From prospective newborn screening for metachromatic leukodystrophy to gene therapy - the German experience

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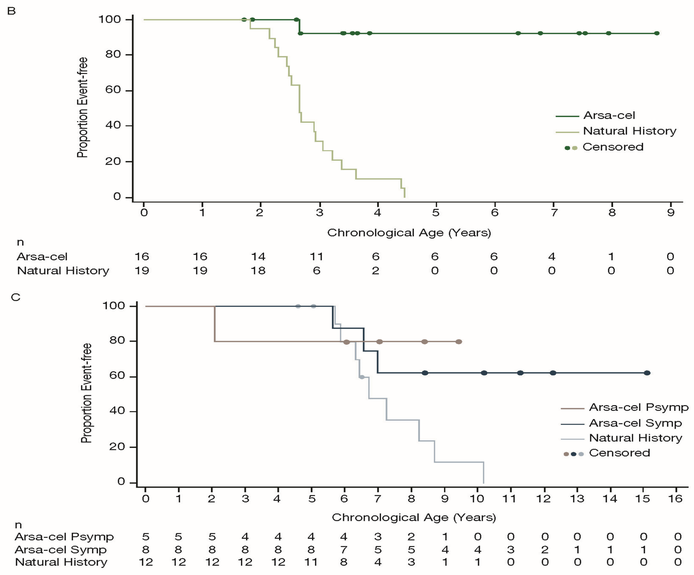
Background

Metachromatic leukodystrophy (MLD) is a progressive neurodegenerative disease leading to severe disability and premature death. Atidarsagene autotemcel (arsa-cel, tradename: Libmeldy Lenmeldy™, Libmeldy™) was approved by EMA in 2020 and by FDA in 2024 for children with MLD with presymptomatic late infantile (LI) and early juvenile (EJ) MLD, and early symptomatic EJ MLD. Allogeneic haematopoietic stem cell transplantation (HSCT) is an available treatment option for late-onset subtypes

We share the German treatment experience in Tübingen, including treatment and monitoring of 4 patients identified by a newborn screening (NBS) pilot study.

Methods

From 2021, a first prospective MLD NBS pilot study using a three-tiered screening[2] (sulfatides, ARSA enzyme activity, genetic sequencing) in DBS was initiated at the Screening center in Hannover, Germany. Identified positive cases were managed and treated according to a consensus-based clinical algorithm[3] at the University Children's Hospital in Tuebingen.



Figures from Fumagalli et al *Lancet* 2022. Kaplan-Meier plot showing age at severe motor impairment or death in patients with LI MLD treated with arsa-cel versus untreated natural history LI MLD (upper) and in patients with pre-symptomatic and early-symptomatic EJ MLD treated with arsa-cel versus untreated natural history EJ MLD (lower). Severe motor impairment-free survival is defined as the interval from birth to the earlier loss of locomotion and sitting without support (GMFC level 5 or 6) or death from any cause;

Results

Out of 109,259 screens from the NBS study, 3 have been identified as screen positives. In all three cases the diagnosis of MLD was confirmed. Based on genotype and enzyme activity, the subtype was predicted as EJ in two cases and late onset in 1 case, respectively. Index case 1 and 2 received arsa-cel at 12 months of age, no unexpected side effects were observed and these children continue to develop age-appropriately. Index case 3 is in close clnical monitoring and planned for HSCT.

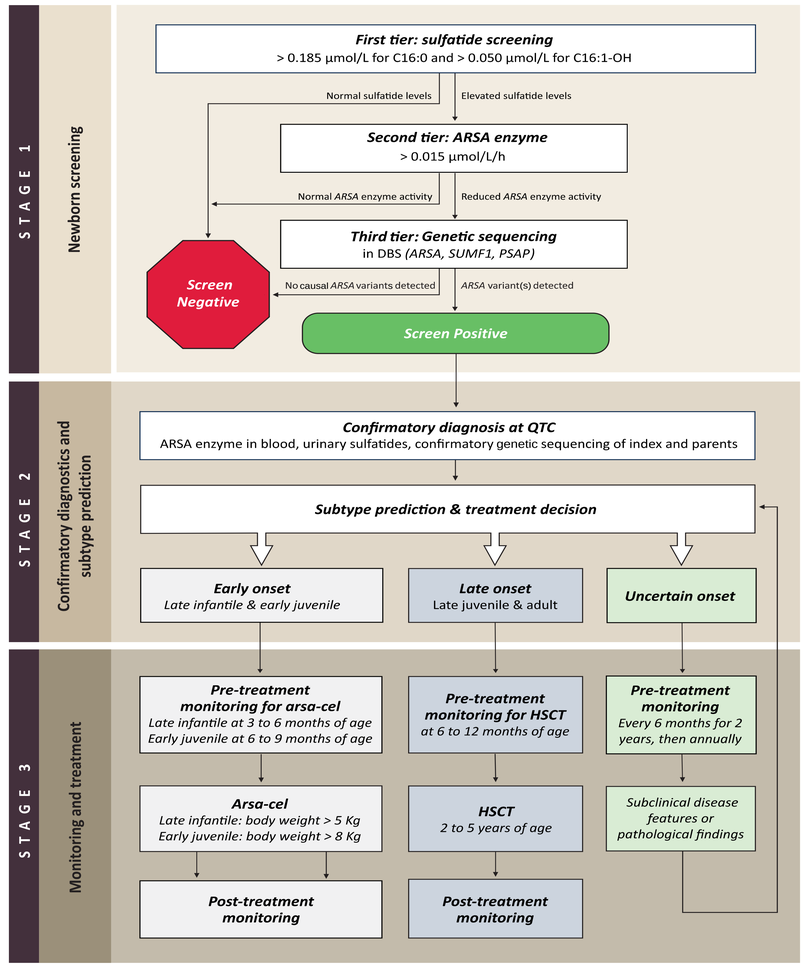


Fig. 2: Screening, management and treatment algorithm for NBS for MLD[2-4]

Literature

[1]Fumagalli et al., 2022, The Lancet. [2]Hong et al., 2021, GiM. [3]Laugwitz et al., 2024, EJPN. [4]*Laugwitz et al., submitted.*