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2012

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Gustavo Saposnik

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Bilateral Medial Medullary Infarction: A systematic review

Authors: Sujatha Parthasarathy MD* ¹, Jitphapa Pongmoragot MD* ¹, Daniel Selchen MD FRCPC ¹, Gustavo Saposnik MD MSc FAHA ¹⁻³

¹ Stroke Research Unit, Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Canada

² Institute of Clinical Evaluative Sciences, Toronto, Ontario, Canada

³ Departments of Medicine and Health Policy Management and Evaluation, University of Toronto, Ontario, Canada

Address for correspondence:

Dr. Gustavo Saposnik

55 Queen St East, Suite 931

St Michael's Hospital, University of Toronto,

Toronto M5C 1R6 Canada

Phone: (416)-864-5155

e-mail: saposnikg@smh.ca

Conflict of interest: Nothing to disclose

* Both equally contributed to qualify as first authors.

Running Title: Bilateral Medial Medullary Infarction: a systematic review

The present manuscript includes one figure and 3 tables.

Abstract

Background: Bilateral infarction of the medial medulla (MMI) is rare. Limited information is available on clinical characteristics, etiology and prognosis. High resolution neuroimaging has a major role in elucidating the underlying stroke mechanism. The aim of this systematic review was to analyze the clinical presentation, stroke mechanism and outcome in patients with bilateral MMI.

Methods: We performed a systematic review of the literature from 1992 to 2011 that reported on clinical presentation, stroke mechanism and/or outcomes in patients with MRI proven bilateral MMI. Medline, EMBASE and Scholars Portal of Web Science were searched without language restriction. Two reviewers independently assessed studies to determine eligibility, validity and quality. The primary outcome was inpatient mortality and secondary outcomes were mortality at 12 months, an illustrative case is also described.

Results: We identified 138 articles from Medline, EMBASE, and Scholars' Portal including the above MESH terms. Twenty-nine articles met the inclusion criteria including 38 cases with bilateral MMI, who were included in our study. The mean age was 62.2 years, predominantly in male(74.2%). The most common clinical presentations were motor weakness in 78.4%, dysarthria 48.6%, and hypoglossal palsy 40.5%. Most common vascular pathology was vertebral artery atherosclerosis 38.5%. The clinical outcome was poor (death rate 23.8%, dependency 61.9%).

Conclusion: Bilateral medial medullary infarction is a rare stroke syndrome. Clinical presentations were mostly rostral medullary lesions. Large artery atherosclerosis and branch disease were the most common stroke mechanisms. The clinical outcome was usually poor.

Background

Medial medullary infarction was first described in the 19th century by Spiller.¹ However, the initial description of medial medullary syndrome was attributed to Dejerine who proposed the clinical triad of ipsilateral hypoglossal paralysis, contralateral hemiparesis sparing face and contralateral loss of deep sensation.² In 1937 Davison first described the underlying vascular mechanism: the occlusion of the anterior spinal artery (ASA) and vertebral artery in MMI.⁴ Infarction of the medial medulla is uncommon and accounts for 0.5- 1.5% of all strokes.^{3,5} Bilateral MMI is even rarer. Previously the diagnosis of bilateral MMI was from autopsies. More recently the advent of MRI revealed an increasing number of bilateral MMI cases. However, limited evidence is available on clinical presentation, stroke mechanism and outcome in patients with bilateral MMI. We have completed a systematic review of the literature analyzing clinical features, imaging, and prognosis in MRI proven patients with bilateral MMI.

Methods:

We reporting an illustrative case and performed a literature search in Medline, EMBASE, and Scholars' Portal Web of Science from 1992 to March 2011 on bilateral medullary infarctions. The search strategy combined the following Medical Subject Heading (MeSH) terms: 'brainstem infarctions', 'Medulla', and 'bilateral'. The results were then filtered to include only those citations with the keywords 'medial'. We also completed computer searches based on key words, and

hand searched for references from previously retrieved articles. Articles were included if they met the following inclusion criteria: i) MRI proven bilateral medial medullary infarctions, ii) reporting on clinical presentation and vascular imaging, and iii) reporting on outcome measures (e.g. mortality or disability). The search was confined to human subjects and no language restriction was placed. We recorded demographic features, clinical presentation and neuroimaging (MRI and MRA brain).

Study identification and validity assessment

Two reviewers (SP, JP) assessed titles and abstracts to determine eligibility. Disagreements between raters were solved by a third reviewer (GS). Two reviewers (SP, JP) independently extracted data using standardized data collection forms. Information was collected on study design, participant characteristics, vascular imaging, and outcome measures. The primary outcome of interest was inpatient mortality. Independence at 2 months was a secondary outcome. Independence was defined by the modified Rankin scale (mRS) 0-2.

Illustrative Case

A 71 year old man with known atrial fibrillation not on anticoagulation, presented with acute onset of right sided weakness and garbled speech, NIHSS 6. CT and CT Angiogram revealed no brain abnormalities or vascular occlusions. IV tPA was administered within 3 hours of symptoms onset, without improvement. The following day he developed contralateral left hemiparesis, right horizontal gaze palsy and worsening of dysarthria, NIHSS 14. Although the tongue was central, he was unable to protrude it outside his mouth. There was no sensory impairment or ataxia. On the third day he became quadriplegic and had marked dysphagia

requiring intubation. DWI MRI revealed acute infarcts in bilateral medial medulla at the rostral level, resembling a heart (“Heart sign”) and an infarct in territory of the right posterior inferior cerebellar artery (PICA), sparing the lateral medulla (Figure 1A and 1B). Both CTA and MRA revealed diffuse intracranial atherosclerosis. The right PICA and anterior spinal arteries were not visualized. The left superior cerebellar artery was occluded on its second segment (Figure 1C). The echocardiogram revealed no obvious intracardiac thrombus. Considering the history of atrial fibrillation and multiple infarcts affecting different vascular territories, the most likely stroke mechanism was embolic either from the non-visualized spinal artery or cardiogenic (e.g. aortic arch). Unfortunately, the patient developed pneumonia and **died**.

Results: Systematic review on Bilateral MMI

We identified 138 articles from Medline, EMBASE, and Scholars’ Portal Web of Science including the above MESH terms. Filtering with keywords yielded 61 citations for review.

Finally, 29 articles met the inclusion criteria, providing information on clinical and radiological aspects. Together these articles accounted for 38 patients with MRI proven bilateral MMI including our present case. We excluded Kim JS. et al⁶ from our analysis due to incomplete clinical information. We found no interventional studies or randomized controlled trial. There were seven articles published in languages other than English. Table 1 summarizes demographic information, clinical findings, imaging, and outcomes. The mean age was 62.2 years (range 42-81). Men were most commonly affected (74.2%).

Clinical findings:

The most common clinical presentation was motor weakness (78.4%), bilateral in 64.9% of patients. Other symptoms at onset included dysarthria and nystagmus in 48.6% (horizontal nystagmus 27%, upbeat nystagmus 13.5%, gaze evoke nystagmus 5.4% and rotatory nystagmus 2.7%). Sensory disturbance was noted in 43.2%. Hypoglossal palsy was present in 40.5% of patients, whereas dysphagia occurred in 16.2%. One fourth of patients with bilateral MMI developed respiratory failure (24.3%).

Vascular imaging:

Most common findings using MR angiography included: vertebral artery atherosclerosis 38.5%, no abnormalities were found in 38.5%, vertebral artery occlusion 15.4%, basilar artery atherosclerosis 19.2%. Dissection was reported in 7.7%. Anterior spinal artery occlusion was noted in 3.8% (from an autopsy case).

Outcome measures: Overall, the prognosis in reported patients with bilateral MMI was poor. In-hospital mortality was reported in 23.8%, almost two third of survivors were dependent (61.9%) at 2-3 months.

Discussion

Bilateral Medial Medullary Infarction (MMI) is a rare stroke subtype, usually presenting with sudden onset of quadriparesis/quadriplegia, loss of deep sensation, hypoglossal palsy, bulbar dysfunction, with or without respiratory failure. The initial diagnosis may be challenging due to the heterogeneity of the clinical presentation. The advent of MRI facilitates the diagnosis of

medial medullary infarction. Most common mechanisms include large atherosclerotic vessel disease, small penetrating artery disease (ie. branch disease), and cardiogenic (e.g. cardiac source, aortic arch) seems the. Thirty-eight percent of patients reported in the literature had no abnormal vascular findings. Limited information is available in the literature regarding clinical presentation, stroke mechanism, and prognosis of bilateral MMI. To the best of our knowledge, our study is the largest systematic review including 38 MRI proven-cases with bilateral MMI (Table1). The most common clinical presentation was bilateral motor weakness (64.9%) which corresponds to the site of the infarction (V shape). Interestingly, only 10% of patients with bilateral MMI presented with hemiparesis and 20% progressed from hemiparesis to quadriplegia within 72 hours. Nystagmus was also a common finding (48.6%), upbeat nystagmus in 13.5% indicating the involvement of the medial longitudinal fasciculus. Respiratory failure was noted in 24.3%, more prevalent than the reported 5% in unilateral MMI series.¹² The most common MRI finding includes rostral medullary infarction (V-shape). Previous studies reported an initial negative DWI MRI in up to 20% of patients.⁵ In the comprehensive Posterior Circulation Stroke registry (New England Medical Centre Posterior Circulation study), cardioembolism was the most likely mechanism to cause distal posterior circulation territory infarcts¹¹. In the largest reported case series of unilateral MMI (n=86)⁶, large vessel disease was found in 62% (similar to our case) followed by small vessel disease in 28%. Kim et al.⁶ also reported, Bilateral MMI (6 cases) vascular pathology was commonly found in atheromatous branch occlusion. Only 1% was found in cardiac embolism. In our study vascular pathology could be categorized in two major groups: large artery atherosclerosis involving the vertebral artery (38.5%) and normal vascular imaging. The anterior spinal artery was non-visualized in 38.5%. In the normal angiogram group the stroke mechanism was likely atheromatous branch occlusion or ASA occlusion which

couldn't be demonstrated by MR angiogram. Bilateral MMI could be related either to extended thrombosis in the vertebrobasilar junction, or be due to the anatomical variability of perforator branches that supply the medulla or variation of anterior spinal artery originating from one of the VA may explain the occurrence of a simultaneous bilateral medial medullary infarction. Dissection of VA was uncommon in our study (7.7%) compared with other reports of unilateral MMI.¹² The clinical outcome was poor compared to unilateral MMI.^{3,6} In our study, one fifth of patients died and two third of survivors remained dependent.

The present systematic review has limitations. Symptoms were reported by different authors in a non-systematic fashion. Although we developed an algorithm to identify all cases with bilateral MMI, we cannot rule out an involuntary omission. Despite these limitations, our study summarizes the clinical presentation, imaging, and outcomes in patients presenting with bilateral MMI. A better understanding of this syndrome will assist clinicians to recognize bilateral MMI early, and to discuss therapeutic interventions and prognosis with patients and their families.

In conclusion, bilateral MMI is an uncommon stroke syndrome usually related to large artery or branch disease, and is commonly associated with poor outcome.

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Legends:**Figure 1**

Figure 1A and 1B: DWI MRI shows restricted diffusion involving bilateral medial medulla ('Heart sign') (arrow) and the right inferior cerebellar hemisphere consistent with an acute infarction.

Figure 1C: MR angiogram demonstrates diffuse intracranial atherosclerosis. The left superior cerebellar artery was occluded on its second segment. There was no significant stenosis or occlusion of the vertebral and basilar arteries. The right PICA, anterior spinal arteries were not visualized.

Table 1: Clinical characteristics, imaging and prognosis of Bilateral MMI reported in the literature

Author	No.	Age (yrs)/sex	Year	Clinical presentation	Vascular Imaging	Outcome
Toyoda K et al (7)	1	71/M	1992	gaze palsy , dysarthria, hypoglossal palsy, quadriplegia, horizontal nystagmus respiratory failure	Left VA and BA irregularity, Small aneurysm middle BA, right VA hypoplasia and atherosclerosis, ASA nonvisualised	persistent quadriplegia at 2 months mRS5
Kleinert G et al (13)	1	59/ M	1993	hypoglossal palsy, quadriplegia, sensory loss, respiratory failure	Autopsy showed VA and BA atherosclerosis bilaterally with occlusions in the ASA branches	Death at 2 weeks (pneumonia)
Ohashi et al (14)	1	61/F	1995	hypoglossal palsy quadriplegia, sensory loss,	NA	NA
Kim JS (25)	1	59/M	1995	facial paralysis, dysarthria, dysphagia motor deficit, paresthesia, impair vibration upbeat nystagmus	VA occlusion	NA
Roh JK et al (15)	1	71/M	1996	impaired deep sensation Sensory ataxia, upbeat nystagmus bilateral dysmetria, truncal ataxia	VA and BA normal	Stand and walk with 2 weeks mRS 3
Wada K et al (8)	1	69/M	1996	gaze palsy, bilateral facial weakness, left hemiparesis, horizontal nystagmus	Right VA occlusion	NA
Toyoda K et al (3)	1	71/M	1996	bilateral facial palsy, dysarthria , right hypoglossal palsy, right hemiparesis, bilateral sensory loss, upward and horizontal nystagmus	Right VA hypoplasia, Left VA atherosclerosis(wall irregularity)	mRS 5 at 2 months
Toyoda K et al (3)	1	47/M	1996	quadriparesis, bilateral sensory loss, horizontal nystagmus	Normal angiogram with nonvisualised ASA	mRS 3 at 2 months
Takizawa S et al(26)	1	70/M	1996	dysarthria, dysphagia, bilateral hypoglossal palsy, quadriplegia gazed evoke nystagmus	Normal VA and BA, Nonvisualised ASA	mRS4 at 7 months

Del Brutto OH et al(16)	1	58/M	1998	hypoglossal palsy quadriplegia,	VA partial occlude, VA dolichoectasia	Quadr iplegia at 2 months mRS5
Bailbe M et al (17)	1	42/M	2000	NA	NA	Favorable outcome
Katoh M et al (18)	1	71/M	2000	horizontal gaze palsy, dysarthria, impaired gag reflex, quadriparesis,	NA	5mth able to walk ,mRS 3 Hemiparesis at 1 year,
Thijs RD et al (19)	1	56/M	2001	dysarthria, quadriplegia, respiratory failure	Right VA occlusion, Non visualized ASA	Quadriplegia at 2 months mRS 5
Kumral E et al (20)	1	57/M	2002	facial palsy,dysarthria hypoglossal palsy quadriplegia, sensory loss, upbeat, horizontal, rotatory nystagmus, gait ataxia	VA dolichoectasia	Quadriplegia at 3 months mRS5
Moon SY et al (27)	1	81/F	2002	anarthria,hypoglossal palsy,quidriplegia, impair vibration	Normal VA and BA, ASA non visualized	Death, (aspiration pneumonia)
Kobayashi Z et al (21)	1	69/M	2003	quadriplegia	NA	NA
Takano K et al (22)	1	63/F	2003	dysarthria, quadriparesis, sensory loss, horizontal nystagmus	Normal angiogram, ASA nonvisualised	Quadriplegia at 2 years, mRS5
Alvarez-Cermeno Jc et al (28)	1	49/F	2003	Bilateral hypoglossal palsy	VA atherosclerosis, BA stenosis	Favorable outcome at 2 months, mRS 1
Kameda W et al (12)	6	NA	2004	sensory loss, horner's syndrome, cerebellar ataxia	VA and PICA atherosclerosis (number patient =2)	NA
Fukuda M et al (9)	1	52/F	2004	hypoglossal palsy, hemiplegia, sensory loss	VA dissection bilaterally	Hemiplegia at 18 months, mRS3
Maeda M et al (23)	1	69/F	2004	dysarthria, quadriplegia, horizontal nystagmus, respiratory failure	VA stenosis/ occlusion	NA
Zickler P et al (33)	1	NA	2005	Quadriparesis, autonomic dysregulation	NA	NA
Jikumaru et al (24)	1	79/M	2006	gaze palsy, Left facial palsy, dysarthria, quadriplegia, respiratory failure	NA	NA

Gondim F et al (29)	1	64/F	2006	hypoglossal palsy, quadriparesis, upbeat nystagmus, respiratory failure	Right VA stenosis, BA stenosis(50%)	Death at 2 months (r/o peritonitis)
Tokuoka K et al (34)	1	62/M	2007	dysarthria, dysphagia, Quadriplegia, Sensory loss	NA	mRS 5
Paliwal VK et al (35)	1	70/M	2009	anarthria, dysphagia, quadriplegia, gaze evoke nystagmus, respiratory failure	Hypoplastic right VA, ASA non visualised	Death, (pneumonia)
Kim JS et al (6)	12	NA	2009	dysarthria, quadriparesis, nystagmus	atheromatous branch occlusion	NA
Liu CL et al (31)	1	54/F	2009	dysphagia, hiccough, quadriparesis, impair vibration	Normal VA and BA	Mechanical ventilation/ persistent quadriplegia at 1 year, mRS5
Shono Y et al (5)	1	57/M	2010	facial palsy, hypoglossal palsy, hemiparesis	Normal VA and BA, ASA nonvisualised	mRS 2 at 3 months
Shono Y et al (5)	1	60/M	2010	dysarthria, bilateral hypoglossal, palsy, quadriparesis, bilateral sensory dysfunction, ataxia	Left VA occlusion after Branching PICA(dissection)	mRS 5 at 3 months
Krishnan M et al(32)	1	70/M	2011	dysarthria, hypoglossal palsy, quadriparesis, impair vibratory, horizontal nystagmus, respiratory failure	Bilateral VA and BA atherosclerosis	Residual spastic quadriparesis at 1 month, mRS5
Ma L et al (36)	1	49/M	2011	dysarthria,quadriplegia, horizontal nystagmus	Normal VA, BA	Motor power gr 3/5 at 18 months,mRS5
Ma L et al (36)	1	48/M	2011	dysarthria, dysphagia hypoglossal palsy, Quadriparesis, bilateral sensory loss horizontal nystagmus,	Left VA occlusion	Motor power gr 4/5 at 1mth. mRS1 at 15 months
Present case	1	71/M	2010	gaze palsy, dysarthria, quadriplegia, Respiratory failure,	Normal VA and BA ASA nonvisualized	Death 1 month (pneumonia)

Abbreviations: M- male; F-female; VA- vertebral artery; BA- basilar artery; ASA- anterior spinal artery; PICA- posterior inferior cerebellar artery; mRS- modified Rankin scale; NA- details not available

Table 2. Clinical Manifestations

Symptoms and signs (Total n=37)	Number	(%)
Motor	29	(78.4)
Bilateral weakness	24	(64.9)
Hemiparesis	4	(10.8)
Unidentified	1	(2.7)
Dysarthria	18	(48.6)
Nystagmus	18	(48.6)
Upbeat	5	(13.5)
Horizontal	10	(27)
Gaze evoked	2	(5.4)
Rotatory	1	(2.7)
Sensory	16	(43.2)
Hypoglossal palsy	15	(40.5)
Bilateral	3	(8.1)
Unilateral	1	(2.7)
Unidentified	11	(29.7)
Respiratory failure	9	(24.3)
Dysphagia	6	(16.2)
Facial palsy	6	(16.2)
Gaze palsy	5	(13.5)
Ataxia	4	(10.8)
Horner Syndrome	1	(2.7)

Table 3. Vascular Imaging

Vascular Pathology (Total n=26)	n	(%)
Normal VA, BA, ASA	10	(38.5)
VA atherosclerosis	10	(38.5)
VA occlusion	4	(15.4)
BA atherosclerosis	5	(19.2)
Dissection	2	(7.7)
VA dolichoectasia	2	(7.7)
ASA occlusion	1	(3.8)
PICA atherosclerosis	2	(7.7)

Abbreviations: VA- vertebral artery; BA- basilar artery; ASA- anterior spinal artery; PICA- posterior inferior cerebellar artery
 From the case report some patients have more than one vascular pathology.

Note: Total percentage is higher than 100 due to more than one vessel affected in some cases.

Figure 1- Illustrative case

A)

B)

C)

Figure 1A and 1B: DWI MRI shows restricted diffusion involving bilateral medial medulla ('Heart sign') (arrow) and the right inferior cerebellar hemisphere consistent with an acute infarction.

Figure 1C: MR angiogram demonstrates diffuse intracranial atherosclerosis. The left superior cerebellar artery was occluded on its second segment. There was no significant stenosis or occlusion of the vertebral and basilar arteries. The right PICA, anterior spinal arteries were not visualized.