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Short communication

Two sisters with macular dystrophy caused by the 3243A>G mitochondrial DNA mutation☆,☆☆

V. Sánchez-Gutiérrez, J. García-Montesinos, A. Pardo-Muñoz*

Departamento de Oftalmología, Hospital Universitario Ramón y Cajal, Madrid, Spain

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ABSTRACT

Case report: Two sisters, 54 and 60 years old, with a history of diabetes and deafness, consulted for decreased visual acuity (VA). Funduscopic examination revealed patchy areas of chorioretinal atrophy with annular arrangement around the fovea. Genetic study identified the heteroplasmic mutation 3243A>G in mitochondrial DNA, which supports the syndrome maternally inherited diabetes and deafness (MIDD) or Ballinger-Wallace disease.
Discussion: The finding of such macular disorders, especially in the presence of diabetes mellitus and deafness, should suggest the performing of a mitochondrial genome screening to identify this unusual syndrome.

Dos hermanas con distrofia macular causada por la mutación 3243A>G del ADN mitocondrial

Palabras clave:
Distrofia macular
Diabetes
Sordera
ADN mitocondrial
Enfermedad mitocondrial
Síndrome de Ballinger-Wallace

RESUMEN

Caso clínico: Dos hermanas de 54 y 60 años, con antecedentes de diabetes y sordera, consultaron por disminución de la agudeza visual (AV). En la funduscopia se observaban áreas parcheadas de atrofia coriorretiniana con disposición anular alrededor de la fóvea. El estudio genético identificó la mutación heteroplásmica 3243A>G en el ADN mitocondrial, compatible con el síndrome *Maternally Inherited Diabetes and Deafness* (MIDD) o enfermedad de Ballinger-Wallace.
Discusión: El hallazgo de tales alteraciones maculares características, especialmente si se acompaña de diabetes mellitus y sordera, nos debe indicar la realización de un cribado del genoma mitocondrial para identificar este inusual síndrome.

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* *Corresponding author.*
E-mail address: verosangu@gmail.com (V. Sánchez-Gutiérrez).

Introduction

Mitochondrial inheritance diseases include the maternal inheritance diabetes and deafness syndrome (MIDD) or Ballinger-Wallace disease, caused by the mutation of the mitochondrial DNA at the 3243A>G position. This mutation can give rise to a broad range of clinical expressions, including macular dystrophy.

Clinic case report

Two sisters, 54 and 60 years old, visited the hospital to discard a diabetic retinopathy after referring for diminished visual acuity (VA). They exhibited diabetes mellitus with over 10 years evolution and both had also been diagnosed with neurosensory deafness. Family history included their mother and one aunt diagnosed with diabetes mellitus and bilateral neurosensory deafness, without genetic assessment.

The youngest sister, 54 years, exhibited VA of 0.6 in the right eye and 0.9 in the left eye. Ocular fundus exploration reveals the presence of large retina pigment epithelium (RPE) atrophy areas in the posterior pole, similar in both eyes. These areas exhibited patch hypoautofluorescence, mainly in the posterior pole and the peripapillary area (Fig. 1). A multifocal electroretinogram (MF ERG) exhibited alterations with amplitude reduction in the central and perifoveal areas (Fig. 2). Family history and the associated disease of the patient prompted the request for a genetic assessment which identified the presence of 3243A>G heteroplasmic mutation in the *tRNALeu* (UUR) gene of mitochondrial DNA, compatible with the MIDD syndrome. The apparent heteroplasmic mutation was of 71–79%, quantified by means of PCR-RLFP direct sequencing with micro-fluid separation in the BioAnalyzer Agilent device.

The second sister, 60 years, exhibited a VA of 0.5 in the right eye and 0.8 in the left eye. The ophthalmological assessment produced findings similar to those of her sister. The ocular fundus exhibited large patch areas of RPE atrophy arranged as a ring around the fovea. As with the sister, said areas exhibited hypoautofluorescence and showed hyperfluorescent dots surrounding the periphery of the atrophy areas (Fig. 3). MF ERG revealed sensitivity reductions matching the ocular fundus findings (Fig. 4). Genetic analysis also showed the presence of a 3243A>G mutation in the mitochondrial DNA, with an apparent mutant heteroplasmy level of 17–25%.

During the 3-year follow-up, VA remained stable in both patients with very similar ocular fundus and autofluorescence appearance found during checkups. To date, none of the 2 sisters have developed diabetic retinopathy signs.

Discussion

The presence of maternal inheritance diabetes and neurosensory deafness, to which macular dystrophy is frequently associated, constitutes the MIDD syndrome, generally produced by a 3243A>G mutation in mitochondrial DNA.[1] This mutation can also give rise to different clinical phenotypes such as the mitochondrial encephalomyopathy syndrome with lactic acidosis and episodes of cerebrovascular accidents (MELAS).[2]

The MIDD syndrome accounts for approximately 1.5% of all diabetes cases.[1,3] The first expressions can appear at any age although the disease is generally diagnosed in young adults.[3] In the majority of cases, said patients exhibit diabetes

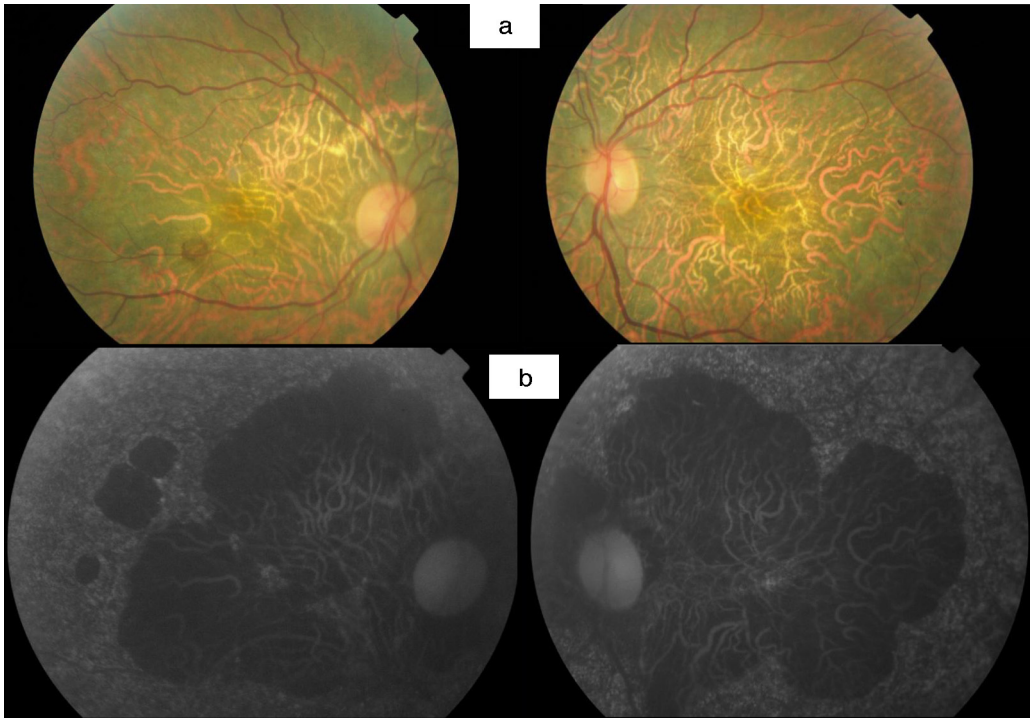

Fig. 1 – Funduscopic findings and autofluorescence of the first sister. (a) Large chorioretinal atrophy area in the posterior pole of both eyes. (b) Confluent hypoautofluorescence patches in the posterior pole.