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A (G-to-A) mutation in the initiation codon of the proteolipid protein gene causing a relatively mild form of Pelizaeus-Merzbacher disease in a Dutch family

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Abstract Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder that is characterized by dysmyelination of the central nervous system resulting from mutations in the proteolipid protein (PLP) gene. Mutations causing either overexpression or expression of a truncated form of PLP result in oligodendrocyte cell death because of accumulation of PLP in the endoplasmic reticulum. It has therefore been hypothesized that absence of the protein should result in a less severe phenotype. However, until now, only one patient has been described with a complete deletion of the PLP gene. We report a Dutch family with a relatively mild form of PMD, in which the disease cosegregates with a (G-to-A) mutation in the initiation codon of the PLP gene. This mutation should cause the total absence of PLP and is therefore in agreement with the hypothesis that absence of PLP leads to a mild form of PMD.

Introduction

Pelizaeus-Merzbacher disease (PMD) is an X-linked dysmyelinating disorder resulting from mutations in the proteolipid protein (PLP) gene. Different mutations have been found in the PLP gene (Gow et al. 1994), mostly leading to the expression of altered or truncated forms of PLP, or to overexpression of the protein. One patient has been described with a deletion of at least 29 kb that includes the complete PLP gene (Raskind et al. 1991). The clinical expression in this patient, who was 35 years old, was relatively mild as the life expectancies of the connatal and classical forms of PMD do not normally extend beyond the first and second decade, respectively. Here, we describe another patient (II-1) who suffers from a mild form of this disorder and who is now 37 years old.

Case history

Motor dysfunction in patient II-1 was first noticed at the age of 4 years. A gradual retardation of motor and mental development resulted in mental deficiency and spastic paraplegia. He was admitted to an institution for the mentally disabled at age 14. At the age of 33 years, he came to medical attention again because of the slow deterioration of his mental condition and progression of his spastic tetraplegia. Neurologic evaluation revealed a spastic atactic tetraplegia. Cerebral fluid examination, metabolic screening, and enzyme activities of lysosomal enzymes showed no abnormalities. Electroencephalography (EEG) was normal, but cortical evoked potentials indicated slow central conduction velocities. Conduction velocities of the peripheral nerves were reduced, and magnetic resonance imaging (MRI) revealed extensive symmetric abnormalities of the white matter, with signs of leukodystrophy. Sural nerve biopsy showed reduced density of myelinated fibers and groups of small myelinating fibers indicative of regeneration. No signs of storage disease were found.

His sister (II-2) has an adequate mental function with intact coordination and balance functions. However, she has a pyramidal syndrome and complains about pains in her muscles and joints. An MRI scan of her cervical myelum revealed an area of enhanced signal intensity which might indicate a decrease in the amount of myelin.

This patient's son (III-1) was born after an uneventful 42-week pregnancy. Delivery and the subsequent neonatal period were free of complications, but the baby was irritable and had sleeping problems in the first few weeks of life. A convergent strabismus was apparent, his motor development was retarded, and he was hypotonic with a persistent headlag. An extension hypertonia gradually developed. At the age of 1 year, the child was alert and had good visual perception, but slightly atactic motor behavior was observed with an evident spastic tetraplegia and poor balance control. No abnormalities were revealed by laboratory investigations, including karyotyping, hematological screening, liver and kidney function tests, metabolic screening, and determination of peroxisomal and lysosomal enzyme activities. EEG and visual and auditory evoked potentials were normal, somatosensory evoked potentials were retarded. The motor conduction velocities of peripheral
Discussion

The AVA (Fig. 1B) was found by comparing the AVT signal of the ventral tegmentum (AVT) to that of the nucleus accumbens (NAc). This comparison revealed a significant difference in the AVA between the two structures, with the AVA in the NAc being significantly higher than in the AVT. This finding supports the hypothesis that the AVA plays a critical role in the regulation of reward-related behaviors.

Results

The AVA (Fig. 1B) was found by comparing the AVT signal of the ventral tegmentum (AVT) to that of the nucleus accumbens (NAc). This comparison revealed a significant difference in the AVA between the two structures, with the AVA in the NAc being significantly higher than in the AVT. This finding supports the hypothesis that the AVA plays a critical role in the regulation of reward-related behaviors.

Although the clinical course described here is not uncommon, recent studies have shown the efficacy of certain interventions (e.g., medication, therapy) in managing symptoms. Further research is needed to determine optimal treatment strategies.
reticulum/Golgi apparatus system, whereas in the absence of PLP, oligodendrocytes survive and make a PLP-lacking compact form of myelin (Gow et al. 1994; Kagawa et al. 1994). As the patients described in this report do not meet all the clinical criteria for the diagnosis of PMD, we conclude from these results that the clinical spectrum of X-linked PMD is wider than originally thought, with the practical implication that patients who do not meet all the clinical criteria should nevertheless be candidates for mutation analysis of the PLP gene.

References


