Eye movement changes in a patient with Zellweger Spectrum Disorder caused by PEX2 gene mutation

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Objective

The Zellweger spectrum disorders (ZSDs) are characterized by an onset in the newborn period or later in childhood, frequently resulting in death during childhood or adolescence, but milder phenotypes are reported. Transmission is autosomal recessive and mutations in any of at least 12 PEX genes is thought to be responsible for ZSDs, which are represented by a continuum of three phenotypes including Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Eye movements characteristics of ZSDs are very poorly investigated. Here we report on eye movements abnormalities in a patients with ZSD caused by PEX2 mutation and mild phenotype.

Materials and Methods

We examined a 56-years-old man, already diagnosed as having a ZSD caused by two heterozigous mutations of the PXMP3 (PEX2) gene (c.355C>T (p.Arg119X) and c.865_866insA (p.Ser289-LysfsX36), with onset at 3 years, mild phenotype and slow progression. Clinical and biochemical aspects of the patient have previously been described [1]. The oculomotor tasks were recorded with eye-tracking technique [2]. Standard saccadic parameters of horizontal and vertical visually-guided saccade and antisaccades, rate of antisaccade errors with relative corrections and fixation abnormalities were carried out.

Results

Clinical examination disclosed gait ataxia, lateral and vertical gaze-evoked nystagmus, hypoacusia, mild dysarthria, slight dysmetria, generalized areflexia, and bilateral pes cavus; brain MRI revealed marked atrophy of cerebellum, cerebellar peduncles and brainstem, particularly of pons, and moderate atrophy of the supratentorial regions of the brain [1]. Visually-guided saccades examination showed increase of saccade latency; saccades were much hypometric and slower than controls, particularly in the horizontal plane. The antisaccade error rate was 100 % with correction rate of 33%. A bilateral gaze-evoked and rebound nystagmus with frequency of 1 Hz was detected; sporadic square wave jerks saccadic intrusions were also evident.

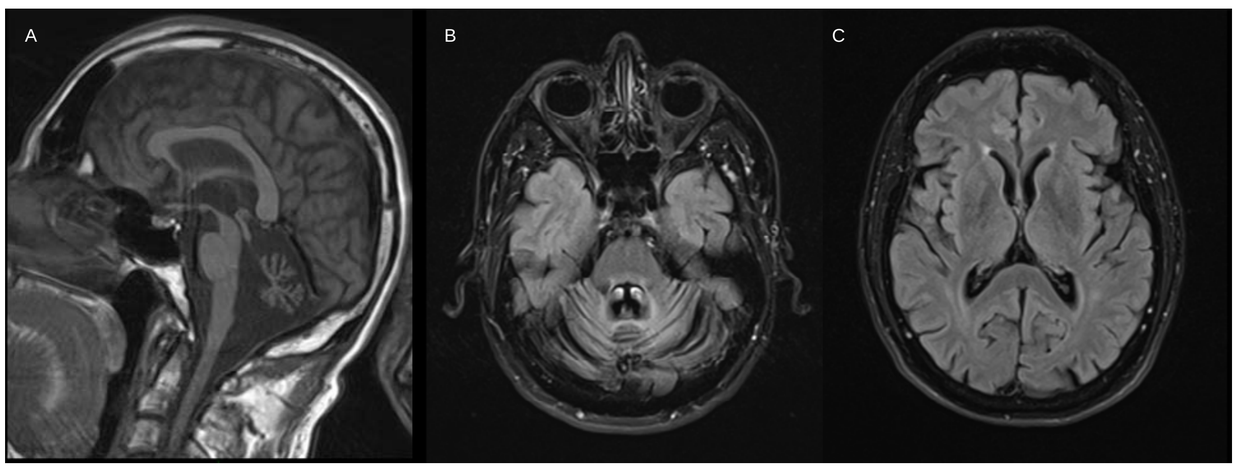

Fig2. Sagittal T1-weighted (A), axial FLAIR (B-C) images showing important subcortical atrophy of braistem and cerebellar structures (A-B) and mild supratentorial atrophy (C). Absence of white matter signal abnormalities.

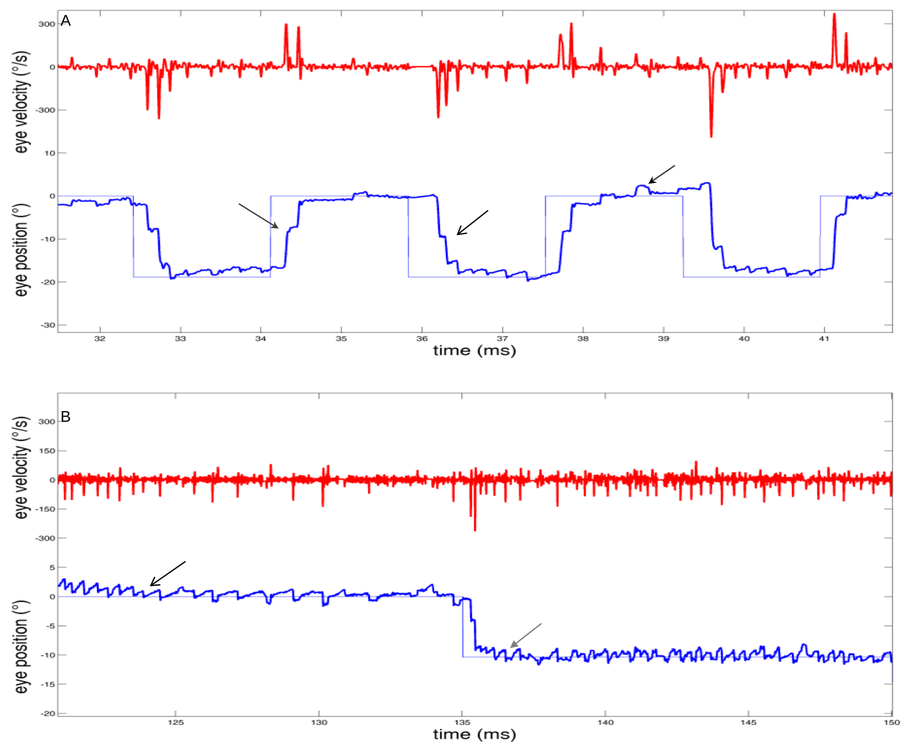

Fig 1 A. Saccade recording. Rightward gaze displacement (18°) and central eye position (0°) are shown. Saccades are hypometric and followed by a corrective saccade both toward eccentric and central position (black and grey arrow). Sporadic square wave jerks intrusions are shown (small black arrow). Fig.1 B. Fixation task recording. Gaze-evoked nystagmus (grey arrow) and rebound nystagmus (black arrow) with a frequency of 1 Hz are shown.

Table1. Saccadic parameters of patient vs controls.

Saccadic values	Latency (ms)	Peak Vel (°/s)	Duration (ms)	Amplitude (°)	Gain
Patient	10° (221±46) 18° (228±71) 8° (237,5±49)	10°: (262±52) 18°: (348±82) 8°: (157±47)	10° (40±6,7) 18° (51,5±13) 8° (43±6,3)	10° (5,7±0,9) 18° (8,8±2,6) 8° (4,2±0,5)	10° (0,5±0,08) 18° (0,5±0,1) 8°(0,5±0,06)
Controls	10° (178±21) 18° (189±44) 8° (199±17)	10° (388±60) 18° (507±78) 8° (289±42)	10° (48±9,2) 18° (65±10) 8° (51±8)	10° (10,3±1) 18° (18±1) 8° (8±0,8)	10° (1±0,1) 18° (0,9±0,07) 8° (1±0,15)

Discussion

The eye movements abnormalities showed by our patient are expression of the diffuse subtentorial atrophy, as revealed by brain MRI; particularly, saccadic dysmetria and slowing of ocular movements are typical of abnormalities in the cerebellum-brainstem circuits, as well as the presence of GEN and rebound nystagmus, indicating an abnormal functioning of gaze-holding structures. However, the presence of increased latency and the very high rate of antisaccade errors, with low spontaneous corrections, likely indicate an involvement of frontal and prefrontal cortex regions. Our findings testify the presence of oculomotor abnormalities in a ZSD patient with mild phenotype. Saccadic evaluation represents a non-invasive tool that could be of help in the diagnosis and follow-up of Peroxisomal disorders.

References:

1) **Mignarri A, Vinciguerra C, Giorgio A, et al. Zellweger Spectrum Disorder with mild phenotype caused by PEX2 gene mutations. JIMD Rep. 2012;6:43-6.**
2) **Rosini F, Federighi P, Pretegiani E, et al. Ocular-motor profile and effects of memantine in a familiar form of adult cerebellar ataxia with slow saccades and square wave saccadic intrusions. PLoS One 2013;8(7):e69522.**