Ataxic Hemiparesis: Neurophysiological Analysis by Cerebellar Transcranial Magnetic Stimulation

**Saeko Kikuchi · Hitoshi Mochizuki · Arata Moriya ·
Setsu Nakatani-Enomoto · Koichiro Nakamura ·
Ritsuko Hanajima · Yoshikazu Ugawa**

Abstract The aim of this study was to investigate physiological mechanisms underlying ataxia in patients with ataxic hemiparesis. Subjects were three patients with ataxic hemiparesis, whose responsible lesion was located at the posterior limb of internal capsule (case 1), thalamus (case 2), or pre- and post-central gyri (case 3). Paired-pulse transcranial magnetic stimulation (TMS) technique was used to evaluate connectivity between the cerebellum and contralateral motor cortex. The conditioning cerebellar stimulus was given over the cerebellum and the test stimulus over the primary motor cortex. We studied how the conditioning stimulus modulated motor evoked potentials (MEPs) to the cortical test stimulus. In non-ataxic limbs, the cerebellar stimulus normally suppressed cortical MEPs. In ataxic limbs, the cerebellar inhibition was not elicited in patients with a lesion at the posterior limb of internal capsule (case 1) or thalamus (case 2). In contrast, normal cerebellar inhibition was elicited in the ataxic limb in a patient with a lesion at sensori-motor cortex (case 3). Lesions at the internal capsule and thalamus involved the cerebello-thalamo-cortical pathways and reduced the cere-bellar suppression effect. On the other hand, a lesion at the pre- and post-central gyri should affect cortico-pontine pathway but not involve the cerebello-thalamo-cortical pathways. This lack of cerebello-talamo-cortical pathway involvement may explain normal suppression in this patient. The cerebellar TMS method can differentiate cerebellar efferent ataxic hemiparesis from cerebellar afferent ataxic hemiparesis.

Keywords Cerebellar efferent ataxic hemiparesis · Cerebellar afferent ataxic hemiparesis · Transcranial magnetic stimulation · Cerebellum

S. Kikuchi · H. Mochizuki (✉) · A. Moriya ·
S. Nakatani-Enomoto · K. Nakamura · Y. Ugawa
Department of Neurology, School of Medicine,
Fukushima Medical University,
1 Hikarigaoka,
Fukushima 960-1295, Japan
e-mail: mochizuki-h@umin.ac.jp

R. Hanajima
Department of Neurology, Division of Neuroscience,
Graduate School of Medicine, University of Tokyo,
Tokyo, Japan

Introduction

Ataxic hemiparesis (AH) is well-recognized lacunar syndrome showing homolateral ataxia with accompanying corticospinal tract impairment [1–3]. It can result from a small brain lesion positioned at various sites, such as at the pons, midbrain, internal capsule, corona radiata, and cerebral cortex [1–6].

Ataxia could be produced by lesions positioned anywhere within the cerebellar loops; cortico-ponto-cerebellar (cerebellar afferent pathways) or cerebello-thalamo-cortical projections (cerebellar efferent pathways). Several previous papers concluded that pontine or internal capsule lesions should affect the cortico-ponto-cerebellar pathways (cerebellar afferent ataxic hemiparesis) [1, 2]. Some recent studies, however, speculated that a lesion at the posterior limb of internal capsule would affect the cerebello-thalamo-cortical pathway (cerebellar efferent ataxic hemiparesis) [3–6]. These

speculations are based on anatomical knowledge about the pathways within the cerebellar loops. The location of cerebello-thalamo-cortical pathways, however, remains to be determined at the internal capsule level [7, 8].

The interaction between the primary motor cortex (M1) and cerebellum could be evaluated by cerebellar TMS in humans [9]. In normal subjects, TMS over the cerebellum reduced motor evoked potentials (MEPs) to TMS over the contralateral M1 when it preceded the motor cortical stimulation by 5, 6, and 7 ms. This cerebellar inhibitory effect was absent or reduced in patients with a lesion involving the cerebello-thalamo-cortical pathways (cerebellar efferent ataxia), and it was normally elicited in ataxic patients with a lesion affecting cortico-ponto-cerebellar pathways (cerebellar afferent ataxia) [9]. In this communication, we applied the cerebellar stimulation to patient with AH to elucidate mechanisms for ataxia in AH.

Patients and Method

Subjects were three patients with AH who were admitted to our hospital from 2008 to 2009. All met the criteria of AH [3]: (1) new onset ipsilateral ataxia and pyramidal signs, (2) dysmetria out of proportion to the weakness, (3) absent or minimal cortical signs, and (4) all signs documented by a neurologist.

Case Presentation

Case 1

A 63-year-old woman visited our hospital because of the right side limb weakness. She showed mild hemiparesis and moderate ataxia on the right side without any sensory abnormalities. Her manual muscle test scales (MMT; Medical Research Council scale) of right side limbs were 5- to 5. Her dysmetria, dysdiadochokinesis, and terminal oscillation were out of proportion to her weakness, and Holmes-Stewart rebound phenomenon was positive.

Diffusion-weighted magnetic resonance images (DW-MRI) of the brain revealed a small infarction in the posterior limb of left internal capsule (Fig. 1a). The median nerve somatosensory evoked potential (SEPs) and central motor conduction times (CMCTs) were all within the normal range.

Case 2

A 75-year-old man visited our hospital with chief complaint of left limb sensory disturbances. He had no weakness (MMT=5) with extensor plantar response on the left side and moderate left side hemi-ataxia. Temperature and pain sensations were mildly impaired, but position and vibration

sensations were normal. On the left side, his dysmetria, dysdiadochokinesis, and terminal oscillation were out of proportion to the sensory disturbances, and Holmes-Stewart rebound phenomenon was positive.

DW-MRI showed a small infarction in the right lateral thalamus (Fig. 1b). The CMCTs were all within the normal ranges, but the N20 onset-peak SEP amplitude was abnormally small in the left median nerve SEP (amplitude of N20; right median nerve 3.4 μV, left 0.2 μV).

Case 3

An 81-year-old woman was admitted to our hospital because of the left upper limb weakness (MMT=5-). She had mild monoparesis and moderate ataxia in the left upper limb. The dysmetria, dysdiadochokinesis, and terminal oscillation were out of proportion to the weakness, and Holmes-Stewart rebound phenomenon was positive.

DW-MRI showed small infarctions in the right pre- and post-central gyri (Fig. 1c). Routine examinations, bilateral CMCTs, and SEPs were all normal.
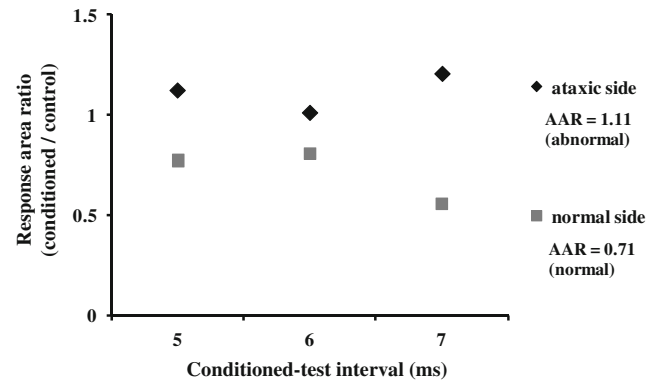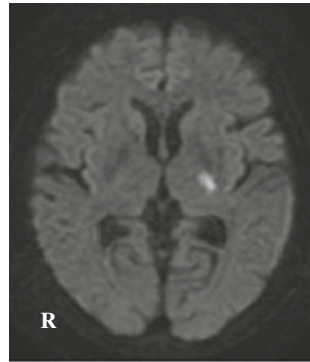
Method

Cerebellar Inhibition Induced by Cerebellar TMS

Paired TMS pulses were given over the cerebellum and the contralateral M1. The details of this method were described in our previous paper [9]. The procedures were approved by the Ethics Committee of Fukushima Medical University and performed in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all the subjects.
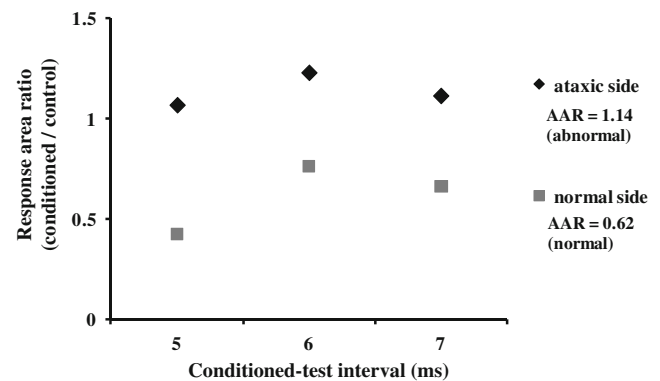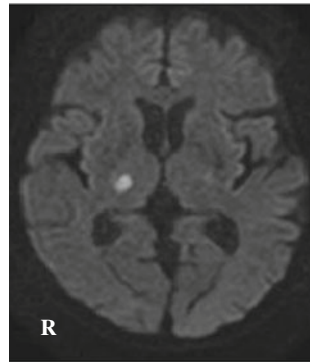
In brief, surface electromyographic activity was recorded from the target first dorsal interosseous muscle (FDI). TMS was performed with two Magstim 200 stimulators (The Magstim Co., Ltd, Whitland, UK). The conditioning magnetic stimulus was given over the cerebellum using a double-cone coil (The Magstim Co., Ltd, Whitland, UK). The center of the junction region of the coil was placed 3 cm lateral from the inion. The coil was held so that currents in the brain flowed upward. The threshold for activation of the descending motor tracts was determined as the lowest intensity eliciting five small responses (MEPs) (about 200 μV) in a series of ten stimuli when the subject made a 5% maximal voluntary contraction (about 50 μV) (threshold of case 1, 58% of maximal stimulator output; case 2, 51%; case 3, 95%) . The intensity of conditioning cerebellar stimulus was fixed at 90% of the threshold. At various times after the conditioning stimulus (ISI=5, 6, or 7 ms), the motor cortex was stimulated by a round coil placed over the vertex. The motor cortical TMS (test
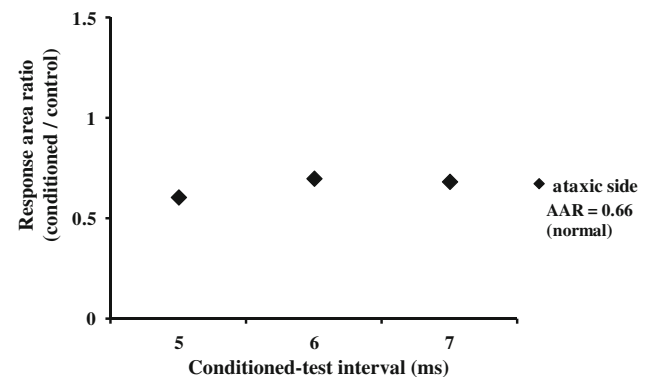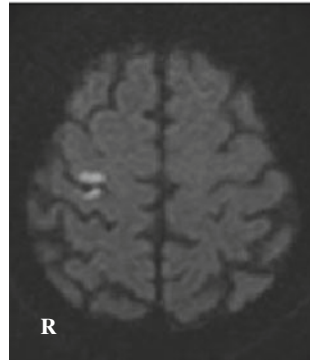
A: Case 1

B: Case 2

C: Case 3

stimulus) was adjusted to produce an MEP of 0.3–0.7 mV peak to peak in the relaxed FDI when given alone.

We used a randomized conditioning-test design as reported previously [9, 10]. Various conditions (the test or conditioning stimulus given alone, or the test stimulus preceded by the conditioning stimulus by various ISIs) were intermixed randomly in one session. ISIs between the conditioning and test stimulus were 5, 6, and 7 ms. Data were analyzed off-line after the experiments. In each session, eight MEPs were collected for each condition in which both stimuli were given, and ten MEPs for the control condition in which the test stimulus was given alone. Since MEPs are often polyphasic, we routinely measured response size in terms of area of MEPs rather than peak–peak amplitude. The area of each single MEP in each condition was measured in order to compare the control and conditioned MEPs in the same session. We calculated the ratio of the mean area of the conditioned MEP to that of the control MEP for every ISI. In normal subjects, conditioned MEPs at ISIs of 5, 6, and 7 ms were suppressed. This suppression effect was considered to be absent or abnormally reduced when the average area ratio

(AAR) (ISIs = 5, 6, and 7 ms) exceeded the upper limit of our normal range (mean ± 2SD, 0.78 [9]).

Results

Figure 1 shows brain DW-MRIs and the time courses of cerebellar suppression for three patients.

In a patient with a lesion at the posterior limb of left internal capsule (case 1), the cerebellar suppression was absent (AAR = 1.11) on the ataxic side (right hand), whereas normal suppression was evoked on the normal side (non-ataxic, left hand, AAR = 0.71) (Fig. 1a).

In a patient with a lesion at the right lateral thalamus (case 2), the cerebellar suppression was absent on the ataxic side (left hand) (AAR = 1.14), whereas normal suppression was evoked on the normal side (non-ataxic, right hand, AAR = 0.62) (Fig. 1b).

In contrast, in a patient with a lesion at the right pre- and post-central gyri (case 3), the cerebellar inhibition was normally evoked in an ataxic limb (left hand, AAR = 0.66) (Fig. 1c).

Discussion

The present electrophysiological study confirmed patho-physiological mechanisms for ataxia speculated from anatomical knowledge in AH, namely cerebellar efferent AH and cerebellar afferent AH.

Previous cerebellar stimulation experiments showed that it can differentiate cerebellar efferent ataxia from cerebellar afferent ataxia physiologically [9, 11]. Figure 2 shows the supposed lesion sites for the present patients. As discussed below, anatomical knowledge suggests that the cerebellar efferent pathways (cerebello-thalamo-cortical pathways) were involved in cases 1 and 2, whereas the cerebellar afferent pathway (cortico-pont-cerebellar pathways) in case 3. The results of cerebellar stimulation (absent cerebellar suppression in cases 1 and 2, and normal suppression in case 3) support the above anatomical speculation.

Lesion Site

In 100 patients with AH, CT, or MRI analyses demonstrated that responsible lesions for ataxia were positioned at the internal capsule (39%), pons (19%), thalamus (13%), corona radiate (13%), lenticular nucleus (8%), cerebellum (4%), and frontal lobe (4%) [4]. Another study showed lesions at pons (8 cases), internal capsule (6 cases), corona radiate (2 cases), internal capsule to corona radiate (7 cases), subcortical frontal lobe (one case) or anterior central convolution (2 cases) in 25 patients with AH [5]. In our three cases, lesions were located at the posterior limb of internal capsule, lateral thalamus and pre- and post-central gyri, all of which were well-known lesion sites for AH [4, 5].

Which Part of Cerebellar Loops Was Disrupted?

Anatomical knowledge revealed that the fronto-ponto-cerebellar fibers descend through the anterior limb of internal capsule, genu, and the anterior one-third portion of the posterior limb of internal capsule [12–14]. Especially, the fibers from primary motor cortex via pontine nucleus to the cerebellum are shown to pass through the anterior one-third portion of the posterior limb of the internal capsule [14]. On the other hand, the tracts from ventro-lateral nucleus of thalamus to pericentral cortices are located at the posterior portion of the posterior limb of the internal capsule [12, 15]. The fronto-pontine pathway is positioned just anterior to the corticospinal tract which is positioned right anterior to the thalamo-motor cortical pathway. The lesion of case 1 was positioned at a posterior portion of the posterior limb of the internal capsule. Taken these all anatomical knowledge together, we speculated that the lesion would involve the thalamo-cortical fibers (cerebellar efferent AH). The lack of cerebellar suppression shown here physiologically supports this anatomical speculation. In case 2, the responsible lesion was positioned at the lateral thalamus (Fig. 2), which should affect the thalamo-cortical fibers (cerebellar efferent AH). The absent cerebellar suppression in this patient also physiologically supports this idea. In case 3, one conspicu-

Fig. 2 The cerebellar loops. Cerebellar efferent pathways were shown by *lines* and afferent pathways by *dotted lines*. Lesion site was indicated by *crosses* for each case (×)
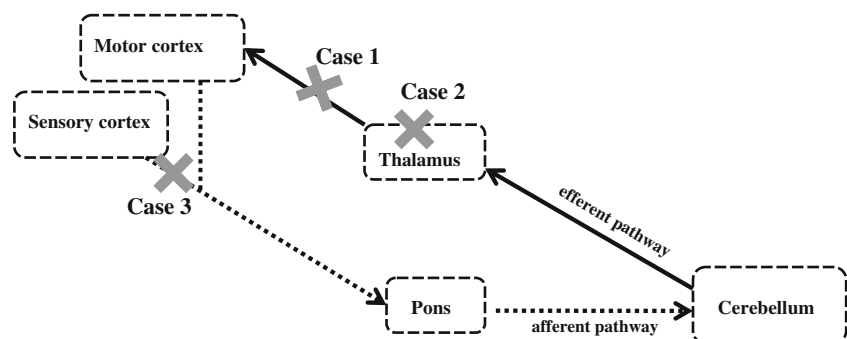
ous finding is that this small lesion produced apparent cerebellar ataxia at the acute phase and it faded out in a week probably because of its small size. We studied this patient when she had apparent ataxia. Based on these, we considered that cerebellar ataxia was caused by a lesion within cerebellar afferent pathways (Fig. 2). However, we could not exclude the following possibility. The small lesion must have involved a part of some cerebellar related pathway without gross impairment of cortico-pontine pathway and it caused clinical ataxia. This lesion, however, was too small to be detected by cerebellar TMS experiment. If so, our experimental results may be of no use for speculating mechanisms of the ataxia in this patient.

Conclusion

Both cerebellar efferent and afferent pathways involvements can produce ataxia in AH. Cerebellar efferent AH must be physiologically differentiated from cerebellar afferent AH by the cerebellar stimulation technique.

Conflicts of interest The authors declare that there are no potential conflicts.

References

1. Fisher CM, Cole M. Homolateral ataxia and crural paresis: a vascular syndrome. J Neurol Neurosurg Psychiatry. 1965;28:48–55.
2. Fisher CM. Ataxic hemiparesis. A pathologic study. Arch Neurol. 1978;35:126–8.
3. Gorman MJ, Dafer R, Levine SR. Ataxic hemiparesis. Critical appraisal of a lacunar syndrome. Stroke. 1998;29:2549–55.
4. Moulin T, Bogousslavsky J, Chopard JL, Ghika J, Crépin-Leblond T, Martin V, et al. Vascular ataxic hemiparesis: a re-evaluation. J Neurol Neurosurg Psychiatry. 1995;58:422–7.
5. Hiraga A, Uzawa A, Kamitsukasa I. Diffusion weighted imaging in ataxic hemiparesis. J Neurol Neurosurg Psychiatry. 2007;78:1260–2.
6. Kelly MA, Perlik SJ, Fisher MA. Somatosensory evoked potentials in lacunar syndrome of pure motor and ataxic hemiparesis. Stroke. 1987;18:1093–7.
7. Dupuis MJ, Evrard FL, Jacquerye PG, Picard GR, Lermen OG. Disappearance of essential tremor after stroke. Mov Disord. 2010;25:2884–7.
8. Mochizuki H, Ugawa Y. Disappearance of essential tremor after stroke: which fiber of cerebellar loops is involved in posterior limb of the internal capsule? Mov Disord. (2011. doi:10.1002/mds.23712.
9. Ugawa Y, Terao Y, Hanajima R, Sakai K, Furubayashi T, Machii K, et al. Magnetic stimulation over the cerebellum in patients with ataxia. Electroencephalogr Clin Neurophysiol. 1997;104:453–8.
10. Mochizuki H, Huang YZ, Rothwell JC. Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol. 2004;561:331–8.
11. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol. 1995;37:703–13.
12. Axer H, Keyserlingk DGv. Mapping of fiber orientation in human internal capsule by means of polarized light and confocal scanning laser microscopy. J Neurosci Methods. 2000;94:165–75.
13. Parent A. Carpenter's human neuroanatomy. 9th ed. Baltimore: Williams & Wilkins; 1996. p. 682–5.
14. Kamali A, Kramer LA, Frye RE, Butler IJ, Hasan KM. Diffusion tensor tractography of the human brain cortico-ponto-cerebellar pathways: a quantitative preliminary study. J Magn Reson Imaging. 2010;32:809–17.
15. Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci. 2003;6:750–7.