Pearls & Oy-sters: Maternally inherited diabetes and deafness presenting with ptosis and macular pattern dystrophy

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PEARLS

- Ptosis can occur with a variety of mitochondrial syndromes, not just chronic progressive external ophthalmoplegia.
- Macular pattern dystrophy is highly characteristic of maternally inherited diabetes and deafness (MIDD), and funduscopy should be performed on all subjects with personal or family history of diabetes and deafness.

OY-STER

- Only 15% of patients with MIDD have diabetes at diagnosis, and diabetes may start at ages ranging from the teens to the fifth decade.

Mitochondrial disorders can cause an array of neuro-ophthalmologic manifestations such as ptosis, external ophthalmoparesis, nystagmus, pigmentary retinopathy, and optic neuropathy.¹ The m.3243A>G point mutation in the mitochondrial genome, an alanine-to-guanine transition at position 3243 of mitochondrial DNA, in the MT-TL1 gene that encodes the tRNA^{Leu} (UUR), commonly presents as an encephalopathy accompanied by lactic acidosis and stroke-like episodes (MELAS). Many mutation carriers, however, have a wide range of neurologic, cardiac, endocrine, gastrointestinal, and psychiatric symptoms, as well as other mitochondrial syndromes.² Another syndrome also associated with this mutation is maternally inherited diabetes and deafness (MIDD).³ Ptosis and ophthalmoparesis are not generally seen in MIDD,⁴ with only 1 report of 2 patients with ptosis in this condition.⁵ We present another patient with ptosis associated with MIDD and the m.3243A>G mutation, in whom the key diagnostic feature was the macular pattern dystrophy typical of MIDD.

CASE REPORT A 54-year-old woman had right ptosis since her early teens (figure). This was stable for decades but began to worsen at age 40. Surgical correction was attempted twice but ptosis recurred.

She had had hearing loss since her early 20s. An optometrist had noted asymptomatic retinal lesions about 10 years prior, without progression on subsequent visits; a retina specialist considered a diagnosis of early age-related macular degeneration. She did not have cardiac disease or diabetes. Her mother and a younger brother had early-onset deafness and the brother had diabetes.

Her visual acuity was 20/20 in both eyes; color vision and peripheral visual fields were normal. Funduscopy showed an unusual macular dystrophy, with a perimacular ring of retinal atrophy in both eyes. She had a mild ptosis in the right eye with poor lid closure of both eyes. Eye movements were normal. Audiology confirmed moderate sensorineural hearing loss. The rest of her neurologic examination was normal.

Single fiber EMG of the frontalis muscle, EKG, and echocardiogram were normal. Muscle biopsy of the left vastus lateralis muscle revealed only subtle mitochondrial changes, with 1 ragged red fiber. Genetic analysis was positive for 3243 MELAS mtDNA mutation, with 40% heteroplasmy. Investigations by an endocrinologist have so far revealed only an elevated hemoglobin A1c on 1 occasion.

DISCUSSION Among mitochondrial disorders, ptosis is most notably a feature of chronic progressive external ophthalmoplegia (CPEO). However, it can occur with other mitochondrial syndromes also. In a cohort of 153 subjects with the m.3243A>G mutation, ptosis was found in 36 of 45 patients with MELAS, and in 10 asymptomatic carriers.¹ Pigmentary retinopathy and CPEO are the classic neuro-ophthalmologic features of Kearns-Sayre syndrome, but some patients with MIDD can also have similar pigmentary changes.² However, our patient had a more severe and unusual macular pattern dystrophy,^{2,6} sometimes called a “peri-macular annular retinal atrophy”⁷ that is characteristic of many patients with MIDD.^{3,4,8} Overall, about 85% of patients with

(A) Right ptosis. (B) Bilateral orbicularis weakness. (C) Macular pattern dystrophy, right fundus. (D) Macular pattern dystrophy, left fundus. Note the characteristic ring of punched-out pale atrophic lesions surrounding the macula.

MIDD have macular abnormalities.³ Fortunately, visual symptoms are rare, consisting of decreased central vision, poor night vision, or photophobia, and only a minority show a decline in visual acuity with time.^{2,7} Although our patient did not have diabetes, this is true of about 15% of patients with MIDD, in whom diabetes may start at ages ranging from the teens to the fifth decade.^{3,4} Asymmetric ptosis with mild reduction of upgaze has only recently been described in 2 patients with MIDD.⁵ As yet, there is no definitive treatment for MIDD: 1 study of 28 patients reported that 3 years of coenzymeQ10 improved insulin secretion and slowed hearing loss, but had no discernible effect on the retinopathy.⁹ Slow progression of annular visual scotomata is said to be the rule, with patients generally asymptomatic before the age of 50, and reductions in visual acuity rare.^{2,7} There is some evidence that the progression of hearing loss may depend upon the degree of heteroplasmy of the mutation.¹⁰ Family members should be followed for the development of hearing loss, diabetes, renal problems, or cardiomyopathy.³ With the m.3243A>G mutation, Wolff-Parkinson White syndrome, stroke-like episodes, migraine headaches, and seizures may also occur. Genetic counseling is advisable.

There were 3 key features in this case. The first 2 were the personal history of deafness, and the family history of deafness and diabetes, which strongly raise suspicion of a mitochondrial disorder underlying the progressive ptosis. The third and most specific feature was the macular pattern dystrophy, which pointed directly to the diagnosis of MIDD and an m.3243A>G point mutation. Macula pattern dystrophy is not a well-known entity, though its appearance is highly characteristic and it is easily visible on funduscopy. Awareness of its appearance and significance, coupled with careful review of the macula in patients with a personal or family history of deafness, diabetes, or ptosis, will lead to the diagnosis of this condition.

AUTHOR CONTRIBUTIONS

O. Ogun saw the patient, prepared the case report, and wrote the first draft. C. Sheldon saw the patient, collected data, and edited the draft. J. Barton saw the patient, obtained images, and made final revision.

DISCLOSURE

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