Medial Medullary Infarction
Clinical, Imaging, and Outcome Study in 86 Consecutive Patients

Jong S. Kim, MD, PhD; Young S. Han, MD

Background and Purpose—Clinical-imaging correlation and long-term clinical outcomes remain to be investigated in medial medullary infarction (MMI).

Methods—We studied clinical, MRI, and angiographic data of 86 consecutive MMI patients. The lesions were correlated with clinical findings, and long-term outcomes, divided into mild and severe (modified Rankin scale >3), were assessed by telephone interview. Central poststroke pain (CPSP) was defined as persistent pain with visual numeric scale ≥4.

Results—The lesions were located mostly in the rostral medulla (rostral 76%, rostral+middle 16%), while ventro-dorsal lesion patterns include ventral (V, 20%), ventral+middle (VM, 33%), and ventral+middle+dorsal (VMD, 41%). Clinical manifestations included motor dysfunction in 78 patients (91%), sensory dysfunction in 59 (73%), and vertigo/dizziness in 51 (59%), each closely related to involvement of ventral, middle, and dorsal portions, respectively (P<0.001, each). Vertebral artery (VA) atherosclerotic disease relevant to the infarction occurred in 53 (62%) patients, mostly producing atheromatous branch occlusion (ABO). Small vessel disease (SVD) occurred in 24 (28%) patients. ABO was more closely related to VMD (versus V+VM) than was SVD (P=0.035). During follow-up (mean 71 months), 11 patients died, and recurrent strokes occurred in 11. Old age (P=0.001) and severe motor dysfunction at admission (P=0.001) were factors predicting poor prognosis. CPSP, occurring in 21 patients, was closely (P=0.013) related to poor clinical outcome.

Conclusion—MMI usually presents with a rostral medullary lesion, with a good clinical ventro-dorsal imaging correlation, caused most frequently by ABO followed by SVD. A significant proportion of patients remain dependent or have CPSP. (Stroke. 2009;40:3221-3225.)

Key Words: medulla oblongata ■ medial medullary infarction ■ MRI ■ central poststroke pain

Medial medullary infarction (MMI) syndrome was initially described by Spiller more than 100 years ago, and Dejerine proposed a triad of symptoms: contralateral hemiplegia sparing the face, contralateral loss of deep sensation, and ipsilateral hypoglossal paralysis. Pathological examination first conducted in 1937 demonstrated thrombotic occlusion of the anterior spinal artery (ASA) and adjacent vertebral artery (VA). More recently, studies using MRI have rapidly expanded our understanding of MMI syndromes. However, the number of subjects was too small for reliable clinical-MRI correlation study, and no long-term outcome study has ever been performed. Therefore, we examined clinical, imaging, etiopathogenesis, and follow-up outcomes in MMI patients.

Methods

Patients
Between September 1996 and July 2008, we examined 100 consecutive patients at the Asan Medical Center who had clinical and MRI imaging findings consistent with MMI. Those with combined lateral medullary infarction (LMI) were excluded. We excluded the following patients: 5 who were admitted >7 days after symptom onset, 6 who had concomitant major infarction outside of the medulla, and 3 who had significant neurological sequelae attributable to previous strokes. However, we included 5 patients who showed dot-like tiny (<2 mm in diameter) diffusion-weighted MRI (DWI)-identified lesions in the occipital area (n=3) or the cerebellum (n=2). Thus, 86 patients with acute consecutive MMI became the subjects of this study. All patients were examined by the first author, with specific signs and symptoms recorded prospectively, except for 7 patients for whom a retrospective chart review was performed. The sensory sequelae of the 3 patients were used in our previous article. Among the symptoms/signs examined, muscle strength was graded using the Medical Research Council (MRC) scale, and maximal motor deficits during admission of ≤3 in any proximal limb were considered “severe.” Pain, cold temperature, vibration, and position perception was tested and the grade was categorized as “mild,” “moderate,” or “severe” as described elsewhere. The definition of risk factors such as hypertension, diabetes, hyperlipidemia, and heart work-up protocol in our institute were described previously.

Imaging Analysis

Depending on departmental policies, our imaging protocols changed over time. Between 1996 and 2000, we initially performed CT scans on patients with acute (<3 days after onset) stroke, and then conducted follow-up T2- and T1-weighted MRI and MR angiogram.
classified according to the diagram of the upper medulla as: in the rostral medulla (see below), lesions were ventro-dorsally 2.7 days after stroke onset). Lesions were classified by YSH 4.1 /H11006 (either DWI or T2) findings obtained in the subacute stage (mean, patients who underwent imaging evaluation twice, we used the MRI and MRA were performed only once. MRA examinations were performed using either a 1.5 Tesla or 3.0 Tesla MR imaging unit. A horizontal plane at 3-mm intervals from the medulla to the midbrain was obtained. DWI parameters included a repetition time (TR) of 7500 ms, an echo time (TE) of 84 ms, a matrix number of 128×128, and two b values of 0 and 1000 seconds/mm². Three-dimensional (3D)-time-of-flight (TOF)-MRA and 3D-contrast-enhanced (CE)-MRA were also performed at the time of MR imaging with parameters described elsewhere.9

Assessment of Lesion Pattern and Etiologies Distribution of Infarcts Based on MRI Findings

As lesions were often invisible or vague on initial CT or DWI in patients who underwent imaging evaluation twice, we used the MRI (either DWI or T2) findings obtained in the subacute stage (mean, 4.1±2.7 days after stroke onset). Lesions were classified by YSH who was blinded to clinical information. Rostro-caudally, the lesions were categorized as “rostral,” “middle,” and “caudal,” with criteria described previously.10 Because the majority of lesions were located in the rostral medulla (see below), lesions were ventro-dorsally classified according to the diagram of the upper medulla11 as: “ventral (V)” (ventral part, presumably containing the pyramid); “middle (M)” (middle part, presumably including the medial lemniscus); and “dorsal (D)” (dorsal part, presumably including the medial longitudinal fasciculus [MLF] in a lesion extending to the dorsal surface of the medulla) (Figures 1 and 2).

Evaluation of Arterial Stenoses

The degree of arterial stenosis was categorized into mild (less than 50% diameter reduction), moderate (≥50% diameter reduction with complete distal flow), severe (segmental nonvisualization of artery), occlusion, and aplasia (nonvisualization of the entire VA/hypoplasia (diffuse homogeneous narrowing of the entire VA). We interpreted nonvisualization or homogeneous narrowing of the distal VA after the origin of the posterior inferior cerebellar artery as aplasia/hypoplasia, and irregular narrowing as atherosclerotic vascular stenosis.

Presumed Stroke Mechanisms

The presumed mechanisms were categorized by consensus among our stroke team with modification of recent guidelines.12

1. Large vessel disease (LVD), when there was a significant stenosis or occlusion of the relevant artery (VA) that explains the infarction. The LVD was divided into 3 categories: (1) atheromatous branch occlusion (ABO)13 when infarcts were on the territory of one or a few perforating branches arising from stenosed (of any degree) or occluded distal, intracranial VA, or VA-basilar artery (BA) junction that presumably occluded the orifice of perforators (Figure 2); (2) artery-to-artery embolism (AAE) when there was a moderate to severe stenosis or occlusion in the proximal VA with no distal VA disease. Because the degree of stenosis may be exaggerated in V1 segment, only severe stenosis or occlusion was considered as “significant” in V1. Also, if there was any possibility of pulsation or motion artifacts in the V1, we did not consider the lesion as significant; (3) AAE+ABO when there are stenosis or occlusion in both distal and proximal VA.

2. Cardiogenic embolism (CE): CE was determined when there was embolic heart disease without significant atherosclerosis.

3. Small vessel disease (SVD): SVD was defined when patients had (1) hypertension or diabetes; (2) no embolic heart disease; (3) normal angiogram findings.

4. Undetermined etiology was defined when there was (1) presence of 2 or more causes; (2) imaging findings that were hard to differentiate between vascular lesion and hypoplasia/aplasia of VA.

Presumed Stroke Mechanisms

Distribution of Infarcts Based on MRI Findings

Figure 1. Schematic diagram showing structures in the rostral medulla, and the ventral (V), middle (M), and dorsal (D) portions.

Figure 2. Illustrative patients. Diagrams on the right show presumed stroke mechanism of small vessel disease (upper) and branch artery occlusion resulting in unilateral (middle) and bilateral (low) infarcts. VA indicates vertebral artery; ASA, anterior spinal artery; 1-a, T2-weighted MRI showing involvement of “V” portion only (V type), which produced pure motor stroke. 1-b, MRA of Patient 1-a, showing normal vertebral arteries. 2-a, Diffusion weighted MRI showing involvement of V and M portions (VM type), which produced hemisensori-motor stroke. 2-b, MRA of Patient 3-a, showing distal vertebral artery occlusion (VMD type), which produced hemisensori-motor dysfunction, dizziness, and horizontal nystagmus. 3-a, T2-weighted MRI showing involvement of V, M, and D (VMD type), which produced hemisensori-motor stroke. MRA findings were normal. 3-b, MRA of Patient 3-a, showing distal vertebral artery occlusion (VMD type), which produced hemisensori-motor stroke. MRA findings were normal. 4-a, Diffusion-weighted MRI showing bilateral infarcts, producing severe dysarthria, quadriparesis, and nystagmus. 4-b, MRA of Patient 4-a showing focal severe stenosis in the left vertebral artery junction area (arrow).
5. VA dissection when patients had (1) an obvious history of recent head/neck trauma or sudden neck rotation (chiropractic manipulation, golf practicing, yoga, etc); (2) concurrent neck or occipital pain (3); angiogram findings consistent with dissection.

Follow-Up Study
In patients with follow-up periods >6 months, telephone interviews were performed in November 2008 by an experienced stroke research coordinator with the use of structured format, exploring the general neurological outcome using a modified Rankin scale. The scale $\geq 3$ was considered a “severe” outcome. Patients’ subjective sensory complaints were assessed as described previously, with the severity assessed by 10-point markers on a visual numeric scale (1, slight; 10, most severe). When a score was $\geq 4$, and symptoms were irritable, persistent, and not associated with joint problems, we defined this as central poststroke pain (CPSP). Chart review was also performed to reinforce data in 55 patients.

Statistical Analysis
We used $\chi^2$ tests to compare categorical variables and Fisher exact test when the number of cells was small. The $t$ test was used to compare continuous variables. Statistical tests were performed using SPSS version 10.0; probability values $<0.05$ were considered significant.

Results
Demographic and Clinical Features
There were 64 men and 22 women of age 34 to 87 (mean 62±10) years. Risk factors included hypertension in 71 (83%), diabetes in 43 (50%), cigarette smoking in 44 (51%), hyperlipidemia in 21 (24%), and atrial fibrillation in 2 (2%). Nineteen patients had histories of stroke, and 9 had histories of coronary heart disease.

As shown in Table 1, motor dysfunction was the most common symptom occurring in 78 patients; hemiparesis in 68, quadriparesis in 8, and monoparesis in 2. The arm was weaker than the leg in 12 patients, whereas the leg was weaker than the arm in 3. In patients with hemiparesis, the paresis always occurred on the side contralateral to the lesion. The motor dysfunction was severe in 29 patients (37%), in whom there was gradual worsening of limb weakness over several days in 66%. Twenty-one patients showed mild facial paresis on the side of limb weakness.

Sensory impairment could not be reliably assessed in 5 patients because of severe dysarthria or confusion. In the remaining 81, sensory symptoms/signs were seen in 59 patients (73%). Paresthesia (numb or tingling sensation) was complained of by 55 patients. Objective sensory disturbances included impairment in vibration (48 patients, severe in 5), position (41 patients, severe in 4), pinprick (17 patients, severe in none), cold (22 patients, severe in none), and touch (32 patients) sensations. Eight patients had subjective paresthesia without objective sensory deficits. The sensory symptoms/signs usually occurred below the ear, except for 17 in whom the ear was also involved. In 16 patients, mild and short-lasting sensory symptoms were also noted in the face, usually limited to parts of the forehead or cheek.

Limb ataxia was noticed in 36 patients, usually associated with mild weakness (ataxic hemiparesis). Dysarthria was present in 54 patients, mild in 39, moderate (speech, occasionally unintelligible) in 11, and severe (mostly unintelligible) in 3. Generally, patients with dysarthria had bilaterally clumsy tongue movements, and tongue deviation was noted in 12 patients (ipsilaterally in 3 and contralaterally in 9) only, none with tongue atrophy or fibrillation. Dysphagia was noted in 25 patients, 4 of whom required nasogastric tubes for feeding. Vertigo/dizziness (n=51), nausea/vomiting (n=14), and headache (n=9) were usually transient early symptoms. Twenty-eight patients had horizontal nystagmus (27 ipsilateral to the lesion, 1 contralateral to the lesion), 5 upbeat nystagmus, 4 both, and 1 had downbeat nystagmus. Six patients showed skew deviation, 5 ipsilateral lateral rectus paresis, and 3 showed internuclear ophthalmoplegia.

MRI Findings
The infarcts were located in the right in 30 patients, in the left in 44, and bilaterally in 12 (14%). On rostro-caudal classification, because the rostral-caudal extents may differ on the right and left sides in patients with bilateral lesions (n=12), bilateral lesions were separately considered, yielding 98 lesions (74+[12×2]). The lesions were mostly located in the rostral medulla (Table 2), and none had a lesion exclusively occurring in the caudal medulla. Vento-dorsally, all bilateral lesions had the same ventro-dorsal extension except for one who had a VMD- type lesion on the right and a VM lesion on the left. We included this in the VMD group. VMD was most frequent, followed by the VM and V types. Generally, the V portion was involved in 81 patients (94%), M in 59 (69%), and D in 45 (52%; Table 3). We also found that bilateral lesions were more often dorsally extended (VMD-type) than

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<th>Table 1. Clinical Manifestations</th>
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<td>Symptoms and Signs (n=86)</td>
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<td>Motor dysfunction</td>
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<td>Hemiparesis</td>
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<td>Quadriparesis</td>
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<td>Ipsilateral hypoglossal palsy</td>
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<td>Contralateral tongue deviation</td>
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No. in parenthesis indicates percentage.
were unilateral lesions (9/12 versus 26/74, \( P = 0.012 \)). No bilateral lesion involved the V portion only.

**Clinical-MRI Correlation**

Because almost all patients had involvement of the rostral medulla, a clinical-rostrocaudal imaging correlation could not be made. On clinical-ventrodorsal correlation, motor dysfunction was closely related to involvement of V (\( P < 0.001 \)), but not M or D (\( P = 1.000, P = 0.077 \), respectively). Sensory dysfunction was closely related to involvement of M (\( P < 0.001 \)) but not V or D (\( P = 0.127, P = 0.216 \), respectively). Any ocular motor dysfunction (including nystagmus and skew deviation) was related to involvement of D (\( P < 0.001 \)) and M (\( P = 0.004 \)) but not V (\( P = 0.172 \)). Vertigo/dizziness was related to involvement of D (\( P = 0.005 \)) and M (\( P = 0.006 \)) but not V (\( P = 0.666 \)).

**Angiographic Findings and Presumed Stroke Mechanisms**

MR angiography was performed on all 86 patients except for one who underwent CT angiography. Conventional angiography was additionally performed in 10 patients, generally in those who were suspected to have dissection. Fifty-three patients had relevant VA or VA-BA junction atherosclerosis and were categorized as LVD, 50 of them related to ABO (mild stenosis in 17 patients, severe stenosis in 19, occlusion in 14). Two patients had AAE + ABO (severe stenosis in both the proximal VA and distal VA), and 1 had AAE (severe stenosis in the VA orifice). The etiology was unknown in 6 (Table 3). Twenty-four patients were considered to have SVD. One with atrial fibrillation was categorized with CE. Two patients had dissections that occluded the distal VA, probably resulting in occlusion of the perforator orifice. Among patients with either ABO or SVD, the VMD-type (versus the V + VM-type) lesion was more often associated with ABO than with SVD (\( P = 0.035 \)). Bilateral lesions were more often associated with ABO (compared to SVD) than were unilateral lesions, with marginal significance (\( P = 0.053 \)).

**Follow-Up Results**

Of the 86 patients, 3 died during admission from the current MMI (\( n = 2 \)) or recurrent massive MCA infarction (\( n = 1 \)). One was excluded from follow-up examination because the follow-up period was <6 months. Of the remaining 82, follow-up studies could not be performed on 14 patients because of the inability to contact them by telephone (\( n = 10 \)), or patients’ refusal to participate (\( n = 4 \)). For the remaining 68 patients, telephone interviews were conducted 6 to 146 months (mean 71 ± 42 months) after the onset of stroke. Nine patients died (2 from pneumonia; 3 months and 1 year poststroke, respectively), traumatic brain hemorrhage (1; 4 years poststroke), lung cancer (1; 3 years poststroke), Alzheimer disease (1; 7 years poststroke), recurrent strokes (3; 3, 4, and 8 years poststroke, respectively). In 2, the cause of death was uncertain. Including in-hospital stroke, recurrent strokes occurred in 11 patients (15.5%), 4 of which were fatal. Five patients developed newly diagnosed coronary heart disease.

At the time of last follow-up, clinical outcomes were mild in 41 patients and severe in 30. Among variables such as gender, age, various risk factors, stroke mechanism (ABO versus SVD), lesion size (VMD versus others), lesion location (involvement of V, M, or D), severe motor dysfunction, and sensory dysfunction, only age (\( P = 0.001 \)) and severe motor dysfunction at admission (\( P = 0.001 \)) were factors predicting poor prognosis. They remained as significant factors when patients with recurrent strokes were excluded. Among the 59 patients who survived and were contacted by us, 35 had residual motor dysfunction, 38 sensory symptoms, and 21 dizziness. Excluding 3 who had joint pain, 21 patients were considered to have CPSP, described as numb in 16, cold in 8, painful in 6, and burning in none. Symptoms were aggravated by a cold environment in 17 patients, a hot environment in 2, and body movement in 2. Patients with CPSP more often had severe outcomes than those without CPSP (16/21 versus 15/38, \( P = 0.013 \)). The results were similar (\( P = 0.024 \)) when patients with recurrent strokes were excluded (\( n = 54 \)).

**Discussion**

Our data, the largest collection of MRI-identified MMI, showed that lesions mostly involve rostral V area, which is
related to the high prevalence of motor dysfunction (91%). The severe motor dysfunction, along with age, was an important factor predicting poor long-term clinical outcome. Facial palsy seems to be caused by involvement of yet-uncrossed corticobulbar fibers directed to the contralateral cranial nuclei at the upper medulla. Interestingly, we observed definite ipsilateral tongue weakness in only 3 patients, none of whom showed tongue atrophy or fibrillation. Although ipsilateral hypoglossal nerve palsy is one of the triads of MMI, its prevalence has been variably reported as 11% to 18% or 71% to 82%. The discrepancies may be explained by different degrees of lesion extension; in the latter studies, combined lateral and medial medullary infarcts were included, and most patients had lesions extending to ≥2 retro-caudal levels whereas most of our patients and those from the former studies had lesions strictly limited to the paramedian rostral area that could have less severely damaged the hypoglossal fascicle/nuclei. Instead, we more often observed clumsy tongue movements, with occasional contralateral tongue deviation, suggesting that dysarthria/dysphagia are largely caused by involvement of the corticobulbar tract rather than hypoglossal nerve.

Sensory symptoms/signs were closely associated with M involvement. Although lemniscal sensory impairment was characteristic, mild and transient impairment of pain/temperature perception was occasionally present, probably attributable to involvement of the spinoreticulothalamic system that regulates the spinothalamic sensory system. We found that long-term sensory sequelae were quite frequent, related in part to development of joint pain in severely parietic limbs. Nevertheless, CPSP occurred in 21 patients (35.6% of followed patients), a prevalence even higher than CPSP because of posterolateral thalamic (25%) or LMI (25%). Although the prevalence is not comparable because of different CPSP criteria used in each report, our data highlight that CPSP is an important sequela of MMI that should be properly recognized and managed.

Vertigo/dizziness and ocular motor abnormalities were closely related to involvement of D portion, which contains structures such as the vestibular nuclei and MLF. In contrast to LMI, nystagmus was almost always ipsilesional, which could be explained by involvement of crossing ipsilateral climbing fibers from the vestibular nuclei in MMI and crossed fibers in LMI. Upbeat nystagmus, observed in 9, was no more frequent in bilateral MMI than in unilateral MMI (data not shown), suggesting concurrent involvement of decussating fibers from both anterior semicircular canals to ocular motor nuclei at the MLF in the rostral medulla.

Distal VA or VA–BA junction atherosclerosis was the most important vascular pathology, mostly giving rise to MMI by way of ABO. Although ASA occlusion either from atherosclerosis occurring in the distal VA or the ASA per se may have occurred in some of our patients, we do not think this is a frequent occurrence because the lower portion of the medulla, supplied by ASA, was mostly spared in our series (Figure 2). We found that bilateral MMI lesions were mostly associated with ABO (none with SVD) and more often dorsally extended (VMD-type) than were unilateral lesions (no bilateral MMI lesions were limited to the V potion). This may be related to our observation that VMD-type (versus V + VM-type) lesions were significantly more often associated with ABO than with SVD. Therefore, it seems that distal VA atherosclerosis tends to produce larger lesions than does SVD, perhaps associated with either multiple perforator occlusion (Figure 2) or more extensive hypoperfusion in the medial medulla. Bilateral lesions may be related either to extended thrombosis in the verteobasilar junction to the contralateral side (Figure 2) or variability of perforator branches to supply bilateral medulla. Dissection was uncommon as compared to LMI patients, a finding consistent with the observation that dissection occurred more frequently in caudal than in rostral LMI.

Sources of Funding
This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A080201).

Disclosures
None.

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Stroke. 2009;40:3221-3225; originally published online July 23, 2009;
doi: 10.1161/STROKEAHA.109.559864

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