CASO CLÍNICO/CASE REPORT

Mucopolysaccharidosis Type I, Hematopoietic Cell Transplantation and Neurodevelopmental Profile: A Case Report

Mucopolissacaridose Tipo I, Transplante de Células Hematopoiéticas e Perfil de Neurodesenvolvimento: Um Caso Clínico

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Abstract

Type I mucopolysaccharidosis is caused by an alpha-L-iduronidase deficit and has three phenotypic expressions. Hurler syndrome includes dysmorphias, hirsutism, hepatosplenomegaly, hydrocephalus, skeletal deformities, recurrent infections, heart abnormalities, and global developmental delay. Hematopoietic cell transplantation provides a continuous source of alpha-L-iduronidase throughout the body, including the central nervous system and, currently, appears to be the gold-standard therapy for this pathology. We present the case of a six-years-old child with the diagnosis of Hurler syndrome, submitted to hematopoietic cell transplantation and integrated in a structured support plan with special education, speech therapy and early home intervention, who presents a trend of convergence with the normality in all the development areas, except for locomotor skills and eye-hand coordination. These findings highlight the positive impact of the hematopoietic cell transplantation together with the early and structured intervention of a multidisciplinary team in the neurodevelopmental profile of children affected by Hurler syndrome.

Resumo

A mucopolissacaridose tipo I é causada por um défice de alfa-L-iduronidase e tem três expressões fenotípicas. A síndrome de Hurler inclui dismorfias, hirsutismo, hepatoesplenomegalia, hidrocefalia, deformidades esqueléticas, infeções recorrentes, anomalias cardíacas e atraso global do desenvolvimento. O transplante de células hematopoiéticas (TCH) fornece uma fonte contínua de alfa-L-iduronidase em todo o corpo, incluindo o sistema nervoso central e, atualmente, parece ser a terapêutica gold-standard para esta patologia. Apresentamos o caso de uma criança de seis anos com diagnóstico de síndrome de Hurler, submetida a TCH e integrada num plano de apoio estruturado com educação especial, terapia da fala e intervenção precoce domiciliária, que apresenta uma tendência de convergência com a normalidade em todas as áreas do desenvolvimento, exceto na motricidade grosseira e coordenação olho-mão. Estes achados destacam o impacto positivo do TCH juntamente com a intervenção multidisciplinar precoce e estruturada no perfil de neurodesenvolvimento das crianças com síndrome de Hurler.

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Introduction

Mucopolysaccharidosis are rare lysosomal storage diseases caused by specific enzyme deficiencies necessary for the normal degradation process of glycosaminoglycans. Partially degraded glycosaminoglycans accumulate in lysosomes resulting in progressive cell dysfunction that translates into multiorgan failure.[1] Mucopolysaccharidosis are classified as types I to IX and each one represents a specific enzymatic deficit, phenotypic variability and distinct clinical and imaging characteristics.[2]

Type I mucopolysaccharidosis is caused by an alpha-L-iduronidase deficit and has three phenotypic expressions, according to the residual activity of the enzyme and consequent severity of the condition: Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome.[3,4]

Hurler syndrome includes dysmorphias, hirsutism, hepatosplenomegaly, hydrocephalus, skeletal deformities, recurrent infections, heart abnormalities, and global developmental delay/intellectual development disorder.[5,6] Currently recommended treatments are enzyme replacement therapy and hematopoietic cell transplantation (HCT). When performed early, HCT has been showing a particular positive impact on the neurodevelopmental profile of children affected by the disease, with the potential to preserve their neurocognitive function.[7]

This case describes a child diagnosed with Hurler syndrome who underwent HCT and its impact on the neurodevelopmental profile.

Case Report

Male child, 6–years-old, with no relevant family history. The pregnancy was supervised, and a prenatal diagnosis of ventriculomegaly was made. It was a term vacuum-assisted operative vaginal delivery without complications. At 6 months of age a ventricular-peritoneal shunt system was placed because of aggravating hydrocephalus and a correction of left inguinal hernia was performed. At 12 months, due to developmental impairment, hydrocephalus and vertebral alterations with dorsolombar kyphosis and dysmorphias of the vertebral bodies, the patient was observed in a pediatric neurology appointment, where the hypothesis of mucopolysaccharidosis was placed. The genetic diagnosis of Hurler's syndrome was confirmed at 14 months of age with the identification of a compound heterozygosity for pathogenic variants in the *IDUA* gene: c.144_146delGAG (p.R48del) – exon 1; c.1205G>A (p.W402*) – exon 9.

The boy is under follow-up in a neurodevelopment center of a tertiary hospital since the diagnosis. At 16 months of age, he took some steps with support, vocalized and said monosyllables, understood simple orders, had good social interaction and did not make tower of 2 cubes or pincer grasp. At 2 years of age he took few steps on his own, stood up if grabbed, made pincer grasp, had good social interaction, said a few words, understood simple orders and pointed to ask for something or to get help. He was submitted to HCT on two occasions, at 2 years and 2 months (with transplant rejection) and at 2 years and 5 months of age.

From the neurodevelopmental profile point of view, formal and seriated psychological evaluations were performed at 2 years and 10 months, 3 years and 11 months and 5 years and 2 months of age, through the Griffiths Mental Development Scale whose results are shown in **Table 1**. Of these evaluations, we highlight the trend of convergence with the normality in all the development areas, except for locomotor skills and eye-hand coordination, which progressively presented worse results. Since the age of 3 he is integrated in a structured support plan with special education and speech therapy in hospital context and early home intervention, with a total of 3 sessions per week.

In addition to neurodevelopmental profile, the child is stable regarding the other manifestations of the disease with mild aortic and mitral insufficiency, recurrent otitis externa without auditory acuity deficit, mild hepatomegaly without splenomegaly, corrected hyperopia with glasses and facial dysmorphias and hirsutism in improvement. From the musculoskeletal point of view presents with bilateral knee valgism, right-hand claw deformation and mild kyphosis with dorsal rectification and lumbar hyperlordosis.

Table 1. Results of psychological evaluations - Griffiths Mental Development Scale Developmental and Global Quotient.

Griffiths subscales and GQ	2 years and 10 months	3 years and 11 months	5 years and 2 months
Locomotor	70.6	66	57.3
Personal-social	88.3	70.4	74.2
Hearing and Language	75.5	80.4	91.9
Eye and Hand Coordination	83.8	65.9	57.3

Discussion

Hurler syndrome is characterized by being the most aggressive phenotype of type I mucopolysaccharidosis. According to the natural history of the disease, intracellular accumulation of glycosaminoglycans leads to progressive multisystem deterioration. Without institution of therapeutic, the neurocognitive decline is marked and the individuals evolve to severe intellectual development disorders.[8]

HCT provides a continuous source of alpha-L-iduronidase throughout the body, including the central nervous system. On the other side, enzyme replacement therapy is unable to cross the blood-brain barrier, so HCT currently appears to be the gold-standard therapy for this pathology. In addition to the systemic favorable outcomes, there is also evidence that HCT performed at an early stage of disease development can prevent neurocognitive decline.

Of the six areas of neurodevelopment that contribute to global functioning (global motricity, fine motricity, language, performance, practical reasoning, personal-social adaptation), the evidence suggests that, after transplantation, the progression of intellectual capacities in all areas of development is notorious, being maintained over time. On the other hand, in terms of global and fine motricity, the progression is significantly slower, and these are the areas with the worst results.[9]

When interpreting the results of the Griffiths Mental Development Scale it is important to take into account that the value of the score corresponding to the population average is 100 and the standard deviation varies between 12 and 17. Qualitatively, scores between mean and two standard deviations are considered to be within the expected values for normality, and 70 is considered the lower limit of normality.[10]

When analyzing the results of the psychological evaluations performed in the reported case it is possible to notice that the profile of neurodevelopment is in line with the trend that has been described in the literature. The scores for global motricity and eye-to-hand coordination are below the standard values, with a result of 57.3. The other areas evaluated presented scores that are around the values of normality, with emphasis on the areas of language and practical reasoning, with results, in the last evaluation, of 91.9 and 83.9, respectively.

This case aims to highlight the importance of neurocognitive functions of children with Hurler syndrome following HCT. Firstly, given that the severity of organic symptoms and the long-term neurodevelopment profile depend on the early institution of appropriate therapy, it is essential to highlight the importance of clinicians being alert to distinguish between progressive and non-progressive cognitive dysfunction diseases in early development years, especially because, in some of them, the most distinguishing features are non-neurological.

The seriated psychological evaluations recorded in **Table 1** demonstrate the impact that the different therapies confer on the realization of the therapeutic potential established by transplantation. Emphasis should also be placed on the results obtained in the assessment of global and fine motor skills. While this work shows that intervention in these areas cannot be neglected, it is also important that further studies on the understanding of this subject emerge. Furthermore, it is also significant to point up the importance of formal and systematic evaluations of the neurodevelopmental profile of these children after transplantation. Since there is no formal recommendations regarding timings for this assessment, it is fundamental to be aware of the specific needs of every child so that the interventions and therapies can be adapted to maximize the potential gains of HCT.

In conclusion, HCT, together with the early and structured intervention of a multidisciplinary team, has shown great positive impact in the neurodevelopmental profile of children affected by Hurler syndrome and, in this case, is in line with what has been described globally. ■

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RI: Design, writing and final approval.
CBL: Critical review with intellectual input and fianl approval.
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