The syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL): a description of three patients

Kulesh A.A.[1, 2], Starikova N.L.[1, 2], Drobakha V.E.[1, 2], Brokhin L.Yu.[1, 2], Chubarov A.S.[1, 2]

[1]Acad. E.A. Vagner Perm State Medical University, Ministry of Health of Russia, Perm; [2]City Clinical Hospital Four, Perm

[1]26, Petropavlovskaya St., Perm 614990, Russia; [2]2, Kim St., Perm 614107, Russia

Three clinical cases of the syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) are first described in Russian literature. The patients were young (aged 30–35 years), had symptoms characteristic of the prodromal period of infections. In all the patients, the disease started with intense headache, followed by focal neurological symptoms: aphasia and hemihypesthesia in all cases and confusion with psychomotor agitation in two cases. All the three patients showed spontaneous recovery within 2–3 days. Perfusion computed tomography, magnetic resonance imaging, and electroencephalography are compared in one of the cases. The differential diagnosis of HaNDL with acute cerebrovascular accident, herpetic encephalitis, epilepsy, and migraine is discussed.

Keywords: *the syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL); perfusion computed tomography, magnetic resonance imaging, and electroencephalography.*

Contact: *Aleksey Aleksandrovich Kulesh;* ***aleksey.kulesh@gmail.com***

For reference: *Kulesh AA, Starikova NL, Drobakha VE, et al. The syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL): a description of three patients. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2020;12(4):65–72.* ***DOI:*** *10.14412/2074-2711-2020-4-65-72*

Syndrom of transient headache with neurologic deficits and cerebrospinal fluid lymphocytosis (CSF) (Headache with neurologic deficits and CSF lymphocytosis, HaNDL) it is a rare benign, self-resolving disease characterized by recurrent episodes of migraine-like headache combined with focal neurological symptoms and/or confusion [1, 2].

In 1981 J.D. Bartleson et al. [3] first described seven patients with episodes of headache accompanied by neurological deficits and CSF lymphocytosis. In 1995, based on the analysis of 7 own and 33 previously described cases, M. J. Berg and L. S. Williams [4] proposed the term HaNDL and its diagnostic criteria, which included: severe headache, transient episodes of neurological deficit (each no more than 3 days), CSF lymphocytosis (16–350 white blood cells, at least 86% of mononuclear cells, mainly lymphocytes) and spontaneous recovery (within 3 months). Additional criteria were: increased protein levels in the CSF, increased opening pressure, transient non-epileptiform changes on the electroencephalogram (EEG), and viral prodrome or fever. In 1997, F. Gomez-Aranda et al. [5] presented a description of the largest series to date, which included 50 patients with HaNDL. In total, more than 100 cases of the disease have been described in the world, but it is assumed to have a higher prevalence – about 0.2 cases per 100,000 population [1, 6].

In the International classification of headaches third revision (ICHD-3, 2018), HaNDL syndrome is described in section 7.3.5, and its diagnostic criteria include:

A. migraine-like headache Episodes that meet criteria B and C;
B. Both of the following points:
   1. Accompanied or preceded by at least one of the following neurological disorders lasting more than 4 hours:
      a) hemiparesthesia,
      b) dysphagia,
      c) hemiparesis.
   2. Associated with lymphocytic pleocytosis in the liquor (>15 cl/mcl) in the absence of an obvious etiology.
C. the Causal relationship between A and B is confirmed by at least one of the following:
   1. Headache and neurological deficit developed or significantly increased simultaneously with CSF pleocytosis or caused its detection;
   2. Headache and transient neurological deficit significantly decreased in parallel with the decrease in CSF pleocytosis;
D. there are No other explanations for the existing symptoms [7].

This article describes three clinical cases of HaNDL for the first time in the Russian literature. We observed patients in the period from 2015 to 2020 in the neurological Department of the regional vascular center of the clinical hospital (CH) No. 4 in Perm.

Clinical case №1

The patient*, 30 years old, on July 4, 2017, had diarrhea without an increase in body temperature. On July 7, in the morning, there was an intense headache (up to 9 points on the 10-point visual analog scale, VAS) with nausea, vomiting, photophobia, drowsiness and speech disorders (according to her husband, she spoke like a foreigner). The afatic disturbances lasted about two hours. An ambulance team was called, and the patient was taken to the primary vascular Department with suspicion of acute cerebrovascular accident. Computer tomography (CT) of the brain was performed, no structural changes were detected. Intravenous thrombolytic therapy was not performed. To exclude meningoen-*

cephalitis, a lumbar puncture was performed, and a cytosis of 81 cl/mcl (98% of lymphocytes) was detected, with a protein content of 0.41 g/l.

According to the results of the examination, the patient was sent to an infectious diseases hospital on the same day with suspected serous meningitis, where she stayed for three days. Repeated lumbar puncture (July 10) revealed a cell count of 228 cl/mcl (99% lymphocytes). The concentration of protein was 1.4 g/l, glucose – 3.6 mmol/l. The analysis for the presence of antibodies to the tick-borne encephalitis virus and ixodic tick-borne borreliosis showed a negative result. The patient received Ceftriaxone. She was transferred to the neurological Department of clinical hospital (CH) No. 4 in Perm for further examination and treatment. Upon admission, she complained of moderate diffuse headache; right-sided hemihypesthesia was recorded in the neurological status. There was no meningeal syndrome. The patient was prescribed acyclovir at a dose of 30 mg/kg per day (the patient's weight is 64 kg) and dexamethasone at a dose of 0.15 mg/kg, which the patient received for 3 days.

On the next day of treatment in the neurological Department, the headache significantly decreased, but the aching pain in the left frontotemporal area remained. General clinical and biochemical blood tests did not have significant deviations.

The CSF analysis of July 11 showed a cytosis of 66 cl/mcl (95% of lymphocytes), a protein concentration of 1.79 g/l, and glucose – 3.7 mmol/l. CSF analysis from July 17: cytosis 34 cl/mcl (94% of lymphocytes), protein content 0.76 g/l, glucose 2.6 mmol/l. The DNA of herpes simplex virus (HSV) type 1 and 2, tick-borne encephalitis virus, Borrelia burgdorferi were not found in the CSF. Polymerase chain reaction (PCR) to enterovirus RNA is negative. Serological tests for human immunodeficiency virus (HIV), hepatitis B and C, and syphilis were negative.

According to magnetic resonance imaging (MRI) of the brain, performed on July 11, there were no signs of focal damage to brain structures. The patient was discharged after a week with complete regression of headache.

Clinical case №2

***The patient**, 35 years old, 3 weeks before admission to the hospital noted the appearance of diffuse headaches (6–7 points on VAS), periodically accompanied by a decrease in the sensitivity of the right half of the body. Stopped cephalgia with non-steroidal anti-inflammatory drugs (NSAIDs). On June 13, 2016, her sister noticed that the patient began to behave inappropriately, did not enter into speech contact. Sister called the ambulance team, which delivered the patient to the CH №4 in Perm with suspicion of acute violation of cerebral circulation.*

At the time of admission, she was clearly conscious, but verbal contact was impossible due to sensorimotor aphasia. Meningeal syndrome was not detected, cranial nerves are intact, motor functions are not impaired. It was not possible to assess the sensitivity. The severity of neurological deficits on the national institutes of health's stroke scale (NIHSS) was 9 points. A contrast-free CT scan of the brain was performed immediately, and no macrostructural changes were visualized.

Intravenous thrombolysis with Alteplase was initiated, against which the patient developed psychomotor agitation (Richmond scale of agitation and sedation, RASS +3), and after 30 minutes the drug was discontinued. To exclude hemorrhagic transformation, repeated CT of the brain was performed, and no pathology was detected. Diazepam was introduced, and Propofol sedation was initiated. Against the background of stop sedation, neurological status was assessed every 4 hours, and psychomotor agitation remained. On July 14, a lumbar puncture was performed, cytosis was 11 cl/mcl, 100% of lymphocytes, protein concentration – 0.75 g/l, glucose – 4.7 mmol/l. On the same day, an MRI of the brain was performed, which did not reveal any significant abnormalities. The patient was prescribed acyclovir at a dose of 30 mg/kg per day and dexamethasone at a dose of 0.15 mg/kg.

On July 15, sedation was canceled. During the examination, the patient complained of moderate pressure pain in the occipital region, was clearly conscious, and was comprehensively oriented. Speech disorders were not observed. Otherwise, the neurological status was also unchanged. On June 16, repeated lumbar puncture was performed, the cytosis was 71 cl/mcl (93% of lymphocytes), the protein concentration was 0.26 g/l. No complaints, neurological status within normal limits.

On July 17, a negative result of HSV type 1 and 2 PCR was obtained, which allowed to cancel therapy with acyclovir and dexamethasone. A negative result of PCR and serological tests for tick-borne encephalitis virus and ixodic tick-borne borreliosis was obtained. Viral hepatitis and HIV were not detected in the patient.

On June 23, the final lumbar puncture was performed, the cytosis was 41 cl/mcl (98% of lymphocytes), the protein content was 0.2 g/l. The patient was discharged with complete regression of neurological deficit.

Clinical case №3

***The patient**, 30 years old, has been suffering from migraines with visual aura since the age of 22. Approximately twice a month, attacks of intense (up to 9–10 points on VAS), diffuse, pressing cephalgia with photo – and phonophobia, without nausea and vomiting, lasting 5–6 hours, which are preceded by loss of visual fields (more often on the right). He stopped an attack with help of NSAIDs or triptans.*

Since April 9, 2020, he began to worry about atypical headaches: diffuse with initiation in the neck, of a pulsating nature, about 5 points on VAS, without photo-and phonophobia, nausea, vomiting and aura symptoms. He took NSAIDs with a positive effect. The next day, similar cephalgia resumed, the patient noted an increase in body temperature to 37, 1 ℃ in combination with a slight runny nose. The following days were disturbed by the indicated headache, General weakness, and an increase in body temperature to a maximum of 37.4 ℃.

On the morning of April 13, after waking up, the patient suddenly developed a pain in the neck, which quickly turned into a diffuse headache, pulsating, with an intensity of up to 9 points on VAS, without photo-and phonophobia, nausea and vomiting. After 15 minutes, there was numbness in the right leg, which quickly spread to the right half of the torso, arm and cheek; then the patient noticed weakness in the right limbs and was unable to make verbal contact with the mother (motor aphasia).

Accompanied by a friend, he went to the primary vascular Department at the place of residence, where he was examined by a neurologist, and a CT scan of the brain was performed. At the time of examination, the headache has significantly decreased, focal neurological symptoms are not recorded, except for a slight agitation of the patient, and he was released home. Returning home, the patient went to bed, but after a while woke up in a state

of disorientation and psychomotor agitation. An ambulance team was called, taken to another primary vascular Department, where a CT scan of the brain was performed again (also without signs of pathology) and hospitalized in the intensive care unit, and later transported to the regional vascular center of CH №4 in Perm. Delivered in a state of light sedation against the background of Propofol administration, did not enter into verbal contact, did not follow commands, made inarticulate sounds, moaned. Was fixed, when shifting to the table CT struggled with the medical staff, tried to get up. No meningeal symptoms were detected. Pupils equal, mydriasis, of photoreactive saved. Other cranial nerves are intact. According to the degree of resistance, it was possible to conclude that the muscle strength was preserved, although the patient used less of his right arm.

Contrast-free CT of the brain (Fig. 1 a) did not reveal any changes. CT angiography (arteries and veins are passable), as well as CT perfusion (Fig. 1 b, c) were performed to exclude acute disorders of cerebral circulation. According to the latter data, areas of decreased cerebral blood flow rate (CBF) and increased transit time of contrast agent (MTT) in the left temporal region were recorded. MRI of the brain was performed (Fig. 1 d, e, f), the quality of which was low due to the patient's motor activity. However, there was no restriction of diffusion in the brain substance, no significant deviations from the venous vessels on the SWAN MRI-sequence were detected, but a zone of light hyperintensivity of the left temporal lobe cortex was visualized, corresponding to the area of hypoperfusion on CT.

The patient was hospitalized in the intensive care unit, and a lumbar puncture was performed immediately. The pressure was high, and the CSF was transparent. CSF analysis revealed a cytosis of 64 cl/mcl (90% of lymphocytes), a protein of 3.9 g/l.

Therapy with acyclovir at a dose of 30 mg/kg per day (the patient's weight is 120 kg) and dexamethasone 10 mg 4 times a day was started. Psychomotor agitation persisted, so continued sedation with propofol. The neurological status was unchanged at night, and there was no verbal contact.

In the morning, the patient could answer simple questions in monosyllables («yes» or «no»), pronounce his name incorrectly («Takatoliy» instead of «Anatoly»), and there were no motor disorders. When the sedation decreased, he tried to get up. An EEG was performed (against the background of dexmedetomidine sedation to RASS-4), which was analyzed to show a stable interhemispheric asymmetry of Delta activity in amplitude and, to a lesser extent, in index s>d (Fig. 2).

By the evening, the speech began to gradually recover, he could build simple sentences. The next morning, the speech disorders completely regressed, the previous events, starting with the development of confusion, the patient completely amnesic. Thus, focal neurological disorders persisted for about two days.

A negative CSF PCR result was obtained for HSV, after which acyclovir and dexamethasone therapy was canceled.

On April 15, a control study of MRI of the brain with contrast was repeated (Fig. 1 g, h, i). Data for pathological changes in signal characteristics from brain structures were not received. The previously determined increase in the signal from the left temporal lobe cortex was not registered by FLAIR.

EEG monitoring was performed on the same day (Fig. 2). In the waking state, a slowdown in the main activity was detected: up to 6.5–7 Hz, at individual recording sites it reached 8 Hz; pronounced disorganization of the main activity by multi-region-

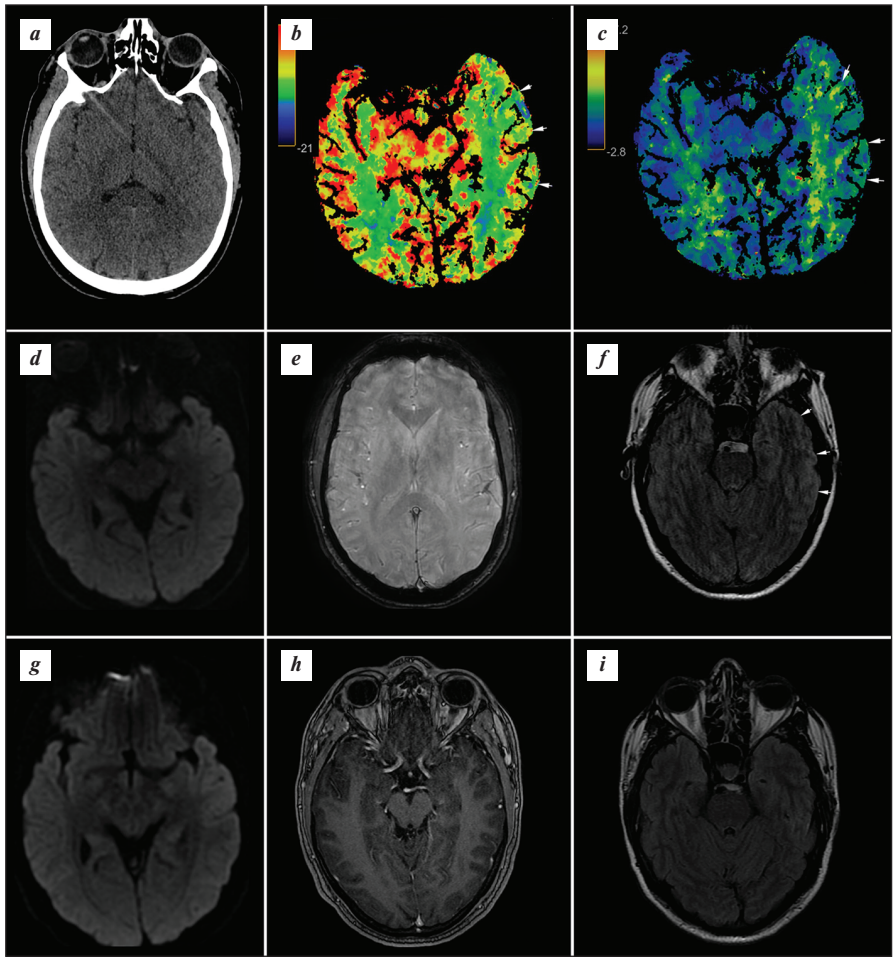

Fig. 1. *Results of neuroimaging of patient №3 at admission: a – native CT of the brain without signs of pathology; b – color map of the speed of cerebral blood flow (CBF); c – color map of the transit time of the contrast drug (Mean Transit Time, MTT). These maps show areas of CBF decrease and MTT increase in the left temporal region; d – MRI sequence DWI. e – MRI-SWAN sequence, without signs of pathology; f – the FLAIR_MRI sequence reflects a low-intensity increase in the MR-signal along the cortex contour of the left temporal lobe, correlating with CT perfusion data. Results of the control study: g – MRI sequence DWI, h –T1 weighted sequence with paramagnetic, no pathological changes were formed; i – MRI-sequence FLAIR, hyperintensivity detected at admission, regressed.*

al rhythmic and non-rhythmic theta activity, beta activity; moderate exaltation of rhythmic beta activity (the phenomenon of «excessive fast») without a stable significant amplitude interhemispheric asymmetry; periodic multi-regional rhythmic and non-rhythmic theta deceleration with a predominance in the right parietal and occipital leads (the index in the background record is up to 30% without sustained significant suppression when opening the eyes); periodic diffuse rhythmic deceleration up to 5 Hz with an amplitude predominance in the frontal, posterior lower frontal, and frontopolar leads (the index in the background record is no more than 10%). Epileptiform activity in the waking state, specific EEG patterns of sleep, as well as clinical and electroencephalographic patterns of epileptic paroxysms have not been registered.

On April 17, the patient showed an increase in the concentration of urea (23 mmol/l) and creatinine (430 mcmol/l) in the blood. After 3 days of hydration, the indicators returned to normal.

The patient was discharged after 10 days with complete regression of neurological deficit, the headache did not recur.

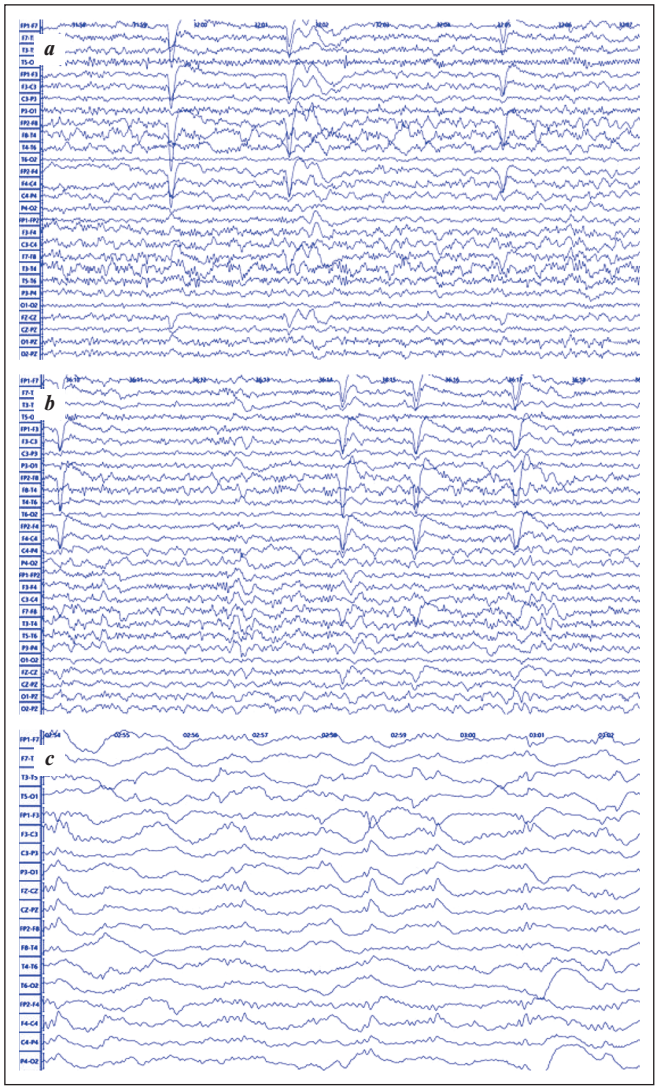

Fig. 2. *Patient №3, a, b, c — EEG in the waking state, c — sedation with dexmedetomidine; 30 mm/s, 7 mcV/mm, 0,5–35 Hz*

Discussion. The article describes three clinical cases of HaNDL, which have a number of similar features: the young age of patients (30–35 years), the presence of an infectious prodrome, the onset of the disease with an intense headache, followed by focal neurological symptoms (in all cases, there was aphasia and hemihypesthesia, in two – confusion with psychomotor agitation), lymphocytic pleocytosis of CSF, and spontaneous recovery within 2–3 days. However, in the cases described, there are a number of significant differences that should be discussed in more detail.

The first patient had prodromus in the form of diarrhea, the second-headache, and the third patient – fever and runny nose. In the development of HaNDL syndrome, the role of a viral infection that causes activation of the immune system is discussed. 25–50% of patients with HaNDL have symptoms of a viral infection or fever within 3 weeks before the attack develops [4, 5, 8]. In particular, the association of HaNDL with herpes virus type 7 is shown [9].

Some clinical similarity between HaNDL and hemiplegic migraine may indicate possible genetic and metabolic (channelopathy) mechanisms of disease development [10], although mutations characteristic of familial hemiplegic migraine, in particular in CACNA1A, were not found in patients with HaNDL [11]. It is noteworthy that the third patient before the present episode suffered from migraines with a typical aura, which in its characteristics significantly differed from the real attack (paradoxically, the pain in HaNDL had a pulsating character). It is assumed that the basis of clinical manifestations of HaNDL is autoimmune aseptic vasculitis of the soft medulla with the subsequent development of migraine-like cortical spreading depression [5, 6, 9, 12], although most patients with HaNDL syndrome do not have a history of migraines [7]. In the second and third patients, the headache was not migrainous, which is in some contradiction with international diagnostic criteria and may indicate its development within the meningeal syndrome.

Aphasia and hemihypesthesia in our observations were the most universal symptoms. Classic manifestations of the disease described by F. Gomez-Aranda et al. [5] include: sensory disorders (78% of episodes), aphasia (66%), and motor disorders (56%). Visual disturbances were observed in only 12% of attacks. The most common combination of symptoms was motor aphasia and sensory/motor central hemisyndrome.

At the same time, in two of the described patients, cephalgia combined with aphasia and hemigypesthesia transformed into confusion with psychomotor agitation, which required treatment in the intensive care unit and prolonged sedation. Confusion is considered as one of the main symptoms of the disease [10, 13, 14, 15], although this symptom is not mentioned in the ICHD-3 diagnostic criteria. The origin of confusion may be related to dysfunction of stem and/or limbic structures [10]. In addition, HaNDL can manifest a catastrophic clinical picture with increased intracranial pressure and the need for resuscitation [6].

The two patients we described had only one episode of focal neurological deficits. At the same time, the second patient had a complex character with a transition to obscurity of consciousness, while the third patient had a «light interval» between the episode of aphasia/hemigypesthesia/hemiparesis and the development of confusion. The duration of the attack in the described patients was 1–3 days. According to classical

data, F. Gomez-Aranda et al. the number of episodes of focal neurological deficit varies from 1 to 12, the average duration of an episode is 5 hours, and there are no violations between episodes [5].

It should be noted that two of the three patients were admitted to the hospital with a suspected acute violation of cerebral circulation, and the second patient intravenous thrombolysis was started. Indeed, HaNDL is considered as one of the stroke masks in the emergency Department [1, 2]. When analyzing data from the Madrid stroke center registry for 10 years (6347 patients), M. Guillan et al. (2016) identified 9 cases of HaNDL (average age 27.6 years) [16]. The issue of timely differentiation is of a fundamental nature, since it determines reperfusion tactics. It is known that intravenous thrombolysis is performed in 55% of patients who are later diagnosed with HaNDL [16]. It is obvious that performing a lumbar puncture immediately upon admission is a contraindication for performing thrombolysis.

Signs in favor of the stroke mask, in particular HaNDL, are: migration of symptoms (reflecting spreading cortical depression), young age, lack of vascular risk factors, isolated aphasia, concomitant headache and vomiting – features that are also true for the described clinical cases. Additional information can be obtained during neuroimaging in the emergency room. Optimal MRI of the brain, which, as in the cases presented, is characterized by the absence of significant changes in FLAIR and, most importantly, DWI. However, MRI may reveal an increased leptomeningeal accumulation of contrast in the temporal and occipital lobes and cerebellum [17, 18], edema of cortical gray matter [17], as well as an increased representation of hypointensive brain veins [2] or, conversely, a reduced venous signal within the involved region on the MR-sequence sensitive to magnetic susceptibility (SWI) [19]. In particular, A. Yilmaz et al. in 2010, we described hyperintensity of the right temporal and occipital cortex on FLAIR in combination with hypoperfusion of this area on perfusion-weighted MRI in a 27-year-old patient with HaNDL, manifested hemiparesis, prosoparesis, hemihypesthesia, visual ignoring, anosognosia, and confusion [17]. The similarity of this picture with the one we found in the third patient (there are no other similar descriptions in the literature) it suggests its pathogenetic connection with the obscuration of consciousness in HaNDL.

The routine practice of vascular centers includes multimodal neurovascular imaging, which is justified in the present case. When performing a CT perfusion study with HaNDL, a change in perfusion status may be observed in the form of an increase in time to peak/MTT indicators in the cortical zone that does not correspond to the arterial pool, which occurred in the third patient. Focal unilateral hypoperfusion, which may be based on metabolic changes in the cerebral cortex, has also been demonstrated in studies using SPECT and transcranial dopplerography [16, 20, 21]. Since in some cases the perfusion pattern may be similar to that of a stroke, CT angiography is necessary to demonstrate the absence of occlusion of a large vessel [1, 16].

With the exception of a vascular catastrophe that requires immediate treatment, differential diagnosis should be carried out with the next most dangerous cause – meningoencephalitis. Note that after excluding the stroke, the first patient was sent to an infectious disease hospital. According to G. R. Tabeeva et al., HaNDL must be differentiated from viral meningitis (especially caused by Epstein–Barr virus, cytomegalovirus, herpes simplex virus and HIV), meningitis associated with cat scratch disease; and benign recurrent serous meningitis Mollare; bacterial serous meningitis (neuroborreliosis, neurosyphilis, neurobrucellosis, tuberculosis, Mycoplasma infection) [22].

The most urgent and responsible, in our opinion, is the differentiation of HaNDL with HSV-encephalitis, which has a similar clinical picture: fever (80% of cases), confusion/disorientation (72%), behavioral disorders (59%), headache (58%), impaired consciousness (58%), focal neurological deficit (41%), aphasia/speech disorders (40%). At the same time, in HSV-encephalitis, generalized convulsions develop in 54% of cases [23, 24].

The picture of the liquor is also similar: increased protein, pleocytosis (on average, about 70 cl/mcl a predominance of lymphocytes (60–98%, on average 80%) [23, 24]. In HaNDL, lymphocytic pleocytosis (from 10 to 760 cl/mcl) is observed, which serves as a key manifestation of the disease [5]. According to the diagnostic criteria of ICHD-3, it is necessary to have more than 15 cl/mcl [7].

The main method of confirming HSV-encephalitis is PCR for detecting HSV DNA, whose sensitivity is 98% for HSV-1, and specificity is 94–99% [25]. PCR is usually positive on the first day and remains so for a week. However, with very early testing, the result may be negative [26]. MRI of the brain is also not an aid in differential diagnosis, since typical changes (unilateral restriction of diffusion with subsequent hyperintensivity on the FLAIR of the medial temporal lobe, cingulate gyrus, orbitofrontal and insular cortex) are present in 95% of patients on day 3, and may be absent in very early periods [23, 27].

If HSV-encephalitis is suspected, intravenous acyclovir therapy is immediately prescribed at a dose of 30 mg / kg per day, which can be discontinued if there is a low probability of this disease (normal MRI, CSF cytosis <5 cl/mcl, normal mental status), a negative PCR result is obtained, or an alternative diagnosis is confirmed [23, 24]. Acyclovir is a nephrotoxic drug, and its parenteral use is associated with acute kidney injury (in 5–18% of patients), especially in the presence of a history of hypertension, diabetes, chronic kidney disease, high doses, as well as prescription with NSAIDs [28, 29, 30]. During acyclovir therapy, adequate hydration and regular monitoring of purification indicators should be performed. Despite these measures, a third patient developed transient acute nephropathy, which is probably due to two contrast studies.

When considering HaNDL in the framework of aseptic meningitis, differential diagnosis should be made with systemic diseases (neurosarcoidosis, Behcet's disease, Shegren's syndrome, systemic lupus erythematosus and Wegener's granulomatosis), drug-associated aseptic meningitis (when taking NSAIDs, certain antibiotics, intravenous immunoglobulin, monoclonal antibodies and antiepileptic drugs) and neoplastic meningitis (carcinomatosis in breast cancer, lung, melanoma; leukemia, lymphoma) [31].

The next stage of differential diagnosis is to exclude epilepsy. EEG in HaNDL is characterized by a number of non-specific non-epileptiform phenomena, such as asymmetric generalized deceleration, intermittent rhythmic Delta

activity, and three-phase waves. Slowing of the main activity and three-phase waves require a differential diagnosis with metabolic encephalopathy, especially against the background of liver diseases [35]. They should also be distinguished from periodic phenomena, such as periodic lateralized epileptiform discharges (PLAIDS), which are characteristic of viral and autoimmune encephalitis, among others [9, 32, 36, 37]. In the initial EEG study of the third patient (against the background of dexmedetomidine sedation), a stable interhemispheric asymmetry of Delta activity in amplitude and, to a lesser extent, in the s>d index was registered. In the second study, episodes of regional deceleration (mainly in the theta range) were significantly more pronounced on the index in the right parietal and temporal, to a lesser extent, in the right posterior lower frontal (anterior) and right mid-temporal leads. Regional non-rhythmic theta and, to a greater extent, Delta deceleration with a change of localization (from left to right) without epileptiform activity indirectly indicates a pronounced transient suppression of the function of the corresponding regions. The low spatial resolution of routine non-invasive EEG does not allow us to locate the damage zone more precisely than within one lobe. Inhibition of alpha activity can be a consequence of diffuse damage to the cortex, mainly occipital localization (the theory of multiple cortical alpha-rhythm generators, the theory of «cortical twins»), as well as disorders of the brain stem (suppression of alpha-rhythm generators or strengthening of ascending activating influences) and the thalamus [38,39]. Last further indicates the pathogenetic significance of the dysfunction of these structures in the development of confusion in HaNDL. Direct comparison of the results of two studies is incorrect due to different physiological conditions.

Finally, the presence of paroxysmal headache with the development of focal neurological symptoms makes it possible to differentiate HaNDL syndrome with migraine with aura (in particular with migraine with stem aura and sporadic hemiplegic migraine) [22]. It should be noted that both HaNDL syndrome and migraine are characterized by the absence of pathological findings in standard neuroimaging, although transient vasogenic edema (MRI-FLAIR) and decreased tracer accumulation (PET) during migraine status in areas correlating with existing symptoms are described [33]. The clinical differentiation of migraine and HaNDL is difficult, and a differential diagnosis can only be made with confidence based on an analysis of the composition of CSF. In addition, it should be borne in mind that migraines are characterized by repeated almost identical cephalgic attacks, and the diagnosis of migraines with aura, according to the International classification, is established only if the patient has a history of at least two attacks that meet international criteria. Differentiation of a developed cephalgic attack, accompanied by General and focal symptoms, with a migraine attack is especially relevant for the third patient, who from the age of 22 suffered frequent (up to twice a month) migraine attacks with aura, which were stopped by triptans. Transient disturbance of consciousness is described in the symptomatology of migraine with a stem aura [7]. However, the clinical picture of the described episode differs from the typical attacks of the patient, and the presence of lymphocytic pleocytosis in the CSF confirms the diagnosis of HaNDL.

HaNDL is characterized by a monophasic course, although clinical deterioration may occur several weeks or months after the initial attack, which necessitates dynamic monitoring of patients; however, neurological symptoms may vary from episode to episode, depending on the involvement of different regions of the brain [6]. Despite the benign nature of the disease, some patients may develop intracranial hypertension syndrome with visual impairment during the recovery period [34].

Thus, at present, HaNDL is considered as a rare benign form of secondary headache [22], which should be the first concern for angineurologist-specialists. To make a timely diagnosis, a thorough analysis of the dynamics of clinical symptoms is necessary and a detailed examination, including multi-modal CT and/or MRI of the brain, lumbar puncture and EEG, is carried out in a short time. Confusion that developed after acute cephalgia and focal neurological deficits is characteristic of HaNDL. Due to the high risk of herpetic encephalitis in the patient, even with a typical clinical picture of HaNDL, acyclovir therapy is advisable with early cancellation after receiving a negative PCR result. The disease has a benign course, but after discharge from the hospital, patients require dynamic monitoring.

REFERENCES

1. Quintas S, Lopez Ruiz R, Trillo S, et al. Clinical, imaging and electroencephalographic characterization of three cases of HaNDL syndrome. *Cephalalgia*. 2018 Jun;38(7):1402-6. doi: 10.1177/0333102417735846

2. Ferrante E, Prone V. Possible clinical marker of first attack of HaNDL syndrome (stroke-like mimics) in emergency room: a case report. *Neurol Sci*. 2018 Nov;39(11):2003-5. doi: 10.1007/s10072-018-3517-9

3. Bartleson JD, Swanson JW, Whisnant JP. A migrainous syndrome with cerebrospinal fluid pleocytosis. *Neurology*. 1981 Oct;31(10):1257-62. doi: 10.1212/wnl.31.10.1257

4. Berg MJ, Williams LS. The transient syndrome of headache with neurologic deficits and CSF lymphocytosis. *Neurology*. 1995 Sep;45(9):1648-54. doi: 10.1212/wnl.45.9.1648

5. Gomez-Aranda F, Canadillas F, Marti-Masso JF, et al. Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. A report of 50 cases. *Brain*. 1997 Jul;120 (Pt 7):1105-13. doi: 10.1093/brain/120.7.1105

6. Babi MA, Applebee A, Shapiro R, et al. Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis presenting as acute neurological emergencies. *Cephalalgia*. 2017 Mar;37(3):284-9. doi: 10.1177/0333102416642733

7. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018 Jan;38(1):1-211. doi: 10.1177/0333102417738202

8. Pascual J, Valle N. Pseudomigraine with lymphocytic pleocytosis. *Curr Pain Headache Rep*. 2003 Jun;7(3):224-8. doi: 10.1007/s11916-003-0077-2

9. Stelten BM, Venhovens J, van der Velden LB, et al. Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL): A case report with serial electroencephalography (EEG) recordings. Is there an association with human herpes virus type 7 (HHV-7) infection? *Cephalalgia*. 2016 Nov;36(13):1296-301 doi: 10.1177/0333102415618616

10. Frediani F, Bussone G. Confusional state as first symptom of HaNDL syndrome. *Neurol Sci*. 2015 May;36 Suppl 1:71-4. doi: 10.1007/s10072-015-2194-1

11. Chapman KM, Szczygielski BI, Toth C, et al. Pseudomigraine with lymphocytic pleocytosis: a calcium channelopathy? Clinical description of 10 cases and genetic analysis of the familial hemiplegic migraine gene CACNA1A. *Headache* 2003 Sep;43(8):892-5. doi: 10.1046/j.1526-4610.2003.03168.x

12. Apetse K, Breynaert L, Butaud C, et al. Transient headache and neurological deficits with cerebrospinal fluid lymphocytosis associated with IgM antibodies to the Epstein-Barr virus viral capsid antigen. *Case Rep Neurol Med.* 2013;2013:975709. doi: 10.1155/2013/975709

13. Nelson S. Confusional state in HaNDL syndrome: case report and literature review. *Case Rep Neurol Med.* 2013;2013:317685. doi: 10.1155/2013/317685

14. Soto-Insuga V, Lopez-Villanueva L, Rodrigo M, et al. Confusion as a presentation symptom of pseudomigraine with pleocytosis in a paediatric patient. *Ann Pediatr (Barc).* 2014 Jun;80(6):394-8. doi: 10.1016/j.anpedi.2013.10.025

15. Lo Re M, di Sapio A, Malentacchi M, et al. Acute confusional state in HaNDL syndrome (transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis). *Neurol Sci.* 2015 Mar;36(3):477-8. doi: 10.1007/s10072-014-2017-9

16. Guillan M, DeFelipe-Mimbrera A, Alonso-Canovas A, et al. The syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis mimicking an acute stroke. *Eur J Neurol.* 2016 Jul;23(7):1235-40. doi: 10.1111/ene.13008

17. Yilmaz A, Kaleagasi H, Dogu O, et al. Abnormal MRI in a patient with 'headache with neurological deficits and CSF lymphocytosis (HaNDL)'. *Cephalalgia*. 2010 May;30(5):615-9. doi: 10.1111/j.1468-2982.2009.01950.x

18. Garcia-Esperon C, Carrera D, Prats-Sanchez L, et al. Focal leptomeningeal uptake, a new radiological finding in pseudomigraine with pleocytosis. Captacion leptomeningea focal, un nuevo hallazgo radiologico en la seudomigrana con pleocitosis. *Neurologia*. 2017 Jan–Feb;32(1):63-5. doi: 10.1016/j.nrl.2015.03.007

19. Rodriguez-Lopez C, Garzo Caldas N, Uriarte Perez de Urabayen D, et al. A new MR radiological sign in HaNDL syndrome. A case report. *J Clin Neurosci.* 2019 Mar;61:274-6. doi: 10.1016/j.jocn.2018.11.018

20. Fuentes B, Diez Tejedor E, Pascual J, et al. Cerebral blood flow changes in pseudomigraine with pleocytosis analyzed by single photon emission computed tomography. A spreading depression mechanism? *Cephalalgia*. 1998 Oct;18(8):570-3. doi: 10.1046/j.1468-2982.1998.1808570.x

21. Kappler J, Mohr S, Steinmetz H. Cerebral vasomotor changes in the transient syndrome of headache with neurologic deficits and CSF lymphocytosis (HaNDL). *Headache*. 1997 Sep;37(8):516-8. doi: 10.1046/j.1526-4610.1997.3708516.x

22. Tabeeva G, Azimova J, Skorobogatych K. Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL). *J Neurol Stroke.* 2018;8(3):147-9. doi: 10.15406/jnsk.2018.08.00299

23. Gnann JW Jr, Whitley RJ. Herpes simplex encephalitis: an update. *Curr Infect Dis Rep.* 2017 Mar;19(3):13. doi: 10.1007/s11908-017-0568-7

24. Rabinstein AA. Herpes virus encephalitis in adults: current knowledge and old myths. *Neurol Clin.* 2017;35(4):695-705. doi: 10.1016/j.ncl.2017.06.006

25. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol.* 2010 Aug;17(8):999-e57. doi: 10.1111/j.1468-1331.2010.02970.x

26. Adler AC, Kadimi S, Apaloo C, et al. Herpes simplex encephalitis with two false-negative cerebrospinal fluid PCR tests and review of negative PCR results in the clinical setting. *Case Rep Neurol.* 2011 May;3(2):172-8. doi: 10.1159/000330298

27. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. *Neurotherapeutics.* 2016 Jul;13(3):493-508. doi: 10.1007/s13311-016-0433-7

28. Ryan L, Heed A, Foster J, et al. Acute kidney injury (AKI) associated with intravenous aciclovir in adults: Incidence and risk factors in clinical practice. *Int J Infect Dis.* 2018 Sep;74:97-9. doi: 10.1016/j.ijid.2018.07.002

29. Richelsen RKB, Jensen SB, Nielsen H. Incidence and predictors of intravenous acyclovir-induced nephrotoxicity. *Eur J Clin Microbiol Infect Dis.* 2018 Oct;37(10):1965-71. doi: 10.1007/s10096-018-3332-5

30. Lee EJ, Jang HN, Cho HS, et al. The incidence, risk factors, and clinical outcomes of acute kidney injury (staged using the RIFLE classification) associated with intravenous acyclovir administration. *Ren Fail.* 2018 Nov;40(1):687-92. doi: 10.1080/0886022X.2018.1487866

31. Tattevin P, Tchamgoue S, Belem A, et al. Aseptic meningitis. *Rev Neurol (Paris).* 2019 Sep–Oct;175(7-8):475-80. doi: 10.1016/j.neurol.2019.07.005

32. Amodio P, Montagnese S. Clinical neurophysiology of hepatic encephalopathy. *J Clin Exp Hepatol.* 2014;5:S60-S68. doi: 10.1016/j.jceh.2014.06.007

33. Barona J, Mulerob P, Pedrazab MI, et al. Sindrome HaNDL: correlacion entre la topografia del deficit neurologico y las alteraciones en electroencefalograma y SPECT en una serie de 5 nuevos casos. *Neurologia*. 2016 Jun;31(5):305-10. doi: 10.1016/j.nrl.2015.03.004. Epub 2015 May 11.

34. Fitzpatrick W, Lowry N. PLEDs: clinical correlates. *Can J Neurol Sci.* 2007 Nov;34(4):443-50. doi: 10.1017/S0317167100007332

35. Masuda T, Kimura N, Nakamura K, et al. A case of limbic encephalitis repeated aphasic status epilepticus with periodic lateralized epileptiform discharges. *Rinsho Shinkeigaku.* 2011 Feb;51(2):135-40. doi: 10.5692/clinicalneurol.51.135

36. Niedermeyer E. Alpha rhythms as physiological and abnormal phenomena. *Int J Psychophysiol.* 1997 Jun;26(1-3):31-49. doi: 10.1016/s0167-8760(97)00754-x

37. Неробкова ЛН, Авакян ГГ, Воронина ТА. Клиническая электроэнцефалография. Фармакоэлектроэнцефалография. Москва: ГЭОТАР-Медиа; 2020. ISBN 978-5-9704-5371-1. [Nerobkova LN, Avakyan GG, Voronina TA. *Klinicheskaya elektroentsefalografiya. Farmakoeletroentsefalografiya* [Clinical electroencephalography. Pharmacoelectroencephalography]. Moscow: GEOTAR-Media; 2020. ISBN 978-5-9704-5371-1 (In Russ.)].

38. Gentile S, Rainero I, Daniele D, et al. Reversible MRI abnormalities in a patient with recurrent status migrainosus. *Cephalalgia*. 2009 Jun;29(6):687-90. doi: 10.1111/j.1468-2982.2008.01803.x

39. Mulroy E, Yap J, Danesh-Meyer H, et al. Symptomatic intracranial hypertension during recovery from the syndrome of headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HANDL). *Pract Neurol.* 2017 Apr;17(2):145-8. doi: 10.1136/practneurol-2016-001539

Received/Reviewed/Accepted
10.05.2020/14.06.2020/20.06.2020

Conflict of Interest Statement
The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Kulesh A.A. *https://orcid.org/0000-0001-6061-8118*
Starikova N.L. *https://orcid.org/0000-0002-8350-7004*
Drobakha V.E. *https://orcid.org/0000-0001-8523-2692*
Brokhin L.Yu. *https://orcid.org/0000-0001-9499-7013*
Chubarov A.S. *https://orcid.org/0000-0001-8657-8281*