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Clinical Features of CASPR2 Autoimmune Encephalitis in Children

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Abstract

Objective: To investigate the clinical features, treatment and prognosis of CASPR2-antibody encephalitis in children.

Methods: One preschool male child diagnosed with CASPR2 antibody encephalitis was admitted to the Department of Neurology of Xuzhou Children's Hospital. The clinical features, laboratory tests, EEG manifestations, treatment and prognosis were retrospectively analyzed. The relevant literature was searched.

Results: The clinical features of this case were mental and behavioral disturbance. His cranial imaging was normal. The abnormal video EEG showed slow waves, multifocal sharp slow wave and spike wave. His serum anti-CASPR2 antibody titer was 1:10. After 3 weeks of treatment with gamma globulin and steroids, visual hallucination and fear disappeared, hypersomnia and hyperhidrosis were alleviated. The patient could communicate with others, but calculation was limited in simple addition and subtraction. After 6 months, there remained only involuntary movements such as shaking hands, the EEG was normal, the antibodies were negative. These symptoms disappeared one month after oral administration of tiapride. In the literature review, there was no similar domestic case reported in child; while foreign literature reported three cases of children with CASPR2 antibody positive, and two cases were diagnosed with CASPR2 encephalitis. They firstly received treatment of methylprednisolone combined with gamma globulin and achieved significant effect. Another case was diagnosed with Kleine-Levin syndrome, and the symptoms were relieved after oral administration of oxcarbazepine.

Conclusion: Children with CASPR2 encephalitis have a variety of clinical symptoms. They respond well to gamma globulin and methylprednisolone, and the short-term prognosis is optimistic after treatment.

Keywords: Children; Autoimmune Encephalitis; CASPR2; Visual Hallucination; Mental Disturbance; Behavioral Disturbance

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Introduction

CASPR2 (Contactin Associated Protein-like 2) is a cell adhesion molecule of the axonin IV superfamily [1], CASPR2 antibodies can cause multiple neurological syndromes, such as Morvan syndrome, acquired neuromyotonia and so on. These diseases are more common in adults than children. In this paper, one child with anti-CASPR2-related encephalitis and its clinical features, imaging features, treatment options and prognosis were analyzed. Besides, literature review was also conducted, in order to improve the understanding of the disease in children, with the aim of achieving early detection and effective treatment to improve the prognosis of this disease.

Material and Method

General information

A 7-year-old boy with subacute onset, chief complaint: Abnormal mental behavior for 1 month, came to our hospital on February 27th, 2020.

Present history: The child began to flash back game scenes since January 2020, accompanied by a sense of fear, and gradually became restless, accompanied by abnormal movements, such as sniffing, squinting, shaking shoulders, and shaking hands aimlessly, language reduction, sleepless at night, sudden laugh, and profuse sweating. Be able to eat and go to the toilet independently, no

fever, no vomiting, no convulsions.

Past history: Epilepsy (focal seizure: Unilateral muscle twitching with salivation) was diagnosed in our hospital 2 years and 9 months ago, taking levetiracetam (0.25 g, po, q12h), and there was no epileptic seizure for 2 consecutive years.

Personal history: Nothing special, but low grades. Family history: Sister was diagnosed with epilepsy in our hospital when she was 4 years old. She took carbamazepine orally for three years without any effect, and gradually reduced the drug does. Currently, the drug has been stopped for 1 year, and she has no seizures. Mother had a history of convulsions when she was young (the specific convulsions and whether the medication was used is unknown). Aunt was diagnosed with epilepsy when she was 4 years old. She took carbamazepine orally. After 3 years of seizure-free, the drug has been stopped for 2 years, and there is no recurrence. The intelligence of his mother and aunt lag behind peers.

Physical examination

Clear, no drooping eyelids, normal pupil light reflex, normal eye movements, fear of strangers, normal face, sniffling for no reason, squinting, shaking shoulders, waving hands (left and right) and other involuntary movements, restless walking, normal gait, limb strength and muscle tone were normal, sensory and motor examinations were normal, neuropathological signs were negative, and meningeal irritation symptoms were negative. Be able to communicate in simple language, complete simple instructions (such as naming objects and colors) and read numbers below 10, unable to complete addition and subtraction.

Aided examination

Cerebrospinal fluid routine, biochemistry, electromyography, brain MRI are normal, and the video EEG is abnormal. Serum anti-CASPR2 antibody is 1:10, cerebrospinal fluid anti-CASPR2 antibody is negative by the cell-based assay. The family's whole exome examination: The child, his sister with epilepsy and his mother has a heterozygous deletion of GRIN2A: chr16: loss1 (EXON: 2), which is a pathogenic mutation according to ACMG guidelines.

Literature review

Using "children"; "CASPR2"; "immune encephalitis" as keywords to search CNKI, Wanfang, PubMed, and Western Biomedical Journal databases, statistics on "children's CASPR2 antibodies" published at home and abroad from 2010 to 2021. There are five articles relevant to "Clinical Study of Encephalitis". Three cases of CASPR2 antibody-positive children were reported, and two cases were diagnosed with CASPR2 encephalitis, and one case was diagnosed with Kleine-Levin syndrome.

Result

Treatment and follow-up

After admission, the child was initially diagnosed as immune-related encephalitis by combining with the clinical symptoms, imaging and EEG characteristics. When the immune encephalitis antibody results came back, the diagnosis was: CASPR2-antibody encephalitis. Then, human immunoglobulin (2 g/kg, 3 days in total) and methylprednisolone (20 mg/kg/d × 3 d) plus prednisone (2 mg/kg/d × 3 d × 3 rounds) was given. After 3 weeks of treatment, hallucinations and fears disappeared, involuntary movements gradually decreased, and sleep and sweating significantly alleviated. This patient was discharged when he could communicate with others and read numbers below 10 fluently, but calculation was limited in simple addition and subtraction, the titer of serum anti-CASPR2 antibody was 1:10. After 6 months of treatment, all symptoms disappeared except for occasional involuntary movements. There was no slow wave activity on the background of EEG, blood and cerebrospinal fluid antibodies were negative, and the brain MRI was normal. Considering that extrapyramidal function may be involved, the involuntary movements disappeared after a month oral administration of sulfur. In the follow-up duration to May 2021, the child had no abnormal movements, no hallucinations, no convulsions, and could communicate with people normally.

Literature review

Foreign literature reported that there were three CASPR2 antibody positive children, and two of them were diagnosed. No similar cases in children have been reported as CASPR2 encephalitis with developmental retardation and seizures by review of relevant domestic literature. Methylprednisolone combined with gamma globulin was the first choice for treatment, and the curative effect was consistent with the treatment of this child. One case was diagnosed as Kleine-Levin syndrome, also known as Sleeping Beauty syndrome, and the symptoms were relieved after oral administration of oxcarbazepine (Figures 1-4).

Discussion

CASPR2 is a cell adhesion molecule of the axonin IV superfamily [1], a transmembrane protein whose C-terminal interacts with 4.1B protein. 4.1B protein is mainly located in neurons of the limbic system, basal ganglia and other motor areas and sensory pathways, and abundant in the temporal lobe. Antibody CASPR2 and antibody

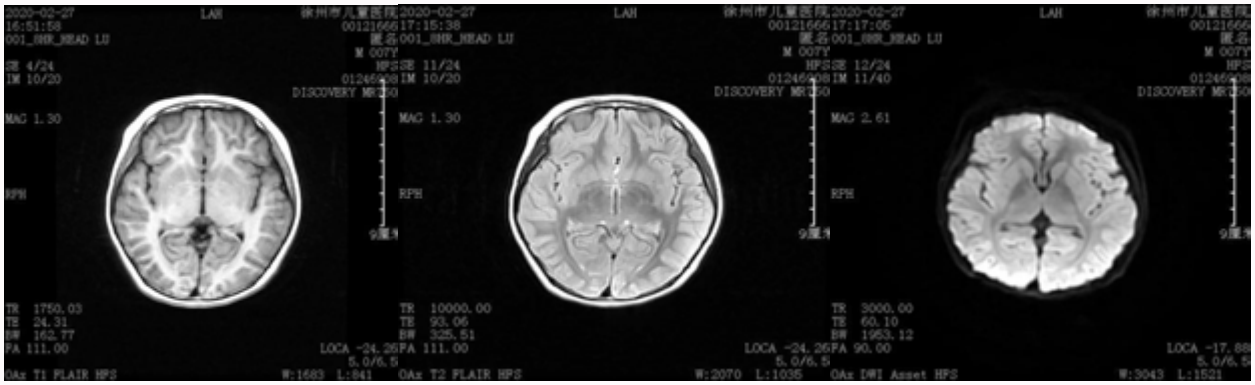

Figure 1: Brain MRI showed no abnormality before treatment.

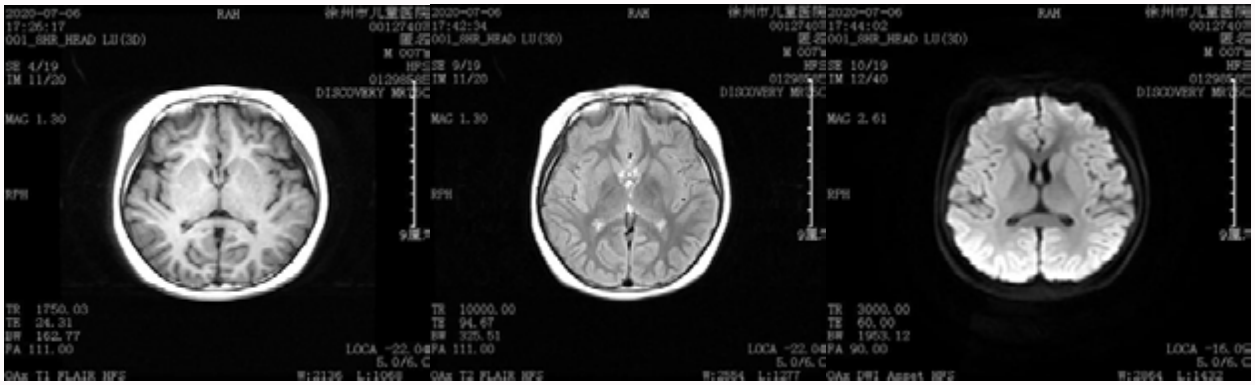

Figure 2: Brain MRI showed no abnormality after 3-week treatment.

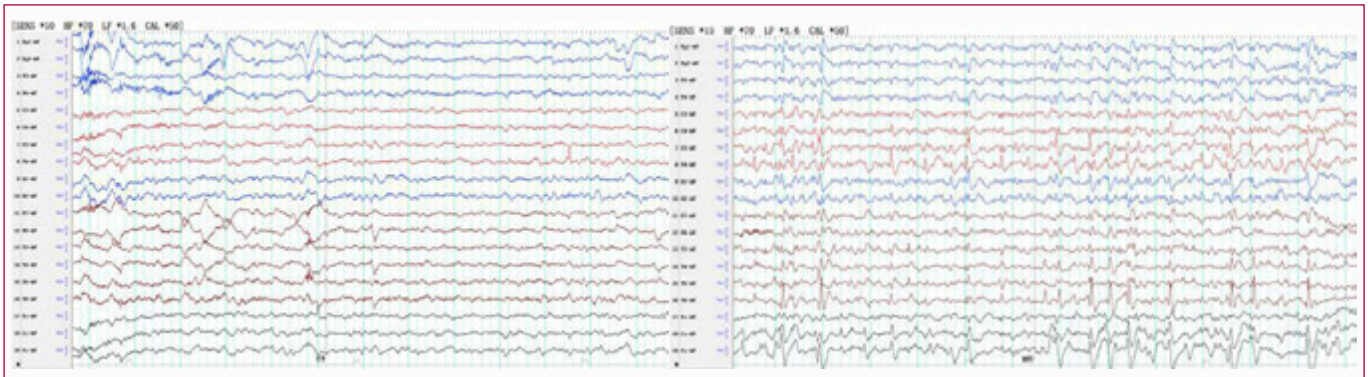

Figure 3: EEG manifestations before treatment: The slow wave of background activity, multifocal sharp slow waves and sharp wave paroxysms can be seen in the central area and posterior cerebrum during the interictal period, the sleep wave is normal, but no EEG in the slow wave sleep phase can be seen, and the parents identified the child with no shaking when EEG manifests seizure.

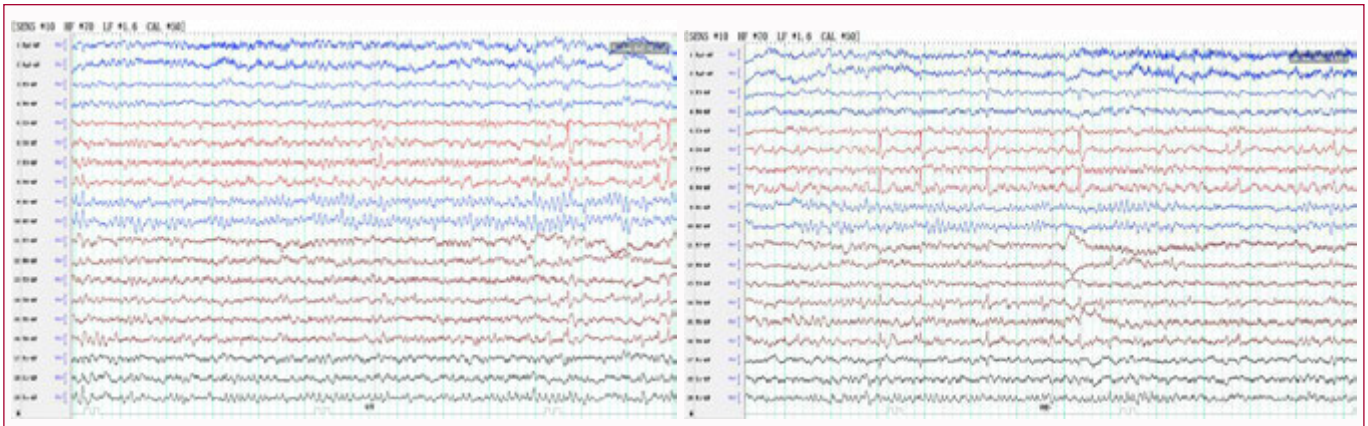

Figure 4: EEG manifestations after 3-week treatment: The slow wave of background activity disappeared, and multifocal sharp slow waves and sharp wave paroxysms can be seen in the central area during the interictal period.

LGI1 (anti-Leucine-rich Glioma Inactivated gene 1) are both anti-VGKC (Voltage-Gated Potassium Channel) antibodies. There is overlap between the two peptides, and they are widely distributed in the central and peripheral nervous system, showing a variety of symptoms. The clinical manifestations of encephalitis caused by CASPR2 in adults are neuromyotonia, Morwan syndrome, limbic encephalitis, cerebellar ataxia, autoimmune Parkinson's syndrome, neuropathic pain, etc. [2-5]. Compared with NMDAR encephalitis, CASPR2 encephalitis in children is relatively uncommon. In 2020, Bien et al. performed a large multi-center study on a sample of 10,919 patients with neurotraumatic symptoms and two neurological antibody tests were conducted in two laboratories. CASPR2 antibody positives are all adult, and most of them are males over 55 years old. No children with CASPR2 positive cases have been found [6], which is consistent with most of the relevant reports. Up to May 2021, there has no pediatric CASPR2 encephalitis in China has been reported. This study is the first case report of CASPR2 encephalitis in children with hallucinatory vision and abnormal mental behavior as the initial symptoms in the preschool age in China.

Neuroimaging studies [7-8] supported that the pathogenesis of anti-CASPR2 antibody-related disease is thought to be due to the blockade of the interaction between CASPR2 and Contactin-2, which

disrupts the expression of KV1 channels, especially in inhibitory interneurons in the hippocampus, which may lead to excessive excitability and network disturbances, which eventually leads to seizures. At the same time, because 4.1B protein bound to the C-terminal part of CASPR2 is mainly located in neurons of the limbic system, basal ganglia and other motor areas and sensory pathways, the clinical symptoms of CASPR2 encephalitis are mainly related with limbic system and basal ganglia damage. For example, the clinical manifestations of this study were related with the increase of extrapyramidal movements, such as hallucinations, abnormal mental behavior, hand shaking, and nuzzling.

Early researches did not differentiate anti-VGKC antibody subtypes. In 2011, 5 children with recurrent epileptic seizures who were positive for anti-VGKC antibodies were reported to have immune encephalitis, but their LgI1 and CASPR2 antibodies in peripheral blood and cerebrospinal fluid were negative [8]. In 2013, among 46 cases of acute severe childhood encephalitis in Taiwan, one child with positive anti-voltage-gated potassium channel antibodies was reported with clinical manifestations of frequent epileptic seizures, cognitive dysfunction, behavioral and psychological changes, while LgI1 and CASPR2 antibody was negative. Furthermore, brain MRI showed bilateral thalamic damage. Even after a sufficient dose of gamma globulin and high-dose methylprednisolone, the child's condition deteriorated significantly in memory, attention and language within a few months. Although the epilepsy was relatively controlled, there remains significant impairment in learning ability. Besides, persistent seizures, cognitive impairment, and behavioral abnormalities persisted during one-year follow-up. The 6 children suffering from immune encephalitis with positive anti-VGKC antibodies in these two studies were all negative for LgI1 and CASPR2 antibodies. The following reasons may be account for that. On the one hand, the antibody titer may be too low. On the other hand, there are other subtypes of anti-VGKC antibodies in addition to LgI1 and CASPR2 antibodies. Which encourage researchers to do in-depth research on anti-VGKC antibodies in the future clinical work. Some researchers also mentioned that in pediatric patients, most VGKC complex antibodies do not bind to LGI1 or CASPR2, thus, detection of anti-VGKC complex antibodies in children has limited diagnostic value [9].

Different from the case in this study, South Korea reported the results of a multi-center study of 1,820 patients with neuroimmune symptoms in 2015, including 5 cases (consist of one child and four adults) of CASPR2 antibody-positive encephalitis, with a median age of 43.5 years. This 8-year-old girl was clinically characterized by fever at the beginning of the disease course, complex partial epileptic seizures with repeated smacking of the lips and unresponsiveness. Secondary progressed with tonic-clonic seizures, status epilepticus, increased sleep. In addition, EEG manifests the θ rhythm of bilateral cerebral hemispheres, brain MRI shows enhancement of meninges, no damaged lesions in brain parenchyma, serum CASPR2 antibody titer 1:10, methylprednisolone (15 mg/kg/d × 5 d) was given. After 18-month follow-up, seizures were significantly reduced, sleep was normal, and EEG shows focal slow-wave activity and epileptiform discharges in the right cerebral hemisphere [10]. In this study, the child had a history of epilepsy before the disease onset, which was clearly caused by the GRIN2A mutation and was well controlled by oral administration of oxcarbazepine. There was no epileptic seizure, and the clinical effect was prominent after combined the usage of gamma globulin and methylprednisolone. After six-month follow-up, other symptoms disappeared except for the occasional shaking and clapping, which disappeared after the addition of tiapride hydrochloride, and there was no sign of recurrence after 15 months of follow-up.

In 2019, a 8-year multicenter study on autoimmune encephalitis antibodies in children (under 18 years old) reported that 241 of 375 enrolled children were positive for cerebrospinal fluid or serum-related antibodies, only a 13-year-old girl was weakly positive for serum CASPR2 with 7 to 10 day's recurrence of confusion, hypersomnia, executive dysfunction, emotional lability, difficulty finding words, and autonomic dysfunction (headache, extremity Cold, etc.), the results of brain MRI and PET were normal, but EEG shows 3 Hz to 5 Hz mixed wave low-frequency activity in the left frontotemporal region. Seizure period PET showed increased blood flow in different brain regions, and routine cerebrospinal fluid examinations (including GAD65-IgG, NMDAR-IgG and CASPR2-IgG) were normal. However, 2 months after the onset, the plasma CASPR2-IgG was weakly positive. After only oxcarbazepine treatment was given, the interval between Seizure period was prolonged and the duration was shortened, and finally diagnosed as Kleine-Levin syndrome, also known as Sleeping Beauty syndrome [11]. The clinical symptoms of the case in this study are similar: Abnormal sleep, emotional instability, speech disorders, autonomic dysfunction, etc. But differences also exist. The case in this study has visual hallucination, abnormal movements, extrapyramidal symptoms. In addition, this case has been diagnosed with focal epilepsy in the past, and has been taking oxcarbazepine and well controlled, suggesting that although these two cases have similar clinical symptoms and positive CASPR2 antibody, the diagnosis and treatment plan of the children are different. Notably, it is inappropriate to diagnose CASPR2 antibody encephalitis merely by laboratory tests, the decision of diagnosis and treatment should be cautious since there are many brain regions involved and the clinical symptoms are diverse.

In 2021, Qin et al. retrospectively studied 25 cases Asian encephalitic patients with serum CASPR2 antibody positive (1:10~1:300) [12], some patients had positive CASPR2 antibody in cerebrospinal fluid, the age range from 3 to 79 years old. The case of children is a 3-year-old child with clinical manifestations of epilepsy, hyperhidrosis, increased sleep, cognitive impairment, etc. The abnormal EEG showed slowed background activity and epileptiform changes. After treatment with gamma globulin and methylprednisolone, the clinical symptoms of the children gradually disappeared except for epileptic seizures. The clinical symptoms and treatment effects were similar to the case in this study, but long-term follow-up was needed to observe whether there is late recurrence. In addition, the sleep disorder in Qin's retrospective study demonstrated increased sleep while our study indicated decreased sleep. Sleep-related brain functional areas include the locus coeruleus, raphe nucleus and thalamus, and the different manifestations of sleep disorders may be related to CASPR2 antibody titers, which are related to different degrees of damage to the autonomic nerve function area.

In conclusion, the incidence of autoimmune encephalitis mediated by CASPR2 antibody in children is extremely low. Currently, there are multi-center studies cooperative worldwide, but the number of cases is very small. Combined with the retrospective analysis of this case and foreign literature reports, it can be concluded as following: CASPR2 encephalitis in children has a variety of clinical symptoms, including cognitive dysfunction, epileptic seizure and autonomic nervous disorder. CASPR2 encephalitis responds well to gamma

globulin and methylprednisolone, and the short-term prognosis after treatment is good. To be more comprehensive, further studies are needed to assess long-term outcomes.

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