



Title	Rare frequency of downbeat positioning nystagmus in spinocerebellar ataxia type 31
Author(s)	Yabe, Ichiro; Matsushima, Masaaki; Yoshida, Kunihiro; Ishikawa, Kinya; Shirai, Shinichi; Takahashi, Ikuko; Sasaki, Hidenao
Citation	Journal of the Neurological Sciences, 350(1-2), 90-92 https://doi.org/10.1016/j.jns.2014.12.042
Issue Date	2015-03-15
Doc URL	http://hdl.handle.net/2115/60844
Rights	© 2015, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International http://creativecommons.org/licenses/by-nc-nd/4.0/
Rights(URL)	http://creativecommons.org/licenses/by-nc-nd/4.0/
Type	article (author version)
File Information	manuscript.pdf



[Instructions for use](#)

Clinical Short Communication

Rare frequency of downbeat positioning nystagmus in spinocerebellar ataxia type

31

Ichiro Yabe¹, Masaaki Matsushima¹, Kunihiro Yoshida², Kinya Ishikawa³, Shinichi Shirai¹, Ikuko Takahashi¹, Hidenao Sasaki¹

1) Department of Neurology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

2) Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan

3) Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence author; Hidenao Sasaki

Department of Neurology, Hokkaido University Graduate School of Medicine, N15 W7 Kita-ku, Sapporo 060-8638, Japan

e-mail; h-isasak@med.hokudai.ac.jp

Text: 712 words (not including acknowledgment, or references)

Running head: Rare DPN in SCA31

Keywords: spinocerebellar ataxia type 31, spinocerebellar ataxia type 6, downbeat positioning nystagmus, dizziness, vertigo, spinocerebellar degeneration, cortical cerebellar atrophy

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Abstract

Spinocerebellar ataxia type 31 (SCA31) and spinocerebellar ataxia type 6 (SCA6) are the most frequent types of spinocerebellar degeneration in Japan. Previous reports described that it was difficult to distinguish SCA6 and SCA31 in clinical situations. There is not much difference except that the onset age of SCA31 is slightly higher than that of SCA6. Therefore we surveyed our medical records retrospectively, and then compared clinical symptoms of SCA6 and SCA31. As previously stated, the onset age of SCA31 is higher than that of SCA6. Gaze-evoked nystagmus is more frequent in SCA6 than in SCA31. The percentage in downbeat positioning nystagmus (DPN) is as high as 63% in SCA6. In contrast, DPN in SCA31 is rare and subtle. Our study suggests that the presence of DPN is an important sign that can differentiate SCA6 from SCA31 clinically.

Introduction

Spinocerebellar ataxia type 31 (SCA31) is one of the most frequent types of spinocerebellar degeneration in Japan [1]. Because the basic symptom is cerebellar ataxia with other symptoms occurring infrequently, SCA31 is classified as a pure cerebellar ataxia. SCA31 develops by long expanded insertions of a TGGAA repeat in the introns of the thymidine kinase 2 and the brain expressed associated with *Nedd4 (BEAN)* genes [1]. Another frequent form of pure cerebellar ataxia in Japan is spinocerebellar ataxia type 6 (SCA6) [2]. SCA6 develops through small expansions of a CAG repeat at the 3' end of the P/Q type Ca²⁺ channel alpha1 subunit gene [3]. Previous reports described that it was difficult to distinguish SCA6 and SCA31 in clinical situations. There is not much difference except that the onset age of SCA31 is slightly higher than that of SCA6 [4, 5].

Among SCA6 and two allelic disorders (episodic ataxia type 2 and familial hemiplegic migraine type 1), downbeat positioning nystagmus (DPN) was recognized at a high frequency [6, 7, 8], and episodes of vertigo and oscillopsia associated with DPN were reported [7, 8]. Symptoms were often noted early in these disorders [7]. However, the frequency of DPN has not been yet reported in SCA31. Therefore we surveyed our medical records retrospectively, and then compared the clinical symptoms of SCA6 and SCA31.

Subjects and Methods

Study subjects were 30 SCA6 patients and 26 SCA31 patients who visited Hokkaido University Hospital, Shinshu University Hospital and Medical Hospital, Tokyo Medical and Dental University. The patients had been definitively genetically diagnosed after informed consents were obtained. In 30 SCA6 patients and 23 SCA31 patients, DPN was

examined according to a previously reported method [7]. DPN was first examined without Frenzel glasses and then with the glasses, with observation being done directly by the examiner. Differences in age at onset and examination between SCA6 and SCA31 were examined by Wilcoxon rank sum test. Each incidence of clinical features including DPN between the two disorders was examined by Fisher's exact test, and the expected value should be more than 5.

Results

The onset symptoms of SCA6 were dizziness: 50%, unsteady walk: 44%, dysgraphia: 3% and dysarthria: 3%. Those with SCA31 had unsteady walk: 67%, and dysarthria 33% (Figure 1). The summary of clinical symptoms is shown in Table 1. As previously stated, the onset age of SCA31 is higher than that of SCA6. Gaze-evoked nystagmus is more frequent in SCA6 than in SCA31. In consideration of the gaze nystagmus severity, patients with moderate to marked nystagmus often had SCA6 although those with nystagmoid to mild nystagmus primarily had SCA31. The percentage in DPN was as high as 63% in SCA6. In contrast, DPN in SCA31 was found in only one of 23 patients examined. With the exception of DPN, the symptoms and severity in this patient were similar to other SCA31 patients. Furthermore, in this patient, DPN was subtle, even when using Frenzel glasses, although that of SCA6 was macroscopic.

Discussion

This study reveals that SCA6 accompanies DPN and its concomitant symptoms at a high frequency. On the other hand, these signs in SCA31 were rare. This fact clearly distinguishes SCA31 from SCA6. Prior studies described the frequency of gaze

nystagmus in SCA31 at 15 to 100% [9, 10]. This variation was presumed to be caused by the difference of whether slight nystagmus in SCA31 was detected.

At present, the role of the cerebellum in developing DPN is not clearly established in Purkinje cells, which are selectively involved in SCA6, and are connected directly with the vestibular nucleus [11, 12]. Previous investigations showed that Purkinje cells located mainly in the cerebellar flocculus and vermis play an important role in vertical vestibulo-ocular reflex (vVOR) cancellation [11, 12, 13]. These regions are known to be severely affected in SCA6 [14]. Furthermore, VOR gain in SCA6 was shown to be within normal limits [15]. Thus, DPN in SCA6 is considered to be due to a dysfunction of vVOR cancellation. The detailed analyses of these neuropathological changes in the flocculus of SCA31 have not yet been done [1, 4, 16]. Future studies should consider vVOR in SCA6 and SCA31.

Conclusion

Although further investigation is needed, the presence of DPN is an important sign that can differentiate SCA6 from SCA31 clinically.

Acknowledgements

We thank Mrs. Mari Kimura for technical support of the genetic analysis. This work was supported in part by a Grant-in-Aid for the *Research Committee for Ataxic Diseases* of the Research on Measures for Intractable Diseases from the Ministry of Health, Welfare and Labor, Japan.

References

- [1] Sato N, Amino T, Kobayashi K, Asakawa S, Ishiguro T, Tsunemi T, et al. Spinocerebellar ataxia type 31 is associated with “ inserted ” pentanucleotide repeats containing (TGGAA) n. *Am J Hum Genet* 2009; 85: 544-557
- [2] Yabe I, Sasaki H, Matsuura T, Takada A, Wakisaka A, Suzuki Y, et al. SCA6 mutation analysis in a large cohort of the Japanese patients with lateonset pure cerebellar ataxia. *J Neurol Sci* 1998; 156: 89-95
- [3] Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, et al. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the $\alpha 1A$ -voltage- dependent calcium channel. *Nat Genet* 1997; 15: 62-69
- [4] Ishikawa K, Toru S, Tsunemi T, Li M, Kobayashi K, Yokota T, et al. An autosomal dominant cerebellar ataxia linked to chromosome 16q22.1 is associated with a single-nucleotide substitution in the 5' untranslated region of the gene encoding a protein with spectrin repeat and Rho guanine-nucleotide exchange-factor domains. *Am J Hum Genet* 2005; 77: 280-296
- [5] Yoshida K, Shimizu Y, Morita H, Okano T, Sakai H, Ohata T, et al. Severity and Progression Rate of Cerebellar Ataxia in 16q-linked Autosomal Dominant Cerebellar Ataxia (16q-ADCA) in the Endemic Nagano Area of Japan. *Cerebellum* 2009; 8: 46-51
- [6] Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca² channel gene CACNL1A4. *Cell* 1996; 87: 543-552
- [7] Yabe I, Sasaki H, Takeichi N, Takei A, Hamada T, Fukushima K, et al. Positional

vertigo and macroscopic downbeat positioning nystagmus in spinocerebellar ataxia type 6 (SCA6). *J Neurol* 2003; 250: 440-443

[8] Yabe I, Kitagawa M, Suzuki Y, Fujiwara K, Wada T, Tsubuku T, et al. Downbeat positioning nystagmus is a common clinical feature despite variable phenotypes in an FHM1 family. *J Neurol* 2008; 255: 1541-1544

[9] Onodera Y, Aoki M, Mizuno H, Warita H, Shiga Y, Itoyama Y. Clinical features of chromosome 16q22.1 linked autosomal dominant cerebellar ataxia in Japanese. *Neurology* 2006; 67: 1300-1302

[10] Basri R, Yabe I, Soma H, Sasaki H. Spectrum and prevalence of autosomal dominant spinocerebellar ataxia in Hokkaido, the northern island of Japan: a study of 113 Japanese families. *J Hum Genet* 2007; 52: 848-855

[11] Fukushima K, Fukushima J, Kaneko CR, Fuchs AF. Vertical Purkinje cells of the monkey floccular lobe: simple-spike activity during pursuit and passive whole body rotation. *J Neurophysiol* 1999; 82: 787-803

[12] Zee DS, Yamazaki A, Butler PH, Gücer G. Effects of ablation of flocculus and paraflocculus of eye movements in primate. *J Neurophysiol* 1981; 46: 878-899

[13] Bertholon P, Bronstein AM, Davies RA, Rudge P, Thilo KV. Positional down beating nystagmus in 50 patients: cerebellar disorders and possible anterior semicircular canalolithiasis. *J Neurol Neurosurg Psychiatr* 2002; 72: 366-372

[14] Iwabuchi K, Tsuchiya K, Uchihara T, Yagishita S. Autosomal dominant spinocerebellar degenerations. Clinical, pathological, and genetic correlations. *Rev*

Neurol 1999; 155: 255-270

[15] Takeichi N, Fukushima K, Sasaki H, Yabe I, Tashiro K, Inuyama Y. Dissociation of smooth pursuit and vestibulo-ocular reflex cancellation in SCA-6. Neurology 2000; 54: 860-866

[16] Owada K, Ishikawa K, Toru S, Ishida G, Gomyoda M, Tao O, et al. A clinical, genetic, and neuropathologic study in a family with 16q-linked ADCA type III. Neurology 2005; 65: 629-632

Table 1. Clinical features of our patients

	SCA6	SCA31	p value
Patients (n)	30	26	
Onset age (average \pm SD)	49.2 \pm 11.3	58.4 \pm 5.9	0.0007*
Age at examination (average \pm SD)	59.4 \pm 10.8	66.5 \pm 7.6	0.0050*
Cerebellar ataxia (n)	30 (100%)	26 (100%)	
Dysarthria (n)	26 (86.7%)	25 (96.1%)	0.3585**
Gaze nystagmus (n)	26 (86.7%)	11 (42.3%)	0.0006**
Nystagmoid to mild nystagmus (n)	2 (7.7%)	11 (100%)	< 0.0001**
Moderate to marked nystagmus (n)	24 (92.3%)	0 (0%)	< 0.0001**
Downbeat positioning nystagmus with Frenzel glasses (positive /examined patients; n)	19 / 30	1 / 23	< 0.0001**
Downbeat positioning nystagmus without Frenzel glasses (positive /examined patients; n)	18 / 30	0 / 23	< 0.0001**
Deep tendon reflex increase (n)	3 (10.0%)	3 (11.5%)	1.0000**
Deep tendon reflex decrease (n)	5 (16.7%)	8 (30.8%)	0.3416**
Babinski's sign (n)	1 (3.3%)	2 (7.7%)	0.5920**

*Wilcoxon rank sum test, **Fisher's exact test

Figure 1. Initial symptoms