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Misdirected horizontal saccades in pan-cerebellar atrophy

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ABSTRACT

Saccadic dysmetria is a sensitive marker of cerebellar dysfunction. We discovered misdirected horizontal saccades due to cross-coupled orthogonal (vertical) saccades in siblings with pan-cerebellar atrophy. There was an upward drift in vertical eye position after each cross-coupled downward saccade. Such drifts brought the eyes back to the desired target. Due to strong upward bias, downward compensatory slow movements did not follow cross-coupled upward saccades. There was minimal horizontal cross-coupling associated with vertical saccades. There was a reduced gain of horizontal pursuit causing lag in the horizontal eye movement and subsequent catch-up horizontal saccades. The horizontal catch-up saccades were also associated with vertical cross-coupled eye movements and subsequent drifts. There was no cross-coupling of pursuit eye movements. Our results support the hypothesis emphasizing adaptive cerebellar control of saccade direction. Commands for horizontal saccades trigger not only the activity of the horizontal burst generators, but also the vertical burst neurons. The activity of orthogonal (vertical) burst neurons is canceled by opposing signals under cerebellar supervision. Cerebellar lesions could disrupt such balance between opposing orthogonal signals leading to vertical cross-coupling during horizontal saccade. We speculate that upward drift might result from an imbalance in opposing orthogonal signals at the level of neural integrators.

1. Introduction

Saccadic eye movements rapidly shift gaze to the target of interest. The information required to generate such visually guided saccades is presented in a spatial map. Superior colliculus neurons convert such spatially distributed signal into temporally modulated activity of the motor system [1]. The motor commands from the superior colliculus are then projected to the saccadic burst generator in the brainstem reticular formation. Paramedian pontine reticular formation has horizontal burst neurons, while rostral intermediate nucleus of medial longitudinal fasciculus contains neurons for the vertical saccades [2–4]. The burst neurons generate high-frequency discharge to steer saccades in desired direction.

Tectal processing of the spatial map into motor commands is nearly precise, but there is some leeway for downstream adjustments in the saccade direction. The saccadic command not only increases the activity of the burst generator for the movement in desired direction, but also increases the activity of the burst neurons responsible for the orthogonal saccade. For example horizontal saccades are associated with a robust increase in the activity of horizontal burst generators but modest increase in the activity of vertical burst neurons [5,6]. It is hypothesized that unwanted increase in the activity of burst neurons responsible for orthogonal movement and skewed saccadic trajectory is actively canceled by adaptable neural circuit under cerebellar supervision [7]. We test this hypothesis in two siblings with pan-cerebellar atrophy.

2. Materials and methods

We studied two patients with pan-cerebellar atrophy and twelve age-matched healthy subjects. The Emory University and The Cleveland Clinic Institutional Review Boards approved the study protocol. The subjects signed informed consent before participation.

2.1. Clinical presentation

Patient 1: She is a 20-year-old woman who was referred to our clinic for progressive worsening of gait, changes in handwriting, and dysarthria. She had mild difficulty with swallowing with occasional choking spells. She had fainting spells but had negative cardio-vascular investigations. She had hypoglycemia on glucose tolerance test. There was a family history of late-onset tremor affecting the patient's maternal grandmother, but speech and gait were not affected. Her biological brother (patient 2) had similar neurological deficits as outlined in the subsequent section. Her examination revealed mild dysarthria of cerebellar origin. She had hypermetric leftward and hypometric rightward saccades. Downward vertical saccades had normal velocity, but upward drift immediately followed it. There was no nystagmus in primary and eccentric gaze position or during ophthalmoscopic

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examination. Vestibulo-ocular reflex was normal, but vestibulo-ocular reflex cancellation was impaired. There was no ocular motor apraxia. There were catch-up saccades during horizontal smooth pursuit. Vertical smooth pursuit was normal. She had normal muscle strength. Sensation was normal to all modalities. Her coordination was assessed with a scale for the assessment and rating of ataxia (SARA) [8]. On SARA, she scored 2 for gait, which corresponds to clearly abnormal tandem walking more than ten feet, but no support required for casual gait. She had mildly slowed, and awkward half turns. She scored 0.5 for stance, which corresponded to sway during tandem stance. She scored zero for sitting, two for speech, two on both sides for finger chase, one on both sides for nose-finger test, one on both sides for fast alternating hand movements. Her brain MRI revealed pan-cerebellar atrophy (Fig. 1). Laboratory tests excluded Friedreich's ataxia. She had unremarkable laboratory tests for cholesterol, albumin, and alpha-fetoprotein, excluding other recessive ataxias. Tests for sporadic ataxia such as anti-GAD antibodies, anti-gliadin antibodies, anti-tissue transglutaminase antibodies, and vitamin E levels were also unremarkable. Testing for autosomal dominant ataxias was not performed due to negative history in patient's parents.

Patient 2: He is a 27-year-old man and a biological brother of Patient 1. We evaluated him for progressive gait difficulty, imbalance, incoordination, slurred speech, and mild dysphagia. His deficit was progressive over two years. He had full range of extraocular movements; horizontal saccades were dysmetric, rightward saccade had hypometria and leftward horizontal saccade was hypermetric. Upward saccade was slow; downward saccade was normal, but a drift followed it. He had mild gaze-evoked nystagmus in extreme lateral eye position; his gaze was otherwise stable. Ophthalmoscopy was unremarkable. Vestibulo-ocular reflex was normal, but its cancellation was impaired. He had saccadic horizontal pursuit, but vertical pursuit was normal. He had mild to moderate ataxia. We used SARA to assess his coordination. He scored three for gait. This score corresponds to considerable staggering, difficulties in half turn but without support. He was able to stand with feet together for more than 10 s, but sways were present (SARA = 2). He scored zero for sitting on SARA. His speech was impaired but easy to understand, corresponding to score of two on SARA. During a finger chase he had dysmetria of less than 15 cm reaching error (SARA = 2). His rapid alternating movements were irregular (SARA = 2), heel to shin slide was also abnormal (SARA = 2). His brain MRI revealed pan-cerebellar atrophy, but there was no brainstem or cerebral involvement.

2.2. Eye movement recordings

We recorded eye movements with corneal curvature tracker (Jazz Novo, Ober Consulting, Poland). The apparatus tracks and averages the horizontal and vertical position of both eyes at the sampling rate of 1000 Hz. We performed in vivo calibration prior to each experiment session.

2.3. Experimental paradigm

Each subject followed a visual target projected on the LCD screen. In each trial, the target first appeared at straight-ahead position then shifted 10° and 20° to the right and left; 10° and 20° up and down. Each subject made total of 96 saccades (24 downward, 24 upward, 24 rightward and 24 leftward), and 32 pursuits (8 downward, 8 upward, 8 rightward, and 8 leftward). The pursuit target velocity was 8°/s.

2.4. Data analysis

We interactively identified the saccades in eye position trace. The eye position was differentiated and smoothed with a Savitzky–Golay filter (polynomial order: 3; frame length: 21) to derive eye velocity. We confirmed the onset of the saccade in eye velocity trace. We used peak velocity and saccade amplitude for further analysis. We took ratio of the saccade amplitude in unwanted (orthogonal) and desired directions. This ratio, called cross-coupling index, was used to quantitatively assess cross-coupled movements. We took the ratio of the eye velocity and target velocity to assess pursuit gain in the desired and orthogonal directions. Latter assessed cross-coupled pursuit gain. Matlab® toolboxes were used for the statistical analyses.

3. Results

We measured eye movements from two biologically related siblings with pan-cerebellar atrophy and two age-matched healthy subjects.

3.1. Saccade

Fig. 2A and B depicts examples of saccades from one patient with cerebellar degeneration (patient # 1) and a healthy subject, respectively. The patient first fixed gaze on straight-ahead target and then made saccades to the visual target that appeared 20° to the right, left, up or down. The traces in Fig. 2A depict simultaneously recorded vertical and horizontal eye positions. As expected, the rightward horizontal saccade (red trace) in the cerebellar patient was hypometric. In addition, there was simultaneous change in the vertical eye position (blue trace, closed black arrow in Fig. 2A). Unwanted vertical movement was subsequently corrected by a drift (open black arrow), bringing the eyes back to the meridian (gray dashed line). In other words, intended pure rightward saccade was not only dysmetric but also misdirected. Corrective saccades followed dysmetria, while drifts corrected displaced trajectory.

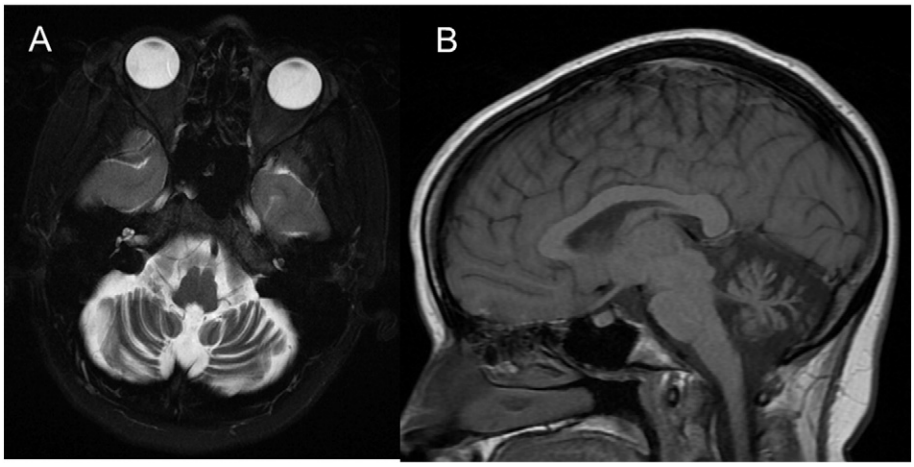

Fig. 1. MRI depicts an example of pan-cerebellar atrophy in the patient 1. Panel A illustrates T2-weighted axial images, while panel B shows sagittal FLAIR sequence.