Differential diagnosis of ischemic stroke in the arteries of the vertebrobasilar system

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Stroke in the arteries of the vertebrobasilar system is characterized by a variety of nonspecific symptoms, many mimickers, and often atypical clinical presentation, which, together with the low sensitivity of CT and MRI of the brain, leads to incorrect and untimely diagnosis. This article addresses in detail the issues of differential diagnosis of this disease with Guillain–Barre syndrome, myasthenic crisis, central pontine myelinolysis, multiple sclerosis, Wernicke encephalopathy, vestibular neuronitis, Meniere's disease, and vestibular migraine.

Keywords: *stroke in the arteries of the vertebrobasilar system; clinical presentation; differential diagnosis.*
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Stroke in the arteries of the vertebrobasilar system (VBS) accounts for 20–25% in the structure of ischemic stroke and is often life-threatening. Stroke in the VBS arteries is characterized by a wide range of nonspecific symptoms, many imitators and often an atypical clinical presentation, which often leads to late or incorrect diagnosis. On the other hand, with a given location of stroke, there are a number of fairly characteristic signs, knowledge of which helps to make the correct diagnosis. The difficulty of diagnosing stroke in the VBS arteries is also associated with the low sensitivity of CT and MRI of the brain, especially at the early stages [1]. In the framework of this article-lecture, we set out to present modern data on the problem of differential diagnosis of stroke in the arteries of the VBS.

Clinical presentation

It is known that stroke in the arteries of the VBS remains undiagnosed at the emergency department level three times more often than stroke in the carotid system. The risk of misdiagnosis is especially high in the presence of headache, dizziness, nausea/vomiting, mild symptoms or complete regression of symptoms, as well as in young patients and women [1–4].

According to the results of an analysis of data from two large registries (New England Medical Center Posterior Circulation Registry, n=407, USA; Chengdu Stroke Registry, n=302, China), the majority of patients with stroke in the arteries of the VBS have nonspecific symptoms in terms of diagnosis and location: dizziness – 19–47%, headache – 18–28%, nausea/vomiting – 27–34% [5, 6]. Headache is more common in women and is associated with the cardioembolic subtype of stroke, localization of the infarction in the cerebellum and mild neurological deficits [7, 8].

The majority of patients with stroke in the VBS arteries are characterized by the following focal symptoms: hemiparesis – 41–54%, dysarthria – 26–31%, paresis of facial muscles/tongue muscles – 31–41%, hemihypesthesia – 36%. Ataxia is observed in 31–32% of patients, nystagmus – in 12–24%, diplopia – in 7%, impaired consciousness (considered as a focal symptom of damage to the ascending activating reticular system) – in 5–10%. Tetraparesis (often asymmetric) occurs in 8% of patients, hemianopsia – in 4%, Horner's syndrome – in 4%, motor alternating syndromes – in 4%, sensory alternating syndromes – in 3% [5, 6].

Despite the rarity of alternating syndromes in the clinical picture of stroke in the arteries of the VBS, they are extremely significant, since their timely identification significantly shortens the path to the correct diagnosis. Alternating syndromes are a combination of symptoms that develop due to the close arrangement of structures in the brain stem. The most commonly observed syndromes are dorsolateral medullary syndrome (Wallenberg–Zakharchenko), inferior ventral pontine syndrome (Millard–Gubler), inferior medial pontine syndrome (Foville), ventral mesencephalic syndrome (Weber) and dorsal mesencephalic syndrome (Parinaud) [9] (Fig. 1, *a–c*).

It is important to note that a stroke in the arteries of the VBS occasionally causes symptoms characteristic of a stroke in the carotid arteries, such as aphasia and neglect, which are associated with damage to the thalamus, temporal and parietal lobes (branches of the posterior cerebral arteries). On the other hand, dysarthria and homonymous hemianopsia, usually associated with stroke in the arteries of the VBS, cannot be considered reliable signs, since they are also observed in a stroke in the carotid system. Typical of a stroke in the posterior cerebral artery is isolated loss of visual fields [6, 9, 10].

Thus, the clinical picture of a stroke in the arteries of the VBS can be represented in the form of an inverted pyramid (Fig. 2). Obviously, the accuracy and speed of diagnosis will depend on the symptoms of what level of the "pyramid" the doctor is faced with: the presence of indicator signs will immediately lead to a correct diagnosis, while nonspecific complaints and symptoms will require differential diagnosis.

Differential diagnosis

Let's discuss the most difficult situations encountered in clinical practice.

Flaccid tetraparesis and brainstem dysfunction (bulbar syndrome, tongue muscle paresis, respiratory disorders). It can develop with a bilateral infarction of the medulla oblongata, which accounts for only 1% in the structure of stroke in the VBS arteries and is associated with occlusion of the anterior spinal artery (usually against the background of atherosclerotic stenosis of the vertebral artery in the V_4 segment). On MRI, the shape of the infarction resembles the heart (see Fig. 1) [11–14]. The described clinical presentation requires differential diagnosis with Guillain–Barre syndrome, which is characterized by progression of symptoms for more than a day (peak – 2 weeks), distal paresthesias at the onset (with or without pain), ascending tetraparesis, areflexia, absence of pathological reflexes; impaired photoreactions of the pupils and bilateral paresis of facial muscles may also be observed. Motor or sensorimotor polyneuropathy is typical according to electroneuromyography, as well as an increase in protein levels in the cerebrospinal fluid from the 2nd week of the disease [15]. Differential diagnosis with myasthenic crisis should also be carried out. Attention should be paid to the history of myasthenia gravis and provoking factors (infectious disease, taking antibiotics and some other medicines, aspiration, surgery, pregnancy, sleep deprivation, physical and emotional stress). Muscle weakness depends on activity (it usually increases in the evening), characterized by weakness of the neck muscles ("drooping head", "drooping jaw"), bilateral ptosis, entry of food and liquid into the nose when swallowing, as well as bilateral paresis of facial muscles [16]. Positive fatigue and ice tests, absence of pathological reflexes and response to proserin indicate myasthenia gravis, which is confirmed by the electromyographic decrement test, but this is not often available in emergency settings. Another cause of the development of the clinical picture under discussion may be osmotic demyelinating syndrome, also known as central pontine myelinolysis. The disease occurs in 2.5% of intensive care unit patients; 30–78% of cases are associated with hyponatremia and/or its rapid correction. Other causes include chronic alcoholism, cirrhosis of the liver, nutritional deficiency, renal failure, burns and tumors. Exposure to the trigger usually precedes symptoms by 1 to 14 days. Symptoms depend on the location of demyelination. The most common manifestation is encephalopathy with impaired levels of wakefulness/consciousness, delirium, memory and attention impairment. Central pontine myelinolysis with a neuroimaging picture of total damage often causes development of locked-in syndrome. Dysarthria, dysphagia, pupillary and oculomotor disorders and suppression of tendon reflexes are also characteristic. The diagnosis is confirmed by MRI of the brain, demonstrating the typical localization of demyelination in the central parts of the brain pons – the "bat wing" or "Trident of Neptune (Poseidon)" symptom (see Fig. 1) [17, 18].

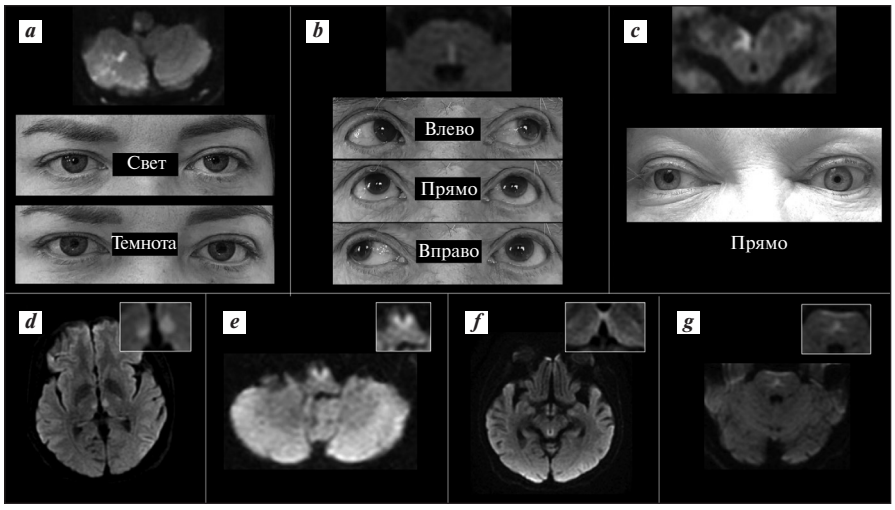

Fig. 1. *Clinical and radiological examples of stroke in the arteries of the VBS and similar conditions*
а – Horner syndrome on the right with dorsolateral medullary infarction due to dissection of the V_4 segment of the hypoplastic vertebral artery; б – internuclear ophthalmoplegia during myocardial infarction involving the medial longitudinal fasciculus on the left; в – right oculomotor nerve dysfunction in Weber syndrome due to ventral mesencephalic infarction on the background of atherosclerotic stenosis of the distal part of the basilar artery; г – bilateral thalamic infarctions due to occlusion of the Percheron artery; д – medial medullary infarction with MRI "heart" sign due to occlusion of the anterior spinal artery; е – MRI image of Wernicke's encephalopathy: limited diffusion around the aqueduct of Sylvius, in frame – "hockey stick" sign; ж – MRI image of osmotic demyelination syndrome (central pontine myelinolysis) – "trident" sign formation. MRI images in all figures are shown in diffusion-weighted imaging mode

Bulbar syndrome ± other "stem" symptoms. As part of vascular pathology, this syndrome can develop with medial [19] and lateral [20] medullary infarction (rarely); usually combined with other symptoms. An alternative diagnosis is myasthenia gravis, which is associated with the presence of autoantibodies to muscle-specific tyrosinekinase (MuSK). This form is observed in 5–8% of patients, usually in young women, and is characterized by bulbar syndrome in combination with neck muscle weakness, respiratory failure, ophthalmoparesis and ptosis [21, 22]. A rare acute bulbar "+" variant of Guillain–Barre syndrome should also be excluded. Young age of the patients and previous infection can be indicative of the diagnosis. Nine out of 10 patients develop ophthalmoplegia, three out of five develop prosoparesis, half develop ataxia, and the same number develop protein-cell dissociation in the cerebrospinal fluid [23, 24].

Internuclear ophthalmoplegia (INO). The key sign of INO is impaired adduction of the eye on the side of the affected medial longitudinal fasciculus, which is usually combined with nystagmus when abducting the opposite eye (see Fig. 1). Infarcts involving the medial longitudinal fasciculus and some adjacent structures may be manifested in a number of oculomotor disorders, referred to as "INO-plus." Thus, combined damage to the reticular formation and/or the center of horizontal eye movement can lead to the development of "one and a half syndrome", which is manifested in concomitant gaze paralysis in one direction and weakness of the adductor muscle when looking in the other direction; when the eye is abducted, monocular nystagmus is observed. In some patients, this clinical picture is combined with prosoparesis due to damage to the nucleus or fibers of the facial nerve. A rare variant of the syndrome is bilateral INO [25]. Stroke is the cause of two out of five cases of INO. More often, the syndrome develops with an anteromedial pontine infarction, rarely as part of Wernicke syndrome with a caudal paramedian mesencephalic infarction. This syndrome is represented by bilateral INO in combination with bilateral cerebellar dysfunction (V-pattern lesion on MRI) and is associated with occlusion of the perforating branches of the main, superior cerebellar or posterior cerebral artery [12, 25, 26]. In one third of patients, INO is associated with multiple sclerosis (the most common saccade disorder in this disease) [27]. History of episodes of neurological dysfunction, young/middle age of onset and radiological signs are key factors in the differential diagnosis during emergency hospitalization of the patient.

Acute attack of dizziness. Dizziness is one of the most common symptoms of cerebellar infarction. Every tenth patient with cerebellar infarction experiences isolated dizziness. Four out of five patients have an infarct in the territory of the medial branches of the posterior inferior cerebellar artery with involvement of the nodule; less often, dizziness occurs with a stroke in the territory of the superior or anterior inferior cerebellar artery. In the latter case (with an infarct in the territory of the labyrinthine artery), acute cochleovestibular syndrome develops [28]. Although stroke in the VBS arteries often manifests as dizziness in combination with focal neurological symptoms, small infarcts involving the inferior cerebellar peduncle, ganglion and vestibular nuclei can cause isolated dizziness [29, 30]. The primary differential diagnosis of acute dizziness is within the framework of acute vestibular syndrome, which, using the HINTS+ algorithm or its modifications, is further divided into central and peripheral [31, 32]. The central variant of the syndrome, usually associated with damage/dysfunction of the cerebellar structures, is characterized by multidirectional gaze-induced nystagmus, vertical nystagmus, torsion nystagmus, negative head rotation impulse test (HRIT), as well as severe trunk ataxia [33]. The presence of the latter is specific for cerebellar infarction [34].

The peripheral variant of acute vestibular syndrome is manifested in unidirectional horizontal torsional nystagmus, which intensifies with the removal of visual fixation and obeys Alexander's law, in combination with a positive HRIT on the side opposite to the direction of the fast phase of nystagmus (test positive on the affected side) [35]. The main cause of acute peripheral dizziness is vestibular neuronitis, a disease associated with selective inflammation (of viral or infectious-allergic origin) of the vestibular nerve. Neuronitis manifests itself as a sudden and prolonged attack of vestibular dizziness, accompanied by nausea, vomiting and imbalance, which, however, does not reach the degree of astasia/abasia. The disease may be preceded by a respiratory viral infection [33]. Sometimes, several hours or days before the development of an acute vestibular attack, patients experience short-term episodes of dizziness or instability, which also requires differential diagnosis with transient ischemic attack [36]. Hearing with neuronitis does not decrease if there are no concomitant diseases or acute labyrinthitis / labyrinthine infarction. There are no symptoms of damage to the brainstem or other parts of the brain. Rarely, infarction with selective damage to the vestibular nerve entry into the medulla oblongata, vestibular nuclei, dorsolateral pons, or cerebellar flocculus may present with dizziness mimicking vestibular neuronitis (pseudoneuronitis syndrome) [35]. A rapid regression of both dizziness and nystagmus is also characteristic, while with neuronitis spontaneous nystagmus persists for a long time (especially when visualized using Frenzel glasses or the VideoFrenzel system). Minimizing errors in the differential diagnosis of peripheral acute vestibular syndrome is achieved using quantitative tests – videonystagmography and video-HRIT [37].

Another disease that requires differential diagnosis within the framework of peripheral acute vestibular syndrome is Meniere's disease. The diagnosis of Meniere's disease is based on the presence of two or more attacks of vestibular vertigo lasting from 20 minutes to 12 hours, sensorineural hearing loss at low and medium frequencies in one ear, auditory disturbances varying in intensity, such as noise, feeling of fullness in the ear in the absence of other causes of dizziness [38]. The problem of diagnosing the disease in emergency neurological care is that the patient often arrives with severe vestibular vertigo and does not complain of hearing loss or tinnitus. Therefore, assessing the dynamics of nystagmus is extremely important. Initially, a fast horizontal irritative nys-

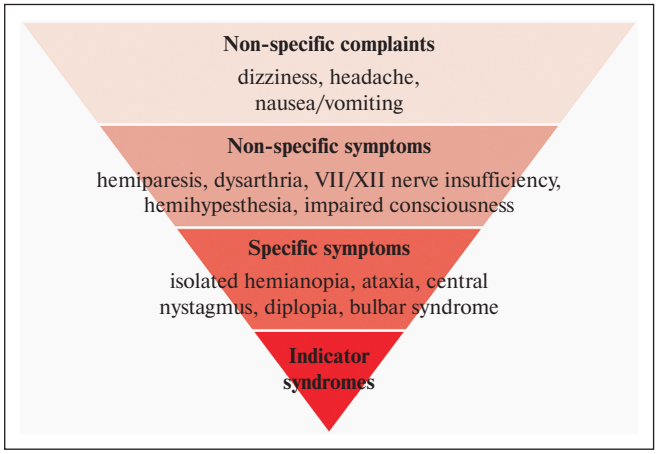

Fig. 2. *Clinical picture of stroke in the arteries of the VBS. Indicator syndromes (Wallenberg–Zakharchenko, Dejerine, Millard–Gubler, Foville, Weber, Benedict, Parinaud, Anton syndromes, Percheron artery syndrome, internuclear ophthalmoplegia, "one-and-a-half" syndrome, "apex" of the basilar artery syndrome, acute cochleovestibular syndrome) indicate a high probability of stroke in arteries of the VBS*

tagmus is observed, directed towards the affected ear (a positive HRIT will also be observed there), after which a reversion occurs with the development of paralytic nystagmus with a fast component towards the healthy ear. In the final phase, recovery nystagmus occurs, again directed towards the lesion [39].

The presence of central acute vestibular syndrome in a patient also does not allow us to unambiguously establish a stroke in the arteries of the VBS. First of all, a differential diagnosis of stroke and Wernicke encephalopathy is necessary, a disease that requires fundamentally different treatment. Wernicke encephalopathy develops as a result of thiamine deficiency in chronic alcoholism, anorexia nervosa and other conditions leading to malnutrition. An important risk factor is vomiting during pregnancy. The classic triad of symptoms (encephalopathy, oculomotor disorders and ataxia) is observed in less than a third of patients. The disease is characterized by horizontal (less often vertical) gaze-evoked nystagmus, which is the earliest manifestation of the disease. Vertical nystagmus is often observed: initially spontaneously upbeating, then changing direction to the opposite, depending on the direction of gaze, convergence and vestibular stimuli. The development of downbeating nystagmus in combination with trunk ataxia indicates a chronic stage of the disease. There may also be a marked bilateral decrease in the horizontal (but not vertical) vestibulo-ocular reflex. The next most common ophthalmological manifestation of Wernicke encephalopathy is bilateral paresis of the external rectus muscles of the eye; concomitant horizontal gaze palsy is less common. The disease is characterized by a typical MRI pattern: T2 hyperintensity and limited diffusion on DWI around the aqueduct of Sylvius and the third ventricle, medial thalamus (hockey stick sign), dorsal medulla, quadrigeminal plate, and mammillary bodies (see Fig. 1) [40–42].

Significant diagnostic difficulties can arise if the patient has isolated positional nystagmus. If there are signs of atypicality (isolated positional nystagmus changing direction, inconsistency of nystagmus characteristics with the presumably involved semicircular canal, absence of a latency period, persistence and lack of response to repositioning maneuvers), cerebellar infarction involving the flocculus or nodule should first be excluded [43].

When excluding the causes of central vertigo described above, it is advisable to think about the presence of vestibular migraine in the patient, which is the most common episodic vestibular disorder, characterized by an extremely variable course. When collecting anamnesis in patients with episodic vertigo, attention should be paid to vestibular symptoms (spontaneous, positional, visually induced and head movement-induced vertigo), cochlear manifestations, as well as the presence and characteristics of headache and related phenomena (auras, photo- and phonophobia). When assessing the neurological and vestibular status at the time of an attack, a detailed analysis of positional nystagmus is important to determine its typicality or atypicality; in the interictal period, an assessment of nystagmus induced by hyperventilation, head shaking, and vibration can also be informative [44].

Depression of consciousness. This symptom in a patient with cardiovascular risk factors first of all requires the exclusion of the basilar artery occlusion. Embolic occlusion, which usually develops against the background of atrial fibrillation, leads to the development of the "top of the basilar artery syndrome" described by L.R. Caplan [45] and accounting for 8.5% in the structure of stroke in the arteries of the VBS. The syndrome often manifests itself as depression of consciousness to the level of coma, so the patient may be admitted to the hospital on artificial ventilation with a diagnosis of "coma of unknown origin" (Fig. 3), which requires mandatory emergency neuro- and angiovisualization. When examining a patient in a coma, pupillary and oculomotor disorders (anisocoria, miosis, strabismus/deviation of gaze, lack of photoreaction of the pupils with intact corneal reflexes), pathological foot reflexes, lateralization of the motor response when pressing on the sternum may indicate a stroke. Also, patients with the top of the basilar artery syndrome are characterized by behavioral disturbances (dream-like behavior), vivid hallucinations (Lhermitte peduncular hallucinosis), cortical blindness / Balint syndrome (optic ataxia, impaired voluntary eye movements while reflexes are preserved, simultaneous agnosia), gaze paresis (more often vertical), hemi/tetraplegia and ataxia [9, 45, 46]. Percheron artery syndrome (bilateral thalamic infarcts involving the medial parts of the midbrain), also characterized by gaze paresis (usually vertical) and cognitive/behavioral impairments [47] (see Fig. 3) can lead to depression of consciousness (usually to the level of somnolence).

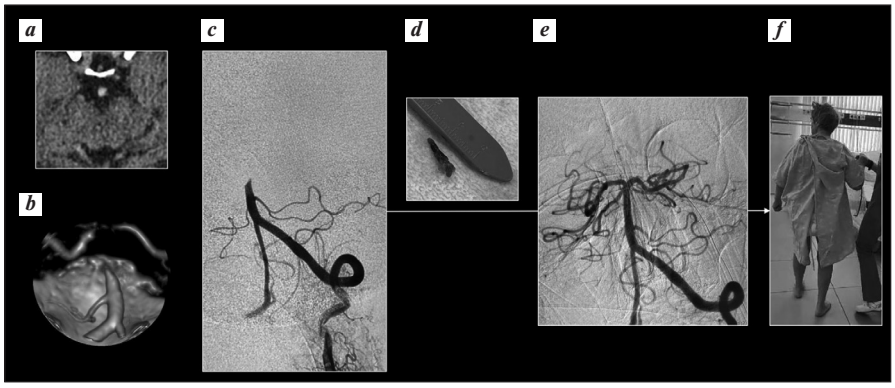

Fig. 3. *Clinical example of "apex" of the basilar artery syndrome. A 74-year-old female patient with arterial hypertension went to the bathroom in the morning, relatives heard her scream, and after opening the door, they found the patient unconscious on the floor. An ambulance was called, the patient was put on ventilation and taken to the hospital in a state of sedation and myoplegia. An initial CT examination of brain without contrast (a) revealed a symptom of hyperdense basilar artery. CT angiography (б) confirmed the presence of occlusion of the distal basilar artery. A similar picture was obtained on selective cerebral angiography (в). The embolus was aspirated (г), and blood flow in the main basilar artery was restored (д). The next morning, the patient was upright again, and her neurological status was normal (е). The search for the cause of the stroke revealed atrial fibrillation, and direct oral anticoagulant was prescribed on day 3 for stroke secondary prevention*

Conclusion

Thus, a stroke in the VBS arteries is characterized by an extremely variable clinical presentation. Despite the fact that most patients have symptoms that are nonspecific with respect to the location of the lesion, this type of stroke can be characterized by syndromes, recognition of which significantly speeds up the diagnosis. The low information content of neuroimaging methods at the early stages of the disease, coupled with the low specificity of the clinical picture, determines the need for differential diagnosis of stroke in the arteries of the VBS with a wide range of diseases, such as Guillain–Barre syndrome, myasthenia gravis, central pontine myelinolysis and multiple sclerosis. Particular difficulties arise when the patient has isolated dizziness. In this case, it is necessary to differentiate stroke in the arteries of the VBS from vestibular neuronitis, Meniere's disease, vestibular migraine and Wernicke encephalopathy. Such manifestations of stroke in the arteries of the VBS, as depression of consciousness (with occlusion of the top of the basilar artery or Percheron's artery) or positional nystagmus, can cause late diagnosis of stroke, and therefore are considered "chameleons" of stroke. There is no doubt that clinical differential diagnosis continues to play a key role in the management of patients with stroke in the VBS arteries.

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