD, suggesting a common etiopathology [14], especially when ASD coexists with intellectual disability [15].

The great preponderance of ASD research has concentrated on genetic causes of ASD [16], despite the fact that inherited single gene and chromosomal defects are only found in the minority of ASD cases [17]. However, unlike idiopathic ASD, many genetic syndromes that have a high prevalence of ASD also frequently have a high incidence of epilepsy [18], and gene mutations associated with ASD are also frequently associated with epilepsy [19]. Epilepsy also frequently co-occurs with ASD in individuals who manifest metabolic abnormalities such as abnormalities in mitochondrial metabolism [16] as well as abnormalities in the regulation of essential metabolites such as folate [20,21], cholesterol [22], and branched-chain amino acid [23]. One interesting aspect of metabolic disorders in relation to ASD is that some children with ASD have clear classic inborn-inherited errors of metabolism, while perhaps more have metabolic abnormalities that

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http://dx.doi.org/10.1016/j.yebeh.2014.08.134

do not have a clear relationship to known inherited genetic abnormalities.

Several reviews have described some of the classic inborn-inherited errors of metabolism that are associated with ASD [17,24]. Other reviews have taken a broader view by including metabolic disorders that do not necessarily have a clear genetic basis [20,25–27]. However, these reviews have not concentrated on metabolic abnormalities associated with ASD with respect to epilepsy. The fact that metabolic disorders are associated with ASD suggests that, in some individuals, ASD symptoms may arise from systemic abnormalities rather than from abnormalities specifically localized to the brain.

Identifying the metabolic abnormalities associated with ASD, especially for individuals with ASD who have comorbid epilepsy, is important as clarifying the underlying comorbid condition that may be causing both the epilepsy and ASD can potentially lead to optimizing treatment options in order to improve outcomes for individuals with ASD as well as their families. In addition, since many metabolic pathways are well understood, identifying metabolic defects can lead to augmenting standard epilepsy treatment with known or novel treatments [4]. Furthermore, by understanding metabolic and genetic biomarkers that can identify these disorders, it might be possible to detect these disorders early in life, even prenatally, so treatment can be started at the earliest possible time, potentially before ASD symptoms or epilepsy develops, in order to improve long-term outcome.

Given the fact that metabolic disorders may be amenable to treatment, it is of paramount importance that physicians are aware of the clinical features that are indicative of a metabolic disorder and appropriately investigate patients with suggestive presentations. However, unlike many diseases, metabolic disorders may not have particular classic presentations, so basing a diagnostic strategy on the search for one or two specific key symptoms is inappropriate. For example, patients with mitochondrial disorders can present with a variety of primary manifestations including neurologic, muscular, multisystemic, or psychiatric. Thus, it is essential for the clinician to become sensitive to the variety of potential symptoms and the patterns to which the symptoms manifest. This is of significant importance when patients manifest primary psychiatric symptomatology as such disorders are classically diagnosed based on symptoms rather than on biochemical, metabolic, or neuroimaging evaluations. Identifying an individual with a psychiatric disorder with underlying metabolic abnormalities can significantly positively alter therapeutic management [28,29].

This article reviews the metabolic syndromes that are associated with individuals with ASD and comorbid epilepsy. As many of these syndromes are rather rare, the more rare syndromes are discussed briefly. However, mitochondrial disease will be discussed in detail as it is of particular interest in children with ASD since it is being increasingly recognized as a cause of epilepsy in individuals with ASD [4,25] and those without ASD [30–32] and novel treatments are being developed for mitochondrial disease which may improve therapeutic options [33,34]. To help better understand some of the metabolic abnormalities underlying epilepsy and ASD, we will discuss the animal models of ASD that manifest epilepsy and metabolic abnormalities. Finally, to facilitate the clinical application of the information presented in the article, we discuss an approach to diagnosing metabolic abnormalities in individuals with ASD and epilepsy.

1.1. Metabolic disorder associated with epilepsy in autism spectrum disorder

Table 1 outlines the metabolic disorders associated with ASD and comorbid epilepsy. This table organizes the metabolic disorders into several categories, including disorders of energy, cholesterol, vitamin, γ-aminobutyric acid (GABA), purine, pyrimidine, and amino acid metabolism and urea cycle disorders. The prominent symptoms for each disorder, not including ASD and epilepsy, along with the diagnostic tests used to identify the disorder are outlined. Each disorder will be reviewed within its category below.

1.1.1. Disorders of energy metabolism

Several disorders affecting energy metabolism have been documented in ASD, including mitochondrial disorders and creatine deficiency syndromes. The prevalence of mitochondrial abnormalities in ASD appears to be unusually high compared with that of typically developing individuals [25], and mitochondrial abnormalities have been implicated in epilepsy in individuals without ASD, especially in individuals with treatment-resistant [31] and temporal lobe [32] epilepsies. Mitochondrial abnormalities in relationship to ASD will be discussed in more detail in a separate section below, while creatine deficiency syndromes are discussed immediately below.

Creatine is synthesized in the liver and kidney and is transported through the blood to high-energy demand tissues, such as the brain and skeletal muscle, where it is actively transported into the tissue against a large concentration gradient by the sodium/chloride-dependent transporter known as CrT1 which is coded by the SLC6A8 gene. Once in tissues, creatine is phosphorylated by creatine kinase to phosphocreatine, the main energy storage molecule of the cell, using adenosine triphosphate (ATP). Without creatine, phosphocreatine cannot be produced, and cells will become rapidly depleted in energy.

Disorders of creatine metabolism have been reported in children with ASD and epilepsy [35,36]. Three inborn disorders of creatine metabolism, collectively known as the creatine deficiency syndromes, have been described since 1994. Two disorders involve deficiencies in enzymes responsible for creatine production, arginine:glycine amidinotransferase (AGAT), and S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase (GAMT), while the third disorder involves a deficiency in the creatine transporter.

The general presentation of children with disorders of creatine metabolism includes developmental delay, regression, ASD features, mental retardation, receptive and expressive language disorders, dyskinesia, and seizures [37]. The severity of the symptoms depends on the specific disorder. Individuals with GAMT deficiency are the most severely affected, with almost invariable development of ASD and seizures, severe delays in language, and magnetic resonance imaging (MRI) abnormalities. Individuals with creatine transporter disorder demonstrate a milder phenotype, while children with AGAT deficiency demonstrate the mildest phenotype [37]. Creatine transporter deficiency is an X-linked recessive disorder, so a family history of X-linked mental retardation is supportive of the diagnosis. Several reports suggest that creatine deficiency disorders can be treated with high-dose creatine monohydrate and a diet containing specific amino acids [38,39].

1.1.2. Disorders of cholesterol metabolism

Smith–Lemli–Opitz syndrome (SLOS) is a congenital disorder caused by mutations in both DHCR7 genes, the genes that encode the Δ-7-dehydrocholesterol reductase enzyme, a precursor step for the production of cholesterol. Metabolically, children with SLOS demonstrate elevated concentrations of 7-dehydrocholesterol and reduced cholesterol concentrations in the blood. Interestingly, 50%–75% of children with this disorder meet the criteria for ASD [40,41]. This disorder is characterized by low birth weight, failure to thrive, poor feeding, eczema, seizures, and congenital structural abnormalities of the heart, gastrointestinal tract, genitalia, kidney, limbs, face, and brain [40,41]. Treatment with cholesterol supplementation in children with SLOS has been reported to improve ASD and associated behavioral symptoms in a case report [42], case series [43], and prospective cohorts [44,45], especially in young children [46], but the effectiveness of such treatment in seizure control has not been studied. This disorder can be diagnosed by measuring 7-dehydrocholesterol and cholesterol levels or by DHCR7 sequencing. It is important not to rely on cholesterol levels alone to diagnose SLOS as depressed levels of cholesterol are rather common in children with ASD who do not have SLOS [22].

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Table 1
Metabolic disorders associated with epilepsy and autism spectrum disorder.

Disorder	Clinical features	Diagnostic testing
Disorders of energy metabolism		
Mitochondrial disease	Developmental regression, gross motor delay, fatigability, ataxia, and gastrointestinal abnormalities	• Fasting serum lactate, pyruvate, acylcarnitine, amino acids, and urine organic acids
Creatine metabolism disorder	Developmental regression, mental retardation, dyskinesia, and family history of x-linked mental retardation	• Magnetic resonance spectroscopy • Urine and serum creatine and guanidinoacetic acid
Disorders of cholesterol metabolism		
Smith–Lemli–Opitz syndrome	Low birth weight, failure to thrive, poor feeding, eczema, and congenital structural abnormalities of the heart, gastrointestinal tract, genitalia, kidney, limbs, face, and brain	• Blood 7-dehydrocholesterol and cholesterol • DHCR7 sequencing
Disorders of cofactor (vitamin) metabolism		
Cerebral folate deficiency	Ataxia, pyramidal signs, acquired microcephaly, dyskinesias, and visual and hearing loss	• Folate receptor alpha autoantibody • Cerebrospinal fluid 5-methyltetrahydrofolate
Pyridoxine-dependent and pyridoxine-responsive seizures	Mental retardation, breath-holding, aerophagia, and self-injurious behavior	• Pyridoxine trial • Plasma and cerebrospinal fluid pipecolic acid • Urine α-aminoadipic semialdehyde • *ALDH7A1 sequencing*
Biotinidase deficiency	Developmental delays, seborrheic dermatitis, alopecia, feeding difficulties, vomiting, diarrhea, brain atrophy, and ataxia	• Biotinidase activity • BTD gene sequencing
Carnitine biosynthesis deficiency	Nondysmorphic male–male siblings with autism spectrum disorder	• Plasma and/or urine 6-N-trimethyllysine, 3-hydroxy-6-N-trimethyllysine, and γ-butyrobetaine.
Disorders of γ-aminobutyric acid metabolism		
Succinic semialdehyde dehydrogenase deficiency	Global developmental delay, myoclonus, hallucinations, ataxia, choreoathetosis, and dystonia	• Urine gamma-hydroxybutyric acid
Disorders of pyrimidine and purine metabolism		
Adenylosuccinate lyase deficiency	Global developmental delay, microcephaly, distinct facies, growth retardation, mental retardation, cerebellar vermis hypoplasia, brain atrophy, excessive laughter, and extreme happiness	• Urine and/or cerebrospinal fluid succinyladenosine
Nucleotidase-associated PDD	Hyperactivity, compulsiveness, speech abnormalities, ataxia, abnormal gait, and frequent infections	• Urine uridine
Hyperuricosuric autism	Altered sensory awareness, ataxia, and fine motor deficits	• 24-hour urine urate
Phosphoribosylpyrophosphate synthetase deficiency	Developmental delay and ataxia	• Urine uric and orotic acids • Complete blood count
Disorders of amino acid metabolism		
Phenylketonuria	Global developmental delay, mental retardation, microcephaly, spasticity, ataxia, poor growth, poor skin pigmentation, and aggressive behavior	• Serum phenylalanine
Branched-chain ketoacid dehydrogenase kinase deficiency	Intellectual disability and consanguinity	• Plasma and cerebrospinal fluid branched-chain amino acids
Altered tryptophan metabolism	No specific features besides autism spectrum disorder	• Reduced cellular generation of nicotinamide adenine dinucleotide
Urea cycle disorders		
Urea cycle disorder	Protein intolerance, temperature instability, ataxia, episodic somnolence and lethargy, cyclic vomiting, and psychosis	• Plasma ammonia and amino acids • Urinary orotic acid

1.1.3. Disorders of vitamin metabolism

Disorders of vitamin metabolism that have been reported in children with ASD and epilepsy include disorders of folate, pyridoxine, biotin, and carnitine metabolism, each of which will be reviewed below.

Several folate metabolism abnormalities have been linked to ASD. Polymorphisms in key folate pathway enzymes such as methylenetetrahydrofolate reductase [47–56], dihydrofolate reductase [57], and the reduced folate carrier [55] have been associated with ASD but have not specifically been associated with epilepsy in individuals with ASD. However, children with cerebral folate deficiency (CFD) are commonly diagnosed with epilepsy and/or ASD [58–60]. Folate is transported across the blood–brain barrier by an energy-dependent receptor-mediated system that utilizes the folate receptor alpha (FRα) [61]. Autoantibodies that can bind to the FRα and greatly impair its function have been linked to CFD [58]. Since this transport system is energy-dependent, a wide variety of mitochondrial diseases [26,62–68] and novel forms of mitochondrial dysfunction related to ASD [69] have been associated with CFD. Recently, Frye et al. [20] reported that 75% of 93 children with ASD were positive for one of the two FRα autoantibodies. The high rate of FRα autoantibody positivity was confirmed by a recent study from Belgium that measured the FRα blocking autoantibody. This study found that 47% of 75 children with ASD were positive for the FRα blocking autoantibody compared with 3% of 30 controls with developmental delays but not autism [70]. Many children with ASD and CFD have marked improvement in clinical status when treated with folinic acid — a reduced form of folate that can cross the blood–brain barrier using the reduced folate carrier rather than the FRα transport system [20,58,59,71]. Folate receptor alpha autoantibody testing can be performed clinically, but a lumbar puncture to measure the cerebrospinal fluid concentration of 5-methyltetrahydrofolate is the gold standard diagnostic test for CFD.

Pyridoxine and its primary biologically active form pyridoxal-5-phosphate play major roles in the proper function of over 60 enzymes. Pyridoxal-5-phosphate is a cofactor for glutamic acid decarboxylase, the enzyme that metabolizes glutamic acid to GABA. Usually, pyridoxine-dependent seizures and pyridoxine-responsive seizures present

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as intractable seizures in the first months of life and are defined by their clinical response to pyridoxine therapy [72,73]. The majority of pyridoxine-dependent seizures appear to result from a deficiency in the enzyme α-aminoadipic semialdehyde dehydrogenase associated with mutations in the ALDH7A1 (antiquitin) gene [74,75]. These mutations result in the excess production of Δ^1-piperideine-6-carboxylate, a compound which complexes with and depletes pyridoxal-5-phosphate [74]. Pyridoxal-5-phosphate depletion reduces glutamic acid decarboxylase activity, resulting in a reduction in GABA synthesis [74,76,77]. Although early-onset intractable tonic–clonic seizures are the usual presentation, late-onset seizures [78–80] and other seizure types [81–83] have been described. It has been suggested that pyridoxine-responsive seizures may be a clinical entity distinct from pyridoxine-dependent seizures [84]. In children with ASD, several studies have reported significant improvement in behavior and cognition attributable to combined therapy with magnesium and pyridoxine [85–88], but others have not been able to document such a response [89,90]. There has been one case report of ASD associated with severe mental retardation, aerophagia, breath-holding, self-injury, and pyridoxine-dependent seizures [91]. According to the report, pyridoxine improved seizures but did not improve ASD features. When suspected, pyridoxine-dependent seizures can be diagnosed by measuring plasma and/or cerebrospinal fluid concentration of pipecolic acid, measuring urine concentrations of α-aminoadipic semialdehyde, or sequencing the ALDH7A1 gene. A pyridoxine trial can also be useful clinically.

Biotinidase deficiency is caused by mutations in both BTD genes which results in a deficiency of the biotinidase enzyme, an enzyme that is needed to recycle biotin, an essential cofactor for several carboxylase enzymes. Typical onset is early in life, between the 1st and 24th months of life. Symptoms include seizures, developmental delays, skin rash, seborrheic dermatitis, alopecia, feeding difficulties, vomiting, diarrhea, brain atrophy, and ataxia. Metabolic testing can demonstrate elevated blood lactate and ammonia as well as abnormal urine organic acids including elevations in β-hydroxyisovalerate, β-methylcrotonylglycine, β–hydroxypropionate, and methylcitrate. Standard treatment is 10 mg of daily biotin. The one reported child with ASD and partial biotinidase deficiency did not respond to treatment, although it was believed that ASD was prevented in his younger brother who also manifested symptoms of partial biotinidase deficiency [92]. Biotinidase deficiency is characterized by neurodevelopment problems and seborrheic dermatitis in children. Biotinidase activity can be tested clinically, and any suspicious case should be confirmed by BTD gene sequencing.

Recently, a defect in the carnitine biosynthesis pathway was described in seven children with ASD, one of whom also had epilepsy [93]. This defect in exon 2 of the X chromosome TMLHE gene encodes the first enzyme in the carnitine biosynthesis pathway, specifically 6-N-trimethyllysine dioxygenase. Interestingly, this genetic change was not more common in children with ASD than in control children overall but was more common in probands from families with male–male multiplex ASD compared with controls, suggesting that this was a risk factor for these families rather than a causative metabolic disease. Carnitine deficiency appears to be common in the wider populations with ASD, but children with ASD and carnitine deficiency have not been well characterized regarding their ASD and medical symptoms such as epilepsy [94]. Given the lack of carnitine genes found to be directly related to ASD, some authors have hypothesized that carnitine deficiency in ASD may be secondary to mitochondrial disease or dysfunction [25,95], while others have suggested that carnitine metabolism abnormalities may be related to the overproduction of short-chain fatty acids resulting from imbalances in enteric bacteria [96,97].

1.1.4. Disorders of γ-aminobutyric acid metabolism

First described in 1981, succinic semialdehyde dehydrogenase deficiency is a rare disorder of GABA metabolism that results from a mutation in both ALDH5A1 genes [98]. Since the enzyme is partially responsible for the degradation of GABA, brain GABA levels are elevated, and GABA is degraded by an alternative pathway that produces γ-hydroxybutyric acid. Elevated γ-hydroxybutyric acid results in many of the neurological manifestations of this disorder. Positron emission tomography studies suggest that elevated GABA levels downregulate brain $GABA_A$ receptors [99]. Symptom onset commonly occurs before 1 year of age with global developmental delay, hypotonia, hyporeflexia, ASD features, seizures, ataxia, choreoathetosis, dystonia, myoclonus, strabismus, nystagmus, retinitis, disc pallor, and oculomotor apraxia [100,101]. Magnetic resonance imaging can demonstrate increased T2 signal in the basal ganglia, subcortical white matter, brainstem, and cerebellum [102,103]. Metabolically, the urine, serum, and cerebrospinal fluid may demonstrate an elevation in 4-hydroxybutyric acid, but this highly volatile compound can be difficult to measure. Sequencing the ALDH5A1 gene can confirm the diagnosis.

1.1.5. Disorders of pyrimidine and purine metabolism

Children with ASD and comorbid seizures have been described to have disorders of purine and pyrimidine metabolism. These include both classic inborn-inherited disorders of metabolism, such as adenylosuccinate lyase deficiency and phosphoribosylpyrophosphate synthetase deficiency, as well as novel disorders of purine metabolism that do not have a clearly genetic basis.

Adenylosuccinate lyase deficiency is a rare disorder of de novo purine synthesis that results in the accumulation of succinyl purines [104,105]. Patients have a unique behavioral phenotype including excessive laughter, a very happy disposition, and stereotyped movements mimicking Angelman syndrome [106]. Patients show a variable combination of mental retardation, epilepsy, ASD features, and cerebellar vermis hypoplasia [104,105]. This disorder can be diagnosed using the Bratton–Marshall assay to measure succinylaminoimidazole carboxamide riboside and succinyladenosine concentration in the urine and/or cerebrospinal fluid.

One patient with developmental delay and ataxia as well as seizures and ASD features has been described with phosphoribosylpyrophosphate synthetase deficiency [107]. Metabolic abnormalities included decreased uric acid and increased orotic acid excretion and megaloblastic anemia and erythrocyte phosphoribosylpyrophosphate synthetase activity that was 10% of normal. Treatment with adrenocorticotrophic hormone reportedly increased erythrocyte phosphoribosylpyrophosphate synthetase activity and improved behavior and seizures.

Others have described some novel abnormalities in the purine pathway. In 1993, hyperuricosuric autism was described in which 24-hour urine urate was above the normal range and half of the patients had comorbid seizures [107]. Although it was believed that the metabolic basis was likely to be an abnormality of purine nucleotide interconversion, no abnormality in enzyme activity could be detected in fibroblasts, and no genetic basis could be identified. A low-purine diet and allopurinol may improve behavior and seizures in these patients.

In 1997, Page et al. [108] described four patients with ASD, seizures, immune system abnormalities, and a decrease in urinary urate. This disorder was later termed nucleotidase-associated pervasive developmental disorder [107]. Fibroblasts from the patients demonstrated decreased incorporation of uridine into nucleotides and an increase in cytosolic-5′-nucleotidase activity, suggesting an increase in nucleotide catabolic activity. All patients treated with oral pyrimidine nucleoside or nucleotide compounds showed a remarkable improvement in speech, behavior, and seizure activity. No genetic basis was found for this disorder.

1.1.6. Disorders of amino acid metabolism

Disorders in the metabolism of phenylalanine, branched-chain amino acids, and tryptophan have been described in children with ASD and comorbid epilepsy and will be reviewed in this section.

Phenylketonuria (PKU), for the most part, has been eliminated in the developed world. Phenylketonuria is an autosomal recessive inborn error of phenylalanine metabolism resulting from deficiency of

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phenylalanine hydroxylase secondary to a mutation in the PAH gene on chromosome 12q23.2. Newborn screening programs identify children with PKU at birth, allowing the implementation of specific dietary intervention. With good adherence to diet, children born with PKU can be expected to lead a normal life [109]. However, children with PKU who go untreated or who do not adhere to the diet adequately may demonstrate poor growth, poor skin pigmentation, microcephaly, seizures, spasticity, ataxia, aggressive behavior, hyperactivity, ASD features, global developmental delay, and/or severe intellectual impairment. For example, Baieli et al. [110] found that no children with classic PKU identified as neonates met the criteria for ASD, whereas 6% of those with late diagnosed classic PKU were identified with ASD. The prevalence of seizures and epilepsy is dependent on metabolic control [111]. Gross et al. [112] demonstrated that children who started treatment later were more likely to have seizures and mental retardation.

Recently an inactivating mutation in the branched-chain ketoacid dehydrogenase kinase was described to be associated with autism, epilepsy, and intellectual disability in three families with two children each who were products of first-cousin consanguinity [23]. In this disorder, phosphorylation-mediated inactivation of branched-chain ketoacid dehydrogenase is deficient, leading to abnormally low levels of branched-chain amino acids. Behavioral and neurological deficiencies were reversed in a mouse model of this disorder but not in the patients.

Using Biolog (Hayward, CA) phenotype microarrays, a recent study demonstrated a reduced production of nicotinamide adenine dinucleotide in cell lines derived from patients with syndromic ASD and from those with nonsyndromic ASD when tryptophan was provided as a sole carbon source, suggesting an abnormality in tryptophan metabolism [113]. Further studies of patients with ASD demonstrated a reduction in the expression of several tryptophan pathway enzymes, including TPH2, a gene that has been linked to both ASD [114,115] and epilepsy [116]. Altered central tryptophan metabolism has also been identified in a mouse model of progressive myoclonic epilepsy [117,118]. The exact biological mechanism by which tryptophan is linked to both ASD and epilepsy is not clear, but there are many possibilities since it is an essential precursor of many neurotransmitters including serotonin, kynurenic acid, and quinolinic acid, and the critical mitochondrial energy carrier nicotinamide adenine dinucleotide.

1.1.7. Urea cycle disorders

The urea cycle disposes of nitrogenous waste derived from the breakdown of protein. The key sign of a urea cycle disorder is a large elevation in blood ammonia after a high-protein meal or during times of illness or physiological stress. Symptoms can range from decreased appetite to cyclical vomiting to lethargy or, in severe cases, coma. In some cases, patients may self-select low-protein diets to minimize symptoms. Psychosis, seizures, and pyramidal signs develop over time. Two cases of children with urea cycle disorders, one with ornithine transcarbamylase deficiency and arginase deficiency [119] and another with carbamyl phosphate synthetase deficiency [120], have been reported. Treatment focused on reducing ammonia through a low-protein diet and ammonia binders and supplementation with specific amino acids and various vitamin supplements [121]. Improvement in ASD symptoms has been reported with treatment.

1.2. Mitochondrial dysfunction associated with epilepsy in autism spectrum disorder

A recent meta-analysis found that 5% of children with ASD met the criteria for classic mitochondrial disease, while as many as 30% of children with ASD may manifest mitochondrial dysfunction [25]. Other studies suggested that 30% to 50% of children with ASD have biomarkers consistent with mitochondrial dysfunction [122,123], and the prevalence of abnormal mitochondrial function in immune cells derived from children with ASD is exceedingly high [124,125]. Mitochondrial dysfunction has been demonstrated in the postmortem ASD brain [126–131] and in animal models of ASD [132]. Novel types of mitochondrial dysfunction have been described in children with ASD [69,96,133] and in cell lines derived from children with ASD [134,135]. Several studies suggest that children with ASD and mitochondrial dysfunction have more severe behavioral and cognitive disabilities compared with children with ASD without mitochondrial dysfunction [136–138]. Interestingly, a recent review of all of the known published cases of mitochondrial disease and ASD demonstrated that only about 25% have a known genetic mutation that can account for their mitochondrial dysfunction [122].

A meta-analysis found that, overall, 41% of children with ASD and documented mitochondrial disease are reported to have seizures [25]. This perhaps should not be surprising as mitochondrial dysfunction has been implicated in seizures and epilepsy, especially in therapy-resistant [31] and temporal lobe [32] epilepsies. The association between ASD and seizures in children with mitochondrial disease was first described as part of the HEADD (hypotonia, epilepsy, autism, and developmental delay) syndrome [139]. These cases demonstrated deficiencies in complexes I, III, and IV or large-scale mitochondrial deoxyribonucleic acid (DNA) deletions. Further case reports and series have linked seizure disorders in ASD with complex deficiencies, particularly complex III deficiencies. For example, seizures have been reported in individuals with complex III deficiency [140] and combined complex I + III deficiency [141]. Since the electron transport chain (ETC) is the final common pathway for producing the common cellular energy carrier, adenosine triphosphate (ATP), deficiencies in ETC function can have profound effects on the production of energy at the cellular level. Interestingly, mitochondrial dysfunction has been reported in many genetic syndromes associated with ASD and epilepsy. For example, mitochondrial dysfunction has been reported in Rett syndrome [142–144], PTEN haploinsufficiency [145], Phelan–McDermid syndrome [146], 15q11-q13 duplication syndrome [140,147], Angelman syndrome [148], Septo-optic dysplasia [149], and Down syndrome [150,151]. Thus, mitochondrial dysfunction may underlie the phenotype of ASD with epilepsy, regardless of the underlying cause.

Some of the novel forms of mitochondrial dysfunction associated with ASD have a high prevalence of epilepsy. Eighty percent of the five children described with complex IV overactivity manifested either generalized seizures or subclinical epileptiform discharges on overnight electroencephalogram [69], and the case with complex I overactivity had complex partial seizures and frequent bursts of predominantly left-sided multispike–wave discharges on electroencephalogram [133]. Another unique form of mitochondrial dysfunction in ASD appears to be associated with an abnormal increase in a particular pattern of short and long acylcarnitines [96]. This pattern of metabolic abnormalities parallels a rodent model of ASD in which these same metabolic abnormalities are induced by propionic acid [97]. Detailed study of children with this biomarker reveals a unique change in ETC and citric acid cycle function consistent with excess metabolic flux of propionic acid [96]. Theoretically, propionic acid can be overproduced by the overrepresented species of *Clostridia* found in the gastrointestinal tract of children with ASD [152,153]. Given that propionic acid is a short-chain fatty acid that can complex with L-carnitine, increased propionic acid production could also explain the relatively common carnitine deficiency documented in children with ASD [96,97,153]. The propionic rodent model of ASD demonstrates epileptiform-like spikes in the hippocampus, neocortex, and basal ganglia, with discharges in the basal ganglia associated with measurable behavioral abnormalities [97]. However, in the published case series of children with ASD, only 27% demonstrated abnormalities on overnight video electroencephalogram, and only 10% reported a history of seizures [96]. Clearly, further research is needed to further elucidate the correspondence between novel forms of mitochondrial dysfunction and epilepsy in ASD.

Abnormalities in mitochondrial function can lead to abnormal development in brain circuits, resulting in both neurodevelopmental disorders and epilepsy through several mechanisms. Mitochondria are

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ubiquitous organelles that are essential for almost every tissue in the body, especially the brain. Abnormalities in mitochondrial biomarkers found peripherally have also been found in the brains of individuals with ASD [131]. Thus, it is very likely that changes in mitochondrial function in the brain affect neural transmission and function in children with ASD. This could occur through several mechanisms. Neural synapses are areas of high energy consumption [154] and are especially dependent on mitochondrial function [155]. Mitochondria are concentrated in the dendritic and axonal termini where they play an important role in ATP production, calcium homeostasis, and synaptic plasticity [156,157]. Mitochondrial dysfunction can compromise neurons with high firing rates, such as GABAergic interneurons [158]. Reduced GABAergic transmission may be relevant in ASD as GABA neurons are essential for the generation and synchronization of high-frequency gamma rhythms — rhythms essential for high-level cortical processing of sensory information and 'binding' that have been shown to be abnormal in children with ASD [159]. The age range when autistic regression typically occurs corresponds to a time when there is an overabundance of cortical excitatory glutamatergic neurotransmitters and receptors [160,161] and rapid brain growth [162]. Thus, this is a developmental window in which mitochondrial energy production is pivotal. Given the importance of glutamate and GABA transmission in the development and progression of epilepsy, these same imbalances of glutamate and GABA neurotransmission could result in seizures and epilepsy in children with ASD [163,164].

Mitochondrial dysfunction is well known to result in increased levels of reactive oxygen species. Reactive species can damage neural tissue and interfere with neural transmission. Glutathione is the principal intrinsic molecule that protects cells against reactive species. Given that glutathione levels in the brain are about 50-fold lower than those in peripheral tissues, such as hepatocytes, neurons may be especially sensitive to increases in reactive oxygen species [165]. Recent studies have suggested that oxidative stress may be involved in the development of epilepsy [166]. In fact, several studies have discussed the use of antioxidants as a treatment for epilepsy [167,168], and several groups have hypothesized that one of the mechanisms for seizure control with the ketogenic diet is through the improvement of oxidative stress [169,170]. Interestingly, studies have demonstrated the connection between reactive oxygen species and mitochondrial dysfunction in brain tissue from individuals with ASD [126]. This may be another mechanism in which mitochondrial dysfunction and disease can lead to the development of epilepsy in children with ASD.

Immune dysfunction has been implicated in the development of epilepsy [171], and evidence of cellular and humoral immune dysfunction has been implicated in ASD [131,172]. In fact, the same autoantibodies to neural antigens have been linked to both autism and epilepsy [173,174]. This is significant as mitochondrial dysfunction in ASD has been repeatedly reported in immune cells [125,134,145] with such mitochondrial dysfunction linked to abnormalities in immune cell function [125]. In addition, abnormalities in microglia have been linked to abnormal brain development in Rett syndrome [175], and studies suggest that the immune system may be essential for synaptic pruning during development [176]. Thus, abnormalities in immune cell function as a result of mitochondrial dysfunction may also result in seizures in children with ASD.

Another physiological abnormality that is becoming increasingly recognized in both ASD and epilepsy is the dysregulation of calcium [177,178]. Its relationship to ASD and epilepsy is best characterized by the novel genetic disorder Timothy syndrome which includes arrhythmias, particular dysmorphology, congenital heart disease, immune deficiency, hypoglycemia, ASD, and seizures [179]. Calcium regulation is important not only in the regulation of the cell membrane potential, where its dysregulation in cardiomyocytes causes arrhythmias, but also within the cell where it regulates enzymes and transcription factors. Most interesting is the connection between mitochondrial function and calcium. Mitochondria have a significant role in the buffering of cellular calcium having multiple calcium transporters. Many mitochondrial enzymes are regulated by calcium, resulting in cellular calcium flux having both short-term and long-term consequences on mitochondrial activity [180]. Evidence suggests that calcium plays a significant role in regulation of cellular bioenergetics, production of reactive oxygen species, and induction of autophagy and apoptosis through its interaction with the mitochondria at endoplasmic reticulum-specific subdomains known as mitochondria-associated membranes [181,182]. Thus, abnormalities in cellular calcium regulation can have significant effects on mitochondrial function and have led some authors to point out the possibility of mitochondrial dysfunction in neurological and neurodevelopmental disorders associated with abnormalities in calcium metabolism [178]. Thus, abnormalities in calcium metabolism related to ASD and epilepsy provide another link to mitochondrial dysfunction in ASD and epilepsy.

Interestingly, treatments that are typically used for patients with mitochondrial disease have been shown to improve functioning in some children with ASD [122]. Several studies, including two double-blind, placebo-controlled studies [183,184], have reported improvements in core and associated ASD behaviors with L-carnitine treatment [140,141,183–188]. Two double-blind, placebo-controlled studies using a multivitamin containing B vitamins, antioxidants, vitamin E, and coenzyme Q10 reported various improvements in ASD symptoms compared with placebo [189,190]. Several other antioxidants [90], including vitamin C [191], methylcobalamin [192–194], N-acetyl-L-cysteine [195–197], ubiquinol [198], and carnosine [199], have also been reported to demonstrate significant improvements in ASD behaviors. However, the effect of these treatments on seizures or epilepsy in these children was not investigated in these studies.

1.3. Animal models of autism and epilepsy

There are several models of ASD that also manifest epilepsy and metabolic abnormalities. As mentioned above, the propionic rodent model of ASD demonstrates mitochondrial, oxidative stress and lipid abnormalities as well as epileptiform-like discharges in the brain [97,153]. However, the majority of biochemical data from the rodent model are derived from adult animals exposed to proprionic acid by intraventicular injections, thereby limiting the generalizability and translatability of the data. Despite this limitation, there appears to be preliminary evidence of a corresponding ASD metabolic subgroup of children with similar manifestations [96]. Ongoing animal studies using prenatal and neonatal exposure to enteric metabolites demonstrated the induction of ASD-like behaviors, lending support for the validity of the adult animal model [200,201]. Several genetic models of ASD syndromes in which epilepsy is common have demonstrated mitochondrial dysfunction including Rett syndrome [142], PTEN haploinsufficiency [145], and Angelman syndrome [148], while abnormalities in oxidative metabolism have been demonstrated in the Rett syndrome mouse model [142]. Classic environmental exposure models of ASD have also been shown to involve mitochondrial dysfunction as ASD behaviors induced by prenatal valproic acid exposure have been shown to be associated with reduced mitochondrial respiration [202]. A new rat model of ASD and ADHD, which has a predisposition toward seizures, manifests aberrant lipid handling [203]. Interestingly, ASD-like symptoms improved when the ketogenic diet, a metabolic diet with therapeutic effect for both epilepsy and mitochondrial disorders, was used therapeutically in several well-established mouse models of ASD that demonstrate comorbid seizure susceptibility, including the BTBR [204], EL [205], and prenatal valproic acid exposure [202] mouse models. Indeed, understanding the metabolic abnormalities in these animal models and how they correspond to children with ASD not only will help us understand the pathophysiology in more detail but also will allow treatment to be optimized on the animal models before launching human clinical trials.

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1.4. Diagnostic approach to metabolic disease

There are several factors that make the diagnosis of metabolic disease difficult, most prominently the heterogeneity of the presentation of metabolic disorders. While many traditional diseases are diagnosed by symptoms that are specific to the disease, it is unusual for metabolic diseases to have specific symptoms. As an example, we will consider mitochondrial disorders. Adult patients with mitochondrial disorders often show obvious gross motor issues, including easy fatigability, myopathies, or cardiomyopathies, while muscular manifestations are seen in a minority of patients with pediatric mitochondrial disease [206], and it is actually unusual for children with mitochondrial disease to present with characteristic hallmarks [207]. Indeed, in the pediatric population, classic biochemical markers such as lactic acidosis and muscle tissue histology such as ragged red fibers are not commonly seen with mitochondrial disease caused by well-established genetic mutations [208]. This makes the diagnosis of metabolic disease rather different from many classic diseases and requires a shift in the diagnostic strategy. Indeed, many times, diagnosis is based on a diagnostic criterion that indicates the probability of a metabolic disorder or a collection of symptoms and biomarkers that are only suggestive of a metabolic syndrome. In addition, many metabolic diseases associated with neurodevelopmental disorders do not appear to have a simply clear genetic fingerprint. In the case of mitochondrial disease, two genomes, the mitochondrial and the nuclear genome, as well as the interaction between the two genomes, need to be considered. In addition, the mitochondrion is sensitive to damage from extrinsic environmental factors as well as intrinsic factors that increase oxidative stress, thus raising the possibility of acquired mitochondrial dysfunction [16,122,131,209,210].

We have some evidence of a clinical phenotype of mitochondrial dysfunction in some children with ASD that may raise our index of suspicion in any particular patient. A recent meta-analysis that reviewed all of the cases of mitochondrial disease reported in children with ASD noted an unusually high prevalence of regression, gastrointestinal dysfunction, and motor delays, as well as seizures, in children with ASD and mitochondrial disease compared with the general population with ASD [122]. Specific mitochondrial disease syndromes associated with ASD have certain clinical symptoms that could be helpful in diagnosing a mitochondrial disorder. The HEADD syndrome includes hypotonia and developmental delays [139]. However, since the prevalence of hypotonia was not found to differ between children with ASD and mitochondrial disease and the general population with ASD, hypotonia may not be a symptom specific enough to differentiate individuals with ASD with mitochondrial disease from those without mitochondrial disease [122]. In a biomarker analysis, individuals with ASD who manifested the unique elevations in short and long acylcarnitine abnormalities showed a high rate of regression [123], consistent with others who have demonstrated that the enteric gut bacteria that produce propionic acid appear to be associated with regressive-type ASD [211,212]. This preliminary biomarker analysis also found that the subset of children with an elevation in the alanine-to-lysine ratio during screening for metabolic disorders tended to have a diagnosis of epilepsy [123]. All of the cases of children with complex I or IV overactivity and epilepsy or subclinical epileptiform discharges demonstrated normal early development followed by a substantial developmental regression with poor developmental recovery despite therapeutic interventions [69,133]. Thus, reviewing the cases of mitochondrial dysfunction and epilepsy associated with ASD does underscore two phenotypes that appear to be associated with mitochondrial disease, either developmental delays from early in life, particularly motor delays, or abrupt regression with the onset of seizures. When these symptoms are found in a child with ASD and seizures, an investigation of mitochondrial disease is warranted.

Given the fact that children with ASD can have a wide manifestation of symptoms, usually affecting many systems other than the brain, and that children with mitochondrial disease can have a wide variety of symptoms and biochemical findings [213,214], several reviews have suggested that mitochondrial disease should be considered in all children with ASD [26,122]. Recently, several algorithms outlining the workup for mitochondrial disease in ASD have been published [26,27,96,122]. Most importantly, it has been pointed out that given the low prevalence of known genetic mutations associated with mitochondrial disease in ASD and the many novel forms of mitochondrial disorders associated with ASD, a mitochondrial disease diagnostic criterion based on symptoms and biochemical findings may be more useful in the diagnostic workup of children with ASD than a diagnostic criterion more specific to classic mitochondrial disease [26,27].

Other metabolic disorders associated with ASD and epilepsy appear to have a much lower prevalence except for disorders that affect the folate pathway, particularly the association with FRα autoantibodies [20]. Thus, in addition to mitochondrial disease and dysfunction, abnormalities of folate metabolism and FRα autoantibodies should be considered in all children with ASD [20]. Children with negative findings given a workup for these disorders and/or those with treatment-resistant epilepsy should undergo further investigation for other metabolic disorders. Many of these disorders do not have specific clinical symptomatology to point toward, while some clinical clues may help for other disorders. For example, X-linked inheritance is seen in creatine transporter disorder and certain urea cycle disorders, and consanguinity has been noted in branched-chain ketoacid dehydrogenase kinase deficiency; recurrent episodes of vomiting and lethargy, particularly after a protein meal, are seen in urea cycle disorders; particular facial dysmorphology is common in adenylosuccinate lyase deficiency and Smith–Lemli–Opitz syndrome; movement disorders are seen in creatine metabolism disorder, CFD, and succinic semialdehyde dehydrogenase deficiency; and recurrent infections are seen in disorders of purine metabolism. Thus, it is difficult to develop a specific diagnostic algorithm to investigate these metabolic disorders systematically since diagnosis requires careful consideration of the individual patient to gather specific clues.

2. Discussion

We have reviewed all of the metabolic disorders that are associated with ASD in which epilepsy has been reported to be a comorbid condition. Interestingly, all of the metabolic diseases associated with ASD appear to include cases of children with comorbid epilepsy. Thus, epilepsy may be a common symptom of metabolic disorders and may be a clue that a metabolic disorder may be underlying the etiology of the neurodevelopmental abnormalities in children with epilepsy and ASD. It is also important to consider many of the metabolic disorders even when genetic disorders are diagnosed. Indeed, CFD can coexist with Rett syndrome [215], and mitochondrial dysfunction has been reported in a wide variety of genetic disorders associated with ASD [140,142–151]. In addition, CFD should be ruled out in the context of mitochondrial dysfunction as it has been shown to coexist with several mitochondrial diseases [26,62–69].

One advantage of investigating and diagnosing metabolic disorders is that treatments for many of these metabolic disorders are available [4]. Preliminary studies suggest that there are a substantial number of children with ASD with these metabolic abnormalities. For example, mitochondrial dysfunction may be seen in 5% to 80% of children with ASD [122–124], and FRα autoantibodies may be found in 47% [70] to 75% [20] of children with ASD. Clearly, further studies will be required to clarify the percentages of these subgroups. As several studies have suggested that treatment for these metabolic disorders can improve seizures, this is an important consideration in the diagnosis and treatment of epilepsy in children with ASD.

Many of the metabolic diseases described have only been reported in case reports or case series, so the prevalence of these metabolic abnormalities in children with ASD and epilepsy is not fully known. Given the small number of patients described with some disorders, it is not

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always clear if epilepsy is strongly linked to the disorder or whether the epilepsy simply coexists with the underlying neural dysfunction that has resulted in the ASD features. Further studies will be needed to determine the exact relationship between certain metabolic disorders, ASD, and epilepsy. However, some disorders like mitochondrial disorders are clearly prevalent in children with ASD and epilepsy and, thus, deserve consideration during the diagnostic workup. Clearly, many children with ASD and their families may be able to benefit from treatments which are focused on addressing metabolic abnormalities.

Conflict of Interest

The authors declares no conflict of interest.

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Please cite this article as: Frye RE, Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder, Epilepsy Behav (2014), http://dx.doi.org/10.1016/j.yebeh.2014.08.134

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Please cite this article as: Frye RE, Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder, Epilepsy Behav (2014), http://dx.doi.org/10.1016/j.yebeh.2014.08.134

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Please cite this article as: Frye RE, Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder, Epilepsy Behav (2014), http://dx.doi.org/10.1016/j.yebeh.2014.08.134