Characteristics of audiogram configuration in multiple-system atrophy C and cortical cerebellar atrophy

Running head: Audiogram shape in MSA-C and CCA

Ryotaro Omichi[1)], M.D., Yukihide Maeda[1)], M.D., Ph.D., Akiko Sugaya[1)], M.D., Ph.D., Yuko Kataoka[1)], M.D., Ph.D., Shin Kariya[1)], M.D., Ph.D., Rie Nagayasu[1)], Atsuko Nakagawa[1)], M. Sc., Toru Yamashita[2)], M.D., Ph.D., Koji Abe[2)], M.D., Ph.D., Kazunori Nishizaki[1)], M.D., Ph.D.

Department of Otolaryngology - Head and Neck Surgery[1)] and Department of Neurology[2)], Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-Cho, Kita-Ku, Okayama 700-8558, Japan

Corresponding author:

Yukihide Maeda, M.D., Ph.D.

Department of Otolaryngology - Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-Cho, Kita-Ku, Okayama 700-8558, Japan

Tel: +-81-86-235-7307; Fax: +-81-86-235-7308; email: maedayj@yahoo.co.jp

Abstract

*Conclusion***:** The prevalence of low-tone hearing loss (LTHL) is significantly high in spinocerebellar degeneration (SCD) with cerebellar predominance, including multiple-system atrophy C (MSA-C) and cortical cerebellar atrophy (CCA).

Objective: We aimed to test the hypothesis that SCD with cerebellar predominance, MSA-C and CCA may cause auditory symptoms.

Methods: The shape and threshold of pure-tone audiograms were evaluated for MSA-C (*n*=47; mean (±standard deviation) age, 61.6±8.9 years), CCA (*n*=16; 62.8±9.5 years) and age-matched controls (*n*=169; 62.5±10.7 years). To differentiate specific hearing loss for MSA-C and CCA from presbycusis, the shape of audiograms was examined based on previously established audiological criteria.

Results: When audiogram shape was defined according to audiological criteria, the odds ratio for LTHL in SCD compared to controls was 2.492 (95% confidence interval (CI): 1.208-5.139; $p<0.05$, Pearson's chi-square test) in MSA-C and 2.194 (95% CI: 0.709-6.795) in CCA. When the selection of audiogram shape according to these criteria was verified by 3 certified audiologists, odds ratios for LTHL in MSA-C and CCA were 3,243 (95% CI:

1.320-7.969) and 3.692 (95% CI: 1.052-12.957), respectively, significantly higher than in controls.

Key words: audiogram configuration; sensorineural hearing loss; low-tone hearing loss; spinocerebellar degeneration; multiple-system atrophy C; cortical cerebellar atrophy

Introduction

Spinocerebellar degeneration (SCD) covers a group of neurodegenerative diseases that affect the cerebellum and brainstem. Within this category of neurodegenerative disease, the diagnosis of multiple-system atrophy (MSA) can be subdivided into forms showing a cerebellar predominance (MSA-C), parkinsonism predominance (MSA-P) and predominance in the autonomic nervous system (Shy-Drager syndrome), based on the phenotype. Cortical cerebellar atrophy (CCA) is diagnosed when the pathological phenotype is restricted to cerebellar symptoms. The primary clinical symptoms of these degenerative diseases are ataxia, cranial nerve signs, extrapyramidal signs, and autonomic symptoms, often appearing during adulthood and progressing with age. Detailed characterization of the disease phenotypes is useful for differentiating between these SCD subtypes.

The clinical symptoms of familial SCD with autosomal-dominant inheritance, SCA36 (spinocerebellar ataxia 36), which is prevalent in western Japan and the most common form of hereditary SCD in Galicia, Spain, is characterized by sensorineural hearing loss with late-adult onset. The disease phenotype of SCA36 involves pure cerebellar symptoms such as ataxic dysarthria, truncal and

limb ataxia, and disdiadochokinesia (pure CCA phenotype) and motor neuron involvement [1, 2]. Several neuroimaging studies have proposed an association between the cerebellum and auditory function. Specific regions in the cerebellum may play roles in auditory tasks using controlled acoustic stimuli, as shown by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) [3]. Some reports have indicated a link between auditory brainstem response (ABR) and cerebellar atrophy [4]. In SCD patients, particularly among patients with MSA-C, cerebellar atrophy is associated with ABR abnormalities [5]. However, those studies did not evaluate pure tone audiograms in patients. Based on these observations, we hypothesized that SCD with a cerebellar predominance, such as MSA-C or CCA, may be associated with auditory symptoms, and therefore compared the profiles of audiograms in patients showing those pathologies with those of age-matched controls.

As the phenotype of SCD typically involves adult onset and progression with age, distinguishing hearing loss due to the pathological process of SCD from presbycusis (hearing loss predominantly in the high-frequency regions of the audiogram) is often difficult. In the majority of cases, hearing loss due to the

pathological process of SCD cannot be detected by simple comparison of hearing thresholds between SCD and age-matched control cohorts, because both show significant presbycusis [2]. Progression of presbycusis in the high-frequency range represents a major obstacle to the evaluation of disease-related sensorineural hearing loss in older adults. To this end, previous studies have analyzed audiographic data from older adults (54-66 years old) and established criteria to classify audiogram configurations into “high frequency sloping” (HFS), “flat”, “low frequency ascending” (LFA), “mid-frequency U-shape” (MFU), and “mid-frequency reversed U-shape” (MFRU) [6-8]. In the present study, audiogram configurations were analyzed for MSA-C and CCA patients and age-matched controls. We focused on sensorineural hearing loss at low frequencies (low-tone hearing loss, LTHL; average threshold >25 dB nHL at 125, 250, and 500 Hz with LFA or MFRU configuration), in order to discuss hearing loss with a pathological basis in SCD with cerebellar predominance (MSA-C or CCA).

Materials and methods

Sample collection

This study involved a retrospective chart review of MSA-C and CCA patients who had been referred to our Otolaryngology Department for audiological evaluation between 2006 and 2014. The study protocol was approved by the Institutional Ethics Committee at Okayama University Hospital (#1505-013) and was conducted in accordance with the principles expressed in the Declaration of Helsinki. The diagnosis of MSA-C (*n*=47; 23 males, 24 females; mean (±standard deviation (SD)) age, 61.6±8.9 years) and CCA (*n*=16; 7 males, 9 females; mean age, 62.8±9.5 years) was made by neurologists based on the disease phenotype verified by extensive neurological, serological, neuroelectrophysiological, and neuroradiological (MRI and single photon emission computed tomography) examinations. For age-matched controls (*n*=169; 62.5±10.7 years), subjects with a history of chemotherapy, any ear diseases such as sudden hearing loss or any ear surgery were excluded. For all subjects, pure-tone hearing threshold was examined by both air and bone conduction. Otoscopic examinations and audiograms excluded diseases in the middle ear and tympanic membrane. Air conduction thresholds in pure-tone audiograms of all these MSA-C, CCA, and control subjects were analyzed.

Classification of audiogram shape and definition of LTHL

The shapes of audiograms in the right and left ears were classified into the 5 categories: HFS, High frequency sloping; Flat; LFA, Low frequency ascending; MFU, Mid frequency U; MFRU, Mid frequency reversed U, according to the definitions of audiometric configuration used in previous reports [6]. According to the modified criteria established by Demeester et al [6], HFS was defined when the difference between the mean of the hearing thresholds at 500/1000 Hz and at 4000/8000 Hz was >15 dB. “Flat” audiograms were those with differences among means at 250/500 Hz, 1000/2000 Hz, and 4000/8000 Hz ≤15 dB. An LFA audiogram configuration was classified when the difference between the poorer low-frequency and the best threshold in higher frequencies was >15 dB. MFU was defined when differences between the poorest thresholds in the mid-frequencies and those in the low and high frequencies were >15 dB. MFRU was categorized when differences between poorest thresholds in low and high frequencies, and best thresholds in the mid-frequencies were >15 dB. When the audiogram configuration met the criteria of LFA or MFRU and at the same time, the mean threshold of low frequencies (125, 250, 500 Hz) was >25 dB, the audiogram was considered to show hearing loss specifically in the low frequencies (LTHL). Subjects with LTHL in the right, left, or both ears were

considered to have LTHL.

In addition to these selection criteria, 3 certified experts (audiologist/otoneurologist) with >14 years of experience in clinical audiology were assigned to independently verify audiograms for LFA and MFRU configuration according to experience. Only when all 3 experts judged an audiogram shape as LFA or MFRU and mean threshold at 125/250/500 Hz was >25 dB, the audiogram was considered to show LTHL.

Statistical analysis

Average thresholds (averages of thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz) were compared between controls and MSA-C or CCA using the Kruskal-Wallis test and Mann-Whitney *U*-test (significance level $p<0.05$). The odds ratio for the prevalence of LTHL (average threshold >25 dB nHL at 125, 250, and 500 Hz with LFA or MFRU configuration) and 95% confidence interval (95%CI) was calculated for MSA-C and CCA compared with controls. Pearson's chi-squared test and Fisher's exact test were applied for the number of LFA and MFRU between MSA-C, CCA and control (significance level $p<0.05$). Values in this study are given as mean ±SD, and statistical analyses were performed using SPSS version 22.0 software (SPSS, Chicago, IL).

Results

In the SCD and control cohorts, no differences between males and females were detected in the average hearing threshold (mean thresholds at 250, 500, 1000, 2000, 4000 and 8000 Hz) of the right ear (male SCD: 36.9±17.7 dB nHL vs. female SCD: 32.8±17.5 dB nHL; male control: 36.5±12.9 dB nHL vs. female control: 34.2±14.7 dB nHL) or left ear (male SCD: 36.9±14.5 dB nHL vs. female SCD: 33.1±17.4 dB nHL; male control: 37.2±14.3 dB nHL vs. female control: 36.1±14.3 dB nHL). No male-to-female bias was found in the odds ratio for prevalence of LTHL (male-to-female odds ratio in SCD cohort: 1.06; male-to-female odds ratio in control cohort: 0.98).

Table 1 summarizes the data and results of audiogram configurations and average threshold in the MSA-C, CCA, and control cohorts. Mean thresholds of hearing levels in MSA-C (right: 33.3±16.3 dB nHL; left: 34.9±16.7 dB nHL; mean age, 61.6±8.9 years), CCA (right: 39.9±21.0 dB nHL; left: 36.0±14.7 dB nHL; mean age, 62.8±9.5 years), and age-matched controls (right: 35.9±13.4 dB nHL; left: 36.9±14.3 dB nHL; mean age, 62.5±10.7 years) consistently showed mild hearing loss, but no significant difference was evident among cohorts. When audiogram configurations were classified according to the audiological criteria of

Demeester et al. [6], odds ratios for LTHL (hearing threshold >25 dB nHL with LFA/MFRU audiogram configurations) was significantly higher in the MSA-C cohort than in the control cohort (odds ratio: 2.492; 95%CI: 1.208-5.139; *p*=0.015, Pearson's chi-square test). The odds ratio of LTHL in the CCA cohort compared to controls was 2.194 (95%CI: 0.709-6.795) according to these criteria. Within audiograms classified as LTHL (hearing threshold >25 dB nHL with LFA/MFRU audiogram configurations) by the criteria of Demeester et al., all 3 certified audiologists independently judged 10, 4, and 13 audiograms in the MSA-C, CCA, and control cohorts as showing LTHL (LFA+MFRU configurations). Based on these results, the odds ratio of LTHL in MSA-C compared to the control cohort was 3.243 (95%CI: 1.320-7.969; *p*=0.014, chi-square test). The odds ratio of LTHL in the CCA cohort compared to controls was 3.692 (95%CI: 1.052-12.957; *p*=0.054; chi-square test).

To clearly show the results of the above selection process for audiograms, all audiograms classified as LTHL in the MSA-C and CCA cohorts by the final selection are shown in Figure 1. This showed that the older the MSA-C and CCA subjects, the more severe the hearing loss, at both low and high frequencies. As discussed below, hearing loss in the high-frequency range may represent

presbycusis, but the prevalence of hearing loss at low frequencies was higher in the MSA-C and CCA cohorts than in controls.

Discussion

We revealed that LTHL (hearing threshold >25 dB nHL with LFA/MFRU audiogram configurations) was more frequent with MSA-C and CCA than in the control cohort. Several audiogram configurations have been reported in control populations without otological disease [6-8]. The HFS audiogram is the most common audiogram shape, observed in 65-75% of older adults. LFA and MFRU configurations were very rare (together comprising <1%) according to the data of Deemester et al. from a normal aged population [6]. As the HFS audiogram is often associated with the normal physiological process of presbycusis, we focused on LTHL in MSA-C and CCA patients, with the aim of detecting disease-related hearing loss in these SCD cohorts with predominantly cerebellar symptoms.

The present data focused on pure-tone audiograms and do not provide direct evidence of how LTHL might be mediated in the central or peripheral auditory pathways of SCD with a cerebellar predominance. ABR abnormalities are

reportedly found in 72.7% of 22 MSA-C patients. The interpeak latency of waves I-V is prolonged in MSA-C patients [5]. Chokroverty et al. also observed a delay in wave I for ABR in MSA-C [9]. Reduction in the amplitude of wave I was recognized in a MSA-C patient [4]. Waves I and V in ABR are generated by neural activities in the peripheral cochlear nerve and inferior colliculus of the caudal midbrain, respectively. No correlation was found between click-ABR abnormalities and age, sex, disease duration, degree of clinical involvement, or mode of inheritance [5]. In ABRs of subjects with familial SCD with cerebellar involvement, latency of wave I was delayed and interpeak latencies of waves I-V were prolonged [10]. A pathoanatomical analysis of 6 clinically diagnosed patients showing familial SCD with cerebellar predominance, SCA2, revealed severe atrophy and myelin loss in the peripheral auditory nerve and dorsal and ventral cochlear nuclei in these patients [11]. A meta-analysis of fMRI and PET studies proposed that specific areas of cerebellum, such as the lateral crus I area, play a fundamental role in auditory sensory processing [3]. These observations suggest that both central and peripheral auditory pathways are involved in LTHL in MSA-C and CCA patients. The most interesting point may be the reason why patients with MSA-C and CCA had LTHL. As shown in Figure1, it

is observed in the present data that LTHL in these patients is progressing with age in the adulthood, which accompanies progression of the clinical symptoms in the central nervous systems in MSA-C and CCA. It can be hence speculated that the pathological origin of LTHL at least partly involves central auditory pathway. Sound stimuli with different frequencies (e.g. low-frequency sounds) activate different tonotopically organized neurons within the dorsal, posteroventral, and anteroventral cochlear nuclei, trapezoid body, inferior colliculus of the central auditory pathway [12]. Further evaluation of MSA-C and CCA patients by auditory steady-state response and ABR using tone burst stimuli would be useful to understand the pathology of LTHL in MSA-C and CCA patients, because these electrophysiological methods provide frequency-specific investigations of the central auditory pathway at low frequencies.

To the best of our knowledge, the present study is the first to systematically analyze pure-tone audiograms in MSA-C and CCA patients.

LTHL is more frequent in MSA-C and CCA patients than in age-matched controls. When LTHL is clinically observed in patients with MSA-C or CCA, continued audiological follow-up of the patient by audiological professionals is recommended, because LTHL may reflect an audiological phenotype specific for

the pathology of MSA-C or CCA. Further studies are needed to understand how such LTHL is mediated in the central and peripheral auditory pathways in humans.

Acknowledgements

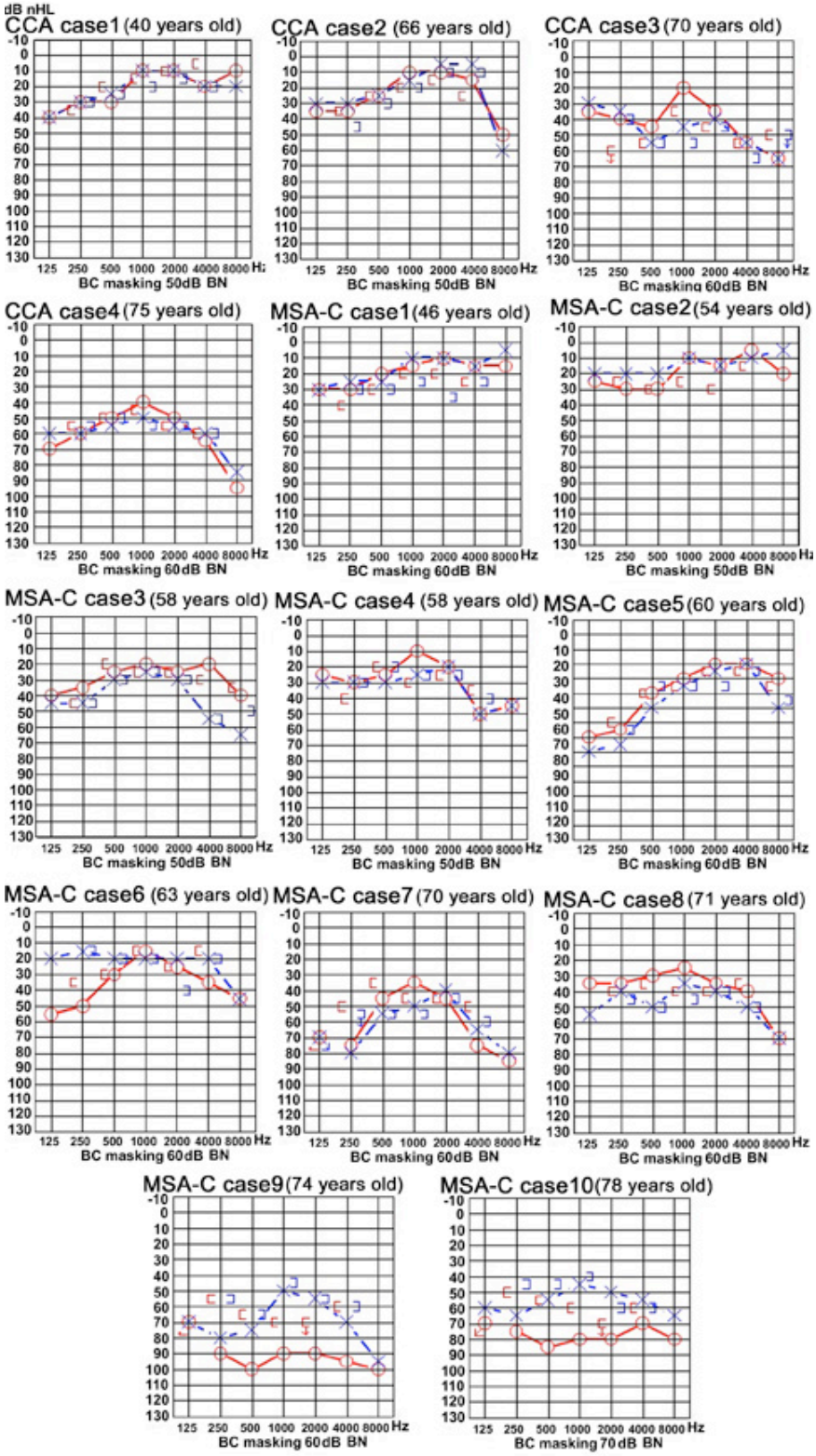
The authors have no conflicts of interest to declare.

Table 1.

Table1. Summary of audiogram configuration and mean threshold in MSA-C, CCA, and control

Audiogram classification based on criteria by Demeester, et al.	MSA-C (61.6±8.9 years old; mean±S.D.; *n*=47)		CCA (62.8±9.5years old; *n*=16)		Control (62.5±10.7 years old; *n*=169)	
	Rt	Lt	Rt	Lt	Rt	Lt
LFA	3(6.4%)	2(4.3%)	2(12.5%)	1(6.3%)	7(4.1%)	5(3.0%)
MFRU	6(12.8%)	7(14.9%)	3(18.8%)	1(6.3%)	16(9.5%)	13(7.6%)
MFU	0	0	0	0	0	0
Flat	27(57.4%)	27(57.4%)	5(31.3%)	5(31.3%)	71(42.0%)	74(43.8%)
HFS	11(23.4%)	11(23.4%)	6(37.5%)	9(56.3%)	75(44.4%)	77(45.6%)
Mean threshold of hearing level	33.3±16.3 dB nHL	34.9±16.7	39.9±21.0	36.0±14.7	35.9±13.4	36.9±14.3
odds ratio for low tone hearing loss vs control (LFA+MFRU; mean of 125,250,500Hz>25dB nHL) Demeester's criteria	2.492 (95% CI:1.208-5.139) Pearson's Chi-square test: p=0.015<0.05		2.194 (95% CI:0.709-6.795) Chi-square test: p>0.05			
odds ratio for low tone hearing loss vs control (LFA+MFRU; mean of 125,250,500Hz>25dB nHL) Demeester's criteria and verified by 3 certified audiologist	3.243 (95% CI: 1.320-7.969) Chi-square test: p=0.014<0.05		3.692 (95% CI:1.052-12.957) Chi-square test: p=0.054			

Figure 1.


dB nHL
CCA case1 (40 years old)
BC masking 50dB BN
CCA case2 (66 years old)
BC masking 50dB BN
CCA case3 (70 years old)
BC masking 60dB BN
CCA case4 (75 years old)
BC masking 60dB BN
MSA-C case1 (46 years old)
BC masking 60dB BN
MSA-C case2 (54 years old)
BC masking 50dB BN
MSA-C case3 (58 years old)
BC masking 50dB BN
MSA-C case4 (58 years old)
BC masking 50dB BN
MSA-C case5 (60 years old)
BC masking 60dB BN
MSA-C case6 (63 years old)
BC masking 60dB BN
MSA-C case7 (70 years old)
BC masking 60dB BN
MSA-C case8 (71 years old)
BC masking 60dB BN
MSA-C case9 (74 years old)
BC masking 60dB BN
MSA-C case10 (78 years old)
BC masking 70dB BN
125 250 500 1000 2000 4000 8000 Hz

Legends

Table 1. Summary of audiogram configurations and mean thresholds of hearing level in MSA-C, CCA, and control cohorts.

Mean thresholds of hearing level in MSA-C, CCA, and controls showed mild hearing loss >25 dB nHL, but no significant differences were detectable among groups. According to the audiological criteria of Demeester et al., odds ratios for low-tone hearing loss (LTHL; hearing threshold >25 dB nHL at 125, 250 and 500 Hz with audiogram configuration of low-frequency ascending/mid-frequency reversed U) were significantly higher in the MSA-C cohort than in controls (odds ratio: 2.492; 95% confidence interval: 1.208-5.139; $p<0.05$, Pearson's chi-square test). The odds ratio for LTHL in CCA cohort was 2.194 (95%CI: 0.709-6.795). When these audiological criteria were verified from judgements of audiogram configuration by 3 certified audiologists, odds ratios for LTHL in MSA-C (3.243; 95%CI: 1.320-7.969) and CCA (3.692; 95%CI: 1.052-12.957) were significantly higher than in the control cohort. Types of audiogram configuration: LFA, low frequency ascending; MFRU, mid-frequency reversed U; MFU, mid-frequency U; HFS, high frequency sloping.

Figure 1. Audiograms selected as low-tone hearing loss (LTHL) by final selection in MSA-C and CCA cohorts.

LTHL was defined as: hearing threshold >25 dB nHL at 125, 250 and 500 Hz with audiogram configuration of low frequency ascending/mid-frequency reversed U by the audiological criteria of Demeester et al. [2009], and verified independently by 3 certified audiologists. The older patients are, the more severe the hearing loss, both in the low and high frequencies of audiograms.

References

[1] Kobayashi H, Abe K, Matsuura T, Ikeda Y, Hitomi T, Akechi Y, et al. Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement. Am J Hum Genet. 2010; 89: 121-30.

[2] Ikeda Y, Ohta Y, Kurata T, Shiro Y, Takao Y, Abe K. Acoustic impairment is a distinguishable clinical feature of asidan/sca36. J Neurol Sci 2013; 324: 109-112.

[3] Petacchi A, Laird AR, Fox PT, Bower JM. Cerebellum and auditory function: An ALE meta-analysis of functional neuroimaging studies. Hum Brain Mapp

2005; 25: 118-128.

[4] Gilroy J, Lynn GE. Computerized tomography and auditory-evoked potentials. Use in the diagnosis of olivopontocerebellar degeneration. Arch Neurol 1978; 35: 143-147.

[5] Sinatra MG, Baldini SM, Baiocco F, Carenini L. Auditory brainstem response patterns in familial and sporadic olivopontocerebellar atrophy. Eur Neurol 1988; 28: 288-290.

[6] Demeester K, van Wieringen A, Hendrickx JJ, Topsakal V, Fransen E, van Laer L, et al. Audiometric shape and presbycusis. Int J Audiol 2009; 48: 222-232.

[7] Allen PD, Eddins DA. Presbycusis phenotypes form a heterogeneous continuum when ordered by degree and configuration of hearing loss. Hear Res 2010; 264: 10-20.

[8] Hannula S, Bloigu R, Majamaa K, Sorri M, Maki-Torkko E. Audiogram configurations among older adults: Prevalence and relation to self-reported hearing problems. Int J Audiol 2010; 50: 793-801.

[9] Chokroverty S, Duvoisin RC, Sachdeo R, Sage J, Lepore F, Nicklas W. Neurophysiologic study of olivopontocerebellar atrophy with or without glutamate

dehydrogenase deficiency. Neurology 1985; 35: 652-659.

[10] Manganelli F, Perretti A, Nolano M, Lanzillo B, Bruni AC, De Michele G, et al. Electrophysiololgic characterization in spinocerebellar ataxia 17. Neurology 2006; 66: 932-934.

[11] Gierga K, Bürk K, Bauer M, Orozco Diaz G, Auburger G, et al. Involvement of the cranial nerves and their nuclei in spinocerebellar ataxia type2 (SCA2). Acta Neuropathol 2005; 109: 617-631.

[12] Saint Marie RL, Luo L, Ryan AF. Effects of stimulus frequency and intensity on c-fos mRNA expression in the adult rat auditory brainstem. J Comp Neurol 1999; 404: 258-270.