Neuro-otological Examinations in Patients With Spinocerebellar Degeneration

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Background: Spinocerebellar-degeneration（SCD）has been reported to show a variety of abnormal neuro-otological findings on electronystagmography（ENG）rather in a late stage of disease developing process, but not in an earlier stage.

Purpose: We have analysed ENG findings derived from 79 patients confirmed with SCD, in order to assess a diagnostic value of ENG and determine which manifestations are helpful in diagnosing SCD.

Results: We observed a high incidence of saccadic pursuit, severely impaired optokinetic nystagmus, and impaired visual suppression; observations that likely to be useful in diagnosing SCD. For each abnormal finding, we compared the data among patients with different types of SCD（olivopontocerebellar cortical atrophy, late cerebellar cortical atrophy, Shy-Drager syndrome, and hereditary SCD）. We also studied the relationship between MRI findings and ocular abnormalities in these patients with SCD. In typical cases, the abnormal neuro-otological findings are effective in an earlier diagnosis of SCD.

Conclusion: In our present study, neuro-otological examinations are demonstrated to be useful for evaluating patients with SCD.

Key words: spinocerebellar-degeneration, neuro-otological examinations, magnetic resonance imaging

INTRODUCTION

Spinocerebellar degeneration（SCD）encompasses a group of neurodegenerative diseases that involve the cerebellum, brain stem, spinal cord, and basal ganglia to various degrees. SCD includes both sporadic and hereditary forms. Most cases of sporadic SCD degeneration are now considered to be instance of multiple system atrophy（MSA）. Although some of these patients have symptoms such as cerebellar cortical atrophy, they may subsequently display extrapyramidal signs and an autonomic disorder similar to MSA［1］. Hereditary SCD consists of autosomal dominant SCD, including spinocerebellar ataxia（SCA）types 1, 2, 3, and 6, and autosomal recessive SCD, such as Friedreich's ataxia［2, 3］. The main clinical findings of SCD include cerebellar, extrapyramidal, and autonomic nerve symptoms, in addition to various oculo-motor disturbances［4-9］. We therefore analyzed neuro-otological findings in patients with confirmed SCD to evaluate their diagnostic value and determine which neuro-otological manifestations are helpful in diagnosing SCD. We also studied the relationship between MRI findings and ocular abnormalities in these patients and showed that neuro-otological examination was useful in the early diagnosis of SCD.

METHODS

The study participants were 79 patients（31males, 48 females; mean age 63.0 years at the initial test, SD 10.1years）who presented at our office with a suspected diagnosis of SCD by our neuro-otological examinations and diagnosed with SCD by Neurologists at Shimane University Hospital. They included 48 cases with olivopontocerebellar cortical atrophy

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(OPCA), 16 cases with late cerebellar cortical atrophy (LCCA), 4 cases with Shy-Drager syndrome (SDS), 11 cases with hereditary SCD without genetic diagnosis (probable hereditary SCD).

Neuro-otological examinations performed during electronystagmography (ENG) included an eye tracking test (ETT), a gaze nystagmus test, a positional nystagmus test, an optokinetic nystagmus (OKN) test, and a caloric test. Abnormal ENG findings were defined as follows: the presence of saccadic pursuit, ocular dysmetria, decreased eye velocity of saccade, gaze-evoked nystagmus, rebound gaze and positional nystagmus, poor OKN responses, to a positioning test, caloric weakness and impaired visual suppression (VS). Decreased eye velocity of saccade was defined by manual measurement of the saccade. Caloric tests were performed in all patients using 20 ml of cold (20°C) water administered over the course of 10 s with eyes open in total darkness. Caloric unilateral weakness was calculated from the manually measured maximal slow-phase eye velocity (maximal SPEV) of the induced nystagmus. Maximal SPEV was corrected by adding or subtracting the SPEV of the spontaneous nystagmus; the normal limit of 25% was employed [10, 11]. VS, which was defined as the percentage reduction in SPEV due to visual fixation, was simultaneously evaluated [11]. The normal limit of 40% was employed. OKN was classified according to visual criteria into four categories: normal (>60°/sec), -borderline impaired (50-60°/sec), slightly impaired (40-50°/sec), moderately impaired (30-40°/sec) and severely impaired (<30°/sec).

Brain MRIs were performed using a 1.5 or 3.0-tesla MRI (Symphony Ultra Gradient, Siemens). The whole head was scanned with a T 2 -weighted image (TR: 4,500 ms, TE: 86 ms), a T 1 -weighted image (TR: 500 ms, TE: 11 ms), a fluid-attenuated inversion recovery image (TR: 8,000 ms, TE: 92 ms) for the transverse plane, and T 1 -weighted image for the coronal plane, with a slice thickness of 5-7 mm. All MRI findings were read and determined by a neuroradiologist who was blinded to the patients' profiles.

RESULTS

Table 1 shows the incidence of abnormal ENG findings in all cases confirmed SCD. Total SCD included all classifications, (OPCA, SDS, LCCA, and hereditary SCD). The common abnormal ENG findings in SCD were ocular saccadic dysmetria,

Table 1. Incidences of abnormal ENG findings in SCD patients

		SCD				
		Total	OPCA	SDS	LCCA	Hereditary
Total number		79	48	4	16	11
		(%)	(%)	(%)	(%)	(%)
Spontaneous nystagmus		42	31	25	50	45
Gaze-evoked nystagmus	Vertical	16	21	0	6	18
	Horizontal	0	0	0	13	0
	Bi-directional	17	10	0	38	18
Rebound nystagmus		11	31	0	19	27
Positioning nystagmus	transient downbeat	27	29	0	38	18
Saccadic pusuit		87	90	100	88	64
OKN	Normal	11	6	33	13	20
	Border	4	2	0	7	10
	Slight	7	4	0	13	10
	Moderate	9	11	0	13	10
	Severe	69	77	67	53	50
VS	Impaired	75	65	25	56	36

OKN; optokinetic nystagmus, VS;visual suppression, SCD;spinocerebellar degeneration,
OPCA; olivopontocerebellar atrophy, SDS;shy-drager syndrome, LCCA;late cortical cerebellar atrophy

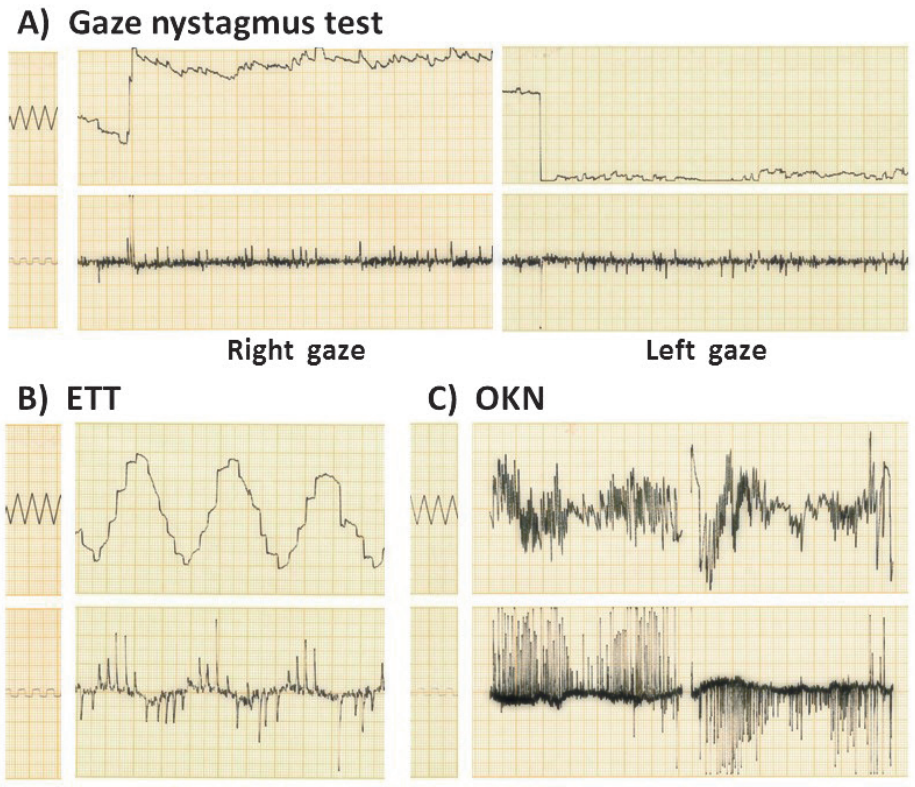

Fig. 1. Raw ENG data sample demonstrating abnormal findings. Multidirectional gaze nystagmus (nystagmus in the direction of gaze) (A) in the gaze nystagmus test, ocular saccadic dysmetria (B) in the eye tracking test (ETT), and severely impaired optokinetic nystagmus (OKN) (C).

impaired OKN and impaired VS. For each abnormal finding, we compared the data for each SCD type with the average data (total SCD). We did not consider SDS, because there were very few patients with this condition. Spontaneous nystagmus occurred in each SCD type, but its frequency was relatively low in OPCA and relatively high in LCCA. Vertical gaze nystagmus was less frequent in LCCA than in other SCD types, and horizontal gaze nystagmus was very rare in our cases. Multidirectional gaze nystagmus (nystagmus in the direction of gaze) occurred more frequently in LCCA than in other SCD types. Rebound nystagmus was elicited more frequently in hereditary SCD than in other types, but positioning downbeat nystagmus (pDBN) and saccadic pursuit were less frequent in hereditary SCD. OKN was more serious in, OPCA but milder in LCCA and hereditary SCD. Impaired VS was less frequent in hereditary SCD than in other types.

We studied the relationship between MRI findings and ocular abnormalities. MRI was performed in all patients. The patients finally showed abnormal findings, consisting brainstem and/or cerebellar atrophy. Fourteen of the patients had no abnormal MRI findings despite having abnormal ENG findings and our suspicion of SCD in our initial neuro-otological examinations. Among these 14 patients, 10 (71%) were diagnosed with SCD by subsequent MRI. Thus, we showed that in typical cases, the neuro-otological test was useful in the early diagnosis of SCD.

Case report

A 64-year-old male who was the son of non-consanguineous parents and had an unremarkable familial and past medical history noticed unsteadiness of gait 8 months before admission, which gradually progressed. On admission, he demonstrated horizontal multidirectional gaze nystagmus (Fig. 1A), saccadic pursuit (Fig. 1B) and severely impaired OKN (Fig. 1C) in our neuro-otological examinations, but no abnormal findings on brain MRI (Fig. 2A). Seven months after the initial MRI, brain MRI demonstrated cerebellar and brain-stem atrophy on the

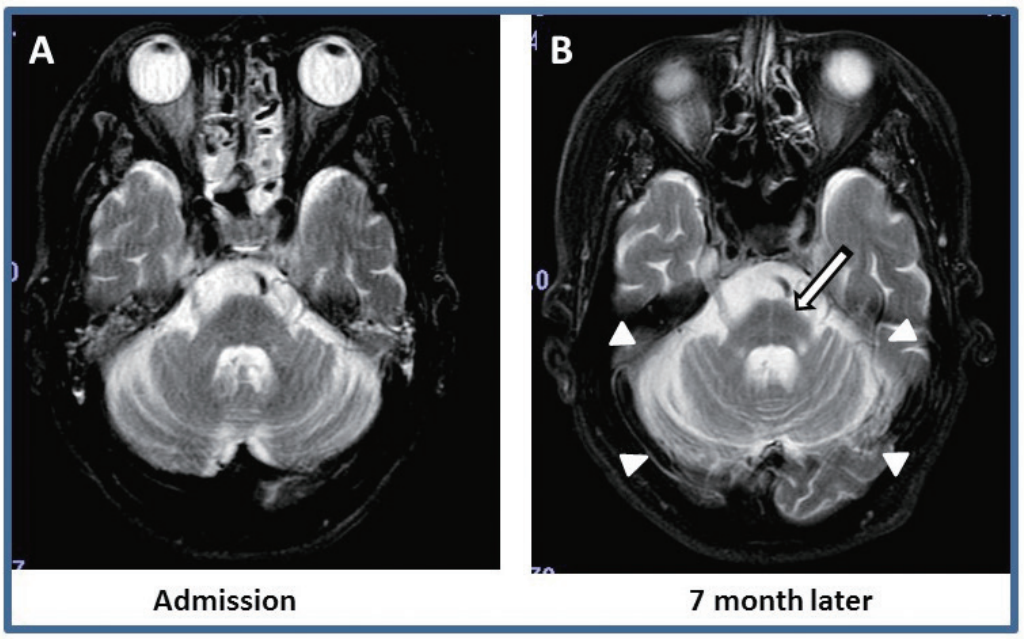

Fig. 2. Brain MRI findings (axial T2 weighted images). The brain stem and cerebellum were normal in appearance on admission (A), but the subsequent MRI (B, 7 months later) demonstrated abnormal findings, of cerebellar and brainstem atrophy (arrow-head) and the hot cross bun sign in the pontine (arrow).

T2 image and clearly showed the hot cross bun sign in the pontine (Fig. 2B).

DISCUSSION

The present observations suggest that neuro-otological testing provides useful information for diagnosing SCD, and that early vestibular dysfunction without abnormal MRI findings contributed significantly to initial symptoms in our patients. Among the abnormal findings in total SCD, we found high incidences of saccadic pursuit (87%), severely impaired of OKN (69%) and impaired VS (75%). These findings are consistent with those previously reported [5, 12, 13]. Therefore, deficits of smooth pursuit, OKN gain, or impaired fixation suppression of vestibule-ocular reflex (VOR) are the most common signs of SCD. However, we found distinctive abnormal findings in each SCD types in our patients. For example, the tendency to observe abnormal findings in hereditary SCD was similar to that in LCCA. It is possible that some patients, reported as having idiopathic LCCA, may have spinocerebellar ataxia type 6 (SCA6) [14], but we found that hereditary SCD had lower frequencies of abnormal findings in all tests compared with other SCD types. And it was not contracted to neuropathological studies [15-18]. The difference in frequencies may be related to the stage of disease. Because SCA patients had a family history of SCD, they may have visited the hospital and have their disease diagnosed at an early stage. In exceptional cases, hereditary SCD showed high frequencies of rebound nystagmus. Hood and coworkers assumed that the underlying pathology in rebound nystagmus is a chronic, slowly progressive, cerebellar degeneration of varied etiology [19]. Hashimoto *et al.* suggested rebound nystagmus should be included as a phenotype in investigations of genotype- phenotype correlations and factors responsible for phenotypic variability in SCA6 [20]. With regard to OKN, previous studies reported activation of the cerebellar hemispheres and structures such as the uvula, nodulus, declive, folium, and parts of the vermal pyramid [21, 22]. In particular, our OPCA patients showed a high frequency of severely impaired OKN. Saccadic slowing has been reported in ataxic syndromes with additional brainstem involvement (e.g. OPCA). On the other hand, saccade velocity has been found to be unaffected in cerebellar atrophy and Friedreich's ataxia [23-25]. Wessel *et al.* suggested that measurements of saccade velocity and VOR gain are

useful in distinguishing between cerebellar atrophy and OPCA [26]. LCCA is a non-hereditary SCD that presents with slowly progressive cerebellar ataxia as a prominent symptom and is characterized neuropathologically by a limited main lesion to the cerebellar cortex and inferior olivary nucleus [27-29]. Our LCCA patients showed a higher frequency of mildly impaired OKN compared with OPCA patients, but we also observed severely impaired OKN in 53% of LCCA patients. Ota *et al*. indicated that there are two types of cerebellar cortex lesions in idiopathic LCCA, vermis dominant and cerebellar hemispheric dominant [29]. Bense *et al*. found no activations or deactivations within other parts of the cerebellar vermis [30]. Therefore, we assume that the seriousness of OKN in LCCA patients depends on the progression of the disease or the site of the lesion. These data support the view that OKN is useful for distinguishing between LCCA and OPCA, but not for advanced LCCA. Interestingly, our LCCA patients showed higher frequencies of pDBN. Neuronal loss, the likely cause of pDBN, primarily encompasses the inferior olives, pontine nuclei, and Purkinje cells of the cerebellar vermis [31, 32]. Anderson *et al.* suggested that pDBN in MSA is due to Purkinje cell dysfunction in the cerebellar vermis [13]. According to the neuropathological features, the cerebellar cortical lesion progresses from Purkinje cell loss in LCCA [29]. Therefore, LCCA patients may show higher frequencies of pDBN.

We studied the relationship between MRI findings and ocular abnormalities in our patients with SCD, and showed that in typical cases, neuro-otological testing was useful in the diagnosis of SCD. Seventy-one percent of the patients diagnosed with SCD by neuro-otological testing but with no abnormal findings in the initial MRI showed abnormal findings in the subsequent MRI.

Notably, one patient was diagnosed as having SCD by MRI more than years after our test raised the suspicion of SCD. Although imaging machines have improved dramatically in recent years, we suggest that the limitations of imaging studies should be considered during examination. Neuro-otological examinations are very sensitive to functional disorders and are useful in the diagnosis of SCD same as others [33-35].

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