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Histiocytic necrotizing lymphadenitis with autoimmune encephalitis in a child: a case report

Yiyun Zhou[1], Sainan Shu[1*]
[1]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030,China

Abstract:
Backgrounds: Histiocytic necrotizing lymphadenitis (HNL) is a rare benign self-limiting inflammatory disease that mainly affects young adults, however, the exact pathogenesis is unknown. A 4-year-old child who was diagnosed with HNL combined with autoimmune encephalitis (AE) was admitted to our hospital. This study aimed to investigate the clinical characteristics, laboratory tests, imaging findings, and treatment outcomes of pediatric patients with HNL+AE.
Case presentation: A 4-year-old male child was admitted to our hospital after presenting with a neck mass persisting for over 2 months and a fever lasting 5 days. The initial symptom was fever accompanied by lymph node enlargement. The patient was diagnosed with HNL, however, the condition did not respond significantly to treatment, and he continued to have lymph node enlargement and intermittent fever. Six months later, the patient developed neurological symptoms, including decreased voluntary activity, impaired speech, and reduced appetite. Subsequent serum testing yielded positive results for CASPR2, leading to a diagnosis of CASPR2 antibody-associated encephalitis. The final diagnosis was HNL+AE, which improved after finding the corresponding treatment. Subsequent follow-ups indicated no recurrence.
Conclusions: This represents the first documented case of HNL+AE in pediatric patients exhibiting typical symptoms of fever, lymph node swelling and pain accompanied by acute neurologic symptoms, and an extended disease course. This report contributes to the theoretical understanding of the disease.

Keywords: histiocytic necrotizing lymphadenitis, autoimmune encephalitis, CASPR2 antibody-associated encephalitis

Introduction

Histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi-Fujimoto disease, is a rare, benign and self-limited inflammatory disease that primarily affects young adults [1-3]. HNL is a non-neoplastic lymphadenitis; and in children, the main symptoms are fever and swollen lymph nodes [4]. Several case reports suggest that HNL may lead to various complications, including meningitis, status epilepticus, interstitial lung disease, myocarditis, acute kidney failure, phagocytic syndromes, sickle cell anemia, and malignancy [5-14]. However, the exact pathogenesis remains unknown [15]. To date, only two cases of adult males with HNL combined with autoimmune encephalitis (AE) have been documented, both of which showed improvement following immunotherapy. However, there are noreport of HNL combined with AE in children.

Currently, there are no established diagnostic criteria for HNL, and laboratory tests lack specificity. Serology, which can detect antibodies to EBV, human herpesvirus 6 and 8, as well as human parvovirus B19 [16]. Similarly, imaging studies such as CT and ultrasound also lack specificity. Therefore, the diagnosis of HNL currently relies on pathologic tissue biopsy. Moreover, there are no specific drugs for the treatment of HNL, and treatment is primarily symptomatic. Antibacterial drugs are typically ineffective. Oral hormone therapy is often the primary choice, and there is no specific guideline for therapeutic dosage [17]. Hydroxychloroquine has also been identified as an alternative treatment [18]. Due to its safety profile, it may present a better alternative to long-term, high-dose hormone therapy.

Recently, a 4-year-old child was diagnosed with HNL combined with contactin-associated protein-2 (CASPR2) antibody-associated encephalitis at our hospital. This case is exceedingly rare. The objective of this study is to analyse the diagnostic and treatment records pertaining to this case, providing a reference for future research on the mechanism and clinical treatment of similar diseases.

Case Presentation

2.1Description of patient, case history, diagnostic assessments, therapeutic interventionsand the actual outcome

The patient, a 4-year-old male, was initially admitted to the hospital on August 20, 2020, presenting with a "neck mass persisting for more than 2 months and fever for 5 days." Prior to this admission, the child had sought medical attention multiple times at external healthcare facilities and our outpatient clinic due to lymph node swelling and pain accompanied by fever, with a peak temperature of 39.2°C. There is also abdominal pain and vomiting. Colour ultrasound examination revealed enlarged lymph nodes, and a puncture indicated reactive hyperplasia of the left lymph node. Despite anti-infection treatment, the symptoms did not show significant improvement.

Upon admission to the hospital for physical examination, multiple enlarged lymph nodes were palpable bilaterally in the neck. The left lymph node, measuring approximately 1.5*1.0 cm, exhibited hardness, tenderness, and localized redness. Auxiliary examination revealed elevated C-reactive protein (CRP) at 13.78 mg/L (↑), increased calcitoninogen levels at 1.40 ng/mL (↑), and albumin at 36.7 g/L, fibrinogen at 4.25 g/L, and blood sedimentation at 24 mm/H. Other test results did not show any significant abnormalities. Despite anti-infective treatment with ticlopidine, there was no substantial improvement. Pathological analysis of the cervical lymph node biopsy indicated HNL of the left cervical tissue. The introduction of dexamethasone anti-inflammatory therapy notably reduced the inflammation. Following the resolution of the fever, the child was discharged from the hospital, with maintenance treatment involving oral prednisone for 1 week. However, after discharge, the child experienced low-grade fever every month which responded to anti-infective treatment, while the cervical lymph nodes remained enlarged.

After six months of intermittent fever, the child's symptoms deteriorated, resulting in a high fever peaking at 39.1°C. The fever occurred frequently, approximately 5 times a day accompanied by chills and abdominal pain. Despite the administration of oral cephalosporin, it proved to be ineffective.

On March 12, 2021, the child was readmitted to the hospital with a chief complaint of "fever." Upon physical examination, multiple enlarged lymph nodes, each approximately the size of a soybean, were palpable in the neck, and similar-sized lymph nodes were also palpable in both groins, exhibiting hardness and mobility. Auxiliary examination revealed a CRP level of 39.04ng/L, PCT level of 1.37ng/ml, and a positive detection of respiratory syncytial virus nucleic acid. No other significant abnormalities were observed.

Five days after admission, the child displayed a diminished spirit, reduced voluntary activity, minimal speech, and poor appetite, which were indicative of neurological symptoms, prompting consideration of AE. The electroencephalogram showed bilateral posterior head background activity with an increased amount of δ slow wave activity, particularly prominent on the right side (Figure 1). Simultaneously, a lumbar puncture was performed, revealing a total protein level of 116mg/L (↓), cerebrospinal fluid albumin level <95mg/L (↓), and no other abnormalities. The serum anti-CASPR2 antibody IgG was detected at a titer of 1:32. Also, enhanced MRI scanning confirmed slight meningeal enhancement. The patient received 7.5g of gammaglobulin (500mg/kg). Following the definitive diagnosis, shock treatment consisting of methylprednisolone at a dose of 290mg (20mg/kg) was administered. Three days later, the child's mood and appetite improved. Then, the methylprednisolone dosage was reduced by 2mg/kg. One week later, the child's mood stabilized, and hand tremors subsided,as well as speech and communication abilities were found essentially normal.

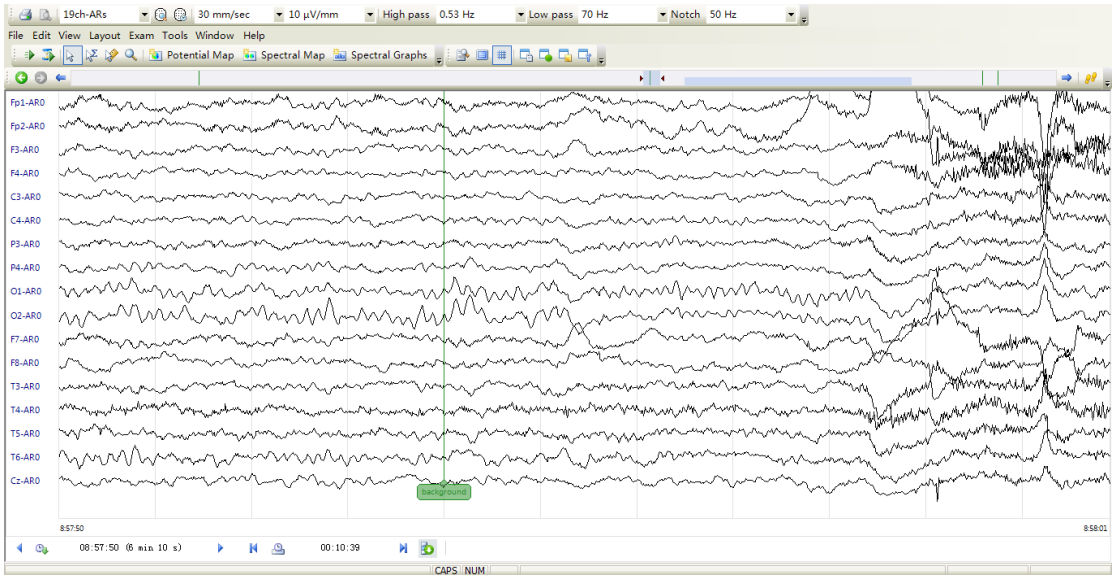

Figure 1. The representative picture of the electroencephalogram showed bilateral posterior head background activity.

After being discharged from the hospital, the patient received maintenance therapy with methylprednisolone (2 mg/kg). Concurrently, the patient underwent monthly gammaglobulin treatment. In addition, a follow-up brain MRI was conducted after the second gammaglobulin treatment. Subsequent to the third gammaglobulin treatment, the serum CASPR2 antibody became negative. A total of 7 treatments were completed, and the process proceeded smoothly.

2.2 Follow-up

Ultimately, the patient returned to the clinic after complete remission of symptoms. The serum biochemical indexes were within normal limits; the cerebrospinal fluid anti-CASPR2 antibody IgG was negative; the cranial MRI scan did not reveal any significant abnormalities, and the mental state was normal.

One year later, following the discontinuation of prednisone, the child's mental development was satisfactory, and no relapse occurred. Subsequent follow-up examinations indicated a negative serum CASPR2 antibody. To date, the child's intellectual development remains positive, and his mental state is stable, as well as there have been no relapses.

2.3 Side effect

After treatment, the child's body temperature returned to normal, with no clinical discomfort and no related clinical side effects. Lymph nodes were not enlarged and did not recur after discharge from the hospital.

Discussion

Chronic autoimmune system dysfunction can lead to neurological and visceral injuries [19,20]. AE involves immune-mediated attacks on intracellular and neuronal surface antigens, resulting in various brain disorders [14,21]. It was previously believed that neuromyotonia, Morvan syndrome (MoS), and limbic encephalitis were caused by antibodies associated with the voltage-gated potassium channel (VGKC) complex. However, an enhanced understanding of autoimmune antibodies has revealed that the causative antibodies are primarily directed against the VGKC complex-associated proteins, specifically the leucine-rich glioma inactivation 1 protein and CASPR2.Overexpression of anti-CASPR2 antibodies can lead to several age-related syndromes, including peripheral nerve hyperexcitability, limbic encephalitis, and MoS. Clinically, autoimmune encephalitis with anti-CASPR2 antibodies is rare. A study at Peking Union Medical College Hospital involving 279 cases of AE found that only 1.8% were CASPR2 antibody positive [22]. However, the etiology of AE is currently unknown. Reports suggest that CASPR2-positive encephalitis may be secondary to staphylococcal and viral infections, indicating potential involvement of infections. Additionally, there are reports of CASPR2-positive autoimmune limbic encephalitis secondary to pembrolizumab treatment, suggesting a possible involvement of immune system disorders [23].

In the early stages of the disease, the persistent lack of cure was attributed to the absence of detectable CASPR2 antibodies associated with AE, as all cerebrospinal fluid CASPR2 antibody tests returned negative results. Instead, serologic testing was employed, revealing an anti-CASPR2 IgG titer of 1:32. It was only after initiating the corresponding therapeutic regimen that the patient experienced significant remission, coinciding with the subsequent negativization of the antibodies. Similar test findings have been reported in previous studies, suggesting that the detection of serum anti-CASPR2 antibodies is more sensitive than that of cerebrospinal fluid [24,25]. Also, studies have identified anti-CASPR2 antibodies in the serum of patients with Morvan syndrome and neurogenic myasthenia gravis [24,26]. Therefore, both serum and cerebrospinal fluid testing are essential for confirming the diagnosis.

It is noteworthy that on both times when the child was admitted to the hospital for exacerbations, gastrointestinal symptoms were present. Given that HNL and AE are both immune disorders, the child should be monitored for potential complications of other immune disorders, such as abdominal purpura or inflammatory bowel disease. Early management is crucial to improve the prognosis in the presence of symptoms.

There are limitations to this study. Firstly, the association between HNL and CASPR2 antibody-associated AE has not been fully elucidated. However, a clinical correlation between the two exists; autoimmune abnormalities may potentially contribute to the development of HNL, and HNL can also cause immune-related reactions leading to CASPR2 antibody-associated AE. Secondly, there is still a lack of relevant diagnostic criteria. Therefore, early diagnosis and treatment can significantly improve patients' symptoms, while delayed treatment may result in irreversible neurological damage or even death. These are all valuable avenues for future research.

Conclusion

In conclusion, HNL may lead to AE or neurologically-related symptoms, and relevant antibody tests should be conducted as early as possible. Early detection and treatment are vital for improving prognosis. This study offers a clinical diagnosis and treatment approach for managing HNL and its associated complications.

Ethics Statement

The disclosure of patient information in this study was reviewed and approved by the Clinical Research Ethics Committee of Wuhan Tongji Hospital.

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