


BRIEF COMMUNICATION

Slowed vertical saccades as a hallmark of hereditary spastic paraplegia type 7

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Introduction

Hereditary spastic paraplegias (HSPs) are neurodegenerative disorders characterized by progressive spasticity and weakness of the lower extremities, resulting from dying back axonopathy of the corticospinal tract.¹ Mutations in the spastic paraplegia type 7 (SPG7, OMIM 602783) gene coding for paraplegin are generally inherited in autosomal recessive manner, resulting in pure or complicated phenotypes.² Although pure phenotypes present with slow progressive spastic paraparesis, the complicated phenotypes additionally exhibit cerebellar involvement,³ followed by anecdotal reports on optic neuropathy,⁴ ptosis,^{5,6} and supranuclear palsy.⁵ Some patients may even mimic Parkinson's disease⁷ or atypical parkinsonism,⁸ delaying the diagnosis. Thus, we investigated the oculomotor and vestibular phenotype in five patients with genetically proven diagnosis of SPG7.

Methods

Patients and clinical examination

Five patients (two females) with genetically proven SPG 7 upon exome-sequencing were retrospectively selected from the databank of the Department for Neurology, Medical University of Vienna. The mutations are referred

Abstract

Anecdotal oculomotor disturbances have been described in spastic paraplegia type 7 (SPG7). We investigated oculomotor and vestibular dysfunction in five patients with genetically verified SPG7. All five patients exhibited significantly slower velocities of vertical saccades compared to controls, but significantly faster than in progressive supranuclear palsy, with upward saccades being particularly affected. Horizontal saccades, cerebellar oculomotor markers, and vestibuloocular reflex seem to be variably affected. Thus, albeit subclinical in some cases, slowing of the vertical saccades may belong to the phenotype of SPG7 and may serve as a valuable biomarker for differentiation from spastic ataxias and atypical parkinsonism.

to the reference sequence NM_003119.2. The summary of demographical and clinical features is given in Table 1. For statistical analysis, we selected retrospectively consecutive 6 age-matched patients with probable progressive supranuclear palsy (PSP)⁹ and 10 aged-matched control cases (unremarkable oculographic reports) from our databank (Table S1). All patients were extensively clinically examined including cranial MRI scans and nerve conduction studies. The Ethical Committee of the Medical University of Vienna approved the study (2029/2018).

Video-oculography

Ocular motor and vestibular functions were tested using video-oculography and rotational chair testing (System 2000, Micromedical Technologies, Illinois, USA) in a dark room enclosure for eyes uncovered recording in all patients with sampling rate of 60 Hz. The stimuli were applied using a laser projector. The patients' head was restrained by positioning the head in a fixed u-shaped headrest, which was placed at suboccipital height. We investigated the presence of spontaneous nystagmus, smooth pursuit (at 0.1, 0.2, and 0.4 Hz), and horizontal and vertical saccades (+/– 10–25 deg). The angular vestibulo-ocular reflex (aVOR) was tested in darkness at 0.32 Hz and VOR suppression at 0.04 Hz sinusoidal rotation. A computer-controlled calibration procedure was

Table 1. Comparison of medical history of five patients with SPG7.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Mutation	c.1552 + 1G>T homozygote	c.1552 + 1G>T homozygote	c.233T> A homozygote	c.1450_1458del9 heterozygote c.1529C> T heterozygote	c.233T> A homozygote
Protein	Direct splice site; splice acceptor site intron 11/exon 12	Direct splice site; splice acceptor site intron 11/exon 12	p.(L78Ter)	p.E484_R486del acceptor splice site exon 11; p.(A510V)	p.(L78Ter)
Gender	Male	Male	Female	Female	Male
Family History	Yes; brother, grandfather (ataxia of unknown origin)	Yes; brother, grandfather (ataxia of unknown origin)	No	Yes; mother had similar complaints	Yes; sister has similar complaints
Age at examination	58	62	54	54	64
Age at onset	39	50	53	Adolescence	56
Symptoms at onset	Unsteady gait	Unsteady gait Impaired coordination of legs	Unsteadiness with falls Pallhyphaesthesia lower extremities Vertical gaze palsy	Clumsiness and pain of lower extremities Difficulties walking up stairs or standing up from a squatting position	Weakness of lower extremities, hypaesthesia of toes and foot soles; gait difficulties and falls
Gait/ lower limb spasticity	Yes	Yes	Yes	Yes	Yes
Lower limb weakness	Yes	No	Yes	Yes	Yes
Lower limb reflexes	Increased	Increased	Increased	Increased	Increased
Muscle wasting	No	No	No	No	No
Ataxia of limbs	Yes	No	Yes	Yes	Yes

Amino acid changes refer to protein accession number NP_003110.1; the mutations are referred to the reference sequence NM_003119.2.

performed using the given calibration program at $\pm 15^\circ$ for horizontal and vertical saccades. Eye movement analysis (including saccadic velocities) was performed automatically by system-specific analysis algorithms (Micromedical Technologies). Additionally, all eye movement recordings were visually re-evaluated and artifacts were removed manually.

Statistical analysis

Velocities of the vertical saccades were compared between the groups using Kruskal–Wallis test. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed by using IBM SPSS version 21.0.

Results

The summary of the clinical history and video-oculographic findings is given in Table 1 and 2, respectively. The absolute values of saccadic velocities are given in Table S1.

Patient one (c.1552 + 1G>T homozygote) is a 58-year-old male and younger brother of patient two. He noticed

gait problems first when he was 39 years old. Video-oculography showed a slight jerky spontaneous nystagmus to the left. Both the horizontal and vertical saccades were slowed. The vertical saccades were elicited with regular accuracies, but prolonged latencies (463 msec for upward saccades, 353 msec for downward saccades; threshold 260 msec). The mean peak velocity for vertical saccades was 189.17 deg/sec, with upward saccades slower than downward saccades (123.57 deg/sec and 243.84 deg/sec, respectively). The horizontal saccades showed slowed velocities, regular accuracies, and prolonged latencies (367 msec to the left, 461 msec to the right; threshold 260 msec). Smooth pursuit was saccadic at all frequencies. The aVOR was symmetrical at 0.32 Hz with regular gain (0.73). The VOR suppression was normal (gain 0.07).

Patient two (c.1552 + 1G>T homozygote) is the older brother of patient one and harbored the same homozygote splice variant. He was 62 years old at the time of examination and had a history of unsteady gait for approximately 5 years. Video-oculography revealed mild spontaneous downbeat nystagmus. The vertical saccades were elicited with slowed velocities (mean peak velocity vertically 156.64 deg/sec) in both directions (downwards

Table 2. Comparison of video-oculographic data of five patients with SPG7.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Mutation	c.1552 + 1G>T homozygote	c.1552 + 1G>T homozygote	c.233T> A homozygote	c.1450_1458del9 heterozygote c.1529C> T heterozygote	c.233T> A homozygote
Spontaneous nystagmus	Slight, left-beating jerky	Downbeat	No	No	No
Saccadic intrusions	No	No	No	No	Square wave jerks
Vertical saccades	Slowed velocities regular accuracies (down 95%, up 94%) prolonged latencies (down 353 msec, up 463 msec)	Slowed velocities normal downward accuracies, undershoot upward (down 93%, up 76%) prolonged latencies (down 324 msec, up 327 msec)	Slowed velocities normal downward accuracies, undershoot upward (down 81%, up 75%) normal latencies (down 217 msec, up 209 msec)	Slowed velocities normal accuracies (down 95%, up 88%) normal latencies (down 215 msec, up 198 msec)	Slowed velocities normal accuracies (down 87%, up 85%) prolonged latencies downward, normal latencies upward (down 287 msec, up 256 msec)
Horizontal saccades	Slowed velocities regular accuracies (left 90%, right 89%) prolonged latencies (left 367 msec, right 461 msec)	Slowed velocities normal accuracies to the left, marginal undershoot to the right (left 93%, right 80%) prolonged latencies (left 285, right 275 msec)	Slowed velocities normal accuracies (left 84%, right 83%) normal latencies (left 197 msec, right 189 msec)	Normal normal accuracies (left 83%, right 91%) normal latencies (left 186 msec, right 195 msec)	Marginal slow velocities normal accuracies (left 86%, right 81%) normal latencies (left 235 msec, right 206 msec)
Smooth pursuit (0.1 Hz; 0.2 Hz; 0.4Hz)	Saccadic at all frequencies	Saccadic at all frequencies	Regular at all frequencies	Slightly saccadic at all frequencies	Saccadic at all frequencies
VOR (at 0.32 Hz)	Regular gain (0.73) regular symmetry regular Phase	Regular gain (0.71) regular symmetry regular phase	High gain (0.9) regular symmetry regular phase	Marginal high gain (0.86) regular symmetry borderline phase	High gain (0.9) regular symmetry regular phase
VOR suppression	Normal (gain 0.07)	Normal (gain 0.06)	Normal (gain 0.1)	Normal (gain 0.14)	Normal (gain 0.11)
cMRI	Cerebellar atrophy	Mild cerebellar atrophy	No atrophies	No atrophies	cerebellar atrophy
Nerve conduction study	Normal	Normal	Axonal lesion of right fibular nerve	Normal	Axonal lesion of right fibular nerve

151.42 deg/sec, upwards 160.25 deg/sec), with normal downward accuracies and undershoot when looking upward. Furthermore, he revealed prolonged latencies of the vertical saccades (327 msec upwards, 324 msec downwards; threshold 260 msec). The horizontal saccades were slowed with normal accuracies when looking to the left and a marginal undershoot to the right. He exhibited long latencies of the vertical saccades as well (275 msec to the right, 285 msec to the left; threshold 260 msec). Smooth pursuit was saccadic at all frequencies. The aVOR was elicited symmetrically and with regular gain (0.71) at 0.32 Hz. The VOR suppression was normal (gain 0.06).

Patient three (c.233T> A homozygote) is a 54-year-old female patient. She was referred to our movement disorder clinic with suspicion of progressive supranuclear palsy. The most prominent clinical finding at first examination was supranuclear gaze palsy affecting primarily upward

saccades, but without extrapyramidal symptoms. Within the next 6 months, she developed lower limb spasticity and weakness. Video-oculography exhibited no spontaneous nystagmus. She had slowed vertical saccades (mean peak velocity 173.11 deg/sec; upward> downward, 164.39 deg/sec and 183.41 deg/sec, respectively) with normal downward accuracies, an upward undershoot, but normal vertical latencies. We noted slowed horizontal saccades with normal accuracies and normal latencies. Smooth pursuit was normal at all frequencies. The aVOR was elicited symmetrically and with high gain (0.9) at 0.32 Hz. The VOR suppression was within the normal range (gain 0.1).

Patient four (compound heterozygote c.1450_1458del9/c.1529C>T) is a 54-year-old female patient, who noted clumsiness of her lower extremities and difficulties walking up the stairs in her adolescence with subsequent slow progression. Video-oculography detected no nystagmus.

She exhibited slowed vertical saccades (mean peak velocity 223.88 deg/sec; upwards > downwards, 204.74 deg/sec and 257.89 deg/sec, respectively) with normal latencies and accuracies. The horizontal saccades were elicited with normal velocities, latencies and accuracies. Smooth pursuit eye movements were slightly saccadic at all frequencies. The aVOR was evoked symmetrically with marginal high gains (0.86) at 0.32 Hz. The VOR suppression was within the normal range (gain 0.14).

Patient five (c.233T>A homozygote) is a 64-year-old male patient, whose symptoms began at the age of 56, when he first noted weakness of the lower extremities resulting in gait difficulties and falls. He was referred to our Department 6 years after the onset with suspicion of extrapyramidal disorder. Clinical examination revealed manifest slowing of vertical saccades. Video-oculography revealed square wave jerks, but no spontaneous nystagmus. He showed slowed velocities of vertical saccades (mean peak velocity 170.33 deg/sec, upwards>downwards, 164.15 deg/sec and 177.75 deg/sec, respectively) with normal accuracies and normal latencies when looking up, but prolonged latencies when looking down (256 msec upwards, 287 msec downwards; threshold 260 msec). We noted marginal slow horizontal saccades with normal accuracies and normal latencies. Smooth pursuit eye movements were saccadic at all frequencies. The aVOR was elicited symmetrically and with high gain (0.9) at 0.32 Hz. The VOR suppression was within the normal range (gain 0.11).

Vertical saccades in SPG 7: slow, but still faster than in PSP

The mean peak velocity of all vertical saccades (all upward and downward saccades) in SPG7 was significantly slower compared to controls ($P < 0.0001$, Fig. 1A).

However, the velocity was still significantly faster compared to the mean peak velocity of vertical saccades in PSP ($P < 0.0001$, Fig. 1A). The mean peak velocity of upward saccades was uniformly slow in all SPG7 patients, resulting in very low standard deviation (Fig. 1B), whereas downward saccades showed higher mean deviation (Fig. 1C). Vice versa, we noted in PSP patients higher variance for upward saccades as compared to downward saccades (compare Fig. 1B and C).

Discussion

The differentiation between complicated phenotypes in SPG7 and other movement disorders may be quite challenging. Similar to previous reports,^{7,8} two of our patients exhibited initially prominent supranuclear saccadic palsy with falls, resulting in suspicion of an extrapyramidal disorder, like PSP. Both patients had clinically manifest supranuclear vertical saccadic palsy at the time of the first clinical examination and presented with repeated unprovoked falls. However, video-oculography revealed slowing of vertical saccades in all five patients with genetically confirmed SPG7, regardless of the mutation type (even in a mildly affected patient). Noteworthy, the velocity of slowed vertical saccades in SPG7 was low for both small saccades ($10 \pm 1^\circ$) and large saccades ($25 \pm 2^\circ$) (Figure S1), but hardly reached the level of saccadic slowing in PSP patients, suggesting an interesting biomarker for differential diagnosis. It is of note that our diagnostic video-oculography system has a sampling rate of 60 Hz. Although this could possibly be regarded as a limited resolution rate for saccade measurement, it was shown in biomedical investigations that even 50 Hz sampling rate is sufficient to record valid saccade peak velocities.¹⁰ Moreover, our observation on PSP-like oculomotor disturbance in SPG7

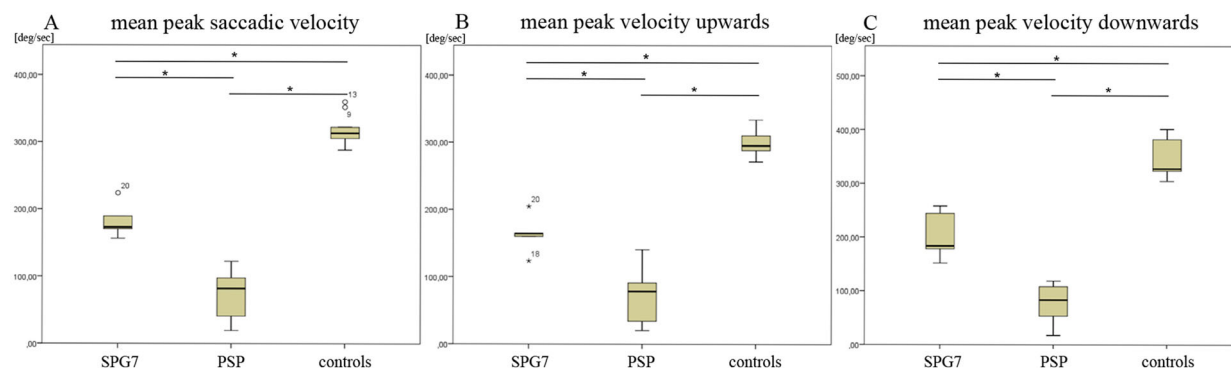


Figure 1. Slowed vertical saccades in SPG7 hardly reaching PSP velocities. (A): Note significantly slower velocities of total vertical saccades in SPG7 patients comparing to controls ($P < 0.0001$), but still significantly faster than in PSP ($P < 0.0001$). Although both upward (B) and downward (C) saccades were slow, upward saccades showed uniformly slow velocities. PSP: progressive supranuclear palsy, SPG7: hereditary spastic paraplegia type 7

is in line with a recent neuropathological report on a SPG7 patient exhibiting PSP-like tau depositions in the brainstem.¹¹ Thus, one can speculate on affection of rostral interstitial nuclei of the medial longitudinal fasciculus (riMLF) in SPG7, similarly to other neurodegenerative disorders affecting vertical saccades, like Niemann-Pick type C or PSP.^{12,13}

The velocities of horizontal saccades seemed to depend on the mutation, as the patient with mild phenotype had normal velocities of the horizontal saccades. Interestingly, we noted in two siblings prolonged latencies of the vertical and horizontal saccades, which are usually associated with attentional or cognitive impairment.¹⁴ However, cognitive dysfunction seems not to be part of the SPG7 phenotype.¹⁵ Hence, further studies are needed to investigate cognitive profile and saccadic system (including antisaccades) in SPG 7. The aVOR could be elicited with normal gains in two patients, marginal high gain in one patient and high gain in two patients, suggesting cerebellar disinhibition of the aVOR. The VOR suppression was normal in all five patients. Saccadic smooth pursuit was observed only in patients with marked cerebellar atrophy. However, further studies are needed to investigate the correlation among them. Thus, the horizontal saccadic abnormalities and cerebellar oculomotor markers may depend on the mutation.

Taken together, video-oculography may be a valuable diagnostic tool to differentiate SPG7 from spastic ataxias¹⁶ (normal vertical saccades) or PSP¹⁷ (more profound slowing of vertical saccades). In particular, more prominent slowing of upward saccades than downward saccades with moderate slowing of the velocity may be considered as a hallmark of SPG7.

Author Contributions

Ivan Milenkovic, MD PhD, designed and conceptualized the study, analyzed the data, and drafted the manuscript. Sigrid Klotz, MD, collected and analyzed the data and drafted the manuscript. Gudrun Zulehner, MD, collected the data and revised the manuscript. Thomas Sycha, collected the data and revised the manuscript. Gerald Wiest, MD, designed the study and carried out revision for intellectual content.

Conflict of interest

None.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Comparison of $10 \pm 1^\circ$ and $25 \pm 2^\circ$ saccades among groups. Note uniform slowing of both small and large saccades upward and downward in SPG 7 as

compared to controls ($P < 0.001$, Kruskal–Wallis test), however, still significantly quicker than in PSP ($P < 0.001$, Kruskal–Wallis test).

Table S1. Comparison of velocities of vertical saccades of 5 SPG7 patients, 6 PSP patients, and 10 control cases. BPPV: benign paroxysmal positional vertigo; Ctrl: control; PSP: progressive supranuclear palsy; PPPD: persistent postural-perceptual dizziness.