

Decreased Wave V Amplitude in Auditory Brainstem Responses of Children with Cerebellar Lesions

Yuka Matsuura,* Masayoshi Oguri,* Yoshiaki Saito,† Yasutaka Aoe,* Ayame Ogawa,* Shota Akiyama,* Nanako Yasuda,* Kengo Sato,* Yoshihiro Maegaki† and Yasuaki Hirooka*

*Department of Pathobiological Science and Technology, School of Health Science, Tottori University Faculty of Medicine, Yonago 683-8503, Japan and †Division of Child Neurology, Department of Brain and Neurological Sciences, Tottori University Faculty of Medicine, Yonago 683-8504, Japan

ABSTRACT

Background This study aims to elucidate the effect of isolated cerebellar lesions sparing the brainstem on the auditory brainstem responses in children.

Methods We enrolled 10 children (aged 1–16 years) with cerebellar lesions on neuroimaging but lacking clinical brainstem involvement signs and with normal brainstem volumes on magnetic resonance imaging.

Results The interpeak latency of waves I and V was normal in 9 patients and was marginally prolonged in 1 patient. While amplitudes of waves I and III were normal, we noted a decreased amplitude of wave V and/or an increased I/V amplitude ratio in 6 patients; these included 5 of 8 patients with cerebellar hypoplasia/atrophy and 1 patient with acute cerebellar ataxia.

Conclusion Our results support the hypothesis of an inhibitory input from the cerebellar fastigial nucleus on the inferior colliculus, which might be disinhibited because of Purkinje cells dysfunction due to cerebellar cortex lesions, especially within the cerebellar vermis.

Key words auditory brain stem response; amplitude; fastigial nucleus; cerebellar vermis

Auditory brainstem responses (ABR) have been extensively used for auditory pathway functional assessments from the distal cochlear nerve (wave I) to the inferior colliculus (IC; wave V) in the clinical setting, including during intraoperative monitoring, while screening for congenital auditory disturbances in neonates, in correlation with disease stages in neurodegenerative disorders, and for investigating brain malformation pathophysiology mechanisms.¹

Apart from these clinical situations, experimental

studies in rats have confirmed that activity in the cerebellar cortex may modify the somatosensory-evoked potentials (SEPs) and visually-evoked potentials (VEPs), in the brainstem and cerebral cortex, and the ABR in the brainstem.² Vermis stimulation and cooling altered the cochlear microphonics and auditory nerve action potentials in guinea pigs.³ Meanwhile, ABR findings in humans with cerebellar alterations have been restricted to cases involving the brainstem.^{4–7}

Against this background, our study aims to investigate the impact of isolated cerebellar lesions on ABR in children with intact brainstems.

SUBJECTS AND METHODS

Data collection

We retrospectively collected data of children with cerebellar etiologies from an outpatient database (from 1992 to 2017) of the Division of Child Neurology, at the Tottori University (Yonago, Japan). We initially identified 20 patients; however, we excluded 10 due to the presence of cerebellar tumors invading the brainstem ($n = 2$), decreased volume on the visual inspection of magnetic resonance images (MRI) or anomalies in the brainstem ($n = 2$), brainstem lesions ($n = 3$), or lack of ABR examinations ($n = 3$). For the remaining 10 patients, we collected data on neurological examinations, including the cerebellar and brainstem signs, from medical charts. In addition, we measured the anterior–posterior diameter on the midline sagittal MR images at the levels of the intercollicular midbrain, the ventral most prominent pontine base, and the pontomedullary junction; and compared the diameters with those from 17 control subjects to confirm the presence of normal brainstem thicknesses (Fig. 1A). The Ethics Committee of the Tottori University approved the study protocol.

Auditory brainstem response

We used the MEB-4208 and MEB-2300 (Nihonkoden, Tokyo, Japan) system to conduct ABR tests. During the examination, patients lied down in the supine position on a bed in a dark room and were subjected to the acoustic stimulation through a headphone. A surface disk elec-

Corresponding author: Yasuaki Hirooka, MD, PhD

yhirooka@med.tottori-u.ac.jp

Received 2018 September 27

Accepted 2018 December 4

Abbreviations: ABR, auditory brainstem response; DCN, deep cerebellar nuclei; FTN, fastigial nucleus; IC, inferior colliculus; IPL, inter peak latency; MRI, magnetic resonance imaging; SEP, somatosensory-evoked potential; VEP, visual evoked potentials

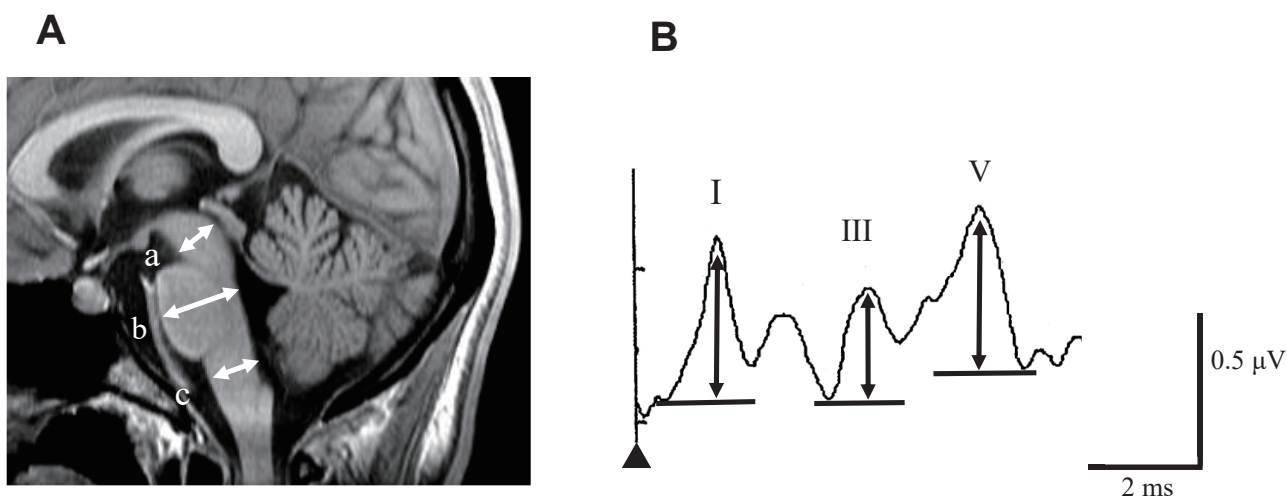


Fig. 1. Diagrams of measurements for the brainstem thickness on magnetic resonance imaging (MRI, **A**) and potential amplitudes on auditory brainstem responses (ABR, **B**). **A:** A sagittal MRI image showing the levels of anterior–posterior diameter measurements at the intercollicular midbrain (a), ventrally most prominent pontine base (b), and the pontomedullary junction (c).

trode with an 11-mm diameter and filled with suitable paste (impedance, < 5000 ohms) was used to record the responses. The positive electrode was placed on Cz, and the negative electrode on ipsilateral and contralateral earlobes; the contralateral ear was stimulated by a white masking noise. An electrode placed on the nasion served as the ground potential. In 8 of 10 patients we performed the ABR test under sedation, and in the others during arousal states. We stimulated ABR using condensate clicks resulting from a 0.1-ms monophasic square electrical pulse, at 90 dB nHL, and a 10-Hz stimulation rate. Then, two consecutive sets of 1000 responses were averaged and superimposed for each with a bandpass of 50–3000 Hz. In addition, we applied artifacts rejection.

We measured the interpeak latency (IPL) between waves I and V in a standard manner.⁸ The amplitudes of I, III, and V waves were determined by the difference between the relevant positive peak potentials and the neighboring negative trough on either side with the lower potential (Fig. 1B).⁹ Although the vulnerability of the wave V amplitude to the influence of IV and VI waveforms may depend on the measurement styles, we found this method used in a previous study analyzing the I/V ratio during normal development⁹ useful in this study for some cases with large slow wave component involving IV and V waveforms. We collected control data of these values from control 41 subjects (Table 1) categorized into six age groups, and we calculated averages and standard deviations for each age group to assess our results in the 10 patients with cerebellar etiologies.

Statistical analysis

We used the linear regression analysis to compare the brainstem anterior–posterior lengths of patients with cerebellar lesions (midbrain, pontine, and pontomedullary) and the mean length and 95% confidence interval (CI) values from 17 control subjects.

We used the GraphPad Prism 6 (GraphPad Software, La Jolla, CA) to perform all the statistical analyses.

RESULTS

Demographic data of patients with cerebellar lesions

In this study, all the 10 patients, aged 1–16 years [mean and standard deviation (SD), 4 years 4 months \pm 4 years 8 months; median, 2 years 11 months; male/female = 6/4], exhibited signs suggestive of the cerebellar involvement with either hypotonia, nystagmus, intention tremor, dysmetria, or ataxic gaits (Table 2).

In addition, 7 patients (cases 1, 4, 5–8, and 10) exhibited varying intellectual disability degrees, and 3 (cases 7–9) had spastic paraplegia. Moreover, 2 patients had a history of febrile convulsions. However, during the period spanning ABR and MRI examinations, none of the patients manifested myoclonus, extrapyramidal signs, or brainstem symptoms (including dysphagia, respiratory disturbance, tongue atrophy, or abducens/ facial nerve palsy). In addition, an oculomotor disturbance in case 4 was interpreted as a cerebellar sign based on its saccadic nature.

The MRIs of the 10 patients revealed cerebellar lesions with a distribution of cortical predominance. Some had additional white matter involvement, includ-

Table 1. Control values of auditory brainstem responses in each age group

	Latency (ms), (mean ± SD, 95%CI)			IPL (ms), (mean ± SD, 95%CI)		Amplitude (µV), (mean ± SD, 95%CI)			I/V ratio, (mean ± SD, 95%CI)	
	I	III	V	I-III	I-V	I	III	V		
0-5M	1.52 ± 0.12 (1.44-1.61)	4.43 ± 0.14 (4.33-4.53)	6.66 ± 0.48 (6.31-7.00)	2.91 ± 0.08 (2.85-2.97)	5.13 ± 0.49 (4.78-5.49)	0.48 ± 0.20 (0.34-0.62)	0.26 ± 0.10 (0.20-0.33)	0.35 ± 0.17 (0.23-0.47)	1.65 ± 1.06 (0.89-2.40)	n = 10
6M-11M	1.53 ± 0.19 (1.37-1.68)	4.15 ± 0.27 (3.92-4.38)	6.25 ± 0.15 (6.13-6.37)	2.62 ± 0.18 (2.47-2.77)	4.72 ± 0.11 (4.63-4.82)	0.40 ± 0.21 (0.21-0.59)	0.28 ± 0.11 (0.19-0.37)	0.42 ± 0.07 (0.37-0.48)	0.97 ± 0.57 (0.49-1.45)	n = 8
1Y	1.51 ± 0.16 (1.41-1.61)	3.95 ± 0.13 (3.87-4.03)	5.92 ± 0.15 (5.83-6.02)	2.44 ± 0.13 (2.36-2.53)	4.42 ± 0.15 (4.32-4.51)	0.62 ± 0.24 (0.47-0.78)	0.46 ± 0.19 (0.34-0.58)	0.58 ± 0.15 (0.49-0.68)	1.10 ± 0.36 (0.87-1.33)	n = 12
2Y-4Y	1.47 ± 0.11 (1.42-1.52)	3.84 ± 0.18 (3.76-3.92)	5.72 ± 0.19 (5.64-5.80)	2.37 ± 0.22 (2.28-2.46)	4.24 ± 0.25 (4.14-4.35)	0.67 ± 0.23 (0.57-0.76)	0.41 ± 0.19 (0.33-0.49)	0.63 ± 0.14 (0.57-0.69)	1.10 ± 0.48 (0.90-1.31)	n = 24
5Y-13Y	1.52 ± 0.11 (1.46-1.57)	3.85 ± 0.12 (3.78-3.91)	5.63 ± 0.18 (5.53-5.72)	2.33 ± 0.17 (2.24-2.43)	4.11 ± 0.23 (3.99-4.23)	0.59 ± 0.30 (0.43-0.75)	0.37 ± 0.16 (0.29-0.46)	0.59 ± 0.21 (0.47-0.70)	1.08 ± 0.52 (0.80-1.36)	n = 16
Adult	1.46 ± 0.09 (1.40-1.51)	3.77 ± 0.10 (3.71-3.83)	5.63 ± 0.28 (5.45-5.81)	2.31 ± 0.10 (2.25-2.37)	4.17 ± 0.31 (3.98-4.37)	0.67 ± 0.16 (0.57-0.77)	0.42 ± 0.17 (0.31-0.53)	0.59 ± 0.17 (0.49-0.70)	1.25 ± 0.58 (0.89-1.62)	n = 12

CI, confidence interval; M, month(s); IPL, inter peak latency; SD, standard deviation; Y, year(s).

Table 2. Clinical profiles of patients with cerebellar lesions

Case	Sex	Age at ABR examination	Age at MRI	Diagnosis/MRI findings	Words	Sentences	Independent gait	DQ	Cerebellar symptoms	Complications	Other neurological signs
1	M	1 y 2 m	0 y 5 m	Cerebellar hypoplasia/atrophy (vermis and inferior hemispheres)	—	n/a	—	50 at 1 y 0 m	Hypotonia, nystagmus		
2	M	1 y 2 m	1 y 2 m	Acute cerebellar ataxia (normal MRI)	12 m	n/a	9 m	Normal	Truncal ataxia, intention tremor	Febrile seizure	
3	M	1 y 2 m	1 y 2 m	Lt. cerebellum infarction	12 m	n/a	13 m	98 at 1 y 2 m	Truncal ataxia, hypotonia/disuse of Lt. extremities		
4	F	1 y 3 m	1 y 3 m	Cerebellar hypoplasia/atrophy (vermis and superior hemispheres)	—	n/a	— (crawl 5 m)	40 at 1 y 2 m	Hypotonia, dysmetria, oculomotor disturbance		
5	M	2 y 10 m	2 y 10 m	Cerebellar hypoplasia/atrophy (diffuse)	2 y 6 m	—	2 y	68 at 2 y 9 m	Hypotonia, intention tremor, ataxic gait	Febrile seizure	
6	F	2 y 11 m	2 y 11 m	Mitochondrial encephalomyopathy; Cerebellar atrophy (vermis predominance)	1 y	—	2 y	76 at 2 y 1 m	Hypotonia		
7	M	3 y 11 m	3 y 11 m	Cerebellar hypoplasia/atrophy (diffuse; including white matter and deep nuclei), arachnoid cyst in the right posterior fossa; cerebral hypoplasia	—	—	—	< 10 at 3 y 11 m	Hypotonia		Spastic paraplegia
8	M	5 y 7 m	5 y 7 m	Cerebellar hypoplasia/atrophy (diffuse), midline arachnoid cyst	—	—	— (stand with aid at 5 y)	12 at 5 y 7 m	Hypotonia, intention tremor, nystagmus		Spastic paraplegia
9	F	7 y 1 m	7 y 1 m	Cerebellar hypoplasia/atrophy (vermis predominance)	12 m	NA	1 y 4 m	Intellect normal at 7 y	Ataxic gait, truncal titubation, dysarthria		Spastic paraplegia
10	F	16 y 4 m	16 y 4 m	Cerebellar hypoplasia/atrophy (hemispheric predominance)	1 y 1 m	3 y	1 y 5 m	Special education since 7 y	Ataxic gait, dysdiadochokinesis, intention tremor		

ABR, auditory brainstem response; DQ, developmental quotient; F, female; M, male; m, month(s); MRI, magnetic resonance imaging; NA, not available; n/a, not applicable; —, not acquired yet; y, year(s).

ing one (case 3) with an infarct involving unilateral deep cerebellar nuclei (DCN). We defined cerebellar hypoplasia/atrophy on MRI as decreased volumes of the cerebellar hemispheres and/or vermis, and/or wide cerebellar fissures, because the distinction or co-existence of prenatal hypoplasia and postnatal atrophy was difficult to ascertain in several enrolled patients. We classified eight patients into this category. Of all, case 6 manifested with hypotonia and delayed motor development in early childhood. His mother had diabetes mellitus in adulthood and experienced a stroke-like episode when the patient was 1-year old. Mutations of A3243G were detected in mitochondrial DNA of samples obtained from the mother and the patient. In addition, ABR and MRI were assessed during that period. However, genetic analyses of the remaining 7 patients were unsuccessful. Moreover, the etiology of 2 other patients included acute cerebellar ataxia after a febrile episode, and cerebellar infarction in the territory of the left superior cerebellar artery (Table 2, Fig. 2).

Quantification of the brainstem thickness

In this study, the anterior–posterior diameters of the brainstem of 9 patients at the levels of the intercollicular midbrain, the ventral most prominent pontine base, and the pontomedullary junction were within the 95% CI of the data obtained from 17 control subjects, except for case 10, with a large diameter at the pontine level (Fig. 3).

Characteristics of ABR findings in patients with isolated cerebellar lesions

We collected normal ABR measurement values for each age group from 41 control subjects (aged 1 month to 18 years; mean \pm SD, 5 years \pm 5 years 2 months; median, 2 years 7 months). Their diagnoses included psychomotor retardation in 18, epilepsy in 7, muscle weakness in 6, strabismus in 1, migraine in 1, daytime sleepiness in 1, gait disturbance in 2, equinus deformity in 1, diplopia in 1, and “normal” in 3 (Table 1).

While the I–V IPL was normal in 9 patients, it was marginally prolonged in case 2. The amplitudes of waves I and III were within 2 SDs from the mean in all patients. In addition, the amplitude of wave V was markedly decreased in 5 of 10 patients (cases 1, 2, 4, 6, and 7) on either or both sides. Their diagnoses were cerebellar hypoplasia/atrophy in 4 patients, including 1 with mitochondrial encephalopathy, and another one with acute cerebellar ataxia. Moreover, the I/V ratio was markedly increased in 5 patients (cases 1, 2, 4, 6, and 8; Fig. 2, Table 3).

DISCUSSION

The commonly preserved I–V IPL and the selective attenuation of the wave V amplitude in various cerebellar pathologies suggest that conduction between the brainstem auditory structures is not being affected and that synaptic activation of the IC is being impaired. Such a dissociation has not been described in humans with cerebellar (or brainstem) lesions,^{4,7} but has been recognized in animal experiments with interventions on the cerebellar cortex.^{2,3} We hypothesize here that the cerebellar fastigial nucleus (FTN) is disinhibited due to disruption of the Purkinje cell signals, resulting in the inhibition on the IC (Fig. 4). These connections may play a critical role in the dissociation, as discussed later.

Although supratentorial structures, such as the auditory cortex, thalamus, and amygdala, can modulate the activity of IC,^{10,11} the degrees of intellectual disability, presence or absence of spastic paraplegia, and history of febrile seizures in our patients did not correlate with the attenuation of wave V. In fact, we excluded patients with abnormalities within the brainstem that could affect the auditory pathway, as far as possible, after clinical and MRI examinations. In addition, we observed the selective attenuation of wave V amplitudes with preserved I–V IPL under different pathologies in this study, including infection-related acute ataxia and cerebellar hypoplasia/atrophy in the chronic phase. On the other hand, the genetic or nongenetic causes of cerebellar atrophy in 8 patients were heterogenous, and we cannot rule out the selective involvement of IC in some patients at microscopic levels. However, these facts led us to interpret wave V changes as associated with cerebellar dysfunction in our patients.

In addition to studies investigating the status of the auditory pathway and structures in its close vicinity, experimental studies have rarely confirmed that the activity in the cerebellar cortex may modify the SEPs and the VEPs in the brainstem and cerebral cortex and ABR in the brainstem.^{2,3} In a study, the stimulation of dorsal vermis lobules in rats augmented the VEP and attenuated the SEP; in addition, while the ABR generally decreased in amplitude, the ratio of waves IV (potential in the IC in rats) and I varied, depending on the interval between the conditional cerebellar stimulation and the acoustic click.² At the peripheral level, a study in guinea pigs showed cochlear microphonics and auditory nerve action potentials being decreased and increased by stimulation and cooling of the vermis, respectively.³ Meanwhile, the explanation for ABR findings in humans in the presence of cerebellar pathologies has been restricted to cases of cerebellar tumors invading or compressing the brainstem,^{4,5} cases of cerebellar atrophy accompanied by

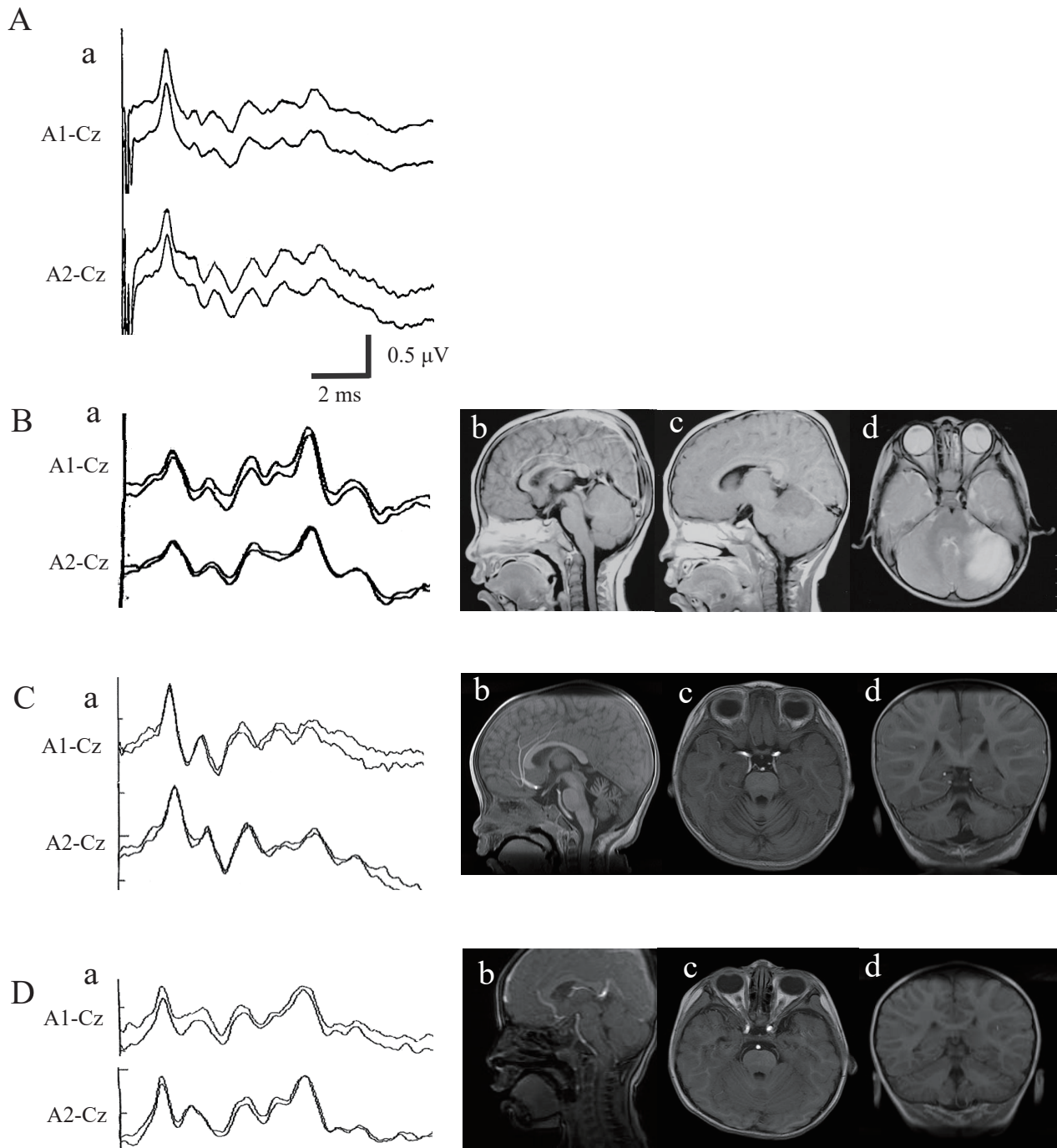


Fig. 2. ABR and T1 or T2-weighted MRI (T1WI or T2WI) findings from case 2 (**A**), case 3 (**B**), case 4 (**C**), and a control subject aged 3 years and 2 months (**D**). **A:** (**a**) On 10 days of illness in acute cerebellar ataxia, wave V is decreased in amplitude, whereas waves I and III appear normal. MRI on day 8 revealed unremarkable findings (exact T1- and T2WI were taken in the 1990s and are currently unavailable but were reported as normal by neuroradiologists and pediatric neurologists). **B:** (**a**) On day 2 of cerebellar infarct, wave V is preserved. (**b–d**) MRI on the same day (**b** and **c**: gadolinium-enhanced T1WI, **d**: T2WI) (**b**: midline sagittal image, **c**: left to midline sagittal slice at the level of left superior peduncle, **d**: axial image at the level of middle cerebellar peduncles) revealed an infarct lesion in the left cerebellar hemisphere with edema in the surrounding areas. In **c**, the infarct possibly involves the left fastigial nucleus in close vicinity of the superior cerebellar peduncle. **C:** (**a**) Wave V is decreased in amplitude. (**b**) Midline sagittal T1WI shows moderate atrophy/hypoplasia of cerebellar vermis with wide sulci. Inferior folia of the vermis are replaced by the cerebellar tonsil, suggesting volume loss of the vermis. (**c**, **d**) Cerebellar hypoplasia/atrophy, predominantly in the upper hemispheres, is noted on the axial (**c**) and coronal (**d**) T1WIs at the level including the superior cerebellar peduncles and the fastigial nuclei. **D:** (**a**) ABRs with normal amplitudes and waveform. (**b–d**) T1WI show no abnormality in midline-sagittal (**b**), axial image at the level of superior cerebellar peduncles (**c**), and coronal image involving the level of deep cerebellar nuclei (**d**). ABR, auditory brainstem response; MRI, magnetic resonance imaging.

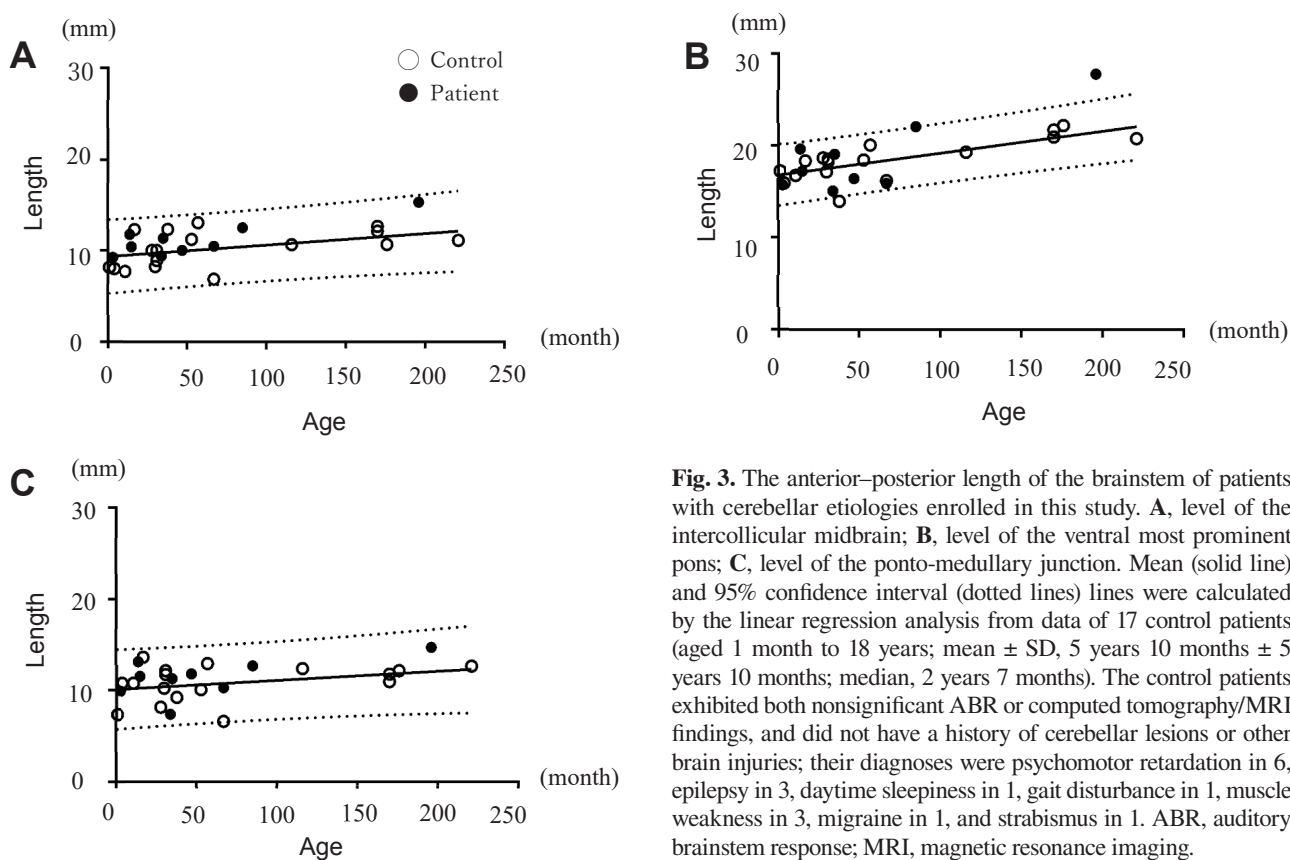


Fig. 3. The anterior–posterior length of the brainstem of patients with cerebellar etiologies enrolled in this study. **A**, level of the intercollicular midbrain; **B**, level of the ventral most prominent pons; **C**, level of the ponto-medullary junction. Mean (solid line) and 95% confidence interval (dotted lines) lines were calculated by the linear regression analysis from data of 17 control patients (aged 1 month to 18 years; mean \pm SD, 5 years 10 months \pm 5 years 10 months; median, 2 years 7 months). The control patients exhibited both nonsignificant ABR or computed tomography/MRI findings, and did not have a history of cerebellar lesions or other brain injuries; their diagnoses were psychomotor retardation in 6, epilepsy in 3, daytime sleepiness in 1, gait disturbance in 1, muscle weakness in 3, migraine in 1, and strabismus in 1. ABR, auditory brainstem response; MRI, magnetic resonance imaging.

Table 3. ABR findings of patients with cerebellar anomalies

Case	IPL (ms), (SD)				Amplitude (μ V), (SD)				I/V ratio, (SD)	
	Wave I-V		Wave I		Wave III		Wave V		Left	Right
	Left	Right	Left	Right	Left	Right	Left	Right		
1	4.3 (-0.80)	4.7 (+1.87)	0.22 (-1.67)	0.17 (-1.88)	0.17 (-1.53)	0.10 (-1.89)	0.12 (-3.07)	0.12 (-3.07)	1.86 (+2.11)	1.43 (+0.92)
2	4.8 (+2.53)	4.8 (+2.53)	0.89 (+1.13)	0.78 (+0.67)	0.44 (-0.11)	0.33 (-0.68)	0.22 (-2.40)	0.33 (-1.67)	4.00 (+8.06)	2.33 (+3.42)
3	4.2 (-1.47)	4.5 (+0.53)	0.50 (-0.50)	0.38 (-1.00)	0.38 (-0.42)	0.44 (-0.11)	0.75 (+1.13)	0.56 (-0.13)	0.67 (-1.19)	0.67 (-1.19)
4	4.6 (+1.20)	4.4 (-0.13)	0.96 (+1.42)	0.79 (+0.71)	0.63 (+0.89)	0.58 (+0.63)	0.17 (-2.73)	0.42 (-1.07)	5.75 (+12.92)	1.90 (+2.22)
5	4.3 (+0.24)	4.3 (+0.24)	0.63 (-0.17)	0.83 (+0.70)	0.58 (+0.89)	0.54 (+0.68)	0.42 (-1.50)	0.58 (-0.36)	1.50 (+0.83)	1.43 (+0.69)
6	4.6 (+1.44)	4.4 (+0.64)	0.41 (-1.13)	0.41 (-1.13)	0.14 (-1.42)	0.21 (-1.05)	0.34 (-2.07)	0.14 (-3.50)	1.20 (+0.21)	3.00 (+3.96)
7	4.5 (+1.04)	4.6 (+1.44)	0.42 (-1.09)	0.33 (-1.48)	0.13 (-1.47)	0.25 (-0.84)	0.42 (-1.50)	0.33 (-2.14)	1.00 (-0.21)	1.00 (-0.21)
8	4.4 (+1.26)	4.2 (+0.39)	0.71 (+0.40)	0.75 (+0.53)	0.42 (+0.31)	0.42 (+0.31)	0.29 (-1.43)	0.33 (-1.24)	2.43 (+2.60)	2.25 (+2.25)
9	4.1 (-0.04)	4.1 (-0.04)	0.69 (+0.33)	0.25 (-1.13)	0.56 (+1.19)	0.50 (+0.81)	0.69 (+0.48)	0.44 (-0.71)	1.00 (-0.15)	0.57 (-0.98)
10	3.8 (-1.19)	3.8 (-1.19)	0.83 (+1.00)	0.63 (-0.25)	0.46 (+0.24)	0.50 (+0.47)	0.46 (-0.76)	0.58 (-0.06)	1.82 (+0.98)	1.07 (-0.31)

ABR, auditory brainstem response; IPL, inter peak latency.

brainstem anomalies,⁶ and cases of metabolic/degenerative disorders with brainstem involvement.⁷

A connection between the cerebellar structures and the brainstem precerebellar nuclei has been reported in the literature;^{12–14} however, a degeneration study reported an efferent pathway from the FTN to the IC as the sole direct projection from the cerebellum in rabbits.¹⁵ In addition, the FTN receives inputs exclusively from the

cerebellar vermis, with unilateral predominance.¹⁶ In addition to the projection to the IC, ascending fibers of the FTN to the superior colliculus conduct vergence and adaptation of saccades and pursuit ocular movements,¹⁷ and descending fibers to the dorsal medulla oblongata are involved in the vasomotor modulation.^{12, 18} Regarding the projection from the vermis, the Purkinje cells send GABAergic inhibitory projections to the DCN, includ-

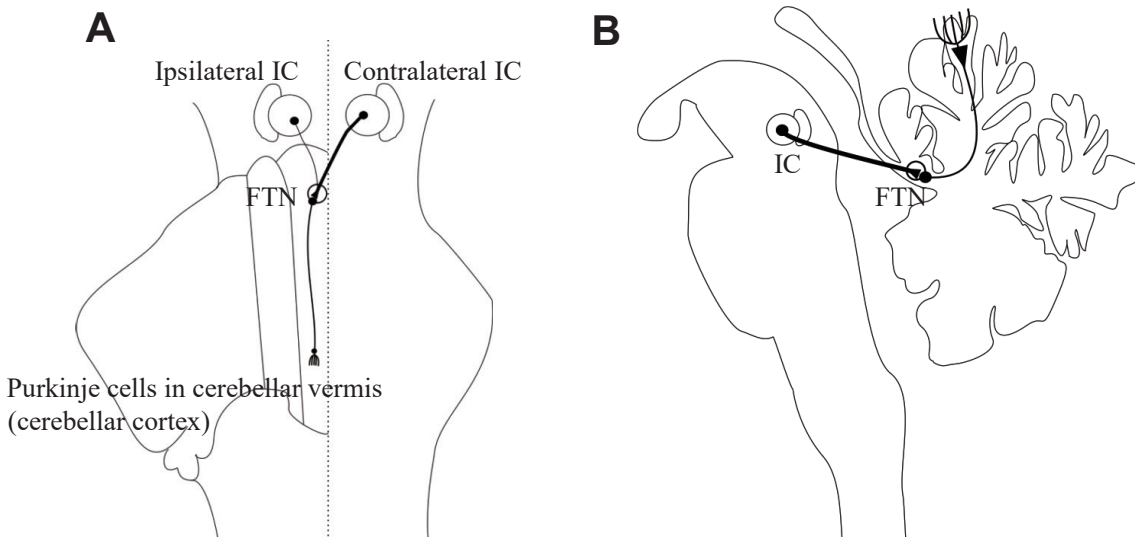


Fig. 4. Hypothetic scheme of cerebellar-fastigial-collicular pathway. **A**, axial view, **B**, sagittal view. Purkinje cells in the cerebellar vermis send inhibitory projections to the cerebellar fastigial nucleus (FTN) bilaterally, with ipsilateral predominance. FTN neurons then project to the inferior colliculus (IC) bilaterally with contralateral predominance, which we hypothesize to be inhibitory. In this scheme, disruption of the cerebellar cortex results in an activation of FTN neurons, leading to the inhibition of IC neurons and the selective attenuation of the wave V amplitudes.

ing the FTN. In addition, neurons in the DCN have pacemaker-like currents and exhibit spontaneous discharges at 20–40 Hz. This spontaneous activity enables the modulation by the inhibitory influence from the Purkinje cells, and the excitatory effects from mossy and climbing fibers; in fact, ablation of the cerebellar cortex results in an increased proportion of high-frequency spontaneously firing DCN neurons.¹⁹

Crispino and Bullock reported that the inhibitory action from the vermis to the FTN may affect ABR potentials, as demonstrated by the general attenuation of ABR upon conditioning stimulation of the dorsal vermis before the acoustic click in rats, resulting from a decline in wave I amplitude.² However, a decrease in wave IV (IC potentials) was shown to be disproportionate to the degree of wave I attenuation; the IV/I ratio was increased at intervals shorter than 10 ms and was decreased at longer intervals.² In other words, potentiation of the IC from the vermis occurs during the short latency, and a suppression emerges during longer latencies. The former could be explained by a disinaptic Purkinje cells–FTN neurons–IC neurons pathway, where the suppression of the fastigial neurons by the Purkinje cells would result in the successive disinhibition of the FTN. To date, the types of inputs from the FTN to the IC have not been elucidated, compared with the glutamate-predominant projections to the vestibular nuclei or the GABA-predominant projection to inferior olive from the FTN.²⁰ However, we hypothesize an inhibitory action in this

connection, which seems consistent with our results, as discussed below. The latter suppression at longer latencies may be invoked by multiple pathways, for example, via the vestibular nucleus²⁰ directly connected to the IC²¹ or through the inferior olivary nucleus^{20, 22} or serotonergic²³ and dopaminergic²⁴ systems.

Compared with the effects of cerebellar stimulation, lesions in the cerebellar vermis would result in increased activity of the FTN. The attenuation of wave V in this study could be attributed to this disinhibition of the FTN. Meanwhile, the preserved wave V in patient 3 (Fig. 2B) might have resulted from the insults on the FTN itself, with a damaged inhibitory projection to the IC.

Otherwise, unilateral cerebellar hemisphere lesions with no injury to the cerebellar vermis may have no impact on the auditory activation of the IC. The latter seems more likely because we observed no laterality in the ABR waveforms in our patients with lesions affecting the unilateral hemisphere, whereas the FTN was projected with contralateral predominance.¹⁵ In fact, stimulation of the cerebellar cortex was not uniformly effective, and the dorsal vermis was the most influential on the modulation of evoked potentials.² Thus, our findings underscore the principal role of the vermis–fastigial module in the modulation of ABR.

Action potentials of the auditory nerve are attenuated by stimulation of the cerebellar cortex and are augmented by cooling of the cerebellar cortex in animals, two phenomena explained by the activation of the supe-

rior olive–cochlear inhibitory pathway by the cerebellar stimulation.³ However, the wave I amplitude remained unaffected in the patients examined in this study, suggesting an interspecies difference, or otherwise, an association to the young age of our patients because the proportion of GABAergic neurons in the superior olive is known to increase with age.²⁵ A trend of higher wave I amplitudes than the average control value in cases 8–10 (Table 2) supports this possibility.

In conclusion, the children with cerebellar lesions lacking auditory brainstem involvement in our study had characteristic ABR findings, including attenuated wave V amplitudes with a normal amplitude of waves I and III, as well as normal I–V IPL. Our results may be explained by assuming an inhibitory projection from the FTN to the IC. Overall, V waves may be regarded as windows to look into (midline) cerebellar lesions.

The authors declare having no conflicts of interest.

REFERENCES

- Chiappa KH. Evoked potentials in clinical medicine. 3rd ed. Philadelphia: Lippincott Raven; 1997.
- Crispino L, Bullock TH. Cerebellum mediates modality-specific modulation of sensory responses of midbrain and forebrain in rat. *Proc Natl Acad Sci U S A*. 1984;81:2917-20. PMID: 6585836; PMCID: PMC345184.
- Velluti R, Crispino L. Cerebellar actions on cochlear microphonics and on auditory nerve action potential. *Brain Res Bull*. 1979;4:621-4. PMID: 487218.
- Kaga M, Nihei K. Appearance of wave III of auditory brainstem response after removal of a cerebellar tumor. *Brain Dev*. 1993;15:305-7. PMID: 8250155.
- Sostarich ME, Ferraro JA, Karlsen EA. Prolonged I-III inter-wave interval in cerebellar astrocytoma. *J Am Acad Audiol* 1993;4:269-7. PMID: 8369545.
- Santo K, Meoka Y, Sugiura C, Nanba Y, Suzaki I, Oka A, et al. Evaluation of brainstem function with multimodality evoked potentials Joubert syndrome. *No To Hattatsu. Brain and development*. 2000;32:281-3. PMID: 10824583. Japanese with English Abstract.
- Tantawy AA, Sherif EM, Adly AA, Hassanine S, Awad AH. Evoked potentials and neurocognitive functions in pediatric Egyptian Gaucher patients on enzyme replacement therapy: a single center experience. *J Inher Metab Dis*. 2013;36:1025-37. PMID: 23508695.
- Musiek FE, Kibbe-Michal K, Geurkink NA, Josey AF, Glasscock M 3rd. ABR results in patients with posterior fossa tumors and normal pure-tone hearing. *Otolaryngol Head Neck Surg*. 1986;94:568-73. PMID: 3088517.
- Jiang ZD, Zhang L, Wu YY, Liu XY. Brainstem auditory evoked responses from birth to adulthood: development of wave amplitude. *Hear Res*. 1993;68:35-41. PMID: 8376213.
- Marsh RA, Fuzessery ZM, Grose CD, Wenstrup JJ. Projection to the inferior colliculus from the basal nucleus of the amygdala. *J Neurosci*. 2002;22:10449-60. PMID: 12451144.
- Winer JA, Chernock ML, Larue DT, Cheung SW. Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey. *Hear Res*. 2002;168:181-95. PMID: 12117520.
- Andrejik JA, Dormer KJ, Foreman RD, Person RJ. Fastigial nucleus projections to the brain stem in beagles: pathways for autonomic regulation. *Neuroscience*. 1984;11:497-507. PMID: 6201783.
- Sugita S, Noda H. Pathways and terminations of axons arising in the fastigial oculomotor region of macaque monkeys. *Neurosci Res*. 1991;10:118-36. PMID: 1710042.
- Teune TM, van der Burg J, van der Moer J, Voogd J, Ruigrok TJ. Topography of cerebellar nuclear projections to the brain stem in the rat. *Prog Brain Res*. 2000;124:141-72. PMID: 10943123.
- Zimny R, Sobusiak T, Deja A, Kotecki A. Cerebellar afferent projection to the inferior colliculus of the mesencephalic tectum. An anterograde degeneration study in the rabbit. *Z Mikrosk Anat Forsch*. 1981;95:197-209. PMID: 7281882.
- Courville J, Diakiw N. Cerebellar corticonuclear projection in the cat. The vermis of the anterior and posterior lobes. *Brain Res*. 1976;110:1-20. PMID: 1276942.
- Beh SC, Frohman TC, Frohman EM. Cerebellar control of eye movements. *J Neuroophthalmol*. 2017;37:87-98. PMID: 27643747.
- Elisevich K, Redekop G. The fastigial pressor response. Case report. *J Neurosurg*. 1991;74:147-51. PMID: 1984498.
- Tarnecki R, Morrison AR, Rajkowski J, Sarna MF, Zurawska I. Spontaneous and evoked activities of interpositus nucleus neurons before and after lesion of the cerebellar cortex. *Acta Physiol Pol*. 1987;38:302-22. PMID: 3452968.
- Diagne M, Delfini C, Angaut P, Buisseret P, Buisseret-Delmas C. Fastigiovestibular projections in the rat: Retrograde tracing coupled with gammaamino-butyric acid and glutamate immunohistochemistry. *Neurosci Lett*. 2001;308:49-53. PMID: 11445283.
- Bácskai T, Székely G, Matesz C. Ascending and descending projections of the lateral vestibular nucleus in the rat. *Acta Biol Hung*. 2002;53:7-21. PMID: 12064781.
- Sastry BR, Morishita W, Yip S, Shew T. GABA-ergic transmission in deep cerebellar nuclei. *Prog Neurobiol*. 1997;53:259-71. PMID: 9364613.
- Obara N, Kamiya H, Fukuda S. Serotonergic modulation of inhibitory synaptic transmission in mouse inferior colliculus. *Biomed Res*. 2014;35:81-4. PMID: 24573204.
- Gittelman JX, Perkel DJ, Portfors CV. Dopamine modulates auditory responses in the inferior colliculus in a heterogeneous manner. *J Assoc Res Otolaryngol*. 2013;14:719-29. PMID: 23835945; PMCID: PMC3767870.
- Jenkins SA, Simmons DD. GABAergic neurons in the lateral superior olive of the hamster are distinguished by differential expression of gad isoforms during development. *Brain Res*. 2006;1111:12-25. PMID: 16919247.