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Crohn's Disease in Hajdu-Cheney Syndrome: Report of Two Cases and Literature Review

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Abstract

Hajdu-Cheney syndrome (HCS) is a rare skeletal disorder caused by heterozygous gain-of-function variants in NOTCH2. In addition to skeletal abnormalities, a mouse model of HCS exhibited splenomegaly and increased marginal zone B cells, but it is unclear whether humans with HCS have immunologic abnormalities. Here, we report two patients with HCS who developed pediatric-onset Crohn's disease (CD). Both children had other features of immune dysregulation, one having immune thrombocytopenia and the other having lymphoproliferation with infectious susceptibility. These cases and others in the literature suggest that HCS is associated with broader immune dysregulation and that NOTCH2 is a CD susceptibility gene.

Keywords: Graves' disease; Immune thrombocytopenia; Inflammatory bowel disease; ITP; Notch2

Introduction

Notch signaling plays a pivotal role in development and disease. Four distinct Notch receptors interact with ligands on adjacent cells, triggering proteolytic cleavage events that culminate in the release and translocation of the Notch intracellular fragment to the nucleus, where it acts as a transcriptional effector [1]. Loss-of-function variants in NOTCH2 or the Notch ligand JAG1 cause Alagille syndrome. Another condition linked to aberrant Notch signaling is Hajdu-Cheney syndrome (HCS), a skeletal disorder characterized by acroosteolysis, osteoporosis, and distinctive facial features [1].

HCS, which has a prevalence of less than 1 per million individuals, is caused by heterozygous gain-of-function (GOF) NOTCH2 variants that generate stop codons upstream of the PEST (proline-glutamic acid-serine and threonine rich) domain, impairing ubiquitin-mediated degradation of Notch2 [1]. Notch signaling in bone has been shown to modulate receptor activator of nuclear factor κB (RANK) induced osteoclastogenesis, and its excess is responsible for the characteristic physical findings in HCS [1]. Notch2 is preferentially expressed in mature B cells and is indispensable for marginal zone B cell (MZB) development [1]. In addition to skeletal abnormalities, a genetically engineered mouse model of HCS exhibits splenomegaly with increased MZBs and decreased follicular B cells, indicative of immune dysregulation [1]. Whether humans with HCS have immunologic abnormalities is unclear. Here, we report two children with HCS, pediatric-onset Crohn's disease (CD), and other features of immune dysregulation.

Case Presentation

Patient 1 is a girl who presented at 6 years of age with excess fractures, micrognathia, high arched palate, hyperflexible joints, and shortening of the distal phalanges on both hands. Skeletal radiographs showed acroosteolysis of the distal phalanges and multiple metatarsal fractures. Bone densitometry confirmed osteopenia. Targeted sequencing identified a heterozygous mutation in NOTCH2 predicted to cause loss of the PEST domain (Table 1). She started bisphosphonate therapy without further fractures. At age 12, she developed diarrhea, and abdominal computed tomography showed pancolitis with normal spleen size. Esophagogastroduodenoscopy and colonoscopy demonstrated chronic active colitis with cryptitis and focal mucosal granulomas in the terminal ileum. She was diagnosed with CD, treated briefly with glucocorticoids, and then transitioned to infliximab. Repeat colonoscopy 10 months later demonstrated good disease control. At age 14, she developed bruising and was found to have a platelet count of 1000/μL without other hematologic abnormalities, consistent with a diagnosis of immune thrombocytopenia (ITP). Serum immunoglobulin levels and peripheral blood B cell counts were normal. B cell phenotyping demonstrated normal percentages of class-switched B cells but mildly decreased plasmablasts ($CD19^+CD38^+IgM^-$; 1.5%, ref. 2.9-51.8%). Her thrombocytopenia did not respond to intravenous immunoglobulin (IVIG) and required romiplostim for a sustained response.

Patient 2 is a male who was born at 32 weeks of gestation with severe hydrops, micrognathia, high-arched palate, synophrys, left iris coloboma and cyst, hearing impairment, cardiovascular defects, isolated bowel malrotation, and hydronephrosis with renal cysts. He developed chronic lung disease, G-tube feed requirements, and global developmental delay. He has suffered from autonomic dysregulation (episodes of diaphoresis, tachycardia, hypertension, cyanosis, and pallor) and ketotic hypoglycemia since 3 years of age. By age 4, osteopenia led to vertebral fractures. He had bacterial infections, including urinary tract infection and sepsis during his first year of life, attributed to complications from surgical procedures and underlying malformations; however, between the ages of 2-5 years, he required multiple ICU admissions for severe respiratory distress in association with viral infections. He was seen by Immunology at 5 years of age and found to have mild hypogammaglobulinemia (4.2 -5 g/L, ref 5.4-16 g/L), inadequate antibody responses to vaccinations, and absent IgD^-27^+ memory class-switched cells and IgD^+27^+ memory non-class switched B cells. He was started on immunoglobulin replacement therapy with significant improvement in infections and has not required hospitalization for infection since. Exome sequencing at age 7 revealed a heterozygous truncating mutation in the last exon of NOTCH2 (Table 1).

B cells were assessed more closely and demonstrated absent memory IgM^+ B cells and virtually absent plasmablasts ($CD19^+CD27^{++}CD38^+IgM^-$; 0.6%, ref. 0.8-5.3%). He has had splenomegaly since birth, suggestive of lymphoproliferation. Other skeletal abnormalities, including acroosteolysis of terminal phalanges of the feet, have manifested over time (Table 1). By 8 years of age, he presented with weight loss, hypoalbuminemia, and mucousy, bloody stools. Endoscopy revealed non-penetrating, non-stricturing ileocolonic CD with upper gut involvement proximal to the ligament of Treitz. Vedolizumab infusion was chosen as treatment with good control one year after diagnosis.

Table 1: Cases of Hajdu-Cheney syndrome with Crohn's Disease.

Skeletal manifestations of HCS	Sex	NOTCH2 variant	CD		Other notable features	Ref
			Age at diagnosis	Treatment(s)		
Typical facial features, acro-osteolysis, excess fractures, osteopenia	F	c.6787C>T p.Gln223*	12 y	Glucocorticoids, infliximab	ITP (age 14 y) controlled with romiplostim	This article
Typical facial features, cervical instability (Os Odontoideum-C2 dens), vertebral fractures, bilateral coxa valga, deformed and bowed fibulas, acro-osteolysis of terminal phalanges of the feet, osteopenia	M	c.7020C>G p.Tyr234*	8 y	Vedolizumab	Cardiovascular defects, renal cysts, splenomegaly, severe respiratory viral infections with hypogammaglobulinemia, and abnormal maturation of B cells requiring IVIG	This article
Typical facial features, acroosteolysis, osteoporosis, vertebral compression fractures	F	ND	37 y	Glucocorticoids, infliximab, and azathioprine		[2]
Typical facial features, clubbed fingers, vertebral compression fractures, osteopenia	F	c.6758G>A p.Trp225*	17 y	Adalimumab, infliximab, vedolizumab, methotrexate, ustekinumab	Functional hypothalamic amenorrhea treated with HRT	[3]

Abbreviations: **CD:** Crohn's disease; **F:** Female; **HCS:** Hajdu-Cheney syndrome; **HRT:** Hormone replacement therapy; **IVIG:** Intravenous immunoglobulin; **M:** Male; **ND:** Not done; **ITP:** Immune thrombocytopenia; ***:** Stop codon leading to truncation upstream of the PEST domain.

Discussion

Along with the cases presented here, two other individuals with HCS and CD have been reported (Table 1) [2,3]. Thus, among the fewer than 200 subjects with HSC described in the literature, a total of 4 have CD, which exceeds the prevalence of CD in the general population [3]. described a Greek family in which six members had HCS and only one developed CD. This kindred suggests that genetic or environmental modifiers may impact the development of CD in the setting of a NOTCH2 GOF variant.

CD is driven by perturbed immune tolerance to intestinal antigens, such as bacteria in the gut lumen. Genome-wide association studies (GWAS) of CD have identified several genetic risk loci that confer an abnormal innate or adaptive immune response to mucosal injury and intestinal microbiota [4]. Linkage disequilibrium mapping of our patient's variant or proxy variants with GWAS of inflammatory bowel disease loci, did not show a correlation. This could be due to rarity of patient variants that makes it statistically difficult to study. Given the established roles of Notch signaling in epithelial homeostasis and the immune response to intestinal bacteria, it is plausible that GOF variants in NOTCH2 contribute to the pathogenesis of CD. Existing mouse models of HCS or colitis could be combined to validate the link between NOTCH2 mutations and CD and to test targeted therapies.

The risk of autoimmunity in HCS may extend beyond CD. Patient 1 developed ITP. The incidence of ITP is higher in patients with CD than in the general population. It often coincides with flares of intestinal inflammation, although ITP developed in our patient when her intestinal disease was quiescent. A literature search for other forms of autoimmunity in HCS identified one individual with Graves' disease [5]. Collectively, these reports reinforce the premise that immune dysregulation manifested as CD, ITP, Graves' disease, recurrent respiratory infections, or splenomegaly is a feature of HCS.

Credit Author Statement

Irem Eldem: Investigation, writing-original draft; **David B. Wilson:** Investigation, writing-original draft, supervision; **Elizabeth C. Utterson:** Investigation; **Dorothy K. Grange:** Investigation; **Iwona T. Wrobel:** Investigation; **Francois Bernier:** Investigation; **Luis Murguia-Favela:** Investigation, writing-original draft; **Megan A. Cooper:** Investigation, writing-review and editing, supervision.

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