Long-term Outcome of a Successful Cord Blood Stem Cell Transplant in Mevalonate Kinase Deficiency

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive inborn error of metabolism with an autoinflammatory phenotype that may be expressed as a spectrum of disease phenotypes, from those with prevailing autoinflammatory syndrome and variable response to anti-inflammatory therapies, to mevalonic aciduria, which is associated with dysmorphic features, severe neurologic involvement, and the worst prognosis. We describe a boy, aged 2 years, 10 months, with severe phenotype of mevalonate kinase deficiency who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from HLA-identical unrelated cord blood because his condition had failed to improve with antiinflammatory treatment as first-line therapy and an anticytokine drug as second-line therapy. The child had a sustained remission of febrile attacks and inflammation after transplant, and during a 5-year follow-up period, psychomotor and neurologic development were normal, without signs of underlying disease or late transplant-related effects. This case confirms that allogeneic HSCT is a safe and effective cure for patients affected by MKD in whom anticytokine drugs alone are insufficient for the management of autoinflammatory syndrome and for the unfavorable outcome of the disease.

Mevalonate kinase deficiency (MKD)[1] is a rare disease caused by recessive loss-of-function mutations of the MK gene.[2] The first phenotype associated with this defect, called mevalonic aciduria (MA), was recognized 30 years ago through organic acid analysis of urine via gas chromatography/mass spectrometry (Online Mendelian Inheritance of Man entry 610377).[3,4] Clinical manifestations of MA show dysmorphic features, cataracts, retinopathy, developmental delay associated with ataxia and dysarthria in the first years of life, recurrent crises of fever associated with hepatosplenomegaly, lymphoadenomegaly, arthritis, uveitis, diarrhea, vomiting, skin rash, and increased acute-phase reactants.[5–7] The prognosis of patients with MA is usually severe: >50% of infants or young children die during a severe multisystemic inflammatory attack. Mevalonate kinase deficiency has also been identified as the cause of an autoinflammatory periodic syndrome called hyperimmunoglobulinemia D (HIDS) or Dutch-type periodic fever syndrome.[8] Patients with HIDS have no dysmorphic or neurologic impairment and display urine excretion of mevalonic acid only during febrile crises (Online Mendelian Inheritance of Man entry 260920).[9,10] Patients with MA display an almost complete enzyme deficiency, whereas patients with HIDS have consistent residual enzymatic activity (up to 30%). Two mutations account for the majority of mutant alleles: the V377I variant is associated with considerable residual enzymatic

abstract

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Dr Giardino managed the patient from the pretransplant period to the present, contributed to the conception and design of the article, drafted the initial manuscript, and conducted the review of the literature; Drs Lanino managed the patient from the pretransplant period to the present, contributed to the conception and design of the article, and reviewed and revised the manuscript; Drs Morreale and Faraci managed the patient from the pretransplant period to the present and contributed to the conception and design of the article; Drs Di Rocco and Gattorno played a central role in diagnosis and management of the patient before the transplant and reviewed the manuscript; Dr Madeo contributed to data collection; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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activity and an HIDS phenotype; the I268T mutation, in contrast, is associated with low residual enzymatic activity and a severe phenotype, especially when the patient is homozygous. Many intermediate phenotypes or unusual presentations[11,12] have been reported in the literature. Therefore, it is better to consider deficiencies in mevalonate kinase as a spectrum of disease phenotypes, with MA lying at the severe end and HIDS at the other[13–15] Antiinflammatory therapies, such as steroids and nonsteroidal antiinflammatory drugs and anticytokine agents including antiinterleukin (IL)-1-β (anakinra, canakinumab, rilonacept) and tumor necrosis factor-α (infliximab, etanercept) monoclonal antibodies, together with supportive care, may control symptoms and reduce the frequency and severity of febrile attacks.[14–21] Their inefficacy in severe phenotypes, however, has frequently been reported.[9,14,23]

Hematopoietic stem cell transplantation (HSCT) represents a consolidated treatment of several hematologic, immunologic, and metabolic inborn errors in children, but only 3 cases of MKD patients treated with HSCT are reported in the literature.[25–27]

This report describes the long-term outcome 5 years after a successful unrelated cord blood (UCB) stem cell transplant in a child affected by MA.

CASE REPORT

We report a male child, born at 37 weeks' gestation after twin monochorionic pregnancy to consanguineous parents of Syrian origin, affected by severe MKD who underwent UCB HSCT at the age 2 years, 10 months.

Intrauterine growth had been delayed, resulting in low birth weight, reduced length, and reduced head circumference. During the neonatal period, the infant presented perimalleolar cellulitis and severe acute enteritis with negative microbiologic assessment with fever and consistent elevation of acute-phase reactants that did not respond to antibiotics, hepatosplenomegaly, and microcytic anemia. Anemia persisted with positive direct antiglobulin test and hepatosplenomegaly, and thus at age 4 months the patient received oral steroid therapy, which led to improvement of hemoglobin values and general conditions.

Precise information concerning the subsequent period is lacking, but recurrent episodes of fever and polyarthritis without clear infective pathogenesis and transient response to steroid therapies were reported.

At age 18 months, the twin brother, during unremitting fever, developed progressive multiorgan failure and died from severe bleeding after a liver biopsy, which showed an unspecific chronic inflammatory infiltrate also observed in the synovial membrane.

At age 2 years, the patient was admitted to our institution. Clinical features are reported in Table 1. An autoinflammatory disease was suspected, and diagnosis of MKD was suggested by clinical features and confirmed by molecular analysis, which revealed a homozygous mutation c.32G>A(p.V8M) of the MVK gene. Mevalonic acid in urine, detected during fever-free interval, was slightly above normal values (23 μmol/mmol of creatinine; normal value <20 μmol/mmol of creatinine), but high levels, typical of classic phenotype of MA, were never detected.

First-line therapy with ibuprofen, prednisone, and supportive care allowed initial clinical and biohumoral improvement; however, these therapies proved insufficient to prevent subsequent attacks of fever. A recombinant IL-1 receptor antagonist (anakinra), added at a dosage of 1.5 mg/kg/daily administered subcutaneously, led to a partial response but was discontinued 1 month later after the onset of severe pneumonia and sepsis caused by *Streptococcus pneumoniae.*

Allogeneic-HSCT was considered the only curative therapy for this patient. Because no related donor was available, a human leukocyte antigen (HLA) -A, -B, -DRB1 matched UCB was selected, and HSCT was performed at age 2 years, 10 months. Transplant features, early complications, and therapeutic interventions are summarized in Table 2.

Neutrophil engraftment was achieved on day 22 after HSCT, platelet engraftment on day 61, with complete

TABLE 1 Clinical Features

Time Point	Clinical Features
At birth (reported)	Wt: 1970 g, <2 SD below the mean Length: 43 cm, <2 SD below the mean Head circumference: 31.5 cm, <2 SD below the mean
Neonatal period (reported)	Fever, elevation of acute phase reactants, perimalleolar cellulitis and severe acute enteritis with no proven infections, no response to antibiotic therapies, hepatosplenomegaly, microcytic anemia
First 2 y of life (reported)	Recurrent attack of fever and polyarthritis without proven infective pathogenesis
At admission to our institute	Severe hypotonia; failure to thrive (below the third percentile for height and weight); atypical craniofacial dysmorphisms (dolichocephaly, frontal bossing, exophthalmos, hypertelorism); microcytic anemia; severe polyarthritis (responsive to steroid therapy); hepatomegaly and splenomegaly; mild psychomotor delay, MRI of CNS: slight aspecific cerebral hypotrophy (probably related to prolonged steroid treatment)

CNS, central nervous system; MRI, magnetic resonance imaging.

TABLE 2 Treatments

Multidrug Antiinflammatory Therapy	Results, Reason for Failure, and Early Complications	
First line		
Ibuprofen + prednisone	Clinical and biohumoral improvement; no prevention of attacks of fever with steroid dependence	
Second line		
Recombinant IL-1 receptor antagonist (Anakinra)	Partial response; severe pneumonia and sepsis	
Allogeneic HSCT (third line therapy)		
Conditioning regimen	Busulfan (16 mg/kg), Cyclophosphamide (200 mg/kg).	
GvHD prophylaxis	Cyclosporin A, ATG (thymoglobulin), MPD 0.5 mg/kg from day +7	
Stem cell source and cell dose	Unrelated cor blood: HLA matching: 6/6; nucleated cells 12.5 $\times$ 10^7/kg; CD34+ cells 0.64 $\times$ 10^6/kg	
Early Complications After Allogeneic HSCT		
Infective complications	Toxicity	Immunologic
• streptococcal sepsis	• oral mucositis (WHO grade 2)	• acute cutaneous GvHD grade 2 steroid resistant
• pulmonary aspergillosis	• thrombotic microangiopathy and PRES due to calcineurin-inhibitor	
• reactivation of cytomegalovirus		

ATG, antithymocyte globulin; HLA, human leukocyte antigen; MPD, methylprednisolone; PRES, posterior reversible encephalopathy syndrome; WHO, World Health Organization.

donor chimerism (short tandem repeat) from day 30, further confirmed every 6 months during the first 5 years after HSCT. Forty days after transplant, the child developed cutaneous acute graft-versus-host disease (GvHD), which resolved after steroids and extracorporeal photochemotherapy.

A complete immunologic recovery (CD4 $>$ 500/mmc) with no further need for immunoglobulin replacement therapy was achieved 6 months after HSCT. The immunosuppressive therapies were stopped 12 months after HSCT, without signs of chronic GvHD and in the presence of stable full donor chimerism.

After HSCT, no episodes of fever triggered by inflammatory activation occurred.

Currently, 5 years after HSCT, clinical conditions and quality of life are good, with normal psychomotor and neurologic development. He is now 7 years old and regularly attends age-appropriate school and speaks fluently. MRI of the brain performed 1 year after HSCT was normal.

Over the years, the child has shown an adequate growth rate, reaching the third percentile for height and weight, although it is 1.6 SD below the genetic target score and his bone age is delayed by 2 years. We observed a progressive improvement and dramatic reduction of dysmorphic features and organomegaly.

DISCUSSION

To the best of our knowledge, this is the first reported case of HSCT from UCB performed in a patient affected by MKD.

Other authors have described their experiences on the therapeutic management of MKD with statins,[16] high-dose glucocorticoids, antitumor necrosis factor-α agents,[17,18] the recombinant homolog of the human IL-1 receptor antagonist anakinra,[19–21] and canakinumab, a human monoclonal antibody directed against IL-1-β.[22,23]

Recently, in a prospective observational study, anakinra treatment was used on demand during febrile attacks in 8 HIDS patients, with reduction of the duration and severity, but not the frequency, of acute inflammatory attacks.[24] The same effect is normally not observed in the more severe form of MA, usually characterized by a chronic inflammatory course that becomes steroid-dependent. At present no replacement therapy is able to correct the severe metabolic defect of MA or to prevent the development of the severe neurologic complications and dysmorphic features.

Neven et al[25] described the first child, aged 3 years, with MA who had obtained control of the autoinflammatory disorder after allogeneic HSCT from a human leukocyte antigen–identical sibling donor, although ataxic gait persisted, reflecting unremitting neurologic damage. Two other children undergoing allogeneic HSCT for HIDS have been reported: the first case with a mild phenotype[26] received HSCT from a sibling donor; the second case[27] had more severe features, including renal and liver failure, and received a liver transplant before HSCT. The authors described the effectiveness of allogeneic HSCT in both patients, with general improvement and without significant neurologic disability after the procedure.

The purpose of HSCT in MKD is to correct the autoinflammatory condition, preventing organ damage and life-threatening events, by replacing the immune system and providing a valid source of the missing enzyme in patients with neonatal onset and severe clinical course despite antiinflammatory therapies. In our patient, the diagnosis was delayed because of

unclear onset and a discontinuous medical support during the first 2 years of age. Allogeneic HSCT was performed because of his severe clinical status, which progressively worsened despite multidrug antiinflammatory treatment, including anakinra.

Our patient did not develop severe acute complications after HSCT, except for posterior reversible encephalopathy syndrome due to calcineurin-inhibitors and mild acute GvHD, that was responsive to steroids and extracorporeal photochemotherapy.

The success of HSCT in our patient is demonstrated by the normalization of inflammatory and MKD biomarkers, prolonged remission of febrile attacks, dramatic improvement in organ function, and reduction of dysmorphic features with normal growth and progressive recovery of psychomotor development. Long-term follow-up (5 years after HSCT) documents a child in good clinical condition, with good quality of life and normalized growth curve and psychomotor skills, without neurologic sequela.

In our opinion, this case is relevant because it confirms that anticytokine drugs alone are not sufficient for the management of patients with severe MKD phenotype and that allogeneic HSCT remains the only effective cure.

Pivotal to the success of HSCT in the treatment of MA is the timing of the procedure, when neurologic involvement has not occurred and organ damage is not yet relevant. Contrary to the first description by Neven et al, despite a considerable delay in diagnosis, at the time of HSCT, our patient did not display severe neurologic or ocular involvement but only mild psychomotor delay. Conversely, the child's clinical picture was characterized by a severe and uncontrolled multiorgan inflammatory condition. Therefore, HSCT could be considered not only in the most severe cases of MKD (ie, MA), but also in intermediate conditions dominated by inflammatory complications, especially when an aggressive biological anticytokine treatment proves ineffective.

In our experience, a conditioning regimen based on busulfan and cyclophosphamide was followed by complete and stable donor engraftment, with acceptable acute and without significant late toxicity. However, since the late onset toxicity after busulfan is well-known,[28] using drugs with lower toxicity profile, but preserved myeloablative properties that allow engraftment,[29,30] could represent a topic of discussion in HSCT for autoinflammatory diseases.[31]

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