Clinical Case Reports

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CASE REPORT

Congenital insensitivity to pain and anhydrosis due to a rare mutation and that is complicated by inflammatory bowel disease and amyloidosis: a case report

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Key Clinical Message

Patients with congenital insensitivity to pain and anhydrosis syndrome are at risk for renal amyloidosis and inflammatory bowel disease. Physicians caring for such patients should be aware of these complications.

Keywords

Amyloidosis, congenital insensitivity to pain and anhydrosis, hereditary sensory and autonomic neuropathy, inflammatory bowel disease, Jordan, nephrotic syndrome, NTRK1 gene, osteomyelitis.

Introduction

Congenital insensitivity to pain and anhydrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN 4) is an extremely rare autosomal recessive disorder of the autonomic and sensory nervous systems [1]. The disorder is characterized by episodes of hyperpyrexia, anhydrosis, insensitivity to pain, and self-mutilation [2].

Here, we report a male patient with CIPA who showed a rare mutation in the NTRK1 gene that was previously reported once [3]. The patient's course was intriguing because it was complicated by inflammatory bowel disease and renal amyloidosis. These findings are rare in the setting of CIPA; to our knowledge, the association of CIPA with renal amyloidosis has been reported one time [4],

and the association with inflammatory bowel syndrome was not previously reported.

Case Report

The patient was born in 1990 from consanguineous parents. His father had renal failure and familial Mediterranean fever (FMF). At 6 months of age, the patient began to have attacks of fever and an absence of sweating. At 8 months, the time of teeth eruption, he would bite his fingers and toes, resulting in tongue and cutaneous injuries. At 6 years of age, he showed difficulties participating in school and had bone fractures due to repeated trauma. At age 9, he was reported as having Lesch–Nyhan syndrome. At 10 years, he underwent multiple reduction surgeries due to recurrent dislocation of the hip joints. By

age 16, he suffered from four deformed limbs, sacral decubitus, and chronic osteomyelitis of the right elbow, both ankles, and both feet. Cultures from right elbow ulcers grew methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter*. At age 19 years, he underwent bilateral below-knee amputation.

In September 2009 and 2 months after the amputation surgery, the patient developed ascites. His uric acid was 4.1 mg/dL (normal, 3.0–7.0 mg/dL), serum creatinine was 0.1 mg/dL, serum albumin was 1.3 g/dL (normal, 3.5–5 g/dL), ascitic albumin was 0.1 g/dL, and total protein in a 24-h urine collection was 6.29 g. In April 2010, he developed generalized edema and new-onset diarrhea. A colonoscopy showed multiple erythematous and ulcerating lesions scattered through the colon. Colon biopsy showed severe crypt abscesses, goblet cell depletion, and severe inflammation of the lamina propria consistent with idiopathic inflammatory bowel disease and suggestive of Crohn's disease (Fig. 1). Therefore, we initiated mesalamine treatment. During the same admission, the patient developed generalized tonic clonic seizures. Brain MRI and electroencephalography were normal. Eventually, following these events, we doubted the primary diagnosis of Lesch–Nyhan syndrome because of the normal uric acid level and the history of recurrent fever and decreased sweating which favor the diagnosis of CIPA. Nerve conduction studies were not performed at the time because the patient had amputation of both lower limbs and deformities and ulcerations in the upper limbs. Genetic testing was performed and subsequently identified homozygous pathogenic variant (c.2125G>T; p.Val709-Leu) in the NTRK1 gene.

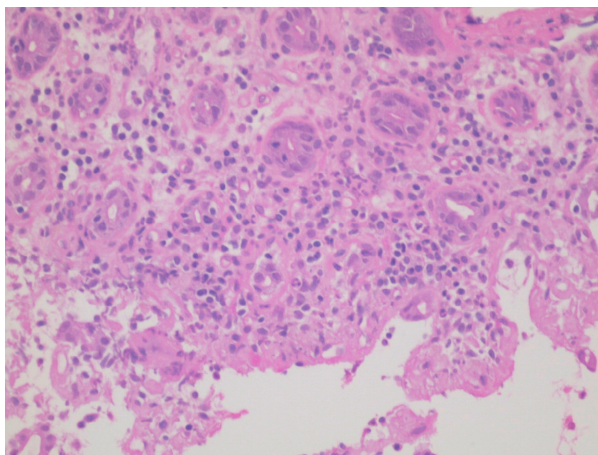In July 2010, the patient was admitted for worsening edema and diarrhea. The diarrhea was bloody with a frequency of seven times per day. His hemoglobin was 4.7 g/dL, creatinine was 1.15 mg/dL, albumin was 0.9 mg/dL, and spot urine protein to creatinine ratio was 1.7 g/day. Urinalysis showed protein + 3 and granular casts. A blood culture grew *Streptococcus canis*. Serum immunoglobulin levels (including IgG subclasses) were normal, with the exception of IgE which was elevated to 822 IU/mL (Normal, <100 IU/mL). A nitroblue tetrazolium test was normal. Transthoracic echocardiogram was normal. Renal ultrasound revealed multiple bilateral renal stones, echogenic kidneys with loss of corticomedullary differentiation, and no hydronephrosis. Renal biopsy showed mesangial expansion by amorphous pinkish material with positive staining for Congo red stain consistent with renal amyloidosis (Fig. 2). The patient went home and died after 3 months.

Discussion

Congenital insensitivity to pain and anhydrosis is a rare autosomal recessive inherited disorder, resulting from the presence of two NTRK1 pathogenic variants [5]. The NTRK1 gene encodes for the high-affinity neurotrophic tyrosine kinase receptor type 1 (NTRK1), an essential part of the pain pathway [3]. Thus far, approximately 50 loss-of-function NTRK1 variants have been associated with CIPA [5].

The differential diagnosis of CIPA includes the following: (i) Hereditary Sensory and Autonomic Neuropathy Type I (HSAN 1), (ii) Hereditary Sensory and Autonomic Neuropathy Type II (HSAN 2), (iii) familial dysautonomia or Riley–Day syndrome or Hereditary Sensory and Autonomic Neuropathy Type III (HSAN 3), and (iv) Lesch–Nyhan syndrome [6]. A diagnosis of CIPA is made according to suggestive clinical features, neurological laboratory tests (such as electrophysiologic studies and sympathetic skin responses), pharmacologic tests for autonomic function (such as the Mecholyl test, which
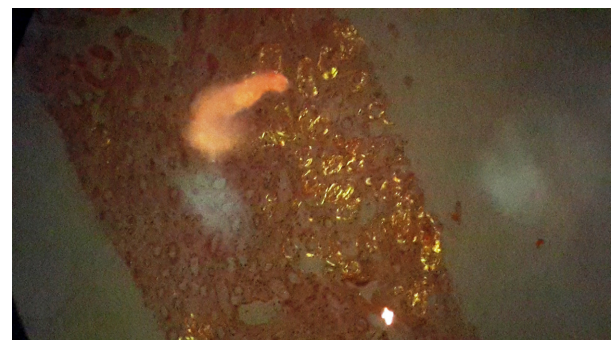

Figure 1. Colon biopsy showing disturbance in crypt architecture and mixed inflammation with focal cryptitis and crypt abscess formation (H&E, 400 X).

Figure 2. Amyloid deposition in renal tubules and blood vessels as highlighted by polarized Congo red stain (200 X).

produces prompt papillary miosis and the sweat test using pilocarpine which reveals a disruption of sweat gland function), histopathologic evaluation (for a hyperplastic epidermis with acanthosis and hyperkeratosis and a decreased amount of sweat and sebaceous glands), and finally, genetic tests for NTRK1 mutations [6].

Here, the diagnosis of CIPA was favored over Lesch–Nyhan syndrome because the patient showed fever, absence of sweating, and normal serum uric acid level. Lesch–Nyhan syndrome is a rare genetic disorder characterized by the overproduction of uric acid, neurologic disability dominated by intellectual disability, dystonia, spasticity, and behavioral problems [7]. Other clinical findings consistent with CIPA in this patient included insensitivity to pain, learning disabilities, seizures, joint dislocation, skin ulcers, and chronic osteomyelitis [3, 8, 9]. We confirmed the diagnosis of CIPA by genetic testing and detected a mutation in the NTRK1 gene; the NTRK1 c.2125G>T (p.Val709Leu) variant has been reported in a Malaysian patient with CIPA [3] and was predicted to be deleterious by in silico analysis using SIFT (http://sift.jcvi.org/), MutationTatster (http://www.mutationtaster.org/), and MutPred (http://mutpred.mutdb.org/) softwares. Additionally, the p.Val709 is completely conserved across different species.

Current therapeutic options for CIPA are limited and include the treatment of symptoms, protection from fractures, and wound infections. However, early surgical treatment enables rapid functional recovery and a reduced risk for accelerated osteopenia due to immobilization [6]. In year 2015, Lopez et al. [6] reported good results in preventing new fractures in a case of CIPA using bisphosphonates to manage osteoporosis. Here, we only provided supportive care such as antibiotics and surgical debridement for the patient. However, these measures could not prevent the progression of infectious and inflammatory complications.

To our knowledge, no previous reports described an association between CIPA and inflammatory bowel disease. However, one previous patient with CIPA was reported to suffer from chronic diarrhea attributed to autonomic dysfunction with sphincter incontinence [10]. Inflammatory bowel disease is a chronic inflammatory disorder that is comprised of both Crohn's disease and ulcerative colitis. It has a multifactorial etiology that has not been fully elucidated [11]. However, inflammatory bowel disease is thought to be the result of a dysregulated immune system in the context of a genetically susceptible individual [12]. Our patient may have developed inflammatory bowel disease due to immune dysregulation because patients with CIPA show several immune abnormalities such as defects in neutrophil chemotaxis [13], hypogammaglobulinemia [14], impaired release of neuropeptides that trigger proinflammatory mediators [15],

defects in lymphocyte signaling [16], and severe *Staphylococcus aureus* infections [17].

Renal manifestations of CIPA are rare and have thus far included focal glomerulosclerosis, interstitial fibrosis, tubular atrophy [18], and renal amyloidosis [4]. To our knowledge, renal amyloidosis was reported only once in association with CIPA [4]. Secondary amyloidosis represents a family of disorders characterized by the extracellular deposition of protein fibrils. Renal amyloidosis is the most frequent type of systemic amyloidosis with a prevalence between 0.5% and 0.86% in various autopsy series [19]. Secondary amyloidosis is associated with a variety of chronic inflammatory diseases such as osteomyelitis, inflammatory bowel diseases, FMF, tuberculosis, bronchiectasis, and rheumatoid arthritis [20, 21].

Here, the following four factors could have caused renal amyloidosis: (i) Inflammatory bowel disease, where amyloidosis is a rare complication of inflammatory bowel disease. The incidence ranges from 0.3% to 10.9% in Crohn's disease and from 0% to 0.7% in ulcerative colitis [22]. The time lapse between the onset of inflammatory bowel disease and an amyloidosis diagnosis is variable: amyloidosis is usually diagnosed 10–15 years after inflammatory bowel disease diagnosis, is sometimes discovered simultaneously with inflammatory bowel disease, and is rarely described before inflammatory bowel disease onset [22]. (ii) Chronic osteomyelitis, where amyloidosis due to osteomyelitis is a late and infrequent complication [20, 23]; in a large series on secondary amyloidosis, osteomyelitis was the etiologic condition in 2% of cases [20]. (iii) CIPA and NTRK1 signaling pathway, where patients with CIPA show several immune and inflammatory abnormalities [14, 15]. Additionally, renal amyloidosis was reported in one patient with CIPA [4]. (iv) Finally, genetic susceptibility, where amyloidosis may be the result of genetic susceptibility in the face of a chronic inflammatory condition [24]. The patient's father, who had renal failure and FMF, may have also suffered from underlying amyloidosis as renal failure in patients with FMF is usually secondary to amyloidosis [20]. Thus, the patient may have inherited a genetic susceptibility to amyloidosis.

In conclusion, we report a rare case of CIPA due to a rare mutation. The patient developed two conditions that are unusual in patients with CIPA: renal amyloidosis and inflammatory bowel disease. Physicians caring for such patients should be aware of these complications. Risk factors for developing these conditions in the context of CIPA could be related to the NTRK1 signaling pathway or repeated inflammation-related injuries during a prolonged period (20 years in this case). However, it is difficult to precisely determine which of these factors caused these two conditions because these factors may have acted either alone or in combination.

Acknowledgment

Conflict of Interest

None declared.

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