Dorsal Medullary Infarction
Distinct Syndrome of Isolated Central Vestibulopathy

Sun-Uk Lee, MD; Seong-Ho Park, MD, PhD; Jeong-Jin Park, MD; Hyo Jung Kim, PhD; Moon-Ku Han, MD, PhD; Hee-Joon Bae, MD, PhD; Ji-Soo Kim, MD, PhD

Background and Purpose—The characteristics of infarctions restricted to the dorsal medulla have received little attention. This study aimed to define the distinct clinical features of dorsal medullary infarction.

Methods—Of the 172 patients with a diagnosis of medullary infarction at Seoul National University Bundang Hospital from 2003 to 2014, 18 patients with isolated dorsal medullary infarction were subjected to analyses of clinical and laboratory findings.

Results—All patients presented acute isolated vestibular syndrome with dizziness/vertigo and imbalance. Almost all patients (17/18, 94%) showed the signs from involvements of the vestibular nuclei, nucleus prepositus hypoglossi, or inferior cerebellar peduncle, which included direction-changing gaze-evoked nystagmus (n=12), negative head-impulse tests (n=8), skew deviation (n=7), central patterns of head-shaking nystagmus (n=6), and spontaneous nystagmus (n=2). Initial magnetic resonance imagings including diffusion-weighted images were negative in 7 patients (39%). Twelve patients (67%) showed a progression and developed additional neurological abnormalities, but the neurological outcomes were favorable.

Conclusions—The presence of central vestibular signs allows bedside differentiation of isolated vestibular syndrome because of dorsal medullary infarction from acute peripheral vestibular disorders. Because initially false-negative magnetic resonance imagings and subsequent progression are frequent in dorsal medullary infarction, early recognition through scrutinized evaluation is important for proper managements.

Key Words: dizziness • infarction • medulla oblongata • vertigo • vestibular nuclei

A cute isolated vertigo has mostly been ascribed to inflammatory disorders, involving the peripheral vestibular labyrinth.1,2 Because the dorsal medulla contains the structures such as the vestibular nuclei (VN), nucleus prepositus hypoglossi (NPH), and inferior cerebellar peduncle (ICP) that are involved in conveying and processing the vestibular and ocular motor signals, lesions involving this area typically cause dizziness/vertigo and imbalance along with ocular motor abnormalities.3 However, the vestibular symptoms and signs from lesions involving the dorsal medulla have mostly been recognized as a constellation of the much more prevalent forms of infarctions involving the medial (medial medullary) or lateral (lateral medullary infarction or Wallenberg syndrome) portion of the medulla.3 Diagnosis of brain stem vestibular syndromes is straightforward when other signs of brain stem involvements are identified.4 However, isolated vestibular syndrome from infarctions restricted to this area provides a difficulty in differentiation from more benign disorders involving the inner ear or the peripheral vestibular nerve.5,6 Previously, clinical features of isolated vestibulopathy from strokes have mostly been reported in patients with cerebellar infarctions,6 and only a few anecdotal reports have described isolated vestibular syndrome from brain stem strokes.7–11

To aid in differentiation of the isolated vestibular syndrome from dorsal medullary infarction (DMI) from peripheral vestibular disorders, we analyzed the clinical features in 18 patients with isolated vestibular syndromes from infarctions restricted to the dorsal portion of the medulla. We hypothesized that DMI would present clinical features distinct from those observed in peripheral vestibular disorders depending on the structures involved.
Subjects and Methods

Subjects

Of the 172 patients with a diagnosis of medullary infarction at Seoul National University Bundang Hospital from 2003 to 2014, 18 patients (8%) had been found to have infarction restricted to the dorsal medulla (14 men: age range, 33–73 years; mean age±SD, 61±12) based on the clinical features and magnetic resonance imaging (MRI) findings. The interval from symptom onset to evaluation ranged from 0 to 10 days (median, 1 day). All patients had full neurological and neuro-otologic evaluation by the senior author (J.-S.K). On the basis of the findings of previous studies, we were able to classify the clinical features observed in our patients into 4 types according to the structure(s) mainly affected, the VN, NPH, ICP, and mixed.9,12,13 This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of Institutional Review Board of Seoul National University Bundang Hospital (B-1109/135-106).

Neurologic Evaluation

In addition to standard neurological examination, all patients had bedside evaluation and video-oculographic recording of spontaneous nystagmus (SN), gaze-evoked nystagmus (GEN), head-shaking nystagmus (HSN), and positional nystagmus; saccades; smooth pursuit; and head-impulse tests (HITs).14–20 HITs were quantified using a magnetic search coil technique in 2 patients using a 70-cm cubic search coil frame (Skalar, Delft, The Netherlands).21–23

Other Neurotologic Evaluation

Patients also underwent bithermal caloric tests, and measurements of ocular torsion and subjective visual vertical (SVV), and cervical and ocular vestibular-evoked myogenic potentials (VEMPs). Detailed methods of each test have been described previously.16–24

MRI and Lesion Analysis

All patients had MRIs to diagnose DMI. The MRI protocol included diffusion-weighted imaging (DWI), T1-, and T2-weighted gradient-echo axial imaging, and T1-weighted sagittal imaging using a 3.0-T (n=3) or 1.5-T (n=15) unit (Intera; Philips Medical Systems, Best, The Netherlands). For the patients with normal MRIs initially, follow-up MRIs were arranged within 7 days of symptom onset. In addition, all the patients had MR angiography of the intracranial vessels. Detailed imaging parameters have been described previously.28

In each patient, we defined the involved structures based on the clinical features.9,12,13 The medulla scanned in the axial plane was divided into the upper, middle, and lower portions by an approximately equal division along its long axis from the pontomedullary junction superiorly to the level of the foramen magnum inferiorly.26

Results

Clinical Characteristics

All 18 patients presented isolated acute vestibular syndrome (AVS) characterized by vertigo or unsteadiness that was the only finding in 15, and it was associated with tinnitus in the ipsilesional (n=2, patients 7 and 11) or contralesional ear (n=1, patient 12) in the remaining 3 patients.

Four patients (patients 6, 7, 9, and 12) reported precedent spontaneous vertigo lasting 1 minute to 6 hours with (n=2) or without (n=1) tinnitus from 2 weeks to 4 months before the infarction. Two of them had brain MRIs within 6 hours of the preceding episode, which were normal.

None of the patients showed any evidence of Horner syndrome, cranial nerve dysfunction, weakness, sensory changes, or cerebellar signs at initial presentation. However, 12 patients later developed additional neurological abnormalities that included limb ataxia (n=10), sensory changes (n=7), Horner syndrome (n=6), dysphagia (n=4), facial palsy (n=3), soft palate palsy (n=2), dysarthria (n=1), limb weakness (n=1), hoarseness (n=1), and hiccup (n=1). These additional neurological deficits developed within 6 days of the initial presentation (median, 1 day; interquartile range, 0–2 days). However, most patients were discharged with only mild functional deficits (modified Rankin Scale score, 0–2 in 15/18 [83%]; Bathel index >90 in 14/18 [78%]).

More than a half of the patients (10/18, 56%) showed the features of both central and peripheral vestibulopathies. Almost all the patients (17/18, 94%) had at least 1 central vestibular sign, including direction-changing GEN (n=12), negative HITs (n=8), skew deviation (n=7), HSN in the opposite direction of SN (n=3), perverted HSN (n=3), and disjunctive torsional nystagmus (n=2). By contrast, features of peripheral vestibulopathy included horizontal–torsional SN increasing with removal of visual fixation (n=13), positive HIT (n=10) in one or both directions, and caloric paresis (n=5). Other findings included decreased or absent responses of cervical (n=4) or ocular (n=5) VEMPs.

Initial MRIs with DWI were negative in more than a half of the patients (11/18, 61%, 10 with 1.5-T and 1 with 3.0-T MRIs) within 10 days of symptom onset (median, 1 day; interquartile range, 0–3 days), but central lesions were suspected because of positive head impulse, nystagmus, test-of-skew in most patients (15/18, 83%). A patient (patient 12) with an initial diagnosis of Meniere disease without any central sign was subjected to MRIs because of prolonged vertigo and unsteadiness lasting for more than 3 days.

Clinico-Anatomic Correlation

**VN Type**

In 5 patients (patients 1–5), the findings could be explained by involvement of the VN, which included (1) contralesional SN, (2) direction-changing GEN during lateral gazes, (3) positive HITs or caloric paresis (Table).9 Representative cases were described in our previous study.9

SN was observed in all 5 patients and was mostly horizontal–torsional with (n=2) or without (n=3) a vertical component, except 1 (patient 3) with a pure horizontal SN. HSN was observed in 3 patients after horizontal head-shaking, and the horizontal component was either ipsilesional (n=1) or contralesional (n=2). The direction of HSN was opposite to that of SN in a patient (patient 4). Positional nystagmus was observed in 1 patient (1/5, 20%) who developed upbeat nystagmus during lying down, straight head hanging, and Dix–Hallpike maneuver to either side, and apogeotropic nystagmus after turning the head to the lesion side while supine. Three patients showed ocular lateropulsion with ipsilesional saccadic hypermetria and contralesional saccadic hypometria. Smooth pursuit was impaired in all 5 patients (ipsilesional in 1, contralesional in 1, and in both directions in the remaining 3). Bedside horizontal HITs were abnormal during ipsilesional head impulses in 4 patients, but recording of HIT using a magnetic search coil technique revealed decreased gains for the contralesional HC and both PCs, but more marked for the ipsilesional ones in 2 patients (patients 1 and 2). Ipsilesional caloric paresis was documented in 4 patients (4/5, 80%).
Four patients showed at least 1 component of ipsiversive ocular tilt reaction (OTR): heat tilt (n=3), skew deviation (n=3), or ocular torsion (n=3). Furthermore, the SVV was tilted in 4 of 5 patients, all ipsiversive. Ocular VEMPs showed decreased or absent wave formation during stimulation of the ipsilesional ear in 2 of the 3 patients who had an evaluation (2/3, 67%), whereas cervical VEMPs showed decreased p13-n23 amplitude during ipsilesional ear stimulation in 3 of the 4 patients evaluated.

Brain MRIs documented lesions in the dorsolateral portion of the medulla, which extended up to the caudal pons in 1 patient (Figure 1).

**NPH Type**

Three patients (patients 6–8) showed the findings from NPH involvement that include (1) ipsilesional SN, (2) direction-changing GEN, and (3) positive HITs during contralateral head rotation in the (4) absence of caloric paresis. One
one of them. The horizontal nystagmus was either ipsilesional (n=3) or contralesional (n=1). HSN was observed in 7 patients (7/9, 78%), and it was ipsilesional in 5 patients and downbeat in 2 patients. HSN occurred in the opposite direction of SN in 2 patients (patients 11 and 17). Five (5/9, 56%) patients showed direction-changing GEN during lateral gazes. Positional nystagmus was observed in 5 patients (5/9, 56%), either (1) vertical (upbeat in 2 and downbeat in 1) nystagmus during lying down, straight head hanging, and Dix–Hallpike maneuver to either side (n=3) or (2) horizontal nystagmus on head turning to either side while supine (ipsilesional in 3). All positional nystagmus developed immediately after head position change and persisted in 4 of them. Saccades were abnormal in 5 patients (5/9, 56%), with an increased latency in 1, and bilateral hypometria in another patient. The remaining 3 patients showed ocular lateropulsion, which was ipsilesional in all. Smooth pursuit was impaired in 5 patients (5/7, 71%), ipsilesional in 3, and contralesional in 2. Bedside horizontal HITs were positive during contralesional head turning in 2 (patients 10 and 11) patients and during ipsilesional turning in 1 (patient 12) patient.

Five patients showed at least 1 component of OTR: head tilt (n=4), skew deviation (n=3), or ocular torsion (n=3). Tilt of SVV was observed in 4 patients, which was all ipsiversive. Ocular (n=2) and cervical (n=6) VEMPs were normal in the patients evaluated.

Brain MRI showed lesions in various portions of the dorsolateral medulla, from the caudal level to the pontomedullary junction (Figure 1).

### Stroke Mechanism
Most patients (15/18, 83%; Table) had at least 1 vascular risk factor, and 7 showed stenosis of the ipsilesional vertebral artery (7/18, 38%). The underlying stroke mechanisms were small artery disease in 10, large artery disease in 7, and vertebral artery dissection in 1 patient.29

### Discussion
The main findings of this study may be summarized as follows: (1) lesions restricted to the dorsal portion of the medulla may present isolated AVS. (2) Almost all the patients with DMI show findings of central vestibulopathy according to the affected neural structures. (3) Brain imaging including DWI may not detect DMI in about a half of the patients at initial presentation with AVS. (4) Patients with DMI usually show neurological deterioration during the acute phase, but long-term prognosis is excellent. (5) Most patients had comorbid vascular risk factors and about a half of them had a stroke mechanism other than small artery disease.

Previously, the vestibular and ocular motor findings in medullary infarctions have mostly been described in the constellation of more prevalent forms of lateral and medial medullary infarctions along with characteristic cranial nerve and sensorimotor findings.30–32 However, our patients with infarctions restricted to the dorsal medulla presented with isolated vestibular syndrome that should be differentiated from benign disorders involving the peripheral vestibular structures.

The prevalence of AVS because of central causes is largely unknown, but is estimated 25% among emergency department visits because of AVS.33 Contrary to the common belief,
the diagnosis of central vertigo/dizziness is often challenging because additional focal neurological deficits are accompanied only in 27% of central vertigo.\textsuperscript{34} Indeed, 10% to 20% of posterior circulation strokes may present with isolated vertigo (pseudo-VN).\textsuperscript{35,36} However, initial MRIs including DWI may be normal especially during the first 24 to 48 hours in ≈14% to 35% of AVS because of central lesion.\textsuperscript{34,35} Furthermore, acute vertigo because of isolated labyrinthine infarction, which may precede infarction in the territory of the anterior inferior cerebellar artery, cannot be detected with current imaging technique.\textsuperscript{8} Indeed, 4 (22%) of our patients with DMI experienced preceding transient vertigo 2 weeks to 4 months before the completed stroke, probably as a manifestation of transient ischemic attacks involving the dorsal medulla.

Because of more than a half of patients showed a progression to develop other cranial or sensorimotor impairments, early recognition and intervention of this distinct isolated central vestibular syndrome are important even though the prognosis is largely benign. Fortunately, almost all the patients showed central vestibular signs, including GEN, normal or contralateral HITs, skew deviation, and central patterns of SN and HSN. Therefore, bedside neurological evaluation is important for early detection and proper management of DMI.\textsuperscript{34}

In a previous study, 3 ocular motor signs, the head impulse, nystagmus, test-of-skew, were more sensitive in detecting acute central vestibular syndrome than early MRIs.\textsuperscript{37} Indeed, 83% of our patients with DMI also showed head impulse, nystagmus, test-of-skew in the presence of normal or equivocal MRIs initially during the acute phase. However, the OTR including skew deviation may be observed in acute peripheral as well as central vestibular lesions.\textsuperscript{1}

**Lesion Location and Involved Structure(s)**

In a half of our patients with DMI, the findings could be explained by involvement of a single vestibular structure located in the dorsal medulla, which included the VN, NPH, and ICP (Figure 2). The findings in the remaining patients, however, could be explained by combined damage to these structures.

The characteristic feature of a lesion involving VN seem to be combined peripheral and central vestibular dysfunction because VN is the immediate recipient of the peripheral vestibular signals, but is also involved in the central modulation and integration of these signals.\textsuperscript{9} The horizontal–torsional SN beating away from the lesion side, positive ipsilesional HITs, ipsilesional caloric paresis, and decreased or absent

**Figure 2.** Schematic illustration of the neural structures involved in our patients with dorsal medullary infarction. AN indicates abducens nucleus; HN, hypoglossal nucleus; ICP, inferior cerebellar peduncle; IVN, inferior vestibular nucleus; LVN, lateral VN; MLF, medial longitudinal fasciculus; MVN, medial VN; and NPH, nucleus prepositus hypoglossi.
VEMP responses during stimulation of the ipsilesional ear were all consistent with unilateral peripheral vestibulopathy.30,39 However, the direction-changing GEN and normal or impaired HITs in the contralesional direction also indicate central vestibular involvements.

NPH lies in the rostral medulla and caudal pons between the hypoglossal and abducens nuclei.40 Because it serves the neural integration for horizontal eye movements, patients with lesions involving NPH may show vertigo, GEN, and unsteadiness.10 NPH has abundant connections with the vestibular system and is adjacent to the midline, just medial to the medial VN.41 Because NPH is commonly irrigated by the arteries that also supply the medial longitudinal fasciculus and abducens nucleus, NPH lesions often accompany horizontal gaze palsies and facial palsy of the peripheral type. However, our patients presented solely with AVS without additional neurological deficits. NPH receives the vestibular signals through afferent branches from the semicircular canals, which also innervate the VN, flocculus, and nodulus and uvula of the cerebellum.42

The role of NPH in vestibular function has been shown in primates and cats with a drug-induced selective injury of the NPH, which produced asymmetrical gain of the vestibulo-ocular reflex during the rotation, and impaired posture and gait.43,44 In cats, unilateral vestibular neurectomy induced cFos expression in the ipsilateral VN, contralateral NPH, and inferior olive. The inferior olive receives an inhibitory projection from bilateral NPHs. These projections are stronger from the contralateral NPH than from the ipsilateral one.45 The inferior olive projects inhibitory fibers to the Purkinje cells of the contralateral flocculus, which inhibit the ipsilateral VN.46 Therefore, NPH lesion would produce contralateral vestibular inhibition to mimic a lesion involving the contralateral VN.47

ICP locates in the posterior portion of caudal pons and rostral medulla between the lower part of the fourth ventricle and the roof of the glossopharyngeal and vagus nerves. It is a thick rope-like neural bundle that contains the afferent and efferent fibers to and from the vestibulocerebellum involved in the integration of the proprioceptive and vestibular function.48 Thus, a lesion involving ICP may also present isolated vestibular syndrome.15 The distinct features of isolated ICP lesions include ipsilesional SN, negative HITs, and directional dissociation between the OTR/SVV tilt and body lateropulsion. Previous studies have consistently reported the occurrence of ipsilesional SN and contralateral OTR in unilateral cerebellar lesions, which is explained by increase in tonic activity of the ipsilesional VN complex probably because of disruption of the inhibitory fibers from the vestibulocerebellum.49,50 Indeed, one of our patient showed ipsilesional SN and normal HITs in the absence of GEN, which are distinct from the findings observed in lesions involving the VN or NPH. Absence of the ipsilesional body lateropulsion in this patient would be explained by sparing of the vestibulospinal or dorsal spinocerebellar tract.48

Vascular Supply and Stroke Mechanism

The VN and ICP, located in the dorsolateral portion of the rostral medulla and caudal pons, are supplied by the perforating arteries from the vertebral, posterior inferior cerebellar, and basilar arteries.49 In contrast, the NPH is supplied by the short anteromedial or lateral perforating arteries from the basilar artery at the level of the medulla and pontomedullary junction.49

The stroke mechanisms in our patients with DMI were mostly small (56%) or large artery disease (39%). The proportion of large artery disease is somewhat lower than that reported in the previous studies on pure lateral or medial type of medullary infarction (50%–60%).30,50 This might be related to the small size of infarctions restricted to the dorsal medulla in our patients.

We defined the involved structures based on the clinical features, not on the radiological data because delineation of the affected structures with imaging findings was nearly impossible in this crowded area. Thus, we should admit that this might have led to creation of artificially well-defined subgroups.

In summary, all our patients with DMI presented isolated AVS. Even though these features mimicked benign inflammatory disorders involving the labyrinth, the presence of central vestibular signs including normal HITs, GEN, skew deviation, and central patterns of HSN allowed differentiation without a difficulty in almost all the patients. Because initially false-negative MRIs and subsequent progression are frequent in DMI, early recognition through scrutinized neuro-otologic evaluation would be important for proper management.

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Disclosures


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