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EDITORIAL

Neurological outcome in patients with inborn errors of metabolism submitted to hematopoietic stem cell transplantation. What should we expect?

Desfecho neurológico em pacientes com erros inatos do metabolismo submetidos a transplante de células tronco hematopoiéticas. O que devemos esperar?

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In the last few years there has been an increasing discussion about the diagnosis and management of rare diseases in Brazil. At this moment, the Brazilian Supreme Court is about to decide on the financial support to the treatment of these disorders.

Balancing the low prevalence of rare diseases in the population (6.6/1,000 inhabitants[1]) and the high impact they pose for the patient/family is an endless discussion poses a quandary, especially if we consider the limited income for the health system, this becomes much harder to equalize. Another important factor is that 4.2% of the years of life lost in the general population are related to rare diseases, which is higher than infectious diseases and diabetes mellitus put together (3.8%)[1].

Out of nearly 8,000 rare diseases classified, inborn errors of metabolism (IEM) represent only but a small group of heterogeneous genetic syndromes, including lysosomal and peroxisomal storage diseases. Some of them can be treated with enzyme replacement therapy (ERT) reducing somatic symptoms; however, until now, the studies with ERT did not demonstrate efficacy in either minimizing or reversing neurological symptoms, probably because ERT does not cross the blood-brain barrier[2]. The currently available treatment option for neurological symptoms is hematopoietic stem cell transplantation (HSCT).

In the current number of Arquivos de Neuropsiquiatria, Saute *et al.* report on the neurological outcome of eleven patients with IEM submitted to HSCT after a median follow up of almost 4 years[3]. The authors evaluated patients with two lysosomal disorders; metachromatic leukodystrophy (MLD) and mucopolysaccharidosis type I-Hurler (MPS-IH); and one peroxisomal disorder, the X-linked cerebral adrenoleukodystrophy (CALD) and they observed non-progression of neurological findings in more than 60% of patients with a mortality rate of 18% in the first year after HSCT[3].

The results of the study by Saute *et al.* bring back to light some issues that should be considered in the decision process of HSCT in IEM, as an early age, at the beginning of the symptomatic phase, as well as the use of stem cells from a related donor[3].

In an individual analyses, for MLD (OMIM #250100), the HSCT performed before symptoms onset could delay the progression of central nervous system compromise, but the response at the peripheral level is still controversial in the litterature[4,5]. For MPS-IH (OMIM #607014), although cerebral damage prior to HSCT remains irreversible, HSCT treatment could still offer an improvement of neurological development, particularly when HSCT is done performed 16 months of age, when a significant reduction of brain atrophy is observed (OR 3.22, 95%CI 1.60–6.50, p = 0.001)[6]. Also, following the procedure, hydrocephalus progression is halted[6]. In CALD (OMIM #300100), HSCT could be considered based on the MRI Loes score and in the early stages of brain demyelination in order to prevent neurological deterioration[7].

Two important issues should also be considered for the HSCT: 1) the graft-versus-host disease observed in 27% of patients (CALD-3, CALD-7, MLD-9) in Saute et al study[3], a major complication that is related to higher mortality rates in a long term follow up after HSCT[8]; and 2) the controversial use of ERT for HSCT MPS-IH as adjuvant therapy[7].

In the future, neonatal screening and the introduction of new technologies, such as gene and chaperone therapies, might provide patients with IEM with earlier diagnosis and greater opportunities of stabilization or even reversal of symptoms, thus improving the clinical outcome with a more specific treatment.

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