Linear high intensity area along the medial margin of the internal segment of the globus pallidus in Machado-Joseph disease patients

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Our new finding on magnetic resonance imaging (MRI) of Machado-Joseph disease (MJD) patients indicates degeneration of the lenticular fasciculus (LF), a major outflow of the internal segment of the globus pallidus (GPI). We examined the clinical, radiological, and autopsy findings of one MJD patient and then retrospectively reviewed the MRI images of another 15 patients looking for a similar abnormal signal intensity. The significance of the clinicoradiological correlation of the MRI finding was confirmed by examining the MRI images of 130 control subjects. In the autopsy case, abnormal linear high intensity areas were observed along the bilateral medial margins of the internal segments of the GPI on T2 weighted, FLAIR, and proton density images, but not on T1 weighted images. Pathologically, this abnormal signal intensity was consistent with degeneration of the LF. The same finding was also observed in the other 15 patients. In two patients the finding was only unilaterally observed. No control subject showed this MRI finding. In MJD patients, abnormal linear high intensity areas indicating LF degeneration are usually observed along the medial margin of the GPI on T2 weighted, FLAIR, and proton density sequences. To our knowledge, this MRI finding has not previously been described.

METHODS
Patients and control subjects
There were 16 MJD patients (table 1). The diagnosis of MJD was made based on clinical presentation, positive family history for autosomal dominant cerebellar degeneration, and DNA analysis. The control subjects consisted of 130 consecutive patients (aged between 12 and 77 years old; mean age 51.7 years), who presented at our hospital during 2003 because of headache or dizziness, but showed no neurological abnormality other than exaggerated deep tendon reflexes.

Molecular analysis of the MJD1 gene
Molecular analysis of the MJD1 gene was performed as described by Kawaguchi and colleagues.3

MRI examination
MRI examinations were performed using two different systems. A 1.0 T system (SMT-100X, Shimadzu, Kyoto, Japan) was used until April 2000, and a 1.5 T system (Magnetom Symphony, Siemens, Munich, Germany) thereafter. Standard brain examinations were carried out using T1 and T2 sequences with contiguous 10 mm thick slices. Proton density and FLAIR sequences were added in some cases. The axial slices were angled to lie parallel to the skull base. The modified coronal slices were angled perpendicular to the posterior limb of the internal capsule in axial slice. No patient had had a previous MRI examination.

Neuropathological examination
The cerebrum was cut into hemispheres on the mid-sagittal line, and sliced coronal (the left hemisphere) and horizontal (the right hemisphere) sections were embedded in paraffin, and subjected to haematoxylin-eosin, Klüver-Barrera, and Holzer staining.

RESULTS
Autopsied patient (patient 4 in table 1)
Physical characteristics
A 48 year old man was admitted to our hospital because of unstable gait of 8 years’ duration. Mild nystagmus, slurred scanning speech, and limb ataxia had been noted when he was 43 years old. He had a family history of a similar neurologic disturbance (his mother’s clinicopathological findings had previously been reported4). Mild lateral and upward gaze palsies, gaze nystagmus, and bulging eyes were noted. He would close the right eye to avoid double vision. Muscle tone was generally decreased, but strength was normal. Deep tendon reflexes were generally increased, and clonus was present in the right wrist and bilateral ankles, but plantar responses were flexor. Limb ataxia was present in all extremities. There were no autonomic disturbances. By age 52, moderate muscle weakness of the limbs had appeared and the patient became unable to walk at age 54. The diagnosis of MJD was confirmed by DNA analysis. At age 56, the first MRI examination was performed. At age 58, near looking reflex became absent. Athetoid movement of the tongue, neck, and extremities, and rapid ballistic movements of the lower limbs were observed. Hypoalgesia of the left side of the face and thermo-hypoaesthesia of the legs were noted. The patient died of aspiration pneumonia at age 61.

Abbreviations: GPI, internal segment of the globus pallidus; LF, lenticular fasciculus; MJD, Machado-Joseph disease; MRI, magnetic resonance imaging
Neuropathological findings
The brain stem and the cerebellum were markedly atrophic. On horizontal section, the GPi showed severe gliosis with relative preservation of neurons (fig 1A). A dense band of fibrillary gliosis was observed along the medial margin of the GPi and appeared to result from the degeneration of the nerve fibres projecting medially through the internal capsule. This gliosis was prominent from the middle to the caudal portion of the GPi, a distribution consistent with that of the LF7 which emerges at the medial margin of the GPi and penetrates the internal capsule. On coronal section, the gliosis was not observed at the level of the putamen (fig 1B), a distribution consistent with the LF running upwards before penetrating the internal capsule.7 The subthalamic nucleus was also degenerated; its dorsal margin was unclear because of the marked myelin pallor of the neighbouring LF. The substantia nigra showed moderate neuronal loss and astrocytosis.

MRI findings
On axial sections, abnormal high intensity areas were observed bilaterally along the medial margins of the GPi on T2 weighted, FLAIR, and proton density images (fig 1C and D), but were not apparent on T1 weighted image. These areas were prominent from the middle to the caudal portion of the posterior limb of the internal capsule and were most clear at the level of the anterior comissure. This finding was observed in both the first MRI at age 56 and the last image at age 60. This distribution of high intensity areas was identical to that of the gliosis on the pathological specimens.

MRI findings in the other patients and control subjects
The same finding as described above was observed in all the other 15 MJD patients. Modified coronal slices were examined in three patients and showed abnormal high intensity areas (fig 1E and F), whose distribution was the same as that of the gliosis on the coronal section of the pathological specimen, and coincided with the distribution of the LF which runs upwards before penetrating the internal capsule.7 This abnormal high intensity area was only weakly observed in patients 8, 11, and 16. In patients 2 and 16, the abnormal high intensity area was demonstrated only on the right side (fig 1G and H). None of the 130 control subjects showed the above finding.

DISCUSSION
Our results showed that an abnormal linear high intensity area along the medial margin of the GPi on MRI in MJD patients; this finding was not observed in control subjects. Our results are supported by the fact that on pathological examination severe LF degeneration is usually observed in the MJD brain.7 To our knowledge this MRI finding has not previously been described.

The abnormal signal probably indicates LF degeneration but could also be due to the degeneration of other fibre systems whose topographical distribution partly overlaps that of the LF. There are two candidates for this possibility because the subthalamic nucleus and the substantia nigra are usually involved14–17 in MJD. The first is the subthalamic fasciculus14–16 which is the main outflow of the subthalamic nucleus to the globus pallidus. The second is the dopaminergic mesostriatal fibres which run along the LF,18 but we have never observed this abnormal signal in Parkinson’s disease patients. On the other hand, the abnormal signal may not be specific for MJD because it probably indicates LF degeneration.

Our results show that the signal is observed in most MJD patients from the early to the end stages of the disease, but may not be present at the very beginning, because the signal was observed only unilaterally in a patient (patient 16) 1 year after the onset of the disease. This result is similar to a radiological report demonstrating that atrophy of the globus pallidus was observed only in patients with an MJD duration of 10 years or longer.13 In addition, the unilateral presentation 16 years after onset of the disease in a patient (patient 2) whose CAG expansion was very small compared to our other patients, suggests that the presentation of the abnormal signal depends on the size of the CAG expansion in the MJD1 gene. This result accords with the fact that the clinical course and the degree of brainstem and cerebellar atrophy in MJD patients are closely correlated with the size of CAG expansion in the MJD1 gene.14–17

No specific correlation was confirmed between the presence of the signal and clinical symptoms. But it is interesting that no rigidity was observed in 13 of our 16 patients. Considering that the substantia nigra of MJD patients is usually severely degenerated,15 and that nigral degeneration results in parkinsonism, it seems likely that MJD patients would usually show parkinsonism. But

Table 1 MJD patient characteristics

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<tr>
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*The autopsied patient; †the sister of the autopsied patient.

Axt, ataxia; Bab, Babinski’s sign; (CAG), the number of CAG repeats; Fasc, fasciculation; IM, abnormal involuntary movement; Lim EM, limitation in eye movement; M atroph, muscular atrophy; n, absent; p, present; Rig, rigidity; Sens, sensory disturbance; Slow EM, slow eye movement; Sp, spasticity.
parkinsonian features are usually absent in MJD patients even in the late stage of the disease. This is a major clinicopathological discrepancy in MJD. However, our results can explain this problem as follows. The early development of the abnormal signal in our patients indicates that GPi degeneration starts at an early stage in MJD. This GPi degeneration can alleviate rigidity by decreasing the output from GPi to the thalamus, and may cancel the influence of the nigral lesion which causes excessive tonic and phasic inhibition of thalamocortical neurons. This effect of GPi lesion in MJD is similar to that of pallidotomy, which alleviates symptoms in Parkinson’s disease.

### References