Germline mutations in the SLC29A3 gene result in a range of recessive, clinically related syndromes: H syndrome, pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome, Faisalabad histiocytosis, and sinus histiocytosis with massive lymphadenopathy. The main symptoms of these diseases are hyperpigmentation with hypertrichosis, sensorineural deafness, diabetes, short stature, uveitis, and Rosai-Dorfman like histiocytosis. Here, we report the case of an 11-month-old boy with early-onset, recurrent episodes of unprovoked fever lasting 7 to 10 days and associated with pericardial effusion, abdominal pain, diarrhea, and inflammation. Physical examination revealed hyperpigmentation with hypertrichosis, dysmorphic features, and spleen and liver enlargement. Failure to thrive, sensorineural deafness, retarded psychomotor development, and a Rosai-Dorfman like cheek lesion developed subsequently. The febrile episodes did not respond to tumor necrosis factor α antagonists and interleukin-1. Sequencing of the SLC29A3 gene revealed a homozygous missense mutation c.1088G>A (p.Arg363Gln). These observations suggest that a newly identified mutation in the SLC29A3 gene may be associated with an autoinflammatory disorder. Genetic defects in SLC29A3 should be considered in patients with autoinflammatory manifestations, recurrent febrile attacks, and 1 or more of the symptoms found in the broad spectrum of SLC29A3-related disorders (especially hyperpigmentation with hypertrichosis). *Pediatrics* 2013;131:e1308–e1313
Monogenic autoinflammatory disorders are characterized by recurrent episodes of fever and inflammatory lesions that mainly affect the skin, joints, bones, eyes, gastrointestinal tract, and heart.1 The number of clinically and genetically identifiable autoinflammatory disorders has grown rapidly over the last decade.2 Here, we report on our observation of an autoinflammatory phenotype in a patient bearing a mutation in the SLC29A3 gene, which encodes the human equilibrative nucleoside transporter 3 (hENT3).

CASE REPORT

Our patient, an 11-month-old boy, had been born to Tunisian first-cousin parents after 38 weeks of uncomplicated pregnancy. The child’s growth was normal until the age of 9 months, when he developed recurrent, idiopathic, febrile episodes. At 11 months of age, he was referred by our hospital’s cardiology department to our tertiary pediatric rheumatology center for evaluation of this periodic fever syndrome. The patient typically experienced 1 febrile episode per quarter. Each episode lasted for 7 to 10 days and was characterized by intense fever (39°C), pericarditis, joint pain, abdominal pain, and/or diarrhea. There were no obvious triggering factors. Laboratory tests revealed a marked elevation of acute-phase reactants during the febrile episodes, including an erythrocyte sedimentation rate (ESR) of between 88 and 120 mm/hour (normal values: <25 mm/hour), a C-reactive protein (CRP) level of between 120 and 354 mg/L (normal values: <5 mg/L), a white blood count of 7–19.4 × 10^9/L (normal range: 6–17 × 10^9/L), IgG levels of 12.9–21.8 g/L (normal range: 4.82–8.96 g/L), and IgA levels of 1.31–2.88 g/L (normal range: 0.33–1.22 g/L). Some attacks were more severe than others and were associated with severe anemia (lowest measured hemoglobin level: 5.4 g/dL). During and between attacks, physical examinations also revealed liver and spleen enlargement, hypertrichosis, hyperpigmented sacral spots (Fig 1), and dysmorphic features. The latter included a triangular face, macrocrania, ptosis, exophthalmia, posteriorly rotated ears, pectus excavatum, wide-set nipples, umbilical hernia, bilateral cryptorchidism, short, square hands, and a sacrococcygeal dimple. Levels of acute-phase reactants did not normalize between the febrile episodes: the CRP level varied between 17 and 137 mg/L, and the ESR varied between 33 to 120 mm/hour. At the age of 2, radiographs revealed wide ribs with intramedullar infiltration; femurs were large without hyperostosis at the onset of the disease, then became curved with metaphyseal flaring, diaphyseal cortical hyperostosis, and flattened epiphysis (Fig 1). Skull radiographs revealed thickening of the calvaria (especially in the frontal and occipital areas) and moderate brachycephaly. Cross-sectional imaging revealed

**FIGURE 1**
Clinical and radiologic data. A, Sacral hyperpigmented spots. B, Skeletal radiographs at the age of 2 years: wide ribs with intramedullar infiltration; large femurs without hyperostosis. C, Skull radiographs at the age of 2 years: frontal and occipital thickening of the calvaria and moderate brachycephaly. D, Cerebral MRI at the age of 20 months (left: bone thickness pointed by arrows 17.4 mm) then 37 months (right: bone thickness pointed by arrows 24.6 mm): thickening and heterogeneous signal of bone marrow. E, Cerebral CT scan at the age of 6 years: thickening and dappled, ground grass infiltration of bone marrow, without cortical hyperostosis.
midface, periorbital, and skull base abnormalities, such as a thickened, heterogeneous bone marrow signal on MRI, thickening and dappled, ground-glass infiltration of the bone marrow (in the absence of cortical hyperostosis) on a computed tomography (CT) scan (Fig 1). The patient failed to thrive (weight, −3 SD; height, −3 SD) and developed psychomotor development delay. Blindness (resulting from anterior uveitis and glaucoma) and bilateral sensorineural hearing loss occurred at 22 and 36 months of age, respectively. All known causes of genetic autoinflammatory syndromes (MEFV, NALP3, MVK, NALP12, and TNFRSF1) were ruled out by sequencing. Lastly, a subcutaneous cheek lesion developed at the age of 4 years and 9 months. Biopsy specimens displayed specific features of Rosai-Dorfman like histiocytosis, with the presence of polymorphous inflammatory cells (lymphocytes, plasma cells, and, in particular, abundant histiocytes with pale cytoplasm and, in some cases, signs of emperipolesis). These histiocytes were positive for CD68 and S100 protein but were negative for CD1a. Our observation of Rosai-Dorfman histiocytosis, hyperpigmented, hypotrichotic cutaneous patches, and sensorineural hearing loss prompted us to screen for mutations in the SLC29A3 gene. Genetic testing (performed after the provision of informed consent by the patient’s parents) revealed a homozygous mutation c.1088G>A (p.Arg363Gln) in both directions in exon 6 of the SLC29A3 gene. Both parents were found to be heterozygous for this mutation. Colchicine (1 mg per day for 1 year), anakinra (5 mg/kg per day for 18 months), canakinumab (4 mg/kg per month for 4 months), and adalimumab (24 mg/m² every 15 days for 6 months) were successively tested and did not decrease the frequency or severity of the episodes and thus were withdrawn. In contrast, administration of nonsteroidal antiinflammatory drugs from the age of 5 did produce a decrease in the frequency of the episodes. At the latest evaluation (at the age of 7 years and 4 months), the patient had experienced 1 febrile attack per year (in the absence of pericarditis) and was suffering from aregenerative anemia (requiring regular blood transfusions). Blood and bone marrow samples tested negative for parvovirus B19 in a polymerase chain reaction assay. A bone marrow aspiration evidenced signs of dyserythropoiesis but no granular dysplasia. A mild inflammatory syndrome persisted (CRP: 90 mg/dl; ESR: 98 mm).

**DISCUSSION**

Here, we reported on an autoinflammatory syndrome in a patient carrying a homozygous missense mutation in the SLC29A3 gene. The syndrome was characterized by recurrent episodes of fever and inflammation, together with pericarditis, abdominal pain, and diarrhea. These observations suggest that SLC29A3-related disorders could be added to the ever-expanding list of monogenic periodic fever syndromes. A large number of clinically identifiable autoinflammatory disorders have been genetically characterized over the last decade. SLC29A3-related autoinflammatory manifestations share some clinical and biological features with chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal onset multisystem inflammatory disease [NOMID]), including dysmorphic facial features, growth and psychomotor retardation, hearing loss, severe anterior uveitis, and bone involvement. Furthermore, persistent leukocytosis and elevation of acute-phase reactants (as observed in our patient) are present in most cases of CINCA/NOMID syndrome. However, the 2 diseases differ significantly in terms of the bone involvement and the response to anti-interleukin-1 (IL-1) agents. In the present case, we observed SLC29A3-related bone manifestations consisting of (1) wide long bones with intramedullar infiltration, metaphyseal flaring, diaphyseal cortical hyperostosis, and a flattened epiphysis and (2) thickening of the calvaria. This situation differs from the overgrowth of the patella and long bone epiphyses (resulting in major joint deformities) that has been reported in some patients with CINCA. Furthermore, the lack of efficacy of anti-IL-1 agents (including canakinumab, a human monoclonal antibody) in our patient contrasted with the sustained remission of most of the symptoms associated with severe IL-1-mediated inflammation in most treated patients with cryopyrin-associated periodic syndrome. The pivotal role of IL-1 in cryopyrin has been evidenced in most of the genetically identified autoinflammatory syndromes, including cryopyrin associated periodic syndrome, IL-1 receptor antagonist deficiency, NALP12-associated periodic fever syndrome, familial Mediterranean fever, mevalonate kinase deficiency, and hyper-IgD syndrome. However, the involvement of other inflammatory pathways was recently highlighted in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome and other syndromes resulting from immunoproteasome dysfunction, all of which are associated with a prominent interferon signature. The complete lack of efficacy of anti-IL-1 agents in our patient suggests that SLC29A3 mutations result in an autoinflammatory syndrome (which is not an IL-1-mediated disorder).

The clinical spectrum of SLC29A3 disorders (Online Mendelian Inheritance in Man #602782 for all subtypes) currently encompasses a broad range of overlapping clinical features and inherited disorders, including H syndrome (hyperpigmentation, hypotrichosis, hepatomegaly, heart abnormalities, hearing...
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<th>Table 1 Phenotype of Patients Already Reported in the Literature With SLC29A3 Mutations</th>
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<td><strong>Faisalabad Histiocytosis</strong></td>
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<td><strong>Puberty delay</strong></td>
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<td><strong>Exocrine pancreatic insufficiency/diabetes mellitus</strong></td>
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<td><strong>Anatomopathology</strong></td>
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<td><strong>Lymphoid follicles and histocytes in dilated sinus RDD-similar</strong></td>
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NR, not relevant; PHID, pigmented hypertrichosis with insulin-dependent diabetes mellitus; RDD, Rosai-Dorfman disease; SHML, familial sinus histiocytosis with massive lymphadenopathy; +, reported; −, not reported.
cases of SLC29A3 defects, and there is no obvious relationship between the severity of tissue involvement and the levels of SLC29A3 expression. A recent study of ENT3 knock-out (ENT3−/−) mice highlighted the role of macrophages in the pathogenesis of the SLC29A3 defects. The animals developed spontaneous lymphadenopathy and splenomegaly as a result of macrophage proliferation. However, ENT3−/− mice have normal serum levels of inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor α). Regulated on Activation, Normal T Expressed and Secreted (RANTES), Monocyte Chemoattractant Protein-1 (MCP-1), and Macrophage Inflammatory Protein 1 alpha (MIP-1α), and their macrophages display the same surface activation markers (CD80, CD83, CD86, CD40, and CD89) as wild-type animals. Hence, further studies are needed to understand the mechanism that underlies autoinflammatory symptoms in SLC29A3-associated disorders.

The fact that this is a single case report limits our ability to extrapolate our findings and definitively prove that autoinflammatory symptoms are associated with SLC29A3 mutation. However, the elevation of acute-phase reactants has been observed in several patients with SLC29A3 disorders and suggests that genetic testing for SLC29A3 mutations should be considered in patients presenting with both recurrent febrile episodes and hyperpigmented, hypertrichotic lesions.

CONCLUSIONS

Our report further expands the clinical spectrum of SLC29A3 disorders and suggests that genetic testing for SLC29A3 mutations should be considered in patients presenting with both recurrent febrile episodes and hyperpigmented, hypertrichotic lesions.

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