Improvement in symptoms of the syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms (MELAS) following treatment with sympathomimetic amines – possible implications for improving fecundity in women of advanced reproductive age

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Summary

Purpose: To evaluate the efficacy of sympathomimetic amine therapy on a mitochondrial abnormality known as the mitochondrial encephalopathy lactic acidosis and stroke-like symptoms syndrome (MELAS syndrome). *Materials and Methods:* Dextroamphetamine sulfate 15 mg extended release capsule was prescribed to a woman with a 25 year history of MELAS syndrome refractory to most other therapies. *Results:* Within one month of therapy the woman noticed considerable improvement in her chronic fatigue, pain, and edema. *Conclusions:* The MELAS syndrome is thus another condition to add to the list of various chronic refractory disorders that improve considerably after dextroamphetamine therapy. This is the first mitochondrial disorder shown to improve with sympathomimetic amines which could suggest that dextroamphetamine could prove useful in decreasing the risk of aneuploidy in women of advanced reproductive age.

Key words: Mitochondria; Chronic fatigue; Encephalopathy; Sympathetic hypofunction; Sympathomimetic amines.

Introduction

The syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a progressive neurodegenerative disorder that is most commonly the result of an A-to-G transition mutation at position 3243 of the mitochondrial genome [1]. It is a multisystem disorder first affecting tissues with high energy consumption, such as brain and skeletal muscle, but then proceeds to cause auditory, visual, psychiatric, renal, gastrointestinal, and dermatological symptoms as well [1-4]. MELAS remains one of the most common mitochondrial disorders, with an incidence as high as 12.48 per 100,000 in one study [4]. However, like all mitochondrial disorders, the concept of hertoplasmy – the presence of two or more different genomes within one cell – makes the disease prevalence and inheritance pattern difficult to appreciate [5, 6].

Since it was first reported by Pavlakis *et al.* in 1984 [7], an abundance of research has been dedicated to MELAS but no clear pathophysiologic mechanism has been linked to the implicated point mutations in the mitochondrial genome. One theory posits mitochondrial neuropathy as the underlying cause of migraines, seizures, and stroke-like symptoms [8]. Iizuka *et al.* report that, despite the name, stroke-like episodes are more likely non-ischemic events. They found that these episodes were characterized by increased capillary permeability, hyperperfusion, neuronal vulnerability, and neuronal hyperexcitability. In subsequent neuroimaging studies, they found that the initial change during acute stroke-like episodes appeared as a focal brain lesion along the cerebral cortex, up to half of which progressively spread to adjoining cortex of the brain beyond the major vascular territories with various degree of vasogenic edema [9]. It is possible that this edema secondary to increased capillary permeability is the direct cause of the characteristic neurologic findings in MELAS patients.

The sympathetic nervous system has been shown to diminish capillary and cellular permeability [10-13]. The importance of the mechanism is evident in idiopathic orthostatic cyclic edema, a state of sympathetic nervous system hypofunction that results in a failure to compensate for the increase in hydrostatic pressure in the orthostatic position. Several anecdotal reports and one controlled study have related idiopathic cyclic edema to decreased sympathetic response and cite sympathomimetic amine therapy as a quick, efficient treatment [14, 15]. Because MELAS and idiopathic orthostatic cyclic edema share the proposed etiology of increased neuronal capillary permeability, one

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would reason that sympathomimetic amine therapy would be effective for patients with MELAS as well as idiopathic orthostatic cyclic edema.

The current study demonstrates the efficacy of sympathomimetic amine therapy for treatment of migraines, seizures, stroke-like episodes, and fatigue associated with MELAS.

Materials and Methods

At the age of 27, shortly after the birth of her second child, this patient began to experience consistent throbbing headache associated with slurred speech, drooping eyelids, and muscle pain. She was admitted to the hospital more than 15 times in order to evaluate these symptoms. Based on her clinical picture of facial muscle weakness, she was diagnosed with myasthemia gravis.

That same year, the patient started to experience stroke-like episodes. Her legs became paralyzed for several days at a time and then spontaneously returned to full strength. She also developed seizures, and began topiramate therapy. She also began to experience narcolepsy, falling asleep in public places such as a restaurant and family gatherings.

Six years after the onset of symptoms, the patient was referred to a molecular medicine specialist. At that time, she was found to have variable lactate and pyruvate levels. Muscle biopsy showed diffuse mitochondrial proliferation. Skeletal muscle oxidative phosphorylation enzymology showed a decrease in the Complex I Assay (CoQ1) (31 nmol/minute/mg mitochondrial protein, normal values 93-325). This combination of this clinical syndrome, muscle biopsy, and enzyme assay led to the diagnosis of MELAS.

As of November 2010, the patient still experienced headaches, stroke-like illness, and extreme fatigue despite treatment with coenzyme Q-10, lidocaine injections, carnatine, and even ketamine therapy. She reported that ketamine therapy helped her extreme fatigue, headaches, and stroke-like symptoms for about four or five weeks after treatment. Directly after her ketamine therapy, she rated her pain as 5 out of 10 in severity; but reports that the pain slowly escalated over the next five weeks and returned to a baseline 10 out of 10.

The woman presented to the present authors at age 52, aware that the group treats chronic fatigue syndrome and was hoping to gain some relief from at least this aspect of her disorder. A trial of dextroamphetamine was started.

Results

The present patient reported improvement in her edema symptoms after the first month of treatment, during which she took 15 mg of dextroamphetamine per day. She also experienced decreased fatigue symptoms and reported decreased pain and increased quality of life. A month after initiating sympathetic amine therapy, she described moderate improvement in her subjective level of pain with no fluctuation.

Encouraged by the initial results, she agreed to increase her dose of dextroamphetamine to 30 mg per day. With the increase, she notes significant improvement still with no fluctuations.

Discussion

Sympathomimetic amines have been found to markedly improve symptoms of chronic neuromuscular disorders that were refractory to standard therapy. Some of these neuromuscular disorders include chronic fatigue which was one of the main debilitating problems of the subject of this case report [16]. Dextroamphetamine sulfate has proven very effective for migraine headaches that were recalcitrant to other therapies [17-19]. One case that was associated with weight gain and edema showed marked improvement in the migraine without improving the edema. This suggests that at least in some cases the headaches may be related to the absorption of chemicals and toxins into brain tissue rather than the edema per se. On the other hand, the present authors recently treated a woman with severe headaches and papilledema diagnosed with pseudotumor cerebri who did not respond to acetazolamide whose severe headaches not only completely disappeared following treatment with dextroamphetamine sulfate, but two months later fundoscopic evaluation showed no signs of papilledema.

The link between these disorders involving a multitude of organ systems seems to be a hypofunction of the sympathetic nervous system [13]. Some other local environmental, genetic or infectious factors may involve certain organ systems over the other. The MELAS syndrome may be another manifestation of this disorder of the sympathetic nervous system, all linked by their positive response to sympathomimetic amine therapy.

Similar to the disorders described above, it is not clear whether the prime reason for the symptoms of MELAS is capillary permeability in cerebral and neurological tissue or cellular permeability and absorption of chemicals and toxins into these tissues or both. Regardless, dextroamphetamine sulfate may prove to be the most effective therapy with the least side effects for MELAS.

Advanced reproductive age is associated with embryos that have a high frequency of aneuploidy related to meiosis I and meiosis II errors, leading to low pregnancy rates and high miscarriage rates [20]. Errors of nondisjunction of chromosomes during meiosis I and meiosis II may be related to mitochondrial errors related to aging of mitochondria, as polymerization of spindle microtubules appears dependant on ATP [21, 22]. With the considerable improvement of this serious mitochondrial disorder with the sympathomimetic amine dextroamphetamine sulfate gives food for thought as to whether this therapy could help reduce meiosis errors in women of advanced reproductive age and possibly improve fecundity and reduce miscarriage rates.

References

[1] Sproule D.M., Kaufmann P.: “Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome”. *Ann. N. Y. Acad. Sci.*, 2008, *1142*, 133.

[2] Santa K.M.: “Treatment options for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome”. *Pharmacotherapy*, 2010, *30*, 1179.

[3] Scaglia F., Northrop J.L.: "The mitochondrial myopathy encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome: a review of treatment options". *CNS Drugs*, 2006, *20*, 443.
[4] Testai F.D., Gorelick P.B.: "Inherited metabolic disorders and stroke part 1: Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes". *Arch. Neurol.*, 2010, *67*, 19.
[5] Schaefer A.M., Taylor R.W., Turnbull D.M., Chinnery P.F.: "The epidemiology of mitochondrial disorders—past, present and future". *Biochim. Biophys. Acta*, 2004, *1659*, 115.
[6] Tritschler H.J., Medori R.: "Mitochondrial DNA alterations as a source of human disorders". *Neurology*, 1993, *43*, 280.
[7] Pavlakis S.G., Phillips P.C., DiMauro S., De Vivo D.C., Rowland L.P.: "Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome". *Ann. Neurol.*, 1984, *16*, 481.
[8] Iizuka T., Sakai F., Suzuki N., Hata T., Tsukahara S., Fukuda M., Takiyama Y.: "Neuronal hyperexcitability in stroke-like episodes of MELAS syndrome". *Neurology*, 2002, *59*, 816.
[9] Iizuka T., Sakai F., Ide T., Miyakawa S., Sato M., Yoshii S.: "Regional cerebral blood flow and cerebrovascular reactivity during chronic stage of stroke-like episodes in MELAS — implication of neurovascular cellular mechanism". *J. Neurol. Sci.*, 2007, *257*, 126.
[10] Engel D.: "The influence of the sympathetic nervous system on capillary permeability". *J. Physiol.*, 1941, *99*, 161.
[11] Engel D.: "The influence of the sympathetic nervous system on capillary permeability in traumatic shock". J. Physiol., 1943, 102, 281.
[12] Check J.H., Katsoff D., Kaplan H., Liss J., Boimel P.: "A disorder of sympathomimetic amines leading to increased vascular permeability may be the etiologic factor in various treatment refractory health problems in women". *Med. Hypoth.*, 2008, *70*, 671.
[13] Check J.H., Cohen R., Katsoff B., Check D.: "Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with symapathomimetic amines". *Med. Hypoth.*, 2011, *77*, 717.
[14] Streeton D.H.P.: "Idiopathic edema: pathogenesis, clinical features and treatment". *Metabolism*, 1978, *27*, 353.
[15] Check J.H., Shanis B.S., Shapse D., Adelson H.G.: "A randomized comparison of the effect of two diuretics, a converting enzyme inhibitor, and a sympathomimetic amine on weight loss in diet refractory patients". Endoc. Pract., 1995, *1*, 323.
[16] Check J.H., Cohen R.: "Sympathetic neural hyperalgesia edema syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue". *Clin. Exp. Obst. Gyn.*, 2011, *38*, 412.
[17] Check J.H., Check D., Cohen R.: "Sympathetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women". *Clin. Exp. Obstet. Gynecol.*, 2009, *36*, 189.
[18] Check J.H., Cohen R., Check D.: "Evidence that migraine headaches in women may be related to a common defect in the sympathetic nervous system as evidenced by marked improvement following treatment with sympathomimetic amines". *Clin. Exp. Obst. Gyn.*, 2011, *38*, 180.
[19] Check J.H., Cohen R.: "Marked improvement of headaches and vasomotor symptoms with sympathomimetic amines in a woman with sympathetic hyperalgesia-edema syndrome". *Clin. Exp. Obst. Gyn.*, 2011, *38*, 88.
[20] Johnson J.A., Tough S.: "Delayed child bearing". *J. Obstet. Gynaecol. Can.*, 2012, *34*, 80.
[21] Van Blersom J., Daavis P., Alexander S.: "Differential mitochondrial distribution in human pronuclear embryos leads to disproportionate inheritance between blastomeres: relationship to microtubular organization, ATP content and competence". *Hum. Reprod.*, 2000, *15*, 2621.
[22] Check J.H., Cohen R.: "Evidence that oocyte quality in younger women with diminished oocyte reserve is superior to those of women of advanced reproductive age". *Med. Hypotheses*, 2010, *74*, 264.

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