

Case Report

A Novel Mutation in the *L1CAM* Gene: A Tale of Two Brothers

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Abstract

L1 syndrome encompasses a spectrum of conditions that includes a common clinical finding of congenital hydrocephalus and X-linked inheritance. *L1CAM* is the only gene implicated in this condition. Approximately 247 different mutations have been reported in 300 families. We present a family with a novel mutation. We also describe the significance and role of congenital hydrocephalus related to perinatal morbidity and mortality. The role of the *L1CAM* gene and significance of mutations is described.

ABBREVIATIONS

VP: Ventriculo-Peritoneal; ALGO® AABR®: Auditory Brainstem Response; BAER: Brainstem Auditory Evoked Response; CSF: Cerebrospinal Fluid; HSAS: Hydrocephalus due to Aqueductal Stenosis; MASA: Mental retardation, Aphasia, Shuffling gait, Adducted thumbs; SP-1: Spastic Paraplegia and some degree of mental retardation; ACC: Agenesis of the Corpus Callosum (ACC); MR-CT: Mental Retardation with Clapsed Thumbs; CRASH: Corpus Callosum Agenesis, retardation, adducted thumbs, Spastic paraplegia, Hydrocephalus; FN: Fibronectin; Ig: Immunoglobulin.

INTRODUCTION

Congenital hydrocephalus associated with *L1CAM* gene mutation is a rare disorder that is inherited in an X-linked fashion. Most mutations are *de novo* that tends to run in families. Although associated morbidity and mortality varies in patients affected children typically have significant neuro-developmental impairment.

CASE PRESENTATION

A routine prenatal ultrasound of a pregnant 26-year-old G₁P₀ (0000) Hispanic female revealed a fetus with severe hydrocephalus. The pregnancy progressed to full term. Baby (JT) was born with a head circumference of 40 cm and anterior fontanel measuring 6x6 cm. He also had adducted thumbs. Brain CT scan showed stenosis of aqueduct of Sylvius and supratentorial non-communicating hydrocephalus. He had a ventriculo-peritoneal (VP) shunt placed soon after birth. At age 5, JT has global developmental delay with hypotonia, lower extremity spasticity and myopia. He is at a 4 year-old level for speech and a 3.5 year-old level in physical development.

The mother received genetic testing and was later diagnosed as a carrier of I1088T mutation in the *L1CAM* gene. Her son was found to have the same mutation in the *L1CAM* gene. She received genetic counseling regarding the risk to subsequent pregnancies. However, she became pregnant with her second son. DT was born in with a head circumference of 51 cm (Figure 1). Prenatal ultrasounds showed severe hydrocephalus but mother had declined amniocentesis. Ultrasound at birth confirmed severe hydrocephalus with stenosis of aqueduct of Sylvius (Figure 2). He was also noted to have adducted thumbs. A VP shunt was placed on Day 3 and head circumference dropped to 48 cm. Eye exam showed optic atrophy. He failed an automated auditory brainstem response (NatusALGO® AABR®) hearing screen and was referred for brainstem auditory evoked response (BAER) test. Genetic studies reported DT was hemizygous for a novel I1088T mutation in *L1CAM* gene. The missense mutation resulted



Figure 1 Photo of DT on Day 3, prior to placement of VP shunt.



Figure 2 Initial head ultrasound of DT at birth.

in T>C nucleotide substitution in exon 24 leading to replacement of an Isoleucine codon (ATC) with a Threonine codon (ACC) at amino acid position 1088. The mutation is denoted as c.3263 T>C at the cDNA level or p.Ile1088Thr at the protein level. The substitution apparently alters a highly conserved position in the FN domain 3.

DISCUSSION

The two brothers were born with congenital hydrocephalus and both were diagnosed prenatally. In the first pregnancy the mother was not aware that she is a carrier of a novel mutation in the *L1CAM* gene that could potentially affect future pregnancies especially in a male fetus. Genetic information from the mother and older sibling provided a clue to the etiology of the congenital hydrocephalus in the younger sibling and later confirmed by genetic testing.

Hydrocephalus can be congenital secondary to events during fetal development or genetics. It can also be acquired at birth or by injury or disease. Communicating hydrocephalus involves impaired re-absorption of CSF. Non-communicating hydrocephalus involves an obstruction of CSF flow. [1,2] Clinical criteria for hydrocephalus includes increased intra-ventricular fluid volume (increased head circumference, imaging showing enlarged ventricles, loss of cerebral sulci) and/or increased intra-ventricular pressure.

Congenital hydrocephalus associated with mutation in the *L1CAM* gene was previously described as four separate neurological conditions with some clinical overlap [3,4]. These four neurological disorders include a) hydrocephalus due to aqueductal stenosis (HSAS); b) mental retardation, aphasia, shuffling gait, adducted thumbs (MASA); c) spastic paraplegia and some degree of mental retardation (SP-1), and; d) agenesis of the corpus callosum (ACC) and mental retardation with clasped thumbs (MR-CT) [3,4]. However, genetic studies proved that these conditions were due to mutation in the L1 gene. Hence, the acronym CRASH syndrome was proposed to refer to the clinical spectrum of **C**orpus callosum agenesis, **R**etardation, **A**dducted thumbs, **S**pastic paraplegia, and **H**ydrocephalus [3,5]. More recently, authors and clinicians have used the term L1 syndrome or L1 disease to refer to this condition. It is an X-linked disorder with a reported incidence of 1 in 30,000 males [2,6].

L1CAM gene encodes for the L1 cell adhesion molecule

(L1CAM) and mutation in this gene is responsible for L1 disease. *L1CAM* is located on the long arm of the X-chromosome at the Xq28 locus. The L1 protein is a trans-membrane glycoprotein belonging to the immunoglobulin super family [7,8]. The structure of a normal L1 gene includes an extracellular surface that contains 6 immunoglobulin (Ig)-like domains and 5 fibronectin (FN) type III-like domains, a single-pass trans-membrane region and a highly conserved cytoplasmic domain [5]. This neural cell adhesion molecule is expressed in the developing nervous system and plays a critical role in the development of the central nervous system. It is mainly expressed on neurons and Schwann cells and has been shown to mediate cell-cell adhesion, axonal growth, path finding and fasciculation, neuronal migration, myelination, cognitive function and memory [4,9].

Mutations in *L1CAM* can occur throughout the gene and tend to be unique in each family. To date, a total of 249 mutations are registered in the *L1CAM* Mutation Database [10]. Site and type of mutation appears to predict the severity of the clinical presentation as suggested by Yamasaki *et al*. In their review of mutations in 129 individuals and their clinical presentation the authors have proposed three classes of mutations in *L1CAM*. Class 1 mutation disrupts only the cytoplasmic domain and is considered the mildest form with some patient having only mild or no hydrocephalus. Class 2 included mutations that alter the structure of the extracellular domain. Class 3 mutation is the most severe as it results in a stop codon that causes a truncation in the extracellular domain. The authors identified severe hydrocephalus in 92% of individuals with class 3 mutations and at least half of the patients died within the first year of life [5]. Michaelis *et al* also identified worse outcome among individuals with missense mutation in FN domain compared to those with mutation in the Ig domains. The authors postulated that mutation in the FN domain might indirectly affect Ig domain function [8]. However, in the cohort of patients that had missense mutation studied by Vos *et al* the authors found no association between the severity of the hydrocephalus and location of the missense mutation [10].

The missense mutation that occurred in this family occurred in exon 24 and involved the FN 3 domain. It resulted in T>C nucleotide substitution and led to the alteration of isoleucine codon (ATC) to a threonine codon (ACC) at amino acid position I1088T. The mutation identified in this Hispanic family is a novel mutation and like most *L1CAM* mutation it is unique to this family. A review of the *L1CAM* Mutation Database showed 5 mutations (2 nonsense, 2 missense and 1 deletion) in exon 24 and all occurring in FN 5 domain. The severity of the hydrocephalus in these two brothers is likely due to the fact the FN domain was involved.

The implications of the finding of the novel mutation in the *L1CAM* gene cannot be overemphasized due to its mode of inheritance and morbidities associated with it. Vos *et al* showed that mutation detection improves when clinical information is combined with family history [10]. Genetic counseling was offered to the mother in this case after the birth of her first son when genetic studies on her and her son detected a mutation in the *L1CAM* gene. Both brothers had severe hydrocephalus requiring VP shunting. Both also exhibit developmental delay.

In summary, *L1CAM* is the only gene implicated in L1

syndrome. Genetic testing is warranted in a newborn male born and sequence analysis of *L1CAM* has 100% mutation detection rate [3]. Majority of the mutations is *de novo* and unique in each family. Genetic counseling should be optimally done prior to a pregnancy with emphasis on the correlation between genotype and phenotype.

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