

## Surviving stiff-person syndrome: a case report

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**Abstract** Stiff-person syndrome (SPS) is a rare condition of progressive muscular rigidity and spasm, frequently accompanied by other autoimmune conditions, an association which has been further strengthened by the discovery of anti-GAD antibodies and the response of SPS to immunotherapies. Intravenous immunoglobulin (IVIg) is the mainstay therapy. Because of the rarity of the GAD antibody associated conditions, most of the information regarding treatment is case series and individual case reports. Here we describe the 15 year long management of a subject with SPS who has had a favourable outcome.

**Keywords** Stiff-person syndrome · GAD antibody · IVIg · Rituximad · Sirolimus

### Introduction

Stiff-person syndrome (SPS) is a rare condition characterised by progressive muscular rigidity and spasm [2], frequently accompanied by other autoimmune conditions, such as insulin-dependent diabetes mellitus and thyroiditis, an association which has been further strengthened by the

discovery of anti-GAD antibodies and the response of SPS to immunomodulatory therapies [3, 4]. However, because of the rarity of SPS and other GAD antibody associated conditions, most of the information regarding treatment is in case series or individual case reports except for one double blind study of intravenous immunoglobulins (IVIg) [4]. Here we describe the 15 year long management of a 45 year old man with SPS who has had a favourable outcome but still requires heavy immunosuppression.

### Case report

He initially presented in 1995, aged 45 years, with a 5 year history of slowly progressive axial stiffness and spontaneous/startle-induced spasms. His past medical history included IDDM, and there is a family history of autoimmunity with Grave's thyrotoxicosis, diabetes and pernicious anaemia. Investigations revealed anti-GAD antibodies and continuous muscle fibre activity on EMG, with no evidence of a peripheral nerve abnormality, MRI or CSF abnormalities.

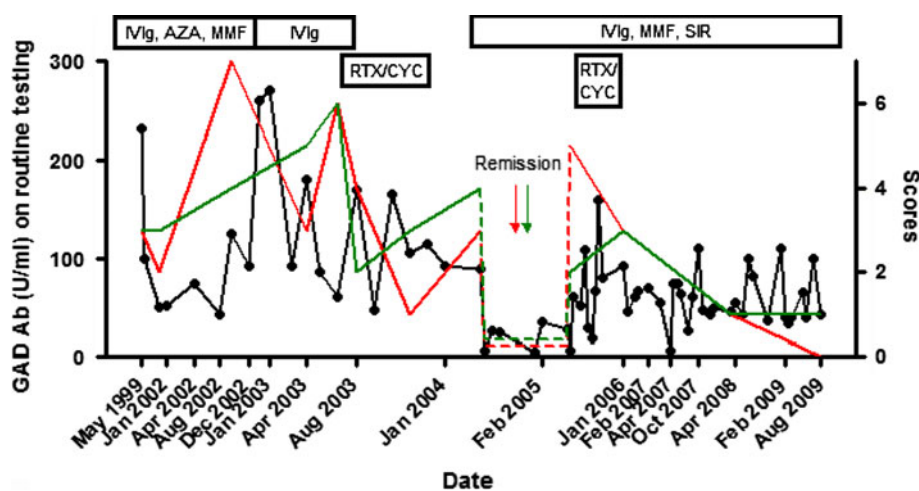
He was tried on a number of medications including diazepam, sodium valproate, and baclofen, before commencing monthly IVIg (0.4 g/kg/day for 5 days) in 1996. Anti-GAD levels fell from 4,000 to 1,600 CPM/μl using a newly developed in-house radioimmunoprecipitation assay [5] (data not shown). There was symptomatic improvement, with stiffness-scores improving from 6/6 in October 1995 to 1/6, and heightened-sensitivity scores improving from 5/7 to 1/7, but he would deteriorate if he delayed the infusions. Azathioprine (75 mg/day), and later mycophenolate mofetil (1 g twice a day), were introduced as supplementary immunosuppressants. Figure 1 shows the details of treatments, sequential clinical assessments (stiffness and heightened-sensitivity scores), and GAD antibody levels since 1999;

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**Fig. 1** GAD antibody levels (1999–2009) measured by radioimmuno-precipitation (RSR Ltd UK) together with periods of treatment. The distribution of stiffness (*in red*) was scored as follows: no stiffness, 0; lower trunk stiffness, 1; upper trunk stiffness, 2; bilateral leg stiffness, 3; bilateral arm stiffness, 4; facial stiffness, 5; and abdominal and back stiffness, 6. Heightened sensitivity (*in green*) was scored as follows: noise, 1; visual stimuli, 2; somatosensory stimuli, 3;

voluntary activities, 4; emotional upset or stress, 5; untriggered, 6; and nocturnal spasms, 7. We have no measures between July 2004 and April 2005 as the patient was in clinical remission. The stiffness and heightened-sensitivity scores record clinical severity [1] AZA azathioprine CYC cyclophosphamide IVIg intravenous immunoglobulin MMF mycophenolate mofetil RTX rituximab SIR sirolimus

GAD antibody levels fluctuated quite widely but with a downward trend.

By 2003, he was not deriving the same benefit from IVIg as previously, i.e. noticing a marked improvement after the infusions with a waning of response in the 2 weeks prior to the next infusions. He had spasms that were so severe as to make it virtually impossible for him to walk properly, often resulting in falls. The decision was made to start anti-CD20 therapy, rituximab (600–700 mg/m<sup>2</sup>), and cyclophosphamide (750 mg). He continued on rituximab (375 mg/m<sup>2</sup>) and cyclophosphamide (1 g) at monthly intervals for 6 cycles, but unfortunately symptoms returned 3 months after the last infusion. Further immunotherapy in the form of sirolimus (2 mg/day) was added, and mycophenolate (1.5 g/day) and IVIg were reintroduced. Although anti-GAD levels fell to the lowest levels recorded in January 2005, a year later he deteriorated with worsening stiffness. Further cycles of rituximab (375 mg/m<sup>2</sup>) and cyclophosphamide (1 g) were again given with noticeable clinical improvement.

By early 2006, for the first time since diagnosis, his SPS appeared to be in long-term remission. Following a prolonged treatment regimen, he had accrued other problems including persistent flu-like symptoms after immunoglobulin infusions, erratic diabetic control and weight loss (which was extensively investigated for the potential development of a neoplasm). Fifteen years from diagnosis, he is well controlled on his maintenance immunotherapy and IVIg with no further RTX or CYC.

## Discussion

Therapies for SPS are largely symptomatic. Long-term management of this disorder is demanding and there exists little guidance regarding the management of difficult cases. Our patient responded very well to IVIg but eventually developed tolerance to the therapy with a failure to respond to the individual courses. A double-blind placebo-controlled trial of IVIg (2 g/kg over 2 days monthly) over 3 months showed improvement in stiffness and heightened sensitivity scores [4]; the beneficial effects lasted anywhere between 6 weeks to a year.

There is evidence to support a role for B cells in autoimmune disorders, and particularly for the use of rituximab which depletes B cells, but may also affect antigen-presentation to T cells [6]. In a case report, rituximab therapy has been shown to be efficacious where other forms of immunosuppressive therapies had failed, including IVIg, cyclophosphamide and mycophenolate [7]. In fact, in our patient effective disease control was achieved only after the introduction of rituximab/cyclophosphamide. We also used sirolimus which inhibits the activation of T cells, and as far as we are aware this is the first case description of its use in the treatment of SPS.

We were able to reliably monitor this patient's clinical response to immunophilins using anti-GAD levels, where declining levels coincided with periods of clinical improvement in most cases, though it should be taken into consideration that these were unblinded observations and

non-drug-related remissions should also be considered. The role of the antibodies in SPS is unclear. Although circulating anti-GAD antibodies can block GABA synthesis in vitro, resulting in dysfunction of GABAergic inhibitory pathways and consequently a shift in the GABA/glutamate balance favouring the latter [8], it is not clear whether this occurs in vivo as GAD is an intracellular enzyme.

This case of SPS has been successfully managed over 15 years using immunomodulatory therapies. Prolonged therapy resulted in immune tolerance and diminished response, and although our subject exhibited remarkable tolerance, the safety of long-term immunosuppression remains unclear. Nevertheless, this long-term study shows that even in treatment-resistant cases, considerable clinical benefit is possible but may require persistent and multiple therapies.

**Conflict of interest** Dr S Gnanapavan reports no disclosures. Prof A Vincent and her department receive royalties and payments for antibody assays, and support from Euroimmun AG for developing antibody tests. Prof G Giovannoni reports having received consulting fees from Bayer–Schering Healthcare, Biogen-Idec, Genzyme, Glaxo-SmithKline, Merck-Serono, Novartis, Protein Discovery Laboratories, Teva-Aventis, Vertex Pharmaceuticals and UCB Pharma; lecture fees from Bayer–Schering Healthcare, Biogen-Idec, Pfizer, Teva-Aventis, Vertex Pharmaceuticals; and Grant support from Bayer–Schering Healthcare, Biogen-Idec, GW Pharma, Merck-Serono, Merz, Novartis, Teva-Aventis and UCB Pharma.

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