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SCIENTIFIC LETTERS

Haematopoietic stem cell transplantation in pyruvate kinase deficiency: When is it indicated?☆

Trasplante de progenitores hematopoyéticos en déficit de piruvato cinasa: ¿cuándo indicarlo?

Dear Editor:

Pyruvate kinase (PK) deficiency is a congenital non-spherocytic haemolytic anaemia characterised by chronic haemolysis that can lead to transfusion dependence. The complications associated with haemolysis, such as cholelithiasis, skin ulcers, folate deficiency or iron overload secondary to transfusion support, are frequent.[1,2]

In severe cases, splenectomy improves the anaemia and reduces the need for transfusions, although it has been associated with an increased risk of thrombosis. The recent literature includes descriptions of cases treated with haematopoietic stem cell transplantation (HSCT) that cured the disease.[2,3]

We present the case of a female patient with anaemia secondary to PK deficiency that underwent transplantation at age 17 years after developing recurrent thromboembolic disease and pulmonary hypertension, which were probably associated with the previous splenectomy.

The patient, who has been described in a previous publication,[4] received an antenatal diagnosis of PK deficiency through umbilical cord blood sampling. Her parents, who were consanguineous and both had a heterozygous mutation in the PK gene, had lost 3 previous children to severe neonatal haemolytic anaemia. The patient developed transfusion-dependent anaemia in the early years of life and underwent splenectomy at age 3 years. Chronic anaemia and hyperbilirubinaemia persisted, and the patient required occasional transfusions that were followed by post-transfusional deferoxamine.

At 14 years she developed extreme thrombocytosis, with more than 1 000 000 platelets per μL, which responded to treatment with hydroxyurea. This was associated with familial hypertriglyceridemia and hypercholesterolaemia and hyperuricaemia. After experiencing several episodes

of acute respiratory failure and heart failure secondary to severe pulmonary hypertension, she received a diagnosis of pulmonary embolism, and required oxygen supplementation at home.

At age 17 years, and given her increased need for transfusions, the possibility of HSCT was contemplated once more, and the donor search focused on relatives outside the nuclear family, as the patient did not have an HLA-identical sibling and her parents were consanguineous. Finally, she underwent an allogeneic HSCT of CD34+ selected cells from peripheral blood of an HLA-identical aunt. Before the transplant, the patient had mild residual pulmonary hypertension and iron overload with a serum ferritin level of 1888 ng/mL that was not assessed radiologically. The pre-transplant conditioning regimen consisted of bulsulfan and cyclophosphamide, after which the patient received an infusion of 2.45×10^6 CD34 + cells/kg and 300 000 CD3 + cells/kg, with no immediate complications. She subsequently developed acute graft-versus-host disease (GVHD) with stage II–III skin involvement, stage II–IV gastrointestinal involvement and stage IV hepatic involvement (with skin and gastrointestinal involvement confirmed by biopsy). She was treated with immunosuppressants, corticosteroids and extracorporeal photopheresis.

On day +121 post-transplant, with evidence of complete donor chimerism in peripheral blood and normal PK activity, the patient was admitted to hospital due to febrile illness. The hepatic GVHD grew progressively worse, accompanied by encephalopathy due to hyperammonaemia and coagulopathy, bronchopneumonia and oral thrush caused by *Candida albicans*, acute diabetes and pancreatitis secondary to steroid treatment, iron overload secondary to transfusion therapy, and kidney failure requiring haemofiltration.

On day +145, the patient had developed signs of anaemia, thrombocytopaenia and schistocytes in peripheral blood, compatible with microangiopathic haemolytic anaemia, which was treated with rituximab. Finally, on day +149 she developed pulmonary haemorrhage and septic shock secondary to infection by *Enterococcus faecium*, and died 48 hours later after of tension pneumothorax.

Pyruvate kinase deficiency is the most frequent cause of congenital non-spherocytic haemolytic anaemia. In this disease, HSCT[2,3] is the only available curative treatment, with recently published studies reporting favourable outcomes with normalisation of PK activity, as observed in our patient. Supportive therapy in the form of transfusion regimens and/or splenectomy in severe cases is associated with long-term complications.[5,6]

Vascular complications, such as arterial or venous thrombosis, pulmonary embolism or pulmonary hypertension have

been described in association with splenectomy, developing years after the procedure, as was the case in our patient. Some of the factors that promote this hypercoagulable state are postsplenectomy reactive thrombocytosis, the increased adherence of red blood cells to the endothelium, and hyperviscosity syndrome associated with chronic haemolysis and iron overload.[1,5,6]

This case demonstrates that HSCT should not be delayed in eligible patients,[2] since the comorbidities that precede transplantation have a considerable impact on post-transplantation morbidity and mortality. Our patient did not undergo HSCT earlier because she did not have an HLA-identical sibling and the donor search was not expanded to other relatives until a later time. The development of pulmonary hypertension, recurrent thromboembolisms and iron overload probably played a role in the patient's deterioration and death after transplantation, despite the cure of the underlying disease.

Diseases that are not life-threatening in the short term pose challenges in the indication of HSCT as to the ideal timing for the procedure. This assessment has to take into account the complications that may result from supportive treatment and their potential impact on the outcome of future curative treatment.[1,2]

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Brachydactyly type C due to a nonsense mutation in the *GDF5* gene☆

Braquidactilia tipo c debida a mutación de parada en el gen *GDF5*

Dear Editor:

The term brachydactyly encompasses a group of bone dysplasias involving the phalanges and/or metacarpal/metatarsal bones of the hands and feet. There are 5 types (A–E) and several subtypes (A1–A4; E1–E3). It has an autosomal dominant pattern of inheritance with variable penetrance. Cases with recessive inheritance are extremely rare.

Brachydactyly type C (BDC) is characterised by a shortening of the middle phalanges of the second, third and fifth finger and the first metacarpal, and may also present with ulnar deviation of the index finger, polydactyly, or a distinctive hypersegmentation of the proximal or middle phalanges of the second and third fingers. The fourth digit is least affected and usually longest.[1–3] ''Angel-shaped'' phalanges (Fig. 1A), while characteristic of BDC, are not pathognomonic, as they may also occur in the disorder known as angel-shaped phalango-epiphyseal dysplasia. It is possible that this disorder and BDC are part of the same clinical spectrum.[1] In BDC, this feature normalises when physeal closure of the hand bones is completed, ending as simple brachydactyly.[1] Other anomalies associated with BDC are short stature with delayed bone age, Madelung deformity, hip dysplasia, talipes valgus or equinovarus or absence of middle phalanges in the toes.[2,3]

We present the case of a boy aged 7 years with radiological features compatible with BDC referred for evaluation of short stature (z-score, −1.8). His father had unilateral post-axial polydactyly, which was also present bilaterally in a paternal uncle. Radiographic examination of the left hand and wrist revealed a bone age that was 2 years younger than chronological age and anomalies that prompted performance of a skeletal survey. The survey detected anomalies in the hands (Fig. 1A) and subtle abnormalities in the feet (mild epiphyseal dysplasia in the proximal phalanges of some toes). The radiological evaluation of a sister aged 6 years revealed lesions in the hand similar to those of the proband, although less pronounced (Fig. 1B). A radiograph of the father's hand (Fig. 1C) only revealed a bone remnant of the post-axial hexadactyly that had been surgically corrected in childhood.

Sequencing of the *GDF5* gene in the proband revealed a heterozygous point substitution in exon 2 (c.1462A>T)