—Case Report—

Correlation of Clinical Improvement with Pontine Lesions in Opsoclonus-myoclonus Syndrome

TSUYOSHI TSUTADA, TORU IZUMI and TATSUYA MURAKAMI

Department of Geriatrics & Neurology, Osaka City University Medical School
1-5-7, Asahi-machi, Abeno-ku, Osaka City, 545, Japan

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Summary

In a case of acute disseminated encephalomyelitis displaying opsoclonus-myoclonus syndrome, magnetic resonance images (MRI) disclosed pontine lesions involving part of the pontine paramedian reticular formation and the raphe nucleus. Shrinkage of the lesions correlated with the patient's clinical state. This observation supports the hypothesis that a pontine lesion can cause opsoclonus-myoclonus syndrome.

Introduction

The term "opsoclonus" was first used in 1913 by Portuguese neurologist K. Orzechowski to describe the abnormal eye movement seen after nonepidemic encephalitis. The original paper cannot be found probably because of a citation error in a later paper (1927) by Orzechowski. The term was used to describe multidirectional conjugated rapid eye oscillations without intersaccadic pause. The activity seemed to be aggravated by emotion, and principally appeared when the patient tried to change the direction of gaze. The abnormal activity was also frequently associated with myoclonic jerking of the face, body or limbs.

Causes reported so far include viral encephalitis, post-infectious syndrome, paraneoplastic syndrome, intoxication, hydrocephalus, trauma, intracranial tumor and thalamic hemorrhage.[1],[2] The location of the lesion responsible for this
abnormal activity has not yet been clearly determined. In 1979, however, Zee and Robinson offered the hypothesis that saccadic oscillations, including opsoclonus, occur due to dysfunction of pause neurons in the pontine paramedian reticular formation (PPRF). Later, pause neurons were identified to be located in the raphe nucleus.

In this paper we present a case with the PPRF and raphe nucleus lesions visualized by MRI, whose shrinkage correlated with improvement of the symptoms.

Case Report

A 26 year-old female was admitted for tremulous movement of the body. One month before admission she experienced general fatigue and loss of appetite for several days, and then recovered. A few days before admission she experienced nausea and vomiting, so rested in bed. The next day she felt a floating sensation while walking, and her symptoms worsened. One day before admission she experienced dysarthria and tremulous movement of the body.

Neurological findings on admission showed a stiff neck and body tremulousness, especially in the presence of nervous tension. The patient also displayed disturbance of left conjugated gaze; her eyeballs showed conjugated but rapid multidirectional movement, especially horizontal saccadic movement without intersaccadic pause. We considered the eye movement to be opsoclonus; it seemed to be particularly intense during attempts to redirect her gaze. The movement diminished, but still occurred, even with her eyes closed. It could also be observed during sleep, although only rarely. Dysarthria was also noted. Manual muscle testing was normal. Deep tendon reflexes were generally hyperactive, without laterality. Plantar reflexes were neutral. Sensory system investigation findings were not remarkable. The patient displayed clumsiness in the finger-to-nose-to-finger test and heel-to-knee-to-shin test, and was unable to walk because of body tremulousness.

Routine laboratory data showed no abnormality. Cerebrospinal fluid (CSF) examination on the third day of admission showed a high protein level of 74.9 mg/dl, but other CSF data, including myelin basic protein, were normal. Brainstem auditory evoked potential (BAEP) recorded a few days after admission was normal.

CT scan on admission revealed no abnormality, but MRI one week after admission disclosed abnormal high-intensity lesions on the T2-weighted image in the white matter of both cerebral hemispheres, and predominantly on the left side of the pontine tegmentum. No abnormal signal intensity was detected in the cerebellum (Fig. 1). Fig. 2 shows a schematic representation of the pontine lesions detected by MRI, and their relationship to the anatomic structure. The most dorsal lesions (Fig. 2-1) involved the pontine reticular nucleus (part of PPRF) and the pontine
Fig 1. Axial T2-weighted MRI one week after admission show abnormal high intensity lesions in both cerebral white matter and predominantly left side of pontine tegmentum. No abnormal signal intensity was detected in cerebellum.

Fig 2. Schematic representation of lesions in pons (right half) and position of pontine reticular nucleus (a) (part of PPRF) and raphe nucleus (b) (left half). Of the lesions in pontine tegmentum (1-3), most dorsal ones (1) involve pontine reticular nucleus and raphe nucleus.
Fig 3. Coronal T2-weighted MRI one week after admission. Disseminated lesions in cerebral white matter are visible in these images as well, with no abnormality in cerebellum.

Fig 4. Axial T2-weighted MRI 6 weeks after admission when opsoclonus showed improvement. Most dorsal pontine lesion in Fig. 1, that involved pontine reticular nucleus and pontine raphe nucleus, almost disappeared. Clinical improvement is associated with shrinkage of pontine lesions.

On the basis of the above findings, we thought that acute disseminated enceph-
Correlation of clinical improvement with pontine lesions in opsoclonus-myoclonus lomyelitis (ADEM) was the most-likely diagnosis, although multiple sclerosis, vasculitis, or encephalitis could not be ruled out. And the dorsal pontine lesions involving the PPRF and the raphe nucleus, produced symptoms of opsoclonus-myoclonus syndrome, left gaze palsy and dysarthria. The patient was treated with a program of steroid and clonazepam. Several days after treatment initiation, her left gaze palsy disappeared and there was gradual improvement in the opsoclonus, body tremulousness and dysarthria. Two months after admission she was discharged, with some remaining opsoclonus-myoclonus syndrome. One year later a follow-up neurological examination showed no neurological deficit.

Fig. 4 shows the MRI obtained 6 weeks after admission, when the opsoclonus-myoclonus syndrome showed improvement. The most dorsal lesions had nearly disappeared. The clinical improvement was associated with disappearance of the lesions involving the PPRF and the pontine raphe nucleus. MRI one year after discharge (Fig. 5) shows that the lesions continued to become more obscure.

Fig 5. Axial T2-weighted MRI one year after discharge. Lesions have continued to become more obscure, with associated clinical improvement.
Discussion

According to Orzechowski, opsoclonus consists of a continual state of ocular agitation with rapid, unequal eye movements that are generally horizontal but also occur in other directions. The term opsoclonus is used to differentiate this movement from other ocular dyskinesias such as ocular myoclonus ("lighting eye movements"), ocular dysmetria, ocular flutter and opsochoria. The activity seems to be exacerbated by emotion and principally appears when the patient tries to change the direction of gaze.

Opsoclonus is frequently associated with myoclonic jerking of the face, body, or limbs. Sometimes, however, the movements cannot be clearly classified as either cerebellar or myoclonic, and are therefore called "dancing," "shivering," or "body tremulousness" as in our case. These atypical movements have features of both cerebellar ataxia and myoclonus, but differ from the usual signs of cerebellar dysfunction because they are present at rest.

Though opsoclonus is known to occur in apparently normal newborns, and opsoclonus-like movement has also been reported as a psychologically related problem, usually it is recognized as a neurological manifestation of remote cancers and toxic, metabolic, infectious, structural, and degenerative disorders. In childhood’s cases it is most often due to the remote effect of a neuroblastoma, and in adult cases to brainstem encephalitis. The mechanism by which opsoclonus occurs is still unclear, but several reports say that in at least some cases it is an immune-mediated phenomenon, since "anti-Ri" antineuronal antibodies have been found in some patients.

With regard to location of the lesion that causes opsoclonus, some authors consider the cerebellum to be the most likely site, in view of associated cerebellar ataxia (the "cerebellar theory"). In fact, many autopsied case reports, such as those of Ellenberger, have indicated that the lesion responsible was in the cerebellum. There are also cases, however, in which no cerebellar lesions were found.

Neurophysiological studies have revealed that there is a neural circuit in the PPRF that produces saccadic eye movement. According to Zee and Robinson, three types of saccadic related neurons (burst cells, pause cells and tonic cells) can be found in the PPRF. Burst cells initiate saccades, and pause cells inhibit burst cells. Pause neurons are of two types, directional pause neurons and omnipause neurons. The latter exert a tonic inhibition on some burst neurons, so act as a trigger for saccades. Zee and Robinson postulate that a disease of the pause cells is responsible for flutter-like oscillation or opsoclonus (the "pontine theory"). The anatomical location of omnipause cells has since been identified in the monkey, and
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homologous cell groups found in the human brainstem; [4], [5] J.A. Büttner-Ennever et al. showed that omnipause neurons in the monkey lie in a morphologically and functionally distinct division of the raphe cell column in the caudal pons, just caudal to the nucleus raphe pontis, which the authors called the nucleus raphe interpositus. They also found a homologous cell group in the human brainstem, clustering around the midline between the abducens nerve rootlets.

Confirmation of the pontine theory requires evidence of omnipause cell dysfunction in opsoclonus-myoclonus syndrome. One piece of evidence that supports the pontine theory is BAEP abnormality in opsoclonus cases, as in the cases described by Araki et al. [13] However, BAEP recorded in our case did not show any abnormality; and considering that the BAEP pathway is the external lemniscus if the causal lesion is in or near the nucleus raphe, [4], [5] the relationship of BAEP abnormality to opsoclonus may be incidental.

Pathological evidence thus far is exceedingly variable, as previously stated. Using MRI, some authors have reported lesions in the pons. [13], [14] Unlike our case, however, they did not show the relation to anatomical site and chronological changes. The lesions in our case involved the omnipause neuron group, and when the opsoclonus was improved, the responsible lesions (Fig. 2-1) had almost disappeared. Although in our case there may have been a cerebellar lesion that was not apparent on MRI because the etiology was ADEM, association of the clinical improvement with the chronological shrinkage of the pontine lesions supports the pontine theory.

References


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