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LETTER

Successful treatment of stiff person syndrome with sequential use of tacrolimus

Stiff person syndrome (SPS) is a rare neurological disease with features of an autoimmune disease. SPS is characterised by severe progressive muscle stiffness of the spine and lower extremities with superimposed muscle spasms triggered by external stimuli such as noise, touch and emotional distress.[1] Patients with SPS respond to high doses of muscle relaxants, such as diazepam and baclofen, several anticonvulsants, and gabapentin. Previous studies have reported that several causal treatments with corticosteroids, plasmapheresis, intravenous immunoglobulin (Ig) and new immunomodulating agents can reduce stiffness and lower sensitivity to stimuli and stress in patients with SPS.[2 3] Because SPS is a chronic disease, patients generally require long-term treatments, which may be effective but difficult to take for long periods.

Tacrolimus (Prograf, FK506) is a macrolide molecule belonging to the same immunosuppressant class as cyclosporine. Tacrolimus has a lower molecular weight and is 100-fold more potent in inhibiting T cell proliferation than cyclosporine. It acts through inhibition of the calcium-calcineurin (CaN) pathway and exerts its immunosuppressive effect by reducing the proliferation of activated T cells.[4] We now report the successful treatment of patients with SPS using tacrolimus as the immunosuppressive agent.

METHODS

Patients

We assigned two patients with SPS who had incomplete responses to conventional therapies and fulfilled the defined clinical criteria (online supplementary table 1).[3]

Clinical evaluations

At baseline and each month thereafter, a neurologist used the distribution of stiffness index, the most consistent indicator of stiffness among patients and within patients, to evaluate the patients with SPS.[3] Scores on this index range from 0 to 6 and reflect the extent of stiffness. The same neurologist also assessed the patients for changes in frequency of spasms with use of the heightened-sensitivity scale, which has been a reproducible and consistent means of assessing the number of factors triggering spasms.[3] Scores range from 1 to 7, with 1 point being given for each type of spasm. A neurologist blinded to the clinical indices and therapeutic regimen.

Measurement of anti-GAD Ab titres

Antiglutamic acid decarboxylase (anti-GAD) antibody (Ab) titres were measured by radioimmunoassay in the sera obtained before and after each 3-month treatment period.

Brain GABA changes in MRS (case 1)

Levy *et al* reported that MR spectroscopy (MRS) showed a prominent and significant decrease in γ-aminobutyric acid (GABA) level in the sensorimotor cortices of patients with SPS.[5] We performed proton MRS studies before and after administration (after 1 month and after 2 years) of tacrolimus using the Signa Horizon (3T GE, Milwaukee, Wisconsin, USA) scanning system. Proton MRS was performed using the STEAM sequence with water suppression by CHESS pulses (TE=18 ms, TR=5000 ms, acquisition=64 times) to minimise the longitudinal and transverse relaxation effects, and LCModel was used for the postprocessing of obtained spectrum.[6] Neurochemical compounds that can be identified in short-echo proton MRS include GABA. The voxel of interest for MRS was set at the sensorimotor cortex.

Assessment for the excitability of motor cortex (case 2)

Koerner *et al*[7] used transcranial magnetic stimulation (TMS) to investigate intracortical inhibition and intracortical facilitation in patients with SPS. They found significantly enhanced motor cortex excitability in the SPS patients. We tested motor cortex excitability using TMS to confirm the hyperexcitability in our SPS patients before and after administration (after 1 and 6 months) of tacrolimus in the same manner as done by Koerner *et al*.

Treatment regimen

Initial medical treatment in other hospitals, oral diazepam (6 mg/day), provided only subjective benefits in both cases. Second, intravenous Ig (400 mg/kg body weight/day) was administered for 5 days in case 1 (figure 1A), whereas the patient in case 2 underwent a course of three plasma exchange (PE) of 2000 ml each for a 7-day period (figure 1B). Intravenous Ig and PE resulted in clinical improvements; the patients were able to perform daily activities independently, and anti-GAD Ab titres in the sera were remarkably decreased (figure 1A,B). However, these treatments produced only short-lived benefits for the first month after intravenous Ig or PE, and the patients experienced recurrences of prolonged painful spasms. In addition, anti-GAD Ab titres in the sera were elevated for short periods. Therefore, the patient in case 1 was given once-monthly infusions of intravenous Ig for 3 months in an attempt to suppress the relapse. In case 2, prednisolone was orally administered because this patient needed continuous immunosuppression therapy to prevent recurrences. Subsequently, tacrolimus was administered orally at a dose of 3 mg once daily after obtaining informed consent. Safety was evaluated at each monthly visit and was based on physical examinations, the incidence of treatment-emergent adverse events and the results of clinical laboratory tests (with an emphasis on creatine, blood urea nitrogen, glucose and haemoglobin A1C because of the previous experience in transplant patients in which tacrolimus use was associated with changes in these laboratory values). And trough levels of tacrolimus were monitored during the study. The Local Ethical Committee approved tacrolimus for use in these cases.

RESULTS

At the start of the tacrolimus treatment, the patients showed symptoms of muscle stiffness, rigidity, and spasms and had high titres of anti-GAD Ab (online supplementary table 1). We used low-dose tacrolimus combined with bimonthly intravenous Ig for case 1 and orally administered prednisolone for case 2; both patients had intractable SPS and uncontrollable muscle symptoms. Consequently, the distribution of stiffness index and heightened-sensitivity scale scores gradually improved with these combination therapies in both cases. The patients' symptoms were alleviated within 4 weeks after commencement of tacrolimus, accompanied by a decrease in serum anti-GAD Ab titres. The motor ability of the patients increased and they became completely self-dependent. No deterioration in both cases has been noted over 3 years. We found higher GABA concentration in the sensorimotor cortex in case 1 after the combination immunotherapy as compared with the pretreatment level (figure 1A). In case 2, we found a significantly high ratio of condition/test motor evoked potential amplitudes before the administration of tacrolimus; after treatment with tacrolimus, intracortical facilitation was significantly reduced (figure 1B).

DISCUSSION

SPS is thought to be the result of an immune-mediated deficiency of GABA, a

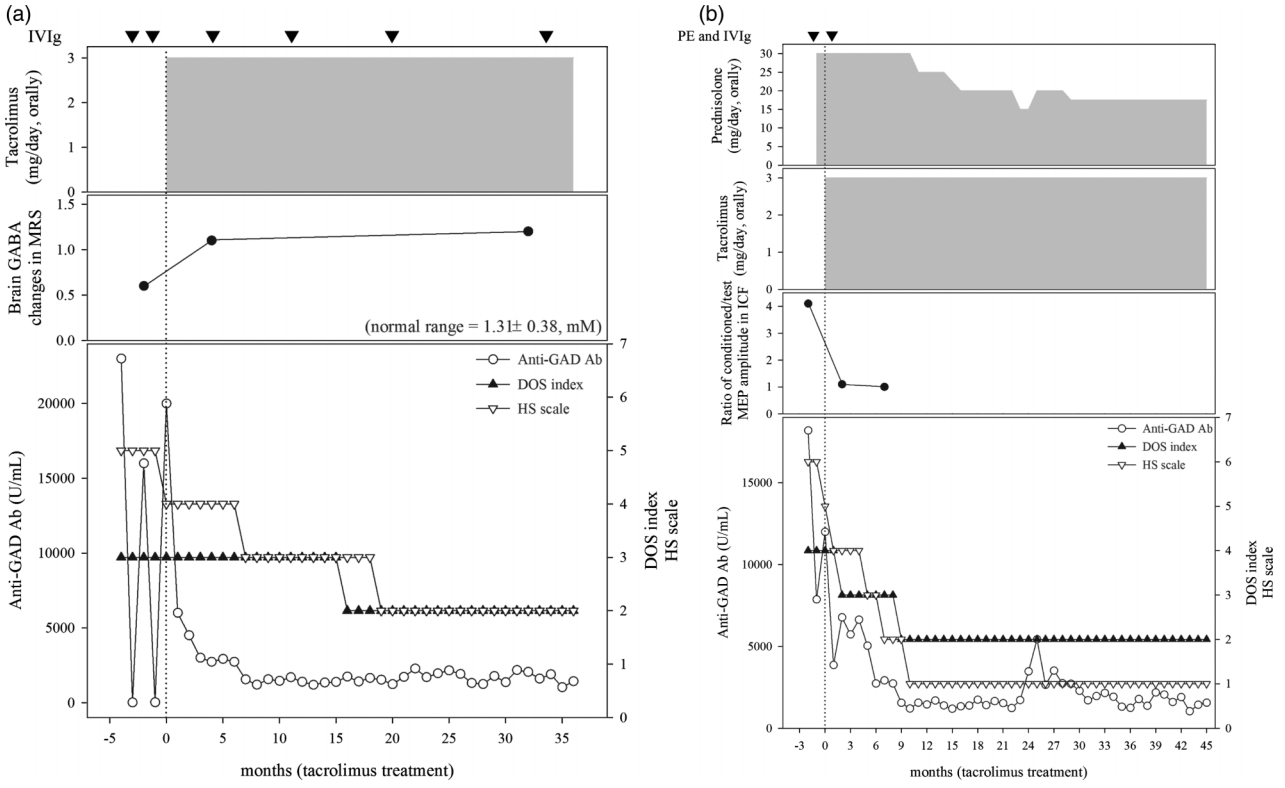

Figure 1 Patient (case 1, A) was given once-monthly infusions of intravenous immunoglobulin (IVIg) for 3 months in an attempt to suppress the relapse. In case 2 (B), prednisolone was orally administered because this patient needed continuous immunosuppression therapy to prevent recurrences. Subsequently, tacrolimus was administered orally at a dose of 3 mg once daily after. Both patients had intractable stiff person syndrome and uncontrollable muscle symptoms. Consequently, the distribution of stiffness (DOS) index and heightened-sensitivity (HS) scale scores gradually improved with these combination therapies in both cases. The patients' symptoms were alleviated within 4 weeks after commencement of tacrolimus, accompanied by a decrease in serum antiglutamic acid decarboxylase (anti-GAD) antibody (Ab) titres.

major inhibitory neurotransmitter in the central nervous system. The majority of SPS patients have high titres of autoantibodies directed against both isoforms of GAD, GAD65 and GAD67.[1] Our cases had favourable responses to intravenous Ig or PE against SPS symptoms. However, they had relapses within a few months after intravenous Ig or PE; thereafter, we needed alternative strategies for the recurrent attacks.

To our knowledge, our study is the first report on successful use of tacrolimus in the treatment of SPS. Tacrolimus has been used for the suppression of immune reactions in organ transplantations and for the treatment of autoimmune disorders such as myasthenia gravis and rheumatoid arthritis. Possible mechanisms of immunological action of tacrolimus in the therapy of SPS include: (1) an immunomodulatory effect, (2) inhibition of CaN and (3) a neuroprotective effect. First, tacrolimus hydrate exhibits strong immunosuppressive activities by inhibiting the synthesis of inflammatory cytokines, such as tumour necrosis factor, interleukin-2 and interferon-γ interacting with helper T cells,[5] and consequently decreasing the production of anti-GAD Ab by B cells. The decline in serum anti-GAD Ab in both cases following treatment suggests the successful targeting of helper T cells. Tacrolimus has been used with success in the treatment of other autoimmune conditions, including myasthenia gravis, ulcerative colitis, rheumatoid arthritis and lupus nephritis.[8–11]

Second, it is presumed that the direct effect of blocking CaN on the GABAergic inhibitory system could lead to immediate improvement. It has been previously reported that tacrolimus suppresses in vivo the activation of CaN, which contributes to hyperexcitability due to downregulation of GABAergic neurones.[12] In addition, anti-GAD Abs also block GABAergic neurotransmission and interfere with the synthesis of GABA. Tacrolimus can suppress this function of the antibody.

Third, tacrolimus may have neuroprotective effects in SPS. Ishizawa *et al* reported the neuropathological analysis of an SPS case. In the spinal cord of the SPS patient, they found a reduction in the density of neurones with somal areas with improvement in the pathological conditions.[13] Tacrolimus might have non-immunosuppressive properties in SPS, as macrolide antibiotics inhibit the function of the immunophilins and provide neuroprotective and neuroregenerative actions.[14]

For the reasons stated above, our results suggest that tacrolimus has pleiotropic effects in patients with SPS. Adverse events were not reported in these two cases; the trough tacrolimus levels were approximately 10 ng/ml and tacrolimus did not accumulate over the duration of the study. We observed short- and long-term recovery of GABA levels in MRS of the brain and suppression of motor cortex excitability in a TMS study. In patients with SPS, MRS and TMS are good tools for the evaluation of therapeutic efficacy, although the accuracy as tools needs to be validated in the future. Important limitations to this study are the retrospective design, the small group of subjects. A prospective, multi-centre, randomised clinical trial is necessary to confirm the relationships among Ab titres, results of tests and symptoms.

In conclusion, in the patients reported here, tacrolimus at low doses was safe and effective in the treatment of SPS in association with reduction of intravenous Ig and

corticosteroids. This drug can be safely used with careful monitoring of plasma concentration in the long term. Tacrolimus should be considered as an alternative treatment for patients with disabling SPS who are not responsive to conventional treatments for this syndrome.

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Contributors Conceived and designed the study: SN. Performed the treatments: KF, YS, NM, YN. Performed and assessed the tests: MH (MR spectroscopy), RU (transcranial magnetic stimulation) and YI. Analysed the data: SN, KF. Wrote the paper: SN, KF, RK.

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