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Phenotypic heterogeneity of the mitochondrial DNA A8344G variant presenting with dorsal midbrain syndrome

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ABSTRACT

Purpose: To describe a neuro-ophthalmic presentation of a phenotypically heterogeneous mitochondrial DNA variant.

Observations: A 10-year-old female with gross motor developmental delay, absence seizures and ataxia subacutely developed poor near acuity and asthenopia. She was found to have accommodative insufficiency, impaired supraduction and convergence retraction nystagmus leading to a diagnosis of dorsal midbrain syndrome. Brain MRI showed highly symmetrical lesions involving the dorsal pons. Genetic testing revealed a previously undiagnosed mitochondrial DNA (mtDNA) pathogenic variant, adenine to guanine at nucleopeptide pair 8344 (A8344G).

Conclusion and importance: The authors describe a unique, neuro-ophthalmic manifestation of mitochondrial disease in a pediatric patient. This report discusses the phenotypic heterogeneity of the mtDNA A8344G variant, which may include 'stroke-like episodes' involving the brainstem, thus presenting with ophthalmic manifestations.

1. Introduction

The mitochondrial deoxyribonucleic acid (mtDNA) adenine to guanine point mutation at nucleotide pair 8344 is commonly identified as the causative pathogenic variant in multisystem mitochondrial disorders. This variant is found in over 80% of patients with myoclonic epilepsy with ragged red fibers (MERRF) syndrome, which is characterized by myoclonus, ataxia, generalized seizures, and ragged red fibers on muscle biopsy.[1,2] Additional clinical findings associated with MERRF syndrome are wide-ranging and may include hypoacusis, optic atrophy, cutaneous lipomas, and cardiac arrhythmia.[3] Although the A8344G variant was previously thought to be specific to MERRF syndrome, current literature review shows phenotypic variability that extends well beyond what is traditionally seen in MERRF syndrome. Distinct mitochondrial disorders such as Leigh disease and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) have been linked to this pathogenic variant, as well as various clinical findings including ophthalmoplegia, spinocerebellar degeneration, and atypical Charcot-Marie-Tooth disease.[4,5] Acute neurological events affecting the brainstem are seldom reported in association with this variant. This case report describes a ten-year-old female carrying the A8344G variant who presented with dorsal midbrain syndrome as a manifestation of her mitochondrial disease.

2. Case report

A 10 year old female presented to the ophthalmology clinic with complaints of difficulty reading at near and "eye strain" for the past three days. Blurred vision at near was present both monocularly and binocularly. She denied any changes in distance vision, diplopia, or oscillopsia. Over the same time course, she was noticed to have increase difficulty with coordination and was falling frequently.

The patient had an extensive past medical history. As a toddler, she was diagnosed with gross motor developmental delay. Negative work up at that time included MRI head and brain, muscle enzymes, serum amino acids, lactic acid, uric acid, carnitine and vitamin E. High resolution karyotype was normal. In early childhood, the patient was diagnosed with absence seizures, supported by electroencephalogram spike-and-wave discharges at a frequency of 3 Hz. The seizures were well controlled with ethosuximide. Six weeks prior to onset of vision complaints, the patient had an episode of supraventricular tachycardia that was ultimately diagnosed as Wolff-Parkinson-White syndrome (WPW).

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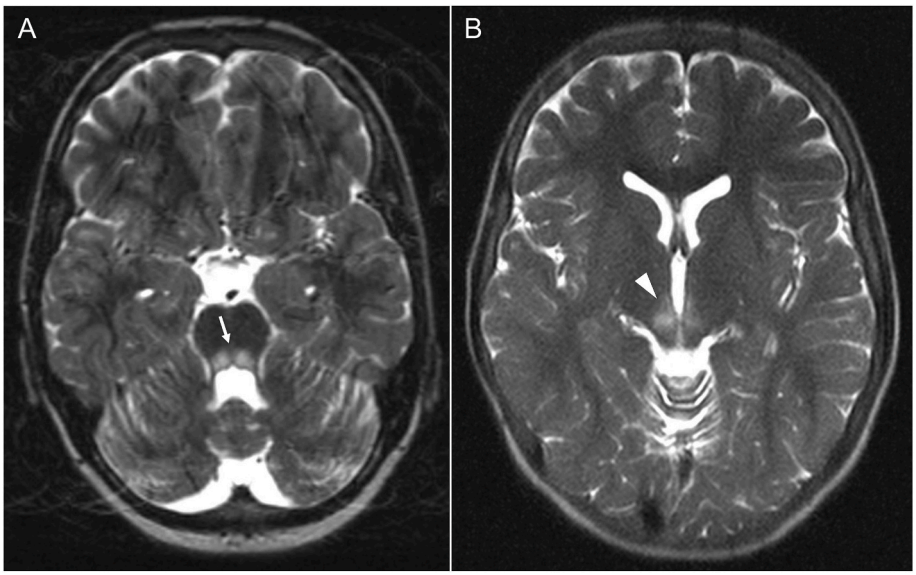

Fig. 1. MRI brain with intravenous contrast four days after symptom onset
A) Axial T2 sequence showing abnormal hypertense signal symmetrically involving the posterior midbrain, pons and B) the medial margin of the right and left thalami.

Despite investigations, no unifying diagnosis had been previously made which explained the patient's medical history.

On exam, distance visual acuity with correction was 20/30 in the right eye (OD) and 20/25 in the left eye (OS). Near visual acuity was 20/100 in both eyes and improved to 20/40 with a +3.00 diopter reading add. Poor accommodation was noted with dynamic retinoscopy. Ishihara color plates were 13/15 OD and 14/15 OS. Confrontation visual fields were full to finger counting. Pupils were mid dilated and sluggish to light without definitive light-near dissociation and without an afferent pupillary defect. Motility examination revealed a −3 elevation deficit in both eyes. Vertical saccades caused convergence retraction nystagmus. Slit lamp exam was unremarkable and dilated fundus exam revealed mild optic nerve pallor. Clinical presentation at this time was most consistent with dorsal midbrain syndrome.

Four days after symptom onset, MRI brain revealed increased T2 and fluid attenuated inversion recovery imaging (FLAIR) signal intensity in a highly symmetric distribution with diffusion restriction involving the periaqueductal gray, medial thalamus, tectum and dorsal midbrain and pons (Fig. 1). The highly symmetrical lesions on MRI were suggestive of a metabolic etiology, prompting an extensive laboratory work up. Laboratory testing that was within normal limits included thiamine, cobalamine, biotin, carnitine, pyruvic acid, urine acylglycines, urine organic acids, lactic acid, creatine phosphokinase, ammonia, and liver function tests. Testing of amino acid profiles revealed that four-hour postprandial alanine and glycine were elevated relative to other amino acids, suggestive of mitochondrial respiratory chain dysfunction. Further mitochondrial genetic testing using targeted variant analysis identified an adenine to guanine mtDNA variant in neuropeptide 8344. The subacute neurological change was thought to be a metabolic 'stroke-like episode,' which can be associated with mitochondrial disorders. The patient was started on a mitochondrial cocktail including coenzyme Q, vitamin E, vitamin C, lipoic acid, pantothenate, selenium and carnitor.[6]

Upon reevaluation two months later, the patient's distance visual acuity and color vision were stable. Accommodative insufficiency was still present, but near acuity was 20/20 in each eye with a +2.00 diopter add. Motility exam showed improvement in elevation in both eyes. There was no longer evidence of convergence retraction nystagmus. MRI brain was essentially unchanged. Accommodative insufficiency continued to slowly improve with time. By two years after her initial brainstem stroke, near acuity was 20/20 in each eye without a reading add. At this time, the MRI brain still showed increased signal intensity of the posterior midbrain and pons, however much less prominently. No new lesions developed over this time.

3. Discussion

Mitochondrial diseases are multisystem disorders that may display striking phenotypic variability, even when caused by the same genetic variant.[4,5] This case describes a 10-year-old female with non-specific motor delay and ataxia during early childhood who subacutely developed dorsal midbrain syndrome and worsening ataxia, ultimately leading to her diagnosis of mitochondrial disorder due to the A8344G pathogenic variant.

While this patient's clinical phenotype, which includes myoclonic seizures and WPW, is most consistent with MERRF syndrome, the episode of mitochondrial encephalopathy manifesting as dorsal midbrain syndrome is more typical of MELAS. This particular presentation may represent a separate entity that involves features of both syndromes and falls under the umbrella of "overlap syndromes." Reported cases describe young patients with the A8344G variant who present with metabolic-stroke-like episodes but phenotypically are otherwise consistent with MERRF syndrome.[7,8]

Of particular interest in this case is the initial, subjective complaint of difficulty reading and asthenopia. Careful ophthalmologic examination revealed accommodative insufficiency, impaired supraduction, and convergence retraction nystagmus, leading to a diagnosis of dorsal midbrain syndrome. Ophthalmic abnormalities most commonly reported in mitochondrial disorders include optic neuropathy, ophthalmoplegia with ptosis, pigmentary retinopathy, and retrochiasmal vision loss.[9] To our knowledge, dorsal midbrain syndrome has not been associated with the A8344G variant. In summary, this case describes a unique, neuro-ophthalmic presentation of a primary mitochondrial disorder existing on a spectrum of MELAS and MERRF syndrome.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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