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Review

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

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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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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].