Genetic Leucoencephalopathies

Antonio Federico

Dept Medicine, Surgery and Neurosciences, Medical School

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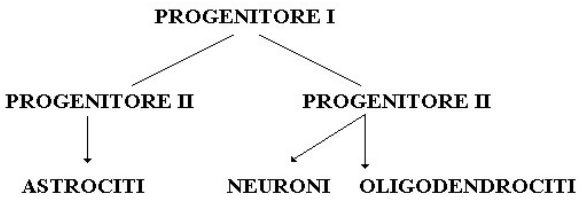
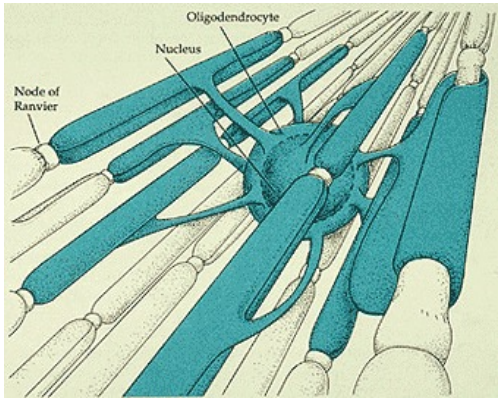
Learning objective n.1:
Informations on Myelin and its pathology

Leukodystrophies are a group of orphan genetic diseases that primarily affect the white matter (WM) of the brain.

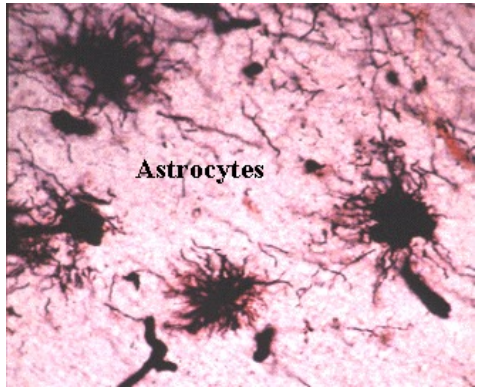
The WM is a complex structure composed of a vast number of nerve fibers (axons) sheathed with a compact lipid-rich membrane (myelin).



Beside myelinated axons, WM contains a variety of supporting cells known as neuroglia or glial cells (astrocytes, microglial cells, and oligodendrocytes)



Glial cells play a major role in the structural, metabolic and trophic support of axons.



Diversity of the genetically determined defects that interfere with glial cell functions explain the large heterogeneity of leucodystrophies.

LEUKODYSTROPHIES
A neuropathological concept

Learning objective n.2:
Neuropathologic concept of leucodystrophy

- **Primary and prevalent involvement of white matter with demyelination**
- **Low amount of myelin, with evidence of its degradation products (ortochromatic, metachromatic, sudanophilic)**
- **Sometimes, spairing of some myelin structures (U fibers)**
- **Tigroid aspect, absence of oligodendrocytes, evidence of globoid cells**

GENETIC LEUCOENCEPHALOPATHIES
Classification

- **According to neuropathology (staining: ortochromatic, metachromatic, sudanophilic; site of demyelination: sparing U fibres, etc; associated findings)**
- **According with clinical aspects (peripheral nerve, muscle, eye involvement, macrocephaly, tendinous xanthomas, premature aging,, skin and bone changes, endocrine involvement: adrenocortical or ovarian insufficiency, diabetes, etc)**
- **According to biochemical abnormalities**
- **According to molecular genetic abnormalities**

Learning objective n.3: Genetic Leucoencephalopathies

LEUKODYSTROPHIES AND LEUCOENCEPHALOPATHIES

Clinical Aspects

Cognitive and behavioural changes of different severity

Predominant motor changes (pyramidal tract and cerebellar system involvement)

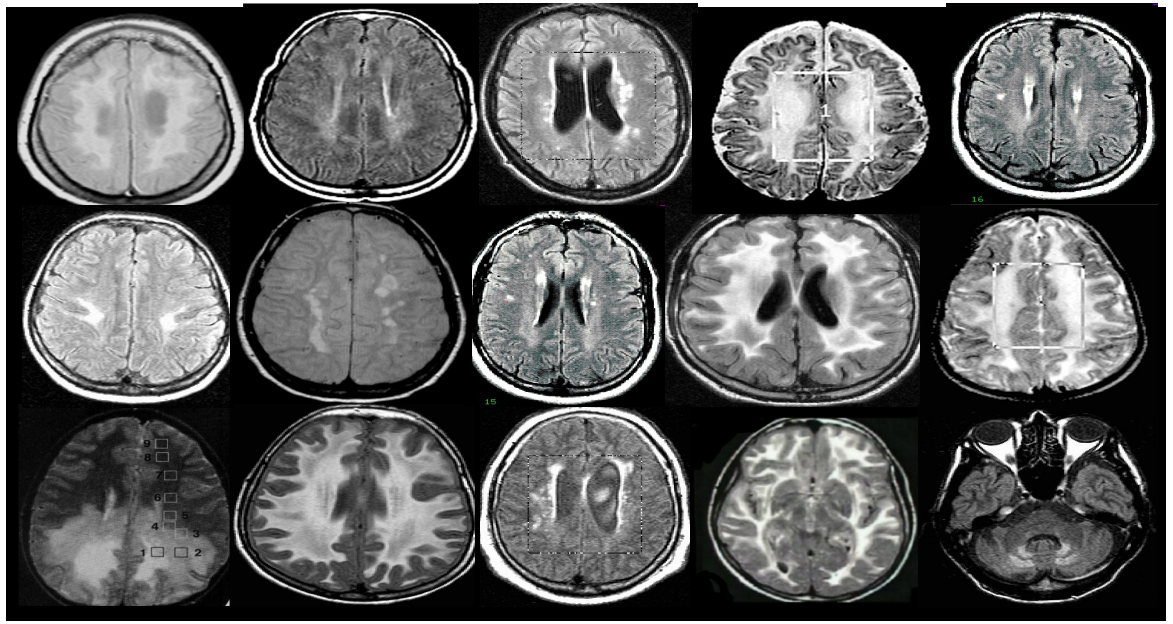
Not constant epilepsy and myoclonus

Neuroimaging

CT: White matter hypodendity

MR T1: Low signal of the white matter for low amount or absence of myelin

MR T2: Hyperintensities in the same areas (increase of water and gliosis)



Learning objective n.4: Genetic Leucoencephalopathies, clinical and neuroimaging

Glial cells dysfunctions

Learning objective n.4

- Storage material for a primary lysosomal dysfunction of lipid or glycoconjugates metabolism
- Plasma membrane lipid changes due to peroxisomal impairement
- Cell lipid trafficking disturbancies
- Energy metabolism impairment
- Chromosomal instability and Dna repair changes
- Cell metabolic deficiency (aminoacid, etc)
- Abnormalities in regulation of protein synthesis
- Small brain vessels dysfunction
- Immune mediated conditions

Table 1 A new classification of genetic white matter disorders

Myelin disorders

Hypomyelination

a. Pelizaeus-Merzbacher disease [224]

b. Peripheral neuropathy, central hypomyelination, Waardenburg-Hirschsprung [36]

c. Cx47-related Pelizaeus-Merzbacher-like disease [36]

d. Hypomyelination of early myelinated structures [104]

Demyelination

a. Metachromatic leukodystrophy [214]

b. Multiple sulfatase deficiency [214]

c. Globoid cell leukodystrophy (Krabbe disease) [214]

d. X-linked adrenoleukodystrophy, cerebral from [173]

Myelin vacuolization

a. Mitochondrial diseases with leukoencephalopathy [159]

b. Phenylketonuria [94]

c. Canavan disease [91]

d. Other selected disorders of amino acid metabolism [2]

e. Cx32-related (X-linked) Charcot-Marie-Tooth disease [45]

Astrocytopathies

a. Alexander disease [25]

b. Megalencephalic leukoencephalopathy with subcortical cysts [23]

c. ClC-2-related disease [45]

d. Vanishing white matter [48]

e. Aicardi-Goutières syndrome and variants [255]

f. Oculodentodigital dysplasia (Cx43) [1]

g. Giant axonal neuropathy [135]

Leuko-axonopathies

a. Hypomyelination with atrophy of the basal ganglia and cerebellum [80]

b. Hypomyelination with congenital cataract [66]

c. Early-onset neuronal degenerative disorders

1. Gangliosidosis GM1 and GM2 [75, 250]

2. Infantile neuronal ceroid lipofuscinosis [79]

3. *AGC1*-related disease [265, 268]

4. *AIMP1*-related diseases [58]

5. *HSPD1*-related disease [134]

d. Pol III-related leukodystrophies [269]

e. Leukoencephalopathy with brainstem and spinal cord involvement and high lactate [231]

f. Hypomyelination with brainstem and spinal cord involvement and leg spasticity [216]

g. Giant axonal neuropathy [135]

Microgliopathies

a. *CSF1R*-related disorders [153, 179]

1. Hereditary diffuse leukoencephalopathy with spheroids

2. Pigmentary ortochromatic leukodystrophy

b. Nasu-Hakola disease [193]

Leuko-vasculopathies

a. Cerebral AD arteriopathy with subcortical infarcts and leukoencephalopathy [162]

b. Cerebral AR arteriopathy with subcortical infarcts and leukoencephalopathy [162]

c. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy [31]

d. Cerebral amyloid angiopathy [162]

e. Leukoencephalopathy with calcifications and cysts [98]

Learning objective n.5: Modern classification of genetic leucoencephalopathies

Acta Neuropathol (2017) 134:351–382
DOI 10.1007/s00401-017-1739-1

REVIEW

Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms

Marjo S. van der Knaap[1,2] · Marianna Bugiani[1,3]

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