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REVIEW

Wallenberg–Zakharchenko syndrome in vascular neurology emergency care: A review

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Abstract
Wallenberg–Zakharchenko syndrome associated with lateral medullary infarction has been known to neurologists since the end of the 19th century. However, to this day, its diagnosis is challenging due to the polymorphic, atypical, and rapidly changing clinical manifestations. Timely verification of the syndrome provides essential information regarding its etiology and also prevents serious complications. The paper presents clinical and anatomical correlates of lateral medullary infarction, its etiology, features of the clinical presentation, complications, and prognosis. In conclusion, a diagnostic algorithm that can be used in everyday practice is given.

Keywords: lateral medullary infarction, Wallenberg–Zakharchenko syndrome, diagnosis
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ОБЗОР

Синдром Валленберга–Захарченко в неотложной ангионеврологии

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Аннотация
Синдром Валленберга–Захарченко, связанный с латеральным медуллярным инфарктом, известен неврологам с конца XIX в., однако и по настоящий день его диагностика является трудной клинической задачей. Это связано с полиморфизмом, атипичностью и динамичностью клинических проявлений заболевания. При этом своевременная верификация синдрома несет важную информацию в отношении его этиологии, а также позволяет предотвратить серьезные осложнения. В статье представлены клинико-анатомические корреляты латерального медуллярного инфаркта, рассмотрены его этиология, особенности клинической картины, осложнения и прогноз. В завершение приведен диагностический алгоритм, который можно использовать в повседневной практике.

Ключевые слова: латеральный медуллярный инфаркт, синдром Валленберга–Захарченко, диагностика
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The first known description of the symptoms of lateral medullary infarction (LMI) was published in 1810 by Gaspard Vieusseux [1]. However, it was not until 1895 that the German neurologist Adolf Wallenberg (1862–1949) associated this set of symptoms with damage to the lateral parts of the me-dulla oblongata supplied by the posterior inferior cerebellar artery (PICA) [2], proving this during a pathological examination in 1901 [3]. The first patient described by A. Wallenberg was a 38-year-old man who developed acute dizziness with pain and hyperesthesia of the left half of the face, im-paired pain and temperature sensitivity on the right half of the trunk, bulbar syndrome, ataxia in the left extremities, and bradycardia. In 1911, Russian neurologist Mikhail Alexandrovich Zakharchenko described five variants of this syndrome, demonstrating its clinical polymorphism associated with the possible expansion of the affected area beyond the lateral parts of the medulla oblongata [4]. In 1993, R. Sacco et al. (USA), using magnetic resonance imaging (MRI), for the first time presented clinical and radiological correlations in 22 patients with LMI [5], and 10 years later, J. Kim (South Korea) published an analysis of 130 cases of MRI-confirmed LMI [6]. In recent years, interest in this syndrome has increased due to the identification of stable LMI patterns, etiological features, and the description of many atypical variants, as well as the development of structured approaches to clini-cal and instrumental diagnostics, which are addressed in our paper.

Anatomy

The anatomy and blood supply of the medulla oblongata are presented in Figure 1.

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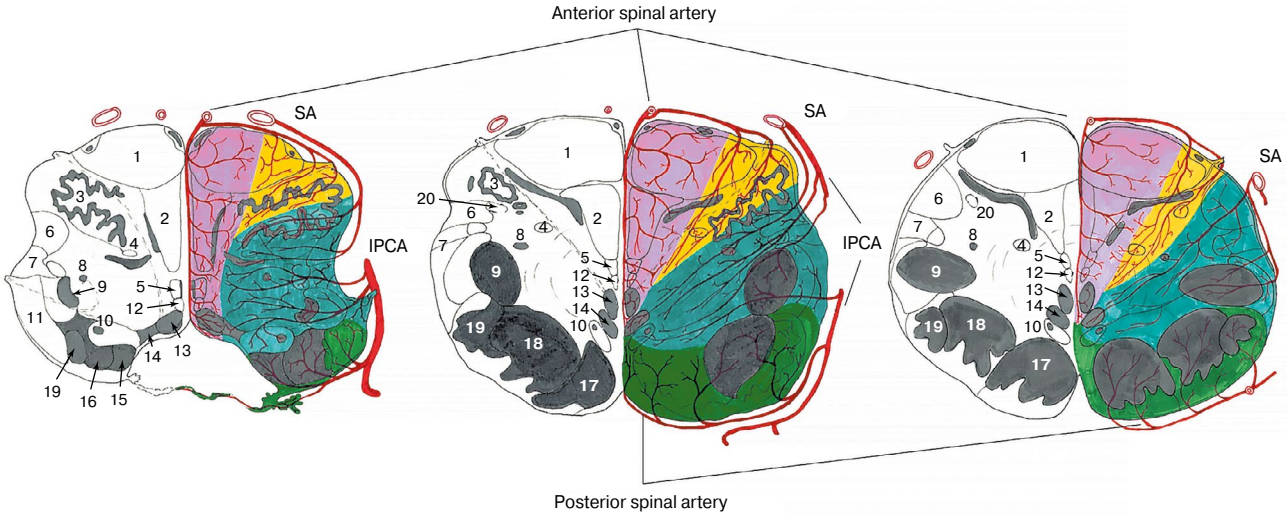
Fig. 1. Anatomy and blood supply of the medulla oblongata.



Note. 1 – pyramidal tract, 2 – medial lemniscus, 3 – inferior olive, 4 – trigeminothalamic tract, 5 – tectospinal tract, 6 – spino-thalamic tract, 7 – spinocerebellar tract, 8 – ambiguous nucleus, 9 – spinal trigeminal nucleus, 10 – solitary tract nucleus, 11 – inferior cerebellar peduncle, 12 – medial longitudinal bundle, 13 – hypoglossal nerve nucleus, 14 – dorsal nucleus of the vagus nerve, 15 – medial vestibular nucleus, 16 – inferior vestibular nucleus, 17 – Goll's nucleus, 18 – Burdach's nucleus, 19 – lateral nucleus cuneatus, 20 – lateral vestibulospinal tract; VA – vertebral artery, IPCA – inferior posterior cerebellar artery.

Table 1. Clinical and anatomical correlates in LMI [6–8]

Anatomical structure	Complaints	Features of neurological sta-tus
Nucleus and descending spinal tract of the trigeminal nerve	Tingling or stabbing pain in the eye and half of the face; feeling of numbness of half of the face on the side of the lesion	Reduced pain and temperature sensation, reduced corneal re-flex
Vestibular nuclei and their connections	Dizziness or instability, nausea, vomiting	Nystagmus, ocular lateropul-sion
Spinothalamic tract	Patient rarely have active com-plains; some patients report re-duced temperature sensation	Decreased pain and tempera-ture sensation in the contrala-teral half of the body and ex-tremities
Endorestiform nucleus (inferior cerebellar peduncle)	Deviation towards the lesion side, clumsiness in the ipsilateral limbs	Hypotonia and an increase in the rebound phenomenon (Stewart-Holmes test) in the ipsilateral arm; pronounced in-tentional tremor is not com-mon; in a sitting or standing position, the patient often devi-ates towards the lesion side
Descending sympathetic tract in the lateral parts of the reticu-lar formation		Ipsilateral Horner syndrome
Dorsal motor nucleus of the vagus nerve		ECG conduction abnormalities, BP lability
Ambiguous nucleus (with me-dial spread of the infarction)	Hoarseness and dysphagia; cough ('croaking' cough)	Weakness of the muscles of the pharynx and palate on the af-fected side. The patient has food retention in the pyriform sinuses

Note. ECG, electrocardiography; BP, blood pressure

The structures involved in LMI and associated symptoms are provided in Table 1.

Epidemiology

A medullary infarction accounts for approximately 4% of ischemic stroke cases and, in 9 out of 10 cases, is represented by LMI [8]. The average age of patients is 57 years, with a male-to-female ratio of 2:1 [6].

Etiology

Most cases of LMI (46–59%) have atherothrombotic genesis (which explains the male-dominated gender distribution) and are associated with intracranial atherosclerosis and stenosis of the IV verte-bral artery segment. In 13–37% of patients, this syndrome was associated with cerebral microangi-opathy [6, 7, 9]. Vertebral dissection is a significant cause of LMI (2.6-15%), particularly in young patients (Fig. 2). The dissection-related mechanism of stroke is indicated by the presence of head/cervical pain, a mechanical trigger, and the subacute occurrence of symptoms observed in eve-ry 4th case of LMI [10]. Due to neuroanatomy features, LMI is rarely cardioembolic (1.2–5%).

Features of the clinical presentation

The frequency of LMI symptoms, based on an analysis of four large cohorts, is shown in Table 2. In 1 out of 3–4 patients, the affected area extends beyond the lateral parts of the medulla oblongata (more often involving the cerebellum — the PICA basin), which leads to additional symptoms and worsens the short-term prognosis [8, 9].

Sensory impairment

Depending on the involvement of the face/limbs (and trunk), J. Kim et al. (2003) identified five patterns of sensory impairment (observed in 96% of patients): ipsilateral trigeminal hypoesthesia and contralateral hypoesthesia in the extremities/trunk (26%), contralateral hemihypoesthesia (25%), bilateral trigeminal hypoaesthesia and hypoaesthesia in the extremities/trunk (14%), isolated contralateral hypoaesthesia in the extremities/trunk (21%), and isolated trigeminal hypoaesthesia (10%). It is essential to note that approximately 20% of patients experience a gradient or a certain level of sensory disorders, with a greater severity in the lower extremities [6]. A case of isolated con-tralateral impairment of surface sensitivity below

Fig. 2. LMI due to vertebral artery dissection. Female patient, 41 years old. Her medical history includes Wolff-Parkinson-White syn-drome, radiofrequency catheter ablation, and a sinus venosus atrial septal defect. On January 24, 2024, after a long car trip, the patient experienced dizziness, pain in the occipital region, rhinophonia, numbness on the right side of the face, decreased sensitivity, and a burning sensation in the left extremities. For a month, she experienced neck pain; 5 days before admission, she was treated by a den-tist. She presented 2 hours after the onset of the disease. Upon admission, the patient had Horner syndrome on the right (*a*), horizon-tal-torsional nystagmus directed to the left, a positive OLD test on the right, mild dysarthria and dysphagia, decreased pain and tem-perature (to a greater extent) sensitivity in the left half of the body, and a pronounced trunk ataxia. A CT scan of the brain was per-formed, and a pronounced conjugate deviation of the eyes to the right was revealed — RadOLD (*d*). CTA showed occlusion of seg-ments III and IV of the right vertebral artery with the 'peanut shell' sign (hypodense lumen and contrast accumulation in the wall of the artery horizontal segment) (*b*), as well as medial displacement of the right vocal cord, indicating its paresis (*c*). After 3 days, the dysphagia regressed. On Day 5, brain MRI showed right-sided dorsolateral medullary infarction (*d*) and intramural hematoma of segment III of the left vertebral artery as a sign of dissection (*e*).

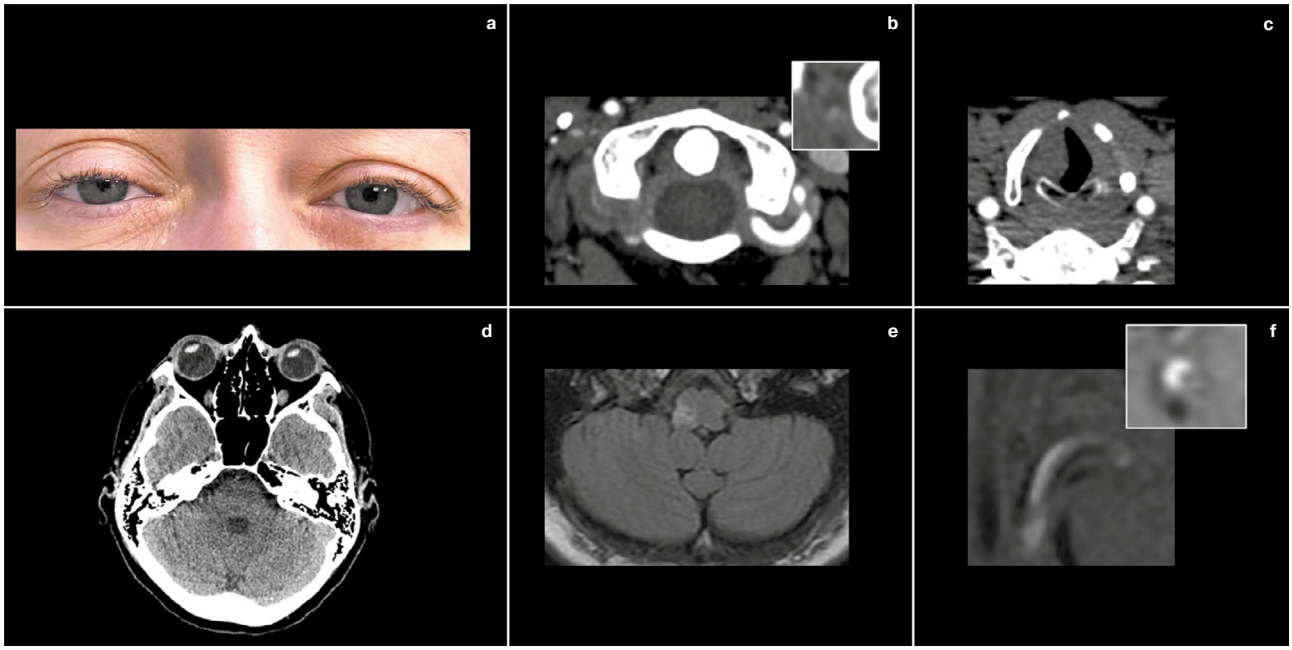


Table 2. Frequency of LMI symptoms, % [6, 7, 9, 11]

Symptom	J. Kim, 2003 (n=130)	W. Kameda, 2004 (n=167)	H. Kang, 2018 (n=248)	L. Tao, 2021 (n=266)
Sensory impairment	96	89	83	72
Horner syndrome	88	72	–	43
Hoarseness	63	–	37	41
Dysphagia	60	57	60	44
Dysarthria	22	75	58	41
Dizziness	57	73	79	76
Nystagmus	56	57	–	21
Ataxia	92	69	85	56
Nausea/vomiting	52	58	–	41
Neck pain/headache	7/52	47	–	21
Hiccups	25	15	20	–
Facial palsy	21	18	32	40
Central respiratory failure	–	2	–	–

the thoracic level has been described [12], as well as only in the contralateral leg [13]. In LMI, isolated thermanalgesia can be observed [14], which must be considered when assessing sensitivity.

A significant proportion of patients with LMI have head and/or cervical pain; its presence may in-dicate both the cause of the disease (ipsilateral persistent cervical pain during vertebral dissection) and the specific features of sensory structure lesions [15]. Cases of LMI manifestation with trigemi-nal neuralgia [16] and trigeminal autonomic cephalgia [17], particularly SUNCT syndrome [18], have been reported.

Oculomotor disorders

Nystagmus. Patients with LMI typically have spontaneous horizontal-torsional nystagmus directed to the intact side [19].

Ocular lateropulsion. Most patients with LMI exhibit lateropulsion of the eyeballs towards the fo-cus (ipsipulsion) upon elimination of gaze fixation, which can be observed in computed tomography (CT), brain MRI (eyeball deviation), the video Frenzel test, or the ocular lateral deviation (OLD) test. In 1969, L. Hagström et al. first described conjugate deviation of eyes towards the LMI focus while blocking gaze fixation by closing the eyes [20]. OLD is currently understood as a

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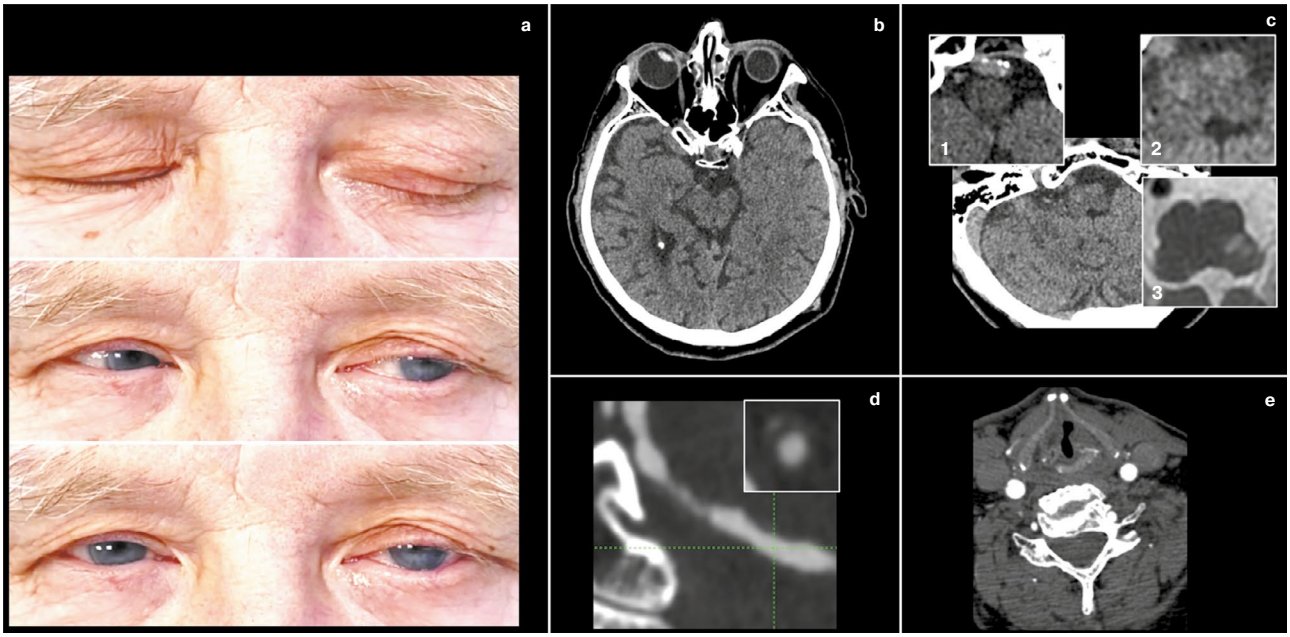
Fig. 3. Clinical case of a typical LMI. Male patient, 61 years old. He has a history of a myocardial infarction in 2021; he is receiving clopidogrel. On February 25, 2024, his wife noticed that the patient had slurred speech; soon, he developed nausea, vomiting, and instability when walking. He presented 6 hours after the onset of the disease with dizziness. Upon admission, the patient had Horner syndrome on the left (*a*, lower image), horizontal-torsional nystagmus directed to the right, a positive OLD test on the left (a), mild dysarthria and dysphagia, decreased pain and temperature (to a greater extent) sensitivity in the right half of the body, and a pro-nounced trunk ataxia. A CT scan of the brain was performed, the forming zone of low density in the lateral parts of the medulla ob-longata on the left was visualized (c2), calcifications in the projection of segment IV of the left vertebral artery (c1), and a pronounced conjugate deviation of the eyes to the left (*b*). CTA revealed pronounced stenosis of segment IV of the left vertebral artery (*d*), as well as medial displacement of the left vocal cord, indicating its paresis (*e*). The next day, dysphagia progressed to severe, and a nasogas-tric tube was placed. After 2 weeks, bronchoscopy with swallowing assessment revealed that grade 1 dysphagia persisted, along with paresis of the upper third of the larynx and the left vocal cord. A month later, an MRI (T2-weighted image) of the brain showed cystic lesions in the lateral parts of the medulla oblongata on the left (c3).



conjugate horizontal deviation of the eyeballs with the eyelids closed, usually towards the focus (ipsipulsion). In some cases, lateropulsion can even be triggered by blinking [21]. To assess OLD, a test is per-formed in which the patient is asked to fix their gaze on the target in front of them, then gently close their eyes for 3–5 seconds. Then, upon the eyes opening, the doctor observes the appearance of a corrective saccade that returns the eyes to the median position (Fig. 3).

According to J. Kattah et al. (2020), OLD occurs in 12% of patients with central acute vestibular syndrome, 40% of patients with LMI, and 11% of patients with pontine infarction. This symptom is most pronounced on Day 2. In acute dizziness, OLD has 100% specificity for the central lesion, as it does not occur in vestibular neuritis. The symptom is usually accompanied by lateropulsion of the trunk; three-quarters of patients cannot sit without support. It must be stressed that in 1/3 of patients with OLD, the infarction focus is not visible on the primary diffusion-weighted (DWI) MRI. Howev-er, the OLD test result correlates with the deviation of the eyes during neuroimaging [22].

It should be noted that minimal lateral deviation can also be observed in vestibular neuritis; how-ever, with a short-time closure of the eyes (no more than 5 s), it does not exceed 5°. A longer closure of the eyes leads to an increase in the deviation, which is seen as a deviation of the eyeballs during neuroimaging [22]. Therefore, the recently proposed VES (Vestibular Eye Sign) radiological test, which demonstrated 89% sensitivity, 75% specificity, and 99% negative predictive value in differen-tiating vestibular neuritis from "non-neuritis" [23], should be interpreted with caution, given its po-tential to yield a positive result in LMI.

To summarize, the combination of ocular ipsipulsion and contralateral spontaneous nystagmus is an important symptom of LMI [24].

Other oculomotor disorders. With lesions of the rostral parts of the medulla oblongata, ipsilateral impairment of the vestibular-ocular reflex can be observed, determined in a video head impulse test (vHIT) [25], which further complicates differentiation with vestibular neuritis. When the medulla oblongata is affected, the subjective visual vertical (in the basket test) is inclined ipsilateral by 7–13° [26].

Coordination and postural disorders

Gait ataxia usually prevails over limb ataxia; more severe symptoms may indicate a caudal loca-tion of LMI [27]. The combination of severe trunk ataxia (inability to sit independently) and OLD is indicative of LMI [28]. The lesion of the lateral parts of the medulla oblongata causes the development of lateropulsion, where the patient feels that an external force pushes them towards the lesion. As a result, the patient may deviate towards an infarction side when standing [29] and occupy an oblique position in the bed [30]. Severe limb ataxia can be observed with a coexisting cerebellar in-farction (PICA basin).

Horner syndrome. When assessing Horner syndrome, it is essential to remember that in bright light, parasympathetic tone is minimal, and sympathetic tone is maximized so that anisocoria may be imperceptible. In the dark, the pupil dilates due to slow, passive sphincter relaxation, resulting in a dilation lag (Fig. 4) [31]. Along with ipsilateral ataxia and contralateral hypoaesthesia, Horner syndrome is included in the clinical triad of LMI proposed by R. Sacco et al. [5].

Bulbar syndrome. Three out of 5 patients with LMI develop dysphagia. Swallowing disturbance is more pronounced in rostral lesions than in caudal [15]. Patients in LMI usually have a pharyngeal swallowing phase, so the Repetitive Saliva Swallowing Test and the Modified Water Swallowing Test are more informative [32]. Approximately half of patients

with LMI who develop dysphagia require nasogastric tube placement.

Hiccups. Hiccups develop in approximately one-third of patients with LMI and are associated with involvement of the dorsolateral region of the middle part of the medulla oblongata, the solitary tract nucleus, the ambiguous nucleus, the reticular formation, the trigeminal nucleus, and their connec-tions [33].

Specific manifestations. In rare cases, LMI can lead to syndrome of inappropriate antidiuretic hor-mone secretion [34], dystrophic ulceration in the trigeminal nerve innervation zone (trigeminal trophic syndrome) [35], dystrophic keratopathy [36], paroxysmal sneezing [37], lateralized change in body surface temperature [38], and secondary cervical dystonia [39].

Opalski syndrome

A rare variant of LMI is Opalski syndrome (described by Polish neurologist Adam Opalski in 1946), which is characterized by ipsilateral hemiparesis associated with damage to the pyramidal tract below the pyramidal decussation [40] (Fig. 5). The syndrome must be distinguished from Ba-binski–Nageotte syndrome, in which the typical pattern of LMI is combined with contralateral hem-iparesis due to involving the pyramidal tract above the pyramidal decussation [41].

Cardiorespiratory disorders

LMI is a "black widow" in vascular neurology since, with such a small size of infarction, a fatal outcome is possible. Death can occur through several mechanisms: dysphagia and aspiration, central hypoventilation, or life-threatening arrhythmias.

The nuclei of the medulla oblongata (n. tractus solitarius, n. dorsalis nervi vagi, n. ambiguus, and the intermediate reticular zone) play an important role in the autonomic regulation of the cardiovas-cular system by modulating sympathetic and parasympathetic activity. In LMI, the inhibition of n. tractus solitarii may be impaired, which causes its disinhibition and an increase in the parasympa-thetic effect. It can lead to bradycardia and asystole (sinus arrest), manifested by syncope, presynco-pe, as well as sudden cardiac death, which may occur in apparently stable patients [42]. According to a study by J. Hong et al. (2013), which included 25 patients with LMI, the presence of a ventral lesion increased the risk of parasympathetic dysfunction by 16 times [43]. Thus, patients with LMI need close monitoring of the heart rhythm, as early detection of conduction disorders can be life-saving (temporary or permanent pacing) [44]. LMI can lead to damage to the respiratory centers rep-resented by three groups of neurons in the brain stem (dorsal and ventral respiratory groups, para-brachial Kölliker–Fuse complex). Involvement of the ventral group of the medulla oblongata leads to central hypoventilation syndrome, a life-threatening disorder characterized by hypoventilation (hypopnea/apnea) during sleep (Ondine's curse) while maintaining voluntary breathing [45]. Meth-ods for diagnosing this syndrome include polysomnography ("gold standard"), as well as monitoring blood gases, specifically pCO2 (hypercapnia) [46]. The pCO2 measurement is mandatory in patients with LMI who have developed impaired consciousness (agitation/decreased consciousness), as this may be associated with hypercapnia [47]. It is important to note that the first manifestations of cen-tral hypoventilation syndrome may be observed after the patient is transferred from the intensive care unit, where respiratory symptoms were not apparent due to the patient's limited sleep (e.g., alarms, ward lights at night, etc.). Therapy options include mechanical ventilation (BiPAP), phrenic nerve stimulation, as well as several pharmacological agents aimed at stimulating intact respiratory neurons by inducing metabolic acidosis (acetazolamide, trazodone, caffeine, clomipramine, etc.) [48].

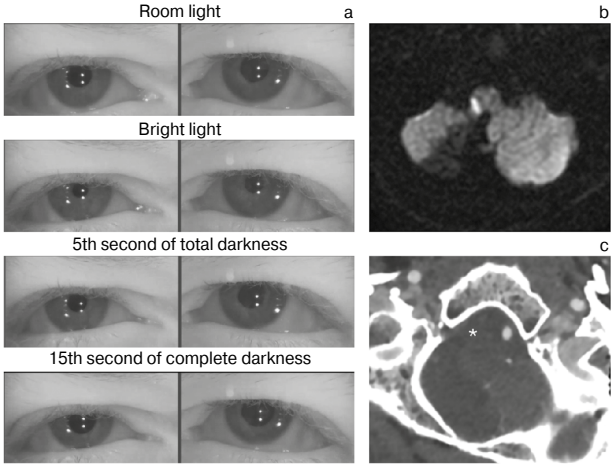
Neuroimaging

CT of the brain has low sensitivity in LMI due to the small size of the infarction and artifacts from the bone structures of the posterior fossa; however, it can give a clue—calcification of the seg-ment IV of the vertebral artery. Brain MRI also cannot be considered a sufficiently informative study since every third or fourth patient with LMI has a false negative result of DWI MRI performed on the first day of the disease. In half of these patients, visualization of the lesion is possible only with the use of thin slices in the coronary view. The probability of detecting the lesion increases when sagittal sections are assessed [49–51]. In patients with LMI and neck pain, it is recommended to lower the scanning frame to capture segments III and IV of the vertebral artery. Detection of sig-nal enhancement in the projection of the concerned artery on the DWI can be an early sign of dissec-tion [52].

When evaluating primary CT or MRI, attention should be paid to the position of the eyeballs: LMI is characterized by ipsilateral conjugate deviation of more than 20° (radiological OLD test); Fig. 6 [53].

Evaluation of CT angiography (CTA) performed from the aortic arch to verify atherosclerotic or dissection stenosis of the vertebral artery ('target' sign and 'peanut shell' sign) can be complement-ed by visualization of the vocal cords (medial displacement of the paretic cord), arytenoid cartilage (anteromedial deviation), pyriform sinuses (enlargement), and soft palate (deviation). CT signs of vocal cord paresis have 100% sensitivity and 80–87% specificity for LMI (see Fig. 6) [54].

Fig. 4. Dynamic anisocoria associated with Horner syndrome in a patient with LMI. Using Frenzel video glasses, pupil dilation lag during a rapid transition from bright light to complete darkness was demonstrated in a patient with LMI (*a* – DWI MRI) due to chron-ic occlusion of segment IV of the right vertebral artery (*c* – CTA, occlusion is indicated by an asterisk).



Diagnostic algorithm

The LMI diagnostic algorithm is shown in Figure 6.

Prognosis

The average NIHSS score on admission is 2, and 3 out of 4 patients have NIHSS scores of 1–4, which does not accurately reflect the actual severity of LMI [8]. To improve the objective assess-ment of neurological deficit in vertebrobasilar stroke, a modified version of the NIHSS, postNIHSS score, can be used, considering trunk ataxia and bulbar syndrome often observed in LMI. One in 5 patients with LMI has a poor functional outcome (mRS>2) and a long-term mortality rate of 7.3% (median follow-up of 3.5 years), with pneumonia and recurrent stroke being the leading causes of death [55]. These findings emphasize the importance of careful clinical evaluation of patients, fo-cusing on the "problem areas" of LMI (such as risk of aspiration and cardiorespiratory disorders), as well as the rapid identification of the etiology of stroke to plan optimal secondary prevention measures. Within the scope of this article, it is not possible to

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Fig. 5. Clinical case of Opalski syndrome. Male patient, 51 years old. He has a long-term history of arterial hypertension and type 2 diabetes mellitus, and in 2018, he had a myocardial infarction. On the evening of December 2, 2022, he experienced dizziness and shakiness while walking. The next day, he noticed weakness in his left leg. The patient was admitted a day after the onset of the first symptoms. His neurological status at admission included intensive horizontal nystagmus directed to the right, a positive OLD test on the left, Horner syndrome on the left (*a*, upper image), mild left-sided hemiparesis (a, lower image), dysarthria, and hiccups. A CT scan of the brain was performed, calcifications in the projection of segment IV of the left vertebral artery were visualized, and a pro-nounced conjugate deviation of the eyes to the left (*b*). CTA revealed pronounced stenosis of segment IV of the right vertebral artery (*c*), as well as medial displacement of the left vocal cord, indicating its paresis (*d*). An MRI performed the next day showed a dorso-lateral medulla infarction on the left extending below the pyramidal decussation (*e*). When the contrast agent was injected, its inten-sive concentric accumulation in the wall of segment IV of the left vertebral artery was found, indicating unstable substenotic atheroma (*f*).

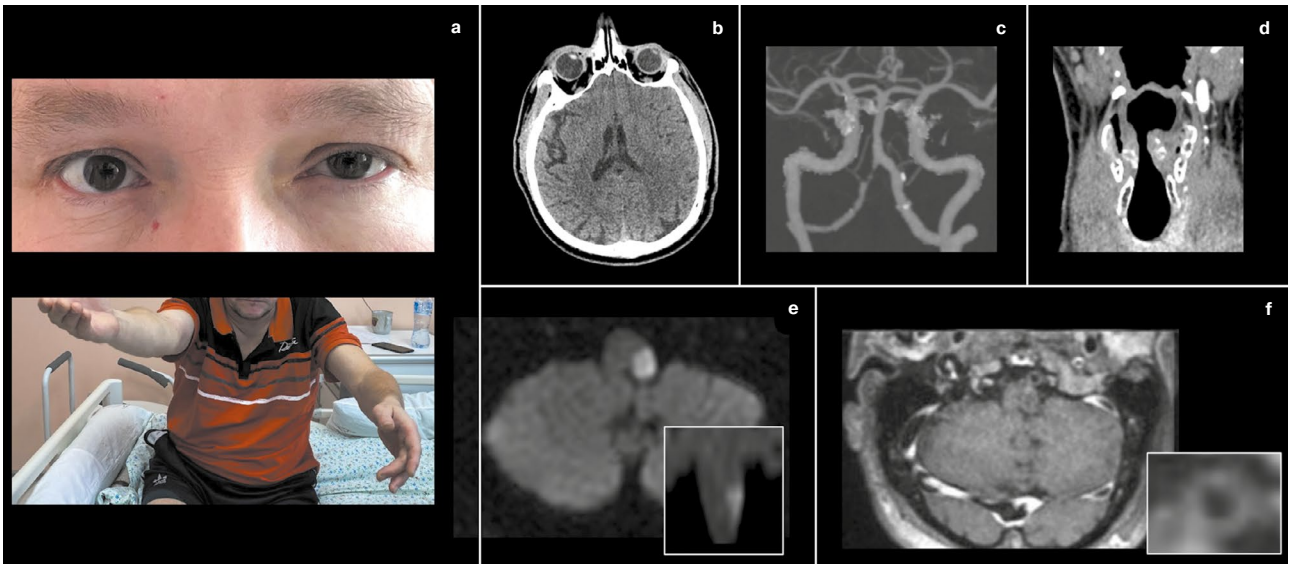
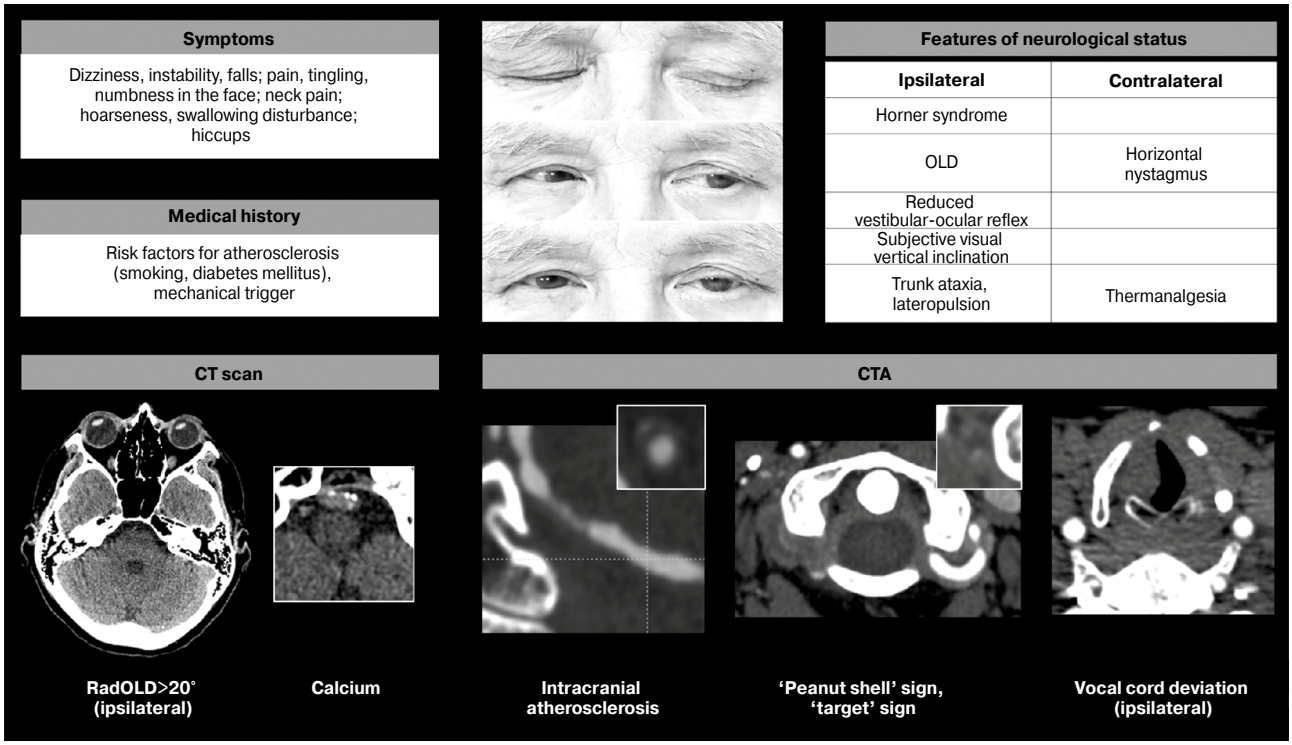


Fig. 6. Algorithm for early diagnosis of LMI.



discuss this issue in detail; however, approaches to managing neurological patients with high cardiovascular risk have been thoroughly discussed elsewhere [56, 57].

Conclusion

The following symptoms may indicate the development of LMI: dizziness, instability, pain, tin-gling, numbness in the face, neck pain, hoarseness of the voice, swallowing disturbance, and hic-cups. When assessing neurological status, Horner syndrome (transition from light to dark), nystag-mus, OLD, trunk ataxia, and thermanalgesia should be actively detected. The analysis of these symptoms is informative regarding the topography of the lesion.

When evaluating a native CT scan of the brain, attention should be paid to the conjugate deviation of the eyeballs and the

presence of calcifications in the projection of segment IV of the vertebral ar-tery. CTA can visualize stenosis of the intracranial segment of the vertebral artery, signs of dissec-tion ('target sign' and 'peanut shell' sing), and also the vocal cord paresis. LMI patients need careful heart rate monitoring and timely diagnosis of central hypoventilation syndrome. The prevalence of atherosclerosis, particularly intracranial atherosclerosis, in the etiology of LMI highlights the need to intensify secondary prevention efforts.

Disclosure of interest. The authors declare that they have no competing interests.

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