MODERN UNDERSTANDING OF THE CLIPPERS SYNDROME: DIFFICULTIES OF DIFFERENTIAL DIAGNOSIS AND APPROACH TO THERAPY

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Abstract

The CLIPPERS syndrome is a rare inflammatory disease of the central nervous system, which is based on lymphocytic inflammation of the pons Varolii. Diagnosis of this pathology is a difficult task and relies primarily on neuroimaging and immunological methods. The key diagnostic criteria also include regression of the pathological process after treatment with glucocorticosteroids. In this literature review, special attention is paid to the features of therapy and differential diagnosis of the CLIPPERS syndrome with two clinically similar diseases of the central nervous system: primary vasculitis of the central nervous system and the PRES syndrome.

Keywords: CLIPPERS syndrome, primary vasculitis of the central nervous system, PRES syndrome, inflammatory disease of the central nervous system, glucocorticosteroids

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Introduction

The CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) syndrome is a rare inflammatory disease of the central nervous system (CNS) with predominant lymphocytic inflammation of the pons Varolii [1, 3]. For the first time, this pathology was described by a research team led by S. Pittock (Mayo Clinic College of Medicine, USA) as one of the forms of stem encephalitis, where the most pronounced damage to the brain bridge caused by T-lymphocytic dysfunction and treatable with glucocorticosteroids (GCS) was observed [5]. Currently, more than 50 clinical cases have been described by different authors [2, 4, 6].

This work aimed to identify the features of therapy and differential diagnosis of CLIPPERS syndrome with two clinically similar diseases of the CNS: primary vasculitis of the CNS (PVCNS) and posterior reversible encephalopathy syndrome (PRES) [7, 8].

Materials and methods

In the course of the study, we reviewed studies and described clinical cases published over the past ten years in peer-reviewed scientific journals. The search for works was carried out in the Pubmed database using the following search terms: "CLIPPERS syndrome", "primary vasculitis of the central nervous system", and "PRES syndrome"

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Results and discussion

The CLIPPERS syndrome is characterized by a subacute onset and a variety of clinical manifestations associated with damage to the brain stem, cranial nerves, and cerebellum [9, 10]. The most frequent and early symptoms in this pathology are ataxia and diplopia [11]. In addition, some other clinical manifestations are observed in the clinical findings of the disease, usually associated with damage to the brain stem [12, 13]. These include sensitivity disorders and paresthesia on the face, dysarthria, nystagmus, and dizziness [14]. Besides the main clinical manifestations, there are additional symptoms that are much less common. Thus, the symptoms caused by the involvement of the conductive tracts of the brain stem and spinal cord in the pathological process are described as conductive disorders of superficial and/or deep sensitivity, para-/tetraparesis, pyramidal signs, pseudobulbar disorders, and sphincter dysfunction [1, 17-19]. In some cases, mnestic disorders and executive function disorders were detected, as well as headache and pathological fatigue. The age of onset of the disease varies widely with averages of 43, 46, and 52 years, according to different authors [15, 16]. The CLIPPERS syndrome occurs with equal frequency in males and females. In the absence of treatment, the initial symptoms progress over several weeks and tend to alternate between exacerbations and remissions. The prolonged absence of therapy can lead to persistent neurological deficits. During neuroimaging studies, which are of key importance, characteristic signs of inflammation of stem structures are found in this pathology [18-21]. Thus, magnetic resonance imaging (MRI) detects multiple foci localized mainly in the pons Varolii, hyper-intensive in T2 and fluid-attenuated inversion recovery (FLAIR) modes and hypo-intensive in T1 mode. The foci accumulate contrast. Therefore, with contrast enhancement using gadolinium, a characteristic pattern is visualized during scanning, called "salt and pepper, speckles, and stippling" [22, 24]. In the description of subsequent clinical cases, other foci of pathological changes were also identified [21, 23]. Thus, the perivascular spaces of the medulla oblongata and cerebellum were involved in the inflammatory process, and in isolated cases, the pathological process could spread to the spinal cord. In addition, inflammatory changes were also found in supratentorial structures such as basal ganglia and corpus callosum [19, 25]. Changes in the cerebrospinal fluid are nonspecific and unstable. Moderate pleocytosis and proteinorachia are possible, as well as the presence of oligoclonal bands. During the biopsy, patients with CLIPPERS syndrome are found to have predominantly T-lymphocytic infiltration of the white matter of the pons Valorii and other infratentorial structures, with the spread of the inflammatory process mainly in the area of perivascular spaces [20, 21]. In addition, a moderate number of histiocytes and activated microglyocytes were detected in the foci. An important diagnostic sign of the disease is a pronounced response to the administration of high doses of glucocorticosteroids, which is expressed in the regression of clinical symptoms and

positive dynamics during neuroimaging [23]. However, in most cases, patients required prolonged maintenance therapy with corticosteroids or other immunosuppressants. Thus, at the moment, CLIPPERS syndrome is considered an immune-mediated inflammatory disease of unknown etiology [26].

Another similar pathology is **PVCNS** (also known in the Russian-language literature as isolated angiitis), a poorly studied and rare disease that damages the vessels, mainly of the brain (less often spinal cord) of exceptionally small and medium size, sometimes involving the inflammatory process of the meninges [31, 32, 34]. It is believed that, at present, the etiological cause of PVCNS remains unclear, as with CLIPPERS syndrome [33]. It is reliably known that the disease is primary, that is, it does not originate from other pathologies, and also differentiates with vascular lesions resulting from infection with microorganisms. There are three main types of the course of PVCNS, subdivided according to the pathomorphological findings: the granulomatous form, with the formation of mononuclear infiltrates, multinucleated giant cells, and accumulation of b-A4 amyloid in the layers of vascular walls in 24 to 50% of cases (ABRA, amyloid beta related angiitis); the necrotic form, where transmural necrotic lesions are observed in the membrana elastica interna and there is an increased risk of cerebral hemorrhage (including microaneurotic hemorrhage); and the lymphocytic form associated with a defect of the normal functioning of the vascular wall due to its multiple infiltrations by lymphocytes [35, 36]. According to the literature, the main pathogenetic mechanisms are immune inflammation mediated by some infectious agents (for example, the herpes virus family), where the microorganism acts as a provoking factor and initiates the inflammatory process in the vascular walls, penetrating the latter transaxonally, with a decrease in the immunity of the body and/or other contributing factors. The dendritic cells also might play a role, as they are located in large numbers in the intermediate and outer layer of the arteries and are stimulated through the Toll-Like receptor system, which leads to an influx of T cells into the arterial wall and promotes the activation of cytokine clusters, with further changes in vascular conformation [32, 36, 37]. The clinical symptoms are quite variable and depend on the diameter of the vessels involved in the pathological process, most often developing subacutely. At the onset of the disease, patients complain of a progressively increasing headache and show symptoms of cognitive dysfunction, followed by manifestations of focal symptoms like ataxia, aphasia, transient and acute disorders of cerebral circulation, optical disorders, and the possible development of epileptic seizures [38-41]. The greater the damage to the cerebral vessels, the more diverse the clinical manifestations (average lesions result in focal and circulatory disorders, and with smaller lesions, the disease takes a course similar to encephalopathy). With further development of pathology, according to the reports of some authors who studied small cohorts of patients (52, 102, or 163 patients included in the study) mortality reaches from 5 to 15% of cases [33, 33].

The PRES syndrome is a rare clinical and radiological syndrome manifested by vasogenic edema of the white matter of the parietal-occipital lobes of the brain, which is characterized by the following clinical findings: headache, mental status disorders (encephalopathic manifestations), epileptic seizures, and decreased or complete loss of vision [39, 40]. For the first time, this pathology was described by a research group led by J. Hinchey in 1996 [40]. Over the past decades, due to the improvement and wider spread of magnetic resonance imaging, significant progress has been made in the diagnosis of this syndrome. In most cases, PRES is associated with hypertension. However, to date, PRES is associated with other pathological conditions like autoimmune diseases, chemotherapy of malignant neoplasms, preeclampsia/eclampsia, acute glomerulonephritis, infection and septic shock, organ transplantation, including bone marrow and stem cells, sickle cell anemia, hyperammonemia, ventriculoperitoneal bypass surgery, as well as with the toxic effect of certain medications (cyclophosphamide, erythropoietin, interferon, cyclosporine, azathioprine, cisplatin, tacrolimus, L-asparaginase, ustekinumab, and filgrastim). The neurotoxic effect in this pathology is a consequence of a defect in the autoregulation of blood circulation of the vessels feeding the posterior parts of the brain in response to sharp fluctuations in blood pressure [39, 41]. As a result, due to hyperperfusion, the normal permeability of the haematoencephalic barrier is disrupted, which leads to vasogenic cerebral

edema, usually most pronounced in the parietal-occipital lobes [42, 46]. There are two more possible mechanisms of PRES development: cerebral vasoconstriction with the subsequent development of cerebral ischemia and endothelial damage with a defect of the haematoencephalic barrier, leading to the development of edema [39, 43]. At the beginning of the course of PRES, vasogenic edema without inflammation prevails, which in later stages is followed by ischemia with neuronal damage and demyelination, laminar necrosis, and hemorrhages in the white matter and cerebral cortex. During neuroimaging, the pattern usually reflects vasogenic edema of the brain [44]. Thus, on MRI in T1 mode, the areas of edema are displayed as zones of hypo-intensive signal, and in T2 mode, as hyper-intensive. In the diffusion-weighted imaging (DWI) mode, zones of the iso- or hyper-intensive signal are detected, and in the apparent diffusion coefficient (ADC) mode, due to increased diffusion, edema zones are visualized as hyper-intensive [41, 43]. Nevertheless, in this pathology, vasogenic edema is often not limited to the parietal-occipital regions and is often found in the frontal, lower parietal regions, and sometimes in the cerebellum and brainstem [45, 46].

Differential diagnosis in the study of such pathologies is extremely difficult, due to the non-specificity of many symptoms and relatively rare occurrences in clinical practice [20, 35]. When examining and analyzing the cerebrospinal fluid, it can be found that with CLIPPERS syndrome, an increase in lymphocytes and oligoclonal immunoglobulin G (IgG) is characteristic, and with PVCNS, one observes more indicators of aseptic meningitis and it is also characterized by pleocytosis, sometimes predominant due to the neutrophil component, slightly elevated levels of protein and glucose. However, in both cases, the presence of an infectious agent is excluded [47, 50]. The MRI findings in patients with CLIPPERS are characterized by a point linear-nodular enhancement in the perivascular spaces, accumulation of contrast agent mainly in the area of the pons Varolii and cerebellum, while PVCNS is more manifested by subcortical and periventricular foci of white matter ischemia, and MRI with biopsy is of great diagnostic value, during which it is possible to assess the characteristic morphological findings [32, 48, 49]. The PRES syndrome on MRI is characterized by signs of vasogenic edema localized in the parietal-occipital lobes, often with a transition to the area of the upper frontal sulcus, and, as a rule, having a bilateral and relatively symmetrical arrangement [42, 46, 58].

Possible treatment options

In most cases, patients with CLIPPERS syndrome respond positively to corticosteroid therapy, the lack of response to which can be regarded as grounds for alertness and the possible need to reassess the diagnostic approach (the so-called red flag) [29, 53-55]. Long-term use of GCS in this pathology leads to a distinct and gradual decrease in clinical and radiological manifestations [22, 56]. Some patients are prescribed the combined use of corticosteroids with immunosuppressants, which, according to some data, helps to achieve the leveling of exacerbations to a greater extent than monotherapy [50, 52]. However, there is evidence of the use of other medications in cases where the patient has a long history of the CLIPPERS syndrome and the generally accepted treatment algorithm does not contribute to reducing the frequency of exacerbations. Thus, T. Rempe et al. (2019), report on the management of a 39-year-old patient with this pathology who has been receiving treatment with methylprednisolone and azathioprine for four years with a positive response, but with further development of exacerbation of symptoms; tocilizumab was prescribed for five years (480mg IV, monthly) and, then, it was replaced with maintenance therapy (162 mg subcutaneously, weekly). A distinct regression of neurological disorders has been demonstrated, both in clinical observation and instrumental research [25]. Probably, in this case, the use of tocilizumab as an effective means of reducing the expression of pro-inflammatory cytokines and inducing the production of B-regulatory cells, as well as differentiation of T-cells, is justified and can be considered as a means of choice in a resistant CLIPPERS syndrome. In the work of Parada-Garza et al. (2018), leflunomide was used to treat a patient taking corticosteroids in the acute phase of the disease, without a previous clinically significant effect [27]. Teriflunomide is a metabolite of the above-mentioned medication used mainly for the treatment of rheumatological pathologies, and has a pronounced immunosuppressive effect, affecting the modulation of T-cells. In the

described clinical observation, leflunomide, from the first two months of the start of therapy, allowed to achieve complete clinical remission, after which the patient was transferred to maintenance therapy with azathioprine. There are also isolated reports of the successful use of rituximab and other medications from the group of monoclonal antibodies, but the experience of their administration in this pathology is very limited [26, 57].

Conclusion

Currently, the diagnosis of CLIPPERS syndrome can be made based on the clinical findings, first of all, if it is impossible to explain the patient's symptoms in any other way, as well as a combination of pathomorphological and neuroimaging techniques, with a response to ongoing GCS therapy. Difficulties in carrying out differential diagnostics with several similar pathologies indicate the relevance of studying this topic and the need, as new clinical cases appear, for further systematic reviews and meta-analyses.

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