Vestibular Imbalance Associated With a Lesion in the Nucleus Prepositus Hypoglossi Area

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Background: The nucleus prepositus hypoglossi (NPH) is known to be a neural integrator of horizontal eye movements. Although the role of the human NPH is not well known, it may also function in postural balance, in view of its anatomic connections with the vestibular nuclei and vestibulocerebellum and of lesion studies in experimental animals.

Objective: To show that the human NPH contributes to vestibular function in addition to eye movement control.

Design: Case series.

Setting: University hospital.

Patients: Six patients with small and discrete brainstem infarctions that predominantly involved the NPH region.

Main Outcome Measure: Findings on magnetic resonance images.

Results: The NPH was affected at the lower pontine level in 2 patients and at the upper medullary level in 4. In addition to gaze-evoked nystagmus, all patients had vertigo, vomiting, and postural ataxia, suggesting vestibular dysfunction. The patients typically fell contralaterally or bilaterally to the lesion side.

Conclusion: The NPH serves a vestibular function in addition to its oculomotor control function.

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The nucleus prepositus hypoglossi (NPH), one of the perihypoglossal nuclei, is located rostral to the hypoglossal nucleus and extends to the abducens nucleus. The NPH and the medial vestibular nucleus (MVN), which is located lateral to the NPH and serves a vestibular function, are reciprocally connected and have afferent and efferent connections with the vestibulocerebellum and with most parts of the oculomotor system, including the abducens nucleus and the paramedian pontine reticular formation. Since the NPH was first suggested to serve a vestibular or oculomotor function, and studies in subhuman primates and cats have focused on its role in eye movement control and have shown that the NPH and the MVN are involved in the neural integration of horizontal eye movements. While the exact role of the NPH in humans is uncertain because cases with an isolated NPH lesion are rare, it is possible that the NPH functions in postural balance, as does the MVN, in view of its anatomic connections with the vestibular system and of lesion studies in experimental animals.

Herein we present our observations in 6 patients with small and discrete brainstem infarctions that predominantly involved the NPH region. All patients had vertigo, postural ataxia, and gaze-evoked nystagmus. Clinical findings associated with the NPH lesions, particularly in relation to its role in postural ataxia, are described.

Methods

During a 3-year period, 6 patients with small infarctions involving the NPH area were identified from among those admitted to our neurology department. The subjects included 2 men and 4 women with a median age of 67 years (range, 55-80 years). We reviewed clinical and magnetic resonance imaging (MRI) findings in these patients.

Results

Demographic and clinical findings are shown in the Table.

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All patients had small lesions in the medial portion of the pontomedullary junction. The lesion was at the lower pontine level in 2 patients and at the upper medullary level in the other 4 (Figure 1). The NPH appeared to be involved in all patients. All patients had vertigo as a presenting symptom, as well as gaze-evoked nystagmus or a mixed horizontal-torsional nystagmus that was intensified when looking in the direction of quick phases. A spontaneous upbeat nystagmus accompanied these symptoms in 1 patient (Table). Platelet antiaggregating drugs were given to all patients. A complete improvement of the postural ataxia was observed in all patients during the ensuing weeks.

Lesions in the subjects as demonstrated by MRI were small and discrete, and located in the medial tegument of the pontomedullary junction. A careful review of the MRIs showed that all lesions commonly involved the NPH region (Figure 2).

The NPH is known to be a component of the neural integrator of horizontal eye movements along with the MVN and flocculus, and to be important for normal gaze holding. Experimental lesions of the NPH were found to impair the ability to hold eyes in eccentric gaze. Moreover, gaze-evoked nystagmus was induced by pharmacologically inactivating the NPH-MVN region in the monkey. In concert with findings in primates, gaze-evoked nystagmus was present in all of our patients. A spontaneous upbeat nystagmus was observed in 1 patient. The present study adds MRI evidence to the previously suggested theory that the damage in the paramedian rostral medulla, involving the perihypoglossal nuclei, may be responsible for a spontaneous upbeat nystagmus.

Of note, all patients had postural ataxia with vertigo and vomiting, which suggests vestibular dysfunction. Although previous studies on experimental animals have concerned the role of the NPH in eye movement control, several lines of evidence suggest that vestibular dysfunction may be attributed to an NPH lesion. First, the NPH has reciprocal and extensive connections with the vestibulocerebellum and the vestibular nuclei, which serve a vestibular function, as well as the oculomotor system. The projection areas within the cerebellum, which include the anterior lobe, entire vermis, flocculus, nodulus, and fastigial nuclei, may also result in postural ataxia when damaged. Second, selective injury of the NPH has produced vestibular imbalance in experimental animals. Drug-induced selective damage of the NPH and of the adjacent perihypoglossal and reticular nuclei in primates produced a profound impairment of posture and gait. In cats, the selective inhibition of the NPH by muscimol microinjection caused a moderate vestibular imbalance and a failure of the horizontal neural integrator. This prior evidence, in combination with the findings of the present study, strongly suggests that the NPH serves a vestibular function as well as an oculomotor control function.

In this study, the NPH lesion typically produced contralateral or bilateral falls. The NPH has extensive and reciprocal connections with vestibular nuclei directly and indirectly via the vestibulocerebellum. An experimental study showed that a lesion of the NPH decreased the activity of the contralateral vestibular nuclei as a result of a reduction in the inhibition of inhibitory Purkinje cells of the contralateral flocculus, which projects to the vestibular nuclei (Figure 3). Thus, contralateral falls induced by an NPH lesion may be a reasonable explanation, because a lesion of the vestibular nuclei produces ipsilateral falls. Lesions of the commissural connections between the 2 NPHs at the midline were found to result in a reduction of both vestibular activities, which again may cause bilateral falls.

### Table. Demographic and Clinical Features of Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Risk Factors</th>
<th>MRA/DSA</th>
<th>TEE</th>
<th>Nystagmus</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/79</td>
<td>Hypertension</td>
<td>BA, MCA, ICA stenosis</td>
<td>Aorta plaques (9 mm)</td>
<td>GE, horizontal, right</td>
<td>Dysphagia</td>
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<tr>
<td>2/F/62</td>
<td>Hypertension, smoking</td>
<td>Both VA stenosis</td>
<td>Aorta plaques (5 mm)</td>
<td>Spontaneous upbeat, and GE, horizontal, right</td>
<td>Skew deviation, ocular tilt reaction</td>
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<td>3/F/55</td>
<td>Previous stroke</td>
<td>BA stenosis</td>
<td>ND</td>
<td>None</td>
<td></td>
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<tr>
<td>4/F/58</td>
<td>Hypertension, DM, previous stroke</td>
<td>BA, ICA stenosis</td>
<td>ND</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>5/F/80</td>
<td>None</td>
<td>Normal PCA stenosis</td>
<td>Normal (TTE)</td>
<td>GE, horizontal, bilateral</td>
<td>None</td>
</tr>
<tr>
<td>6/F/66</td>
<td>Hypertension, previous stroke</td>
<td>Normal</td>
<td>Normal (TEE)</td>
<td>GE, bilateral</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: BA, basilar artery; DM, diabetes mellitus; DSA, digital subtraction angiography; GE, gaze-evoked; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; ND, not done; PCA, posterior cerebral artery; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VA, vertebral artery.
Patient 6 had horizontal conjugate gaze palsy and facial palsy. The abducens nucleus and the facial nerve fascicles could be simultaneously involved, because they are located just above the NPH.

The present study has limitations. Because the involvement of the MVN or of the NPH was determined on the basis of MRI, exact microanatomic localization of the lesions was not possible. Therefore, when the proximity of the NPH and the MVN is considered, the possibility exists that the adjacent MVN might actually be involved. However, when the MVN is involved in the development of vestibular imbalance, patients are expected to fall ipsilaterally to the lesion side. However, in the present study, no patient showed an ipsilateral fall, which indicates that the MVN was unlikely to be responsible for the postural ataxia of our patients. As the majority of studies have examined the role of the NPH, the roles of the other perihypoglossal nuclei, the nucleus intercalatus, and the nucleus of Roller, which might be involved in our patients, are uncertain. Although it is conceivable that other perihypoglossal nuclei might contribute to vestibular dysfunction, no evidence is available on this topic. Another limitation of our study is that electro-oculographic studies were not undertaken. Therefore, we did not obtain more accurate information on the relationship between human NPH and horizontal eye

Figure 1. Magnetic resonance images (MRIs) of the patients. Axial MRIs show small high-signal-intensity lesions (arrows) in the medial tegmentum of the upper medulla (patients 1, 2, 3, and 5) and the lower pons (patients 4 and 6), which are consistent with infarctions. DWI indicates diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery.
movement control. Moreover, gaze-evoked and vestibular nystagmus, which may have been superimposed in some patients, could not be differentiated. Nevertheless, this study presents, to our knowledge, the first case series involving a discrete lesion predominantly affecting the NPH and describes our attempts to unveil and then demonstrate the role of the human NPH in vestibular balance.

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REFERENCES