SHORT REPORT

Epilepsy and cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies

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J Neurol Neurosurg Psychiatry 2007;**78**:187–189. doi: 10.1136/jnnp.2006.089268

Anti-glutamic acid decarboxylase (GAD) antibodies are described in stiff-person syndrome and also in other neurological syndromes, including cerebellar ataxia and epilepsy. This paper reports the case of a patient who had chronic focal epilepsy, upbeat nystagmus and cerebellar ataxia, associated with a polyautoimmune response including anti-GAD antibodies. Both gait and nystagmus improved markedly after immunosuppressive treatment with corticosteroids and azathioprine. After the introduction of benzodiazepines, previously refractory seizures were completely controlled. Anti-GAD antibodies should be actively sought out in pharmacoresistant epilepsy, particularly if other neurological abnormalities are present. Combined treatment with immunosuppressants and γhydroxybutyric acidergic agents may be highly effective.

Glutamic acid decarboxylase (GAD) catalyses the transformation of glutamate into γhydroxybutyric acid (GABA). Both are major neurotransmitters of the central nervous system that are also present in peripheral organs. Increased titres of autoantibodies against GAD (GAD-Ab) are found in insulin-dependent diabetes mellitus (IDDM) and as well as in various neurological diseases, such as stiff-person syndrome (SPS),[1] cerebellar ataxia with polyendocrine autoimmunity (CAPA)[2] and epilepsy,[1 3–6] and in more rare conditions, such as progressive encephalomyelitis with rigidity.[7] In addition, GAD-Ab have been found in association with other organ-specific antibodies and autoimmune diseases such as myasthenia gravis, thyroiditis and pernicious anemia.[1 2] Paraneoplastic GAD-Ab have also been described. Treatment focuses on modification of the immune response and enhancement of GABAergic activity.

CASE REPORT

In July 2004, a 58-year-old man of central African origin was referred to us for chronic focal epilepsy of unknown origin. Since the age of 40, he had weekly complex partial seizures (impaired consciousness, orofacial and manual automatic movements and postictal amnesia) and rare secondary generalised seizures. Previous treatments with carbamazepine and phenytoin had been unsuccessful. Apart from arterial hypertension, his personal and familial medical history was unremarkable.

The clinical neurological examination was normal, except for signs suggesting a mild sensory neuropathy, which was confirmed by nerve conduction studies. A 5-day video electroencephalogram recording showed occasional left frontal spikes. Despite complete carbamazepine withdrawal, however, no seizures were recorded. Magnetic resonance imaging (MRI) of the brain and interictal positron emission tomography (PET) results were normal. A vitamin B_{12} deficiency with atrophic gastritis was detected and parenteral substitution was initiated. The treatment for epilepsy was changed to gabapentin (2700 mg daily), but weekly seizures persisted.

Beginning in January 2005, he developed a severe gait disorder and, within a few weeks, required a cane and permanent help from another person. He reported a new slight slurring of speech and pain in the left lateral lower leg and foot induced by stance and gait. Another neurological examination showed an upbeat nystagmus, left-sided hemiataxia and gait ataxia. Muscle tone was slightly diminished, but strength was normal. The sensory neuropathy was unchanged. Blood tests showed normal blood cell counts, corpuscular volume, erythrocyte sedimentation rate, glucose, electrolytes, creatinine, hepatic and pancreatic enzymes and thyroid tests, as well as normal levels of vitamins and serum immunoglobulins. Comprehensive tests for autoantibodies were positive for the following: anti-intrinsic factor, anti-thyreoglobulin, anti-thyreoperoxydase and anti-Langerhans islet cells (table 1). Indirect immunofluorescence on cerebellum slices of monkey (fig 1) and rat showed cytoplasmic reactivity of the patient's serum, which was compatible with the presence of high titres of GAD-Ab and was confirmed by immunoblot.[2] Tests for connective tissue disorder, coeliac disease, syphilis, Lyme disease, HIV, other neurotropic viruses and paraneoplastic antibodies were negative. No neoplasia was detected by cerebral and spinal MRI or by total-body PET imaging.

Analysis of the cerebrospinal fluid (CSF) showed the presence of 1% plasma cells with normal cell counts, and isoelectric focusing showed two oligoclonal bands. Whereas the immunoglobulin G index was within the normal range, high titres of GAD-Ab specific for both 65-kDa and 67-kDa isoforms were present, as well as trace amounts of anti-thyreoperoxidase antibody. The intrathecal synthesis index was 28.8 for GAD-Ab and <3 for anti-thyreoperoxidase antibody.

Because of the coexistence of a cerebellar syndrome and seizures in a patient with a polyautoimmune disorder, including GAD-Ab, corticosteroid treatment was initiated: 500 mg intravenous methylprednisolone was given for 5 days, followed by 60 mg oral prednisone daily, and gabapentin was replaced by valproate. At the end of the methylprednisolone treatment, the nystagmus, hemiataxia and gait had improved and the leg pain had disappeared. Azathioprine (1.5 mg/kg/day) was introduced and tolerated well, allowing slow tapering of prednisolone to 5 mg/day. None the less, control of seizures remained unsatisfactory, prompting replacement of valproate with levetiracetam, and clobazam was added after 5 months. Eight months later, at the last follow-up in November 2005, the nystagmus had disappeared and the hemiataxia and gait ataxia had improved markedly. The patient was able to walk for

Abbreviations: CAPA, cerebellar ataxia with polyendocrine autoimmunity; GABA, γhydroxybutyric acid; GAD, glutamic acid decarboxylase; GAD-Ab, autoantibodies against GAD; IDDM, insulin-dependent diabetes mellitus; MRI, magnetic resonance imaging; PET, positron emission tomography; SPS, stiff-person syndrome

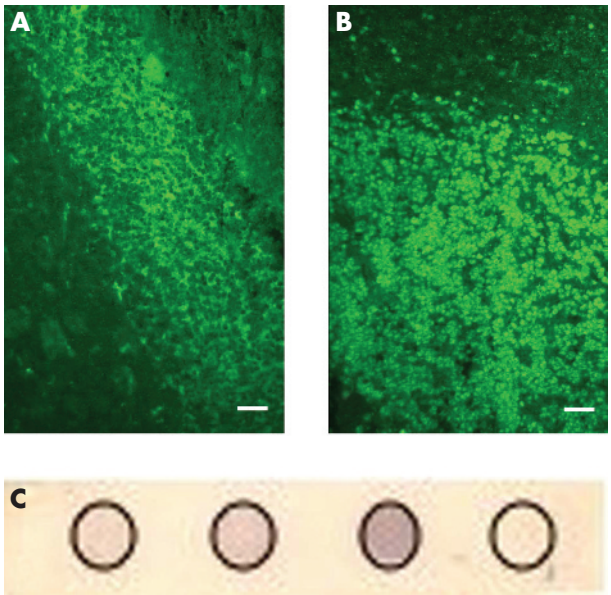

Figure 1 (A) Cytoplasmic reactivity of the patient's serum on primate cerebellar granular cells (bars measure 20 μm). Indirect immunofluorescence was carried out using the patient's serum diluted to 1:10. The serum reacted positively up to a dilution of 1:8000. (B) Anti-nuclear fluorescence was obtained with a reference anti-Hu serum (titre 1/320), diluted to 1:20. This shows the different reactivity of the patient's serum compared with anti-Hu autoantibodies. (C) Immunoblot confirming the glutamic acid decarboxylase (GAD) reactivity. From left to right: control reaction, GAD67, GAD65, cut-off. Positivity is indicated by intensities of blue (appearing as dark rose). The test is clearly positive for GAD65, but only weakly positive for GAD67 (reproduced by the permission of Professor J Honnorat).

1.5 miles without a walking stick and had had no seizures for the past 6 months. No diabetes had developed.

DISCUSSION

We report a patient with different neurological syndromes that occurred successively in the presence of GAD-Ab. He was successfully treated with immunosuppressants and benzodiazepines. To our knowledge, this is the first reported case of progressive occurrence of pharmacoresistant late-onset cryptogenic epilepsy, cerebellar ataxia and upbeat nystagmus related to GAD-Ab.

Although alternating nystagmus[8] and downbeat nystagmus[9] have been described, so far no upbeat nystagmus has been reported in association with GAD-Ab. The cerebellar ataxia associated with high GAD-Ab titres matches that in previously described cases of CAPA,[2] which were also associated with other antibodies of unknown significance, notably antithyroid antibodies. Lack of vitamin B_{12} reportedly causes cerebellar ataxia and epilepsy[10]—yet our patient was well substituted for vitamin B_{12} when the ataxia developed, had no white matter lesions and continued to have seizures after substitution. Other causes of late-onset cerebellar degeneration (alcohol, coeliac disease, paraneoplastic or hereditary syndrome) were not present. An immunological origin was therefore considered, which was corroborated by clinical improvement under immunosuppressants. Arguably, our patient did not fulfill the criteria for CAPA, as he did not have overt polyendocrinopathy in addition to his neurological conditions. He had, however, high titres of anti-intrinsic factor antibodies, with low serum levels of B_{12} and atrophic gastritis, as well as anti-thyreoperoxidase autoantibodies, thus being similar to patients described by Honnorat *et al*.[2]

Contrary to SPS and CAPA, which are clearly associated with the presence of GAD-Ab, the spectrum of epilepsy syndromes related to GAD-Ab and the relevance of these antibodies in epilepsy are less clear. Epilepsy affects 10% of patients having SPS with GAD-Ab,[1] and has been described with or without other neurological conditions. Very high titres of GAD-Ab have been associated with cases of temporal lobe epilepsy (with or without hippocampal sclerosis) and extratemporal epilepsy (with cortical dysplasia or without lesion), as well as with juvenile myoclonic epilepsy.[3–6] Prevalence studies have shown no major association between GAD-Ab positivity or titres and the severity of epilepsy, neither in focal nor in generalised epilepsy.[3 6] Thus, epilepsy associated with GAD-Ab encompasses a wide spectrum of epilepsy syndromes with or without abnormality seen on MRI. The pathophysiological importance of GAD-Ab in these patients is not clear. Low levels of GABA in

Table 1 Titres and index of intrathecal synthesis of the autoantibodies tested in the serum and CSF

	Serum	CSF	Index
Albumin, mg/l	41 200	354	
IgG, mg/l	13 000	56	
GAD-Ab dilution end titres (IIF)*	1/8000	1/1000	
Anti-thyreoperoxydase (EIA), UI/ml	>1000 (<35)	12.9	
Anti-thyreoglobulin (EIA), UI/ml	66 (<40)	Negative	
Anti-Langerhans islet cells U JDS	>5000 (<10)	640	
Anti-intrinsic factor, UI/ml	11.1 (<1.1)		
IgG intrathecal synthesis: $(IgG_{CSF}/IgG_{serum})/(albumin_{CSF}/albumin_{serum})$			0.5 (<0.65)
GAD intrathecal synthesis: $(GAD\text{-}Ab_{CSF}/GAD\text{-}Ab_{serum})/(IgG_{CSF}/IgG_{serum})$			28.8
Anti-thyreoperoxydase intrathecal synthesis $(TPO\text{-}Ab_{CSF}/TPO\text{-}Ab_{serum})/(IgG_{CSF}/IgG_{serum})$			<3.0

Cut-off values are in parentheses.
CSF, cerebrospinal fluid; ENA, extractable nuclear antibodies; GAD, glutamic acid decarboxylase; GAD-Ab, autoantibodies against GAD; IgG, immunoglobulin G; TPO-Ab: anti-thyreoperoxydase antibodies.
Methods used for the various antibody testing are: IIF, indirect immunofluorescence; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; UJDS, Unit Juvenile Diabetes Society.
The following additional autoantibodies tested negative in the serum: anti-nuclear antibodies (IIF), extractable nuclear antigens (ELISA), anti-smooth muscle (IF), anti-striated muscle (IF), anti-liver kidney microsome (IF), anti-surrenal (IF), anti-gliadin (IF), anti-endomysium (IF), anti-transglutaminase IgA, anti-amphiphysin, anti-CV2, anti-Hu, anti-Ri, anti-Yo.
*For GAD-Ab, numbers refer to the reciprocals of end point titres determined by IIF. For GAD-Ab, the index of intrathecal synthesis was calculated similarly to other reports on cerebellar ataxia with polyendocrine autoimmunity.[2]

the brain and CSF are, however, associated with uncontrolled epilepsy,[11] indicating that GABA is crucial in seizure suppression.

In our patient, refractory epilepsy was present for 18 years before ataxia developed and the immunological tests were carried out. It is, however, possible that his epilepsy was also related to GAD-Ab. Consistent with this hypothesis, the clinical picture strongly resembled other GAD-Ab-related epilepsies[4] and the seizure frequency was reduced after starting immunosuppressants and GABAergic drug treatment.

The underlying molecular mechanism is thought to be different in the various medical conditions associated with GAD-Ab. GAD-Ab titres are much higher in SPS and CAPA than in IDDM, and the cellular (epitope recognition) as well as humoral (immunoglobuline isotypes) responses to GAD65 are different.[10] GAD-Ab in SPS reduce GABA production in vitro but those in IDDM do not, indicating selective inhibition of the enzymatic activity.[12] Serum samples from patients having IDDM with neurological diseases (SPS, ataxia, epilepsy, palatal myoclonus) stain the cytoplasm of cerebellar granular neurones, whereas those from patients with uncomplicated IDDM do not.[13] Thus, GAD-Ab related to neurological conditions seem to be different from those related to IDDM.

In addition, the epitopes recognised by GAD-Ab seem to differ in the various associated neurological manifestations, which may have implications for the immunological pathogenesis and treatment.[13 14] In our patient, ataxia and nystagmus responded better to corticosteroids and azathioprine than did seizures. The longer duration of the epilepsy may explain the weaker response to this treatment, but different immunological mechanisms related to ataxia and nystagmus versus seizures may have also been responsible.

Two different isoforms of GAD exist (GAD65 and GAD67). In SPS and CAPA, GAD65 is most often found.[13 15 16] Isoforms prevalent in epilepsy are less well characterised. GAD65 is found preferentially in the axon terminals and synaptic vesicles, whereas GAD67 is more uniformly distributed in the neurones.[17] Mice deficient in the 65-kDa isoform have epilepsy,[18] whereas the 67-kDa isoform seems to be crucial for cerebral development.[17] Autoreactivity against both isoforms was found in our patient, with predominance against the 65-kDa isoform.

The treatment of GAD-Ab-related neurological conditions relies either on enhancement of GABA activity or on immunosuppression. The treatment for SPS,[16] CAPA[19] or epilepsy[5 20] associated with GAD-Ab has included corticosteroids, immunosuppressants, plasma exchange, intravenous immunoglobulins and GABAergic drugs, resulting in variable success. Our patient showed remarkable and lasting improvement of ataxia with prednisolone and azathioprine. Their effect on epilepsy was limited, and it was not until the introduction of benzodiazepines that the patient had no more seizures. It should be emphasised that GABAergic drugs used to treat epilepsy alone did not provide complete seizure control in previously reported cases.[6 20]

We recommend an active search for GAD-Ab in polymorphic neurological presentation, including atypical refractory epilepsy, ataxia and nystagmus. A combination of immunosuppressants and GABAergic agents may lead to dramatic improvement.

ACKNOWLEDGEMENTS

We thank Professor J Honnorat for GAD-Ab measurement in his laboratory in Lyon, France; Dr M Chofflon, Department of Neurology, Geneva University Hospital, for helpful suggestions on the analysis; L Fontao, Department of Dermatology, Geneva University Hospital, for immunofluorescence microphotography; and L Cameron for careful revision of the manuscript.

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Funding: This study was supported by SNF grants IB74B0-111086, 3200B0-104146, 3200-068105 and 3200-113766.

Competing interests: None declared.

Informed consent was obtained for publication of the patient's details described in this report.

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Received 22 January 2006
Revised version received 26 April 2006
Accepted 5 May 2006

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