

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?

Marcos C. Lange¹

¹ Universidade Federal do Paraná, Hospital de Clínicas, Serviço de Neurologia, Curitiba PR, Brasil.

Correspondence:

Marcos C. Lange; Hospital de Clínicas, Serviço de Neurologia; Rua General Carneiro, 181 / 4º andar; 80060-900 Curitiba PR, Brasil; E-mail: langeneuro@gmail.com

Conflict of interest:

There is no conflict of interest to declare.

Received 26 October 2016

Accepted 03 November 2016



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 inhabitants¹) 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 barrier². 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 years³. 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 HSCT³.

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 donor³.

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 literature^{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 halted⁶. 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 deterioration⁷.

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 study³, a major complication that is related to higher mortality rates in a long term follow up after HSCT⁸; and 2) the controversial use of ERT for HSCT MPS-IH as adjuvant therapy⁷.

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.

References

1. Mazzucato M, Visonà Dalla Pozza L, Manea S, Minichiello C, Facchin P. A population-based registry as a source of health indicators for rare diseases: the ten-year experience of the Veneto Region's rare diseases registry. *Orphanet J Rare Dis.* 2014;9:37. doi:10.1186/1750-1172-9-37
2. Valayannopoulos V. Enzyme replacement therapy and substrate reduction therapy in lysosomal storage disorders with neurological expression. *Handb Clin Neurol.* 2013;113:1851-7. doi:10.1016/B978-0-444-59565-2.00055-1
3. Saute JAM, Souza CFM, Poswar FO, Donis KC, Campos LG, Deyl AVS et al. Neurological outcomes after hematopoietic stem cell transplantation for cerebral X-linked adrenoleukodystrophy, late onset metachromatic leukodystrophy and Hurler syndrome. *Arq Neuropsiquiatr.* 2016;74(12):953-63. doi:10.1590/0004-282X20160155
4. Solders M, Martin DA, Andersson C, Remberger M, Andersson T, Ringdén O et al. Hematopoietic SCT: a useful treatment for late metachromatic leukodystrophy. *Bone Marrow Transplant.* 2014;49(8):1046-51. doi:10.1038/bmt.2014.93
5. Boucher AA, Miller W, Shanley R, Ziegler R, Lundt T, Raymond G et al. Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report. *Orphanet J Rare Dis.* 2015;10:94. doi:10.1186/s13023-015-0313-y
6. Aldenhoven M, Wynn RF, Orchard PJ et al. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. *Blood.* 2015;125(13):2164-72. doi:10.1182/blood-2014-11-608075
7. Chiesa R, Wynn RF, Veys P. Haematopoietic stem cell transplantation in inborn errors of metabolism. *Curr Opin Hematol.* 2016;23(6):530-5. doi:10.1097/MOH.0000000000000289
8. Eapen M, Ahn KW, Orchard PJ, Cowan MJ, Davies SM, Fash A et al. Long-term survival and late deaths after hematopoietic cell transplantation for primary immunodeficiency diseases and inborn errors of metabolism. *Biol Blood Marrow Transplant.* 2012;18(9):1438-45. doi:10.1016/j.bbmt.2012.03.003