Severe Early-Onset Colitis Revealing Mevalonate Kinase Deficiency

abstract

Hyperimmunoglobulinemia D is the less severe form of mevalonate kinase deficiency (MKD) caused by recessive inherited mutation in the mevalonate kinase gene. Hyperimmunoglobulinemia D is characterized by febrile attacks, often associated with transient digestive manifestations, such as abdominal pain, diarrhea, and vomiting. Here we report for the first time 2 patients with MKD revealed by severe neonatal colitis. Both patients had chronic bloody diarrhea and failure to thrive; 1 patient since the age of 1 month and the other since the age of 12 days. Total parenteral nutrition was required. A marked elevation of acute phase reactants was present, and no evidence of infection was found. In patient 1, ileocolonoscopy revealed ulcerative colitis at the age of 5 months. Patient 2 suffered from enterocolitis and shock, associated with multiple bowel adhesions at age 5 weeks; the rectosigmoidoscopy showed aphtoid lesions of the sigmoid colon. Pathologic findings of colonic biopsies revealed a dense polymorph inflammatory infiltrate associated with deep ulcerations. Febrile attacks occurred 2 months after the onset of digestive symptoms in patient 1, and at onset of disease in patient 2. Genomic sequencing of the mevalonate kinase gene revealed compound heterozygous mutations in both patients. Anti-interleukin-1 agent produced long-term remission of all digestive features and laboratory parameters. This report emphasizes that MKD may be the cause of severe early-onset inflammatory colitis, and must be considered by physicians, even in the absence of fever, after ruling out infections. Anti-interleukin-1 therapy may result in a dramatic improvement of MKD-related inflammatory bowel disease.

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KEY WORDS
Mevalonate kinase deficiency, colitis, infant, anti-interleukin-1

ABBREVIATIONS
anti-IL1—anti-interleukin 1
HIDS—hyperimmunoglobulinemia D syndrome
IBD—inflammatory bowel disease
IL—interleukin
MA—mevalonic aciduria
MKD—mevalonate kinase deficiency
MVK—mevalonate kinase
TPN—total parenteral nutrition

Drs Bader-Meunier and Jung contributed equally to this work.

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Mevalonate kinase deficiency (MKD; MIM 251170) is a rare autosomal recessive disease caused by mutations in the gene encoding mevalonate kinase (MVK), an enzyme involved in the biosynthesis of cholesterol and isoprenoids. It results in a continuous spectrum of clinical manifestations ranging from recurring febrile attacks associated with inflammatory symptoms, known as hyperimmunoglobulin D syndrome (HIDS; MIM 260920), to a more severe form, known as mevalonic aciduria (MA; MIM 610377). HIDS is characterized by excessive disease caused by mutations in the gene encoding mevalonate kinase, an enzyme involved in the biosynthesis of cholesterol and isoprenoids.

CASE REPORTS

Patient 1

Patient 1 was a 14-month-old girl born to healthy unrelated parents after an uneventful pregnancy. From 1 month of age, she had bloody and mucoid diarrhea (6 stools per day), protein-losing enteropathy leading to hypoalbuminemia, failure to thrive, and a marked elevation of acute phase reactants (Table 1). From the age of 3 months, she had febrile attacks lasting 1 to 7 days and recurring every 1 to 3 weeks without any trigger. She was admitted for fever and persisting bloody diarrhea at 3 months of age. Her weight was below the 10th percentile, she had normal psychomotor development and no dysmorphic features. Laboratory investigations are summarized in Table 1. Digestive endoscopy showed severe ulcerative pancolitis with disappearance of the normal vascular markings, visualization of the colonic submucosa and fibrin depositions, particularly in the transverse colon (Fig 1A). Macroscopically, the ileum, esophagus, stomach, and duodenum were normal. Pathologic analysis revealed ulcerated colonic mucosa and a diffuse dense cellular infiltration (Fig 2A). This cellular infiltration was mainly composed of CD3+, CD4+, and CD8+ lymphocytes (Fig 2B and Supplemental Fig 3 A–C); macrophages; and eosinophils. There were also some rare neutrophils. Crypt damage was apparent with increase of apoptosis highlighted by immunostaining with caspase-3 antibody (Supplemental Fig 3D). Gastritis was also present. Blood, urine, and stool culture tests detected no evidence of bacteria; *Clostridium difficile* toxin was absent. Adenovirus, rotavirus, cytomegalovirus, and Epstein-Barr virus were not detected by polymerase chain reaction on stool, blood, and/or colonic samples. Perinuclear antineutrophil cytoplasmic antibodies and antisaccaromyces cerevisiae antibodies were negative. Total parenteral nutrition (TPN) and blood transfusions were required and albumin infusions were administered every 10 days. Intravenous methylprednisolone (1 mg/kg per day for 3 weeks) had no effect. After infliximab infusions (5 mg/kg at day 0, day 15, and then 10 mg/kg at day 45 and at week 8) and tacrolimus treatment (0.5 mg/kg per day), the quantity of blood transfusion requirement and albumin infusions decreased (every 3 weeks). However, the infant still had chronic bloody diarrhea; recurrent febrile attacks with elevated inflammatory markers; and attacks of polyarthritis, edema of hands and feet, and urticarial rash since the age of 9 months. Colonoscopy at the age of 12 months showed left-side colonic stricture and a rectum fistula (Fig 1B and C). Additional studies were carried out to better define and characterize this autoinflammatory syndrome. During febrile attack, urinary excretion of mevalonic acid was elevated (Table 1). MVK enzyme activity in lymphocytes was below 1% and genomic sequencing of the *MVK* gene revealed 2 compound heterozygous mutations: p.[Val377Ile]+[Tyr116His]. The patient’s mother carried the heterozygous p.Tyr116His mutation, whereas the father had heterozygous p.Val377Ile mutation. Anakinra (2 mg/kg per day) treatment was started at the age of 14 months and the administration of infliximab and tacrolimus were stopped. This resulted in clinical remission and improvements in laboratory test results (Table 1) within 30 days. The infant continued to receive TPN infusions, but less, because of oral feeding difficulties. Three months after the start of anakinra, colonoscopy showed complete mucosal healing, and disappearance of both stenosis and fistula (Fig 1D). Inflammatory infiltrate decreased and epithelial cell apoptosis significantly reduced compared with the previous colon biopsies (Fig 2C and D). This digestive improvement and absence of recurrent febrile attacks were reported with a 6-month follow-up.

Patient 2

Patient 2 was a boy born to healthy unrelated parents after an uneventful pregnancy and delivery. He was admitted on the 12th day after birth. He had fever, failure to thrive, persistent diarrhea, and vomiting. There was no documented history of maternal-fetal infections. Physical examination revealed hepatomegaly and mouth ulcers. He had normal psychomotor development and no dysmorphic features. There was a marked elevation of acute phase reactants (Table 1). Blood, cerebrospinal fluid, urine, and stool culture tests detected no evidence of bacteria; the tests for *Clostridium difficile* toxin, rotavirus, and adenovirus in stool were negative. Perinuclear antineutrophil cytoplasmic antibodies and antisaccaromyces cerevisiae antibodies were negative. Treatment with amoxicillin, cefotaxim, and gentamicin was administered. Fever
resolved in 4 days, but diarrhea, abdominal pain, and vomiting were persistent and even worsened since the age of 1 month. TPN was administered. Rectosigmoidoscopy showed aphtoid ulcerations of the sigmoid colon. Upper gastrointestinal endoscopy was normal. Pathologic analysis of duodenal and colonic biopsies revealed deep ulcerations, diffuse and dense infiltration of lymphocytes, and plasma cells in the mucosa. At 5 weeks of age, the patient suffered from shock and enterocolitis. Laparotomy identified inflammation and dilated perforated jejunum with multiple adhesions. Jejunostomy and TPN were required. During the next month, 2 febrile attacks lasting 2 to 4 days occurred. At the age of 2.5 months, intestinal continuity restored after surgery, but the infant suffered from fever up to 39°C, bloating, abdominal pain, and vomiting.

After treatment with intravenous methylprednisolone for 5 days, these symptoms disappeared. During febrile attack, the urinary mevalonic acid level was elevated (Table 1). Genomic sequencing for the \textit{MVK} gene revealed compound 2 heterozygous mutations: p.Gly326Arg+Val377Ile. Each healthy parent has 1 heterozygous mutation. Anakinra (3 mg/kg per day) treatment was started when the infant was 3 months old, and steroid treatment was stopped. This resulted in digestive improvement over a follow-up period of 7 months. TPN was discontinued 5 days after starting anakinra.

**DISCUSSION**

We report here for the first time, to our knowledge, that early-onset severe ulcerative colitis revealing MKD can be treated successfully with anti-IL-1 agents. Biochemical and genetic testing confirmed the diagnosis of MKD in these 2 patients. Urinary excretion of mevalonic acid was elevated in both patients during febrile attacks. Serum immunoglobulin D concentrations were normal in both cases, highlighting the fact that, as previously described, hyperimmunoglobulin D could be absent. Genomic studies of \textit{MVK} revealed missense mutations that have been already reported in patients with MKD, with the p.Val377Ile mutation as the most frequent. Digestive manifestations are frequent during the course of HIDS. They are mostly transient; occur during

<table>
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<th>TABLE 1 Laboratory Investigations at Onset of Digestive Manifestations and During Treatment With Anakinra</th>
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<td><strong>Patient 1</strong></td>
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<td><strong>Before Anti-IL-1</strong></td>
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<td><strong>Erythrocyte sedimentation rate, mm/h</strong></td>
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<td><strong>Protein-C reactive, mg/L</strong></td>
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<td><strong>MVK gene mutations</strong></td>
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**FIGURE 1**

Colonoscopy features from patient 1 before and after the treatment with anakinra. A, Deep colonic ulcerations with white fibrin deposition. B, Orifice of the rectal fistula. C, Stenosis on the left colon. D, Mucosal healing on the left colon 3 months after anakinra therapy.
febrile attacks; and consist of abdominal pain (62% to 85%), vomiting (44% to 70%), and/or diarrhea (65% to 86%). Repeated peritonitis is a rare cause of abdominal adhesions, and some patients may develop moderate colitis or proctitis several years after the onset of HIDS. Jejunal obstruction and intestinal perforation have also been reported in MA. Conversely, in these 2 patients, severe persistent colitis was early onset and revealed MKD, and the absence of neurologic symptoms and dysmorphic features ruled out MA. Clinical features were not absolutely typical in patient 1, who developed febrile attacks only 2 months after the onset of digestive symptoms.

The present report highlights that MKD should be included in the monogenic causes of neonatal-onset severe inflammatory colitis. The most common diagnoses responsible for colonic inflammation in the first few months of life are either allergy or infectious diseases. Other causes can include early-onset inflammatory bowel disease (IBD), autoimmune enteropathies (similar to immune polyendocrinopathy X-linked syndrome, X-linked inhibitor of apoptosis deficiency, and defect in the IL-10/IL-10 receptor), chronic granulomatosis disease, glycogenosis 1b, carbohydrate-deficient glycoprotein syndrome, or Hermansky-Pudlak syndrome. Enteropathy was severe in both patients. Moreover, the presence of transmural inflammation was suggested by the development of a rectal fistula in patient 1 and a jejunal perforation in patient 2. They had mucosal ulceration and a dense inflammatory infiltrate, which were both atypical, so we searched for another etiology.

This report demonstrates for the first time that treatments with anti-IL-1 agents can result in complete disappearance of symptoms in patients with severe inflammatory colitis. Conversely, anti–tumor necrosis factor therapy, which is effective in most cases of severe IBD, resulted in only partial remission of gastrointestinal disorders caused by MKD. Possible efficacy of IL-1 agents to treat and prevent attacks in some patients with MKD has been highlighted. MK is an enzyme committed in the isoprenoid biosynthesis pathway that produces cholesterol and a number of nonsterol isoprenoids, including geranylgeranyl groups. Impairment of this pathway results in a shortage of geranylgeranylated proteins, which induces activation of caspase-1, an enzyme cleaving proIL-1β into its active form. Thus, the increased production of IL-1β in patients with MKD may show a possible link between MKD and inflammation. That was supported by the fact that anti-IL-1 agents were effective against those symptoms that were related to MKD. Recent studies and these 2 cases suggest that MKD is a predisposing cause to the development of some chronic inflammatory diseases responding to anti-IL-1 agents.

This report emphasizes that physicians should consider the diagnosis of MKD in neonates with severe colitis associated with a marked elevation of acute phase reactants, even in the absence of fever and after ruling out the presence of infections. Anti-IL-1 therapy can cause dramatic improvement in symptoms of IBD related to MKD.

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