Leukodystrophies — much more than just diseases of myelin

Marjo S. van der Knaap and Marianna Bugiani

A Review article in the February 2018 issue of *Nature Reviews Neurology* (Adult leukodystrophies. *Nat. Rev. Neurol.* **14**, 94–105; 2018)[1] highlights adult presentations of leukodystrophies. This is an important topic, as leukodystrophies are commonly associated with childhood, and adult neurologists may be undereducated on the subject[1]. The paper starts with a broad definition of leukodystrophies as inherited disorders that affect the white matter of the CNS; cells involved in the axon–glia unit, including oligodendrocytes, astrocytes, ependymal cells and microglia, are specifically affected. The authors explain that underlying pathological mechanisms vary widely, and that in many cases pathological assessment is not feasible because of lack of brain tissue, so clinicians must rely on the molecular aetiology of the disorder and the appearance of the white matter on neuroimaging to define and classify the various disorders.

Surprisingly, the authors then classify leukodystrophies into only two categories: hypomyelinating leukodystrophies, which are primary deficits in myelin development, and demyelinating leukodystrophies, where myelin develops normally but subsequently undergoes progressive disruption. The Review is built on this concept[1].

We dispute the concept of progression as inherent to leukodystrophies. It is increasingly apparent that some disorders, widely accepted as leukodystrophies[2], are associated with transient neurological signs, followed by improvement and sometimes recovery. Examples include megalencephalic leukoencephalopathy with subcortical cysts, caused by dominant *HEPACAM* mutations[2–4], and leukoencephalopathy with thalamus and brainstem involvement and lactate elevation, caused by *EARS2* mutations[5].

More importantly, we wish to draw attention to the fundamental concept that white matter integrity and function are determined by all constituents of the white matter, not just the myelin. This concept is supported by identification of leukodystrophies caused by defects in proteins not related to myelin biology and by increasing knowledge on the diversity of white matter pathology underlying leukodystrophies, as we have described in a previous review[6] and illustrated in FIG. 1. Numerous disorders discussed by Köhler et al.[1] are neither hypomyelinating nor demyelinating. An example is hereditary diffuse leukoencephalopathy with spheroids, caused by a defect in the microglia-specific colony-stimulating factor 1 receptor (CSF1R) and characterized pathologically by a predominant axonopathy[7]. Another example is vanishing white matter, a complex disorder that leads to total white matter degeneration[8] and can be classified neither as hypomyelinating nor as demyelinating. We recently proposed a classification that recognizes the following categories: oligodendrocytopathies, astrocytopathies, microgliopathies, leuko-axonopathies and leuko-vasculopathies[6].

Why is classification of the leukodystrophies so crucial? A classification system encapsulates our view of the pathological mechanisms underlying the leukodystrophies and has important implications for therapy. The concept of inherent progression underestimates the potential of innate repair systems, which might be harnessed as part of the therapeutic strategy. Also, the incorrect belief that all leukodystrophies revolve around myelin implies that therapy should be focused on remyelination[9]. This approach will fail if the underlying pathology is an axonopathy, vasculopathy or total white matter degeneration. We have nothing to gain from oversimplification, because we will miss out on what needs to be achieved, namely, total white matter repair.

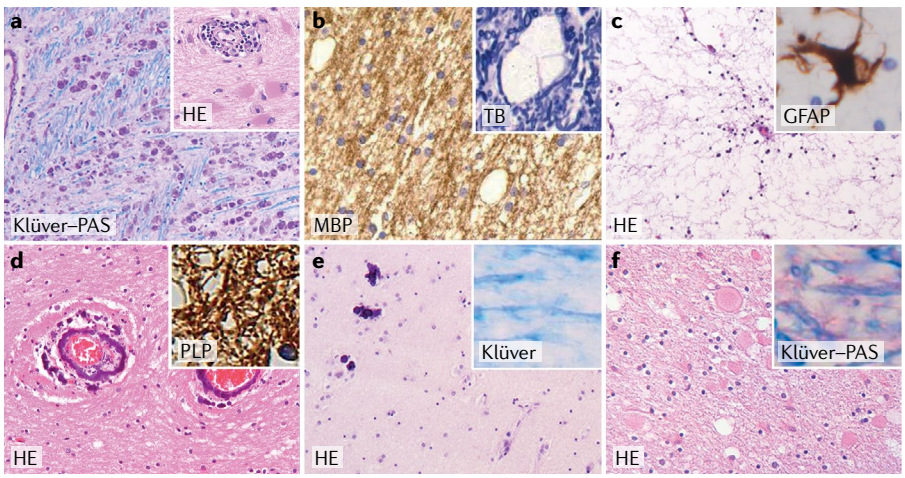

Fig. 1 | **Multifaceted neuropathology of leukodystrophies. a** | Metachromatic leukodystrophy (main image) and cerebral X-linked adrenoleukodystrophy (X-ALD, inset) are characterized by loss of myelin (Klüver–periodic acid–Schiff (PAS), blue), myelin debris in macrophages (pink) and reactive astrocytes. In X-ALD, lymphocytes accumulate around blood vessels and in brain parenchyma. **b** | Megalencephalic leukoencephalopathy with subcortical cysts is characterized by white matter vacuolization. Vacuoles are lined by myelin and represent intramyelinic oedema (myelin basic protein (MBP) stain). No myelin loss is observed (Toluidine blue (TB), inset). **c** | Vanishing white matter is characterized by total white matter degeneration, with combined lack of myelin and axons and loss of all white matter cell types, and meagre astrogliosis but relative abundance of oligodendrocyte precursor cells. Astrocytes have abnormal morphology (glial fibrillary acidic protein (GFAP) stain). **d** | Aicardi–Goutières syndrome is a combined astrocytopathy and microangiopathy with calcification of blood vessels and capillaries but little myelin loss (proteolipid protein (PLP) stain). **e** | GM1 gangliosidosis is a primary neuro-axonopathy with axon loss. Infantile-onset variants are characterized by secondary failure of myelination (blue, inset) and intraparenchymal small calcifications (purple, haematoxylin and eosin (HE)). **f** | Hereditary diffuse leuko-encephalopathy with axonal spheroids is a microgliopathy causing prominent axonal pathology with axonal swellings and secondary loss of myelin (blue, inset). Magnifications: main images and X-ALD: ×200; other insets: ×400. Part **b** inset adapted with permission from REF[10], Springer Nature Limited.

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Competing interests
The authors declare no competing interests.