Metachromatic leukodistrophy

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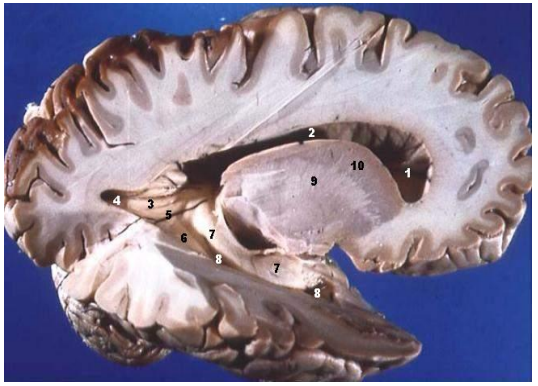
Metachromatic leukodistrophy

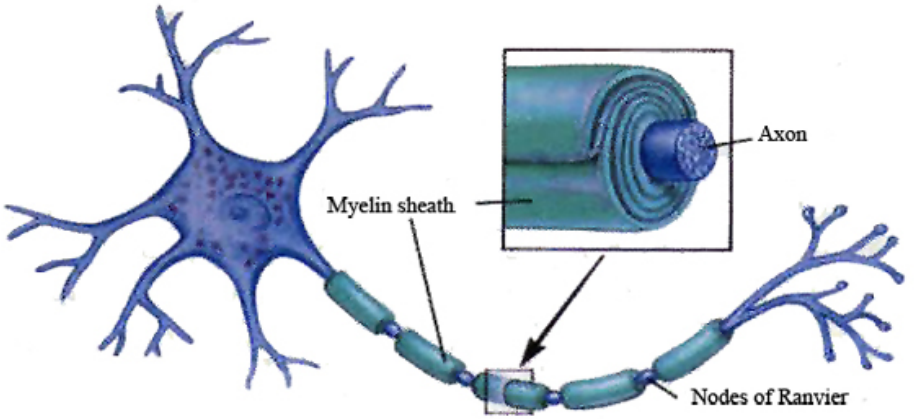
caused by a mutation in the enzyme Arylsulfatase A (ARS A)

incurable, autosomal recessive inherited lysosomal storage disease

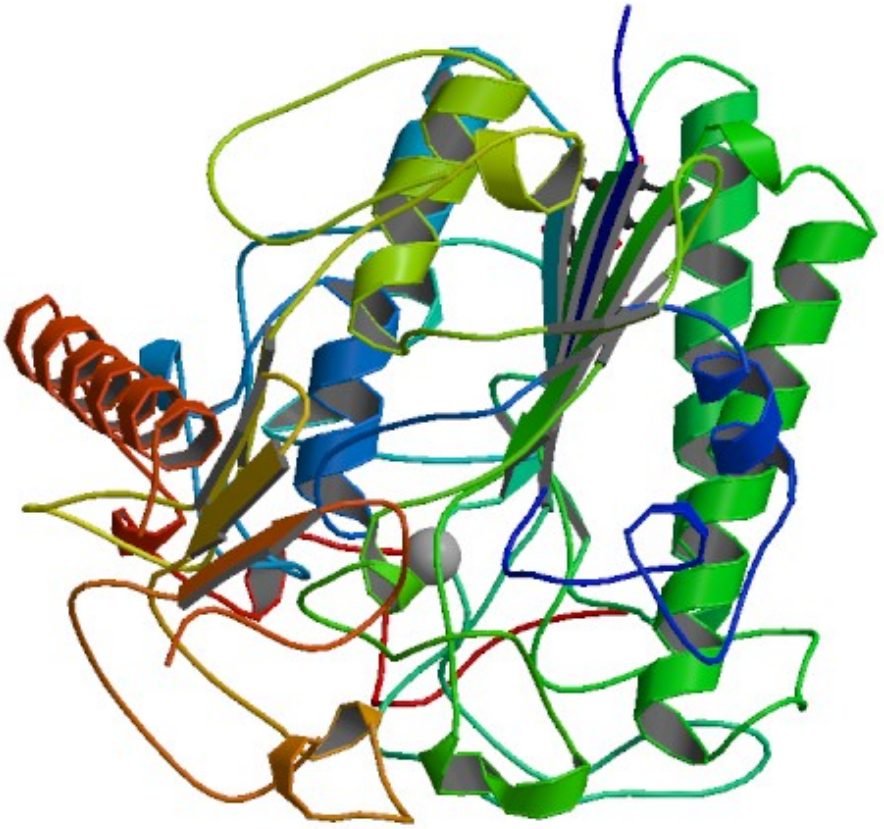
Affects growth/developement of myelin sheath around Axons

White matter abnormalities





Arylsulfatase A



Protein Arylsulfatase A

Breaks up sulfatides in the lysosome

Problem in MLD: not enough enzyme activity of ASA → sulfatides are not digested → toxic level →myelin damage

Another toxic molecule

Lipids Health Dis. 2011 Feb 7;10(1):28.

Accumulation of lysosulfatide in the brain of arylsulfatase A-deficient mice.

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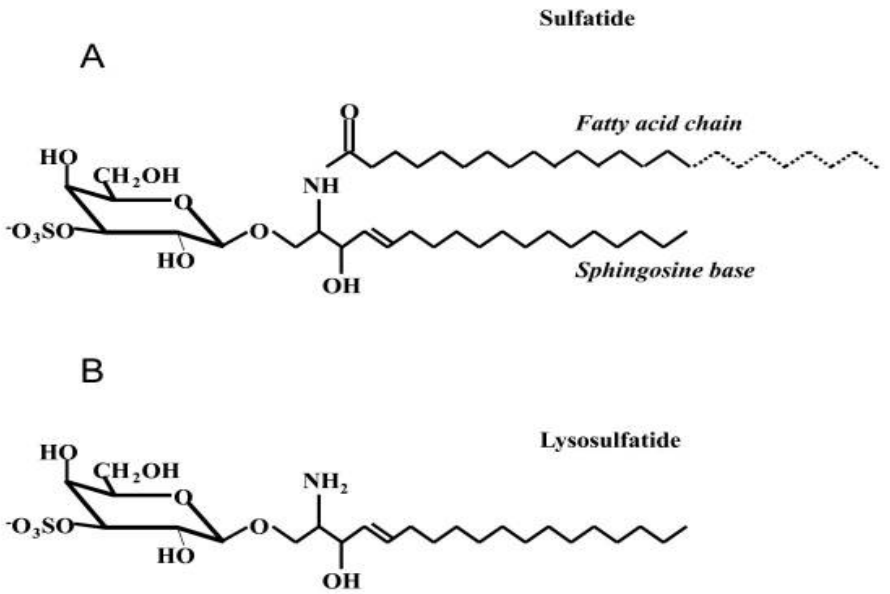
Abstract

Lysosomal storage diseases are a group of disorders where accumulation of catabolites is manifested in the lysosomes of different cell types. In metachromatic leukodystrophy (Arylsulfatase A [EC.3.1.6.8] deficiency) storage of the glycosphingolipid sulfatide in the brain leads to demyelination, resulting in neuromotor co-ordination deficits and regression. In a mouse model for metachromatic leukodystrophy, the ASA null mutant mouse, the accumulation of sulfatide in correlation to phenotype has been thoroughly investigated. Another lipid species reported to accumulate in patients with metachromatic leukodystrophy is the sulfatide related lipid lysosulfatide. Lysosulfatide was shown to be a cytotoxic compound in cell culture experiments and thus suggested to be involved in the pathology of metachromatic leukodystrophy. In this study, we further investigated the developmental profile of lysosulfatide in the brain of ASA null mutant mice by using high performance liquid chromatography. Lysosulfatide could be detected in the brain of normal mice (ASA +/+) from 1.8 months up to 23.1 months of age. From the age of 8.8 months the lysosulfatide levels remained constant at 1 pmol/mg wet tissue. The developmental change (< 20 months) of brain lysosulfatide showed an accumulation in ASA null mutant mice at ages above one month compared to its normal counterpart (ASA +/+). Thus, the ASA null mutant mouse might be a suitable model to further investigate the role of lysosulfatide in the pathogenesis of metachromatic leukodystrophy.

Toxicity caused by

- Sulfatide
- Lysosulfatide



ARSA gene

ARSA gene codes for Arylsulfatase A

Located on the long arm of chromosome 22, base pair 51,063,448 to base pair 51,066,606

Over 60 mutations are known to cause Metachromatic leukodystrophy

Forms of Metachromatic leukodistrophy

5 different allelic forms:

- Late infantile
  - become diseased two years after birth
  - motor symptoms, rigidity, mental deterioration
  - Death occurs five years after breakout of the disease at the latest
- Juvenile
  - Onset is between 3–10 years of age
  - Usually begins with impaired school performance, mental deterioration and dementia. Then, symptons strongly resemble the late infantile form.

Forms of Metachromatic leukodistrophy

Adult forms

- onset after the age of 16.
- commonly psychiatric symptoms and can lead to the diagnosis of schizophrenia.
- Disorders in movement and posture appear very late.
- patients may live for another several decades after onset of the symptoms.

Pseudoarylsulfatase A deficiency

- Carriers show apparent ARS A enzyme deficiency, but without neurologic abnormalities.

Partial cerebroside sulfate deficiency

- Partial defect of ARS A (10-20 % normal activity)
- Symptoms similar to adult form

Treatment

No effective therapy is available yet

- can only slow down progression

Prospectives:

- Enzyme replacement therapy:
  - compensates deficiency, e.g. by infusion
- Gene therapy:
  - e.g. repopulate affected tissues with donor-derived myeloid cells,