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CASE REPORT

L1CAM mutation in association with X-linked hydrocephalus and Hirschsprung's disease

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Abstract X-linked hydrocephalus (XLH) is characterized by increased intracranial ventricle size and head circumference secondary to aqueduct of Sylvius congenital stenosis. Exceedingly rare is the concurrence of XLH and Hirschsprung's disease (HSCR) with a theoretical incidence of 1 in 125–250 million cases. Herein, we are describing a case of a patient with concurrent XLH and HSCR. The patient was delivered via cesarean section at 37 weeks gestation and underwent uneventful ventriculoperitoneal shunt placement. As a part of a workup for constipation, we performed a rectal biopsy, which was consistent with HSCR. Genetics testing showed hemizygous for R558X hemizygous mutation in the L1CAM gene. A C → T nucleotide substitution in exon 13 resulted in replacement of an arginine codon with a stop codon, a nonsense mutation. Although it is widely accepted that HSCR represents the failure of early embryonic neural crest cells to migrate properly, the exact mechanism is not known. The association of HSCR with XLH in the presence of L1CAM mutations remains quite interesting because cell adhesion molecules are involved in the proper migration of neural components throughout the body. Additional studies are necessary to fully elucidate the relationship between XLH and HSCR in the presence of L1CAM mutations.

Keywords Hirschsprung's disease · Constipation · Hydrocephalus · Neonate

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Introduction

X-linked hydrocephalus (XLH) is characterized by hydrocephalus with enlargement of the third and lateral ventricles due to stenosis of the aqueduct of Sylvius. Classical clinical features include mental retardation, bilateral adducted thumbs, upper and lower extremity hypotonia and spasticity, and minor craniofacial abnormalities [1]. Hypoplasia or complete absence of the corpus callosum as seen on MRI is an associated malformations. XLH is quite rare, with a frequency between 1:25,000 and 1:50,000. Exceedingly rare, but clinically significant, is the concurrence of XLH and HSCR with theoretical incidence of 1 in 125–250 million cases [2, 3]. Notwithstanding, there have been eight reported cases of XLH in association with HSCR in the presence of a multiplicity of L1 CAM (L1 cell adhesion molecule) gene mutations. Herein, we present an additional case of XLH and HSCR with confirmed L1CAM mutation.

Case presentation

The patient is the second child born to a G2P2 mother in good health receiving excellent prenatal care. The patient's mother is an only child of European ancestry. The patient's

maternal grandmother has one sibling, a healthy brother. The patient's father is of Persian and European ancestry. The patient has a healthy brother. The family history is otherwise negative for birth defects, mental retardation and neurological disorders. Consanguinity is denied.

Fetal ultrasound examination in the third trimester revealed hydrocephalus. The patient was delivered via cesarean section at 37 weeks gestation and admitted to the neonatal intensive care unit (NICU) for respiratory support. He was noted on physical examination to have prominent hydrocephalus, global hypotonia and spastic paresis of bilateral lower extremities. Bilateral thumbs were adducted. On day 4 of life he underwent uneventful ventriculoperitoneal shunt placement. The patient could not be sustained on oral nutrition and was maintained on nasogastric feedings for nutritional support. Moreover, as a part of a workup for severe constipation requiring periodic enemas dating back to birth, a rectal biopsy was performed. The biopsy results were consistent with Hirschsprung's disease as demonstrated by the absence of ganglion cells and hypertrophy of nerve fibers with enhanced acetyl cholinesterase activity. He was discharged from the NICU on day of life 30 and shortly thereafter did tolerate gastrostomy tube placement at month 2 of life. The family was anxious to take the child home and felt comfortable to perform rectal irrigations. The child was allowed to recuperate and grow for an additional 10 months after which he underwent aganglionic bowel resection with rectosigmoid (Soave) pull-through and diverting ileostomy. In the immediate postoperative period, the patient exhibited new onset seizure activity that responded rapidly to intravenous barbiturate. As per neurology recommendations the child was not maintained on this anti-seizure medication. The remainder of the postoperative period proceeded without event and the child was discharged to home. The patient is now tolerating consolidated gastric tube feeding. Following discharge, he was seen by ophthalmology for nonreactive and asymmetrical pupils suggesting optic nerve hypoplasia, a condition which is defined as a congenital deficiency of retinal ganglion cells [4]. This suspected deficiency of retinal ganglion cells is particularly interesting in a patient with HSCR who demonstrates rectal absence of ganglion cells. The child did receive vision therapy, but has since stopped and is tracking well with normal focusing.

Additional workup

Genetics consultation was obtained. The patient was found to be hemizygous for R558X mutation in the *L1CAM* gene. This is indicative of a C → T nucleotide substitution in exon 13, resulting in the replacement of an arginine codon with a stop codon at amino acid position 558. This creates a nonsense mutation that is predicted to cause loss of normal protein function either through premature protein truncation or through nonsense-mediated mRNA decay. The patient's mother declined DNA carrier testing for personal reasons.

Discussion

Previous reports have described instances of XLH secondary to stenosis of the aqueduct of Sylvius [5–8]. XLH is associated with any of a number of largely private mutations of the L1CAM gene, with more than 180 mutations reported to date [9, 10]. L1CAM, or neural cell adhesion molecule 1, is a member of the immunoglobulin super family of cell adhesion molecules expressed widely in developing neurons [11]. The gene is located on chromosome Xq28, and the condition is inherited in an X-linked recessive pattern, with a minority of cases representing new mutations. Some genotype–phenotype correlations are possible, as mutations affecting different regions of the gene, and therefore the protein, are classified as to their type with loose correlations as to their clinical significance. Within a family, however, two individuals with the same mutation might have a different degree of severity, so other factors are clearly responsible for part of the clinical presentation. Mutations affecting different regions of the protein will have different effects and have been classified accordingly [12]. Class I L1CAM mutations affect the cytoplasmic domain, while class II mutations are missense point mutations or deletions affecting the extracellular domain. Class III mutations are nonsense mutations leading to premature stop codons with truncation of the extracellular domain which are the most severe L1CAM defects. The patient described in the report has a class III mutation.

With this report, we add to the literature with an additional case report of a patient with XLH and HCSR with an L1CAM mutation [1, 2, 13]. Although it is widely accepted that HSCR represents the failure of early embryonic neural crest cells to migrate properly, the exact mechanism is not known. Defects in many genes have been implicated in HSCR, including RET proto-oncogene, endothelin receptor b, endothelin-3, SOX-10, and SIP1 [1] and L1CAM mutations alone certainly do not account for HSCR. Even so, the association of HSCR with XLH in the presence of L1CAM mutations remains quite interesting because cell adhesion molecules are involved in the proper migration of neural components throughout the body. Perhaps, L1CAM acting as an X-linked modifier gene somehow allows for the manifestation of additional errors in genes known to be associated with HSCR [14]. While L1CAM mutation in the presence of XLH cannot independently predict HSCR, the multidisciplinary medical and surgical teams should proactively rule out the diagnosis of HSCR in the child with

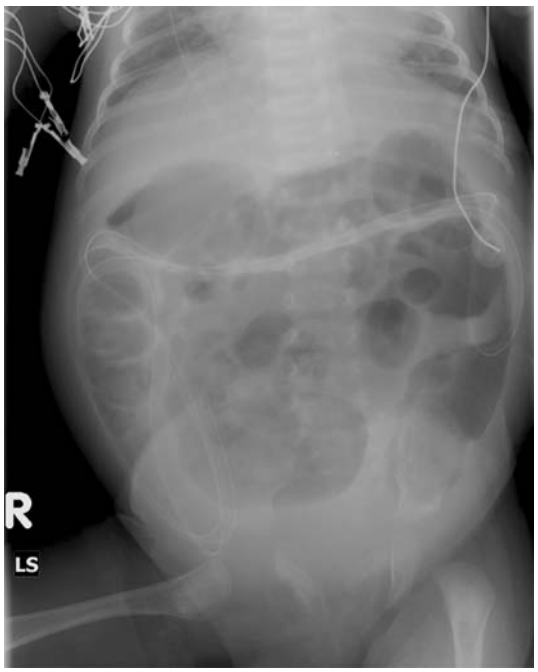

Fig. 1 Plain radiograph demonstrating multiple, dilated loops of bowel

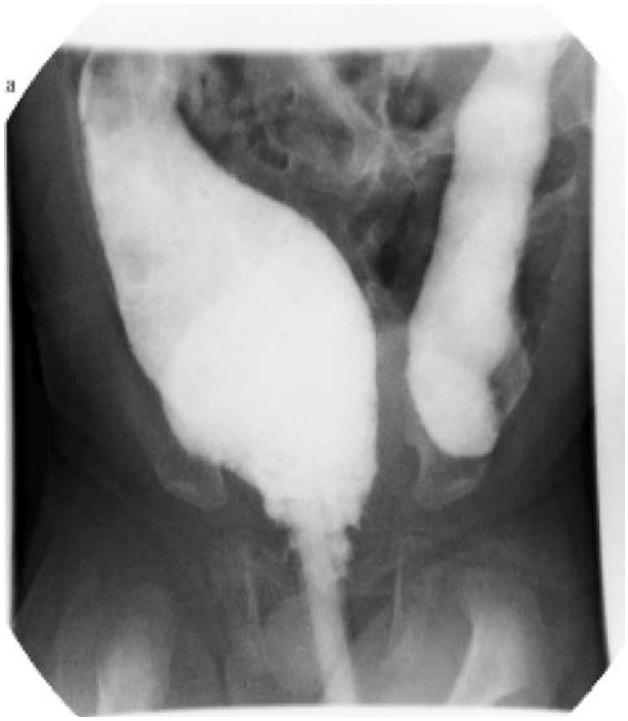

Fig. 2 Barium enema demonstrating proximal dilated bowel with collapsed distal segment

signs of feeding intolerance, vomiting, constipation or abdominal distention. A barium enema can quickly identify the presence of a small colon as well as rectal caliber change. Surgical consultation for suction or open rectal biopsy with acetyl cholinesterase activity level assay should be performed to confirm the diagnosis of HCSR. The goal of staged surgical intervention is to remove the aganglionic bowel segment with anastomosis of normal proximal bowel to rectal tissue just above the anus coupled with a diverting ostomy to allow healing of the fresh suture line. This ostomy is later reversed to re-establish bowel continuity. While it is obvious that additional studies are necessary to fully elucidate the true relationship between XLH and HSCR in the presence of L1CAM mutations, we are compelled to recognize the association in an effort to optimize outcomes in this rare, but all too often fragile patient population (Figs. 1, 2).

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