Abstract A novel missense mutation of the L1CAM gene (Xq28) is described in an adult patient affected with severe mental retardation, spastic paraparesis, adducted thumbs, agenesis of corpus callosum and microcephaly (L1 disease). We detected a transition c2308G→A in exon 18 that caused an amino acid change in codon 770. The patient’s mother and two sisters were heterozygous for the same mutation. This newly described mutation predicts the substitution of an aspartate by asparagine (D770N) in the second fibronectin (Fn2) domain of the extracellular portion of the mature L1 protein. Even if amino acid substitution does not significantly change the physico-chemical properties of the Fn2 domain, it seems clear that the integrity of this domain is required to maintain the biological functions of the protein. The feature peculiar to this patient is the decelerated head growth post-natally, leading to microcephaly. Mutations of L1CAM associated with prolonged survival may hamper post-natal brain and head growth.

Key words L1 disease • L1CAM gene • Fn2 domain • Genetic heterogeneity • Post-natal brain growth

Introduction

The L1 cell adhesion molecule (L1CAM) gene is located near the telomere on the long arm of the X chromosome (Xq28) and encodes a 1125-amino acid, transmembrane glycoprotein of about 200 kDa. It contains 6 immunoglobulin and 5 fibronectin type III domains in the extracellular portion of the protein, a transmembrane domain and one short cytoplasmic stretch. It is expressed on the surface of glial cells and neurons, and is involved in several cellular events during the development of the central nervous system (CNS), such as neuronal migration, neurite growth and fasciculation, myelination, axonal guidance and synaptic plasticity [1]. Mutations of the L1CAM gene in humans are responsible for an X-linked syndrome, which encompasses 3 diseases that can be associated with CNS malformations [2]. The most frequent is hydrocephalus secondary to stenosis of the aqueduct of Sylvius (HSAS, MIM 307000), a life-threatening condition often with a fatal outcome within the first year of life. MASA (MIM 303350) is the acronym for mental retardation, aphasia, shuffling gait and adducted thumbs, and it is characterised by severe mental retardation and motor function impairment; it can be associated with CNS malformations such as callosal agenesis and enlarged ventricles [3]. Another less common condition related to L1CAM mutations is complicated spastic paraparesis type 1 (SPG1, MIM 312900). The clinical spectrum within each condition is extremely variable; even members of the same family may be affected with the different phenotypes encompassed by the L1-associated syndrome [4, 5]. This suggests that environmental and genetic factors can act epistatically in this type of disorder [6]. To overcome the difficulties in the nosography of L1-associated diseases, they have been lumped together and can be referred to as CRASH (Corpus callosum agenesis, mental Retardation, Adducted thumbs, Spastic paraparesis and Hydrocephalus) syndrome [7]. So far 143 private mutations of L1CAM gene
have been detected, and they are spread among the different phenotypes (check at LICAM mutation database: http://dnalab-www.uia.ac.be/dnalab/l1/). The missense mutations are the most common and, although their distribution over the functional L1 protein domains are highly heterogeneous, there is a tendency to clustering in the second, third and fourth immunoglobulin-like domain and in the second fibronectin domain [8]. Herein we report the identification of a novel missense mutation of LI involving the second fibronectin (Fn2) domain of the gene in a young adult affected with MASA, callosal agenesis and microcephaly. In our opinion, the defective growth of head and the brain malformation account for his severe disability, whereas his survival to adulthood can be related to the lack of congenital hydrocephalus.

Case report

A 10-year-old boy affected with severe mental retardation and significant gait disturbances was referred to us for a diagnostic work-up. He was born in the 35th week of gestation by natural delivery. Body weight was 2450 g, length 48 cm and head circumference 33 cm. Malformed hands and feet were reported at birth. By the 4th month developmental delay was evident. When 13 months old he underwent a CT scan, which showed callosal agenesis with ventricular enlargement. At the age of 10 years clinical evaluation revealed microcephaly (-2SD) with bilateral proptosis, low-set, small ears and arched palate. Thumbs were adducted at the metacarlo-phalangeal joints and there was syndactyly of III and IV fingers of both hands; adducted toes were present along with II and III toe syndactyly of feet. He could walk only if supported bilaterally, because of foot deformities and severe retraction of ankles; his gait was shuffling. Muscle tone was markedly increased and responses of deep reflexes were brisk. He had no speech, but he could communicate by crying and waving his arms. He displayed autistic features, showing several stereotyped movements of hands and upper limbs. He was fully dependent on his carers. MRI of the head showed enlarged third ventricle, marked dilatation of the occipital horns of the lateral ventricles (colpocephaly) and complete callosal agenesis; myelination was regular for his age (Fig. 1a,b). EEG recording was unremarkable. At 20 years he developed sporadic absence seizures, responsive to valproic acid. EEG recordings showed slow waves without epileptic activity. He is now 24 years old; his clinical condition is unchanged. Molecular investigation of the LICAM gene was performed on the proband, his two sisters and mother following informed consent. Genomic DNA was purified by peripheral blood leukocytes and screening of mutations for all exons of LICAM gene were performed on amplimers obtained with appropriate primers designed by...

Fig. 1 Head MRI: T1-weighted scans. a Coronal section showing callosal agenesis, persistence of Probst’s fascicles (arrows) and enlarged third ventricle. b Axial section revealing enlarged posterior ventricles (colpocephaly). Molecular genetic analysis of LI gene. c Mutation detected in the patient affected with MASA and callosal agenesis: the transition c2308G→A within exon 18 causes an amino acid change in codon 770.