



CASE REPORT

Autism in the Son of a Woman with Mitochondrial Myopathy and Dysautonomia: A Case Report

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Innov Clin Neurosci. 2015;12(9–10):29–32

FUNDING: No funding was received for the preparation of this manuscript.

FINANCIAL DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.

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KEY WORDS: Autism, autism spectrum disorder, ASD, mitochondria, mitochondrial disease, mitochondrial myopathy, dysautonomia, neurocardiogenic syncope

ABSTRACT

The relationship between autism spectrum disorders and mitochondrial dysfunction, including mitochondrial myopathies and other mitochondrial diseases, is an area of ongoing research. All autism spectrum disorders are known to be heritable, via genetic and/or epigenetic mechanisms, but specific modes of inheritance are not well characterized. Nevertheless, autism spectrum disorders have been linked to many specific genes associated with mitochondrial function, especially to genes involved in mitochondrial tRNA and the electron transport chain, both particularly vulnerable to point mutations, and clinical research also supports a relationship between the two pathologies. Although only a small minority of patients with autism have a mitochondrial disease, many patients with mitochondrial myopathies have autism spectrum disorder symptoms, and these symptoms may be the presenting symptoms, which presents a diagnostic challenge for clinicians. The authors report the case of a 15-year-old boy with a history of autism spectrum disorder and neurocardiogenic syncope, admitted to the inpatient unit for self-injury, whose young mother, age 35, was discovered to suffer from

mitochondrial myopathy, dysautonomia, neurocardiogenic syncope, Ehler-Danlos syndrome, and other uncommon multisystem pathologies likely related to mitochondrial dysfunction. This case illustrates the need for a high index of suspicion for mitochondrial disease in patients with autism, as they have two orders of magnitude greater risk for such diseases than the general population. The literature shows that mitochondrial disease is underdiagnosed in autism spectrum disorder patients and should not be viewed as a “zebra” (i.e., an obscure diagnosis that is made when a more common explanation is more likely).

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social behavior and language development and restricted or repetitive patterns of behavior or obsessive interests. ASD may present, in some cases, without the language or intellectual impairment symptoms; this condition was formerly known as Asperger’s syndrome, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, but is now contained within the single diagnosis of ASD, according to

the fifth edition of the *DSM* (*DSM* 5).^{1,2} This form of ASD is known to be heritable, as are all forms of ASD, despite the previous belief to the contrary, though the mechanisms of inheritance, both genetic and epigenetic, are not well characterized.³ The genetic loci responsible are heterogeneous, and the penetrance is highly variable and influenced by complex psychosocial gene-environment interactions.⁴ Despite the incomplete state of our knowledge of the pathophysiology underlying ASD, there is some emerging evidence that connects the genetic etiology of this disorder to mitochondrial disease.⁵

Mitochondrial myopathies are a diverse and poorly understood set of diseases that include the mitochondrial deoxyribonucleic acid (DNA) depletion syndromes, pure myopathies, Kearns-Sayre syndrome, and syndromes named for common symptom clusters, such as myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Due to their histological picture, they are commonly and historically referred to as ragged red fiber diseases, or simply the mitochondrial disorders. Over 200 specific genes have been linked to transfer ribonucleic acid (tRNA) mitochondrial disease alone, and tRNA is not the only mechanism by which mitochondria cause clinical disease.⁶ For example, genetic dysfunctions in the amino acid carriers, such as the glutamate-aspartate shuttle of the mitochondrial membrane, are now known to be associated with ASD.⁷ Mitochondrial tRNA (mt tRNA) is known to be especially vulnerable to point mutations, which produces a broad array of pathology.⁸

Although neurological symptoms have long been strongly associated with mitochondrial disease, from motor function symptoms to epilepsy, encephalopathy, and stroke, the psychiatric aspect of mitochondrial disease is only

recently beginning to be elucidated.⁹ Imaging techniques like spectroscopic brain magnetic resonance imaging (MRI) are only just now allowing researchers to compare mitochondrial function in individuals with autism to that of neurotypical persons, and it has been found that patients with ASD have higher lactate levels (a proxy of mitochondrial function) in the cingulate gyrus, corpus callosum, and other brain areas compared to controls.⁹

CASE REPORT

A 15-year-old boy with a past history of oppositional defiant disorder, attention deficit hyperactivity disorder (ADHD), anxiety, major depressive disorder, and ASD (formerly diagnosed with Asperger's syndrome) presented to the emergency department due to self-injury (superficial cuts on forearms and fingers from scissors or a box cutter) secondary to depression. He denied suicidal ideation and attributed his recent depressed mood to awareness of his autistic symptoms, and he was afraid of the social stigma related to autism. He also reported increased anxiety over the past four weeks relating to fears that he might misbehave at school, and he expressed fear of authority. He denied any psychotic symptoms or substance abuse. His psychiatrist prescribed risperidone, fluoxetine, and citalopram, but discontinued the selective serotonin reuptake inhibitor (SSRI) for reasons unclear to the patient. He also took atenolol and midodrine for neurocardiogenic syncope, and fludrocortisone for autonomic insufficiency.

During the interview, his affect was blunted and his speech pattern was monotonous, but his thought process was logical and his vocabulary was extensive—both classic findings in ASD without impairment in language or intellect. When asked about stressors at home, he mentioned his mother's declining health due to a mitochondrial disease

as well as his own concerns about his future health, given his previous "spells" (syncopal episodes secondary to his diagnosis of neurocardiogenic syncope). The patient stated in an incongruently flat affect that he was going to "end up just like" his mother. He was kept on the inpatient unit for four days until he denied any further thoughts of self-harm, and was discharged with sertraline added to his medications.

It was discovered that the patient's mother, age 35, also suffered from neurocardiogenic syncope, along with mitochondrial myopathy, dysautonomia, Ehler-Danlos syndrome, and a Budd-Chiari type 2 malformation that required surgical decompression. She received care at a tertiary academic medical center from a cardiac electrophysiologist and a neurologist, with care coordinated by medicine faculty. She suffered from recurrent and severe hypoglycemic episodes, likely secondary to adrenal insufficiency, which resulted in many emergency department visits. Cardiology's workup discovered that she also suffered from central sleep apnea, paroxysmal atrial fibrillation, a patent foramen ovale, hypothyroidism, Raynaud's disease, and early onset cataracts. This extensive, multisystem litany of symptoms and diseases is typical for a patient with a mitochondrial disease.

DISCUSSION

The literature on mitochondrial dysfunction in ASD is growing rapidly. A recent literature review found that patients with autism had a risk of mitochondrial disease two orders of magnitude greater than the general population, and that the rate of mitochondria-associated lab abnormalities (pyruvate, carnitine, ubiquinone, and lactate) is even higher.¹⁰ There are data to suggest that lab values correlate to clinical severity of ASD symptoms and that some patients have symptomatic improvement on co-enzyme Q10,

carnitine, and B complex vitamin supplements—all nutrients that could ameliorate mitochondrial dysfunction.¹⁰

Specific pathophysiological mechanisms have been discovered to explain the relationship between ASDs and mitochondrial function, though given the heterogeneity of both disorders it is difficult to estimate the significance of these findings. In one case study, the authors took a buccal swab from a boy with autism and an unexplained set of unusual neurological symptoms and found that a gene region for complex IV and I of the electron transport chain was deleted.¹¹ In another case study of a boy with autism and progressive muscle weakness, the authors found a novel mutation in a tRNA gene.¹² Population studies back up the implications of these case reports. A significant Chinese study to find a genetic basis for autism in their population implicated a gene for mitochondrial complex 1.¹³ A 2008 cohort study examining patients originally diagnosed as having idiopathic ASD but later found to have a co-occurring mitochondrial disease demonstrated that 24 out of the 25 examined had clinical evidence of a mitochondrial disease that was misattributed to another organic cause before the correct diagnosis was made.¹⁴ This suggests that mitochondrial disorders may be underdiagnosed in patients with autism. Both clinical and basic science literature is trending toward support for the idea that many forms of autism are related to mitochondrial disease.^{15,16} Some clinicians have debated whether all children with autism should be evaluated for mitochondrial disorders, though most are hesitant to recommend this.¹⁷

Although there is no consensus on indications for a complete mitochondrial workup in patients with autism and nonspecific symptoms, the generally accepted workup for a mitochondrial disorder in a patient with nonspecific

symptoms suggestive of mitochondrial disease begins with a clinical examination for cardiac enlargement; optic atrophy and retinopathy; central nervous system findings such as cerebellar ataxia, sensorineural hearing loss, and movement disorders; and peripheral nervous system symptoms such as hypotonia and muscle weakness.^{18,19} Labs to measure plasma lactate, plasma amino acids, plasma acylcarnitines, cerebrospinal fluid (CSF) lactate, and urinary organic acids should be included as well.^{18,19} In addition to the physical exam and labs, electromyography is recommended to look for subclinical myopathy and neuropathy, electrocardiogram to assess for any arrhythmias, and a brain MRI to evaluate for leukoencephalopathy.¹⁹ Because some mitochondrial dysfunction is only apparent when the body is under stress, exercise testing to evaluate for plasma lactate levels can be helpful in establishing a mitochondrial myopathy diagnosis.²⁰ While these laboratory and imaging studies are recommended to begin a workup in patients with nonspecific symptoms, the most definitive studies for mitochondrial disease remain muscle biopsy²¹ and genetic testing,²² both of which can be expensive and for which insurers have different policies for approving. It is not uncommon for insurance coverage to depend on the specific mutation for which testing is sought, and clinicians should be prepared to discuss the matter with the patient's insurer prior to any testing being performed.

The benefits of evaluating a patient for mitochondrial disease and providing a specific diagnosis can include better supportive management and anticipation of specific sequelae of mitochondrial disease, such as audiology and ophthalmology screening, better seizure control, and cardiology assessments.²³ The evidence for pharmacological therapy in mitochondrial disease is weak, but supplementation with coenzyme q10,

creatinine, and L-carnitine is recommended, despite lack of efficacy, due to their plausible mechanism of action, benign side effect profile, and safety.²⁴ Diagnosis also provides a rationale for the patient to avoid certain drugs, such as those that are ototoxic (aminoglycosides), can precipitate lactic acidosis (metformin), or are known to interfere with the electron transport chain (such as chloramphenicol, barbiturates, phenytoin, statins, and valproic acid).²⁵ Future benefits of diagnosis may include the opportunity for gene therapy, although mitochondrial gene therapy is still in its infancy.²⁶

CONCLUSION

Given emerging evidence that mitochondrial dysfunction, particularly in the electron transport chain needed for cellular energy production, is an underlying pathophysiological mechanism for some varieties of ASD, clinicians should have a high index of suspicion for mitochondrial disease, especially when they encounter a patient with unusual neurological or constitutional symptoms. The prevalence of mitochondrial disease in ASD patients may be as high as five percent, which means that it is not the “zebra”²⁷ diagnosis that it might be in a non-ASD patient, where prevalence is about 0.01 percent.¹⁰

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