Midbrain Ataxia: An Introduction to the Mesencephalic Locomotor Region and the Pedunculopontine Nucleus

OBJECTIVE. Although gait ataxia is usually associated with cerebellar lesions, we review a less familiar cause. We present three patients with dorsal midbrain lesions and correlate these presentations with recent findings in the functional anatomy of the midbrain.

CONCLUSION. We suggest that these lesions involve a well-studied but generally unfamiliar area of the dorsal midbrain known as the mesencephalic locomotor region. More specifically, we hypothesize that involvement of the pedunculopontine nucleus, a major component of the mesencephalic locomotor region, may be at least partially responsible for producing midbrain ataxia.

When a patient presents with gait ataxia, the neurologist and the neuroradiologist reflexively think of possible lesions in the cerebellum. We review a less familiar cause of ataxia: dorsal midbrain lesions.

Ataxia as a sign of midbrain abnormality has been previously described, predominantly as part of Claude’s syndrome and Nothnagel’s syndrome [1]. These descriptions putatively link the ataxia to a dorsal midbrain abnormality involving or adjacent to the decussation of the superior cerebellar peduncles, disrupting cerebellar efferents to the thalamus, and hence producing ataxia.

Since the publication of the original descriptions of brainstem anatomy and neuroanatomic–functional correlations in the late 1800s and early 1900s, there have been tremendous advances in our understanding of neuroanatomy. Given the paucity of reports in the recent literature regarding the neuroanatomic basis of midbrain ataxia, we sought to correlate some of these recent neuroanatomic discoveries with the cases of three patients who presented with ataxia and dorsal midbrain lesions. We suggest that these lesions involve a well-studied but generally unfamiliar area of the dorsal midbrain known as the mesencephalic locomotor region [2, 3]. More specifically, we hypothesize that involvement of the pedunculopontine nucleus (PPN), a major component of the mesencephalic locomotor region, may be at least partially responsible for producing midbrain ataxia [4, 5].

Before a previous report on one of our patients [6], there had been, to our knowledge, only one clinical report suggesting the involvement of the PPN in a patient with gait deficits [7]. However, a wealth of animal and human data now suggests that it is time to familiarize ourselves with the mesencephalic locomotor region and the PPN and their possible roles in gait disorders.

Subjects and Methods

Case 1

A 66-year-old man with a history of poorly controlled diabetes and hypertension presented to the emergency department with complaints of gait unsteadiness and blurred vision. Findings at physical examination were significant for a profound truncal ataxia that was most pronounced when the patient was attempting to walk but was present even when
he was sitting. The patient was able to stand but only with a wide stance. When asked to walk, he had marked start hesitation in his gait and generated short, irregular, unsteady steps, lacking rhythmicity and a uniform direction. Although he initiated his gait with difficulty, the patient showed no signs of festination, shuffle, stooping, or other characteristics seen in the Parkinsonian gait. He was unable to perform tandem gait. The results of Romberg’s test were negative. Peripheral cerebellar functions, such as those used in the finger-to-nose test, were intact. Eye movement examination showed the upward gaze to be more restricted than the downward gaze, impaired convergence, and skew deviation of the eyes in the primary position, with the left being hypertropic. No nystagmus, lid lag, or pupillary abnormalities were observed. No eye-patching was attempted. T2- and diffusion-weighted MRI showed a lesion consistent with infarct, measuring about 6 mm, in the left dorsal midbrain, anterior to the aqueduct of Sylvius and dorsal to the red nucleus (Fig. 1). Repeated examination 3 days later showed significant gait improvement; however, the ocular findings remained unchanged.

Case 2
A 52-year-old man with diabetes and hypertension presented to the emergency department 2 days after a sudden onset of blurred vision and difficulty in walking. At examination, the patient was found to have dense, pupillary-involving palsy of the left third nerve. The patient was also mildly dysarthric, with some slurred speech. Although functions used in finger-to-nose testing were intact, the patient showed disturbances in gait, with unsteadiness; a broad-based stance; swaying, short, irregular steps with variable amplitude and some high-stepping; and some difficulty initiating locomotion. The patient was unable to attempt tandem gait. We observed no Romberg’s sign and saw no evidence of truncal ataxia while the patient was sitting. No stooping or shuffling was observed in the patient’s gait, and no evidence of mask facies or resting tremor was seen. The third nerve palsy produced an inferolateral deviation of the globe and a dense ptosis. This simulated eye-patching because the left eye was completely closed. The patient’s gait ataxia significantly improved over the ensuing 3 days, although there was little change in the ocular findings. The third nerve palsy was significantly improved at 6 weeks. T2- and diffusion-weighted MRI showed a recent infarct in the posterior left midbrain tegmentum, just dorsal to the red nucleus (Fig. 2).

Case 3
An 80-year-old hypertensive man presented to the emergency department with a 1-day history of
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ever, none of the patients displayed positive Romberg’s signs or showed evidence of peripheral cerebellar dysfunction such as positive results on finger-to-nose or heel-kneeshin tests. Only one patient had significant truncal ataxia while seated. All the patients displayed oculomotor abnormalities, with either third nerve palsies or vertical gaze deficits. Patients with acute ocular motor nerve palsy may present with gait instability. However, their gait unsteadiness tends to vary depending on the severity of the diplopia, and they do not exhibit hesitation or lack of rhythmicity, as seen in our patients. In fact, most patients with diplopia compensate well in their gait and do not usually present with predominant gait instability. These cases thus suggest that there may be some unique features of gait disturbances caused by dorsal midbrain lesions that are specific to the midbrain tegmental structures and not secondary to cerebellar dysfunction caused by involvement of the adjacent decussation of the superior cerebellar peduncles or to associated oculomotor abnormalities.

As we stated, all the lesions in our patients were isolated to the posterior midbrain tegmentum, likely involving the mesencephalic reticular formation. A functionally defined mesencephalic locomotor region containing the PPN is located in this region. The mesencephalic locomotor region was first described by Shik and Yagodnitzy in 1966 [8] and has been studied extensively in animal models thereafter [2, 3]. The mesencephalic locomotor region is located in the dorsal midbrain, lying in the posterior tegmentum just ventral to the inferior colliculus (Fig. 3).

Discussion

Our three patients had isolated lesions in the dorsal midbrain, consistent in appearance and presentation with infarcts. All the patients also presented with gait hesitation and gait ataxia as prominent parts of their symptom complex. The ataxia was characterized by steps that lacked uniform direction, amplitude, and rhythmicity, with an unsteadiness and an inability to perform tandem gait. Although gait hesitation is typical of Parkinsonism, none of the patients displayed other typical Parkinsonian features such as bradykinesia, rigidity, festination, or a stooped and shuffling gait. Gait ataxia, conversely, is typical of cerebellar lesions. However, none of the patients displayed positive Romberg’s signs or showed evidence of peripheral cerebellar dysfunction such as positive results on finger-to-nose or heel-kneeshin tests. Only one patient had significant truncal ataxia while seated. All the patients displayed oculomotor abnormalities, with either third nerve palsies or vertical gaze deficits. Patients with acute ocular motor nerve palsy may present with gait instability. However, their gait unsteadiness tends to vary depending on the severity of the diplopia, and they do not exhibit hesitation or lack of rhythmicity, as seen in our patients. In fact, most patients with diplopia compensate well in their gait and do not usually present with predominant gait instability. These cases thus suggest that there may be some unique features of gait disturbances caused by dorsal midbrain lesions that are specific to the midbrain tegmental structures and not secondary to cerebellar dysfunction caused by involvement of the adjacent decussation of the superior cerebellar peduncles or to associated oculomotor abnormalities.

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In animal experiments, it is found physiologically by placing electrodes in this approximate location and advancing them until controlled locomotion on a treadmill is obtained with stimulation [3]. More recently, subtraction brain single-photon emission CT has shown an area of activation in the ventrolateral midbrain, most likely involving the mesencephalic locomotor region [9]. This finding confirms the role of the mesencephalic locomotor region in both initiating and modulating locomotion.

A careful study in the cat revealed that the predominant output of the mesencephalic locomotor region is through the reticulospinal system, including portions of the ventral and anterior parts of the nucleus gigantocellularis and posterior and ventral portions of the nucleus reticularis ventralis and nucleus reticularis magnocellularis [3]. These efferents to the medioventral medulla in turn modulate spinal locomotor pathways [10]. In primates, moreover, there appear to be additional direct projections from the mesencephalic locomotor region to the spinal cord [11]. The output of the mesencephalic locomotor region seems to be bilaterally distributed to the reticulospinal cells in the ventromedial medulla, with an ipsilateral predominance [3]. This bilateral projection may account for a general gait ataxia rather than a unilateral deficit. Most reticulospinal cells in the ventromedial medulla receiving mesencephalic locomotor region input project to the spinal cord through the ventrolateral funiculus ipsilateral to the mesencephalic locomotor region—that is, through the medullary reticulospinal tract. Lesions of the medullary reticulospinal tract, in turn, have been shown to cause deficits in locomotion and to cause imbalance [12, 13]. This growing body of evidence suggests that the mesencephalic locomotor region plays an important role in human locomotion.

A main component of the mesencephalic locomotor region is the PPN, which is thought on the basis of animal studies to be involved in the initiation and modulation of gait, among other functions [5]. The PPN is a heterogeneous population of neurons, lying in the dorsal midbrain as part of the mesencephalic reticular formation. In the human brain, it is bordered medially by fibers of the superior cerebellar peduncle and the peduncular decussation and is bordered laterally by the medial lemniscus [4]. Rostrally, the anterior portion of the PPN contacts the substantia nigra, whereas the most caudal pole is adjacent to the locus ceruleus [4].

Two main subdivisions of the PPN have been recognized: a pars compacta of the PPN (PPNc), located in the caudal part of the nucleus, and a second part known as the pars dissipata (PPNd). These have been described in humans and monkeys [14]. Most of the PPNc neurons are cholinerergic. The PPNd has a higher proportion of glutaminergic neurons [14]. Much work in humans remains to be done on the precise connectivity of the PPN. However, primate data suggest that the main inputs to the PPN are from the internal segment of the globus pallidus and the pars reticularis of the substantia nigra [15].

Other proposed inputs are from the subthalamic nucleus and the cerebral cortex [4]. Proposed outputs of the PPN in primates are to the globus pallidus, pars compacta of the substantia nigra, subthalamic nucleus, striatum,
dorsal midbrain, resulting in stepping with ataxia [20].

Thus, the combination of gait hesitation and gait ataxia previously described, without other significant Parkinsonian or cerebellar features, may reflect a characteristic symptom complex of dorsal midbrain lesions related to the mesencephalic locomotor region and the PPN. This association may also explain the reason that other lesions in this area, such as the periaqueductal abnormalities associated with Wernicke’s encephalopathy, present with gait ataxia along with oculomotor symptoms. Interestingly, however, lesions of multiple sclerosis involving the dorsal midbrain seem to present differently, with deficits such as intranuclear ophthalmoplegia (from involvement of the medial longitudinal fasciculus) being prominent features. From the foregoing facts, we may hypothesize that this difference is seen because infarcts would tend to involve the neuronal structures, such as the PPN, whereas multiple sclerosis would tend to involve the white matter tracts, such as the medial longitudinal fasciculus. Such hypotheses, of course, require significant further study for their validation.

Although this series is far too small to speculate on the prognosis of infarcts in the dorsal midbrain, we note that the gait ataxia resolved fairly quickly in all three patients and with a significantly faster time course than the associated oculomotor abnormalities in the first two patients, who had the larger midbrain lesions.

In conclusion, we presented the cases of three patients with lesions in the posterior midbrain tegmentum which exhibited gait ataxia among other findings (predominantly third nerve deficits or vertical gaze palsy). We hypothesize the involvement of the mesencephalic locomotor region of the posterior midbrain tegmentum, and in particular the PPN which lies within it, in gait ataxia in such patients. We believe that this association represents an important level of refinement over the few early descriptions of midbrain ataxia. Thus, for neuroradiologists, the dorsal midbrain should be a “focus area” in patients presenting with gait ataxia, especially when this symptom is accompanied by third nerve deficits or vertical gaze palsy.

References