SHORT REPORT

Fluid attenuation inversion recovery (FLAIR) images of dentatorubropallidoluysian atrophy: case report

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Abstract

The white matter lesions in a patient with late adult onset dentatorubropallidoluysian atrophy (DRPLA) were studied in detail by MRI using the fluid attenuation inversion recovery (FLAIR) technique. The patient was a 60 year old woman with a family history of DRPLA, in whom the number of CAG repeats in the DRPLA gene on chromosome 12 was expanded to 59 (normal allele 10). In addition to atrophy of the cerebral cortex, cerebellum, and pontomesencephalic tegmentum, the cerebral white matter and a part of the white matter tracts within the brainstem showed prominent high signal intensities on FLAIR images. These MR findings suggest that, in addition to the degeneration of the dentatorubral and pallidoluysian systems, the pathological process extends to the white matter in DRPLA. This could be important for differentiating DRPLA from other clinically similar diseases such as Machado-Joseph disease or Huntington's disease.

(*J Neurol Neurosurg Psychiatry* 1998;**65**:396–399)

Keywords: FLAIR image; dentatorubropallidoluysian atrophy; cerebral white matter; brainstem

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Received 11 November 1997 and in revised form 6 February 1998
Accepted 16 February 1998

Dentatorubropallidoluysian atrophy (DRPLA), first described by Smith *et al* in 1975,[1] was established as an autosomal dominant neurodegenerative disease by Naito and Oyanagi in 1982.[2] The clinical symptoms are variable depending on the age of onset of the disease—myoclonus, epilepsy, and mental retardation are the main symptoms in juvenile onset, whereas cerebellar ataxia, choreoathetosis, and dementia are seen in adult onset. Neuropathologically, a combined degeneration of the dentatorubral and pallidoluysian systems is a characteristic feature of DRPLA.[3] In 1994, Koide *et al*[4] and Nagafuchi *et al*[5] identified an unstable expansion of the trinucleotide (CAG) repeats in the DRPLA gene on the short arm of chromosome 12, which made possible a genetic diagnosis of DRPLA.

Fluid attenuation inversion recovery (FLAIR) MR images are heavily T2 weighted, allowing easy detection of small and relatively low contrast lesions. At the same time, the long inversion recovery (IR) pulse nulls or greatly reduces the CSF signal, which minimises artifacts arising from CSF motion and partial volume effects of CSF. Thus, FLAIR sequences are superior to conventional or fast spin echo T2 weighted sequences in visualising a wide range of lesions, particularly those in the periventricular or subcortical areas.[6 7] FLAIR images also disclose anatomical details and have the advantage of allowing disease detection in the white matter tracts within the brainstem.[8]

We report here FLAIR images of a patient with late adult onset DRPLA, diagnosed definitively by DNA analysis, and we discuss the neuroradiological characteristics of the cerebral white matter and the brainstem lesions of DRPLA.

Case report

The patient was a 60 year old woman with five affected siblings in three successive generations. Her elder brother had died from DRPLA (confirmed at postmortem). She had been well until the age of 48, when she noticed dizziness and unsteady gait. Dizziness recurred and gait disturbance slowly progressed. At the age of 53, she began to twist her face, shoulders, and limbs. Neurological examination at that time showed disturbance of memory and calculation, slurred speech, limb, and gait ataxia, choreoathetosis of the face and limbs, and hyperreflexia of the lower limbs. Brain CT showed mild cortical atrophy and diffuse low density areas around the lateral ventricles with slight dilatation of the ventricles. She had no risk factors for cerebrovascular disease such as hypertension, diabetes mellitus, or hyperlipidaemia. Her neurological symptoms gradually worsened thereafter, and she began to fall and had a general decline in cognitive abilities. She had neither myoclonus nor seizures during the entire course of her illness.

MOLECULAR STUDY

The method reported by Koide *et al*[4] was used for DNA diagnosis of DRPLA. Informed consent was obtained for the study. Genomic

Figure 1 Polyacrylamide gel analysis of the PCR amplified product containing the trinucleotide repeat tract in our patient (lane 1), a normal control (lane 2) and a patient with DRPLA (disease control, lane 3). One expanded allele with a CAG repeat number of 59 is seen in our patient.

DNA, extracted from peripheral blood lymphocytes, was subjected to polymerase chain reaction using a primer set (A: 5'-CACCAGTCTCAACACATCACCATC-3', B: 5'-CCTCCAGTGGGTGGGGAAATGCTC-3') targeted at the region containing (CAG)n. The PCR products were analysed by polyacrylamide gel electrophoresis to determine the number of CAG repeats. One expanded allele had 59 CAG repeats at the DRPLA locus, whereas the normal allele contained 10 (fig 1). The number of CAG repeats at the DRPLA locus of healthy Japanese was reported to range from 8 to 25.[4]

MRI STUDY

Brain MRI was performed at a magnetic field strength of 1.5 T with 5 mm slice thickness. Spin echo T1 weighted images (TR 350 ms, TE 17 ms) and T2 weighted images (TR 5000 ms, TE 140 ms) were obtained in axial and sagittal planes. The FLAIR images were obtained with a TR of 6000 ms, TE of 150 ms, and inversion time (IT) of 2000 ms. T1 weighted MRI disclosed cerebral atrophy predominantly in the frontotemporal region with dilatation of the lateral ventricles and atrophy of the cerebellum and pontomesencephalic tegmentum accompanied by dilatation of the fourth ventricle and the aqueduct. The T2 weighted images showed diffuse confluent high signal intensities in the bilateral periventricular white matter and centrum semiovale, as we reported previously.[9] The cerebral high signal intensity lesions were clear in FLAIR images, appearing as extensive irregularly shaped high signal intensity areas around the entire lateral ventricle (fig 2 A). Subcortical white matter was less involved. Furthermore, the axial and sagittal FLAIR images showed high signal intensities in the corpus callosum, the central portion of the bilateral thalami, the cerebral peduncles, the decussation of the superior cerebellar peduncles, the ventrolateral portions of mesencephalopontine tegmentum, and a central region of the pontine base (fig 2 B, C, D). We have never seen such thalamic and brainstem findings in FLAIR images of healthy subjects or patients with other types of spinocerebellar degeneration.

Discussion

Diffuse high signal intensities throughout the periventricular white matter and centrum semiovale on T2 weighted MRI, mimicking leukoaraiosis or leukodystrophy, seem to be characteristic findings in DRPLA.[9] The FLAIR images disclosed the pathological changes in white matter more clearly than did conventional T2 weighted images. These changes in white matter are considered to reflect the histopathological features of diffuse myelin pallor in the periventricular white matter and centrum semiovale and seem to be found in association with the progression of personality changes and dementia. Although Uyama *et al*[10] reported that abnormal MRI signals in the cerebral white matter were only seen in patients with late adult onset DRPLA, we have often found white matter lesions in patients with juvenile or early adult onset, and we suggested that these lesions may precede neurological symptoms even in patients with late adult onset.[11]

In our experience with MRI, involvement of the thalamus and brainstem are common in patients with DRPLA, and tend to parallel the degree of changes in cerebral white matter.[11] However, thalamic degeneration has rarely been noted in necropsied cases in which a spongy appearance was marked in and around the centromedial nucleus.[12] Our findings, together with the previous notion that the fibres of the dentatorubral tract end at the thalamus, may imply that the changes in the thalamus are an outcome of changes in the cerebellar afferent projections from the dentate nucleus. Abnormally high signal intensities within the brainstem are best appreciated on FLAIR images and might be identical with previously described neuropathological lesions of DRPLA, such as central grey matter, superior cerebellar peduncle, central tegmental tract, medial longitudinal fascicles, and medial lemniscus. On the axial images of the midbrain, there is a distinctive signal difference between the red nucleus and the surrounding fasciculi, which, we contend, is characteristic of this disease. It is also noteworthy that the central portions of the pontine base, which are not usually involved in DRPLA, were visualised as high signal intensity areas. By contrast with olivopontocerebellar atrophy,[13] axonal atrophy was the major change in the pontine transverse fibres, accompanied by little axonal degeneration and no marked demyelination or gliosis in a case of DRPLA.[14] As almost all patients with DRPLA show pyramidal signs to a variable extent,[2] further work is needed to analyse the pathological findings in more detail in relation to the MR findings.

Although the pathogenesis of these changes in white matter is still unclear, there are two theories; systemic degeneration due to DRPLA and changes secondary to cerebral ischaemia. The appearance of the lesions in cerebral white matter in FLAIR images is diffuse and not uneven or flecked, as is often seen in cerebrovascular disease. In addition, our patient had no risk factors for cerebrovascular disease . Mizoi *et al*[15] carried out a single photon emission computed tomography (SPECT) study, which failed to disclose any relative decrease in cerebral blood flow, even in patients with DRPLA with abnormal findings in the cerebral white matter. They also found no decrease in cerebral blood volume in an MRI perfusion study. Histopathological investigation has disclosed diffuse decrease of myelin sheaths and axons, but no fibrillary gliosis, infarcts, or arteriolar thickening or hyalinisation.[3 15 16] Furthermore, Takano *et al*[17] analysed the size of expanded CAG repeats of the DRPLA gene by dissecting necropsied DRPLA brains into the cortex and white matter, and found that the CAG repeats were consistently expanded in the white matter as well as in the cortex. These findings suggest that the lesions in the cerebral white matter or white matter tracts within the brainstem in DRPLA are not attributable to

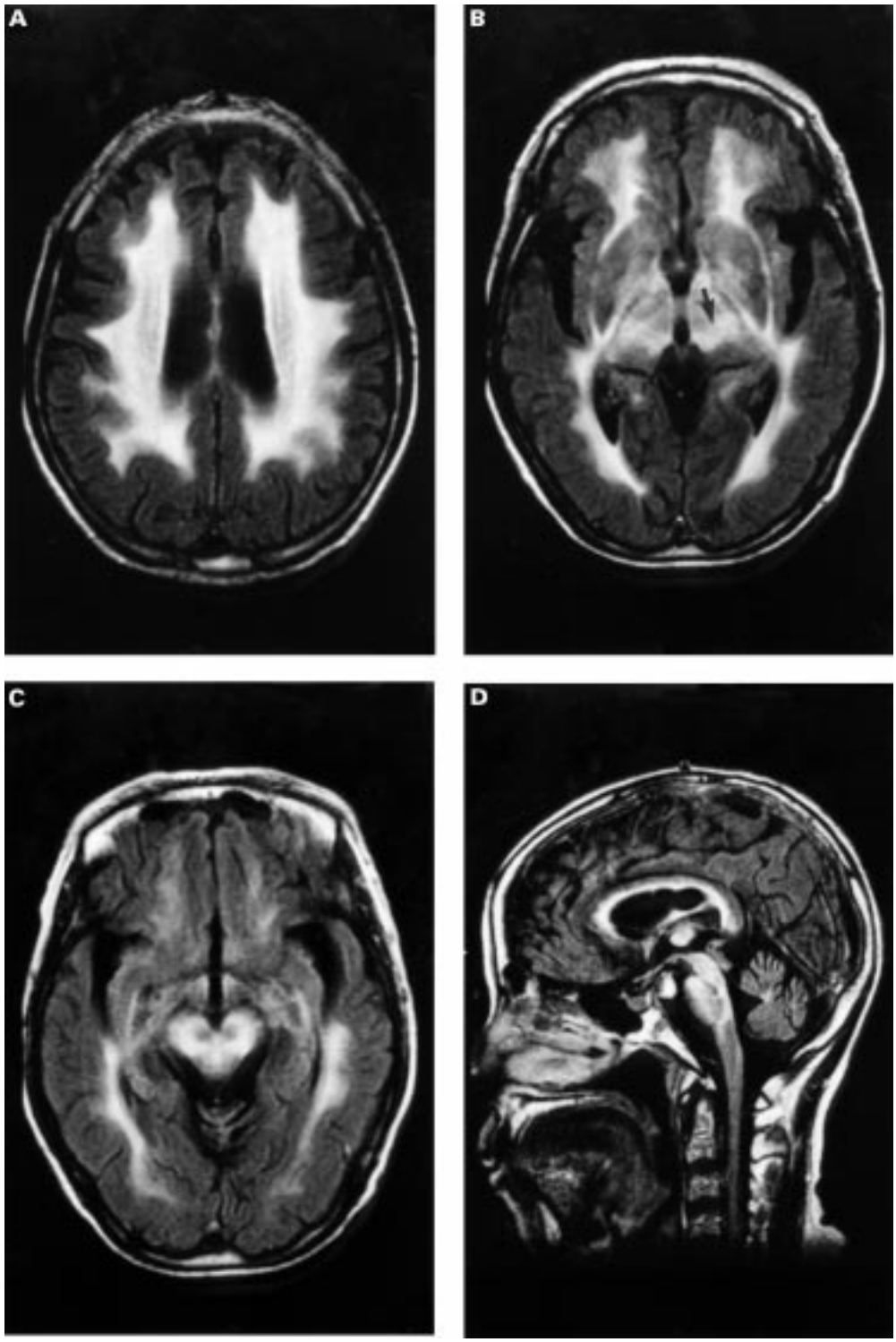

Figure 2 Axial (A, B, C) and sagittal (D) FLAIR images of the patient. Prominent confluent high signal intensities in the periventricular white matter are seen (A). High signal intensity is also present in the bilateral thalami (B, arrow), areas that are not commonly involved in DRPLA. In the midbrain, the surrounding fasciculi around the red nucleus are distinctively visualised as high signal intensity areas (C). The sagittal image shows high signal intensities in the corpus callosum, the cerebral peduncles, the decussation of the superior cerebellar peduncles, and the ventrolateral portions of the mesencephalopontine tegmentum, as well as a central region of the pontine base (D).

xcerebral ischaemia and that the abnormal MRI changes may originate from the disease process of DRPLA itself.

Recent molecular identification and characterisation of gene mutations now permit rapid molecular confirmation of many neurological disorders. Expansion of CAG repeats in a protein coding region has been identified in SCA-1, SCA-2, SCA-3/Machado-Joseph disease, SCA-6, and DRPLA, which constitute a group of diseases termed hereditary spinocerebellar degeneration. They are clinically similar, being characterised by cerebellar ataxia and other neurological symptoms. When 27

patients with Machado-Joseph disease and two patients with SCA-1 diagnosed by DNA analysis were examined, none of them showed changes in the cerebral white matter or the brainstem of the type found in our patient with DRPLA.[11] Huntington's disease, which is often misdiagnosed as DRPLA on the basis of the appearance of choreic movements and psychiatric symptoms in the early stage of the disease, also shows no changes in white matter.[18] Therefore, we suggest that changes in these areas of the cerebral white matter and brainstem may be a useful criterion for distinguishing DRPLA from other types of hereditary spinocerebellar degeneration or Huntington's disease.

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J Neurol Neurosurg Psychiatry 1998 65: 396-399
doi: 10.1136/jnnp.65.3.396