## Pendular nystagmus, palatal tremor and progressive ataxia in GM2-gangliosidosis

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Progressive ataxia and palatal tremor (PAPT) is a neurodegenerative disorder described in both sporadic and familial cases [1,2]. Nystagmus is commonly associated. So far, only two genetic disorders (Alexander's disease and SCA20) are recognized causes of familial PAPT, whilst most cases remain undiagnosed [1–3].

We report a 71-year-old man with adult-onset GM2-gangliosidosis type II (GM2-II, Sandhoff disease) who developed ocular pendular nystagmus and palatal tremor (OPT) besides progressive cerebellar ataxia, extrapyramidal signs and mild cognitive impairment.

GM2-II results from *HEXB* mutations causing deficiency of β-hexosaminidase A and B, clinically indistinguishable from the more frequent Tay–Sachs disease (GM2-gangliosidosis type I) where *HEXA* mutations lead to sole β-hexosaminidase A deficiency [4]. GM2-ganglioside accumulates in neuronal as well as non-neuronal tissues causing a heterogeneous neuro-degeneration. Late-onset GM2-gangliosidosis progresses more slowly and more mildly than infantile GM2-gangliosidosis with rare occurrence of retinal cherry-red spot and startle myoclonus, and with extrapyramidal and cerebellar dysfunction, upper and lower motor neuron impairment and neuro-psychiatric manifestations as the most prevalent symptoms [4]. Diagnosis may be difficult.

Our patient belongs to a family of seven siblings, three of them affected by GM2-II and whose history and clinical features have been reported elsewhere [5]. In addition to his syndromic symptoms, the patient complained of gradually worsening oscillopsia and dysarthria. His recent history was negative for traumas, infections, inflammations or drugs associated with OPT [1,2]. Furthermore, clinical examination revealed a small amplitude vertical pendular nystagmus, masked by frequent blinking. Rhythmic palatal tremor was associated with tremor of the chin and branchial-derived muscles (Video S1). Surprisingly, despite a long history of progressive cerebellar impairment leading to clinically evident gait ataxia, dysmetria and blurred speech, brain magnetic resonance imaging (MRI) performed 14 years before (Fig. 1Aa), some weeks after, and several months after (Fig. 1Ab–e) did not show cerebellar or pontine atrophy and ruled out lesions in the Guillain–Mollaret triangle as well as inferior olivary (pseudo) hypertrophy. Long echo time MR spectroscopy showed low NAA/Cr and Cho/Cr ratios in both pons and cerebellar white matter. Therapy with clonazepam reduced the ocular tremor remarkably so that, after some weeks, it was possible to record the patient's saccades. Horizontal saccades were hypometric with respect to healthy controls (Fig. 1B). The target was often reached through multistep saccades, suggesting a fastigial disinhibition as already hypothesized for hypometric saccades in late-onset Tay–Sachs disease [6]. Vertical saccades were hypometric and slow, indicating moderate supranuclear vertical gaze palsy.

This report extends to GM2-II the spectrum of inherited syndromes associated with PAPT. Notably, MRI was negative for lesions commonly associated with monophasic OPT [1,2,7], indicating GM2-II as the most likely cause of OPT. Interestingly, investigation for GM2-gangliosidosis in undiagnosed PAPT is also suggested by the finding of typical features of late-onset GM2-II in several cases of idiopathic PAPT. Indeed, optic atrophy without the macular cherry-red spot, pyramidal and extrapyramidal signs, autonomic failure and psychiatric disturbances characterize typical GM2-gangliosidosis, particularly its late-onset variant, but they have often been reported also in sporadic and familial undiagnosed cases of PAPT [1,3,4]. The patient provided written informed consent.

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### Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

### Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Video S1.** Oculopalatal tremor, hand resting tremor and cerebellar signs. Small-amplitude vertical pendular nystagmus masked by frequent blinking, rhythmic tremor of the palate and branchial-derived muscles, cerebellar and extrapyramidal signs.