

6-12-2005

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## Repository Citation

Ahn, Mary S.; Sims, Katherine B.; and Frazier, Jean A., "Risperidone-induced psychosis and depression in a child with a mitochondrial disorder" (2005). *Psychiatry Publications and Presentations*. 395.

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## Case Report

# Risperidone-Induced Psychosis and Depression in a Child with a Mitochondrial Disorder

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### ABSTRACT

**Objective:** To our knowledge, this is the first published case report of an adolescent girl with a mitochondrial disorder and depression who displayed both new-onset psychotic and increased mood symptoms during treatment with risperidone.

**Data:** A 16-year-old girl was treated with risperidone for mood lability and impulsivity at a community hospital. Within days, she developed paranoid ideation, profound psychomotor retardation, increased depression, and fatigue. She was transferred to an inpatient psychiatric hospital, where she was taken off risperidone. Within 48 hours after discontinuation of the medication, she had complete resolution of psychotic symptoms, fatigue, and psychomotor retardation, and her depression improved.

**Conclusions:** This observation of “on-off” risperidone treatment suggests that risperidone may have worsened both psychiatric and physical manifestations of the mitochondrial disorder in this adolescent. These findings are consistent with recent *in vitro* literature, which implicate a series of neuroleptic medications with mitochondrial dysfunction. Furthermore, the authors provide diagnostic and treatment options that are available for mitochondrial disorders, which are of interest to child psychiatrists due to the central nervous system manifestations of these disorders.

### INTRODUCTION

**M**ITOCHONDRIAL DISORDERS were first described by Rolf Luft in 1962 (Luft et al. 1962) and refer to dysfunction of energy metabolism by different pathways including: (1) oxidative phosphorylation, (2) fatty acid oxidation, and/or (3) Krebs Cycle. Oxidative phosphorylation creates adenosyl triphosphate (ATP), which is

essential for energy metabolism and vital for the normal function of bodily organs. Therefore, mitochondrial disorders may lead to clinical manifestations involving almost any organ system (Zeviani and Di Donato 2004). The most common clinical presentations in a recent retrospective review of 113 children with mitochondrial disease include cardiomyopathy (40%) and nonspecific encephalopathy (39%). The chil-

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dren without cardiomyopathy were further studied and 100% had developmental delays, 79% had hypotonia, 20% had hypertonia, 50% had seizures, 12% had movement disorders, 6% had ataxia, 21% had sensorineural hearing loss, and 32% had ophthalmologic abnormalities (Scaglia et al. 2004). (Please refer to Table 1, which lists the most common presentations of mitochondrial disorders.) Mitochondrial disorders have been also implicated in neurodegenerative disorders, as neurons are susceptible to oxidative damage. By extension, one would expect that neuropsychiatric manifestations would occur secondary to mitochondrial disorders, though this remains an understudied area. A recent study estimates the prevalence of mitochondrial disorders to be 1 of 5000 births, although the authors argue that this is a conservative estimate, given their heterogeneous genotypic and phenotypic presentations (Thorburn 2004).

Typical and atypical neuroleptics are commonly prescribed for a variety of childhood psychiatric conditions, including psychotic disorders, mood disorders, and disruptive behavior disorders (Armenteros et al. 1997; Grcevich et al. 1996; Frazier et al. 1999; McDougle et al. 1997; Snyder et al. 2002; Horrigan and Barnhill 1997; Schreier 1998; Buitelaar 2000; Buitelaar et al. 2001; Gaffney et al. 2002). They have also been used to treat emotional and behavioral dysregulation in youth with underlying mitochondrial disorders. However, *in vitro* data using rat liver have shown that both typical and atypical neuroleptics inhibit mitochondrial oxidative phosphorylation (Modica-Napolitano et al. 2003). Also, *in vitro* neuroleptic medications (haloperidol, chlorpromazine, and thiothixene) have been shown to inhibit electron transport chain complex I enzyme activity in rat brain mitochondria (Burkhardt et al. 1993) and human brain

(haloperidol, chlorpromazine, risperidone and, to a much lesser extent, clozapine) (Maurer and Moller 1997). As such, neuroleptics might be expected to exacerbate the very neuropsychiatric symptoms that they are being used to treat in people with already compromised dysfunction of energy metabolism owing to a mitochondrial disorder.

We present the following case of a young woman with a mitochondrial disorder whose subsequent clinical course may illustrate the complications that can arise from treatment with an atypical neuroleptic in individuals with these disorders. We also use the case as a way to discuss the recognition and management of a mitochondrial disorder within a neuropsychiatric context.

## CASE REPORT

A 16-year-old girl, JM, with a low-average IQ, speech and motor delays, and a significant medical history of a mitochondrial and seizure disorder, was brought in by her mother to a community hospital's psychiatric emergency program for parasuicidal behavior.

### *History of mitochondrial disorder*

JM's mitochondrial disorder first came to light as part of an evaluation for seizures. She experienced tonic-clonic seizures at 5 years of age, with seizures occurring three to four times per week. JM underwent a thorough neurological workup, including magnetic resonance imaging (MRI), which was within normal limits. During her seizures, JM experienced profound muscle weakness that made the neurologist suspicious of an underlying mitochondrial disorder. Her lactate level (one of the tests for diagnosing

TABLE 1. COMMON PRESENTATIONS CONSISTENT WITH MITOCHONDRIAL DISORDERS  
(MUNNICH ET AL. 1996; DiMAURO ET AL. 2004)

Central nervous system	seizures, myoclonus, ataxia, psychiatric symptoms, cognitive decline, headaches
Cardiac	cardiomyopathy, heart block
Endocrine	diabetes, growth-hormone deficiency/short stature, hypothyroidism, hypoparathyroidism
Muscle	muscle weakness
Optic	ptosis, visual changes
Otic	deafness

mitochondrial disorders) was elevated, and, therefore, a muscle biopsy was performed. The presence of ragged red fibers confirmed the diagnosis of a mitochondrial disorder. Clinically, JM improved on a cocktail for mitochondrial disorders, consisting of carnitine supplementation (Carnitor) and Coenzyme Q-10 supplementation. Her seizures dramatically decreased to once or twice annually.

#### *Psychiatric history*

When JM was brought to the emergency room, she had been depressed, cutting herself superficially on the arms and taking extra ibuprofen and extra seizure medication to relieve psychic pain. The self-mutilation began after learning that a close relative was diagnosed with cancer, and that her brother had been sexually molested. In addition to cutting herself, JM had sleep disturbance, poor appetite, and decreased interests. There was no history of psychomotor retardation, increased fatigue or guilt, decreased concentration, or manic or psychotic symptoms. JM began contemplating suicide but never thought of a plan. She took excessive amounts of ibuprofen and levetiracetam (Keppra) the night before her presentation as a way to "numb the pain," rather than as a suicide attempt. Prior to the recent stressors, she and the family denied any psychiatric problems.

#### *Family history*

An uncle had a history of posttraumatic stress disorder and depression after the Vietnam War. There was no other psychiatric family history. The medical family history was positive for seizure disorders and asthma. There was no family history of developmental delay or mitochondrial disorders.

#### *Treatment history*

JM's medications included: Levetiracetam (Keppra) 1000 mg twice-daily prescribed for her seizure disorder; carnitine (Carnitor) 700 mg three times a day; multivitamin daily; and Coenzyme Q-10 200 mg twice-daily. The carnitine, multivitamin, and Co-Q were taken for her underlying mitochondrial disorder, and there

were no changes in this medication regimen for over 1 year. Her primary care physician had prescribed paroxetine 1 week prior to her presentation to the community hospital owing to concerns of depression, but she had not filled the prescription.

#### *Hospital course*

Because of the unavailability of inpatient psychiatric beds in the area, JM boarded on the pediatric service of a community hospital for 4 days awaiting transfer. On the first hospital day, a psychiatric consultant recommended starting the paroxetine 10 mg daily for her depression and risperidone 0.5 mg twice-daily to address impulsivity. Admission laboratory data showed a negative urine toxicology screen. Her complete blood count, electrolytes, liver profile, vital signs, and electrocardiogram were all within normal limits. Her urine pregnancy test was negative. No lactate or pyruvate levels were drawn.

On hospital day 5, JM was transferred to the in-patient child psychiatric unit and received an evaluation by the first author. At this time, JM's mental status examination was notable for a clear change from the report of her mental status prior to starting risperidone. She presented as irritable, guarded, and with severe psychomotor retardation. She denied hallucinations but appeared to be attending to internal stimuli. She displayed paranoid ideation towards her family and staff members. JM complained of fatigue and of an acute deficit in concentration. There was worsening of her depressed mood. Her admission Abnormal Involuntary Movement Scale (AIMS) examination was zero.

Later that day, JM was taken off risperidone because of questionable clinical indication and concerns about its effects on her underlying mitochondrial disorder, as the examiner was familiar with the recent literature about neuroleptics and mitochondrial dysfunction. JM continued on the same doses of her other medications, including the paroxetine.

Within 48 hours after stopping the risperidone, JM showed complete resolution of her paranoid ideation, was no longer attending to internal stimuli, and was no longer feeling fatigued. Her concentration improved. She still

complained of urges to cut herself and received skills therapy on the unit to address these maladaptive behaviors. Her mother, who had noticed a dramatic deterioration in her daughter's mental status while on risperidone and paroxetine, also noted the improvement once the risperidone was stopped.

JM was discharged home in stable condition after 13 inpatient psychiatric hospital days.

## DISCUSSION

In this case report, we present an adolescent girl with a history of developmental delays, and a mitochondrial disorder who, prior to acute stressors, had no psychiatric history. She responded to her acute stressors with depression and maladaptive coping skills. There was no history of psychosis prior to taking the psychotropic medications. She was started on risperidone, and within 48 hours of initiating the medication she experienced paranoid ideation, profound psychomotor retardation, and worsening of her depression. There was no indication of extrapyramidal symptoms (EPS) secondary to risperidone. These symptoms of psychosis resolved after the risperidone was discontinued.

Lactate and pyruvate levels, as well as amino acid and organic acid levels, might have confirmed the relationship of JM's clinical status to risperidone, but were not obtained during this "on-and-off" evaluation. There are, of course, other possible reasons for worsening of her clinical status. These include: (1) a drug-drug interaction in this patient between risperidone and paroxetine; (2) an idiosyncratic reaction to risperidone unrelated to worsening of mitochondrial functioning; (3) a progression of the patient's underlying depression; and/or (4) a neuropsychiatric progression of the patient's underlying mitochondrial disorder unrelated to the medication treatment. However, given JM's rapid resolution of psychiatric symptoms after the risperidone was discontinued, the most likely reason for the symptom exacerbation involved exposure to risperidone, whether it represented a drug-drug interaction with paroxetine, an unrelated idiosyncratic reaction to risperidone, or a direct effect of the risperidone

done on mitochondrial function. Given JM's history of mitochondrial dysfunction and the data suggesting that neuroleptics can worsen mitochondrial function, it is not unreasonable to conclude that her deterioration was related to risperidone's effect on mitochondrial oxidative phosphorylation.

There have been published case reports of increased psychiatric and physical difficulties in adults with mitochondrial disorders who were treated with neuroleptics (Kaido et al. 1996; Yamazaki et al. 1991; Spellberg et al. 2001; Iizuka et al. 2003). For example, Yamazaki et al. report a 37-year-old male with an 8-year history of psychosis and dementia, who later developed hyperpyrexia and dystonia after haloperidol administration. Both his dystonia and psychiatric symptoms resolved after being diagnosed with a mitochondrial disorder named MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like syndrome) and being placed on Coenzyme Q-10 and taken off haloperidol (1996). Of note, MELAS has been described together with psychiatric symptoms even before stroke-like episodes have taken place (Suzuki et al. 1990). These findings raise the question whether mitochondrial dysfunction increases vulnerability to psychiatric symptoms in certain primary mitochondrial disorders.

### *Clinical implications*

This case report brings up several issues in the clinical treatment of children with psychiatric symptoms. Firstly, children with psychosis are often evaluated for organic pathology as a part of routine clinical practice, but mitochondrial disorders screening is not commonly part of that organic work-up. Although mitochondrial disorders are relatively rare, clinicians should be mindful that evidence of: (1) developmental delays; and/or (2) multiple comorbid medical problems (i.e., other organ or multiorgan dysfunction); and/or (3) chronic, intermittent, or progressive medical and psychiatric disorders with episodes of exacerbation; and/or (4) positive family history (both maternal and Mendelian inheritance) for mitochondrial diseases or multiorgan pathology without an identifiable etiology, should raise the suspicion that new-onset psychiatric symptoms may be

the result of an underlying mitochondrial disorder. If a mitochondrial disorder is present or even suspected, the risks of worsening the underlying mitochondrial dysfunction should be weighed against the benefits of neuroleptic medications. If clinically necessary, neuroleptics with the least risk of EPS should be considered first, as the degree of mitochondrial dysfunction associated with neuroleptic treatment is associated with extrapyramidal symptom (EPS) risk. Furthermore, children with mitochondrial disorders need to be carefully evaluated for EPS, tardive dyskinesia, psychosis, and worsening of neuropsychiatric symptoms and progression of physical symptoms associated with their underlying mitochondrial disease.

With respect to evaluation, there is no pathognomonic test for mitochondrial disorders. Although adult diagnostic criteria have been proposed, childhood diagnostic criteria are not yet formalized (Bernier et al. 2002; Skladal et al. 2003; Scaglia et al. 2004). However, important initial screening tests for mitochondrial disorders include: (1) serum lactate and pyruvate levels, although only 60% of cases with mitochondrial disorder exhibit elevated levels of lactate and serum pyruvate; (2) a nonfasting urinalysis positive for ketones; and (3) serum ammonia, fasting glucose, serum for quantitative amino acids, and urine for quantitative organic acids (Munnich et al. 1996; Spellberg et al. 2001; Bernier et al. 2002; Prietsch et al. 2002; Smeitink 2003; Hunter et al. 2004; DiMauro et al. 2004).

In cases with a compelling clinical history and/or positive screening tests consistent with mitochondrial disorder, neurological consultation should be sought to pursue additional studies. The neurologist may recommend muscle biopsy in order to examine for the presence of histological abnormalities (including ragged red fibers), or histochemical changes by light microscopy and anatomic mitochondrial findings (crystalline inclusions, subsarcolemmal clustering) in skeletal muscle. Histological skeletal muscle abnormalities can support a diagnosis of a mitochondrial disorder, but are not sensitive, as 17% of patients had normal findings in Scaglia et al. (2004). Direct assay of electron chain complexes may highlight specific deficiency. Other diagnostic tests include genetic

testing (nDNA or mtDNA), or organ-specific provocative testing.

There is no singular cure for mitochondrial disorders, and treatment is based on supportively managing symptoms. Supplementation with enzyme cofactors (Coenzyme Q-10, Vitamin K, B Vitamins), important mitochondrial transport factors (carnitine), dietary changes, and a "vitamin cocktail" rich in antioxidants may be warranted. Medications, which are known to inhibit oxidative phosphorylation, should be avoided if possible, including valproic acid, barbiturates, tetracyclines, chloramphenicol, and certain neuroleptics (Munnich et al. 1996; Modica-Napolitano et al. 2003). If neuroleptics are clinically necessary, olanzapine (Zyprexa) and clozapine (Clozaril) should be considered, followed by quetiapine (Seroquel), owing to the fact that these agents show the least amount of mitochondrial dysfunction in animal studies (Modica-Napolitano et al. 2003).

## CONCLUSIONS

Taken together, these findings lend further support for the need to systematically investigate psychiatric phenotypic expression of mitochondrial disorder and highlight the need to systematically evaluate the safety and efficacy of neuroleptic treatment in youths who suffer from these disorders.

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