MR of childhood-onset dentatorubral-pallidoluysian atrophy.

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MR of Childhood-Onset Dentatorubral-Pallidoluysian Atrophy

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Summary: MR findings in a 14-year-old boy with progressive myoclonic epilepsy, who was diagnosed as having dentatorubral-pallidoluysian atrophy by DNA analysis, were compared with those of his father, who had adult-onset dentatorubral-pallidoluysian atrophy. Besides showing severe brain atrophy, especially of the brain stem tegmentum and cerebellum, MR showed diffuse periventricular hyperintensity on T2-weighted images. As compared with the proband, the father had a mild case.

Index terms: Children, diseases; Degenerative disease; Familial conditions

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal-dominant neurodegenerative disorder particularly prevalent in Japan (1–3). This disorder involves mainly the dentatorubral and pallidoluysian systems of the central nervous system, as indicated by pathologic examination (1, 2). The age of onset ranges from the first to seventh decades. Clinical symptoms may vary even within a single family with multiple affected members (2). Although most childhood-onset patients (ie, younger than 20 years old), have progressive myoclonic epilepsy and mental retardation (1, 2), adult-onset patients usually have cerebellar ataxia, choreoathetosis, and dementia, which can resemble those of Huntington disease. Recently, unstable expansion of a CAG trinucleotide was identified on chromosome 12p of patients with DRPLA (4, 5), making it possible to diagnose definitively DRPLA without pathologic examination.

We report a family with DRPLA in both a 14-year-old boy and his father, diagnosed by DNA analysis (4). In the present study, to evaluate the brain structure of childhood-onset DRPLA, the child underwent magnetic resonance (MR) imaging, and the results were compared with those of his father.

Case Reports

Patient 1 (Proband)

A 14-year-old boy was diagnosed as having DRPLA by DNA analysis (4). His father was known to have adult-onset DRPLA. Two paternal uncles had died during early childhood, and his grandfather on the same side of the family was noted to have an unstable gait at the age of approximately 60 years. The subject achieved normal developmental milestones in the neonatal and infantile periods. At the ages of 15 and 16 months, he could walk alone and pronounce a few meaningful words, respectively. Thereafter, however, he pronounced few additional meaningful words. At the age of 4 years began the onset of seizures and myoclonus. It gradually became evident that he also had psychomotor regression. By the age of 11 years, he had become bedridden and was admitted to our hospital.

Patient 2

The proband's father was 44 years of age at the time of presentation. He began to have choreoathetosis and cerebellar ataxia at the age of 38 years. At that time, he had had atypical absence seizures twice. The above neurologic symptoms advanced slowly and became increasingly severe. In addition, when he was 43 years of age, dementia also developed, characterized by emotional disturbances and personality change.

DNA analysis for DRPLA was performed in both patients using a method reported previously (4). Whereas the number of the CAG repeat of CAG-B37 (DRPLA) locus of a healthy Japanese population ranged from 7 to 28 (4), that of patient 1 was 87, and that of patient 2 was 65 at the expanded allele, indicating changes diagnostic of DRPLA.

Results

MR of the child (Fig 1) showed severe cerebral atrophy predominant in the frontotemporal region, severe brain stem atrophy, especially of

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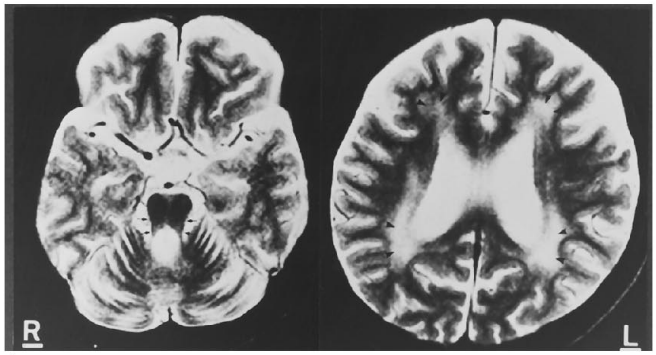

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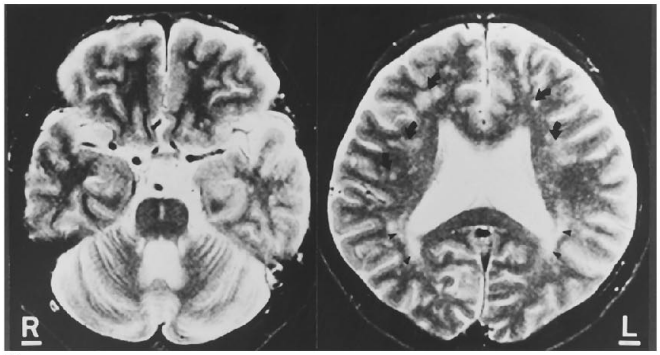

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Fig 1. Patient 1. T2-weighted spin-echo MR sequence (3000/80/1 [repetition time/echo time/excitations]). *Left,* transaxial image through the level of superior pons shows severe brain atrophy, especially of the pontine tegmentum (*arrows*) and cerebellum. *Right,* transaxial image through the level of the body of the lateral ventricle shows cerebral atrophy predominant in the frontal lobes and diffuse periventricular hyperintensity (*arrowheads*).

Fig 2. Patient 2. T2-weighted spin-echo MR sequence (3000/80/1). *Left,* transaxial image through the level of superior pons shows mild cerebral and brain stem atrophy, as well as severe cerebellar atrophy. It is noted that the degree of abnormalities, apart from the cerebellar region, is milder than that of patient 1 (see Figure 1, left, for comparison). *Right,* transaxial image through the level of the body of the lateral ventricle shows some patchy hyperintensity (*arrows*) and periventricular hyperintensity (*arrowheads*).

the midbrain and pontine tegmentum, severe cerebellar atrophy, and diffuse periventricular hyperintensity on T2-weighted images. There were no definite abnormalities of the globus pallidus, subthalamic nucleus, or red nucleus. All of the above abnormalities were also found in the father (Fig 2), with the exception of two major differences. First, apart from the cerebellar atrophy, the MR changes in patient 1 were more severe than in patient 2; and second, as seen on T2-weighted images, whereas patient 1 showed diffuse periventricular hyperintensity, only patchy rather than diffuse hyperintensity was disclosed in patient 2.

Discussion

DRPLA is a neurodegenerative disorder reported by Smith and colleagues (6) based on the pathologic findings. Afterward, Naito and Oyanagi (1) confirmed that DRPLA was a clinical entity with an autosomal-dominant inheritance pattern. Recently, patients with DRPLA in two different Japanese groups (4, 5) presented with unstable expansion of a CAG trinucleotide in a gene on chromosome 12p. In addition, they also noted that the greater the number of CAG repeats, the earlier the onset and severity of a patient's condition (4, 5), as indicated by the present patients. In this way, the DNA analysis for DRPLA can be a valuable tool for the prediction of a patient's prognosis in addition to making an early definitive diagnosis.

Although previous MR studies for DRPLA showed variable findings (7), the cardinal features were strikingly similar among different reports and are compatible with those seen in previous pathologic studies (1, 2). Although previous reports focused mainly on adult-onset DRPLA, the characteristic MR findings of DRPLA were (7): atrophy of the brain stem tegmentum, especially of the midbrain and superior pons; cerebellar atrophy, including the dentate nuclei; periventricular and/or deep white matter hyperintensity on T2-weighted images; and absence of definitive abnormalities involving the globus pallidus, subthalamic nucleus, and red nucleus. In patient 1 with childhood-onset DRPLA characterized by progressive myoclonic epilepsy, the MR study was consistent with the above four findings. Similar abnormalities were identified in patient 2; however, it was noted that, apart from the cerebellar lesion, the abnormalities in patient 1 were more severe than those in patient 2. Thus both the MR and clinical manifestations correlated with what is known about a more-severe course for childhood-onset DRPLA compared with adult-onset DRPLA in the same family.

Because MR often discloses cerebral white matter lesions such as periventricular and/or deep white matter hyperintensities in patients with DRPLA (8), the significance of such lesions has been the subject of recent intense study. Pathologic studies indicate that the cerebral white matter lesions in DRPLA correspond to

reduced myelin fibers evident as pallor of myelin sheaths and gliosis (8). Some articles (7, 8) reported that DRPLA was often associated with subcortical dementia characterized by emotional disturbances and personality change, and the cerebral white matter lesions were most likely to play an important role in the onset of the above dementia symptoms. However, because some previous reports (9) indicate that even healthy persons older than 50 or 60 years of age have periventricular and/or deep white matter hyperintensities, the possibility remains that in adult-onset DRPLA the cerebral white matter lesions may not be specific to DRPLA but are associated with aging. In the pediatric population, cerebral white matter lesions (10) also may not be specific for DRPLA, but may be associated with other metabolic or neurodegenerative disorders such as congenital myotonic dystrophy and Fukuyama-type congenital muscle dystrophy. Although MR findings of progressive myoclonic epilepsy exhibit only nonspecific changes, predominantly atrophy (11), a few previous reports (11, 12) indicated that neuronal ceroid lipofuscinoses and myoclonic epilepsy with ragged red fibers showed periventricular hyperintensity and/or brain stem atrophy on MR. The present study indicates that although the MR findings are not necessarily specific (7), childhood-onset DRPLA should be considered in any child with both progressive myoclonic epilepsy and the above MR findings, that is, periventricular hyperintensity and brain stem atrophy, and should undergo the DNA analysis for DRPLA.

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