

Anti-GluK2 Encephalitis in an Asian Child: A Case Report and Literature Review

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Background: Anti-glutamate kainate receptor subunit 2 (anti-GluK2) antibodies mediated encephalitis is very rare in both children and adults. This study aimed to describe the second report of the anti-GluK2 encephalitis worldwide, the first youngest patient worldwide, and the first case ever in Asia. Besides, this study provides a summary of the clinical manifestations of all previous reported cases.

Methods: The patient was attended at the Department of Pediatrics, Xiangya Hospital, Central South University. Anti-GluK2 antibodies were tested in the serum and cerebrospinal fluid (CSF) by the indirect immunofluorescence on cell-based assays. The clinical information of the patient was collected. In addition, a literature search was carried out in the PubMed.

Results: Our patient was a male who presented with lethargy, recurrent dizziness and vomiting, headache and cerebellar ataxia at the age of 13 years. Prodromal illnesses included Herpes Zoster infection and Mycoplasma pneumonia. The anti-GluK2 antibodies and elevated IL-6 levels were detected in serum while high oligoclonal bands levels were found in the CSF. The intravenous methylprednisolone, immunoglobulin, antibiotics and other symptomatic treatments helped the patient to recover full. We could only find one previous report in the literature (from Barcelona). The literature review plus our report unveiled eight patients with pure anti-GluK2 antibodies related encephalitis. The median age of onset was 28.50 years and majority were males (75.00%). Most of the cases (87.50%) presented with acute cerebellitis symptoms and signs. Preceding or concurrent infection was observed in two patients, while paraneoplastic tumors were observed in two patients. Patients had non-parenchymal brain lesions; the commonest anomalies were those localized in the cerebellum (62.50%).

Conclusion: Our report provides more evidence that anti-GluK2 antibodies may be pathogenic for the autoimmune encephalitis (cerebellitis). Immunotherapy can be used to treat it with good outcome.

Keywords: anti-glutamate kainate receptor subunit 2 (anti-GluK2) antibodies, encephalitis, cerebellitis, immunotherapy

Introduction

Autoimmune encephalitis is a collection of central nervous system inflammatory disorders that can be caused by antibodies against neuronal cell-surface proteins, receptors and ion channels, nevertheless, some patients do not have antibodies.¹ It can affect adults and children. Children usually present with seizures, movement disorders, focal neurological deficits, psychiatric and behavioral symptoms.¹ Autoimmune encephalitis can be diagnosed when patients present with altered mental status (lethargy, personality change or altered level of consciousness) without alternative cause of altered mental status plus 2 of the minor criteria for possible encephalitis and 3 or greater of minor criteria for probable or confirmed encephalitis.^{2,3} Minor criteria include fever > 38 degrees that happened 72 hours prior or after disease manifestation, new focal neurologic findings, new seizures not attributed to an earlier seizure disorder, cerebrospinal fluid (CSF) with ≥ 5 WBC per cubic millimeter, new abnormality on electroencephalograph (EEG) that is consistent with encephalitis, brain image demonstrating an abnormality in the brain parenchyma consistent with encephalitis.^{2,3}

Human autoantibodies against excitatory synaptic transmission (N-methyl-D-aspartate receptors (NMDAR), the alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptors (AMPA), and the kainate receptors) can cause different syndromes.⁴ Anti-NMDAR and anti-AMPA encephalitis are common in pediatric population,⁵ however, anti-kainate receptors encephalitis is very rare in both children and adults. The anti-NMDAR antibodies lead to encephalitis by selectively and reversibly reducing NMDAR surface density and synaptic localization, which in turn abolishes NMDAR-mediated synaptic function, resulting to the observed manifestations such as learning, memory and behavioral deficits.⁶ The anti-AMPA antibodies cause encephalitis by inducing receptor internalization and decreasing AMPARs, which impair long-term synaptic plasticity, learning and memory.⁷ One-third of children diagnosed with autoimmune encephalitis remain with chronic psychiatric and behavioral problems months to years after disease onset.⁸

Kainate receptors include GluK1, GluK2, GluK3, GluK4 and GluK5.⁹ They act as presynaptic regulators of neurotransmitter release at both excitatory and inhibitory synapses by unknown mechanisms.^{10,11} Landa et al reported for the first time 14 cases from Barcelona (of whom three were children aged below 18 years) with anti-glutamate kainate receptor subunit 2 (anti-GluK2) antibodies mediated encephalitis: seven patients had pure anti-GluK2 antibodies, while the rest had mixed types of antibodies.¹² Consequently, they were the first people ever to report the anti-GluK2 encephalitis.¹² The anti-GluK2 antibodies cause encephalitis by internalizing GluK2 receptors resulting to a reversible reduction of synaptic and extrasynaptic clusters of GluK2 as well as a decrease of GluK2-mediated currents.¹² Some patients with this type of encephalitis can respond to steroids or first-line immunotherapy, however, the long-term outcome is not clear due to the rarity of the condition.¹²

In this report, we describe the first Chinese case of the anti-GluK2 encephalitis. We further summarize the previous reported cases and discuss them along with our case to help clinicians and researchers to understand this rare condition better. To the best of our knowledge, this is the second report about anti-GluK2 encephalitis worldwide, the first youngest patient worldwide, and the first case ever in Asia.

Case Report

A 13 years old Chinese boy was admitted at our hospital with chief complaints of lethargy, dizziness and vomiting for half a month, which reoccurred again two days prior to the admission. Prodromal symptoms included fever and cough, which led to his first admission in another hospital. He had a history of being diagnosed with herpes zoster infection two months before the occurrence of the prodromal symptoms. Mycoplasma pneumoniae antibody titer was elevated (1:1280) and the computed tomography (CT) showed evidences of the respiratory infection. Consequently, he was treated with cefoperazone sulbactam, doxycycline, intravenous methylprednisolone (IVMP, unknown low dose for 8 days), ambroxol, nebulization, and rehydration; thus, fever and cough disappeared. Two weeks after the respiratory infection, he experienced dizziness and headache that was followed by non-projectile vomiting of food contents and lethargy. His condition worsened and he was transferred to the second hospital two days later after the onset of dizziness. The frequency of vomiting increased (3–4 times in a day); dizziness and vomiting were more obvious when standing upright and were relieved by lying down. These symptoms were accompanied with ataxic gait; however, he had no other complaints. The mycoplasma pneumoniae antibody titer was lower than before (1:640). Brain magnetic resonance imaging (MRI) showed a slightly larger left ventricle than the contralateral but brain parenchyma was normal. Patient took ceftriaxone, and other symptomatic treatments and got improvement. The family felt that the child was better than before; consequently, they refused lumbar puncture along with autoimmune encephalitis-related antibodies test. Moreover, they refused immunotherapy (IVMP and intravenous immunoglobulin (IVIG)) and requested to be discharged from the hospital five days later.

Patient experienced increased frequency of non-projectile vomiting of food contents again without other obvious cause (5–6 times per day) which was accompanied by severe dizziness, lethargy, and ataxic gait seven days after the discharge. Consequently, his parents decided to bring him to our hospital. On examinations, he had ataxic gait, positive finger-nose test, nystagmus and could fall down easily. Cerebrospinal (CSF) opening pressure during lumbar puncture was 105mmH₂O, however, WBC, protein and glucose levels were normal, and there was no evidence of any pathogen. He had elevated levels of the IL-6 (31.75 pg/mL) in the serum. Electroencephalography (EEG) was normal but the chest CT scan showed infection lesions in the right middle lung and enhanced anterior superior mediastinal patchy density.

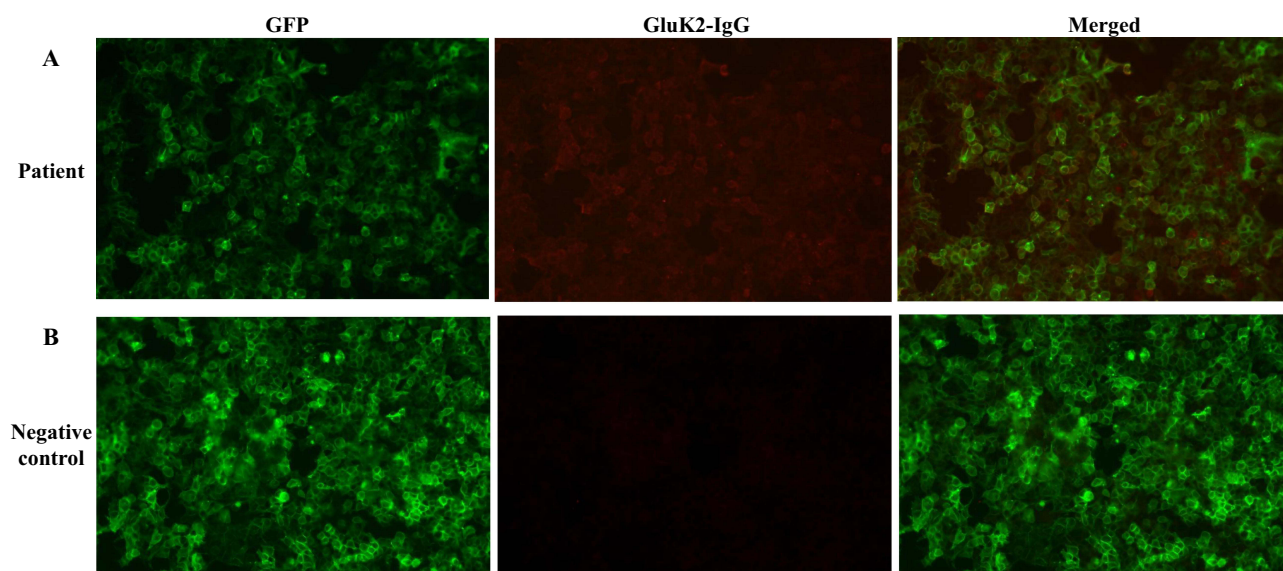


Figure 1 Positive anti-GluK2 antibodies in serum. **(A)** The titer of the patient; **(B)** the negative control. The results above were detected by indirect immunofluorescence on cell-based assays.

Abbreviations: GFP, green fluorescent protein; anti-GluK2, anti-metabotropic-glutamate receptor 2.

We gave him IVIG 20g/day for five continuous days (2g/kg in total), symptomatic treatments and continuous rehydration. The following day, dizziness and vomiting improved a little bit. At that point, he was given low-dose IVMP (1mg/kg per day for two days) as a diagnostic immunotherapy, consequently, the other symptoms improved considerably but the unsteady gait was still present. CSF and serum were screened for the autoantibodies. As a result, anti-GluK2 antibodies IgG were positive (1:32+) in serum (Figure 1) as detected by indirect immunofluorescence on cell-based assays (detections were carried out by Jiangsu Simcere Diagnostic Laboratory) but were negative in CSF. Other screened antibodies included anti-NMDAR/LGI1/CASPR2/GABABR/AMPA1/AMPA2/IgLON5/DPPX/GAD65/mGluR5/GlyR/D2R/MOG/GFAP/GABAAR α 1/GABAAR β 3/NMDAR GluN2A/NMDAR GluN2B/mGluR1/mGluR2/Neurexin-3 α /Cav α 2 δ /KLHL11/PDE10A/AK5/KCTD16/NCAM1, nevertheless, they were all negative (either in serum or CSF). Oligoclonal bands type 2 were positive in the CSF. Otherwise, brain MRI was unremarkable. Based on his clinical presentation and investigations results, the diagnosis of cerebellar ataxia associated with anti-GluK2 antibodies was established. Thus, the IVMP dosage was increased to 250 mg (5mg/kg) for one day, 500 mg/day for 3 days, and then sequential oral prednisone (50 mg once a day initially but was tapered off after the discharge). The addition of the IVMP to IVIG led to the significant improvement of the vomiting, dizziness, and ability to walk. Therefore, our patient met the diagnostic criteria for the possible autoimmune encephalitis: altered mental status (lethargy), fever and cerebellar ataxia, and he responded very well to the first-line immunotherapy. We followed him up for 5 months, and he was doing well according to the last follow-up.

Written informed consent was obtained from the parents to have the case details and any accompanying image published. The study was approved by the ethical committee of Xiangya Hospital, Central South University according to the tenets of the Declaration of Helsinki. The institutional approval was not required to publish the case details; consent was waived due to the retrospective nature of the review, therefore, data was anonymized and maintained with confidentiality.

Literature Review

A literature search was carried out in the PubMed. The key words for searching included: GluK2 and encephalitis or cerebellar ataxia. One published report was retrieved. Fourteen cases with anti-GluK2 antibodies mediated encephalitis have been reported so far: seven patients had pure anti-GluK2 antibodies while seven patients had mixed types of

antibodies. Thus, we now have 15 cases with anti-GluK2 antibodies if we add our patient. The median age of onset for all 15 cases was 41.00 ±24.01 SD (range, 13–75) years. Of those 15 cases, 8 (53.33%) were females.

Differences between patients with pure anti-GluK2 antibodies and those with anti-GluK2 antibodies plus other autoantibodies exist. On the one hand, pure anti-GluK2 antibodies were found in eight cases. The median age of onset was 28.50 ±26.70 SD (range, 13–75) years. Of those eight cases, 6 (75.00%) were males. Seven (87.50%) presented with acute cerebellitis symptoms and signs. Other clinical manifestations included fever (n=3), cough (n=1), dizziness (n=2), vomiting (n=5), headache (n=4), abnormal reflex (n=4), abnormal or reduced level of consciousness (n=5), hydrocephalus (n=2), abnormal behavior (n=1), seizures (n=1), movement disorders (n=4) including myoclonus, opsoclonus, bradykinesia, saccadic pursuit, choreoathetosis and limb weakness. Some cases presented with tumors: Hodgkin lymphoma (n=1) and retroperitoneal teratoma (n=1). Other patients had prodromal or concurrent infection/abuse: Herpes Zoster infection and Mycoplasma pneumonia (n=1) as well as HIV infection and alcohol abuse (n=1). Patients had non-brain parenchyma related abnormalities including abnormal cerebellum (n=5), hydrocephalus (n=2) and brain atrophy (n=2). Therapies used included steroids (n=2), IVIG (n=1), chemotherapy and radiotherapy (n=1). The mean duration of follow up was 25.00 (range, 5–60) months and treatment outcome was as follow: full recovery (n=2), partial recovery (n=3), died (n=2) and unknown (n=1). On the other hand, GluK2 antibodies plus other autoantibodies were found in 7 cases. The mean onset age was 44±22.57 (range, 14–70) years. Of those 7 patients, 85.71% (6/7) were females. The clinical manifestations included cerebellitis (n=1), limbic encephalitis (n=3) and anti-NMDAR encephalitis (n=1). Some cases had tumors: thymoma (n=3) and ovarian teratoma (n=1) and small-cell lung carcinoma (n=1). In addition to anti-GluK2 antibodies, some patients had additional antibodies: AMPAR (n=6), NMDAR (2), glycine receptor antibodies (n=1), CRMP5 (n=2), GABAB (n=1) and CASPR2 (n=1). Brain MRI results included enhanced signal in medial temporal lobes (n=2). The mean duration of follow-up for cases with information was 22.5 (range, 3–39) months. None of the patients had information about the therapies used, however, at the end of follow-up the outcome was as follow: improvement (n=1), partial recovery (n=2), died (n=1) and unknown (n=3). Table 1 summarizes this information.

Table 1 Differences Between the Clinical Features of the Pure Anti-GluK2 Antibodies and Anti-GluK2 Antibodies Plus Other Autoantibodies

Characteristics	Pure GluK2 Antibodies (N=8)	GluK2 Antibodies Plus Other Autoantibodies (N=7)
Age of onset	28.50 ± 26.70 SD (range, 13–75) years	44±22.57 (range, 14–70) years
Sex	6 males and 2 females	1 male and 6 females
Clinical manifestations	Fever (n=3), cough (n=1), dizziness (n=2), vomiting (n=5), headache (n=4), abnormal reflex (n=5), abnormal or reduced level of consciousness (n=5), cerebellitis (n=7), hydrocephalus (n=2), abnormal behavior (n=1), seizures (n=1), movement disorders (n=4) including myoclonus, opsoclonus, bradykinesia, saccadic pursuit, choreoathetosis and limb weakness.	Cerebellitis (n=1), ovarian teratoma (n=1), limbic encephalitis (n=3), anti-NMDAR encephalitis (n=1), small-cell lung carcinoma (n=1).
Tumors	Hodgkin lymphoma (n=1), and retroperitoneal teratoma (n=1)	Thymoma (n=3)
Other antibodies	None	AMPA (n=6), NMDAR (2), glycine receptor antibodies(n=1), CRMP5 (n=2), GABAB (n=1) and CASPR2 (n=1)
Other associated diseases	Herpes Zoster infection and Mycoplasma pneumonia (n=1), HIV infection and alcohol abuse (n=1)	None
Brain magnetic resonance imaging findings	Abnormal ventricle (n=1), abnormal cerebellum (n=5), hydrocephalus (n=2), brain atrophy (n=2),	Enhanced signal in medial temporal lobes (n=2) and normal (n=2)
Therapies for known cases	Steroids (n=2), IVIG (n=1) and Mannitol (n=2), chemotherapy and radiotherapy (n=1)	Unknown
Mean duration of follow up for cases with information	25.00 (range, 5–60) months	22.5 (range, 3–39) months
Treatment outcome	Full recovery (n=2), partial recovery (n=3), died (n=2) and unknown (n=1)	Partial recovery (n=2), unknown (n=3), died (n=1), and improvement (n=1)

Abbreviation: HIV, human immunodeficiency virus.

Discussion

In addition to the previous report,¹² our report provides more evidence that anti-GluK2 antibodies are pathogenic and are related to encephalitis or cerebellitis of unclear etiology. Our patient was the youngest ever reported and presented with acute cerebellitis, altered mental status, anti-GluK2 antibodies and showed response towards steroids and IVIG. Our report has showed for the first time that patients with this type of encephalitis can have elevated IL-6 levels. There are some evidences that IL-6 secretion usually gets stimulated during inflammatory response secondary to infection, leading to the elevation of body temperature.¹³ It is also a growth factor for B cells as it induces their maturation and differentiation into plasma cells and increases their survival, and stimulates B-cell IgG production by modulating the expression of IL-21.¹³ It has been shown that the IL-6 dysregulation is an integral part of the inflammatory pathways of the autoimmune diseases such as neuromyelitis optica spectrum disorder, autoimmune epilepsy, rheumatoid arthritis, Castleman's syndrome, idiopathic juvenile arthritis, and others.¹³ Thus, we assume that infection of our patient triggered the production of the IL-6, which was involved in the pathogenesis of the anti-GluK2 encephalitis, however, more studies are need to explore this connection.

We have observed that pure anti-GluK2 antibodies mediated encephalitis seems to be different from the anti-GluK2 antibodies mediated encephalitis accompanied by other antibodies. Pure anti-GluK2 antibodies mediated encephalitis is characterized by an early adulthood onset age, male predominance, acute cerebellitis and brain imaging abnormalities localized in the cerebellum, whereas, anti-GluK2 antibodies mediated encephalitis accompanied by other antibodies is featured by the late adulthood onset age, female predominance, limbic and anti-NMDAR encephalitis, different types of tumors and non-specific brain abnormalities. Consequently, it seems that the anti-GluK2 antibodies are likely to cause acute cerebellitis with good outcome, while the presence of the anti- GluK2 antibodies plus other autoantibodies might be the accidental finding since most of these patients presented with manifestations related to the additional antibodies rather than anti-GluK2 antibodies.¹² Besides, patients with anti- GluK2 antibodies plus other autoantibodies presented with limbic encephalitis and anti-NMDAR encephalitis, thymoma and ovarian teratoma and small-cell lung carcinoma suggesting the contribution of other antibodies in the clinical manifestations.¹² Future studies can investigate these differences more and their possible causes.

Study Limitations

The fact that we assessed our patient retrospectively and reported only one case, limits our study. We followed our patient for a short duration of time, therefore, it is hard to tell the long-term outcome and predict if he will relapse or not since it has been observed that patients with autoimmune encephalitis often relapse. Since the existing literature is scarce due the rarity of the entity, we cannot tell much about the prognosis of the disease. Future studies are needed to confirm the pathogenicity of the anti-GluK2 antibodies in causing autoimmune encephalitis.

Conclusions

In summary, our report provides more evidence that anti-GluK2 antibodies may be pathogenic in patients with autoimmune encephalitis (cerebellitis). Immunotherapy can be used to treat it with a good outcome. Our case has clinical implications in raising awareness regarding autoimmune encephalitis, and improving the knowledge regarding the diagnostics and treatment of these rare disorders. Although, it is a case report, the documentation of case reports and small case series for rare diseases are important as they provide a basis for future studies.

Abbreviations

Anti-GluK2, anti-glutamate kainate receptor subunit 2; CSF, cerebrospinal fluid; NMDAR, N-methyl-D-aspartate receptors; AMPAR, alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptors; CT, computed tomography; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

The study including all methods adhered to the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board and Research Ethics Committee of Xiangya Hospital, Central South University, Changsha, Hunan. Written consent was obtained from the parents of the subject, which was approved by the Institutional Ethics Committee of Xiangya Hospital, Central South University.

Consent to Publication

The consent for publication was obtained from the parents of the subject.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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None of the authors has any conflict of interest to disclose. The manuscript has been read and approved by all the authors, the requirements for authorship as stated in the journal guideline have been met, and each author believes that the manuscript represents honest work.

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