

## Dentatorubral pallidoluysian atrophy in a Turkish family

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Dentatorubral pallidoluysian atrophy is a neurodegenerative disease that generally presents in adulthood. Although rare, it can be observed in childhood due to extreme expansion of the triplet repeat size during spermatogenesis. The diagnosis in childhood is very difficult in the absence of family history. Here we describe a 12-year-old girl with dentatorubral pallidoluysian atrophy who presented with progressive myoclonic epilepsy and ataxia. Family history exhibited similarly affected cases on the paternal side. Molecular testing for dentatorubral pallidoluysian atrophy revealed abnormal "cytosine-adenine-guanosine" expansion in the atrophin-1 gene.

**Key words:** child, progressive ataxia, myoclonic epilepsy, autosomal dominant inheritance.

Dentatorubral pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterized by ataxia, dementia, choreoathetosis, myoclonus, epilepsy, and psychiatric symptoms<sup>1</sup>. The disease is caused by the unstable expansion of CAG repeats in the atrophin-1 gene, located on chromosome 12p<sup>2</sup>. Paternal transmission of the disease results in more prominent anticipation than maternal transmission<sup>3</sup>. DRPLA is generally viewed as an adult-onset disease, and the diagnosis is very difficult in childhood with no family history. There is an inverse correlation between the age at onset and the size of the expanded CAG repeats.

### Case Report

A 12-year-old girl was referred for progressive myoclonic epilepsy and ataxia. She was the first child of nonconsanguineous parents. The pregnancy was not complicated and resulted in a normal vaginal delivery of a term female infant with a birth weight of 3,500 g.

The psychomotor development was normal. At the age of nine years, she began to have myoclonic seizures followed by ataxia, choreiform movements and cognitive deficits. The child's neurological status worsened in the following years and at the age of 12, she

was not able to walk because of severe ataxia. The seizures of the patient were refractory to antiepileptic drugs. Neurological examination at that time revealed severe mental retardation, choreiform movements prominent in the upper extremities and brisk deep tendon reflexes. The patient could not stand or walk because of severe ataxia. Cranial nerve and the remainder of the physical examinations were normal.

Electroencephalography of the patient revealed slowing of background with multifocal polyspike pattern. Photomyoclonic bursts were also seen during photic stimulation (Fig. 1). The brain magnetic resonance imaging of the patient revealed atrophic changes in the cerebral cortex, cerebellum and brainstem (Fig. 2).

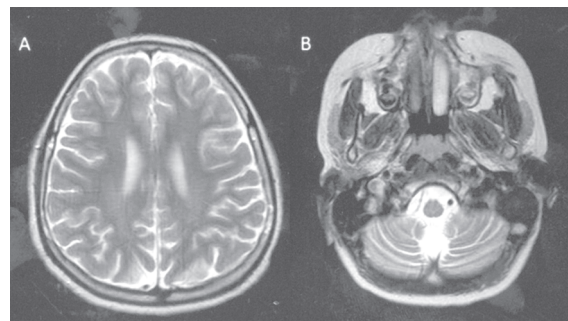


Fig. 1. Brain magnetic resonance imaging showing atrophic changes in the cerebral cortex (A), brainstem and cerebellum (B).

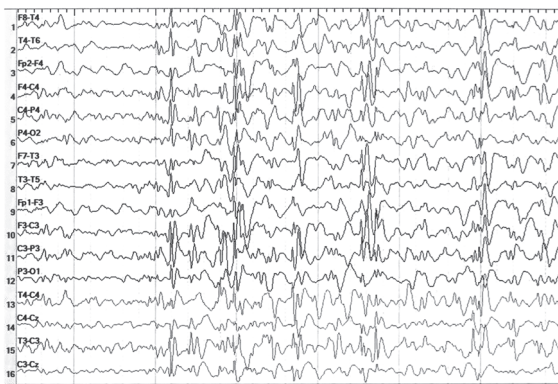


Fig. 2. Electroencephalography showing slowing of background with multifocal polyspike pattern.

The father, a paternal uncle and a paternal aunt began to develop ataxia, myoclonic seizures and dementia when they were about 25. They progressively became bedridden and died at about 30 years of age. The paternal grandmother also developed the same symptoms at about 35 years of age and died at the age of 40. Her father also died with the same symptoms at 50 years of age (Fig. 3). None of these cases had a specific clinical diagnosis previously.

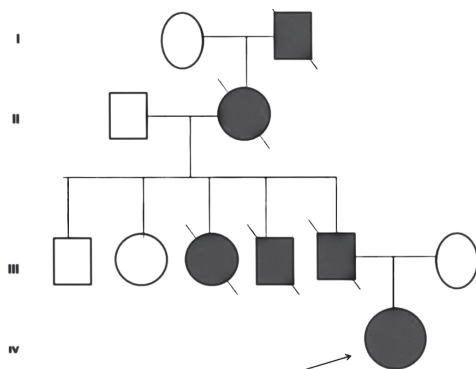


Fig. 3. Family tree showing the prominent vertical dominant transmission.

The clinical findings and family history of the patient suggested DRPLA. Molecular analysis, based on polymerase chain reaction (PCR) amplification of the atrophin-1 gene and followed by agarose gel electrophoresis, revealed the presence of an expanded band in the proband (Fig. 4). Further analysis by sequencing of the PCR products showed 22 repeats in the normal allele (20 CAG+ 2 CAA) and 73 repeats (pure CAG) in the expanded allele of the patient. The child still continues to show progression of her neurological symptoms.

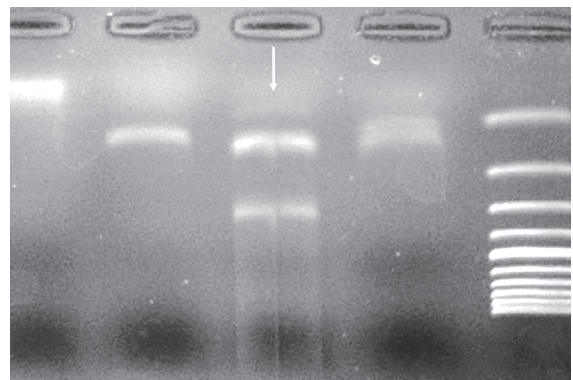


Fig. 4. The CAG repeat region of the atrophin-1 gene was amplified using the primers: forward 5' cac cag tct caa cac atc acc atc 3' and reverse 5'cct cca gtg ggt ggg gaa atg ctc c 3'.

The PCR product was run on a 1% agarose gel, together with control samples. The index case has two bands of different sizes, indicating the presence of a normal allele and an expanded allele (arrow).

## Discussion

Dentatorubral pallidoluysian atrophy is an autosomal dominant neurodegenerative disease first described in Japan. The prevalence in Japan is approximately 0.2-0.7/100,000 persons. Molecular analysis of the disease allowed the detection of DRPLA in other populations, but the prevalence outside Japan is not known. Adult-onset, early adult-onset and juvenile-onset types of the disease have been described. Ataxia, choreoathetosis and dementia are cardinal features in adult-onset types, whereas juvenile-onset type frequently presents with progressive myoclonic epilepsy followed by ataxia, choreiform movements and dementia<sup>3</sup>. The symptoms of our patient also started with myoclonic epilepsy, and the epileptic seizures were refractory to antiepileptic drugs. Ataxia followed the seizures and she became unable to walk alone within three years. Cognitive deficits developed more prominently in the second year of the disease, and she lost the ability of speech and social interaction. Although autistic spectrum disorder and obstructive sleep apnea resistant to surgery are described in juvenile-onset cases<sup>4</sup>, we did not observe these findings in our patient.

Many clinical syndromes like Unverricht-Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers, neuronal ceroid lipofuscinosis and sialidoses are included in the differential diagnosis of DRPLA<sup>5</sup>. The diagnosis is difficult in the absence of family

history and in sporadic cases. Although DRPLA is commonly seen in adult patients, juvenile-onset may occur because of prominent tendency to anticipation. Severe infantile DRPLA with extreme expansion of CAG repeats was also described<sup>6</sup>. In our case, autosomal dominant inheritance with typical clinical findings allowed us to establish the exact diagnosis.

In normal individuals, the CAG repeat segment ranges in size from 7 to 34 repeat units and in affected individuals, the size has been reported to range from 53 to 88 repeats. There is apparently no intermediate range<sup>7-9</sup>. Like other trinucleotide repeat disorders, DRPLA is characterized by anticipation. The anticipation is more prominent in paternal transmission than maternal transmission. The clinical severity of the disease increases from one generation to the next, as observed in our patient.

The characteristic magnetic resonance findings of DRPLA are atrophy of the brainstem tegmentum, especially of the midbrain and superior pons, and cerebellar atrophy, including the dentate nuclei. Globus pallidus, subthalamic nucleus and red nucleus are preserved<sup>10</sup>. Periventricular and/or deep white matter hyperintensity on T2-weighted images is a radiologic feature of adult cases, but it is rarely detected in childhood cases<sup>10</sup>. If periventricular white matter changes are present in addition to generalized atrophy in childhood cases, congenital muscular dystrophies and especially neuronal ceroid lipofuscinoses and myoclonic epilepsy with ragged red fibers should be investigated in the differential diagnosis.

In conclusion, although DRPLA is generally accepted as a neurodegenerative disease of adulthood, it can be observed in childhood because of extreme expansion of the repeat size during spermatogenesis. Young patients present with more serious symptoms and have more rapid progression than adult patients. The most important clue to reaching the diagnosis in childhood is taking a detailed family history. Molecular genetic analysis of the related gene

should be performed to confirm the diagnosis, and families must undergo precise genetic counseling and prenatal molecular genetic diagnosis in a subsequent pregnancy.

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### REFERENCES

1. Naito H, Oyanagi S. Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy. *Neurology* 1982; 32: 798-807.
2. Nagafuchi S, Yanagisawa H, Sato K, et al. Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p. *Nature Genet* 1994; 6: 9-13.
3. Tsuji S. Dentatorubral-pallidoluysian atrophy: clinical features and molecular genetics. *Adv Neurol* 1999; 79: 399-409.
4. Licht DJ, Lynch DR. Juvenile dentatorubral pallidoluysian atrophy: new clinical features. *Pediatr Neurol* 2002; 26: 51-54.
5. Shafwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. *Lancet Neurol* 2005; 4: 239-248.
6. Shimojo Y, Osawa Y, Fukumizu M, et al. Severe infantile dentatorubral pallidoluysian atrophy with extreme expansion of CAG repeats. *Neurology* 2001; 56: 277-278.
7. Nagafuchi S, Yanagisawa H, Ohsaki E, et al. Structure and expression of the gene responsible for the triplet repeat disorder, dentatorubral and pallidoluysian atrophy (DRPLA). *Nat Genet* 1994; 8: 177-182.
8. Ikeuchi T, Igarashi S, Takiyama Y, et al. Non-Mendelian transmission in dentatorubral-pallidoluysian atrophy and Machado-Joseph disease: the mutant allele is preferentially transmitted in male meiosis. *Am J Hum Genet* 1996; 58: 730-733.
9. Komure O, Sano A, Nishino N, et al. DNA analysis in hereditary dentatorubral-pallidoluysian atrophy: correlation between CAG repeat length and phenotypic variation and the molecular basis of anticipation. *Neurology* 1995; 45: 143-149.
10. Miyazaki M, Kato T, Hashimoto T, Harada M, Kondo I, Kuroda Y. MR of childhood-onset dentatorubral pallidoluysian atrophy. *AJNR Am J Neuroradiol* 1995; 16: 1834-1836.