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Effect of edaravone on acute brainstem–cerebellar infarction with vertigo and sudden hearing loss

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ABSTRACT

We report 2 cases with acute brainstem and brainstem–cerebellar infarction showed improvement of their signs and symptoms after administration of edaravone. Case 1, a 74-year-old woman who experienced sudden vertigo, also had dysarthria and left hemiplegia. Magnetic resonance imaging (MRI) showed an abnormal region in the right ventrolateral medulla oblongata. The patient's vertigo and hemiplegia improved completely after treatment. Case 2, a 50-year-old man who experienced sudden vertigo and sensorineural hearing loss (SNHL), developed dysarthria after admission. MRI revealed acute infarction in the right cerebellar hemisphere. Magnetic resonance angiography revealed dissection of the basilar artery and occlusion of the right anterior inferior cerebellar artery. The patient's vertigo and hearing remarkably improved. We have described 2 patients whose early symptoms were vertigo and sudden SNHL, but who were later shown to have ischemic lesions of the central nervous system. Edaravone is neuroprotective drug with free radical-scavenging actions. Free radicals in the ear are responsible for ischemic damage. Edaravone, a free radical scavenger, may be useful in the treatment of vertigo and SNHL.

1. Introduction

Edaravone (3-methyl-1-phenyl-pyrazolin-5-one), a free radical scavenger, is a clinical drug that has been widely used in Japan since 2001 to reduce neuronal damage after acute cerebral infarction [1]. Edaravone has been reported to inhibit lipid peroxidation, vascular endothelial cell injury, brain edema, tissue injury, and delayed neuronal death, and consequently to reduce neurological deficits [1].

Free radicals in the ear are responsible for ischemic damage. Recently, edaravone has been reported to markedly reduce the loss of inner hair cells after cochlear ischemia in gerbils [2]. But, its effectiveness for treating cochlear ischemia has not yet been revealed in humans.

In this paper, we report 2 cases in which acute brain infarction was accompanied by vertigo and sudden sensorineural hearing loss (SNHL). Treatment of the infarction with edaravone also improved the inner ear symptoms; therefore, edaravone also appears to be effective for treating inner ear problems associated with brain infarction in humans.

2. Case report

In Case 1, the patient was a 74-year-old woman who experienced sudden vertigo accompanied by nausea, numbness and coldness in the left limb when she got up. She had a past history of hypertension, spinal canal stenosis, and a cataract. Electrocardiography revealed that she had atrial fibrillation. Computed tomography (CT) scans of the brain revealed no abnormalities. On physical examination, she had right and left lateral gaze nystagmus. She showed dysdiadokokinesis, finger to nose and heel to knee tests were dysmetric and diminished pain and temperature sensation on the left side. She did not complain about hearing loss, so a pure-tone audiogram was not performed.

During the initial 6 h of hospitalization, she appeared dysarthria and incomplete left hemiplegia. Left Babinski reflex were observed. Axial T2- and diffusion-weighted magnetic resonance imaging (MRI) of the brain revealed no obvious abnormalities. However, we strongly suspected a cerebral embolism and administered heparin and edaravone for 2 weeks. Fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed an abnormal region in the right ventrolateral medulla oblongata on day 10 (Fig. 1). Subsequently, the patient's vertigo and hemiplegia improved completely.

In Case 2, the patient was a 50-year-old otherwise healthy man who experienced sudden vertigo that occurred when he started office work. On physical examination, we observed left-beating horizontal torsional spontaneous nystagmus, which was enhanced

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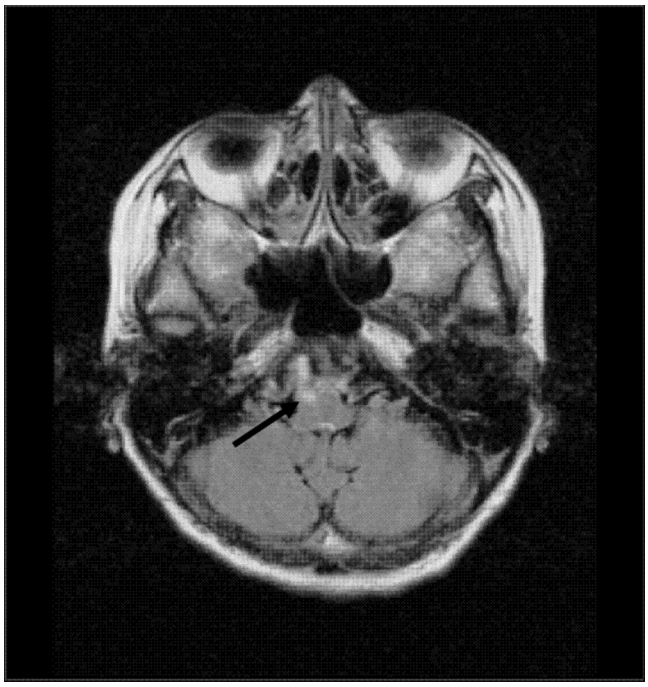

Fig. 1. Axial magnetic resonance imaging (MRI) of the brain performed 10 days after the onset of vertigo in patient 1. Fluid-attenuated inversion recovery MRI of the brain revealed an abnormal region in the right ventrolateral medulla oblongata (filled arrow).

when the patient gazed to the left. He had no ophthalmoplegia, facial paralysis or numbness, Horner's syndrome, or cerebellar dysmetria. CT scans of the brain revealed no abnormalities. In the course of waiting to be examined, he presented with sudden deafness on the right side. The eardrums appeared normal. A pure-tone audiogram showed profound right-sided SNHL (Fig. 2A). Despite we considered right sudden SNHL with vertigo, he developed dysarthria, numbness in the left hand, and slight dysdiadokokinesis, finger to nose and heel to knee tests were dysmetric after 5 h of hospitalization. Diffusion-weighted MRI of the brain showed acute infarction in the right cerebellar hemisphere (Fig. 3A). Magnetic resonance angiography (MRA) revealed dissection of the basilar artery and occlusion of the right anterior inferior cerebellar artery (AICA) (Fig. 3B). From the same day, the patient was begun administering heparin, glycerol and edaravone. High-dose steroid therapy was started from the same day, it was discontinued on the same day. Two weeks later, a second brain MRA showed reperfusion of the AICA (Fig. 3C). After 22 days later, the patient's hearing remarkably improved (Fig. 2B). Subsequently, the patient's vertigo and numbness improved completely. An eye-tracking test and an optokinetic pattern test revealed no abnormalities. The caloric test to cold water revealed normal responses of 30°/s on the right side and 20°/s on the left side.

3. Discussion

We have described 2 patients whose early symptoms were vertigo and sudden SNHL, but who were later shown to have ischemic lesions of the central nervous system. In both cases, edaravone given for the ischemia also resolved the vertigo and associated SNHL. Sudden SNHL and vertigo are potentially caused by cerebrovascular disorders [3]. Distinguishing between peripheral and central lesions is important for ruling out potentially life-threatening conditions. Diffusion-weighted MRI of the brain is usually an invaluable procedure for early detection of acute ischemic stroke. However, in Case 1, diffusion-weighted MRI of the brain initially revealed no obvious abnormality. Only in later follow-up scans, after neuro-otological examination indicated aggravation of symptoms, was an infarction of the ventrolateral medulla oblongata revealed. FLAIR MRI of the brain can be used to estimate the onset time of an acute ischemic stroke within 24 h of the onset [4]. A patient suspected of acute ischemic stroke should be examined using both diffusion-weighted and FLAIR MRI of the brain. If MRI shows no definite abnormalities, we suggest neuro-otological examinations – in particular nystagmus assessment – as highly valuable tools for clinical diagnosis.

Case 2 is an instance of AICA infarction because of the basilar artery dissection. In 1943, Adams first described the clinical symptoms of an AICA infarction [5]. Occlusion of the AICA is rare. Roquer et al. reported that AICA infarcts were diagnosed in 0.9% of all acute strokes in their department and accounted for 5.2% of those affecting the vertebrobasilar system [6].

Edaravone is regarded as a readily available neuroprotective drug with free radical-scavenging actions. A randomized controlled study, in which 30 mg of edaravone was infused twice a day for 14 days to patients within 72 h after the onset of ischemic stroke, showed significant improvement of functional outcome in the edaravone group [1]. For patients treated within 24 h, the difference between the edaravone and placebo groups was even clearer. Thus, patients suspected of having an ischemic stroke should be administered edaravone as soon as possible. We suggest that in the cases reported here, the early judgment and treatment prevented the occurrence of serious conditions in both cases.

Maetani et al. reported that edaravone had a protective effect against the deterioration of auditory brain response (ABR) thresholds and inner hair cell death by intravenous administration (1 mg/kg) 1 h after cochlear ischemia in Mongolian gerbils [2]. These findings suggest that preventing free radical generation may attenuate ischemia-induced hearing dysfunction. Moreover, they suggest that edaravone might protect against aminoglycoside ototoxicity. A similar result was also observed regarding damage due to noise exposure [7]. Cochlear ischemia and reperfusion dysfunction, inflammation could be possible pathogenesis of sudden SNHL. One previous case in which edaravone was used the treatment of AICA syndrome with acute SNHL has been reported [8]. This is thus the second report of edaravone treatment for severe HL with AICA infarction, and the first case in which edaravone was effective against AICA syndrome with severe SNHL without steroid therapy. The current standard treatment for idiopathic sudden SNHL is systemic steroid therapy. Table 1 shows a summary of comparison between edaravone and steroid treatment. Unlike edaravone, Steroid has been reported to support a beneficial role of anti-inflammatory and immunosuppressive agents in reducing hearing loss and cochlear damage [10]. Intratympanic steroid therapy was not inferior to systemic steroid therapy [11]. One previous report has compared the efficacy of intratympanic steroid therapy, systemic steroid therapy, and combined therapy. No difference in the level of hearing gain or ratio of hearing improvement was observed among the three groups [12]. If steroid therapy proves inadequate, edaravone administration might be one treatment option for acute SNHL.

In the cases reported here, heparin was administered with edaravone. Heparin is also used as common medical treatment for acute ischemic stroke. In a prospective study by Mattox and Simmons, 60% of patients with sudden idiopathic SNHL were found to recover with heparin treatment, which is no significant advantage independent of the type of medical therapy [13]. Therefore, we guess edaravone has more effect than heparin for acute SNHL.

In a randomized controlled study to investigate whether adding edaravone could improve treatment outcomes in patients