PostScript

LETTERS

Transient neonatal Lambert–Eaton syndrome

The Lambert–Eaton myasthenic syndrome (LEMS) is caused by serum IgG anti-voltage-gated calcium channel (anti-VGCC) antibodies.[1] Although transient neonatal myasthenia gravis, caused by passive placental transfer of maternal anti-acetylcholine receptor (anti-AChR), is well recognised,[2] as far as I am aware, this phenomenon has not previously been reported in LEMS.

A diagnosis of LEMS was made in a woman at the age of 25 years. She had noted difficulty in keeping up with other children since she was 13. Two years later, she became aware of ptosis. In her late teens, she developed weakness in the limb and had difficulty in speech, chewing and swallowing. She was noted to have bilateral ptosis, facial weakness, poor palatal movements and weakness of neck flexion and extension. The limbs were hypotonic with global weakness, worse proximally, and tendon reflexes were absent.

Anti-VGCC antibodies were positive on three occasions (titres 105–282 pmol/l : positive >50 pmol/l) and anti-AChR antibodies were negative. Neurophysiological studies strongly supported the diagnosis of LEMS with up to a 15-fold increase in compound muscle action potentials after maximum voluntary contraction (MVC). Treatment with plasma exchanges and prednisolone and azathioprine showed marked improvement, although marked residual disability was noted.

She was first seen by BRFL in 1999 when she was 30 years old. At this time, she had fluctuating facial, neck and limb weakness and also a dry mouth. She could walk slowly, for about 200 m. At this stage, she was taking azathioprine 100 mg/day and prednisolone 7.5 mg/day.

The tendon reflexes were depressed with marked post-MVC potentiation. The compound muscle action potential of abductor digiti minimi increased 178% after MVC. After treatment with 3:4 diaminopyridine 10 mg four times daily, increasing to six times daily, she showed marked improvement and the prednisolone was tapered off. The improvement in her disability was maintained.

A positive pregnancy test was noted in April 2004, and she had an uneventful pregnancy. Treatment with azathioprine and 3:4 diaminopyridine was continued. The baby was born by normal delivery at full term and birth weight was 3050 g, with an Apgar score of 10 at 5 min. Mild persistent hypotonia was seen with preserved tendon reflexes, but there was no problem with feeding. Anti-VGCC antibodies were not measured. At 3 weeks, the hypotonia had fully resolved and the infant has remained well.

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References

1 **Motomura M**, Lang B, Johnston I, *et al*. Incidence of serum anti-P/Q-type and antiN type calcium channel autoantibodies in the Eaton-Lambert myasthenic syndrome. *J Neurol Sci* 1997;**47**:35–42.
2 **Keesey J**, Lindstrom J, Cokeley H, *et al*. Anti-acetylcholine receptor antibody in neonatal myasthenia gravis. *N Engl J Med* 1977;**296**:55.

Fulminant Devic disease successfully treated by lymphocytapheresis

Devic disease is a demyelinating disease characterised by acute optic neuritis and transverse myelitis. Although there are differences in the pathogenesis of Devic disease and multiple sclerosis, the treatment for Devic disease is the same as that for multiple sclerosis. We report a patient with Devic disease who was resistant to high-dose intravenous methylprednisolone and intravenous immunoglobulin (Ig) treatments, but was effectively treated with lymphocytapheresis (LCP). The profiles of cytokines during the clinical course are discussed.

Case report

In August 2001, a 27-year-old woman developed acute loss of vision and sensory disturbance in both lower extremities after coughing. The next morning (day 2), she was totally blind and was admitted to our hospital. Neurological examination showed total blindness, papilloedema, moderate muscle weakness of the hip and thigh muscles, positive pathological reflexes of the limbs, hyper-reflexia and sensory loss below the T4–5 level. Loss of vesicorectal function and perspiration below the chest were also observed.

Laboratory examination disclosed a normal C-reactive protein level, positive antinuclear (titre 1/160) and antithyroglobulin antibodies (0.8 U/ml (normal range <0.3)) in serum, normal CD4:CD8 ratio (0.90 (normal range 0.69−1.74)) and an increased percentage of CD8 T cells (45% of total T cells (normal range 12−30%)). Anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies and rheumatoid factor were negative. No significant increase of antibodies in the serum or CSF was seen against the following microorganisms: herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, enterovirus, hepatitis B virus, mumps, measles, rubella, coxsackie virus, *Borrelia burgdorferi*, syphilis, chlamydia, legionella and *Mycoplasma pneumoniae*. Neuromyelitis optica (NMO)-IgG[1] was negative. CSF analysis was normal except for an increased concentration of myelin basic protein (660 pg/ml (normal limit <102 pg/ml)) on day 2, but pleocytosis (112/mm^3) and increased protein concentration (152 mg/dl) were observed on day 12. MRI of the brain showed enlarged optic nerves without enhancement. T2-weighted MRI of the spinal cord showed high signal intensity in the cervical cord (C6–7) on day 3, and diffuse swelling in the whole spinal cord with T2 hyperintensity on day 15.

Two courses of methylprednisolone treatment (1 g/day for 3 days) were given from day 3, and, in addition, intravenous Ig (0.4 g/kg/day for 5 days) was given from day 16. The patient, however, showed no response to these treatments. Thereafter, she fell into complete tetraplegia, with sensory loss below the neck and frequent sharp pains from the shoulder to neck, which were considered to be painful tonic spasms. Then, on day 23, we performed LCP with a centrifuge, ''COBE Spectra'' (GAMBRO, Tokyo, Japan), that processed 7–8 l of blood and removed about $3–4\times10^9$ lymphocytes per procedure. On the day of treatment the sharp pain disappeared immediately after the first LCP, and the following day her vision showed improvement, going from total blindness to the level of finger counting. Thereafter, LCP was performed once or twice weekly for a total of 11 LCP treatments. Her vision was almost normalised, with improvement of the sensory deficit and recovery of weakness of the upper extremities to grade 4 or 5 on the manual muscle test.

The T-helper (Th)1:Th2 balance represented by the ratio of intracellular interferon γ to interleukin (IL) 4 in the CD4 T cells increased markedly both before the first LCP (22.2 (normal limit <10)) and after the last LCP (17.5). CSF IL-6 and serum IL-12 levels were markedly reduced after the first LCP, even when compared with those on the same day before treatment (table 1). No relapse has occurred in 4 years.

Comment

Devic disease presents with a poor prognosis, including death, and frequent sequelae, including visual disturbance or paralysis.[2] Marked improvement was achieved by 2–5 treatments a week over about 6 weeks in only one other reported case of Devic disease that was treated by lymphocytoplasmapheresis, including the removal of both lymphocytes and plasma.[2] In our patient, who was resistant to methylprednisolone and intravenous Ig treatments, remarkable improvement of the symptoms, especially visual loss, was immediately obtained by LCP, which removed only lymphocytes but not plasma. LCP might reduce clonally expanding pathogenic T lymphocytes in the peripheral blood, and has been used as an adjunct to standard immunosuppressive treatment for acute transplant rejection. The removal of lymphocytes may therefore augment immunosuppression.[3] LCP may have induced the improvement in our patient through these mechanisms.

Table 1 Cytokine profile during the clinical course

	IL-6 (pg/ml)		IL-12 (pg/ml)	
	Serum	CSF	Serum	CSF
Before the first LCP	3.2	5660	18.5	<7.8
After the first LCP	3.0	121	<7.8	<7.8
After the last LCP	2.8	6.1	<7.8	<7.8

IL, interleukin; LCP, lymphocytapheresis.

In our patient, an infectious aetiology was unlikely, and positive antinuclear antibody suggested an autoimmune mechanism. The specific biomarker for NMO, NMO-IgG, has been reported in NMO and opticospinal multiple sclerosis, suggesting an autoantibody-driven pathogenesis.[1] The sensitivity of NMO-IgG for diagnosing NMO is 73%,[1] and our patient would be classified as being in the seronegative group. It has, however, been reported that opticospinal multiple sclerosis, which seems to be similar to NMO with respect to NMO-IgG,[1] is associated with the Th1-dominant condition during both the relapse and remission phases.[4] In our patient, a shift in the Th1:Th2 balance towards Th1 dominance was shown during both the acute and remission phases. Th1 cells possibly play an important part in the pathogenesis of Devic disease. An investigation of this will require further study with more patients.

It has been reported that a proinflammatory cytokine, IL-6-secreting cells, or a critical cytokine for T cell-mediated autoimmunity, IL-12-secreting cells, are increased in both the CSF and blood from patients with NMO.[5] In our patient, increased levels of CSF IL-6 and serum IL-12 were consistent with those previously reported, but levels of serum IL-6 and CSF IL-12 were normal. Levels of CSF IL-6 and serum IL-12 correlated well with disease activity. These cytokine levels may therefore serve as markers of therapeutic effects as well as disease activity in Devic disease. Levels of CSF IL-6 and serum IL-12 were reduced immediately after the first LCP, suggesting the direct effect of LCP on cytokines. Clinical improvement is thought to have been induced by LCP, because of the extremely rapid improvement within 1 day after LCP.

In conclusion, LCP may be a therapeutic option in fulminant Devic disease that is unresponsive to other treatments, including methylprednisolone treatment.

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References

1 **Lennon VA**, Wingerchuk DM, Kryzer TJ, *et al.* A serum autoantibody marker of neuromylitis optica: distinction from multiple sclerosis. *Lancet* 2004;**364**:2106–12.
2 **Aguilera AJ**, Carlow TJ, Smith KJ, *et al.* Lymphocytaplasmapheresis in Devic's syndrome. *Transfusion* 1985;**25**:54–6.
3 **Kleinman S**, Nichols M, Strauss F, *et al.* Use of lymphoplasmapheresis or plasmapheresis in the management of acute renal allograft rejection. *J Clin Apheresis* 1982;**1**:14–7.
4 **Ochi H**, Wu XM, Osoegawa M, *et al.* Tc1/Tc2 and Th1/Th2 balance in Asian and Western types of multiple sclerosis, HTLV-I-associated myelopathy/tropical spastic paraparesis and hyperIgEaemic myelitis. *J Neuroimmunol* 2001;**119**:297–305.
5 **Correale J**, Fiol M. Activation of humoral immunity and eosinophils in neuromyelitis optica. *Neurology* 2004;**63**:2363–70.

Repetitive transcranial magnetic stimulation of the motor cortex for hemichorea

Hyperkinetic disorders such as chorea, ballism and dystonia can be observed after lesions (usually small strokes) affecting the thalamus, basal ganglia and related circuits.[1] Neural circuit models of basal ganglia circuitry suggest that these result from disinhibition of thalamo-cortical projections because of a reduction in inhibitory output from the internal pallidal segment. Increased thalamocortical drive may lead to an increase in the excitability of excitatory and inhibitory circuits of the frontal areas of the cortex,[2 3] including M1, that may contribute to hyperkinesia.

Circuits of the human motor cortex can be activated non-invasively with transcranial magnetic stimulation (TMS) of the brain,[4] and because the excitability of neural circuits in the cerebral cortex is not static, repetitive TMS (rTMS) can produce changes in neurotransmission that outlast the period of stimulation.[5–7]

rTMS has been proposed as a therapeutic tool in several psychiatric and neurological disorders, and a recent review suggested that the best effects of therapeutic rTMS are seen when protocols that depress network excitability are used to treat disorders characterised by cortical hyperexcitability.[8]

A recent study showed that excitability of the motor cortex can be reduced for 30–60 min after application of a novel paradigm of rTMS termed continuous θ burst stimulation (cTBS).[9 10] This protocol leads to a decrease in the excitability of excitatory and inhibitory cortical circuits that is long lasting. Thus, after TBS, there is a decrease in the amplitude of the corticospinal volleys evoked by transcranial stimulation,[10] and the size of the resulting motor-evoked potentials.[9] In addition, a reduction in excitability of intracortical inhibitory circuits was shown by a decrease in short latency intracortical inhibition, a putative marker of γ aminobutyric acid transaminase-A activity.[9]

The aim of this preliminary study was to investigate whether cTBS of the motor cortex could reduce involuntary movements in a patient with hemichorea-ballism.

We hypothesised that the reduced excitability in excitatory and inhibitory circuits of the motor cortex that follows cTBS[9] could normalise excitability of frontal areas and improve hyperkinesias.

A 68-year-old woman with a history of hypertension and glaucoma suddenly presented with severe involuntary movements of the left arm, leg and face. An MRI of the brain, carried out a week after the stroke, showed a lesion with signal characteristics of subacute haemorrhage in the midbrain and the caudal diencephalon on the right side, and thus conceivably affecting the subthalamic nucleus or the substantia nigra, or both these structures (fig 1). A lesion of these structures would remove excitatory drive to the internal segment of the globus pallidus and the resulting decrease in pallidal inhibition of thalamus would lead to a consequent increase in thalamo-cortical excitation. Treatment with levetiracetam (500 mg twice daily) produced no benefit.

In the weeks after the stroke, there was mild improvement in the severity of dyskinesias. Movements on the left, and particularly in the arm, however, never resolved completely, and caused pain in the left shoulder.

Ten weeks after the stroke, neurological examination showed left hemichorea, particularly affecting the arm, with ballistic movements at the shoulder and distal choreoathetoid movements. Mild choreatic movements were also observed in the left hemifacial muscles and leg. Posture, voluntary movements or tasks requiring concentration increased intermittent dyskinesias at rest. The rest of the neurological examination was unremarkable apart from blindness of the left eye secondary to glaucoma. Treatment with increasing doses of tetrabenazine up to a dose of 25 mg thrice daily failed to produce any benefit after 2 months. At this time, rTMS of the motor cortex was carried out as an add-on treatment.

The patient gave informed consent to the study that was performed with the approval of the appropriate Institutional ethics committee.

rTMS was applied over the left-hand motor area by using a MagPro (Medtronic A/S, Copenhagen, Denmark) stimulator and a figure of eight-shaped coil. The stimulation intensity was 80% of the active motor threshold (AMT), defined as the minimum single pulse intensity required to produce a motor evoked potential >200 μV on more than five out of ten trials from the contracted contralateral first dorsal interosseous.

rTMS was carried out using the cTBS pattern in which three pulses of stimulation are given at 50 Hz and repeated every 200 ms, for a total of 600 pulses.[9] This protocol leads to pronounced and prolonged suppression of cortical excitability that reaches a maximum about 5–10 min after the end of the protocol.[9]

Sham rTMS was performed by using the same stimulator connected to the placebo butterfly coil MCF-P-B-65, which has no stimulating effect on the cortex but produces auditory and tactile sensations similar to those produced by the real coil. The site of the stimulation and the number of stimuli were identical to those used for the real magnetic rTMS.

Two sessions of real rTMS (the first and the third) and one session of sham rTMS were