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Anterior temporal white matter lesions in myotonic dystrophy with intellectual impairment: an MRI and neuropathological study

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Abstract We studied 12 patients with myotonic dystrophy using MRI and the Mini-mental state examination (MMSE), to see it specific MRI findings were associated with intellectual impairment. We also compared them with the neuropathological findings in an autopsy case of MD with intellectual impairment. Mild intellectual impairment was found in 8 of the 12 patients. On T2-weighted and proton density-weighted images, high-intensity areas were seen in cerebral white matter in 10 of the 12 patients. In seven of these, anterior temporal white-matter lesions (ATWML) were found; all seven had mild intellectual impairment (MMSE 22–26), whereas none of the four patients with normal mentation had ATWML. In only one of the eight patients with intellectual impairment were white-matter lesions not found. Pathological findings were severe loss and disordered arrangement of myelin sheaths and axons in addition to heterotopic neurons within anterior temporal white matter. Bilateral ATWML might be a factor for intellectual impairment in MD. The retrospective pathological study raised the possibility that the ATWML are compatible with focal dysplasia of white matter.

Key words Myotonic dystrophy · Intellectual impairment · Magnetic resonance imaging · Neuropathology

Introduction

In myotonic dystrophy (MD) a characteristic myopathy is accompanied by abnormalities of other systems, including the brain. Despite the fact that clinical reports have shown mental deficiency in 50–70% of cases of MD [1, 2], its pathogenesis has not been clearly explained. Recent studies of the brain with MRI have shown white matter lesions in addition to cerebral atrophy [1–7]. We investigated whether any specific cerebral MRI lesions were associated with intellectual impairment in MD. We also compared these MRI features with neuropathological findings of an autopsy case of MD with intellectual impairment.

Patients and methods

We studied 12 patients with the characteristic clinical and electrophysiological pictures of MD, using MRI and the Mini-mental state examination (MMSE) [8]. Their age was 28–59 years (average 41 years). We compared the findings with those of 10 normotensive age-matched patients whose chief complaints were headache or nonspecific dizziness, who had no abnormal neurological findings. The controls had no hyperlipidaemia or diabetes mellitus. They were aged 32–55 years (average 42 years).

MRI was performed on a 1.5-T imager. Section thickness was 5 mm. T1-weighted images (500–600/15–20/1, repetition time/echo time/excitations) and double-echo proton density-weighted (2500–3000/15–30/1) and T2-weighted images (2500–3000/80–90/1) were obtained with spin-echo sequences.

We reviewed the autopsy specimen of a 42-year-old man with MD for brain lesions which might explain intellectual impairment. The patient had not been hypertensive, and laboratory data were normal. His clinical course was approximately 12 years. The

Table 1 Clinical data and MRI findings

Case	Age (years) at study/sex	Age (years) at onset	Mini-mental state score	White matter lesions on T2-weighted images			Other MRI findings
				Anterior temporal lobe[a]		Other cerebral regions[b]	
				Right	Left		
1	41/M	36	22	+++	++	III	No abnormal contrast enhancement
2	47/M	44	24	+	–	I	Mild ventriculomegaly
3	28/M	14	26	+++	+++	II	Patchy enhancement of uncus, hypothalamus and gyrus rectus
4	42/F	34	26	++	+++	IV	No abnormal enhancement
5	41/M	36	26	++	+	III	Mild ventriculomegaly and sulcal widening
6	50/F	43	26	+	++	II	
7	59/F	37	26	±	+	IV	Mild ventriculomegaly and moderate sulcal widening
8	42/M	24	26	–	–	0	
9	28/M	25	30	–	–	0	Mild ventriculomegaly and sulcal widening
10	37/F	29	30	–	–	I	
11	43/F	27	30	–	–	I	
12	34/M	23	30	–	–	II	

[a] No abnormal intensity area, ± equivocal high-intensity lesion (smaller than 5 mm), + small high-intensity area (5–10 mm) ++ high-intensity area of medium size (11–20 mm), +++ large high-intensity area of large size (more than 20 mm)

[b] *0* no lesions, *I* equivocal high-intensity lesions (smaller than 5 mm), *II* several small high-intensity areas, *III* a few medium-sized high-intensity areas or more than nine small high-intensity areas, *IV* more than three medium-sized high-intensity areas or large high-intensity areas (including diffuse periventricular lesions)

MMSE score was 22, suggesting mental deficiency. He died suddenly, probably of a pulmonary embolus.

Moderate distal muscle weakness and atrophy were observed in all 13 patients with MD, including the autopsy case, but all these patients could walk and maintain an active daily life unaided. Motor deficits therefore did not have an impact on the performance on the MMSE.

Results

Table 1 summarises the clinical and MRI features of the patients with MD. The MMSE is useful for assessing overall mental function quickly and easily, and correlates with the WAIS scores. An MMSE score of 28–30 is normal, while 20 or less definitely represents dementia. Intellectual impairment (MMSE score 22–26) was detected in 8 of them, in a somewhat intermediate range between definitely demented and definitely normal. Disturbance of recent memory was found in all eight, but none had noticed intellectual impairment, because the deficiency was mild. We could not therefore assess the interval from the onset of intellectual impairment to the MRI examination. There was no correlation between the time from the first symptom to MRI and the severity of intellectual impairment, suggesting that the latter is different from a progressive dementia such as Alzheimer's disease. In 10 patients with MD, high-intensity areas were found in cerebral white matter on T2-weighted and proton density-weighted images, which varied in size, number and location. It was not possible to compare the severity of intellectual impairment with the size of the brain lesions, because the MMSE revealed only mild intellectual impairment. Anterior temporal white matter lesions (ATWML) were demonstrated in seven patients, all of whom had intellectual impairment; no ATWML were detected in four patients with normal mentation (MMSE 30). In only one patient with MD and intellectual impairment white matter lesions could not be found. There were no ATWML in the 10 controls. The ATWML were areas of high signal on T2-weighted images (Figs. 1–3), slightly high intensity on proton density-weighted images, and slightly low intensity on T1-weighted images (Fig. 2), with neither mass effect nor focal atrophy. High-intensity areas were seen in periventricular and subcortical white matter in 7 patients with MD. A third of the patients also hat mild ventriculomegaly. Contrast-enhanced MRI revealed no abnormal enhancement in three patients with ATWML.

The pathological examination revealed an ill-defined lesion where the myelin sheaths were decreased in the

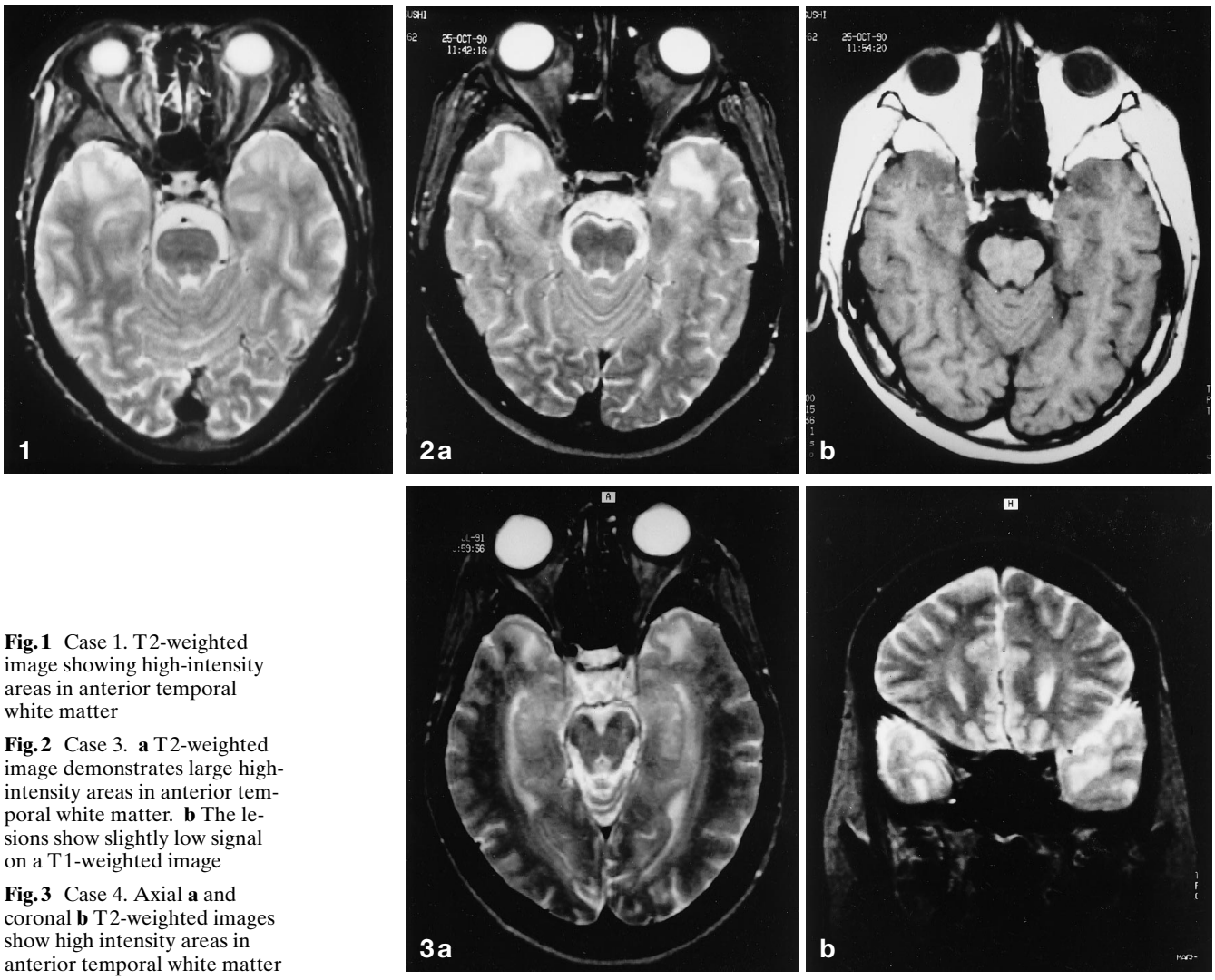

Fig. 1 Case 1. T2-weighted image showing high-intensity areas in anterior temporal white matter

Fig. 2 Case 3. **a** T2-weighted image demonstrates large high-intensity areas in anterior temporal white matter. **b** The lesions show slightly low signal on a T1-weighted image

Fig. 3 Case 4. Axial **a** and coronal **b** T2-weighted images show high intensity areas in anterior temporal white matter

anterior temporal white matter, and microscopically severe loss and disordered arrangement of both myelin sheaths and axons in addition to heterotopic neurons (Fig. 4).

Discussion

After the first clear description of MD by Steinert in 1909 [9], Curschmann [10] was the first to take an interest in the intellectual impairment in the disease. Thereafter, brain lesions, including thalamic neuronal inclusions [11], ventriculomegaly [1–3], abundant Alzheimer's neurofibrillary tangles [12, 13], disturbed cortical architecture and cortical heterotopia [11, 14, 15] were demonstrated by necropsy and neuroradiological studies. Some of these findings may be associated with intellectual impairment, but do not adequately explain its mechanism. Recent papers have described focal white matter anomalies [1–4, 6, 7] and intracranial arachnoid cysts [16] on MRI, indicating developmental anomalies. It was postulated by Rosman and Kakulas [15] that cerebral abnormalities in MD with intellectual impairment result from an interference with nerve cell migration and development of the cerebral cortex during early embryonic life. Fiorelli et al. [17] reported that cortical dysfunction may originate from the above-mentioned anatomical abnormalities. However, disturbed gyral architecture and clusters of heterotopic neurons in the white matter were observed only in small parts of the brain. It is doubtful whether small periventricular white matter lesions on MRI in MD [3, 4] are closely related to intellectual impairment.

Pathologically, we found severe loss and disordered arrangement of myelin sheaths and axons, with many heterotopic neurons in the anterior portions of both

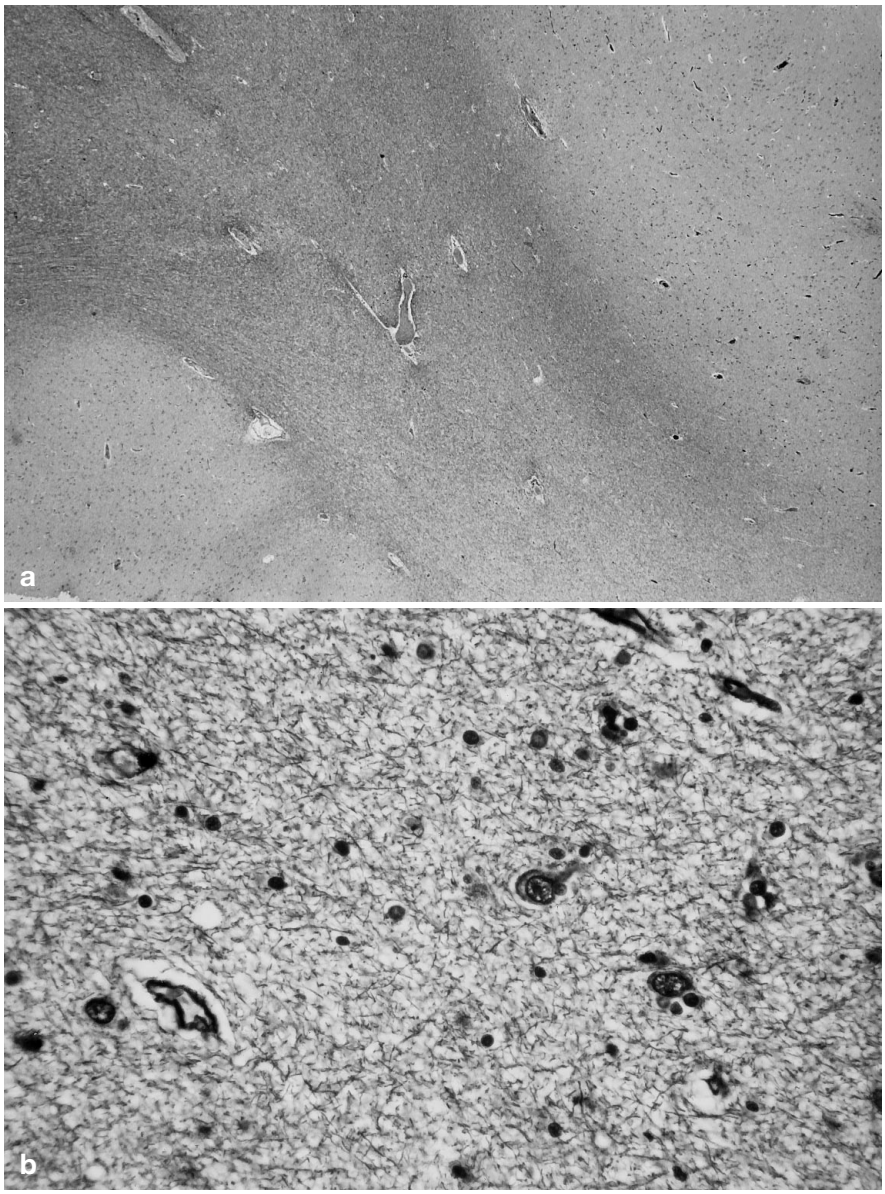

Fig. 4 **a** Low-power photomicrograph (original magnification × 40, Klüver-Barrera stain) of the anterior temporal white matter reveals an ill-defined lesion with decreased myelin sheaths. **b** High-power photomicrograph (original magnification × 200, Bodian stain) of the anterior temporal white matter reveals severely disordered arrangement of axons with microscopically heterotopic neurons

temporal lobes. The ATWML could functionally interrupt the fibre tracts connecting the anterior temporal cortex (area 38) to the amygdala, part of the basolateral limbic system, associated with memory [18].

We observed ATWML bilaterally in the autopsy case and in six of the seven patients examined by MRI, suggesting that ATWML are specific to MD [9]. Furthermore, the bilateral ATWML might suggest an explanation for the intellectual impairment in MD. Huber et al. [1] indicated that patients with severe intellectual impairment in MD had MRI abnormalities related to the degree of skull thickening and focal white matter lesions. Abe et al. [6] reported a significant association between the extent of white matter lesions and the degree of intellectual impairment. Hashimoto et al. [19] suggested a causal relationship between the mental retardation and endocrine dysfunction and the decreased volume of the brain and pituitary gland. Our findings, although limited by small sample size, suggested that ATWML are one of the important factors in the aetiology of the intellectual impairment in MD patients. The pathologic study raised the possibility that ATWML are consistent with focal dysplasia of white matter. The reason the anterior temporal lobes are involved is not clear. It may be that anatomically complicated structures like the temporal lobe are more prove to defective neuronal migration.

On T2-weighted images, focal high-intensity areas in the cerebral white matter can be found in many disorders and in healthy individuals [20, 21]. However, they are not common in the anterior temporal lobe. In our study, the ATWML involved subcortical white matter. Some reports have drawn attention to white matter lesions in the temporal lobes [1, 2, 7], similar to the ATWML in our patients: they were somewhat linear and fingerlike, involving the anteromedial portion of the lobe. The lesions were subcortical, judging from the published images. Miaux et al. [7] detected temporal lobe lesions in 5 of their 13 patients (38%), and considered them characteristic of the disease [7]. Because ATWML were found in 7 of 12 patients (58.3%) in our study, we also think them rather specific to MD.

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