



Lateral medullary infarction with cardiovascular autonomic dysfunction: an unusual presentation with review of the literature

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Abstract

Purpose We report an unusual case of lateral medullary infarction presenting with orthostatic hypotension with pre-syncope without vertigo or Horner's syndrome.

Methods Case report with review of the literature.

Results A 67-year-old man presented with pre-syncope and ataxia without vertigo. Initial brain CT and MRI were normal. Neurological evaluation revealed right-beating nystagmus with left gaze, vertical binocular diplopia, right upper-extremity dysmetria, truncal ataxia with right axial lateropulsion, and right-facial and lower extremity hypoesthesia. Bedside blood pressure measurements disclosed orthostatic hypotension. He had normal sinus rhythm on telemetry and normal ejection fraction on echocardiogram. A repeat brain MRI disclosed an acute right dorsolateral medullary infarct. Autonomic testing showed reduced heart rate variability during paced deep breathing, attenuated late phase II and phase IV overshoot on Valsalva maneuver, and a fall of 25 mmHg of blood pressure at the end of a 10-min head-up tilt with no significant change in heart rate. These results were consistent with impaired sympathetic and parasympathetic cardiovascular reflexes. He was discharged to acute rehabilitation a week later with residual right dysmetria and ataxia.

Conclusion Lateral medullary infarctions are usually reported as partial presentations of classical lateral medullary syndrome with accompanying unusual symptoms ranging from trigeminal neuralgias to hiccups. Pre-syncope from orthostatic hypotension is a rare presentation. In the first 3–4 days, absence of early DWI MRI findings is possible in small, dorsolateral medullary infarcts with sensory disturbances. Physicians should be aware of this presentation, as early diagnosis and optimal therapy are associated with good prognosis.

Keywords Lateral medullary infarction · Lateral medullary syndrome · Wallenberg syndrome · Dorsolateral medullary infarction · Cardiovascular autonomic dysfunction

Introduction

Lateral medullary syndrome (also known as posterior inferior cerebellar artery syndrome, and formerly known as Wallenberg syndrome) is a well-described vascular disorder classically characterized with vertigo, dissociated crossed sensory deficits, ipsilateral ataxia, bulbar palsy, and Horner's syndrome. The lateral medullary syndrome was initially described by the Swiss physician, Gaspard Vieussieux, in

1808, and pathologically characterized in autopsy by the German neurologist, Adolf Wallenberg, in 1901 [40]. Although sensorimotor deficits are the most common manifestations of the lateral medullary syndrome, cardiovascular autonomic dysfunction has been anecdotally reported. We report here the case of a man with an unusual presentation of lateral medullary syndrome with pre-syncope due to orthostatic hypotension without vertigo or Horner's syndrome. We also performed a systematic review of the literature on the occurrence of cardiovascular autonomic dysfunction as part of the lateral medullary syndrome.

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Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to throughout this study. Our workflow is summarized in Fig. 1. Institutional Review Board approval was not required for this study. Electronic searches of the PubMed and Web of Science databases were performed by two independent authors (T.H. and B.D.). Strategic search term combination was used as follow: lateral medullary infarct OR lateral medullary syndrome OR dorsolateral medullary infarction OR wallenberg syndrome AND autonomic. English full text articles involving humans were included. Title and abstract views were screened for relevance to the topic and duplicate articles were removed. A total of 16 studies were included in the analysis. Autonomic testing was performed on WR Medical Testworks Autonomic testing equipment.

Case report

A 67-year-old man with a past medical history of hypertension, coronary artery disease, prior stroke due to small vessel disease without residual deficits, and current tobacco smoker presented to the emergency department with sudden onset orthostatic pre-syncope and ataxia without vertigo. Initial

neurology exam per admitting internal medicine team was unremarkable except for mild difficulty with finger-to-nose testing, slight ataxia, and pre-syncope upon standing. CT and MRI of the head at presentation were normal.

Over the following 3 days, the patient's symptoms worsened, prompting a neurology consultation, which revealed the following pertinent findings: right-beating nystagmus with left gaze, vertical binocular diplopia, right upper extremity dysmetria, truncal ataxia with right axial lateropulsion, right-facial impaired pinprick sensation, right-lower extremity impaired proprioception and pinprick sensation. Bedside blood pressure measurements disclosed orthostatic hypotension.

An echocardiogram showed an ejection fraction of 65%. Telemetry revealed a normal sinus rhythm. Hemoglobin A1c at presentation was 4.9%. A repeat MRI showed a right-sided dorsolateral medullary infarct on day 3 (Figs. 2 and 3). A computed tomography angiography showed an occluded right posterior inferior cerebellar artery and 60% stenosis of the right internal carotid artery. Autonomics nervous system testing demonstrated the following:

Heart rate to deep breathing

There was blunted heart rate variation with an average of 4.0 beats per minute (BPM) on one trial and 3.8 BPM on a second trial. The 5th percentile lower limit of normal for patients of his age is 7 beats per minute.

Valsalva maneuver testing (Fig. 4)

The patient produced a good respiratory effort during each Valsalva response. The heart rate variation was blunted on both trials. Heart rate variation on one trial was 1.03 and, on a second trial, 1.15, with a 5th percentile cut-off of 1.29 for age. The late phase II BP response was present but blunted, not attaining the baseline BP on either of the two trials. There was a modest phase 4 overshoot.

Tilt-table test (Table 1; Fig. 5)

The baseline HR was 77 BPM and the baseline BP by finger cuff was 114/80 and, by auscultation at the antecubital fossa, 115/78. During the tilt, patient noted mild dizziness and mild generalized weakness. His heart rate varied from 82 to 101 BPM and his BP from 90–130 systolic and 70–83 diastolic, with both techniques recording similar pressures. His minimal BP occurred at the end of the tilt (90/70). When the patient was placed supine again, the BP rose to a maximum of 140/80 at 3 min. This represented a 25-mmHg drop in blood pressure when compared to his pre-tilt pressure (115/78).

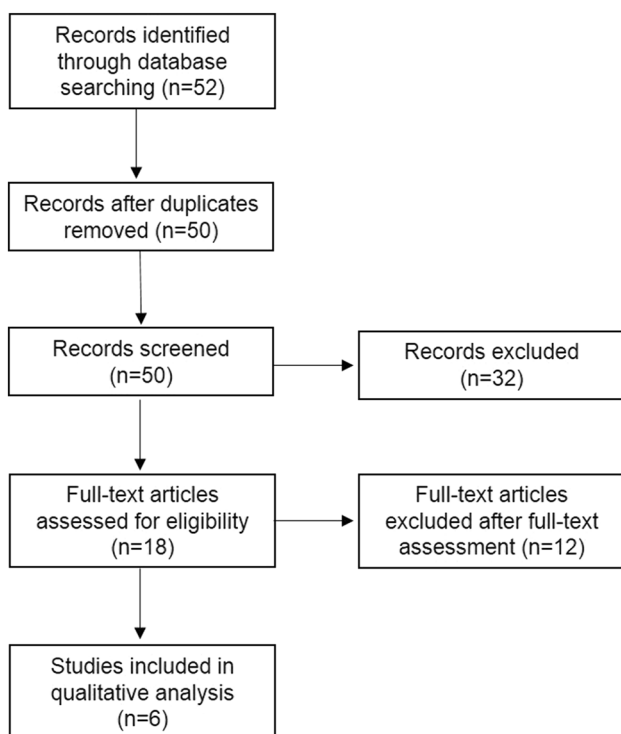


Fig. 1 Flowchart according to PRISMA statement

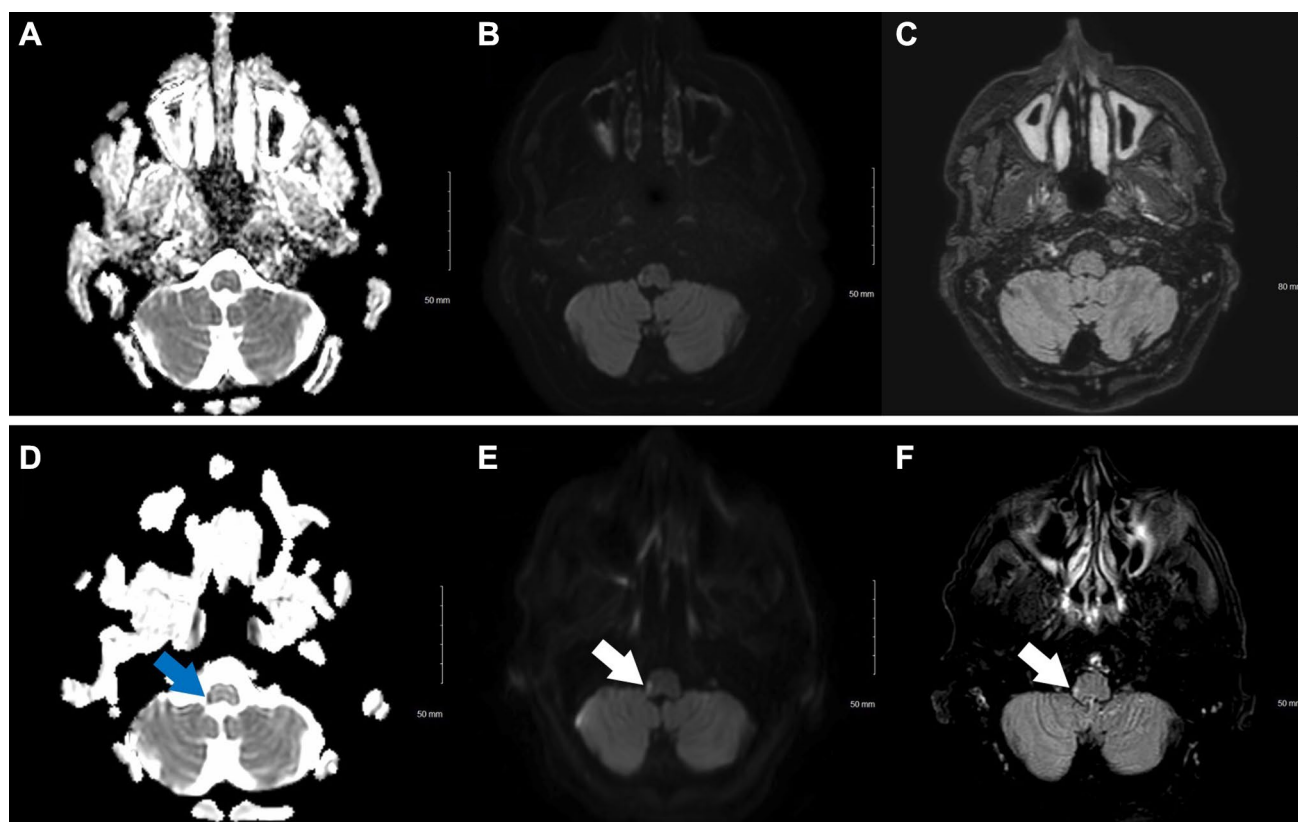


Fig. 2 Axial MRI images on day 0 (**a** ADC, **b** DWI, **c** FLAIR) and day 3 (**d** ADC, **e** DWI, **f** FLAIR). Location of infarct marked with *arrows* on day 3 images



Fig. 3 Sagittal MRI with level of infarct demonstrated

These results are consistent with impaired cardiovascular and parasympathetic cardiovascular reflexes. The only drug taken with cardiovascular autonomic activity

was Amlodipine at a dosage of 10 mg, with the last dose taken 14.5 h prior to the autonomic tests.

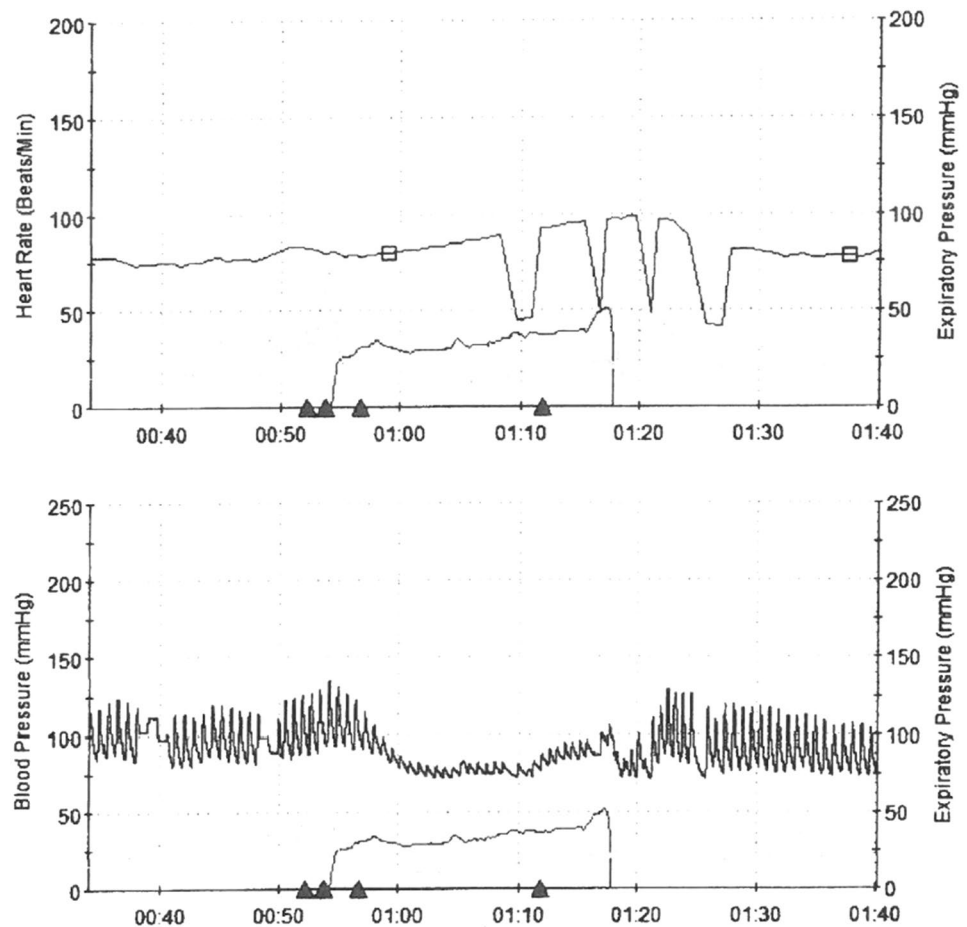
He was discharged to acute rehabilitation a week later with residual right dysmetria, ataxia, and minimal orthostasis. The patient cancelled a follow-up appointment when a repeat MRI and autonomic nervous system testing were planned. Per the latest neurology progress note 2 months after the stroke, he is doing well with only some residual minimal orthostasis, unsteadiness on tandem gait, and a positive Romberg test.

Literature review

A total of 50 articles were identified through database searches after duplicates were removed. A total of 32 articles were excluded after abstract review due to lack of relevance, and 18 full texts were assessed for eligibility. Six of them were included in the final qualitative analysis (Fig. 1) [1, 2, 13, 23, 25, 31].

Cardiovascular autonomic instability is rarely reported in lateral medullary infarctions, with most of the reports coming from single case reports, the exception being with Hong et al., who showed in a prospective cohort study of 69

Fig. 4 Valsalva maneuver graph showing blunted phase 2 and modest phase 4 overshoot



patients that infarction in the ventral part of the right medulla was highly correlated with parasympathetic dysfunction of the baroreceptor reflex. They postulate that impaired heart rate control through disruption of the nucleus ambiguus' cardiovagal efferent pathway resulted in the autonomic cardiovascular dysfunction [13].

As for the case reports, Haltavilla et al. described a case of left dorsolateral medullary infarct in the rostral medulla resulting in orthostatic hypotension combined with Horner's syndrome and hyperlacrimation. In this case, the orthostatic hypotension was postulated to be a result of disruption of descending sympathetic fibers in the hypothalamospinal tract [2]. Phillips et al. reported a large left lateral medullary infarct complicated by paroxysmal hypertension. These episodes of hypertension were attributed to intermittent blockade of baroreceptor afferents, which in turn would lead to disinhibition of sympathetic activity [31]. In another case of large left lateral medullary infarct, Alsaad et al. describe a patient with recurrent syncopal episodes due to recurrent sinus arrests secondary to his lateral medullary infarct [1]. Finally, Lassman et al. report a case of right dorsolateral medullary infarct complicated by paroxysmal apnea and labile hypertension 3 months after the stroke. They postulate

that hypoventilation-induced respiratory acidosis triggered an exaggerated reflex sympathetic outflow, leading in turn to labile hypertension [25].

Discussion

Lateral medullary infarctions (LMI) usually present as partial constellations of classical lateral medullary syndrome with the possibility of a wide range of accompanying unusual symptoms including trigeminal neuralgia, hiccups, neurotrophic keratopathy, and central sleep apnea, among others [9, 14, 15, 30, 33, 41].

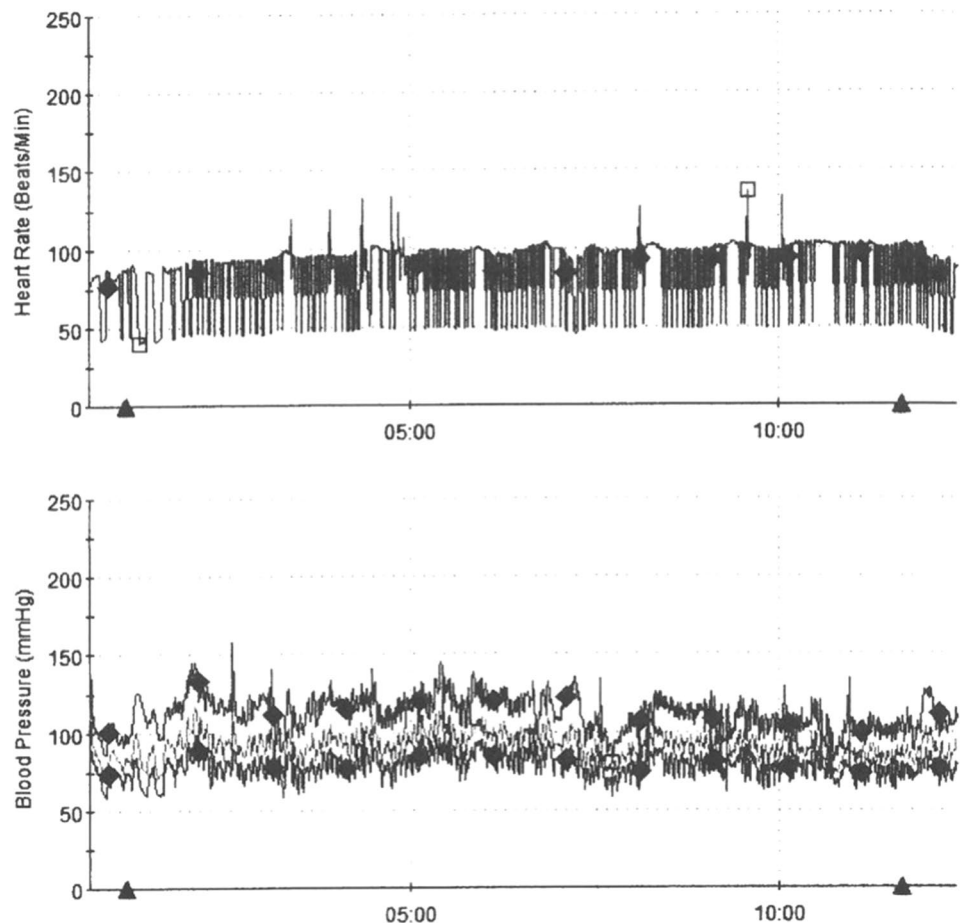
Though efforts have long been made to topologically correlate clinical presentation to anatomical location of infarct in the medulla through retrospective reviews, the complexity and diversity of neural pathways in the medulla as well as the unique distribution of each infarct make this a challenging endeavor [4, 7, 8, 16, 18–21, 35]. Such studies have generally focused on the sensorimotor presentations of LMI, with few reports looking at autonomic dysfunctions in LMI. Cardiovascular autonomic dysfunction secondary to a stroke is a rare occurrence, despite the fact that the

Table 1 Tilt-table test data demonstrating a minimum blood pressure of 90/70 at the end of the tilt. This represented a 25-mmHg drop in blood pressure when compared to his pre-tilt pressure (115/78)

Time (min)	Manual blood pressure	Finipress blood pressure	Heart rate	Symptoms
Pre-tilt	115/78	114/80	80	–
0.5 min tilt	130/80	114/82	82	Mild dizziness
1	120/75	134/93	83	
1.5	125/75	116/83	82	
2	125/78	119/87	94	
3	120/80	122/86	87	
4	125/75	115/75	90	
5	128/80	126/92	99	
6	110/75	101/74	91	Dizzy, weak
7	120/78	118/89	101	
8	125/83	114/83	88	
9	–	93/71	81	Dizzy, weak
10	90/70	100/75	100	
1 min post-tilt	118/75	108/74	91	Improved
2 min post-tilt	–	141/95	82	Ok
3 min post-tilt	140/80	135/88	85	Ok

medulla contains the regulatory centers of the baroreceptor reflex. Brainstem infarctions have been known to have a potential effect on the cardiovascular autonomic system with reports of baroreflex failure presenting with labile hypertension, arrhythmia, hypotension, and bradycardia [6, 10, 12, 24, 25, 31, 37].

The baroreceptor reflex has been well-studied, and it is generally understood as follows. The baroreflex is a feedback loop receiving continuous inputs from stretch-sensitive baroreceptors located in the aortic arch and carotid sinuses. These inputs are carried to nucleus tractus solitarius (NTS) neurons in the brainstem by way of cranial nerves IX and X. NTS neurons, in turn, project excitatory fibers to the caudal ventrolateral medulla (CVLM), which then sends inhibitory fibers to the rostral ventrolateral medulla (RVLM). The RVLM is the primary regulator of cardiovascular autonomic outflow by way of the intermediolateral nucleus in the spinal cord. The parasympathetic branch of the baroreceptor reflex is mediated by the nucleus ambiguus and dorsal nucleus of the vagus nerve, which are innervated by NTS neurons receiving tonic inputs from arterial baroreceptors. This pathway mainly targets the heart, with an activation leading to decreased chronotropy and ionotropy [5, 29].

Fig. 5 Heart rate and blood pressure tracings during head-up tilt, showing minimal heart rate variation. The deflections exceeding 100 beats per minutes are premature ventricular contractions confirmed by Holter monitor

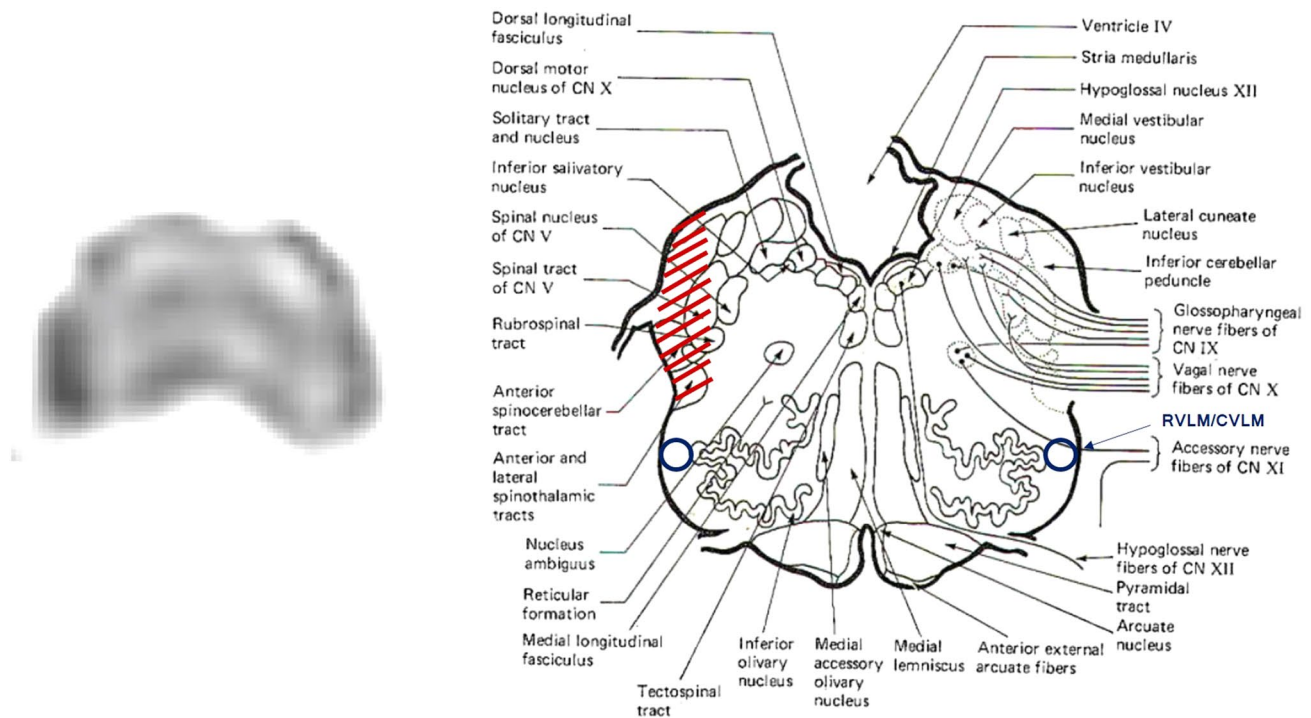


Fig. 6 Zoom-in axial MRI ADC at the area of infarct in the medulla with schematic diagram. Area of infarct (*red hashes*) show putative pathways involved. Diagram from humanneurophysiology.com

Pre-syncope from orthostatic hypotension is a rare presentation of LMI. In our present case, though the autonomic findings could entirely be attributed to Amlodipine, the fact that the patient had been stable on the drug coupled with his sudden onset of pre-syncope feelings coincidental with the acute finding of the lateral medullary infarct make us believe that there is a component of autonomic dysfunction in the present case. We believe that the parasympathetic and sympathetic dysfunctions observed in this case are a result of disruption of entering cranial nerves IX's and X's baroreceptor afferent fibers to the nucleus tractus solitarius. It is also possible that efferent fibers of dorsal motor nucleus of X were affected (Fig. 6) [32]. It would seem that the RVLM/CVLM complex is spared, as it is located more ventrally than the area of infarct (labelled in Fig. 6) [3, 28, 36].

We believe that the lack of Horner's syndrome or miosis observed in this present case is due to sparing of the descending autonomic hypothalamospinal tract (from the hypothalamus paraventricular nucleus to the intermediolateral cell column), which is widely dispersed throughout the rostral medulla around the dorsal motor nucleus of X, the nucleus tractus solitarius, and the nucleus ambiguus [11, 34]. This tract ultimately carries sympathetic fibers to the superior cervical ganglion responsible for pupillary dilation, levator palpebrae muscle tone, and innervation of the lacrimal glands.

The lack of arrhythmia on telemetry, the finding of an occluded posterior inferior cerebellar artery on subsequent computed tomography angiography, and the fact that large vessel disease is the most common cause of LMI suggest a thrombotic etiology behind this present case of LMI, though a cardio-embolic or athero-embolic etiology cannot be ruled out [22, 27].

Interestingly, Tsukuyasi et al. have described patients with infarcts in the dorsolateral location of the medulla, a small stroke volume, and sensory disturbances to be more prone to develop "invisible" brain stem infarctions in the first 3–4 days, as seen in this present case [8, 39]. Axial lateropulsion and nystagmus have been attributed to lesions to the inferior vestibular nucleus or vestibulo-cerebellar fibers [7, 26]. Thomke et al. postulated that limb ataxia with body lateropulsion is probably the consequence of impaired proprioceptive information from the ascending dorsal spinocerebellar tract [38].

Kim et al. showed in several patients with LMI that ipsilateral sensory symptoms were restricted to the upper extremity, except when the infarct was significantly larger. She attributes this phenomenon to involvement of decussating lemniscal fibers [17]. Regarding the ipsilateral lower extremity involvement, it would seem that the patient's lesion was restricted to the lateral portion of the spinothalamic tract, which carries afferents superficial sensory fibers from caudal (sacral, lumbar) dermatomes.

Conclusion

Pre-syncope and orthostatic hypotension is an unusual presentation of lateral medullary infarction resulting from baroreflex failure secondary to disruption of sympathetic and/or parasympathetic tracts in the medulla. In the first 3–4 days, the absence of early DWI MRI findings are possible in small, dorsolateral medullary infarcts with sensory disturbances.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Human and animal rights The manuscript does not contain clinical studies or patient data.

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