CASE REPORT

Cerebellar ataxia and epilepsy with anti-GAD antibodies: treatment with IVIG and plasmapheresis

Zoya Georgieva,¹ Matthew Parton²

¹Queen Elizabeth Hospital
King's Lynn, King's Lynn, UK
²Centre for Neuromuscular
Disease, National Hospital for
Neurology and Neurosurgery,
London, UK

Correspondence to
Dr Matthew Parton,
Matt.Parton@uclh.nhs.uk

SUMMARY

Glutamic acid decarboxylase autoantibody (GAD-65) catalyses glutamate conversion into γ -aminobutyric acid (GABA) in the central nervous system and in the pancreatic β cells. Antibodies targeting GAD-65 are of uncertain pathogenic significance and occur in stiff person syndrome, cerebellar ataxia, epilepsy, limbic encephalitis and combinations thereof and diabetes mellitus. A 45-year-old man with a cerebellar gait ataxia, dysmetria, nystagmus and mild cerebellar dysarthria was diagnosed with insulin-dependent diabetes mellitus a year after the onset of neurological symptoms. He also developed complex and tonic-clonic seizures, resistant to anticonvulsant medication and deteriorated cognitively. Blood and cerebrospinal fluid serology, and imaging supported the diagnosis of GAD-65 cerebellar ataxia and epilepsy. He was treated with intravenous immunoglobulin and subsequently plasmapheresis. We report the outcome of 3 years of treatment, which resulted in the improvement of cerebellar signs (particularly gait), with some ultimate decline of efficacy.

BACKGROUND

Antiglutamic acid decarboxylase autoantibody-65 (GAD-65) cerebellar ataxia is rare and evidence for its management is lacking, other than in case reports. The rationale for the use of intravenous immunoglobulin (IVIG) is best supported by a recent small randomised controlled trial (RCT) in patients with stiff person syndrome (SPS). This report contributes a long duration of follow-up and discusses plasmapheresis in combination with IVIG as a potentially effective treatment for GAD-65 associated ataxia and epilepsy.

CASE PRESENTATION

A 45-year-old right-handed man noticed problems with gait, balance and coordination, abnormal eye movements and trembling of his hands in 2002. He was diagnosed with insulin-dependent diabetes mellitus in 2003 after losing 25 kg weight in 6 months. Since 2006 he has had complex seizures up to thrice weekly at night (preceded by visual hallucinations, typically losing awareness for 10 min) and occasional generalised tonic-clonic seizures.

Complex seizures still occur once monthly and convulsions every 2–3 months despite high doses of anticonvulsants. His cognitive function has gradually declined since 2007, requiring him to stop working as a company director and his walking has deteriorated to 40 m with support.

There is no family history of ataxia, epilepsy or dementia but a maternal aunt suffers from multiple sclerosis.

Neurological examination reveals multidirectional gaze-evoked nystagmus, with an oblique component on lateral gaze, and downbeat nystagmus in the primary position. Cerebellar dysarthria is minimal and gait is ataxic (broad-based and he cannot stand or walk heel-to-toe). There is bilateral dysidiadochokinesia, intention tremor and positive heel-shin test. Upper limb deep tendon reflexes are mildly exaggerated, lower limb reflexes are normal and plantars are down going. Neurological and general examinations are otherwise unremarkable.

INVESTIGATIONS

Differential diagnoses and investigations are listed in table 1.

DIFFERENTIAL DIAGNOSIS

Primary progressive multiple sclerosis was suspected, given the cerebellar syndrome and positive cerebrospinal fluid (CSF) oligoclonal bands. Of 301 patients with MS in a series, 11% had cerebellar symptoms at the onset¹ but patients most severely ataxic also have spasticity and weakness and the lack of demyelination disseminated in time/space on MRI fails to satisfy MacDonald's criteria.

Multiple system atrophy (MSA) represented 29% of 112 cases of late-onset ataxia² but autonomic features at presentation are common (41%), and a pure cerebellar syndrome is not (9%).³ Along with the absence of typical MRI features, this refuted an MSA diagnosis.

A toxic or metabolic cause appeared unlikely without excess alcohol consumption, drug history (eg, lithium, phenytoin) or symptoms of hypothyroidism. Vitamin deficiencies are often accompanied by further signs, for example, ophthalmoplegia in thiamine deficiency, areflexia and proprioception loss in vitamin E deficiency. Rare neurodegenerative causes of ataxia like Creutzfeldt-Jacob disease would also exhibit additional features (faster-progressing dementia, psychiatric disturbance, myoclonus and sensory symptoms).

This patient's age and predominantly cerebellar signs are compatible with being the index case of an autosomal dominant spinocerebellar ataxia type 3 (Harding classification), for example, SCA6. The lack of family history could also be explained by an autosomal recessive condition, or the phenomenon of genetic anticipation seen in trinucleotide repeat disorders, such as Friedreich's ataxia and some

CrossMark

To cite: Georgieva Z,
Parton M. *BMJ Case Rep*
Published online: [please
include Day Month Year]
doi:10.1136/bcr-2013-
202314

Table 1 Differential diagnoses and investigations

Differential diagnosis	Investigation	Results and conclusion
Stroke	► T2W MRI ► History	► No focal lesions ► Insidious onset of symptoms ► Sudden vascular event unlikely
Intracerebral mass	► T2W MRI	► Minimal cerebellar more than cerebral volume loss between 2006 and 2007, stable by 2010 ► No mass lesions
Multiple sclerosis	► T2W MRI	► No evidence of demyelination
Multiple system atrophy	► T2W MRI	► No typical signs (eg, 'hot cross bun' sign)
Paraneoplastic syndrome	► History ► FDG-PET (whole body and brain) ► Onconeural antibodies (against voltage-gated calcium channels, glycine receptors, NMDA receptors, Purkinje cells, Yo, Ri, Ma1, Ma2, amphiphysin, Tr, CRMP5/CV2)	► No clinical pointers to malignancy ► No FDG-avid lesions ► Negative onconeural antibodies
Inherited cerebellar syndrome	► SCA6 genetic testing	► Normal
Autoimmune cerebellar syndrome	► GAD65 antibody ► CSF analysis	► GAD65 antibodies strongly positive in serum and CSF ► Oligoclonal bands in CSF but not in serum ► All other CSF constituents normal

Full blood count and blood biochemistry normal at baseline except for mean corpuscular volume (103- on azathioprine) and glycated haemoglobin 68 mmol/L or 8.4% due to diabetes mellitus.

CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose-positron emission tomography; GAD-65, glutamic acid decarboxylase autoantibody.

spinocerebellar ataxias, meaning that previous generations showed only mild disease.

However, cerebellar ataxia with GAD antibodies was diagnosed based on the examination, autoantibody detection and MRI findings, with further support from the patient's response to treatment.

TREATMENT

Concluding this was an immune-based illness, regular IVIG (2 g/kg over 5 days) was started in 2009, with concomitant azathioprine (100 mg once daily) to minimise the need for IVIG. Plasmapheresis was first performed in late 2011 (5 sessions over 5 days, replacing plasma with a total of 19 L human albumin solution). The period of follow-up presented herein is between 2009 and December 2012.

OUTCOME AND FOLLOW-UP

Figure 1 outlines the course of treatment. Initially, IVIG infusion was at 10 weekly intervals as cerebellar signs improved

maximally within 8 weeks and then declined rapidly. The effectiveness of IVIG gradually decreased to 6–7 weeks presently, and current treatment is at eight weekly intervals.

Plasmapheresis in 2011 resulted in a dramatic improvement in walking and a complete lack of seizures for 12 weeks. After subsequent IVIG and plasmapheresis, the patient subjectively felt no better but both treatments had a measurable small-to-moderate effect on examination.

The current plan is for plasmapheresis at every 4 months, occurring 3 weeks before the regular eight weekly IVIG infusions.

DISCUSSION

GAD catalyses glutamate conversion into γ -aminobutyric acid (GABA) in the central nervous system (CNS) and in the pancreatic β cells. Autoantibodies in CNS disease and diabetes mellitus target the GAD-65 isoform but differ, for example, sera from patients with SPS but not from patients with diabetes recognise a linear epitope at the N-terminal of GAD-65⁴ and anti-GAD-65

Figure 1 Standardised Ataxia Rating Assessment (SARA, maximum score 40, higher scores indicate worse ataxia; scale by Schmitz-Hübsch¹¹).

titres are significantly higher in patients with cerebellar ataxia than controls or patients with diabetes.⁵

Intrathecal production of GAD antibodies has been detected in patients with ataxia⁵ but their role in pathogenesis remains unknown. CSF from GAD antibody-positive patients reduces GABA synthesis and inhibits postsynaptic currents in Purkinje cells of rat cerebellar slices,⁶ possibly representing a reduction in the GABA-mediated inhibitory activity of basket cells on Purkinje neurons. Conversely, how GAD-65 antibodies access this intracellular antigen remains uncertain, and antibody titre does not correlate with the disease severity in SPS, challenging their pathogenic role.⁷ Pathogenesis may therefore be mediated by a presently unknown, immune-generated factor in serum or CSF.

In a series of 14 patients the commonest clinical features were gait ataxia, nystagmus, dysarthria and a history of autoimmune disease (primarily, late-onset insulin-dependent diabetes).⁵ Our patient had cerebellar ataxia and epilepsy, and another report describes SPS with accompanying ataxia. Therefore, these syndromes may represent a continuum of anti-GAD-associated CNS disease.

Steroids and azathioprine may improve cerebellar ataxia and reduce seizure frequency⁸; however, the use of high-dose steroids may compromise the glycaemic control in a patient with diabetes.

Learning points

- ▶ Diagnosis of the rare glutamic acid decarboxylase autoantibody-associated cerebellar ataxia is aided by examination, serology (including onconeural antibodies), genetic testing and MRI.
- ▶ The differential diagnosis is wide including demyelination, inherited, neurodegenerative and metabolic disease and prion disease.
- ▶ Intravenous immunoglobulin and plasmapheresis can demonstrably improve the cerebellar signs and symptoms, though effectiveness may wane over time.

The only report of rituximab (an anti-CD20 monoclonal antibody which depletes B cells) for anti-GAD CNS disease is a crossover trial in two monozygotic twins with SPS, in whom it was ineffective.⁹

IVIg reportedly reduced stiffness and improved walking in SPS patients for 6–12 weeks,¹⁰ and clinical improvement over 1 year has been observed in anti-GAD-positive patients with ataxia (with varying underlying causes, including MSA and SCA).

Contributors MP is the formal treating physician of the patient described in the case. He provided information and supervised ZG (his medical student at the time of writing) and edited the manuscript. ZG compiled information about the case by using case notes, meeting and examining the patient and she wrote the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Matthews B. Symptoms and signs of multiple sclerosis. In: Compston A, Ebers G, Lassman H, McDonald I, Matthews B, Wekerle H. eds. *McAlpine's multiple sclerosis*. 3rd edn. London: Churchill Livingstone, 1998:145–90.
- 2 Abele M. The aetiology of sporadic adult-onset ataxia. *Brain* 2002;125:961–8.
- 3 Wenning GK. Clinical features and natural history of multiple system atrophy: a study of 100 cases. *Brain* 1994;117:835–45.
- 4 Raju R. Analysis of GAD65 autoantibodies in stiff person syndrome patients. *J Immunol* 2005;175:7755–62.
- 5 Honnorat J. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. *Arch Neurol* 2001;58:225–30.
- 6 Takenoshita H. Presynaptic inhibition of cerebellar GABAergic transmission by glutamate decarboxylase autoantibodies in progressive cerebellar ataxia. *J Neurol Neurosurg Psychiatry* 2001;70:386–9.
- 7 Rakocevic G. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff person syndrome: correlation with clinical severity. *Arch Neurol* 2004;61:902–4.
- 8 Nociti V. Refractory generalized seizures and cerebellar ataxia associated with anti-GAD antibodies responsive to immunosuppressive treatment. *Eur J Neurol* 2010;17:e5.
- 9 Venhoff N. Monozygotic twins with stiff person syndrome and autoimmune thyroiditis: rituximab inefficacy in a double-blind, randomised, placebo controlled crossover study. *Ann Rheum Dis* 2009;68:1506–8.
- 10 Dalakas M. The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. *J Neurol* 2005;252(Suppl 1):I/19–25.
- 11 Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006;66:1717–20.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow