

BRIEF REPORT

Allogeneic Bone Marrow Transplantation in Mevalonic Aciduria

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SUMMARY

Mevalonic aciduria is a rare, inborn error of isoprene biosynthesis characterized by severe, periodic attacks of fever and inflammation, developmental delay, ataxia, and dysmorphic features. This autosomal recessive disease is caused by a mutation in the mevalonate kinase gene that severely reduces mevalonate kinase activity. A 3-year-old boy with mevalonic aciduria whose condition had failed to improve with anti-inflammatory treatment underwent allogeneic bone marrow transplantation from an HLA-identical sister who was a heterozygous carrier of the mutant gene. We observed sustained remission of febrile attacks and inflammation during a 15-month follow-up period.

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MEVALONIC ACIDURIA (NUMBER 251170 IN THE MENDELIAN INHERITANCE IN MAN [MIM] DATABASE) is a rare inborn error of isoprene biosynthesis.¹⁻⁵ The typical clinical picture in children is one of recurrent attacks of fever, developmental delay, ataxia, dysmorphic features, failure to thrive, cataracts, and retinal dystrophy.³ The prognosis for patients with mevalonic aciduria is poor; more than 50% of patients die during an inflammatory crisis in infancy or early childhood, and very few survive to adolescence.⁶ This autosomal recessive disease is caused by a severe deficiency of mevalonate kinase (residual activity, <1%) that results from a mutation in the mevalonate kinase gene.⁷ Mevalonate kinase is ubiquitously expressed and plays a crucial role in the early stages of the isoprenoid biosynthesis pathway. The enzyme catalyzes the phosphorylation of mevalonic acid to 5-phosphomevalonate. The main end products include prenylated proteins, heme A, dolichol, ubiquinone (coenzyme Q-10), and cholesterol. As a result of mevalonate kinase deficiency, mevalonic acid accumulates and is excreted in the urine.

Mutations in the same gene are also responsible for the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) (MIM number 260920),^{8,9} an autosomal recessive disorder characterized by recurrent febrile attacks.¹⁰ Classically, HIDS is not associated with dysmorphic features or neurologic impairment. In addition, mevalonic acid is excreted in the urine only during febrile attacks, and mevalonate kinase activity is less severely impaired in HIDS than in mevalonic aciduria (residual activity, >1%).^{11,12} In a subgroup of patients with HIDS, neurologic abnormalities (e.g., mental retardation, ataxia, and epilepsy) may develop with increasing age.^{5,6} These findings suggest a continuum between mevalonic aciduria and HIDS. The two syndromes belong to the group of autoinflammatory syndromes,

all of which are characterized by recurrent episodes of inflammation without major involvement of the adaptive immune system.

The treatment of mevalonate kinase deficiency is mainly supportive. Treatment with simvastatin (an inhibitor of hydroxymethylglutaryl coenzyme A reductase, the enzyme that catalyzes the formation of mevalonic acid) worsened the clinical status of two patients with mevalonic aciduria.¹³ The drug has also been tested recently in six patients with HIDS, five of whom had a reduction in the number of febrile days.¹³ Anakinra, an interleukin-1-receptor antagonist, and tumor necrosis factor α (TNF- α) antagonists (e.g., etanercept) have also been used with a degree of success in patients with HIDS.¹⁴

The mechanism by which mevalonate kinase deficiency causes recurrent episodes of fever and inflammation is unclear. Serum levels of proinflammatory cytokines increase during attacks, and mononuclear cells from patients with HIDS produce high levels of interleukin-1 β after in vitro stimulation.¹⁵ Given the role of inflammation in the pathogenesis of mevalonate aciduria and HIDS, we hypothesized that replacement of the hematopoietic system by allogeneic bone marrow transplantation from a healthy donor with genetically identical HLA would improve symptoms of inflammation in a patient with mevalonic aciduria.

CASE REPORT

A 3-year-old boy, born to consanguineous parents, received a diagnosis of mevalonic aciduria at the

age of 3 months. His intrauterine growth had been retarded, leading to a low birth weight (2.5 kg, or <2 SD below the mean), a reduced length (46 cm, or <2 SD below the mean), and a reduced head circumference (33.5 cm, or 2 SD below the mean). At birth, the main clinical features were fever, hepatosplenomegaly, signs of hepatitis, anemia, thrombocytopenia, and elevated serum levels of markers of inflammation (Table 1). He had recurrent, life-threatening episodes of fever about every 2 weeks. Failure to thrive during the first year of life required enteral feeding. Hepatosplenomegaly persisted, and the boy had mildly dysmorphic features. His psychomotor milestones were somewhat delayed, with axial hypotonia, a small motor delay, and a slightly ataxic gait. His neuropsychologic evaluation (on the Brunet-Lezine scale) showed a normal overall developmental quotient, at 87.

Magnetic resonance imaging (MRI) of the brain at the age of 7 months showed ventricular dilatation but no other supratentorial or posterior fossa anomalies. Serum C-reactive protein levels and the erythrocyte sedimentation rate were persistently high, as were levels of proinflammatory cytokines (interferon- γ , TNF- α , interleukin-1 β , and interleukin-6) (Table 1). Cellularity in the cerebrospinal fluid was normal, whereas levels of proinflammatory cytokines (especially TNF- α) were highly elevated during attacks.

The diagnosis of mevalonic aciduria was established on the basis of persistently elevated levels of mevalonic acid in urine, as determined by capillary gas chromatography followed by iden-

Table 1. Clinical and Biologic Features before and after Bone Marrow Transplantation.*

| Feature | Before Transplantation | After Transplantation | | |
|--|------------------------|-----------------------|------|-------|
| | | 3 Mo | 6 Mo | 12 Mo |
| Febrile attacks | Every 2 to 3 wk | None | None | None |
| Hepatosplenomegaly | Persistent and severe | Mild | Mild | None |
| C-reactive protein (mg/liter) | 80–250 | 6 | 6 | 6 |
| Tumor necrosis factor α (pg/ml) | | | | |
| In serum | 50–120 | 7.6 | ND | 26 |
| In cerebrospinal fluid | 5–60 | 15 | ND | ND |
| Interleukin-1 β in serum (pg/ml) | 1–70 | 4.2 | ND | 4.5 |
| Mevalonate kinase activity in lymphocytes (% of normal controls) | 0.6 | ND | 15.0 | 64.0 |
| Mevalonic acid in urine (mmol/mole of creatinine) | 40–180 | 34 | 17 | 15 |

* Normal laboratory values are as follows: C-reactive protein, less than 6 mg per liter; tumor necrosis factor α in serum and cerebrospinal fluid, 0 to 20 pg per milliliter; and serum interleukin-1 β , 0 to 15 pg per milliliter. ND denotes not determined.

tification and quantification with an ion trap (Saturn 2000, Varian). Mevalonate acid in the urine increased up to 180 mmol per mole of creatinine during febrile attacks and dropped to 40 mmol per mole of creatinine during remission. Mevalonate kinase activity in the patient's lymphocytes was severely impaired, as compared with lymphocytes from healthy controls (Table 1). Molecular analysis revealed the homozygous missense mutation 976G→A in exon 10 of the mevalonate kinase gene, leading to the substitution of arginine for glycine at position 326 at the protein level (G326R).

The TNF- α inhibitor etanercept (at a dose of 0.4 mg per kilogram of body weight) was administered twice a week for 3 months but had almost no effect on the febrile attacks. Anakinra, an interleukin-1 receptor antagonist, was given for 6 months, with a maximum dose of 1 mg per kilogram per day subcutaneously; there was a partial response to this treatment. Administration of anakinra at a higher dose caused liver abnormalities.

Given the child's severe condition and the poor prognosis with this disease, we suggested bone marrow transplantation from an HLA-identical sister who was heterozygous for the 976G→A mutation. The parents gave their written informed consent for the procedure, which was approved by the ethics committee at Necker Hospital. The conditioning regimen consisted of busulfan (at a dose of 19.2 mg per kilogram) and cyclophosphamide (200 mg per kilogram). Prophylaxis against graft-versus-host disease (GVHD) consisted of cyclosporine (at an initial dose of 3 mg per kilogram per day, given as a continuous intravenous infusion before transplantation, and then orally after 1 month for 5 months) and methotrexate (at 15 mg per square meter of body-surface area beginning 1 day after transplantation and 10 mg per square meter on days 3, 6, and 11). Cyclosporine was stopped 1 month after transplantation because of a suspected microangiopathy and was replaced by mycophenolate mofetil (60 mg per kilogram per day given orally from day 35 to day 120 after transplantation). Anti-inflammatory treatment with anakinra (1 mg per kilogram per day given subcutaneously) was maintained until day 25 after transplantation.

The patient received 26.2×10^6 CD34 cells per kilogram from his HLA-identical sister in December 2005. The clinical course after bone marrow

transplantation was relatively uneventful. Streptococcal sepsis occurred during the aplastic phase and was successfully treated with antibiotics. Hematologic recovery was achieved on day 21 after transplantation, with 96% donor chimerism (as judged by the detection of X and Y chromosomes by fluorescence in situ hybridization of peripheral-blood leukocytes). Neither acute nor chronic GVHD occurred. Immunosuppressive drugs were stopped 4 months after transplantation.

Fifteen months after transplantation, the child had not had a recurrence of fever or inflammatory attacks. Inflammatory markers in serum returned to normal levels after hematologic recovery. Levels of proinflammatory cytokines in serum and cerebrospinal fluid also returned to normal (Table 1). Urinary mevalonate acid levels decreased from 34 mmol per mole of creatinine at 3 months to 15 mmol per mole at 12 months. Levels of mevalonate kinase activity in lymphocytes 6 months and 12 months after bone marrow transplantation were 15% and 64%, respectively, as compared with lymphocytes from healthy controls, whereas the activity in the donor's lymphocytes was 50%. The 100% donor chimerism was stable up to the last analysis, performed 12 months after transplantation. Neurologic and psychosocial examinations performed 15 months after transplantation showed a slight, persistent ataxic gait and good language skills. MRI of the brain performed 10 months after transplantation showed no change from the pretransplantation scan.

DISCUSSION

The diagnosis of mevalonic aciduria in our patient was confirmed on the basis of persistent mevalonic aciduria, a very low level of mevalonate kinase activity in the lymphocytes, and the identification of a homozygous mutation in the mevalonate kinase gene (G326R). This mutation corresponds to a region between amino acids 234 and 334 in the enzyme, where all mutations identified thus far in mevalonic aciduria are clustered. It is close to a highly conserved region with characteristics of an ATP-binding site between amino acids 329 and 344.⁷ Transplantation was proposed because of the neonatal onset, the severe clinical course, and the life-threatening, recurrent febrile episodes despite antiinflammatory therapies. The bone marrow transplantation procedure itself was relatively uneventful; there were no unforeseen

complications. Full, stable chimerism was shown by *in situ* hybridization for X and Y chromosomes in peripheral-blood samples. Mevalonate kinase activity in blood lymphocytes increased from 0.6% before transplantation to 64.0%, as compared with control lymphocytes, a year afterward, a level similar to that found in the heterozygous sister. During the same period, we observed a decrease by a factor of 10 in mevalonic acid excretion in the urine.

The patient's clinical condition improved dramatically immediately after bone marrow transplantation. In addition, all the biologic markers of inflammation returned to normal values in the month after transplantation and remained normal up to the last follow-up visit, 15 months after transplantation. This sustained effect was clearly not due to the immunomodulatory effects of the conditioning regimen and the immunosuppressive drugs used for GVHD prophylaxis. Instead, it was probably the consequence of readily detectable mevalonate kinase activity in hematopoietic cells. All the inflammatory symptoms disappeared, even though low levels of mevalonic acid were still detectable in the urine. Since mevalonate ki-

nase is ubiquitously expressed, the residual mevalonic aciduria was probably due to the persistence of mevalonate kinase deficiency in nonhematopoietic cells.

The clinical manifestations of mevalonic aciduria that occur in sites outside the hematopoietic system may result from accumulation of mevalonic acid or the absence of downstream products. However, we cannot rule out the possibility that they also result from inflammation. The long-term effects of bone marrow transplantation on cells and tissues outside the hematopoietic system are unknown and warrant further follow-up. The optimal conditioning regimen also remains an open matter. The use of anakinra during the procedure in this patient might have prevented early complications of transplantation (notably GVHD) associated with elevated levels of proinflammatory cytokines. At this stage, the procedure is investigational and potentially applicable to patients with mevalonic aciduria whose condition is resistant to therapy with antiinflammatory drugs (e.g., inhibitors of TNF- α and interleukin-1 β).

No potential conflict of interest relevant to this article was reported.

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