Ophthalmological and electrophysiological findings in monozygotic twin sisters with phosphomannomutase 2 deficiency (PMM2-CDG) over a period of 37 years

Abstract

**Aims:** To describe the evolution of ophthalmological and electrophysiological findings in monozygotic twin sisters with phosphomannomutase 2 deficiency (PMM2-CDG).

**Methods:** A clinical ophthalmological examination with visual acuity measurement, fundoscopy and flash electroretinogram (fERG) was performed at the age of 4, 18 and 41 years.

**Results:** Ophthalmic examination in both girls at the age of 4 years showed an alternating convergent squint and a saccadic pursuit, with visual acuity of 6/9 in both eyes (Ffooks symbols test). Fundoscopy revealed a normal aspect of the optic discs, narrowed blood vessels and a mild irregular pigmentation in the peripheral retina. Flash ERG in one girl showed a recognisable a, b1 and b2 wave, but with a reduction of the amplitude to less than 40% of the normal amplitude. In the other twin girl, the amplitude was more reduced, but a small b1 wave for the white flash was still noticeable. At the age of 18 years, vision had remained stable. Fundus examination revealed a pink aspect of the optic discs, with moderately narrowing of the vasculature and bone spicules in the mid peripheral retina. fERG showed obvious progression with a completely extinguished trace bilaterally. At the age of 41 years, vision had slightly diminished to 6/12 in both women. Fundoscopy and electroretinogram did not show any changes.

**Conclusions:** Despite obvious deterioration of the fERG between the age of 4 and 18 years, the central vision showed only a minor decrease between the age of 18 and 41 years with still a good functional visual acuity.
Introduction

Congenital disorders of glycosylation (CDG) encompass a group of genetic, mostly multisystem disorders with involvement of the nervous system and the eyes caused by a defective glycoprotein and glycolipid glycan synthesis and attachment. The large majority has an autosomal recessive inheritance. Some 130 different CDG cases have been reported since the first clinical description of phosphomannomutase deficiency (PMM2-CDG) in 1980 by Jaak Jaeken [1], [2], [3]. PMM2-CDG is by far the most frequent protein N-glycosylation disorder. A recent review on ophthalmological findings in protein N-glycosylation disorders has been published by Morava et al. [4], and on protein O-glycosylation disorders by Francisco et al. [5]. Characteristic ophthalmic findings of PMM2-CDG are convergent strabismus and retinitis pigmentosa with abnormal electroretinography and visual evoked potential findings [3], [4], [6], [7], [8], [9], [10], [11], [12], [13]. We report the ophthalmic findings and evolution over a period of 37 years – both ocular and electrophysiological – in monozygotic twin sisters with PMM2-CDG, in follow-up of a 1996 report by Casteels et al. [14].

Case description

The pricnceps patients (monozygotic twin girls) with an intermediate form of PMM2-CDG (compound heterozygous with mutations C.338C>T (p.P113L) and C.422G>A (p.R141H)) presented to the ophthalmic department at the age of 4 years [15]. Clinical examination of the eye movements showed an alternating convergent squint and a saccadic pursuit. Vision in both eyes was 6/9 (logMAR 0.22) measured with the Ffooks symbols test; there was no refractive error on retinoscopy. In both subjects, fundoscopy revealed a normal aspect of the optic discs, with no refractive error on retinoscopy. In both subjects, fundoscopy revealed a normal aspect of the optic discs, with

Discussion

Characteristic ophthalmic findings in PMM2-CDG include convergent squint and retinal dystrophy with abnormalities on electroretinography. The majority of patients also show visual field loss with consequently progressive loss of vision. Other reported ocular manifestations include progressive myopia, hyperopia, cataract, nystagmos, delayed visual maturation and abnormal eye movements [4], [6], [18], [19]. The importance of CDG as a metabolic cause of retinal dystrophy with bony spicule pigmentary deposits has been reported by Fiumara et al. According to these authors, CDG should be considered in cases with early onset of strabismus followed by unexplained
Figure 1: Electroretinographic findings in twin sisters (patient 1 and patient 2) with PMM2-CDG at the age of 4 years (A), 18 years (B) and 41 years (C).

A: 1980: Adapto ERG revealed decreased amplitudes, more obvious for patient 2.

B: 1995: On adapto ERG, responses were entirely extinguished bilaterally. This exam was now completed with an ERG using the ISCEV standard; no recordable dark adapted or light adapted response was observed.

C: 2018: ERG revealed unchanged findings.
Figure 2: Fundus appearance in twin sisters with PMM2-CDG at the age of 18 and 41 years.

(A,B) At the age of 18 years, a pink aspect of the optic discs and a moderate narrowing of the vasculature could be seen in addition to bony spicule pigmentary deposits in the mid peripheral retina, both in patient 1 (A) and patient 2 (B). In patient 1, a wrinkling of the macular retinal surface was noticed (A).

(C,D) At the age of 41 years, findings of fundoscopy had remained the same for patient 1 (C) and patient 2 (D).

Figure 3: OCT examination in twin sisters with PPM2-CDG at the age of 41

For patient 1 (A) and patient 2 (B), severe attenuation of the outer retina starting from the perimacular area is shown. In the central macular area, the normal outer retinal structure was preserved. Drusenoid like changes can also be observed, more obvious in the second patient.
The findings on OCT, namely preservation of normal outer retinal structure in the central macular area, are consistent with the study of Messenger et al. and could explain the maintenance of central vision in both patients [19]. In a study of Thompson et al., pattern VEP showed functional preservation of the macular pathways to the recipient layer 4 of the striate cortex. They propose that this finding could be the reason why most patients keep a functional vision [11]. These findings are congruent with previous reports that the retinal dysfunction spares the central part of the retina that is responsible for visual acuity [20].

In conclusion, this report is a follow-up report to the publication by Casteels et al. in 1996 describing the evolution of visual function and electrophysiological findings in twin sisters with PMM2-CDG over a period of 37 years [14]. Despite obvious deterioration of the retinal function on flash ERG between the age of 4 years and 18 years, the central vision showed only a mild deterioration between the age of 18 years and 41 years with continuing good functional visual acuity. To our knowledge, this report describes the longest ophthalmological follow-up of patients with PMM2-CDG.

Notes

Competing interests

The authors declare that they have no competing interests.

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Please cite as
Van Hees I, Jaeken J, Meersseman W, Casteels I. Ophthalmological and electrophysiological findings in monozygotic twin sisters with phosphomannomutase 2 deficiency (PMM2-CDG) over a period of 37 years. GMS Ophthalmol Cases. 2019;9:Doc37.

DOI: 10.3205/oc000126, URN: urn:nbn:de:0183-oc0001266

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Published: 2019-11-20

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