CASE REPORT

Glycine receptor antibody-associated epilepsy in a boy aged 4 years

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Accepted 7 October 2016

SUMMARY

Our patient was a previously normal boy who presented to his local hospital with an explosive onset of prolonged seizures and encephalopathy. He was treated for a presumed central nervous system infection and initial neuroimaging was normal. Despite treatment with antibiotics and antiepileptic drugs (AEDs), he remained encephalopathic and became ataxic over the next 48 hours, not related to medication. The seizures also proved resistant to treatment despite polytherapy with AEDs, and he required immune-modulatory treatment, intravenous methylprednisolone and intravenous immunoglobulin, in addition to the AEDs to achieve seizure control. The ataxia also improved following treatment. The initial EEG was normal but subsequent EEGs, separated by a week each, were abnormal and revealed subtle atypical 'delta-brush-like waves'. The patient's serum and cerebrospinal fluid were tested for autoantibodies, and he was found to be positive for glycine receptor antibodies that are neuronal antibodies.

BACKGROUND

Glycine receptor antibodies have been reported in adults with progressive encephalomyelitis, rigidity and myoclonus (PERM), but there are only a few cases reported in children with glycine receptor antibody-associated epilepsy, and to the best of our knowledge, none with encephalopathy, ataxia and a 'delta-brush' pattern on EEG.

Previously normal children who present with an explosive onset of seizures and encephalopathy warrant urgent investigations to look for a potentially treatable pathology. In the absence of identifiable aetiologies such as structural brain malformations, central nervous system infections and head injury—a diagnosis of autoimmune-mediated epilepsy should be considered in the differential diagnosis. Additional clinical features that suggest autoimmune-mediated epilepsy disorder may include movement disorders, which occurs in over three-quarter of cases, dyskinesia and/or dystonia in one-tenth of cases and behavioural disorders in one-third of patients. MRI abnormalities can be found in approximately one-third of cases.¹

Prompt recognition of the clinical features of autoimmune epilepsy and subsequent testing can lead to an early definitive diagnosis. This often results in initiation of additional treatment (such as steroids, intravenous immunoglobulin and/or plasma exchange), which can improve the outcome for these children as the seizures can be resistant to standard antiepileptic drugs (AEDs).

Ataxia is an uncommon presenting symptom in children with epilepsy (provided it is not as a result of the AED side effects) and its presence should alert the clinician to consider a neuronal autoantibody-mediated process such as glycine receptor-associated epilepsy.

CASE PRESENTATION

Our patient was a boy aged 4 years, twin one of two, who was born at term by caesarean section. There was no significant medical history and his development was appropriate for age. A week prior to his presentation, he had hand, foot and mouth disease and probably a reflex anoxic seizure following a minor head injury.

He presented to his local hospital with a prolonged afebrile generalised tonic clonic seizure which required treatment with phenobarbitone and phenytoin. He was also empirically treated with intravenous ceftriaxone, acyclovir and oral clarithromycin, and had an urgent CT head which was normal.

Despite emergency treatment, he continued to have several short-lived seizures over the following 24 hours, including generalised tonic clonic and focal seizures. He was therefore started on a course of clobazam. Despite this, the seizures continued and he was started on levetiracetam following discussion with the regional neurological centre. The initial EEG was normal and an MRI brain was undertaken which was also normal.

On day 4 of admission, he developed significant limb and truncal ataxia and was unable to sit unaided or walk. He also developed dysarthria, but there were no other cerebellar signs such as nystagmus or dysmetria. His tone, power and reflexes were normal.

The repeat EEG on day 5 was abnormal, showing diffuse encephalopathic changes.

On reaching adequate doses of clobazam and levetiracetam, the seizure control improved. Over the next 2 weeks, the ataxia also improved; however, he continued to have dysarthria and behavioural difficulties.

He was discharged home with planned follow-up visit within 2 weeks; however, he represented to the hospital within 14 days with a severe escalation of his seizure frequency (~20 seizures per day). At this stage, he was transferred to the tertiary neurology centre where his serum was sent for autoantibodies against N-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel (VGKC), contactin-associated protein-like 2 (CASPAR2),

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To cite: Ude C, Ambegaonkar G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216468

leucine-rich glioma-inactivated protein 1 (LGI-1) and glycine receptors (Gly-R).

He was treated with a 3-day course of intravenous methyl prednisolone followed by a 6-week course of oral prednisolone. He also received a course of intravenous immunoglobulin. Along with optimising the doses of clobazam and levetiracetam, sodium valproate was added to his drug regimen. With the above treatment, his seizure frequency improved from over 20/day to ~1–3 seizures/day.

INVESTIGATIONS

A summary of relevant investigations during his second admission to the tertiary Neurology unit is summarised in [table 1](#).

Our patient was positive for Gly-R antibodies in his serum. A repeat serum Gly-R antibody test performed 2 months later was also positive.

A repeat EEG during his second admission was abnormal with asymmetrical high-amplitude slowing over the right hemisphere. There were epileptiform discharges over the right anterior region. In addition, there were brief bursts of fast/polyspike activity over the right hemisphere showing a ‘delta-brush’ appearance ([figure 1](#)).

Table 1 Summary of investigations

Investigations	Results
Plasma lactate	0.9
Plasma amino acids	Normal
Plasma biotinidase	8.3 (4.4–12 mol/L/min)
NMDAR, VGKC, CASPAR, LGI-1 serology	Negative
TPO antibodies	40 (20–60 µm/mL)
GAD	2 (1–5 units/mL)
Serum Gly-R antibodies	Positive
CSF Gly-R antibodies	Positive

CASPAR, contactin-associated protein; CSF, cerebrospinal fluid; GAD, glutamic acid decarboxylase; Gly-R, glycine receptor; LGI-1, leucine-rich glioma-inactivated protein 1; NMDAR, *N*-methyl-D-aspartate receptor; TPO, thyroid peroxidase; VGKC, voltage-gated potassium channel.

OUTCOME AND FOLLOW-UP

At 6-month follow-up, the patient continues to have short live generalised and focal seizures with up to 3 consecutive seizure-free days. The ataxia has completely resolved and he has mild problems with motor skills.

Inattention, aggressive behaviour, emotional lability and developmental delay have remained major issues and he has developed learning difficulties at school. He is under close follow-up with support from his local community-based multi-disciplinary teams.

DISCUSSION

Introduction

Antibody-mediated epilepsies are a group of neurological disorders whose symptoms appear to be mediated by antibodies to certain neuronal receptors. The causal link between these antibodies and encephalitis is now established.² The majority of case reports have been in adult patients, but in recent years this heterogeneous group of conditions has become well recognised in children. The estimated incidence of NMDAR autoimmune encephalitis (the most frequently reported of the neuronal antibodies) is ~0.85 per million children per year but with features similar to those in adults; some children can also present with partial phenotypes of the disorder.³

In the past decade, various other neuronal antibodies have been linked to autoimmune-mediated epilepsy and encephalopathies. These include VGKC, GAD, LGI-1, CASPAR, thyroid peroxidase and Gly-R antibodies. In paediatric patients, Gly-R antibody-positive autoimmune encephalopathy is relatively less common than the other types as in a large cohort of children with antibody-positive encephalopathy; none was shown to be positive for Gly-R.⁴ It is also the least well defined in terms of its clinical spectrum and phenotypes.

The phenotype of glycine autoimmune encephalopathy in children

Various clinical syndromes associated with Gly-R antibodies have been reported in adults in the literature, most commonly—PERM and Stiff Person Syndrome.^{5 6} Ataxia, as seen in our patient, is not a common presenting clinical feature and was

Figure 1 Delta-brush-like pattern on EEG.

reported in only 9% of patients in a mixed adult/paediatric population study of patients with Gly-R seropositive encephalopathy.⁷

Various EEG changes have been described in autoimmune epilepsies such as delta-brush pattern in NMDAR receptor antibody-positive cases, but these findings are not pathognomic.⁸ At a time when our patient was not taking barbiturates, he demonstrated high-amplitude slowing over the right hemisphere with superimposed brief bursts of fast polyspike activity giving the slowing a subtle delta-brush-like appearance. A study of 23 adults with anti-NMDAR encephalitis showed extreme delta-brush activity on continuous EEG monitoring.⁹ These patients had a more prolonged illness/hospital stay compared with those who did not. In our case, the significance of the EEG findings was unclear. However, its appearance did prompt us to investigate for autoimmune epilepsy.

Treatment and outcome

The typical presentation in antibody-mediated epilepsies is that of multifocal seizures with an explosive onset, that is, rapidly increasing in frequency within a few days of onset. The seizures that are usually refractory to standard antiepileptic medications

require rapid escalation of therapy. There is evidence in literature that early treatment with steroids, intravenous immunoglobulin and plasma exchange and immunomodulatory drugs (such as rituximab) is beneficial. About two-third of patients who received immune therapy show complete recovery while up to 50% of cases still have persisting emotional and behavioural problems at medium long-term follow-up.¹⁰

At the 6-month follow-up, our patient showed significant improvement of his epilepsy following treatment with steroids and immunoglobulin, but had persistent emotional and behavioural difficulties. It has been difficult to ascertain whether this is a side effect of steroid treatment or that of the autoimmune epilepsy, and he will require detailed neuropsychological assessment to prognosticate his neurodevelopmental outcome.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Autoimmune-mediated epilepsy must be considered in patients presenting with explosive onset epilepsy, especially when there is no evidence of other symptomatic causes for the seizures.
- ▶ When these seizures also present with unexplained encephalopathy, ataxia and other movement disorders, an autoimmune cause should be considered and investigated for.
- ▶ EEG findings may be normal at initial presentation, but the abnormalities evolve over time. It is worth repeating the EEG if seizures continue and if new features develop.
- ▶ Abnormal patterns on EEG, such delta-brush activities, should raise the suspicion for an autoimmune cause.
- ▶ Early recognition of symptoms and aggressive treatment with steroids and other immune-modulatory treatments improves outcome for patients.

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