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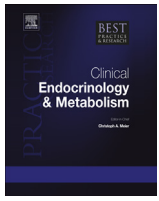

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Metachromatic leukodystrophy: Disease spectrum and approaches for treatment

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Metachromatic leukodystrophy is an inherited lysosomal disorder caused by recessive mutations in *ARSA* encoding arylsulfatase A. Low activity of arylsulfatase A results in the accumulation of sulfatides in the central and peripheral nervous system leading to demyelination. The disease is classified in a late-infantile, juvenile and adult onset type based on the age of onset, all characterized by a variety of neurological symptoms, which eventually lead to death if untreated. There is no curative treatment for all types and stages. This review discusses diagnostic process and efficacy of current and possible future therapies such as hematopoietic stem cell transplantation, enzyme replacement therapy and gene therapy. A systematic evaluation regarding the efficacy of hematopoietic stem cell transplantation and a longer follow up period for gene therapy are needed to come to a general conclusion and improve treatment options for metachromatic leukodystrophy.

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Introduction

In this review, the pathology, diagnosis and possible treatment of metachromatic leukodystrophy (MLD) (250100), a rare disorder with an estimated birth prevalence of 1.4–1.8 per 100.000 [1], is described. At present, no curative treatment is available for all types of MLD. This is an emerging field in which several clinical trials looking for a possible cure for this devastating disease are ongoing. Recently published data on patient care and treatment are discussed.

Metachromatic leukodystrophy is an autosomal recessive inherited lysosomal disorder caused by mutations in the *ARSA* gene located on chromosome 22q13.33, resulting in a deficiency of the enzyme arylsulfatase A (ASA). Some mutations result in pseudodeficiency alleles [2] that result in 10–15% of normal enzyme activity, which is sufficient to physiologically hydrolyze sulfatides and does not lead to disease symptoms [2]. This implies that sulfatide degradation can function normally in the presence of only 10–15% functional ASA enzyme; which is an important consideration for the development of treatment options for MLD. Mutations in *PSAP*, encoding prosaposin, an activator protein of ASA, also lead to MLD (249900), but are rare [3]. In multiple sulfatase deficiency (272200), caused by mutations in the sulfatase-modifying factor-1 gene (*SUMF1*) [4], the function of the whole family of sulfatase enzymes is affected, leading to symptoms of MLD in addition to features of various mucopolysaccharidoses [5].

ASA is essential for sulfatide metabolism through the hydrolysis of the 3-O ester bond of galactosyl and lactosyl sulfatides [1]. Its deficiency results in the accumulation of sulfatides into lysosomal storage deposits in the central and peripheral nervous system, which exhibit accumulation of sulfatides and metachromatic staining characteristics [6]. In the nervous system, sulfatides accumulate in the oligodendrocytes, Schwann cells, phagocytes, astrocytes and also neurons (Fig. 1) [3]. Sulfatides are the most abundant sphingolipids in myelin, accounting for 4% of its composition. They have important functions in

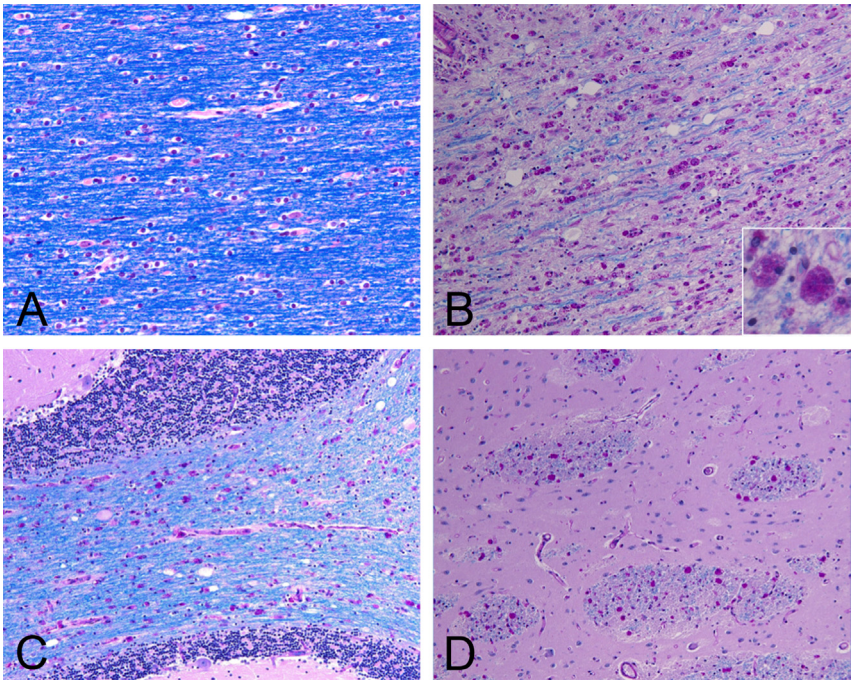

Fig. 1. Klüver-PAS staining of white matter in a control (A, 200×) and a patient with MLD (B–C, 100×). (B) Demonstrates loss of the normally blue-stained myelin and enlarged macrophages accumulating sulfatides (see also inlay). (C) Demonstrates relatively spared white matter in the cerebellum. (D) Shows pencil fibers in the basal nuclei, again with myelin loss and storage cells, within relatively spared grey matter.