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RESEARCH **CASE REPORT**

Case Report: Hemi Dystonia from A Mitochondrial Mutation in MT-ND6

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INTRODUCTION

Mitochondrial DNA mutations (mtDNA) can lead to varied clinical phenotypes. A mutation in the MT-ND6 (m.14459 G>A p.A72V) has previously been reported in patients with various phenotypes even within same family members. We report a family that demonstrates this phenomenon, and we provide details of 2 siblings from this family that have distinct unilateral symptoms and imaging findings.

CASE

A 10-year-old girl presented to our clinic for evaluation of progressive gait abnormality. Following an uneventful perinatal course, she achieved developmental milestones without delays. Around the age of 6 years, she started noticing a difficulty in using her left hand, and had difficulty walking due to tightness of her left leg. No diurnal variation of her symptoms was noted. Her symptoms continued to progress despite physical therapy. She had no other neurological symptoms, and no other chronic medical conditions. Physical exam showed increased tone and dystonic posture of the left arm and leg, hypertrophy of the left biceps, and an abnormal asymmetrical gait (see video, part 1). Her 18-year-old brother had similar left sided symptoms starting at the age of 5 years (see video, part 2). Her maternal cousin had generalized dystonia, cognitive impairment, and developmental delay. There is an extensive family history of neurological disorders on the mother's side, including various combinations of impaired vision, cognitive abnormalities, and abnormal gait (see Figure 1).

Brain MRIs of the patient and of her brother showed unilateral abnormalities of the basal ganglia (figure 2). Brain MRI of the affected cousin showed bilateral basal ganglia abnormalities. Genetic testing showed a homoplasmic pathogenic mutation in the MT-ND6 (m.14459 G>A p.A72V) that was maternally inherited. This leads to deficiency in the Respiratory Chain Complex I. Functional analysis and In-silico analysis demonstrated a deleterious effect, and it has been classified as a pathogenic mutation. Her brother and affected cousin carried the same mutation, and we believe this variant is likely the cause of symptoms in other family members.

Figure 1. Family pedigree showing multiple family members on the maternal side with various combinations of symptoms. (*) Denotes individuals with unilateral symptoms.

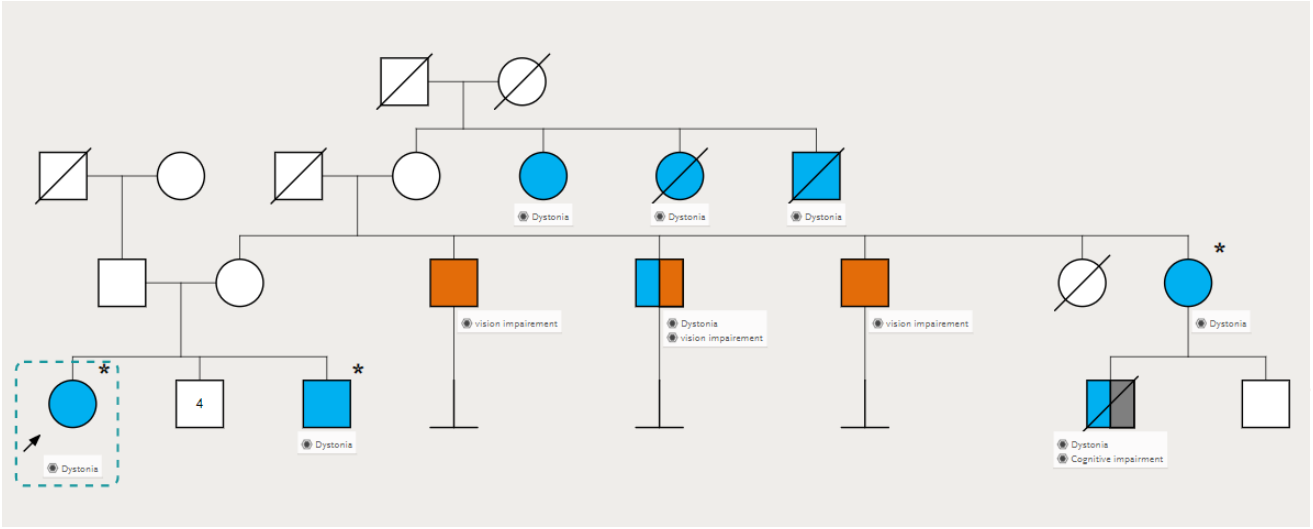
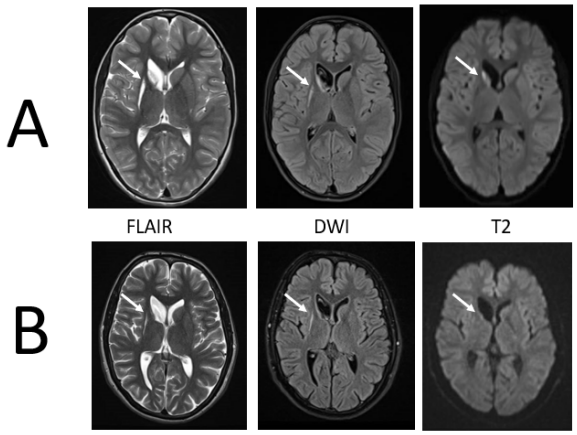


Figure 2. (A) Brain MRI of patient showing abnormal T2/FLAIR signal in right caudate and putamen, restricted diffusion in right caudate. (B) Brain MRI of patient's brother showing marked atrophy of right caudate, putamen and globus pallidus, and with no associated diffusion restriction.



DISCUSSION

Heteroplasmy is a condition where two or more different variants of mtDNA (both normal and mutated) can exist in the same cell. Clinical symptoms usually appear when a significant proportion of mtDNA is mutated. The uneven distribution of mutant mtDNA in different tissues can lead to abnormalities in different organs.

A mutation in the MT-ND6 (m.14459 G>A p.A72V) has previously been reported in patients with various phenotypes including Leigh or Leigh-like syndrome, pure dystonia, spasticity, pure Leber Hereditary Optic Neuropathy (LHON), (LHON) plus dystonia, or clinically asymptomatic cases [1-5]. Unilateral and bilateral symptoms have been described [2]. These wide variations in clinical phenotypes have been reported even within same family members [2,5].

Jun et al. (1994) identified the variant m.14459G>A in heteroplasmy in a family with LHON and dystonia [1]. Kirby et al. (2000) identified the mutation in 3 patients with Leigh syndrome in whom there was no evidence of LHON or dystonia [4]. Shoffner et al. (1995) identified the mutation in a mother and daughter with isolated LHON (the daughter also had unilateral basal ganglia lesions on MRI) [2]. Gropman and colleagues (2004) identified the mutation in a family with a broad spectrum of clinical manifestations. The proband presented with anarthria, dystonia, spasticity, and mild encephalopathy; other family members with the mutation were asymptomatic and others were symptomatic with varying clinical and laboratory characteristics [5].

CONCLUSION

A mutation in the MT-ND6 (m.14459 G>A p.A72V) is notorious for variable clinical expressions. This includes various combinations of LHON, spasticity, dystonia, Leigh's syndrome, as well as asymptomatic cases. Any of these manifestations can occur even within the same family members. This can result in a variety of symptoms between family members and limits the value of genetic testing in other relatives.

AUTHORS' CONTRIBUTIONS

(1) A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

AA: 1A, 1B, 1C, 2B
AU: 1C, 2A

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ETHICAL COMPLIANCE STATEMENT

The institution's IRB committee approved this article. Written informed consent was obtained per institution guidelines for videotaping the subjects and publishing their videos and history. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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