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Rapidly progressive dementias — leukodystrophies as a potentially treatable cause

In their Review on rapidly progressive dementias (Hermann, P. & Zerr, I. Rapidly progressive dementias — aetiologies, diagnosis and management. *Nat. Rev. Neurol.* **18**, 363–376; 2022)[1], Hermann and Zerr provide a comprehensive summary of the manifold causes of fast cognitive decline, including treatable causes such as autoimmune encephalitis and CNS lymphoma. They also mention leukodystrophies, among other genetic CNS disorders, without specifying differential diagnoses and, more importantly, possible treatments.

Leukodystrophies that present with rapidly progressive cognitive decline in adults comprise a range of entities with different modes of inheritance[2]. In the recently delineated cognitive presentation of metachromatic leukodystrophy (MLD), patients can present with profound dementia while motor function remains intact for many years. MLD can be treated with allogenic haematopoietic stem cell transplantation (HSCT), although its efficacy is less well established in adults than in children[3]. For early-onset MLD, ex vivo gene therapy is approved in Europe. Once the disease has progressed beyond a certain threshold, however, these treatments are no longer effective[4]. Cognitive function is the most important criterion for decisions on treatment eligibility. MLD shows an autosomal recessive pattern of inheritance, meaning that siblings of an index patient need to be tested and, if affected, assessed for HSCT eligibility. This recommendation holds true for both older and younger siblings, as age at MLD onset is variable even within a family, especially for the adult-onset form[5].

Another disease for which HSCT is an emerging treatment option is adult-onset leukodystrophy with spheroids and pigmented glia[6] (ALSP). ALSP is caused by dominant variants in *CSF1R*, which lead to cognitive and motor decline, usually starting in the fourth or fifth decade of life (although onset in the third decade has been reported). Mean survival after diagnosis is 6.8 years, although both more rapid and more protracted forms have been reported[7]. Patients with ALSP are sometimes diagnosed with other forms of dementia, such as frontotemporal dementia, before the correct diagnosis is established. Again, even if the index patient is too far advanced for HSCT, family members at risk can be identified through genetic testing and closely monitored to enable HSCT to be implemented when MRI starts to show the white matter involvement that is typical of ALSP. As ALSP has an autosomal dominant pattern of inheritance, identification of an index patient almost invariably means that more family members — including siblings, offspring and cousins — will be diagnosed on genetic testing.

Vanishing white matter (VWM) in adults is another form of leukodystrophy that usually presents with cognitive deterioration. In women, early ovarian failure can provide a clinical clue for this diagnosis[8]. No causal treatment is yet available for VWM in adults, although timely diagnosis raises the possibility of enrolment in natural history studies. A trial of the ISR inhibitor guanabenz is ongoing in children with VWM, and further trials, also including adult patients, are anticipated, underlining the importance of early diagnosis[9].

In summary, clinicians need to be aware of leukodystrophies as potentially treatable diagnoses in people who present with rapidly progressive cognitive impairment. Even if the disease in the index patient is too advanced for treatment, affected family members might qualify for established or emerging therapies.

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References

1. Hermann, P. & Zerr, I. Rapidly progressive dementias — aetiologies, diagnosis and management. *Nat. Rev. Neurol.* **18**, 363–376 (2022).
2. van der Knaap, M. S., Schiffmann, R., Mochel, F. & Wolf, N. I. Diagnosis, prognosis, and treatment of leukodystrophies. *Lancet Neurol.* **18**, 962–972 (2019).
3. van Rappard, D. F. et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience. *Blood* **127**, 3098–3101 (2016).
4. Fumagalli, F. et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet* **399**, 372–383 (2022).
5. Elgün, S. et al. Phenotypic variation between siblings with metachromatic leukodystrophy. *Orphanet J. Rare Dis.* **14**, 136 (2019).
6. Gelfand, J. M. et al. Allogeneic HSCT for adult-onset leukoencephalopathy with spheroids and pigmented glia. *Brain* **143**, 503–511 (2020).
7. Papapetropoulos, S. et al. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: review of clinical manifestations as foundations for therapeutic development. *Front. Neurol.* **12**, 788168 (2022).
8. Parihar, J. et al. Vanishing white matter disease presenting as dementia and infertility: a case report. *Neurol. Genet.* **8**, e643 (2022).
9. van der Knaap, M. S. et al. Therapy trial design in vanishing white matter: an expert consortium opinion. *Neurol. Genet.* **8**, e657 (2022).

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Competing interests

N.I.W. is an advisor and/or co-investigator for trials in metachromatic leukodystrophy, adult-onset leukodystrophy with spheroids and pigmented glia and other leukodystrophies (Shire/Takeda, Orchard, Ionis, PassageBio, VigilNeuro), without personal payment. M.S.v.d.K. is a consultant for Calico regarding trials in vanishing white matter and co-investigator for Ionis regarding a trial in Alexander disease, without personal payment. She is named on patent P112686US00 "Therapeutic effects of guanabenz treatment in vanishing white matter" and on pending patent P112686CA00 "The use of guanabenz in the treatment of VWM", both for the VU University Medical Center, Amsterdam, Netherlands. Y.A.L.P. declares no competing interests.