psychoses. The short interval between the operation and the psychiatric manifestation also supported this view. K KANEMOTO
Kansai Regional Epilepsy Centre, Utsunomiya National Hospital, Kofu, Japan
Correspondence to: Dr Kosuke Kanemoto, Utsunomiya National Hospital, Utsukou, Narutaki, Ondoyama-cho, Kofu, Yamanashi, Japan.

Machado-Joseph disease mutations as the genetic basis of most spinocerebellar ataxias in Germany

Machado-Joseph disease is an autosomal dominant inherited neurodegenerative disorder pathologically characterised by neuronal loss and gliosis in the cerebellum (especially the dentate nucleus), the spinal cord (spinocerebellar tracts, anterior horn cells, posterior columns, and Clarke’s columns) and to varying degrees in the substantia nigra, the subthalamic nuclei, cranial motor nuclei, and peripheral nerves. Clinically Machado-Joseph disease presents with a broad range of symptoms including variable combinations of cerebellar ataxia, pyramidal and extrapyramidal features, peripheral neuropathy, progressive external ophthalmoplegia, and faciolingual fasciculation.1 Machado-Joseph disease was originally described in Portuguese-Azorean descendants and has rarely been encountered in ethnic groups other than Portuguese.1 Up to now, no patients with the clinical diagnosis of Machado-Joseph disease have been reported in Germany. Recently, the Machado-Joseph disease gene locus has been mapped to chromosome 14q and the disease causing mutation has been identified as an unstable and expanded (CAG) trinucleotide repeat.2

We investigated the Machado-Joseph disease mutation in 38 families with dominant cerebellar ataxias and in 21 patients with sporadic forms of ataxia of German ancestry. In 19 of 38 families an expanded trinucleotide repeat in the Machado-Joseph disease gene has been identified. Analysis of the (CAG) repeat length and the age of onset disclosed an inverse correlation, with the longest repeats in patients with juvenile onset (figure). None of the sporadic patients carried the Machado-Joseph disease mutation indicating that new mutations occur rarely.

Prominent clinical features of the German patients with ataxia and bearing the Machado-Joseph disease mutation (table) included cerebellar symptoms such as ataxia of limbs, gait, and stance, dysarthria, ophthalmoplegia, ocular motility disturbances, and a varying combination of dysphagia, spasticity, and peripheral neuropathy with amyotrophy and sensory loss. Characteristic signs of Machado-Joseph disease as described in patients of Portuguese or Oriental descent, such as dystonia, extrapyramidal rigidity, faciolin-

Clinical characteristics of patients with (SCA3), (MJD), and (SCA1)

<table>
<thead>
<tr>
<th>SCAS/MJD</th>
<th>MJD USA *</th>
<th>MJD Japan *</th>
<th>SCA3 France</th>
<th>SCA1 Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of families</td>
<td>19</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No of patients</td>
<td>30</td>
<td>25</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Age of onset (mean (SD))</td>
<td>37 (7)</td>
<td>36 (17)</td>
<td>31 (10)</td>
<td>33 (7)</td>
</tr>
<tr>
<td>(range)</td>
<td>(19-51)</td>
<td>(10-64)</td>
<td>(20-44)</td>
<td>(20-47)</td>
</tr>
<tr>
<td>Disease duration (mean (SD))</td>
<td>12 (5)</td>
<td>12 (7)</td>
<td>11 (5)</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

Clinical signs (%):

- Cerebellar: gait ataxia 100 100 ? ? 100
- Limb ataxia and dysmetria 97 97 90 90 97
- Dysarthria 96 96 90 90 96
- Cerebellar oculomotor signs 93 96 90 90 93
- Pyramidal: spasticity 57 54 50 50 57
- Increased tendon reflexes 40* 40* 92** 92** 33 13
- Extensor plantar responses 40 40 58 50 13
- Extrapyramidal: rigidity 13 40 25 25 0
- Dystonia 3* 3** 36* 67** 6 0
- Ankylostrophy 23 32 42 42 23
- Decreased vibration sense 43* 43* 80** 80** 44 11
- Ophthalmoplegia 37 58 39 39 38
- Faciolingual fasciculation 63* 63* 56* 56* 63* 25
- Dysphagia 63 7 8 8 25

- *P < 0.05; **P < 0.01; ***P < 0.001 comparison of percentages with a corrected z2 test.
- a: comparison between SCA3/MJD Germany and MJD USA; b: SCA3/MJD Germany and MJD Japan; c: SCA3/MJD Germany and SCA1 Germany; d: MJD USA and MJD Japan; e: MJD USA and SCA3 France; f: MJD USA and SCA1 Germany; g: MJD Japan and SCA3 France; h: MJD Japan and SCA1 Germany; i: SCA3 France and SCA1 Germany. Data presented in this paper. Schols et al, unpublished data.
Oculographic findings in traumatic unconsciousness: prognostic implications

The analysis of saccadic eye movements can assist in the diagnosis and anatomical localization of several neurological and psychiatric disorders. Spontaneous and reflexive eye movements may also be of value in the neurosurgical assessment of traumatic brain injury. Organised spontaneous eye movements require integrity of the motoric brain stem, and some reflexive movements need reciprocal connections with visual and auditory cortical centres. Traumatic brain injury results in a graded centripetal disconnection of cortical and subcortical structures in a rostrocaudal direction. Much of the mortality and morbidity associated with head injury is thought to be due to neural disconnection caused by diffuse axonal injury. Taking advantage of the standing corneo-retinal potential of the eye, it is relatively easy to record orbital movements electrophysiologically with periorbital electrodes. Ocular microtremor, which is due to the constant interplay between oculomotor centre oscillations, has been correlated with the clinical state of comatose patients and related to prognosis.

With informed consent from the next of kin, we prospectively studied the electrophysiologic oculograms of 60 comatose patients (47 male and 13 female; age range 1 to 80, mean 36±4 (SD 19-10) years) after severe, non-penetrating head injuries (range one to 23 days postinjury, mean 3±2 days). All patients were sedated with propofol (1.0-3.0 mg/kg) and morphine (0.02-0.15 mg/kg), and mechanically ventilated to maintain a PaCO2 of about 35 mm Hg. Spontaneous and auditory reflexive eye movements were recorded electrophysiologically from bipolar pairs of periorbital silver/silver chloride electrodes, attached to the infraorbital margins referenced to F7 and F8 (international 10/20 system of electrode placement), with a paper speed of 30 mm/s, gain of 50 μV/cm, and filter bandwidth of 0.3 to 35 Hz. The spontaneous and reflexive eye movements in speech (a greeting and the patient’s first name) were assessed by visual inspection of the oculogram and graded according to abnormalities of the eye, it and conjugate the saccades were classified as “normal”; when present but disconjugate they were classified as “asymmetric”; and no movement on the oculogram was classified as “absent”. In 35 patients (58±3%) the saccades were judged to be normal, in 15 (25.0%) they were asymmetric, and in 10 (16.7%) they were absent (table). The patient’s Glasgow coma scale scores were determined several times at the same time, and they were correlated with the oculogram grading (Spearman’s correlation coefficient, r = 0.37, P = 0.007). Patient outcome was assessed by personal interview at three months on the five point Glasgow outcome scale (table 1). Sixteen patients (26.7%) died, five (8.3%) were in the vegetative state, 17 (28.3%) were severely disabled, 14 (23.3%) were moderately disabled, and eight (13.3%) had made good recoveries. There was a good correlation between oculogram grade and outcome category at three months (r = 0.50, P = 0.0003). Of the ten patients without electrographic eye movements seven died, all of whom had histopathological evidence of diffuse axonal injury involving the upper brain stem; the presence of eye movement is therefore significantly associated with non-survival (*2 = 11.52, P = 0.001).

It is well known that eye movements have prognostic significance in brain injury, in particular when spontaneous and reflexive movements are absent, suggesting midbrain and brain stem dysfunction respectively. Indeed the clinical categorisation of eye movements has been based in the intrabulbar coma scale for predicting non-survival after head injury. This simple electrodiagnostic test and classification allows quantification of eye movements, and may assist clinicians in their objective monitoring of severe, coma producing traumatic brain injury. It is relatively easy to include the technique as part of the routine prognostic electrophysiological assessment of cerebral function, and it does not suffer from some of the limitations or risks associated with eliciting oculcephalic and oculovestibular reflexes in patients with trauma affecting the cerebral and/or brainstem areas. The test cannot supplant clinical diagnosis, however, as in our experience its sensitivity is only 43.7% and its specificity is 93.2%, and we do not know exactly how eye movements are affected by the local brain insults. Because spontaneous and reflexive eye movements require an intact neural circuitry, we suggest that their asymmetry or loss reflect increasingly extensive neural dysfunction or disconnection. It is possible that widespread diffuse axonal injury may provide the pathological substrate for this loss of functional integrity.

This study was supported by the Francis and Augustus Newman Foundation and the Resparc Charity. We gratefully acknowledge the technical expertise of the Department of Neuropathology, Frenchay Hospital.
Machado-Joseph disease mutations as the genetic basis of most spinocerebellar ataxias in Germany.
L Schöls, G Amoiridis, M Langkafel, T Büttner, H Przuntek, O Riess, A M Vieira-Saecker and J T Epplen

*J Neurol Neurosurg Psychiatry* 1995 59: 449-450
doi: 10.1136/jnnp.59.4.449

Updated information and services can be found at:
http://jnnp.bmj.com/content/59/4/449.citation

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/