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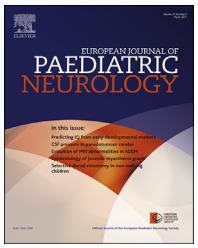

Case study

Focal status epilepticus and progressive dyskinesia: A novel phenotype for glycine receptor antibody-mediated neurological disease in children

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ABSTRACT

Background: Antibody-associated disorders of the central nervous system are increasingly recognised in adults and children. Some are known to be paraneoplastic, whereas in others an infective trigger is postulated. They include disorders associated with antibodies to N-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel-complexes (VGKC-complex), $GABA_B$ receptor or glycine receptor (GlyR). With antibodies to NMDAR or VGKC-complexes, distinct clinical patterns are well characterised, but as more antibodies are discovered, the spectra of associated disorders are evolving. GlyR antibodies have been detected in patients with progressive encephalopathy with rigidity and myoclonus (PERM), or stiff man syndrome, both rare but disabling conditions.

Case Report: We report a case of a young child with focal seizures and progressive dyskinesia in whom GlyR antibodies were detected. Anticonvulsants and immunotherapy were effective in treating both the seizures and movement disorder with good neurological outcome and with a decline in the patient's serum GlyR-Ab titres.

Conclusion: Glycine receptor antibodies are associated with focal status epilepticus and seizures, encephalopathy and progressive dyskinesia and should be evaluated in autoimmune encephalitis.

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1. Introduction

Antibody-mediated encephalitis is now a well-described entity in adults and children.[1] In children and young adults the commonest antibody-mediated encephalitis is associated with N-methyl-D-aspartate (NMDA) receptor antibodies. The patients present with neuropsychiatric disturbance, seizures, movement disorders (including orofacial dyskinesias), encephalopathy and autonomic disturbance.[2] Phenotypes associated with the antibodies to the VGKC-complexes, and the component proteins (leucine-rich, glioma inactivated 1, LGI1) and CASPR2, include limbic encephalitis (memory loss, seizures, hyponatremia) and the syndrome of facio-brachial dystonic seizures (frequent focal dystonic episodes involving one arm and ipsilateral hemiface, FBDS) both predominantly with VGKC-complex/LGI1 antibodies and, so far, only in older adults. Much rarer is Morvan's syndrome (neuromyotonia, autonomic dysfunction and sleep and circadian rhythm disturbance) with mainly VGKC-complex/CASPR2 antibodies.

Also considered very rare is progressive encephalomyelitis with rigidity and myoclonus (PERM); sometimes called Stiff Person Syndrome Plus (SPS Plus) and with antibodies to glutamic acid decarboxylase (GAD).[3] However, PERM is now increasingly found with glycine receptor antibodies (GlyR-Ab), in adults[4,5] and has been described in children.[6,7] The phenotypes associated with GlyR-Abs are beginning to widen as more patients are identified.[8,9]

We describe a child presenting with seizures and encephalopathy who subsequently developed dyskinesias. He responded to treatment for antibody-mediated encephalitis. Antibodies to GlyR alpha1 subunits were identified. Falling serial titres correlated with the clinical improvement following immunotherapy. This patient illustrates that GlyR-Ab mediated encephalitis requires and is responsive to immunotherapy and titres correlate with severity of dyskinesias.

2. Case report

A previously-well 3 year 5 month old Chinese boy experienced increased moodiness and agitation for 4–5 days, urinary incontinence in sleep and two focal seizures starting with left upper limb twitching; one with blank unresponsive staring for 15 min and a second with slurred speech and nodding of head to questions, lasting 45 min and aborted with benzodiazepines in hospital. There was no fever, coryzal symptoms, vomiting, diarrhoea, headaches, dysuria or preceding head injury, trauma, recent travel or infective contacts. Development was age-appropriate with no past or family history of seizures, epilepsy or developmental delay. He was well hydrated and afebrile with no neurocutaneous stigmata and normal systemic examination apart from a papular rash over the left temporal region and atopic eczema. Initial investigations including electroencephalogram (EEG) were normal (Table 1). The patient was incidentally noted to have nasopharyngeal aspirate briefly positive on immunofluorescence for Parainfluenza 3, and Beta thalassaemia minor.

No further seizures occurred but paroxysmal behavioural outbursts persisted lasting 5–35 min, with screaming, sudden awakening from sleep, non-specific pain, agitation, obsessive hand-cleaning and picking up non-existent rubbish. He received intravenous levetiracetam followed by oral lorazepam due to concerns that levetiracetam might exacerbate his behaviour. He was discharged well after 4 days but was readmitted on day 25 of illness with three new focal left upper limb seizures: two 2–3 min tonic seizures and one 10-min tonic-clonic seizure. Post-ictal sleepiness and left upper limb weakness and clumsiness were noted. There was no inter-current illness, fever, vomiting, headaches, photophobia, loss of appetite or loss of weight. Cranial nerve

Table 1 – Summary of investigations.

Full blood count	Haemoglobin 13.7 g/dL White cell count 9.11 × 10^9/L Platelet count 392 × 10^9/L MCV 57.3
Iron studies	Normal
Hb electrophoresis	Consistent with Beta thalassaemia minor. No HbH inclusion bodies seen. Testing for the five common Alpha thalassaemia gene mutations showed no abnormality.
Serum electrolytes	Normal, no acidosis
Calcium, magnesium, phosphate	Normal
Liver function tests	Normal
Creatine Kinase	176 U/L
Urinalysis and microscopy	Normal. No pyuria.
Erythrocyte sedimentation rate (ESR)	5 mm/50 min
C-reactive protein	0.7 mg/L
Anti-nuclear antibody	Negative
Double stranded DNA antibody	Negative
Anti-cardiolipin antibody (IgM & IgG)	Negative
Throat swab mycoplasma PCR	Negative
Mycoplasma serology	No elevation of or rise in titre
Nasopharyngeal immunofluorescence	Parainfluenza 3 Positive (Day 2), Repeat negative (Day 9)
Stool enterovirus	Negative
Ammonia	Normal
Lactate, serum	Not elevated
Acylcarnitine profile	Normal
CSF white cell count	0
CSF protein	0.14 g/L
CSF culture	Negative
CSF Herpes simplex PCR	Negative
CSF Enterovirus PCR	Negative
CSF Mycoplasma PCR	Negative
Paired plasma & CSF Amino acids	Normal
CSF Lactate	Not elevated
CT brain	Normal
MRI brain with contrast	Normal
Abdominal ultrasound	Normal
EEG (day 3 of illness)	Normal interictal EEG
Continuous EEG monitoring (day 44)	Interictal spikes over C4. No ictal rhythms