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

Sang Won Seo, MD; Ha Young Shin, MD; Seo Hyun Kim, MD; Sang Won Han, MD; Kyung Yul Lee, MD; Seung Min Kim, MD; Ji Hoe Heo, MD, PhD

Background: 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.1 Since the NPH was first suggested to serve a vestibular or oculomotor function,2 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.3 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.4,5

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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METHODS

During a 3-year period, 6 patients with small and discrete brainstem 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.
key.7 In concert with findings in primates, gaze-evoked over, gaze-evoked nystagmus was induced by pharma-
tments that were not overcome by the oculocephalic ma-
neuver (Table). Platelet antiaggregating drugs were given
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ot be determined because the lesion was found in the
central portion (Figure 1). Associated neurologic signs
included dysphagia, skew deviation and ocular tilt reac-
tion, dysarthria, facial weakness of the peripheral type,
and disturbances of conjugate horizontal eye move-
tions that were not overcome by the oculocephalic ma-
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to all patients. A complete improvement of the postural
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Lesions in the subjects as demonstrated by MRI were small and
discrete, and located in the medial tegmentum of the
pontomedullary junction. A careful review of the MRIs
demonstrated that all lesions commonly involved the NPH re-
region (Figure 2).

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). All patients showed marked postural ataxia, but
no other cerebellar dysfunctions were observed. The di-
rection of falls was contralateral to the lesion side in 2
patients and bilateral in 2. In another 2 patients with
lesions at the medullary level, the laterality of falls could
not be determined because the lesion was found in the
central portion (Figure 1). Associated neurologic signs
included dysphagia, skew deviation and ocular tilt reac-
tion, dysarthria, facial weakness of the peripheral type,
and disturbances of conjugate horizontal eye move-
tions that were not overcome by the oculocephalic ma-
neuver (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.

COMMENT

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 med-
ullary level in the other 4 (Figure 1). The NPH ap-
ppeared to be involved in all patients.

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discrete, and located in the medial tegmentum of the
pontomedullary junction. A careful review of the MRIs
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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.8 More-
over, gaze-evoked nystagmus was induced by pharma-
cologically inactivating the NPH-MVN region in the mon-
key.8 In concert with findings in primates, gaze-evoked
nystagmus was present in all of our patients. A sponta-
aneous upbeat nystagmus was observed in 1 patient. The
present study adds MRI evidence to the previously sug-
gested theory that the damage in the paramedian rostral
medulla, involving the perihypoglossal nuclei, may be re-
sponsible for a spontaneous upbeat nystagmus.9

Of note, all patients had postural ataxia with vertigo
and vomiting, which suggests vestibular dysfunction. Al-
though previous studies on experimental animals have con-
cerned the role of the NPH in eye movement control, sev-
eral lines of evidence suggest that vestibular dysfunction
may be attributed to an NPH lesion. First, the NPH has
reciprocal and extensive connections with the vestibulo-
cerebellum and the vestibular nuclei, which serve a ves-
tibular function, as well as the oculomotor system. The
projection areas within the cerebellum, which include the
anterior lobe, entire vermis, flocculus, nodulus, and fas-
tigial nuclei,9 may also result in postural ataxia when dam-
aged. 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 pro-
duced a profound impairment of posture and gait.10 The
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induced selective damage of the NPH and of the adjacent
perihypoglossal and reticular nuclei in primates pro-
duced a profound impairment of posture and gait.10 In cats,
the selective inhibition of the NPH by muscimol micro-
jection caused a moderate vestibular imbalance and a
failure of the horizontal neural integrator.7 This prior evi-
dence, 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 con-
tralateral or bilateral falls. The NPH has extensive and
reciprocal connections with vestibular nuclei directly and
indirectly via the vestibulocerebellum.9 An experiment-
al study showed that a lesion of the NPH decreased the
activity of the contralateral vestibular nucleus as a re-
sult of a reduction in the inhibition of inhibitory Pur-
kinje cells of the contralateral flocculus, which projects
to the vestibular nucleus (Figure 3).10 Thus, contra-

Table. Demographic and Clinical Features of Patients

| Patient No./Sex/Age, y Risk Factors MRA/DSA TEE Nystagmus Other Features |
|---|---|---|---|---|---|
| 1/M/79 Hypertension | Aorta plaques (9 mm) | GE, horizontal, right | Spontaneous upbeat, and | Dysphagia |
| 2/M/62 Hypertension, smoking | Aorta plaques (5 mm) | GE, horizontal, right | Mixed horizontal and | None |
| 3/F/55 Previous stroke BA stenosis | Normal | GE, horizontal, right | None | None |
| 4/F/58 Hypertension, DM, previous stroke | BA, ICA stenosis | ND | SD | None |
| 5/F/80 None | Normal | Normal (TTE) | GE, horizontal, bilateral | Dysarthria |
| 6/F/66 Hypertension, previous stroke | Normal | Normal | GE, horizontal, right | Conjugate gaze palsy, facial palsy |

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 movement.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Medullary Level</th>
<th>Pontine Level</th>
<th>Direction/Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>Left</td>
<td>Central</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>Central</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>Bilateral</td>
<td>Right</td>
</tr>
</tbody>
</table>

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.
Acquisition of data: Shin, S. H. Kim, Han, Lee, S. M. Kim, and Heo.

Drafting of the manuscript: Heo.

Critical revision of the manuscript for important intellectual content: Seo, Shin, S. H. Kim, Han, Lee, S. M. Kim, and Heo.

Obtained funding: Heo.

Administrative, technical, and material support: Seo, Shin, Han, Lee, S. M. Kim, and Heo.

Study supervision: S. H. Kim and Heo.

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REFERENCES


Figure 1. Axial diagrams of the upper medulla (A) and the lower pons (B) showing the location of the nucleus prepositus hypoglossi and adjacent structures. 1 indicates nucleus prepositus hypoglossi (gray area); 2, medial vestibular nucleus; 3, medial longitudinal fasciculus; 4, paragigantocellular reticular nucleus; 5, gigantocellular reticular nucleus; 6, parvocellular reticular nucleus; 7, medial lemniscus; 8, facial motor nucleus; 9, pars oralis, spinal tract nucleus of trigeminal nerve; 10, nucleus interpositus; and 11, nucleus raphes magnus.

Figure 2. Schematic diagram showing the relevant connections responsible for contralateral postural ataxia by the nucleus prepositus hypoglossi (NPH) lesion. The commissural connections between the 2 NPHs are predominantly inhibitory. The inferior olive (IO) receives inhibitory projections from the NPH (strong from the contralateral and weak from the ipsilateral NPH) and sends inhibitory projections to Purkinje cells of the contralateral flocculus. Then, the Purkinje cells inhibit the ipsilateral vestibular nucleus (VN). A lesion of the NPH increases net inhibitory input to the ipsilateral VN because removal of the inhibitory commissural connection leads to disinhibition of the contralateral NPH. This increase reduces inhibitory input to the contralateral flocculus, thereby disinhibiting inhibitory projections to the VN.

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Correspondence: Ji Hoe Heo, MD, PhD, Department of Neurology, Yonsei University College of Medicine, Shinchon-dong 134, Seodaemoon-ku, Seoul, 120-752, Korea (jhh@yumc.yonsei.ac.kr).

Author Contributions: Study concept and design: Seo and Heo.