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Guest Editorial

Mitochondrial and metabolic abnormalities in neurodevelopmental disorders

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Neurodevelopmental disorders such as autism spectrum disorder (ASD), dyslexia, learning disabilities and developmental delays affect a significant percentage of children and are associated with long-term psychological and physical disability. Despite decades of research on these disorders, their etiologies are still poorly understood and treatments are limited in number and efficacy. The prevalence of the prototypic neurodevelopmental disorder, ASD, continues to rise at an alarming rate. ASD research has primarily concentrated on and continues to concentrate on genetic causes of ASD [1]. Although genetics are an important aspect of ASD research, genetic studies have found that single gene and chromosome defects account for only a minority of ASD cases [2]. This is also true for other cognitive disorders such as a wide variety of psychiatric disorders. Although linkage studies have identified many candidate regions of certain chromosomes which could be associated with many psychiatric diseases, findings have been inconsistent across studies. For example, recent studies have identified genetic polymorphisms associated with susceptibility to psychiatric disease such as schizophrenia, but most polymorphisms identified are in the non-coding regions of the genome, making the understanding of how these genetic changes cause psychiatric disease opaque [3,4].

Several recent studies have identified rare *de novo* mutations in ASD children, thereby pointing to acquired mutations and/or mutations secondary to errors in the maintenance of DNA integrity rather that inherited genetic syndromes [5,6]. A recent study of dizygotic twins estimated that the environment contributes a greater percent of the risk of developing autistic disorder (55%) as compared to genetic factors (37%) with the risk between genetic and environmental factors about equal for the wider ASD diagnosis [7]. This suggests that complex interactions between the environment and a susceptible genetic background during critical developmental windows may underlie the etiological mechanisms and disabilities associated with ASD.

Recent studies have expanded the recognition of the abnormalities associated with ASD, implicating broader systemic issues involving immune and redox dysregulation, oxidative stress and impaired energy generation systems [1,8–10]. Interestingly, these physiological abnormalities do not only apply to ASD but are shared by a wide variety of both psychiatric, neurodevelopmental and neurodegenerative disorders. Mitochondrial dysfunction has been implicated in schizophrenia [11–14], bipolar disorder [11–13], depression [12,13] and dementia [12,13]. In addition, mitochondrial dysfunction has been documented in a wide variety of genetic syndromes associat-

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ed with neurodevelopmental problems, including Rett syndrome [15–17], PTEN mutations [18], Phelan-McDermid syndrome [19], 15q11-q13 duplication syndrome [20,21], Angelman syndrome [22], Septo-optic dysplasia [23] and Down's syndrome [24,25]. Oxidative stress has been implicated in schizophrenia [26,27], depression [28], bipolar disorder [29,30], Alzheimer's disease [31] and Parkinson's disease [31]. Neuroinflammation has been implicated in Alzheimer's disease [32], schizophrenia [33], bipolar disorder [34] and depression [35]. Interestingly, a review of gene expression abnormalities found in ASD, Rett syndrome and Down syndrome demonstrated a convergence on immune genes rather than neurodevelopmental genes [36].

Thus, it is clear, at least in ASD, that physiological abnormalities exist which can be linked to developmental, cognitive and medical disability. For example, children with ASD and mitochondrial dysfunction have more severe behavioral and cognitive disability than children with ASD without mitochondrial dysfunction [37,38]. In addition, mitochondrial dysfunction can lead to abnormal cognitive development through several mechanisms. For example, neural synapses are areas of high energy consumption [39] that are especially dependent on mitochondrial function [40] and mitochondrial dysfunction can lead to reduced synaptic function, and neurons that have high firing rates, such as GABAergic interneurons, can be severely compromised [41]. In addition, children with ASD and mitochondrial disease appear to have a higher prevalence of medical disorders such as gastrointestinal problems, seizures and gross motor delays [9].

In order to highlight the significance of metabolic disorders in contributing to neurodevelopmental problems, we have put together a special issue of the *Journal of Pediatric Biochemistry* with leaders in the field of metabolic abnormalities in neurodevelopmental disorders. The articles in this issue will provide examples of how this field is rapidly growing and expanding as well as the complexities in diagnosing and understanding metabolic abnormalities in neurodevelopmental disorders.

The special issue starts with an article that provides an overview of metabolic disorders associated with the prototypic neurodevelopmental disorders, ASD. In an article entitled "Metabolic Disorders and Abnormalities Associated with Autism Spectrum Disorder" Frye and Rossignol outline the many metabolic diseases and metabolic abnormalities that have been linked to ASD. The article discusses the most prevalence metabolic disorders, mitochondrial dysfunction and cerebral folate abnormalities, both of which are discussed in more detail in this issue, and then goes on to discuss less common metabolic disorders which have been associated with ASD. Metabolic abnormalities that have been documented in ASD, specifically disorders of cholesterol and tetrahydrobiopterin metabolism, are discussed despite the fact that specific cases have not been officially described. A general algorithm for working up patients for these various metabolic disorders is outlined.

The next section of this special issue features several papers specifically pertaining to mitochondrial disorders. Mitochondrial disease is a relatively new and evolving field of medicine [42]. Although the clinical and histological features of mitochondrial disorders were recognized in the 1960s, it was not until 1988 that specific mitochondrial disease could be linked to a causative genetic mutation. From that point on, specific mitochondrial diseases have been described by their associated genetic alterations. However, patients with neurodevelopmental disorders such ASD who manifest mitochondrial disease or dysfunction do not commonly demonstrate a specific genetic defect to explain their metabolic abnormalities [9]. This finding has presented uncertainty and complexity to the study of mitochondrial metabolism in neurodevelopmental disorders.

In the article entitled "Mitochondrial Disorders: Overview of Diagnostic Tools and New Diagnostic Trends" Dr Fran D. Kendall provides an excellent synopsis of the significance of mitochondrial function in health and disease as well as basic genetics and provides a detailed discussion of diagnostic methods and tools. Dr Kendall also outlines the limitations and future trends in mitochondrial disease diagnosis. The article "New Approaches to Diagnosing Mitochondrial Abnormalities: Taking the Next Step" by Dr Rodenburg's group extends the discussion of advanced and new methods for diagnosing mitochondrial disease. With advances in molecular testing, whole mitochondrial genome sequencing and whole exome sequencing with next-generation sequencing techniques have become commonplace for individuals with mitochondrial abnormalities in which known genetic mutations cannot be found. However, these techniques can reveal a larger number of novel changes in the genome of any one individual that needs to be interpreted with care. This article addresses the complexities of discovering and verifying novel genome alterations in the context of mitochondrial disorders.

As mentioned above, mitochondrial dysfunction has been implicated in a wide variety of disease that ef-

fect brain function, including neurological, neurodegenerative and psychiatric disease. The article "Mitochondrial Respiratory Chain Defects in Autism and other Neurodevelopmental Disorders" by Chauhan et al. provides a very detailed analysis of the evidence for mitochondrial dysfunction in autism spectrum disorder while also addressing the evidence for similar mitochondrial dysfunction in other neurodevelopmental disorders such as Angelman, Down, Fragile X and Rett syndromes as well as attention deficit hyperactivity disorder and schizophrenia. This paper demonstrates the pervasiveness of mitochondrial dysfunction in disorders that affect brain development and function. However, despite this evidence, mechanisms which cause problems with brain development as a result of mitochondrial dysfunction are not clear. One of the consequences of mitochondrial dysfunction, oxidative stress, can have a profound effect on brain development. In an article entitled "Oxidative stress and mitochondrial dysfunction as key players in neurological disorders of childhood" Dr El-Hatem provides an excellent account of the mechanisms by which oxidative stress can damage the developing brain as well as the evidence for oxidative stress in a wide variety of neurodevelopmental disorders and potential treatments for normalizing oxidative stress. In the final paper related to mitochondrial abnormalities entitled "Treatments for mitochondrial dysfunction associated with autism spectrum disorders", Frye and Rossignol outline an approach for treating individuals with mitochondrial dysfunction with special emphasis on autism spectrum disorders.

The last two articles in this special issue outline the complexity of the relationship between folate metabolism and neurodevelopmental disorders. In an article entitled "Synthetic Folic Acid Supplementation During Pregnancy May Increase the Risk of Developing Autism", Drs. DeSoto and Hitlan reanalyze the large Centers for Disease Control Vaccine Safety Datalink dataset to investigate the relationship between the use of synthetic folate during pregnancy and the risk of ASD to the offspring. Interestingly, the reanalysis of this dataset links synthetic folate use during pregnancy to an increased risk of ASD. The complexities of folate metabolism are discussed and the link to ASD is discussed in light of epigenetic regulation of the genome. In the last article in this special issue entitled "Folate receptor alpha autoimmunity and cerebral folate deficiency in autism spectrum disorders" Drs Rossignol and Frye discuss the significance of the high prevalence of the folate receptor alpha autoantibody in ASD with an emphasis on treatment with folinic acid. This article highlights the importance of the use of reduced folates in the treatment of children with ASD and the folate receptor alpha autoantibody, echoing some of the discussion in the previous paper on the complexities of folate metabolism, especially when synthetic folic acid is used as a folate resource.

Overall, we believe that this special issue will bring to light some of the significant metabolic abnormalities associated with neurodevelopmental disorders such as ASD. Increasing awareness and treatment of these underlying metabolic disorders is one step toward improving the health and related disability associated with neurodevelopmental disorders such as ASD.

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