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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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

carried out at intervals of about 10 days. At each session, the patient was evaluated by a skilled movement disorders neurologist. Both the patient and the neurologist who scored the dyskinesias were blinded to the rTMS protocol (sham or real) used in each session. Dyskinesias were measured before and 10 min after stimulation by means of a Dyskinesias Scale (ranging from 0 to 4, see appendix) scored in all the following conditions: at rest; while performing a distracting mental activity; while walking; and while performing voluntary tasks (pouring water, drinking from a glass, putting on a lab coat, buttoning and finger-to-nose manoeuvre). Drinking was the action on which the worst performance occurred and it was therefore the task chosen to compare the severity of dyskinesias in all the six assessments.

The evaluation of the involuntary movements was carried out live and video recordings of the first and second sessions were obtained.

The patient could not distinguish between real and sham stimulation.

Real rTMS produced a dramatic improvement in dyskinesias during functional tasks requiring the use of the upper limb (for video A and table, see http://jnnp.bmjjournals.com/supplemental).

Scores on the evaluation scale improved from 4 to 1 (pouring, drinking), from 3 to 2 (buttoning), from 3 to 1 (rest, finger-to-nose) and from 2 to 1 (walking) after the first session and similarly after the third session (table). The patient reported that the benefit lasted about 24 h after both sessions, with associated reduction of the pain at the left shoulder. After the sham stimulation (second session), no consistent variations were reported by the patient or by the evaluating neurologist. Basal scores on that day were 3 for pouring, drinking, buttoning and finger-to-nose manoeuvre and 2 for rest and walking: a slight improvement was noticed by the evaluating neurologist but was judged to be insufficient to modify the rating on each of the considered tasks (for video B and table, see http://jnnp.bmjjournals.com/supplemental).

Studies in patients with chorea due to Huntington's disease[3] and in a patient with diabetes with hemiballism–hemichorea[2] suggest that in these conditions increased thalamo-cortical drive may increase excitability of excitatory and inhibitory circuits of frontal areas of the cortex, including M1, and contribute to the development of hyperkinesias. The present study shows that rTMS protocols that suppress the excitability of excitatory and inhibitory circuits of the motor cortex may be useful in the treatment of hyperkinetic disorders. This would be consistent with a recent study in which low-frequency rTMS, which is another way of decreasing cortical excitability, was used on midline frontal cortex to reduce dyskinesias in patients with Huntington's disease.[11]

In this study we cannot determine whether the principal effect of cTBS occurs through its suppression of excitatory or inhibitory circuits, or both. What is more certain, however, is that the effects are likely to have occurred because of a change in cortical rather than subcortical circuits. Thus, cTBS is known to suppress excitatory circuits that generate I waves[4] within the motor cortex. Similarly, cTBS reduces short-latency intracortical inhibition,[9] which again is a cortical phenomenon.[4] Currently, there is no evidence that cTBS leads to any changes in excitability of subcortical circuits.

Because the effects of TMS are short-lived, cTBS is not suitable as a chronic intervention. It can, however, turn out to be useful in selecting patients for implantation with cortical epidural electrodes as both TMS and epidural stimulation appear to activate similar elements in the motor cortex.[12] A similar approach has been suggested by Lefaucheur[13] to select patients with pain who may be candidates for chronic epidural motor cortex stimulation.

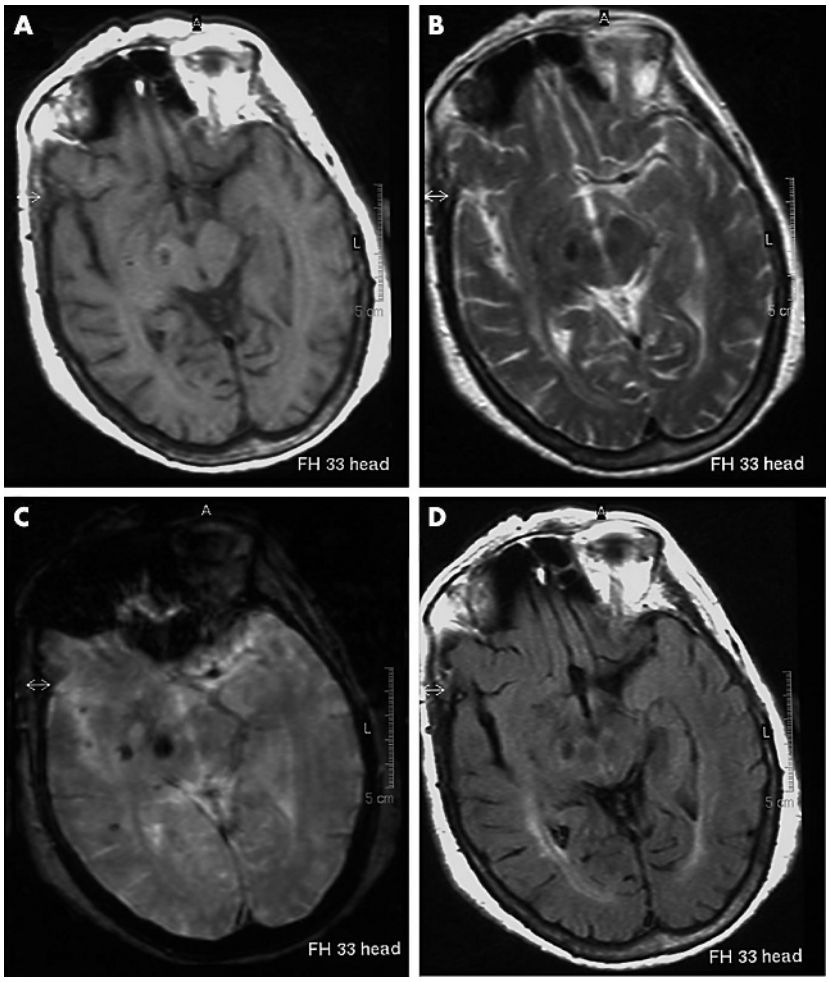

Figure 1 MRI of the brain of the patient. (A) Axial SE T1-weighted image (TR 582/TE 15). (B) Axial TSE image (TR 2200/TE 120). (C) Axial GE T2-weighted image (TR 600/TE 23). (D) Axial T2-FLAIR image (TR 6000/TE 100/TI 2000). The images show a subacute haemorrhagic lesion in the midbrain of the right side.

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An additional table and videos 1 and 2 are available at http://jnnp.bmjjournals.com/supplemental

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Neurogenic pulmonary oedema in a patient with leptomeningeal carcinomatosis

We present the case of a patient with leptomeningeal carcinomatosis from a primary breast adenocarcinoma. On admission to hospital, she developed neurogenic pulmonary oedema due to increased intracranial pressure (ICP), as confirmed by lumbar puncture. Tapping of the CSF resulted in abrupt relief of the clinical sequelae.

A woman in her late 40s, with a medical history of breast adenocarcinoma, for which she underwent a modified radical mastectomy with axillar lymph node resection, was admitted to our hospital for intrathecal chemotherapy. Just 1 month earlier, she underwent craniotomy for a solitary metastatic intracerebral lesion in the left frontal lobe. After this uneventful procedure, she continuously complained of drowsiness, nausea and vomiting. A CT scan showed enhancement of cerebral and cerebellar sulci, typical of leptomeningeal metastasis.

This diagnosis prompted admittance to our hospital, a tertiary care oncology centre, for further treatment. On admittance, the patient had increasing dyspnoea. Pulmonary and cardiac examination showed basilar crepitations on both lungs, tachypnoea (>24/min), tachycardia (145 beats/min) and a blood pressure of 80/40 mm Hg. No cardiac murmurs were heard and the electrocardiograph showed no signs of myocardial infarction. The peripheral oxygen saturation at that time was 80% with no oxygen support. Blood gas analysis showed hypoxia: pH 7.46, partial pressure of carbon dioxide (pCO_2) 4.7, partial pressure of oxygen (pO_2) 5.4, HCO_3^- 24.7, (BE) 1.3 and arterial oxygen saturation (SaO_2) 0.79. A chest radiograph showed a normal heart with evidence of bilateral alveolar filling (fig 1B; fig 1A shows the chest radiograph taken 1 day earlier, which was without abnormalities).

The patient was admitted to the intensive care unit and respiration was supported by mechanical ventilation through a facemask and administration of oxygen. Nevertheless, her neurological condition deteriorated to a Glasgow Coma Scale (GCS) score of 6. On reconsidering the CT scan and the diagnosis of leptomeningeal carcinomatosis, we hypothesised that increased ICP, due to a CSF resorption disturbance, caused neurogenic pulmonary oedema. Therefore, we carried out a lumbar puncture, showing an increased CSF pressure of 60 cm H_2O. We drained 30 ml of the CSF, during which the patient regained consciousness acutely (GCS 13). Cytology showed the presence of malignant cells. The tachypnoea and tachycardia resolved, although the basilar crepitations could still be recognised on pulmonary auscultation. Blood gas analysis showed recovery: pH 7.42, pCO_2 5.2, pO_2 8.0, HCO_3^- 24.8, BE 1.0 and SaO_2 0.93.

The patient was readmitted to the neurosurgical department for a CSF shunt procedure. She was, however, not fit for surgery, and attempts to alleviate the increased ICP with an external lumbar drain failed. Treatment was discontinued when her condition deteriorated again 5 days later, after which she died.

As far as we know, leptomeningeal metastasis has not been described as the cause of neurogenic pulmonary oedema. Although the association of an increased ICP and neurogenic pulmonary oedema has been described previously, the pathophysiological mechanisms remain obscured.[1–3] The medulla oblongata is believed to be the critical anatomical structure responsible for the pathogenesis of neurogenic pulmonary oedema, probably acting through the sympathetic component of the autonomic nervous system.[1 2]

The rapid improvement after the normalisation of the increased CSF pressure is more consistent with neurogenic lung oedema than with other causes of respiratory distress. As reviewed by Fontes *et al*,[4] the clinical features as described in our patient—that is, tachypnoea, dyspnoea, tachycardia and hypotension—often occur in acute neurogenic pulmonary oedema. As Fontes *et al* conclude, we believe that doctors should always be aware of this clinical condition after neurological events, especially when no other causes of pulmonary oedema can be established. Supportive measures are the treatment of choice. In our patient, relieving the increased ICP corrected the respiratory failure.

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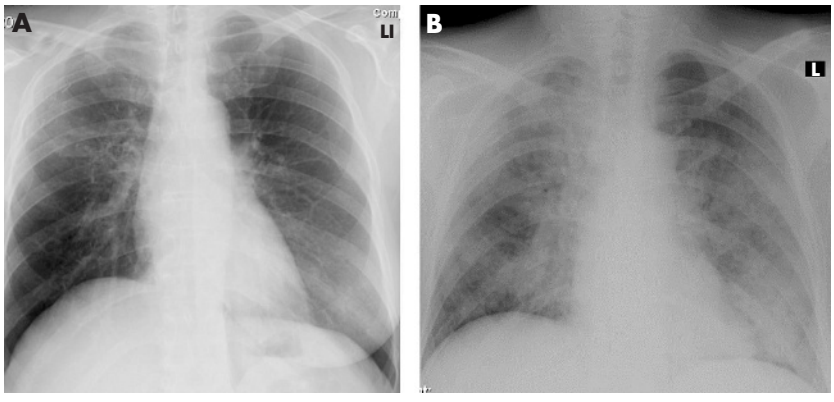

Figure 1 Chest radiograph: (A) taken 1 day earlier; (B) with evidence of bilateral alveolar filling.

Onset of cluster headache triggered by emotional effect: a case report

Cluster headache is a strictly unilateral headache that occurs in association with autonomic symptoms. Stress is a recognised precipitant of migraines, but not of cluster attacks. We describe the case of a patient having migraine for years, in whom extreme emotional stress triggered cluster headache attacks.

Background

Neuroimaging has contributed considerably to the knowledge about the neurobiology of cluster headache. Activation in the region of the posterior hypothalamus is observed,[1] coinciding with subtle structural abnormalities in the same region.[2]

Genetic studies indicate an autosomal dominant inheritance with low penetrance and an increase in risk of 4–18 times for