In stiff person syndrome, anti-GAD antibodies may be detected, but only in a subgroup of patients. The presence of anti-GAD antibodies supports the diagnosis of stiff person syndrome. Our successful use of rituximab in a 41 year old woman with stiff person syndrome resulted in a lasting clinical remission.
the dose was no longer controlling the disease. She was then given once weekly infusions of intrathecal hydrocortisone (500 mg) for four weeks in an attempt to suppress any intrathecal clone of antibody producing cells. This treatment produced short lived benefit and allowed the patient to return home for Christmas, before readmission in January when her symptoms deteriorated.

Rituximab was administered intravenously on 9 January 2004 at a dose of 375 mg/m². Rituximab is an anti-CD20 chimeric human mouse monoclonal antibody that specifically depletes mature B lymphocytes by binding irreversibly and destroying them by apoptosis, antibody dependent cell mediated cytotoxicity (ADCC), and complement mediated lysis. Fifteen days after the infusion the stiffness began to resolve and the patient was able to sit up and shower herself for the first time in more than two years. Figure 1B illustrates the normalisation of the right vastus lateralis EMG following this treatment. The CSF was re-examined on the day of discharge, 17 days after treatment with rituximab, and no anti-GAD antibodies were detectable. One month after discharge she was stable and symptoms were easily managed by small doses of oral benzodiazepines and anxiolytics.

Symptoms began to reappear after the sixth week and she was readmitted and given a four week course of intravenous rituximab in the same dosage at weekly intervals and mycophenolate mofetil was reintroduced at a dose of 1 g twice daily. Her condition again improved after 14 days and she was discharged at the end of the course, at which time she was able to stand and walk with help, sit, and shower.

**DISCUSSION**

Stiff person syndrome is a rare progressive autoimmune disease of the central nervous system (CNS). The diagnosis is made, after exclusion of other known pathologies, primarily on clinical criteria of stiffness, predominantly in axial muscles, with co-contraction of agonist and antagonist muscles and paroxysmal spasms. The diagnosis is supported by investigations including neurophysiological examination, which demonstrates spontaneous motor unit activity at rest simultaneously from agonist and antagonist muscles, and immunological examination, which reveals high serum and CSF titres of anti-GAD antibodies. In addition to these antibodies, anti-iaiophosphoryl antibodies,1 antigenephry and anti-Ri antibodies are often found in paraneoplastic stiff person syndrome.

The mechanism of stiffness in stiff person syndrome is assumed to be a consequence of the interaction between the anti-GAD antibody and the CNS. GAD is the rate limiting enzyme in the production of γ-aminobutyric acid (GABA), which is the most abundant inhibitory neurotransmitter within the CNS. Anti-GAD antibody is known to block the synthesis of GABA in vitro, but whether there is internalisation of anti-GAD antibody and inhibition of GABA synthesis, or whether the antibody attacks and destroys interneurones expressing surface GAD is not clear. However, it is generally accepted that the stiff person syndrome phenotype is the consequence of the functional impairment of inhibitory interneurones as evidenced by the effectiveness of the various GABAergic agents used in the symptomatic treatment of stiff person syndrome.

Electrophysiological methods have been employed to investigate more precisely the locus of GABAergic dysfunction within the CNS in stiff person syndrome, and excitability changes have been described at the level of cortex and spinal cord, and brainstem. Increased excitability within the brainstem and cortex might explain tonic muscle stiffness to some extent but is more likely to explain the presence of the startle response often described in stiff person syndrome. Post mortem histopathological reports have described reduced numbers of GABAergic cells within the cerebellum and a reduction in the size of Renshaw’s cells within the spinal cord. Symptomatic treatment relies upon GABA enhancing agents, and as a putative B cell mediated disease, immunomodulatory therapies have been tried with varying success. The most compelling evidence for immunomodulatory treatment comes from a placebo controlled crossover trial of high dose intravenous immunoglobulin in 16 patients with stiff person syndrome. In addition to significant improvement in objective scores of function there was a significant reduction in anti-GAD in the treatment arm.

Further evidence that stiff person syndrome is a B cell mediated disease is its strong association with other autoimmune diseases. Although our patient had none of the more recognised autoimmune diseases, she did have autoimmune granulocytopenia. Antineutrophil antibodies have been described in association with both systemic lupus erythematosus (SLE) and idiopathic thrombocytopenic purpura. Rituximab has been used with success both in the treatment of other autoimmune conditions (for review see Silverman and Weisman), including rheumatoid arthritis and SLE, and combined with cytotoxic chemotherapeutic agents in the treatment of non-Hodgkin’s lymphoma. Rituximab specifically targets cells expressing the surface antigen CD20 and therefore depletes mature B lymphocytes, but spares plasma cells and early pre-B cells, which do not express CD20. Some trials of rituximab therapy in autoimmune disease (e.g. idiopathic thrombocytopenic purpura) and non-Hodgkin’s lymphoma (NHL) have failed to show clinical improvement. In autoimmune disease, this is usually because of the low doses used in the initial trials, and in NHL, this has been attributed to reduced expression of CD20 in lymphoma cells in advanced disease. With long term treatment there are the theoretical concerns of sensitisation and diminished effectiveness. This is the first report of the successful use of a monoclonal anti-B cell antibody in the treatment of stiff person syndrome. The rapid decline of intrathecal anti-GAD following treatment suggests the successful targeting and elimination of autoantibody producing B cells within the CNS. The association of anti-GAD decline with clinical improvement supports the suggestion that SPS is a B cell mediated autoimmune disease. The rapidity and extent of recovery following treatment might suggest that there is minimal neuronal destruction, and therefore that the syndrome is due to functional inhibition of GABAergic neurones by autoantibodies.

**Table 1 Results of blood and cerebrospinal fluid (CSF) analysis of the patient**

<table>
<thead>
<tr>
<th>Date</th>
<th>Oligoclonal bands</th>
<th>Serum anti-GAD (units/ml) (normal range)</th>
<th>CSF anti-GAD (units/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Jul 2001</td>
<td>Negative</td>
<td>1.1 (1)</td>
<td>Negative</td>
</tr>
<tr>
<td>07 Aug 2001</td>
<td>Negative</td>
<td>0.2 (1)</td>
<td>Negative</td>
</tr>
<tr>
<td>16 May 2002</td>
<td>–</td>
<td>– (1)</td>
<td>–</td>
</tr>
<tr>
<td>10 Dec 2002</td>
<td>–</td>
<td>– (1)</td>
<td>–</td>
</tr>
<tr>
<td>31 Oct 2003</td>
<td>Negative</td>
<td>0.2 (1)</td>
<td>3.2</td>
</tr>
<tr>
<td>09 Jan 2004</td>
<td>Intravenous rituximab (375 mg/m²) administered</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>26 Jan 2004</td>
<td>–</td>
<td>– (1)</td>
<td>–</td>
</tr>
<tr>
<td>02 Apr 2004</td>
<td>Negative</td>
<td>0.3 (1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Intravenous rituximab (375 mg/m²) per week x 4</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>30 Apr 2004</td>
<td>Negative</td>
<td>0.3 (1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

anti-GAD, antiguaminobutyric acid decarboxylase.

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