CASE REPORT

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X LINKED- ALD: SHOULD LOES SCORE BE THE ONLY BENCHMARK FOR HSCT ELIGIBILITY?

HSCT IN X LINKED ALD WITH HIGH LOES SCORE

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ABSTRACT

Hematopoietic stem cell transplant (HSCT) is the only modality that, if performed in the early- stages of cerebral X-linked adrenoleukodystrophy(X-ALD) can lead to good outcomes. Loes- score, calculated based on the findings of the magnetic resonance imaging (MRI) of the brain, helps in the selection of patients for HSCT. As per recommendations, the Loes-score should be <10 for a patient to be eligible for HSCT. Here we report a child of cerebral X-ALD with Loes of 12, but a good neurological function score (NFS), who was treated with HSCT, and had good outcomes. It is therefore important to utilize other parameters along with the Loes score, in selecting patients for HSCT in X-ALD.

Keywords: Adrenoleukodystrophy. Hematopoietic Stem Cell Transplantation. Magnetic Resonance Imaging.

INTRODUCTION

X-linked adrenoleukodystrophy(X-ALD) is a rare genetic disease classified as a peroxisomal disorder caused by mutations in the *ABCD1* gene. There is a deposition of very long chain fatty acids(VLCFA) in tissues including the white matter of the brain, spinal cord, and adrenal cortex.[1]

In 35-40% of patients, X-ALD causes rapid cerebral demyelination leading to cerebral X-ALD which presents in childhood or adolescence and has rapid neurological decline with high morbidity and mortality.[2] To date hematopoietic stem cell transplant(HSCT) remains the mainstay for cure of cerebral X-ALD, provided it is performed in the early stages of the disease.[3] If performed at later stages it can, on the contrary, accelerate the neurologic decline.[4]

Loes score is a 34-point imaging-based severity scale that helps in the prediction of the disease course and selection of patients for HSCT in X-ALD. As per existing recommendations if done for patients with a Loes score of <10 significant improvement is possible.[5]

Here we present a case of an 11-year-old boy with childhood cerebral X-ALD, for whom HSCT was performed despite the Loes score being 12. The child had good long-term outcomes, making this case worth reporting.

RESULTS

Case Description

The child initially presented at 4 years of age with hyperpigmentation of nails and lips. On evaluation, he was found to have hypothyroidism and cortisol deficiency. He was started on thyroxine and replacement doses of corticosteroids. At ten years of age, he presented with acute febrile encephalopathy and vision loss. The seizures were controlled with antiepileptics and the vision loss completely improved over the next 12 hours. The magnetic resonance imaging(MRI) of the brain showed hyperdensities in white matter, parts of corpus callosum, visual tracts and internal capsule. This made us suspect an adrenoleukodystrophy which was then confirmed later exome sequencing to be due to a mutation of the *ABCD1* gene (Exon-10/c.2002A>G/Hemizygous/Likely pathogenic)which confirmed the diagnosis of X-ALD. The family was given the option for an allogeneic HSCT, which they opted for. The child had three episodes of right focal seizures in the time leading to the HSCT, which were managed with adjustment of antiepileptic doses. The baseline Loes score at diagnosis was 9 and it progressed to 12 pre- HSCT. The VLCFA levels in serum were elevated (Table 1).

The child had a younger sister who was 6/6 human leukocyte antigen(HLA) matched and she was not a carrier of the implicated mutation. The HSCT was done seventeen months after the diagnosis using the sister as a donor. The Loes score pre-HSCT had increased to 12, however the neurological functional score(NFS) was 1, so we decided to proceed with the HSCT. The prolonged delay to HSCT was due to the COVID-19 pandemic.

The child was administered myeloablative, reduced-toxicity conditioning with Busulfan(16 mg/kg) and Fludarabine(180 mg/m^2) along with rabbit anti-thymocyte globulin(7.5mg/kg). Cyclosporine was used for graft versus host disease(GVHD) prophylaxis. Peripheral blood stem cells harvested from his sister were administered to him at a dose of 6.88 x 10^6/kg CD-34 positive cells. He had complications of febrile neutropenia and engraftment syndrome post HSCT which were managed as per standard protocols. Neutrophil engraftment occurred on day+11 and platelet engraftment on day+14. He was discharged from the hospital on day +19. The child had grade I skin GVHD and grade IIa upper gut GVHD in follow-up, which were managed with topical steroids and oral budesonide respectively. At present, he is three years post-transplant and growing well. The chimerism analysis done using XX/XY fluorescent in situ hybridisation (FISH) was 100% donor at 1m, 3m, 6m and 12m post HSCT. The child presently is more than three years post HSCT and goes to school and has no vision, hearing, speech, or gait abnormalities. He has been seizure-free since the HSCT and is on tapering doses of anti-epileptics presently. The present NFS is one. The Loes score has remained constant at 12 - three months, one year, two years and three years post HSCT (Figure 1) and the NFS is one.

DISCUSSION

X-ALD is an inherited disorder that affects approximately 1 in 20 000 live male births. Cerebral X-ALD represents the most severe phenotype and early stages of the disease are characterised

by white matter lesions on the MRI, which then progress to active cerebral inflammation reflected by gadolinium enhancement on MRI and rapid clinical deterioration.[6]

Allogeneic HSCT is the standard treatment for cerebral X-ALD. A successful HSCT can stabilize the neurological status, provided it is performed early in the disease course. The Loes score which radiologically classifies the disease severity is known to correlate with HSCT outcomes in cerebral X-ALD, with Loes score of >9 correlating with worse outcomes.[7] The Loes score was initially devised in 1994, as a scoring method for brain MRI observations.[5]

Often the decision to transplant a cerebral X-ALD patient is based predominantly on the Loes score. A Loes score of greater than 9 or 10 correlates with poor HSCT outcomes. Raymond et al have reported that in a 5-year follow-up, patient with cerebral X-ALD who underwent HSCT with a baseline Loes score of <5, the progression in the Loes score and NFS was lesser.[8] Peters et al. have also shown that HSCT with early-stage cerebral X-ALD has a clear advantage and they recommended a Loes score of less than 9 for possible benefit from HSCT. Warren et al have recommended an even lower score (<4) in selecting patients for HSCT.[9,10] In a study conducted by Bladowska J et.al in boys with ALD, subjects with higher severity scores before HSCT, clinical and radiological progression was observed even after transplant. They therefore recommended that only children with pre-transplant Loes score below 8 points could benefit from HSCT.[11] Chiesa et al reported the outcomes of HSCT in 53 X-ALD patients and classified them into early disease (Loes <=9 and NFS<=1) and advanced disease (Loes >9 and NFS>1). They demonstrated that the ED group had better disease-free survival.[12]

Although the Loes score remains a good surrogate marker of disease severity, the scoring is subjective. Being a score based on imaging, the clinical condition of the patient is not taken into consideration when calculating the score. The neurological functional status and the cerebral inflammation are important indicators of disease severity.

HSCT outcomes of patients with Loes score of >9 at the time of HSCT have not been described much. Miller et al have reported that the 5-year overall survival for patients with baseline Loes score ≥ 10 was 60% compared to 89% for patients who had Loes scores of <10. Among all patients with a pre-HCT Loes score ≥ 10, significantly greater survival was observed among those who received NAC in the peri-HCT period. The presence of cerebral disease, NFS scores of >=1, performance IQ at time of HSCT of <80 and donor chimerism at day 60 of <80% were associated with worse outcomes.[13] It is now known that even asymptomatic individuals can have high Loes scores. Kumar et al in their series also reported an asymptomatic individual with an advanced Loes score of nine. Thus, the Loes score may not always be a benchmark to assess the clinical condition.[14]

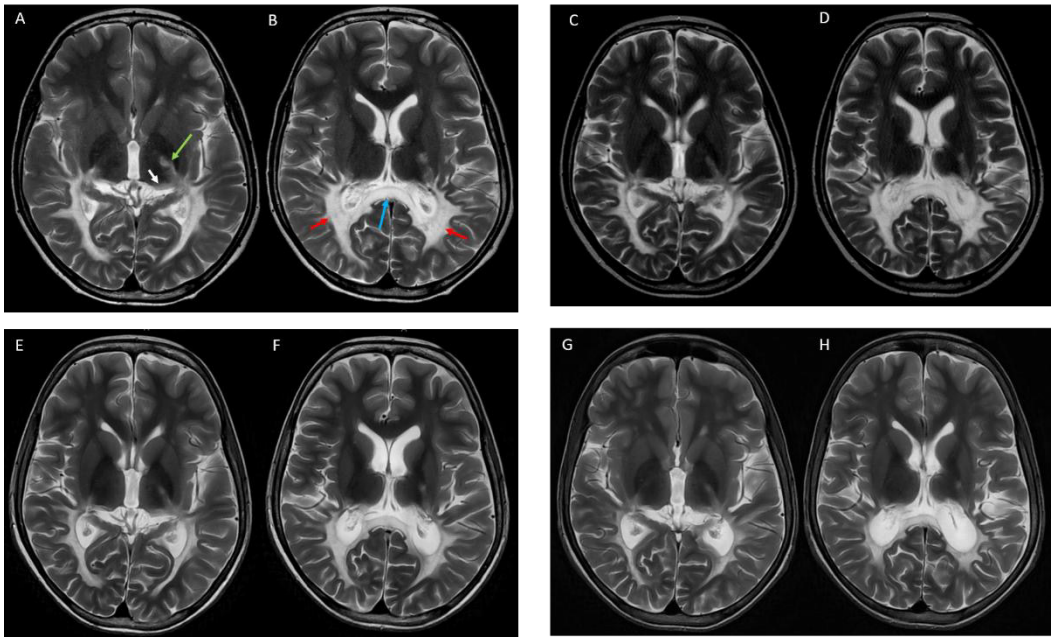
CONCLUSION

In this report, we present a case of a boy with childhood cerebral X-ALD, who had a Loes score on MRI more than the cut-off recommended for HSCT. As the child had a good NFS we proceeded with HSCT. Three years post-HSCT his Loes scores remain stable and the NFS has not worsened. Higher Loes scores are known to correlate with poor outcomes however the scoring remains subjective and observer-dependent. For critical decisions such as HSCT eligibility, other parameters such as the NFS and the presence of cerebral inflammation should be considered along with the Loes score.

TABLE 1: Very long-chain fatty acid levels in the patient pre-HSCT

VLCFA level	November – 2019	December - 2020	Normal range
C26:0 (microgram/milligram)	1.68	1.91	0.45 – 1.32
C24:0/C22:0	1.25	1.32	0.57-0.92
C26:0/C22:0	0.05	0.04	0.01-0.02

FIGURE 1: MRI at different time points in the patient



Legend:

Panels A and B- Baseline MRI 3 months before transplant. MRI brain T2 weighted serial axial images show hyperintense signal changes with involvement of various structures including, the left internal capsule (green arrow in A), medial geniculate body (white arrow in A), splenium of corpus callosum (blue arrow in) and bilateral parieto-occipital white matter (red arrows in B). The total Loes score calculated at this time was 12.

Panels C and D - Follow-up MRI done 3 months after transplant. MRI brain T2 weighted serial axial images, corresponding to the same sections as shown in panels A, and B, do not show any significant interval change. No other new areas of the brain were involved.

Panels E and F- Follow-up MRI done 1 year after transplant. MRI brain T2 weighted serial axial images, corresponding to the same sections as shown in panels A, and B, do not show any significant interval change. No other new areas of the brain were involved.

Panels G and H- Follow-up MRI done 3 years after transplant. MRI brain T2 weighted serial axial images, corresponding to the same sections as shown in panels A, and B, do not show any significant interval change. No other new areas of the brain were involve

REFERENCES

1. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up, and management. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012;7:51.

2. Turk BR, Theda C, Fatemi A, et al. X-linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing, newborn screening, and therapies. Int J Dev Neurosci. 2020;80(1):52-72.

3. Cappa M, Todisco T, Bizzarri C. X-linked adrenoleukodystrophy and primary adrenal insufficiency. Front Endocrinol. 2023;14:1309053.

4. Cartier N, Aubourg P. Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. Brain Pathol Zurich Switz. 2010;20(4):857-62.

5. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. 1994;15(9):1761-6.

6. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. AJNR Am J Neuroradiol. 2000;21(5):839-44.

7. Beam D, Poe MD, Provenzale JM, et al. Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2007;13(6):665-74.

8. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2019;25(3):538-48.

9. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. 2004;104(3):881-8.

10. Warren DJ, Connolly DJA, Wilkinson ID, et al. Magnetic resonance spectroscopy changes following haemopoietic stem cell transplantation in children with cerebral adrenoleukodystrophy. Dev Med Child Neurol. 2007;49(2):135-9.

11. Bladowska J, Kulej D, Biel A, et al. The Role of MR Imaging in the Assessment of Clinical Outcomes in Children with X-Linked Adrenoleukodystrophy after Allogeneic Haematopoietic Stem Cell Transplantation. Pol J Radiol. 2015;80:181-90.

12. Chiesa R, Boelens JJ, Duncan CN, et al. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. Blood Adv. 2022;6(5):1512-24.

13. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: The largest single-institution cohort report. Blood. 2011;118(7):1971-8.

14. Kumar S, Sait H, Polipalli SK, et al. Loes Score: Clinical and Radiological Profile of 22 Patients of X-Linked Adrenoleukodystrophy: Case Series from a Single Center. Indian J Radiol Imaging. 2021;31(2):383-90.