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Vestibular Performance During High Acceleration Stimuli Correlates with Clinical Decline in SCA6

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지도교수 김 지 수

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Abstract

Vestibular Performance During High Acceleration Stimuli Correlates with Clinical Decline in SCA6

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Objective: To determine vestibular dysfunction and correlate ocular motor abnormalities with clinical parameters in patients with spinocerebellar ataxia type 6 (SCA6).

Methods: We examined vestibular responses over a broad range of stimulus acceleration in 11 individuals with SCA6 (6 men, age range=33-72 years, mean age±SD=59±12 years) using bithermal caloric, rotary chair, and head impulse tests. Correlations were also pursued among disability scores, as measured using the International Cooperative Ataxia Rating Scale, disease duration, age at onset, CAG repeat length and ocular motor abnormalities including spontaneous, gaze-evoked,

head-shaking and positional nystagmus, saccades, smooth pursuit and the gain (eye velocity/head velocity) of the vestibulo-ocular reflex (VOR).

Results: In response to relatively low-acceleration, low-frequency rotational and bithermal caloric stimuli, VOR gains were normal or increased regardless of the disease severity. On the other hand, with relatively high-acceleration, high-frequency head impulses there was a relative increase in gain in the mildly affected patients and a decrease in gain in the more severely affected patients; therefore the gains were inversely correlated with the disease severity (Spearman correlation, R=-0.927, p<0.001). Smooth pursuit also deteriorated as the disease severity was increased.

Conclusions: Selective decrease of the vestibular responses during high-acceleration, high-frequency stimuli may be ascribed to degeneration of either the flocculus or vestibular nuclei. The performance of the VOR during head impulses and smooth pursuit may be quantitative indicators of clinical decline in SCA6.

Keywords: Spinocerebellar ataxia, Vertigo, Cerebellum, Vestibulo-ocular reflex, Head impulse test

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Introduction

Spinocerebellar ataxia type 6 (SCA6) is a relatively pure cerebellar form of SCA due to a small CAG repeat expansion in the CACNA1A gene (1). Ocular motor abnormalities of SCA6 include spontaneous, gaze-evoked, head-shaking, and positional downbeat nystagmus, saccadic dysmetria, impaired smooth pursuit (SP), and impaired cancellation of the vestibulo-ocular reflex (VOR) (1-6). In contrast, the gain of the VOR has been reported to be normal (2,7), decreased (8,9), or increased (1). These discrepancies may stem from the different frequencies or accelerations of the stimuli used to evaluate the VOR in these studies. VOR abnormalities that differ depending on characteristics of the stimulus have also been observed in patients with central vestibular lesions (10,11). Recently, a selective reduction in VOR gain during head impulses has been reported in a patient with an isolated floccular infarction (11). In SCA6, the flocculus is more severely affected compared to the cerebellum or pons (12). The disease severity may also have contributed to the discrepancies in VOR gain in SCA6. Indeed, ocular motor abnormalities correlate with the clinical parameters, CAG repeat length or disease severity, in SCA2, 3, and 17 (13-16). However, correlations among the ocular motor impairments and clinical parameters have rarely been reported in SCA6 (6).

Therefore, we sought to determine the vestibular dysfunction in patients with SCA6 using a broad range of stimuli including bithermal caloric, rotary chair and head impulse tests. We also correlated quantitative measurements of the ocular motor abnormalities with

clinical parameters including the age at onset, disease duration and severity, and CAG repeat length.

Methods

Subjects

We prospectively studied 11 patients with genetically confirmed SCA6 (6 men, age range=33-72 years, mean age±SD=59±12 years). Patients had neither a history of peripheral vestibular diseases nor an exposure to ototoxic medication. Medications that could affect ocular motor and vestibular function were not used during the study. All patients had a full neurological and neuro-otological evaluation by one of the authors (J.S.K). The International Cooperative Ataxia Rating Scale (ICARS) was applied at the time of their evaluation. Demographic and clinical details of the patients are presented in table 1. Normative data were obtained from 29 healthy age-matched volunteers (14 men) with the ages ranging from 33 to 73 years (mean±SD=54±11 years).

All experiments complied with the tenets of the Declaration of Helsinki and informed consent was obtained after the nature and possible consequences of this study had been explained to the participants. The study protocol was also approved by the Institutional Review Board of Seoul National University Bundang Hospital.

Oculography

All participants underwent ocular motor studies comprised of spontaneous, gaze-evoked, head-shaking, and positional nystagmus, saccades and SP. Movements of both eyes were recorded at a sampling rate of 60 Hz using 3-dimensional video-oculography (SensoMotoric Instruments, Teltow, Germany). A digitally controlled illuminated target (0.25°) was presented on a LED light bar 1.1 m away. For calibration, subjects were asked to track a sequence of target displaced in the horizontal and vertical directions. Digitized eye position data were analyzed off-line using MATLAB software. During the experiments, patients were seated in a chair and their heads were immobilized by a neck support.

Spontaneous nystagmus (SN) was recorded both with and without fixation in the straight-ahead position. The intensity of SN was determined by its mean slow-phase velocity (°/s) for 10 seconds when the nystagmus was most stable. Gaze-evoked nystagmus (GEN) was induced with horizontal (±30°) and vertical (±20°) target displacements. Head-shaking nystagmus (HSN) was assessed without fixation using a passive head-shaking maneuver in the horizontal plane. Details of the recording methods have been published previously (17). To induce positional nystagmus (PN), patients lay down flat, and the head was turned to either side. The patients also underwent straight head-hanging and the Dix-Hallpike maneuvers in either direction.

Saccades were measured in response to horizontal target steps of 30° (right or left) and 15° (centrifugally or centripetally). The target was presented at 2 second intervals. The participants were instructed to follow the target with their eyes as fast and precisely as possible. The latency, velocity and accuracy of saccades were analyzed (18).

For SP, subjects were asked to track a target moving horizontally in a sinusoidal waveform with maximal amplitude of 40° and peak velocities of 10 and 20 °/s. The mean velocity gain was calculated by the ratio between the peak eye and target velocities.

Evaluation of the vestibular function

The VOR was evaluated using bithermal caloric, rotary chair, and head impulse tests. Caloric stimuli were provided by irrigating the ears for 25 seconds with 50 mL of cold and hot water (30°C and 44°C, respectively) (17). Total sum of the peak responses to each caloric stimulus was defined as the caloric response.

The CHARTR® rotary vestibular test system (ICS Medical, Schaumburg, IL, USA) was used to assess the horizontal VOR during sinusoidal harmonic accelerations. Sinusoidal rotation was about a vertical axis at frequencies of 0.02, 0.04, 0.08, 0.16 and 0.32 Hz and a peak angular velocity of 50°/s. Eye position was detected with electrodes placed using standard methods and was digitized at 160 Hz

with a frequency response of 0-30 Hz and notch filter at 60 Hz. The gain of the slow-phase eye velocity relative to the chair velocity was calculated.

To assess the VOR during head impulse testing (HIT), a magnetic search coil technique was adopted using three-dimensional scleral coils. Rotation of the eye and head was recorded in a 70 cm cubic search coil frame (Skalar, Delft, Netherlands). Digitized eye and head position data were analyzed with MATLAB software. For HIT, the patient was instructed to fix on a red target (0.25°) 1.2 m away. The head impulses were passive and unpredictable head rotations with amplitudes of 20-30°, peak velocities of 200-300°/s, and peak accelerations of 3000-5000°/s^2. They were delivered in the planes of the both horizontal canals (HCs), left anterior and right posterior canals, and right anterior and left posterior canals while the subjects sat upright. A minimum of five impulses were applied in each direction. The VOR gain was calculated for each trial as the ratio between the eye velocity and head velocity, at close to the time of peak head velocity. Detailed methods have been described previously (11).

International Cooperative Ataxia Rating Scale

Disability was scored according to the ICARS, a semi-quantitative ataxia scale (19). ICARS is a 100-point scale that is divided into four subscales, consisting of postural and gait disturbance (34 points), limb

kinetic function (52 points), speech disorder (8 points), and ocular motor function (6 points). Higher scores indicate worse performance.

Statistical analysis

Between the patient and control groups, differences in the parametric variables were analyzed using Student's t-test. Spearman correlation and Mann-Whitney U-test were used for non-parametric data. The level of significance was set at $p<0.05$. Normal values for ocular motor parameters were defined as the mean±2SD.

Results

Clinical characteristics

Detailed demographic and the clinical characteristics of the patients are presented in Table 1. Patients 1 and 6, and patients 2 and 3 were siblings. Fluctuating or episodic symptoms were frequently observed during the early stage of illness (7/11, 64%). Four patients initially presented with recurrent episodes of dizziness, preceding ataxia or dysarthria.

Table 1. Demographic and clinical characteristics in patients with spinocerebellar ataxia type 6

Patient	Sex	Age (years)	Age at onset (years)	Duration (years)	CAG repeats	ICARS	Initial symptoms
1	F	64	44	20	13/23	70	Intermittent dizziness and imbalance
2	M	63	54	9	23/11	58	Imbalance
3	M	60	53	7	23/11	15	Dizziness during walking
4	M	72	60	12	13/22	36	Intermittent ataxia
5	M	48	41	7	10/23	57	Ataxia, dysarthria
6	F	53	52	1	13/23	7	Intermittent dizziness and imbalance
7	F	70	60	10	13/22	65	Intermittent dizziness, aggravated by position
8	F	53	46	7	13/22	13	Intermittent dizziness, aggravated by position
9	M	75	71	4	14/20	39	Intermittent ataxia
10	M	57	33	24	12/25	62	Ataxia
11	F	33	30	3	13/27	48	Fluctuating dysarthria and difficulty in writing
Mean±SD		59±12	49±12	9±7	23±2	43±21	

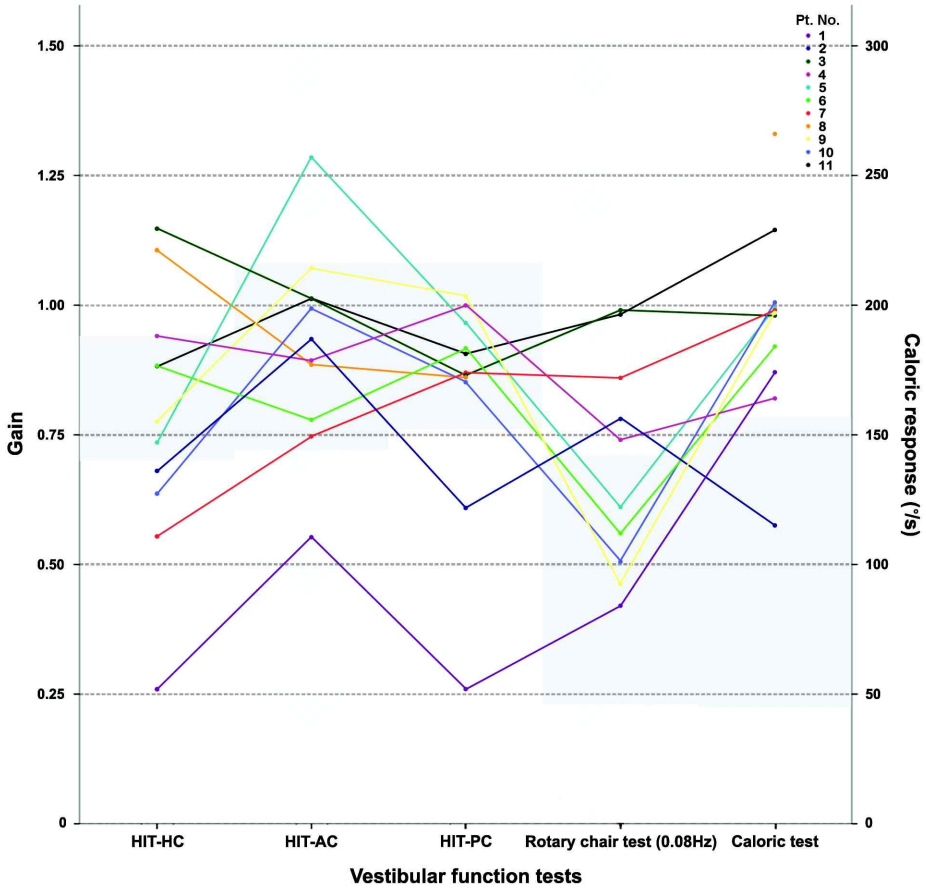
F=female; ICARS= International Cooperative Ataxia Rating Scale; M=male.

Vestibular function (Figure 1 and supplementary table 1)

The caloric responses were significantly increased in 10/11 patients (91%). Rotary chair test was performed in 10 patients, and half (5/10) showed increased VOR gains during sinusoidal rotation at more than 2 stimulation frequencies. The mean VOR gain for each stimulation frequency was symmetric and significantly higher than the normal value except at 0.02 Hz. Small phase leads were observed in 5 patients.

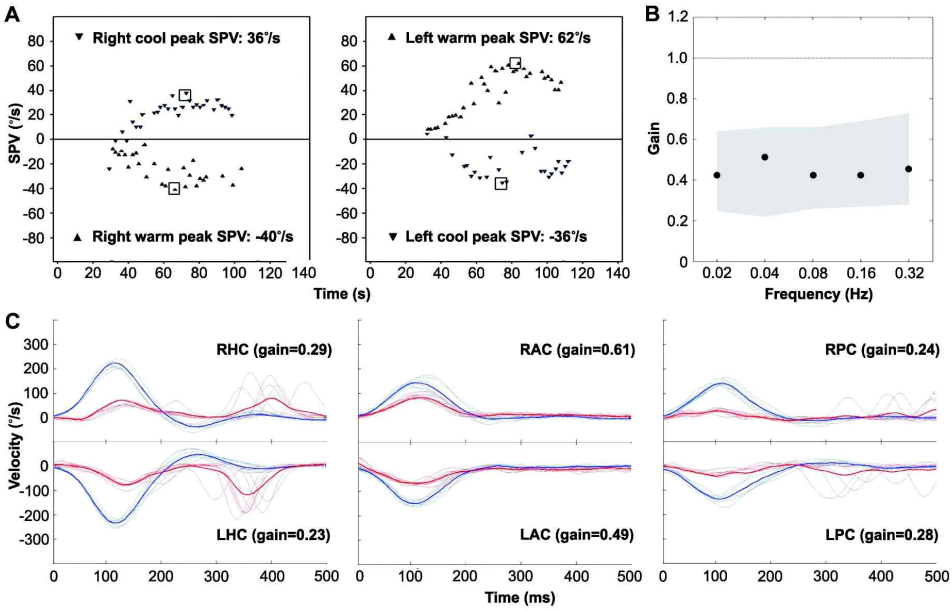
The VOR responses to head impulses were variously affected in the patients. Most patients (10/11, 91%) showed abnormal responses to stimulation of at least one semicircular canal (SCC), increased in 6 and decreased in 4. The head impulse VOR gains also varied according to the SCC stimulated. Head impulses in the HC plane showed abnormal gains in 8 patients (73%), increased in 4 and decreased in 4. The gains for anterior canal (AC) were also abnormal in 4 (36%), increased in 3 and decreased in 1, while those for the posterior canal (PC) were decreased in 2 patients (18%). Even though the head impulse VOR gains did not differ between either side (paired *t*-test, $p>0.05$), 5 patients showed an abnormal gain in only 1 of each SCC pair. The VOR responses to head impulses were normal for all 6 SCCs in only 1 patient (patient 6) whose functional disability was minimal, whereas those were uniformly decreased for all 6 SCCs in the most severely affected patient (patient 1, Figure 2).

Figure 1. Vestibular responses in the patients with spinocerebellar ataxia type 6



The VOR gains during head impulse test (HIT) are variously affected, but those during rotatory chair and caloric tests were generally increased. Vestibular responses of individual patient are illustrated as colored dots with a solid line during HIT, rotatory chair test (gain at 0.08 Hz) and caloric tests. Gray areas represent the normal range (mean±2SD) of each test. Caloric response indicates the sum of the peak slow-phase velocity of the nystagmus induced in the four stimulus conditions of bithermal caloric tests. HIT-AC=head impulse testing in the anterior semicircular canal plane; HIT-HC=head impulse testing in the horizontal semicircular canal plane; HIT-PC=head impulse testing in the posterior semicircular canal plane.

Figure 2. Results of the vestibular function tests in patient 1



(A) Caloric test. The sum of the peak slow-phase velocity (SPV) of the nystagmus in response to each caloric stimulus is increased at 174°/s (normal range=45-157°/s). (B) Rotatory chair test. The gains of the vestibulo-ocular reflex (VOR) are normal during sinusoidal horizontal accelerations. Gray areas represent the normal ranges (mean±2SD). (C) Head impulse tests. Head impulses in the plane of each semicircular canal (SCC) revealed decreased gain of the VOR for all six semicircular canals with overt catch-up saccades during stimulation of the horizontal and posterior SCCs. The blue lines indicate head velocity and the red lines represent eye velocity. LAC=left anterior SCC; LHC=left horizontal SCC; LPC=left posterior SCC; RAC=right anterior SCC; RHC=right horizontal SCC; RPC=right posterior SCC.

Spontaneous, gaze-evoked, head-shaking and positional nystagmus (supplementary table 2)

Six patients (55%) showed SN, downbeat in 5 and upbeat in 1. GEN was observed in 9 (82%), only during horizontal gaze in 5 and during both horizontal and vertical gazes in 4. Horizontal eccentric gaze induced combined horizontal and downbeat nystagmus in 7 (64%) and additional torsional nystagmus in 1. Horizontal head-shaking induced nystagmus in 8 (73%) patients with various patterns, however, when present, the vertical component was always downbeat (5, 45%). Seven patients (64%) showed PN, 4 with downbeat during straight head-hanging, 4 with apogeotropic and 1 with geotropic nystagmus during head turning to either side while supine. All patients with PN also showed HSN.

Saccades (supplementary table 2)

Mean saccadic latency was significantly larger in the patients than in the controls (320±56 vs. 218±17 ms, $p<0.001$) and in most (9/11, 82%), above the normal range (184-252 ms). Dysmetric saccades were observed in all patients. Overall, 54% of all of the horizontal saccades analyzed were dysmetric, hypometric in 34% (gain<0.85) and hypermetric in 20% (gain>1.01). In contrast, saccadic velocities were within normal range.

Smooth pursuit (supplementary table 2)

SP gains were significantly reduced at a peak target velocity of 10°/s (0.42±0.20, normal=0.70±0.10, p=0.001) and 20°/s (0.25±0.20, normal=0.67±0.12, p<0.001). Overall, all patients except 1 (patient 6) showed a decreased SP gain (<mean-2SD) at least at one of the target velocities.

Correlations among the ocular motor findings and other clinical parameters (Table 2)

Correlations among the ocular motor findings and other clinical parameters revealed that the VOR gains during horizontal head impulses inversely correlated with ICARS (R=-0.927, p<0.001, Figure 3) and SP gains decreased with increasing disease duration (R=-0.699, p=0.017). However, no correlation was found between each clinical parameter (age, age at onset, disease duration, CAG repeat length, ICARS) and other ocular motor parameters including the head impulse VOR gains of AC and PC, caloric responses, VOR gains during sinusoidal rotation, and saccades). There was also a positive correlation between ICARS and the disease duration (R=0.706, p=0.015) and a negative correlation between the age at onset and CAG repeat length (R=-0.830, p=0.002).

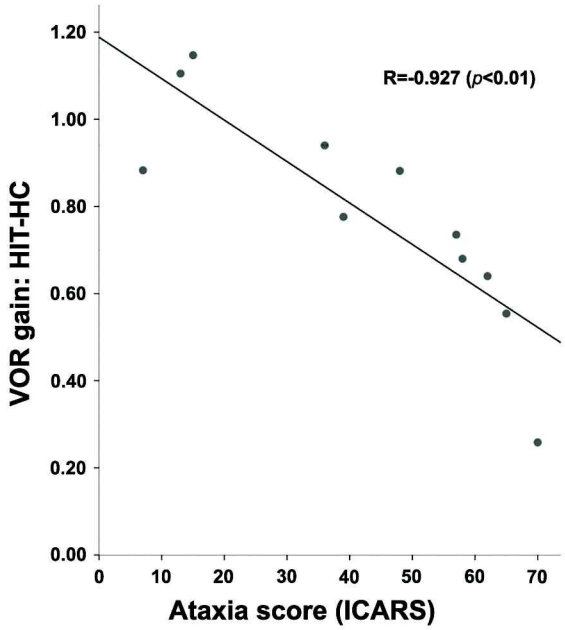
Table 2. Correlations among ocular motor performances and other clinical parameters

	VOR gain				VOR	Saccade	Saccade	Smooth pursuit	ICARS	CAG repeat length
	HIT-HC	HIT-AC	HIT-PC	RCT	CR	Accuracy	Latency	Gain		
ICARS	**-0.927****	-0.191	-0.464	-0.273	-0.082	0.415	0.027	-0.574	1.000	0.222
Disease duration	-0.579	-0.296	-0.469	-0.297	-0.219	0.249	0.301	**-0.699***	**0.706***	0.029
Age at onset	0.123	-0.105	0.364	-0.006	-0.533	0.215	-0.260	0.425	-0.164	**-0.830****
Age at examination	-0.228	-0.223	0.118	-0.273	-0.569	0.249	-0.123	0.094	0.241	**-0.685***
CAG repeat length	-0.164	0.144	-0.414	0.175	0.164	-0.092	0.453	-0.309	0.222	1.000

CR=caloric response; HIT-AC=head impulse testing in the anterior semicircular canal plane; HIT-HC=head impulse testing in the horizontal semicircular canal plane; HIT-PC=head impulse testing in the posterior semicircular canal plane; ICARS= International cooperative ataxia rating scale; RCT=rotary chair test; VOR=vestibulo-ocular reflex.

Figures in bold are significant, *$p \leq 0.05$ and **$p \leq 0.01$.

Figure 3. Correlation between the vestibulo-ocular reflex (VOR) gain during horizontal head impulse test (HIT) and ataxia



VOR gain of the horizontal semicircular canal is negatively correlated with the ataxia score as measured using International Cooperative Ataxia Rating Scale (ICARS). HIT-HC=head impulse testing in the horizontal semicircular canal plane.

Discussion

Our study described several new findings in SCA6. 1) Vestibular responses varied according to the acceleration and frequency of the stimulus even in an individual patient. 2) Vestibular responses elicited by horizontal head impulses (high-acceleration/high-frequency stimuli) strongly correlated with the disease severity. Gains were relatively

increased in patients with milder disability and decreased in more severely affected ones. 3) Vestibular responses during caloric irrigations and sinusoidal rotations (relatively low-acceleration/low-frequency stimuli) were normal or increased regardless of the disease severity. 4) The SP impairment positively correlated with the disease duration. 5) The saccadic latency was prolonged. As in previous studies, we frequently recorded GEN, downbeat HSN, PN, dysmetric saccades and impaired SP. The age at onset was positively correlated with CAG repeat length as described in some previous studies (20).

Abnormal vestibular responses have also been reported in SCA1, 2 and 3 (4,7,15). However, responses were generally reduced for all stimulus accelerations/frequencies (7,15), especially for the lower acceleration stimuli (15). On the contrary, the vestibular responses in our SCA6 patients differed even in a patient depending on the nature of the stimulus. This finding may account for the discrepancies in the VOR gain abnormalities reported in previous studies in which vestibular responses were elicited with relatively restricted ranges of accelerations/frequencies. We found that patients with milder neurological deficits tended to have increased VOR gains across the range of stimuli including head impulses. In addition, the vestibular response to low acceleration/frequency stimuli remained increased irrespective of the disease severity whereas the horizontal VOR gains at higher acceleration/frequency stimuli using head impulses were more reduced in patients with greater disability. These findings indicate that

the horizontal VOR gains to head impulses are increased during the earlier phase and undergo a gradual reduction with disease progression.

The vestibular responses in our patients may be explained based on the cerebellar pathology (1,12), especially the flocculus that is known to have strong influences on the VOR (21). The pathogenesis of SCA6 is not fully understood perhaps due to the diverse effects of CACNA1A mutation on the P/Q type calcium channel (22-24), but deranged calcium signaling in the Purkinje cells may be the key pathogenesis of SCAs (25). Excess of intracellular calcium due to an abnormal increase in the activity of the mutated calcium channels (22) may trigger cerebellar long term depression as a protective mechanism against excitotoxicity in the Purkinje cells (26). Cerebellar long term depression in turn suppresses glutamatergic synaptic transmission and the Purkinje cells activity, resulting in disinhibition and consequent overactivation of the deep cerebellar nuclei (27) and possibly the portions of the vestibular nuclei that receive direct projections from the vestibulocerebellum including the flocculus. These changes would be responsible for the cerebellar dysfunction as well as increased VOR gain in our SCA6 patients during the early stage when the gross integrity of neural pathways is preserved. Changes in the VOR gain in the later stage of SCA6 might be explained based on the response dynamics of the VOR, which can be modeled by two separate pathways, the linear and non-linear (28). The linear pathway is responsible for retaining a constant VOR gain at low-acceleration

stimuli. The non-linear pathway accounts for enhancement of the VOR gain with increase of the stimulus acceleration and works at high-acceleration stimuli. These responses are presumed to arise from separate groups of vestibular afferents and may be controlled by distinctive central vestibular networks, such as the vestibular nuclear neurons (29). Given the neuronal loss with gliosis in the vestibular nuclei observed in SCA6 (30), degeneration in the vestibular nuclei might produce the VOR gain reduction during high-acceleration/high-frequency stimuli and an increased gain during low-acceleration/low-frequency stimuli. Similar patterns of VOR gain changes, a decrease during high-acceleration and normal to increase during low-acceleration stimuli, were also found in animals with experimental cerebellar lesions and human patients with various types of presumably isolated cerebellar pathology (10,11,21).

The VOR gains for the vertical canals during head impulses also tended to be lower in patients with severe disability and vice versa, even though this finding did not reach statistical significance. Remarkably, the VOR gains were dissociated among the SCCs even in individual patients. Since the central VOR pathways are segregated for each SCCs (31), the dissociated vestibular responses for each SCC could provide additional evidence indicating that abnormal vestibular responses in our patients stem from central rather than peripheral vestibular process.

Saccadic latency was significantly prolonged in our SCA6

patients. Few studies have focused on saccadic latency in SCA6 (4,6,32). Prolonged latency has also been reported in other SCAs (4,16). Even though increased saccadic latency has generally been ascribed to disruption of higher level projections from frontal or parietal areas directly, and indirectly via the caudate nucleus and substantia nigra, to the superior colliculus (31), cerebellar degeneration could have been responsible for prolonged latency in our SCA6 patients. Recent studies have shown that saccadic latency is significantly increased in patients with isolated cerebellar dysfunction (33,34). Indeed, marked increase in saccadic latency has been reported in rhesus monkeys when their dorsal cerebellar vermis was selectively ablated (35). Accordingly, cerebellar degeneration might produce prolonged saccadic latencies because of alterations in projections to the superior colliculi mediated by the caudal fastigial nucleus (35) or alterations of cerebellar projections to the cerebral cortex (36).

SP is generally impaired in all SCA subtypes to varying degrees, probably due to dysfunction of the flocculus/paraflocculus or dorsal vermis (1,4,8,13,15,16). Of interest, the reduction of SP gain increased with disease duration in our SCA6 patients. While significant correlations among SP gain and clinical parameters have been reported in other SCA types (13,16), those have rarely been described in SCA6 (6). In view of the positive correlation between ICARS and disease duration, the SP gain may be more affected as disease progresses, even though the correlation between ICARS and SP gain missed significance.

HSN and PN were common findings in our patients, including the perverted downbeat HSN and downbeat PN that have been described as distinctive features of SCA6 (3,5). Given the considerable overlaps in patients with HSN and PN, it is conceivable that those share a common pathophysiology, such as asymmetry or abnormal cross-coupling of the central velocity storage system due to dysfunction of the nodulus/uvula or selective disinhibition over the AC VOR pathway due to floccular dysfunction (17,31).

Finally, we suggest that an impaired VOR during head impulses and possibly impaired SP will be reliable surrogate markers for research on disease modifying therapy as well as for monitoring the progression of disease in SCA6.

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Supplementary table 1 Vestibular findings in patients with spinocerebellar ataxia type 6[a]andcontrols

Patient	CR (°/s)	Sinusoidal rotation (Gain at 0.08 Hz)[b]	Head impulse								
			Horizontal canals (Gain)			Anterior canals (Gain)			Posterior canals (Gain)		
			R	L	mean	R	L	mean	R	L	mean
1	174↑	0.42	0.29↓	0.23↓	0.26↓	0.61↓	0.49↓	0.55↓	0.24↓	0.28↓	0.26↓
2	115	0.78↑	0.70	0.66↓	0.68↓	0.84	1.03	0.93	0.53↓	0.69↓	0.61↓
3	196↑	0.99↑	1.15↑	1.14↑	1.15↑	1.10↑	0.92	1.01	0.87	0.87	0.87
4	164↑	0.74↑	0.96↑	0.92	0.94↑	0.92	0.87	0.89	1.00	1.00	1.00
5	199↑	0.61	0.71	0.76	0.74	1.2↑	1.37↑	1.29↑	1.00	0.93	0.97
6	184↑	0.56	0.88	0.89	0.88	0.77	0.79	0.78	0.96	0.87	0.92
7	198↑	0.86↑	0.64↓	0.47↓	0.55↓	0.77	0.73	0.75	0.87	0.87	0.87
8	266↑	ND	1.10↑	1.11↑	1.11↑	0.90	0.87	0.89	0.90	0.82	0.86
9	197↑	0.46	0.84	0.71	0.78	1.09↑	1.05	1.07	0.95	1.08	1.02
10	201↑	0.51	0.68↓	0.60↓	0.64↓	0.98	1.00	0.99	0.91	0.79	0.85
11	229↑	0.98↑	0.98↑	0.78	0.88	0.98	1.04	1.01	0.85	0.96	0.91
Patient group[c]	193±36	0.69±0.20	0.81±0.23	0.75±0.26	0.78±0.24	0.92±0.16	0.92±0.16	0.92±0.18	0.82±0.22	0.83±0.20	0.83±0.21
Control (mean±SD)	101±28	0.46±0.10	0.82±0.07	0.82±0.06	0.82±0.06	0.93±0.09	0.87±0.09	0.90±0.09	0.94±0.11	0.90±0.06	0.92±0.08
Normal (mean±2SD)	45~157	0.26~0.66		0.70~0.94			0.72~1.08			0.76~1.08	

CR=sum of caloric responses, L=left; R=right, ND= not done

[a] Abnormally increased and decreased responses were denoted with " ↑ " and " ↓ ", respectively.

[b] The VOR gains during sinusoidal harmonic acceleration at a frequency of 0.08 Hz were presented. Similar results were obtained at other frequencies.

[c] Means and standard deviations are presented for the caloric response (see text for the detail), and the VOR gains during rotatory chair and head impulse tests.

Supplementary table 2 Ocular motor findings in the patients with spinocerebellar ataxia type 6

Patient	SN[a](°/s)			GEN		HSN[a](°/s)			PN (°/s)		Saccade				Smooth Pursuit (Gain)	
	H	V	T	Horizontal gaze	Vertical gaze	H	V	T	SHH	HT	Latency (mean± SD, ms)	Accuracy (%) Hypo	Hyper	Total	10°/s (mean)	20°/s (mean)
1	-	D2	-	H-D	V	-	D	-	-	Apo	341±71	27	30	57	0.15	0.05
2	-	-	-	H-D	V	L2	-	-	-	Apo	340±82	54	15	69	0.24	0.08
3	-	-	-	H-D	-	L3	D4	-	D	Apo	284±67	13	25	38	0.58	0.2
4	-	-	-	H-D	-	-	-	-	-	-	397±82	39	30	69	0.35	0.17
5	R1	D2	-	H-D	-	-	D10	-	D	Geo	330±116	39	32	71	0.33	0.19
6	-	-	-	-	-	L7	-	-	D	-	399±166	19	4	23	0.73	0.70
7	L1	D3	-	-	-	-	D6	-	-	-	283±106	62	0	62	0.56	0.4
8	-	D1	-	H-D	V	-	-	-	-	-	244±39	21	25	46	0.30	0.12
9	L1	U1	CCW1	H-D-CCW	-	L22	-	CCW6	-	Apo	238±45	52	5	57	0.73	ND
10	-	-	-	H	V	-	-	-	-	-	370±124	27	12	50	0.27	ND
11	-	D5	CW1	H-D	-	-	D20	-	D	-	294±63	19	42	61	0.39	0.31
Total[b]	3 (27%)	6 (55%)	2 (18%)	9 (82%)	4 (36%)	4 (36%)	5 (45%)	1 (9%)	4 (36%)	5 (45%)	320±56	34	20	54	0.42±0.20	0.25±0.20

Apo=apogenotropic nystagmus beating toward the ceiling (uppermost ear) during head turning while supine, CW=clockwise, CCW=counterclockwise, D=down, GEN=gaze-evoked nystagmus, Geo=geotropic nystagmus beating toward the ground (lowermost ear) during head turning while supine, H=horizontal, H-D=combined horizontal-downbeating, H-D-CCW=combined horizontal-down-counterclockwise-torsional-beating, HSN=head-shaking nystagmus, Hypo=hypometric saccade, Hyper=hypermetric saccade, dysmetric=dysmetric saccade, L=left, ND=not done, PN=positional nystagmus, R=right, SHH=straight head hanging, HT= head turning to either side while supine, SN=spontaneous nystagmus, T=torsional, U=up, V=vertical

[a] Patterns of nystagmus are designated by direction and maximal slow phase velocity (°/s) of each component.

[b] Total sum and frequency of each component are presented for spontaneous, gaze-evoked, and head-shaking nystagmus, and mean or standard deviation are described for saccade and smooth pursuit.

요약(국문 초록)

척수소뇌실조증 6형에서 주로 소뇌기능 이상과 관련된 안구운동이상이 나타나는데 반해, 전정안반사 이득은 형태와 기전이 명확하지 않다. 이에 이번 연구에서는 척수소뇌실조증 6형 환자에서 다양한 범위의 주파수 자극을 이용하여 전정안반사 이득을 측정하고, 이득 이상을 비롯한 안구운동이상과 임상척도와의 연관성을 살펴보고자 하였다.

대상 환자는 유전자 검사상 척수소뇌실조증 6형으로 확진된 11명으로(6 men, age range=32-72 years, mean age±SD=59±12 years), 안구운동검사와 전정안반사 이득을 측정하였다. 전정안반사 이득은 온도안진검사, 회전의자검사, 자기추적코일 장치를 이용한 두부충동검사를 이용하여 다양한 주파수 영역에서 평가하였다. 상관분석을 통해 국제실조증평가척도, CAG 염기 반복수, 발병 연령, 유병기간의 임상척도가 전정안반사와 안구운동이상(자발안진, 주시유발안진, 두진후안진, 자세변환안진, 신속안구운동, 추적안구운동)의 연관성을 분석하였다.

전정안반사는 자극 가속도 및 주파수에 따라 동일한 환자에서도 다양하게 관찰되었다. 저가속도/저주파수 자극의 온도안진검사 및 회전의자검사에서, 전정안반사 이득은 질병의 진행정도와 관계없이 정상 또는 증가되었다. 반면에, 고가속도/고주파수 자극의 두부충동검사에서, 전정안반사이득은 질병의 진행정도에 반비례하여(Spearman correlation, $R=-0.927$, $p<0.001$), 증상이 경미한 척수실조증 6형 환

자는 전정안반사 이득이 증가되었고, 증상이 심한 환자는 이득이 감소되었다. 추적안구운동 이득은 유병기간에 반비례하였다.

질병의 진행에 따른 소뇌타래 또는 전정신경핵의 변성으로 척수소뇌실조증 6형 환자에서 고가속도/고주파수 전정안반사 이득이 감소하는 것으로 설명할 수 있다. 따라서, 척수소뇌실조증 6형 환자에서 두부충동검사의 전정안반사 이득과 추적안구운동 이득은 질병 진행 정도를 정량화하는데 유용할 것이다.

주요어: 척수소뇌실조증, 현훈, 소뇌, 전정안반사, 두부충동검사

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