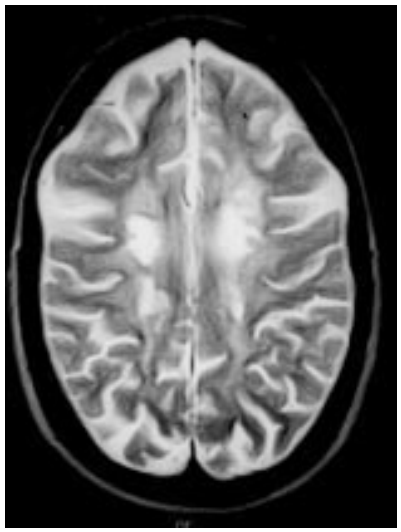
Adult Niemann-Pick disease type C mimicking features of multiple sclerosis

Niemann-Pick disease type C is a panethnic autosomal recessive neurovisceral storage disorder characterised by a unique error in cellular trafficking of exogenous cholesterol. The most typical phenotype is characterised by hepatosplenomegaly, vertical supranuclear ophthalmoplegia, progressive ataxia, dystonia, and dementia and manifests in late childhood. Adult onset Niemann-Pick disease type C often includes psychosis and dementia.[1 2] We report an adult female patient with biochemically verified Niemann-Pick disease type C in whom the initial diagnosis of multiple sclerosis was questionable because of a persistent splenomegaly.

The 33 year old woman was referred to the Psychiatry Department of the University of Heidelberg in December 1994. She complained of progressive difficulties with memory and concentration, increasing social isolation, and problems with daily activities. The patient was unsure about the onset of her problems but suggested that they had started after the birth of her daughter three years previously. History, family history, and the patient's fetal and childhood development were unremarkable. Her parents are non-consanguineous. School performance was satisfactory initially but later her learning behaviour became erratic and she failed her examinations after 10 school years. She worked as a saleswoman and after giving birth she lived on social support. With time she no longer managed to educate her daughter and neglected her housekeeping. The patient´s mother reported that her problems with memory and concentration had been variably apparent since school but progressively deteriorated after her pregnancy.

On neurological examination, cranial nerves were unremarkable. Guided and voluntary eye movements were normal; fast saccadic movements were slightly dysmetric. Optokinetic nystagmus was absent vertically but normal horizontally. The patient had a slight paresis of her left leg, tendon reflexes were brisker in the left than the right leg but symmetric in both arms. Plantar response was flexor. There was a slight ataxia in both legs. Sensory testing was normal. Snout or palmomental reflexes were absent. The patient was inattentive but well oriented to time, person, and place. She had difficulties in retrieving past and storing new information. There was no aphasia or dysarthria but her speech was vague and circuitous with many meaningless phrases. Thinking was slowed, impoverished in content, and reduced in flexibility. She was emotionally labile, her behaviour was disorganised, and her judgment was impaired.

Psychometric tests resulted in an estimated IQ of 71 on the Hamburg-Wechsler test. An amnesia score (Berliner Amnesietest-Kurzform) and the d2 test were highly pathological. Cranial MRI showed considerable cerebral atrophy and multiple non-enhancing hyperintense areas on T2 weighted images localised in the periventricular white matter and the corpus callosum (figure). Follow up examination in spring 1996 showed no changes. Protein concentration (0.36 g/l) and cell count (1 cell/ml) in CSF were normal; oligoclonal bands were positive in CSF but negative in serum. Somatosensory evoked potentials to both legs and transcortical magnetic evoked potential to the left leg were delayed. Abdominal sonography disclosed an enlarged (vertical diameter 17 cm) and inhomogeneously structured spleen. Liver size was borderline. Routine hematological and biochemical analyses were normal except for transient thrombopenia. Vasculitis screening, serum tests for copper, coeruloplasmin, vitamin B12, folic acid, basic endocrinological tests including thyroid function assessment, testing for HIV and syphilis, very long chain fatty acids, arylsulphatase A, and other serum lysosomal enzyme activities were normal.



Axial T2 weighted images show multifocal and partly confluent subcortical areas with pathologically high signal.

Considering the MRI and CSF findings we first diagnosed multiple sclerosis with a prominent picture of progressive dementia. Treatment with steroids did not improve the clinical status. The patient was referred to a rehabilitation hospital. There, CSF analysis was normal and oligoclonal bands were absent.

In August 1995, the patient was readmitted in a state of severe depression and helplessness. Her dementia had deteriorated, neurological examination was unchanged, still showing slight lower limb ataxia and left leg paresis. Because control sonography disclosed persistent splenomegaly, we considered the diagnosis of Niemann-Pick disease type C or Gaucher disease. Cytology of a bone marrow aspirate disclosed so-called sea blue histiocytes and Niemann-Pick cells, a result strongly suggestive of Niemann-Pick disease type B or C. Biochemical studies on cultured skin fibroblasts confirmed the diagnosis of Niemann-Pick disease type C. The intracellular low density lipoprotein induced esterification of cholesterol was reduced (330 (controls 2950 (SD 1200)) pmol/mg cell protein of cholesteryl oleate formed after 4.5 h).

Cytochemical staining with filipin showed a significant but not massive accumulation of unesterified cholesterol in perinuclear vesicles. These combined findings were consistent with an "intermediate" biochemical phenotype of Niemann-Pick disease type C.[2]

The clinical picture in our patient corresponds well to late onset Niemann-Pick disease type C. Although her disease may have insidiously started during childhood or adolescence, definite dementia only developed around the age of 30. Progressive dementia is the most often reported sign, and limb ataxia and splenomegaly are other prominent features in adult onset Niemann-Pick disease type C. Vertical supranuclear ophthalmoplegia, which was absent in our patient, is an important sign in infantile and juvenile Niemann-Pick disease type C, but it is often missing in adult disease[1]

Findings on MRI and in CSF had initially suggested a diagnosis of multiple sclerosis in our patient. Dementia may occasionally be the leading or even only symptom in multiple sclerosis and features of dementia in multiple sclerosis resemble those in our patient. In Niemann-Pick disease type C, neuroimaging is usually normal or shows non-specific cerebral atrophy, but some cases with periventricular white matter lesions have been described.[3] Neuropathological studies occasionally showed demyelination in infantile cases.[2 4] Therefore, clinical and neuroradiological findings in our patient were compatible with a diagnosis of Niemann-Pick disease type C. However, to our knowledge oligoclonal bands have not been reported in the disease. Increased CSF immunoglobulin concentrations are often found in adrenoleukodystrophy,[5] indicating that inborn errors of metabolism can be associated with an immune response. Accordingly, oligoclonal bands in our patient may also represent an immunological response to cerebral damage caused by Niemann-Pick disease type C. In our patient, Niemann-Pick disease type C mimicked features of multiple sclerosis. Therefore, in patients with suspected multiple sclerosis in whom dementia or psychosis are the leading symptoms, Niemann-Pick disease type C should be considered as differential diagnosis.

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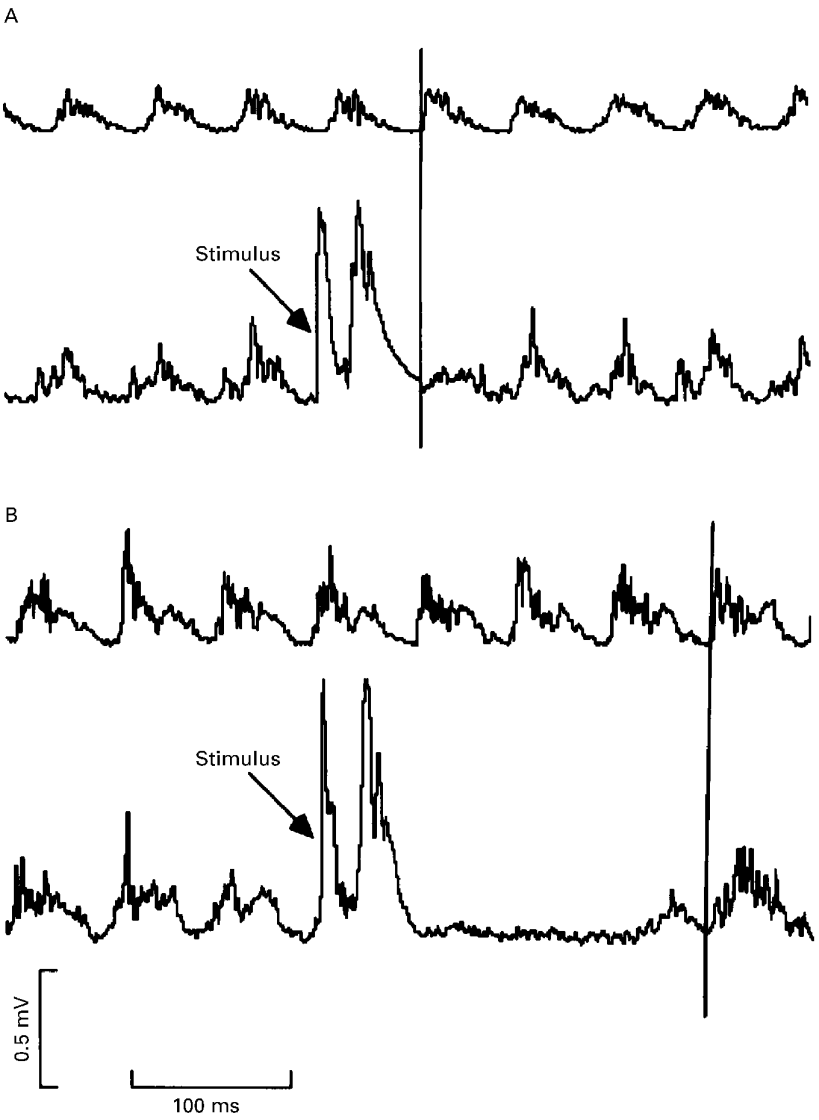
Motor cortex stimulation does not reset primary orthostatic tremor

Primary orthostatic tremor is a rare but well characterised condition.[1–3] The predominant feature is unsteadiness and shaking of the legs, which occurs exclusively on standing. Electromyographic recordings disclose a 13-18 Hz tremor in leg and paraspinal muscles.[2 3] A similar tremor in the arms can be induced by weight bearing actions.

We studied five patients with previously established clinical and EMG diagnoses of primary orthostatic tremor. Surface EMG recordings were made from up to four muscles simultaneously; one muscle (right hamstrings) was recorded from throughout each study to act as a timing reference. Leg muscles were studied with the patients standing and arm muscles with patients leaning forwards on their arms. The effect of different maintained head positions (looking to the left, to the right, upwards, and downwards) was also recorded.

In three patients, while standing, transcranial magnetic stimulation (TMS) was applied using a Magstim 200 with a double cone coil positioned over the vertex. Stimulus intensity was sufficient to produce consistent motor evoked potentials in voluntarily activated leg muscles while seated. The magnetic stimuli were triggered, at a maximum of 0.3 Hz, by EMG bursts. The stimulus delay after an EMG burst was varied between 0 and 50 ms using a precise timing device, to see whether any effect of TMS was dependent on its temporal relation to the tremor cycle. Ten stimuli were applied at each delay setting.

The EMG signals were digitised and data were rectified and displayed in sweep durations of 200-500 ms. The 10 individual trials for a given delay were averaged, using the stimulus as a reference point. In addition all interburst intervals in each individual trial were measured. This allowed calculation of any latency shift in the first poststimulus tremor burst, as well as any subsequent alteration in tremor frequency.



All traces show rectified and averaged (10 trials) EMG data over a sweep duration of 500 ms. (A) and (B) refer to different patients, recording from right quadriceps and right hamstrings respectively. In both cases the upper trace is from a recording without transcranial magnetic stimulation. (A) The stimulus was triggered 45 ms after the start of an EMG burst. The EMG burst after the CMAP is reduced in amplitude, but occurs at the expected latency (vertical line). (B) The stimulus was triggered at the start of an EMG burst. EMG bursts disappear after the CMAP, but then reappear at the expected latency (vertical line).

The frequency of tremor ranged between 14 and 18 Hz. Leg tremor was present in all patients on standing and disappeared on sitting, whereas arm tremor was only seen when patients leant on their arms. Within each patient there was a clear and consistent phase relation of tremor bursts between different muscles. However, comparing all five patients the exact timing of these relations varied. Specifically, there was no overall relation between flexor and extensor muscles or between left and right sides.

We found that changes in head position while standing had no effect on either the frequency or amplitude of the tremor. This would suggest that static vestibular inputs to spinal motor neurons do not modulate the tremor.

In two patients TMS reduced the amplitude of the next EMG burst after the evoked compound muscle action potential (CMAP), but did not alter the frequency of the tremor (figure, A). The magnitude of reduction in amplitude was variable and did not correlate with alterations in stimulus delay. Motor neurons discharged as a result of TMS of the motor cortex would be expected to remain partially refractory and this would explain the reduction in burst amplitude.

In the third patient, EMG bursts were transiently suppressed for between one and three tremor cycles after TMS (figure, B), before reappearing at the expected latency and without any subsequent modulation of frequency. There was no correlation between degree of suppression and stimulus delay. This suppression can probably be attributed to the "silent period", which is thought to be due to activation of both intracortical and spinal inhibitory mechanisms. Significantly, these inhibitory mechanisms did not seem to have modulated the tremor generator, as the EMG burst reappeared at the expected time and the tremor continued at the prestimulus frequency.

The generator site underlying primary orthostatic tremor is unknown. The frequency of the tremor (13-18 Hz) suggests that it is central rather than peripheral. The failure of peripheral stimuli to reset primary orthostatic tremor[2] supports this. The effect of transcranial magnetic stimulation, which has been reported to reset both essential tremor and parkinsonian tremor,[4] has not previously been reported on in this condition.

We suggest that the motor cortex is neither the site nor a modulator of the presumed central generator of primary orthostatic tremor. Furthermore, other intracortical structures activated by transcranial magnetic stimulation (for example, intracortical or transcallosal inhibitory pathways) do not seem to modulate the generator.

This research was funded in part by a Wellcome Trust research grant (KAN).

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