INTRODUCTION

The gamma-aminobutyric acid-A receptor (or $GABA_AR$) is an inhibitory ligand-gated ion channel that plays a role in higher cortical functions such as motor control, vigilance and cognition. Altered $GABA_AR$ function has been identified in anxiety disorders, depression and schizophrenia[1]. Human autoantibodies to the alpha 1 and beta 3 subunits of the $GABA_A$ receptor have been shown to result in autoimmune encephalitis[2].

Studies have shown $GABA_AR$ antibodies may reduce the number of $GABA_AR$ or alter their distribution[3]. $GABA_AR$ encephalitis may present with seizures, cognitive impairment, reduced consciousness, altered behaviour or movement disorders[2]. However, $GABA_AR$ encephalitis is novel and the spectrum of clinical features is not fully defined. This case is unique in that it is the only adult case we are aware of in which the patient has a largely catatonic presentation.

CASE DESCRIPTION

A 22-year old, right-handed Nigerian woman presented to her local emergency department with a four-day history of agitation, confusion, insomnia and repeating words. Two days prior she had developed pharyngitis, and two weeks previous had an uneventful influenza vaccination.

She had a background of mild learning disability and sickle cell anaemia with vasculopathy including, a cerebral infarct and subarachnoid haemorrhage with subsequent hydrocephalus and right ventriculoperitoneal (VP) shunt insertion eleven years previously. She then underwent a left extracranial-intracranial bypass to improve cerebral blood flow. Nine months prior to this presentation she had a further subarachnoid haemorrhage and an external ventricular drain was placed. She was treated with regular exchange transfusions six weekly as part of sickle cell management. Seizure history is unclear but due to her risk of post-stroke seizures, she took carbamazepine modified-release 600mg in the morning, 400mg in the evening. Family denies consumption of illicit or psychoactive substances; urine toxicology was not sent. She was independent, in part-time education and due to start an apprenticeship.

When admitted, a computed tomography (CT) of brain excluded an intracranial bleed. At this stage she was still able to engage in normal conversation. Overnight she deteriorated and a transfer with sedation was arranged to our regional neurosciences centre. Ambulating around the ward, she made eye contact when addressed but produced no coherent speech and did not follow instructions. She recognised her mother but was agitated and often wandered in to other patients' cubicles. A few days later she seemed elated, laughing inappropriately, gesticulating and persistently tapping the table.

A week later she was unable to answer any questions and when called by her name she repeated it without meaning. She displayed automatisms intermittently raising her arms, and would laugh and point to staff that spoke to her. Her agitation was responsive to lorazepam. This progressed to alternating periods of stillness and periods of intense gesticulation and incoherent vocalisations. There was no clear focal neurological deficit. A few days later, she had a self-limiting generalised tonic-clonic seizure lasting two minutes in the context of a Pseudomonas line tip infection.

Aside from a stable macrocytic anaemia, the following blood tests were normal or negative: liver and renal profile, thyroid function, carbamazepine level, serum electrophoresis and immunoglobulins, vasculitis and viral screen (HIV type 1 and 2 antibodies, p24 antigen, hepatitis B and C viruses, herpes simplex viruses, Epstein-Barr, varicella-zoster, cytomegalovirus, adenovirus, parvovirus B19 and treponemal antibodies), anti-neuronal antibodies (Hu, Ri and Yo), voltage gated potassium channel (VGKC) antibodies, and N-Methyl-D-aspartate (NMDA, fixed assay) antibodies.

MRI head (and whole spine) was compared to her CT head scan nine months prior, and showed stable appearances (*Figure 1*). A right trans-occipital ventricular catheter is seen traversing the right occipital horn with right hemispheric encephalomalacia and occipital haemosiderin deposition, diffuse right dural thickening and enhancement secondary to the shunt, and an unchanged Chiari 1 malformation. CT pelvis showed a left adnexal mass but a teratoma was excluded.

Lumbar puncture was challenging with heavily bloodstained CSF, a white cell count above 30/cmm , no growth and no organisms, glucose level 4.3mmol/l (6.3mmol/l in serum), and protein very elevated at 14.2g/l. A viral screen, oligoclonal bands, and NMDA and VGKC antibodies in CSF was negative. Ventricular CSF analysis

after a VP shunt tap that drained 35ml without noticeable improvement, showed white and red blood cells less than 5/cmm, no growth, no organisms, glucose level 3.4mmol/l, protein 0.66g/l and a negative viral screen, immunophenotyping and cytology.

Electroencephalogram (EEG) at presentation showed intermittent slowing over both hemispheres. A further EEG one month later showed slowing over the left temporal area, contralateral to her strokes, but no epileptiform discharges.

The case was discussed at our multi-disciplinary meeting (MDM), with neuropsychiatry input. The clinical presentation was felt to be that of catatonia without evident psychosis. The acute onset, prominent agitation, unusual movements and progression to mutism, in the context of multiple neurological issues suggested an organic rather than psychiatric aetiology. In the absence of evidence to support another cause, autoimmune encephalitis was considered. She was initially treated with intravenous (IV) methylprednisolone (20mg/kg) for three days, followed by oral prednisolone (60mg) tapered over several months.

Four months into her admission, her clinical condition remained largely unchanged. A repeat EEG *(Figure 2)* showed features to support a mild encephalopathy with focal cerebral dysfunction in frontotemporal regions and a liability to focal onset epileptic seizures. The Oxford immunology panel was extended to include VGKC subunits (LGi1 and CASPR2), AMPA receptors 1 and 2, GluR3 and GABA receptor (A and B) antibodies. All were negative except serum $GABA_A$ antibody with a titre of 2.5. The range is between 0 and 4; if below 1 the result is negative, with increasing levels of positive binding from 1.5 to 4. Unfortunately, $GABA_AR$ was not requested in the CSF.

We decided to treat this as an unusual presentation of $GABA_AR$ encephalitis with IV immunoglobulin (2g/kg) over five days, increased prednisolone back to 60mg daily, and a week later, two infusions of rituximab (1g each), two weeks apart.

Following this there was gradual improvement. Over three months she became more interactive and could speak intelligibly enough to communicate her needs. The Bush-Francis Catatonia Rating Scale *(*BFCRS, *Bus*h, *Fink, Petrides, Dowling, & Francis, 1996*), a 23-item screening tool to assess for extent of catatonia, improved from 18 to 12 (normal 0, moderate >9, *Table 1).* Six months later, following neurorehabilitation, she has fully recovered and plans to go to university.

Table 1

Bush-Francis Catatonia Rating Scale				
1) Excitement	6) Grimacing	11) Rigidity	16) Automatic obedience	21) Perseveration
2) Immobility/ stupor	7) Echolalia/ Echopraxia	12) Negativism	17) Mitgehen	22) Combativeness
3) Mutism	8) Stereotypy	13) Waxy flexibility	18) Gegenhalten	23) Autonomic abnormality
4) Staring	9) Mannerisms	14) Withdrawal	19) Ambitendency	
5) Posturing/ cataplexy	10) Verbigerations	15) Impulsivity	20) Grasp reflex	

DISCUSSION

$GABA_AR$ encephalitis

Typically presents with refractory seizures, with high $GABA_AR$ antibody titres in serum and CSF and MRI abnormalities[3]. Insufficient evidence exists regarding whether titres in serum or CSF are more valuable as antibodies have been found in serum but not CSF in some cases[2]. Low antibody titres have been observed in patients with a wide range of symptoms in the presence of comorbidities including autoimmune disorders. In these cases the pathogenic relevance of the antibody is uncertain. In one case, high titres in a symptomatic patient fell once treated, supporting a pathogenic role for the antibody[4].

Multifocal cortical and subcortical changes are often seen on MRI[2] which may be caused by the immune response or by prolonged seizures[3]. The correlation between MRI changes and disease severity is unclear: asymptomatic patients have shown imaging abnormalities[2], in other cases MRI changes resolved with successful treatment. The lack of MRI correlation in our patient may be attributed to significant pre-existing cerebral disease, or to the absence of frequent seizures. EEG classically shows periodic epileptiform discharges in the

temporal lobes with slowing. The absence of frequent seizures in our patient may relate to antiepileptic premedication.

Vaccination is proposed as a possible trigger for a $GABA_AR$ immune response[2]. Previous studies suggest $GABA_AR$ encephalitis in children tends to be viral-related, whilst in adults is tumour-driven[2.] Another study states 39 per cent of patients with $GABA_AR$ antibodies are under 18 years, whilst other encephalitides (except NMDA) largely affect adults; and most patients with $GABA_AR$ antibodies do not have a tumour[3]. Our patient had a preceding pharyngitis and influenza vaccination but no evidence of an underlying tumour.

Most cases in the literature received corticosteroids, immunoglobulin or plasmapheresis first line, and rituximab, azathioprine, ciclosporin or cyclophosphamide as second line immunotherapy.

Catatonia

A psychomotor disorder of varied aetiology that features diffuse motor hypoactivity and stereotyped motor hyperactivity. According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, diagnosis of catatonia requires the presence of two of the following: rigidity, waxy flexibility, stupor, excitement, mutism, negativism, withdrawal, posturing/cataplexy, mannerisms, stereotypy, staring, grimacing, echolalia/echopraxia and verbigeration. The causes of catatonia are summarised in *Table 2*. Catatonia can be assessed with the BFCRS, a standardised, quantifiable examination of catatonia, scoring 0 to 3 to give a measure of severity (*Table 1)*.

Table 2: Causes of catatonia

Infection	Viral encephalitis
Autoimmune	NMDA receptor encephalitis $GABA_AR$ encephalitis
Drug-related	Ciprofloxacin Ketamine Neuroleptic malignant syndrome due to antipsychotics Withdrawal from alcohol, benzodiazepines, clozapine
Metabolic	Hyponatraemia Hypercalcaemia Hepatic encephalopathy Diabetic ketoacidosis
Non-convulsive status epilepticus	
Other brain insults	Stroke Head injury Neoplasm
Neurodegenerative disorders	Parkinson's disease
Psychiatric	Psychosis Post-traumatic stress disorder Severe depression Bipolar disorder

$GABA_AR$ and catatonia

Catatonia is very common in NMDAR encephalitis, occurring in up to 88% of cases[5]. The possible association with $GABA_AR$ antibody encephalitis is less well described. A paediatric case of catatonia without seizures in the presence of $GABA_AR$ antibodies in serum and CSF[6], is described in the literature. She had a preceding viral meningitis as well as pre-existing autoimmune disease (primary hypoparathyroidism), and presented with a 5-day history of fever, fatigue and reduced appetite. An adolescent case of catatonia (BFCRS 13) in a patient with $GABA_AR$ antibodies in serum (in which CSF was not tested) is also described. In this case, CSF, MRI, PET and EEGs were normal. Serum $GABA_AR$ became negative after treatment with plasmapheresis alongside resolution of the catatonia[7]. This patient then showed re-emergence of $GABA_AR$ in serum, undetectable in CSF, with a relapse that again became negative after treatment. Improvement in catatonia was strongly linked with disappearance of $GABA_AR$ antibodies with immunotherapy[7].

Catatonia has been associated with a reduced density of $GABA_AR$ in the left sensorimotor cortex on iomazenil single-photon emission computed tomography (SPECT), suggesting that GABAergic hypofunction may be central to the disorder[8]. With this in mind, lorazepam, a known $GABA_A$ potentiator, is an established treatment for catatonia.

Conclusion

The causative role of the $GABA_AR$ antibody in this case remains uncertain, as catatonia has also been reported in association with sickle cell disease[9] and stroke. However, there was no recent vascular event at the time of this patient's acute presentation, and other organic causes of catatonia were excluded as far as possible. The patient's improvement with immunomodulatory treatment supports the notion that this may have been an atypical presentation of $GABA_AR$ encephalitis.

KEY POINTS

1) Autoimmune encephalitis can present with catatonia and should be suspected in the presence of seizures or autonomic instability.

2) The Bush Francis Catatonia Scale is a useful tool as a measurable assessment of response to treatment in patients with catatonia.

3) Prior anticonvulsant use may delay or conceal a presentation of $GABA_AR$ encephalitis.

4) A viral trigger may precede an autoimmune neurological response, particularly where there is pre-existing blood-brain barrier dysfunction.

5) GABAergic hypofunction may have a causative role in catatonia.

References

[1]Fatemi SH, Folsom TD. GABA subunit distribution and FMRP-mGluR5 signaling abnormalities in the cerebellum of subjects with schizophrenia, mood disorders, and autism *Schizophr Res* 2015; 167 (1-3): 42-56

[2]Spatola M, Petit-Pedrol M, Simabukuro M, et al. Investigations in $GABA_A$ receptor antibody-associated encephalitis *Neurology* 2017; 18(11*):* 1012-1020

[3]Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the $GABA_A$ receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies *Lancet Neurol* 2014; 13: 276-86

[4]Ohkawa T, Satake SI, Yokoi N et al. Identification and Characterisation of $GABA_A$ Receptor Autoantibodies in Autoimmune Encephalitis *J Neurosci* 2014; 34(24): 8151-8163

[5]Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis *Lancet Neurol* 2011; 10(1): 63-74

[6]Nikolaus M, Knierim E, Meisel C, et al. Severe $GABA_A$ receptor encephalitis without seizures: A paediatric case successfully treated with early immunomodulation *Eur J Paediatr Neurol* 2018; 22 (3): 558-562

[7]Pettingill P, Kramer HB, Coebergh JA, et al. Antibodies to $GABA_A$ receptor α1 and γ2 subunits – Clinical and serologic characterization *Neurology* 2015; 84:1233-1241

[8]Northoff G, Steinke R, Czcervenka C et al. Decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia: investigation of in vivo benzodiazepine receptor binding. *J Neurol Neurosurg Psychiatry* 1999; 67(4): 445-50

[9]Dhossche DM, Shettar SM, Kumar T, Burt L. Electroconvulsive therapy for malignant catatonia in adolescence *Southern Medical Journal* 2009; 102(11): 1170-2