

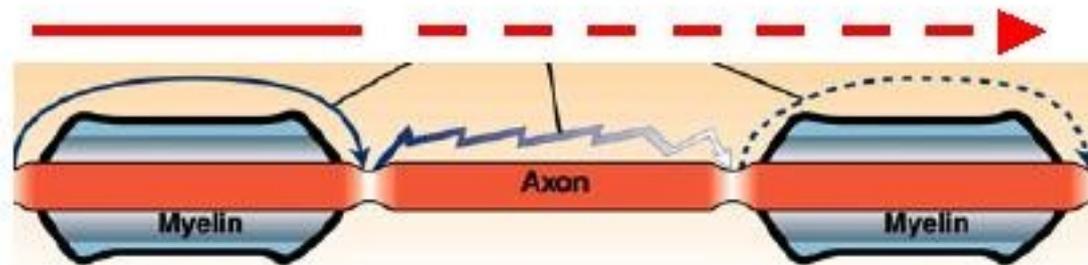
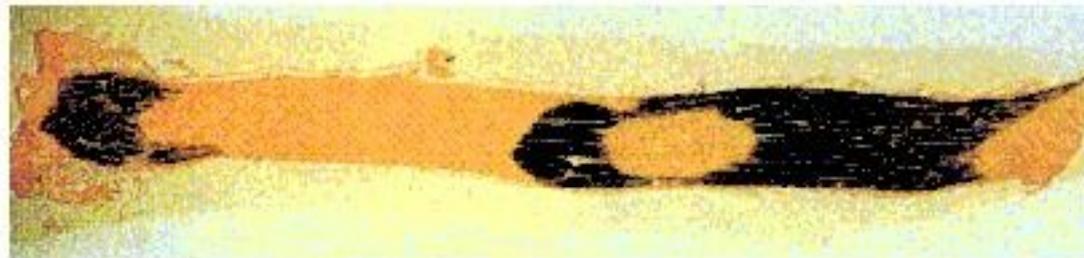
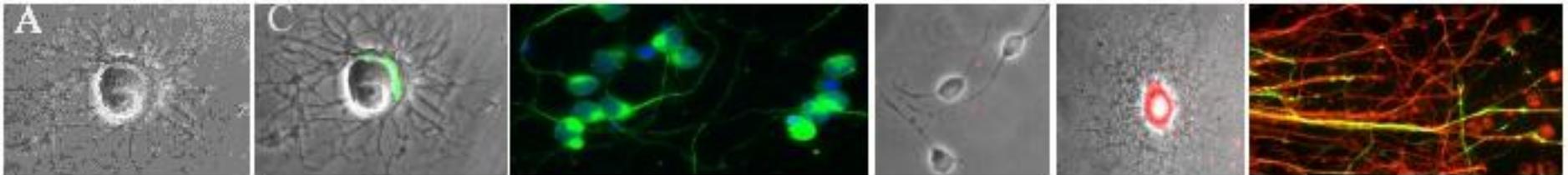
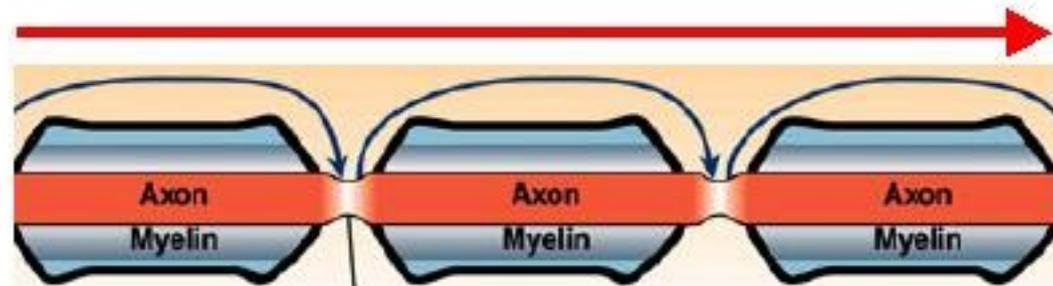
**Clinical spectrum of CNS demyelinating  
disease**

**Alastair Compston**

**Bergamo**

**March 12<sup>th</sup> 2003**

# Axon-glia interactions and demyelinating disease



# The classification of demyelinating disease

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## Isolated demyelinating syndromes

Acute haemorrhagic leuco-encephalomyelitis - Hurst's disease

Acute disseminated encephalomyelitis

Optic neuritis

## Cord lesions

acute necrotising myelitis

transverse myelitis

chronic progressive myelopathy

radiation myelopathy

HTLV 1 associated myelopathy

Monophasic isolated demyelination- site unspecified

## Multiple sclerosis

relapsing remitting

secondary progressive

primary progressive

benign

malignant or Marburg variant

childhood

silent multiple sclerosis

Devic's disease

Balo's concentric sclerosis

combined central and peripheral demyelination

## Central pontine myelinolysis

pontine

extrapontine

## Leucodystrophies

### Schilder's disease

myelinoclastic diffuse sclerosis

transitional diffuse sclerosis

Globoid cell (Krabbe's disease) leucodystrophy

### Adrenoleucodystrophy

X linked childhood adrenoleucodystrophy

X linked adult onset adrenomyeloneuropathy

autosomal recessive neonatal adrenoleucodystrophy

autosomal recessive Zellweger's syndrome

### Metachromatic leucodystrophy

late infantile

juvenile

adult

multiple sulphatase deficiency

### Pelizaeus Merzbacher disease

classical

connatal form

late onset

### Adult onset leucodystrophies

# Acute disseminated encephalomyelitis

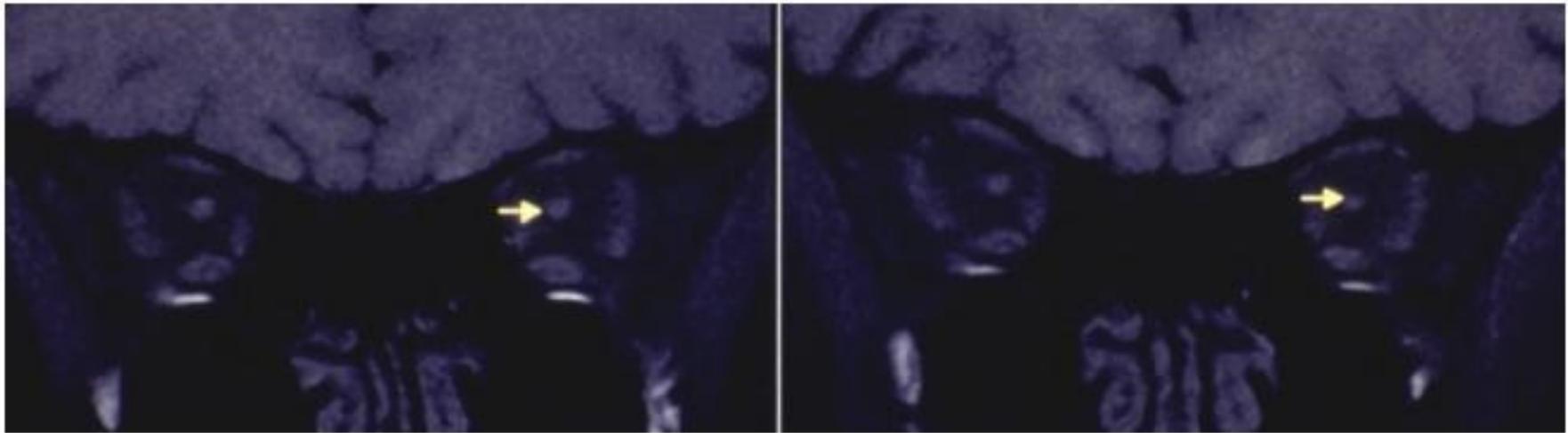
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**Multifocal but monophasic**  
**Children > adults**  
**Hyperacute and fatal (Hurst's disease)**  
**.. focal with recovery**  
**Large white matter MR lesions**  
**CSF pleocytosis**  
**Transient oligoclonal bands**  
**Triggered by infections > vaccinations**  
**immunologically mediated**  
**Uncertain status of *MDEM***  
**Rx corticosteroids and ivIG**



# Optic neuritis

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**Unilateral, recurrent, bilateral sequential > bilateral simultaneous**  
**Subacute onset with recovery > progressive**  
**Dissociation between functional and structural recovery - plasticity**  
**Recurrence risk for development of multiple sclerosis**  
**Optic neuritis – *a window on the brain***

# Transverse myelitis

**Pain .. motor, sensory and sphincter disturbance with spinal shock**

**Adults > children**

**Longitudinal > transverse MR lesions**

**Poor recovery ...**

**.. especially in necrotising myelitis**

**Recurrence risk for multiple sclerosis**

**Devic's disease**

**optic nerve or chiasm .. spinal cord lesions in either order**

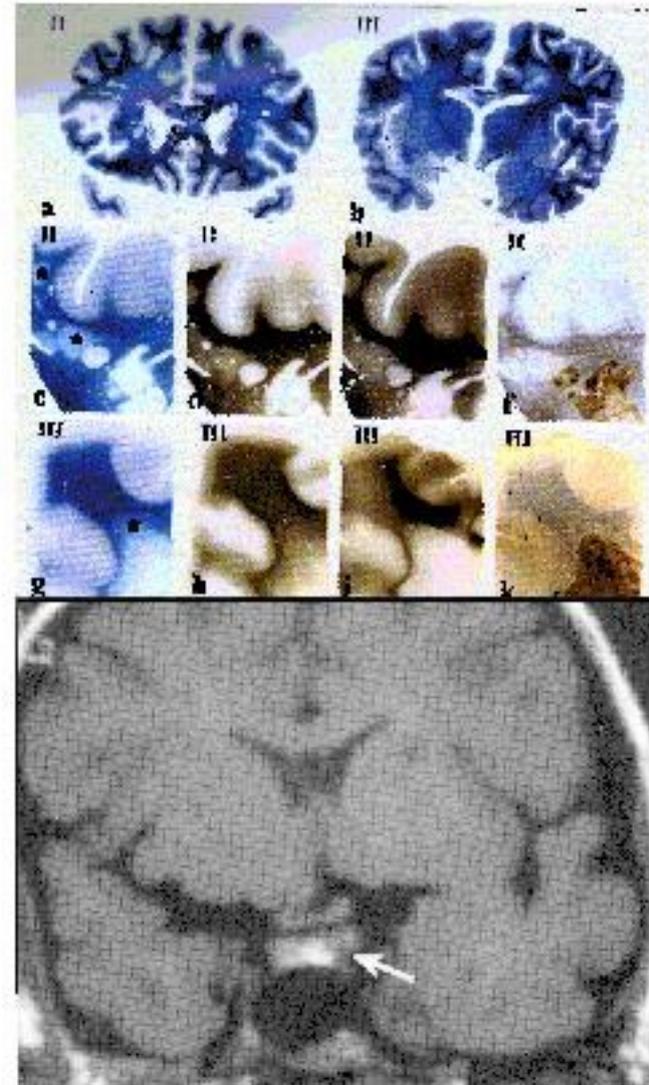
**Associated diseases and causes**

**Oriental and African phenotype**

**Transient oligoclonal bands**

**Antibody and complement mediated**

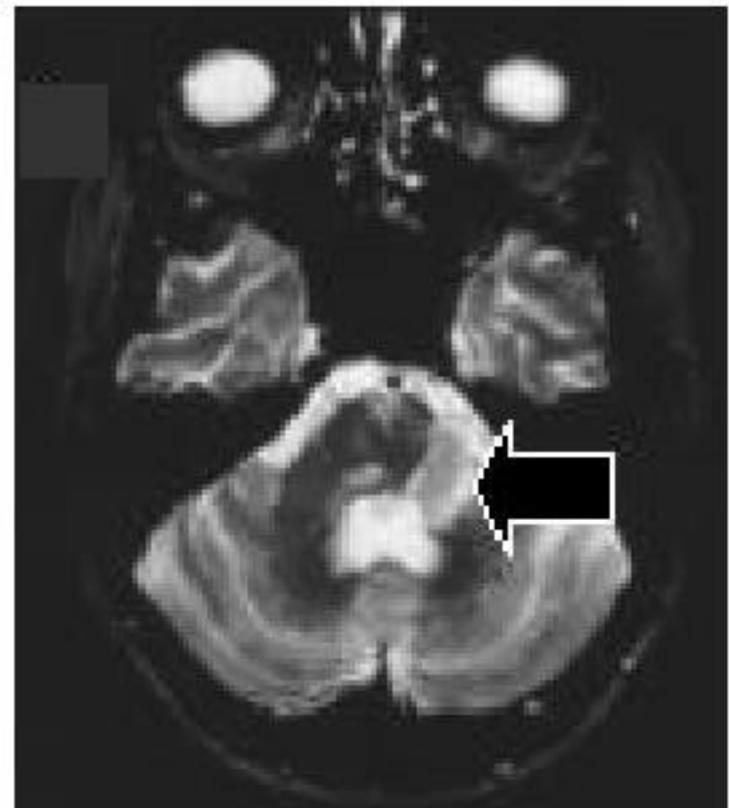
**Rx: plasma exchange**



# Isolated brain stem lesions

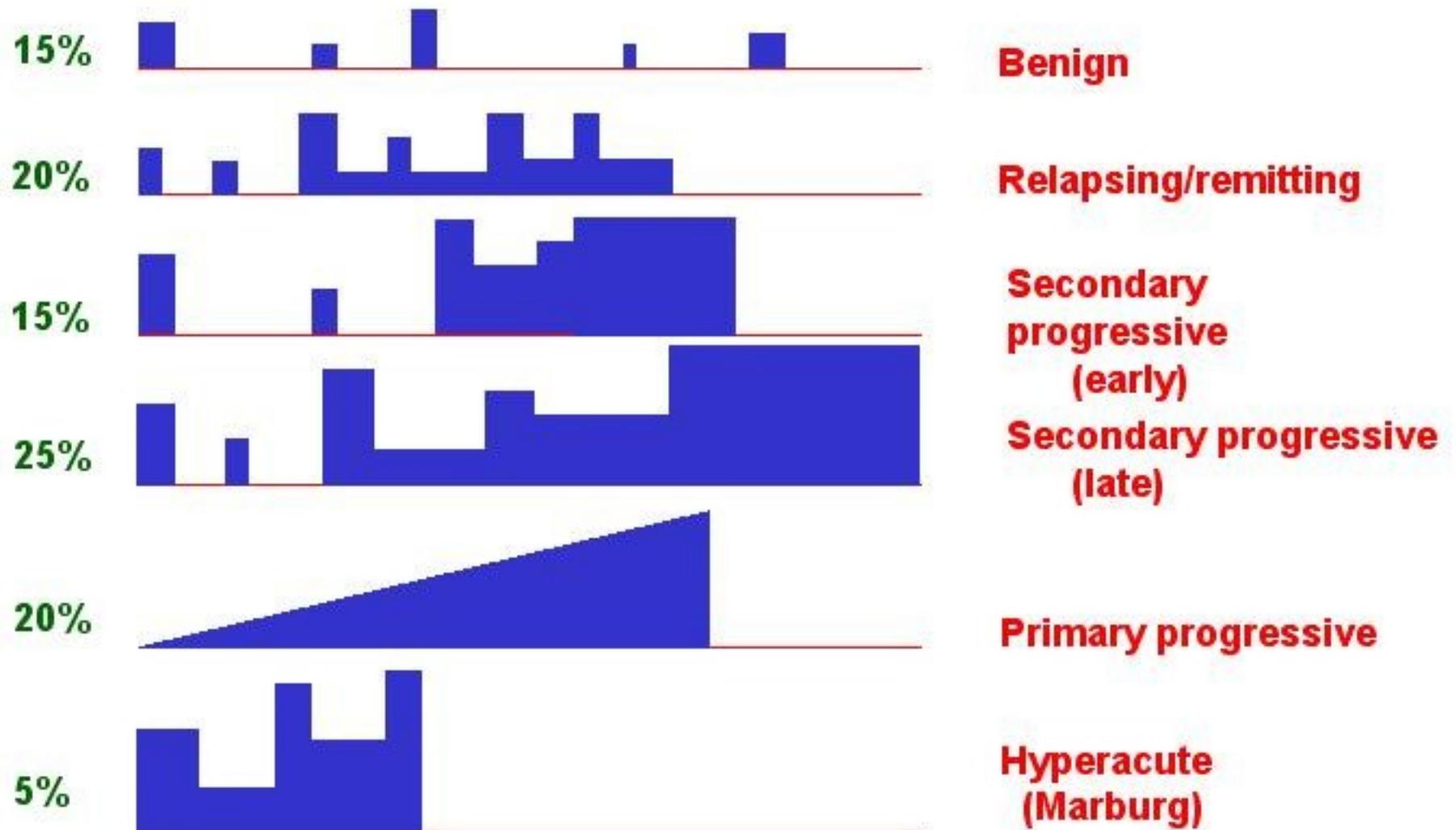
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- Predictable symptoms and signs + headache
- High recurrence risk for multiple sclerosis
- Nuclear palsies and long tract signs



# The clinical course of multiple sclerosis

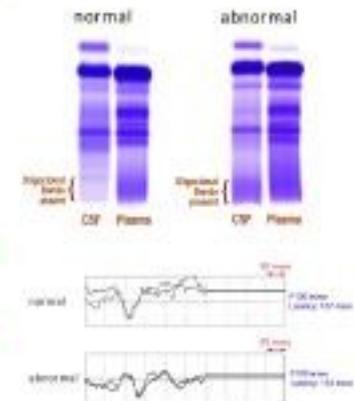
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# The McDonald (2001) criteria for the diagnosis of Multiple Sclerosis

One or more episodes? ... Two	First clinical episode	Subsequent clinical episode	Paraclinical Data
	one or more sites affected	different sites affected	not required
	one site affected	same site affected	lesions disseminated in space on MRI
	two sites affected	none	(if CSF positive, MRI criteria less rigorous) lesions disseminated in time on MRI
	one site affected	none	lesions disseminated in space on MRI (if CSF positive, MRI criteria less rigorous) <b>AND</b> lesions disseminated in time on MRI
	insidious progression suggestive of MS	none	positive CSF <b>AND</b> lesions disseminated in space on MRI (if VEP abnormal, MRI criteria less rigorous ) <b>AND</b> lesions disseminated in time on MRI <b>OR</b> continued progression for one year

## Investigations



## Childhood multiple sclerosis

*A female child had acute disseminated encephalomyelitis at aged 8 years*

*MR scan was abnormal (A)*

*She made a partial symptomatic recovery and subsequent images became normal (B)*

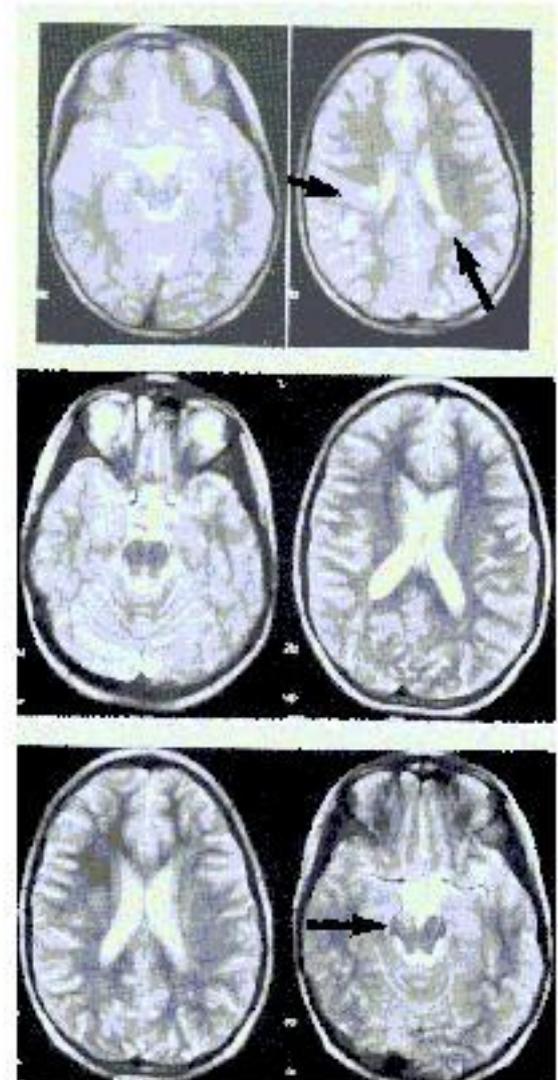
*One month later she had an acute midbrain lesion*

*She has since remained well for 6 years*

**Females > males**

**Often with encephalitic presentation**

**Prognosis surprisingly good by comparison with adult cases**



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## Central pontine myelolysis

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**Follows correction of hypo- or (less frequently) hypernatraemia**

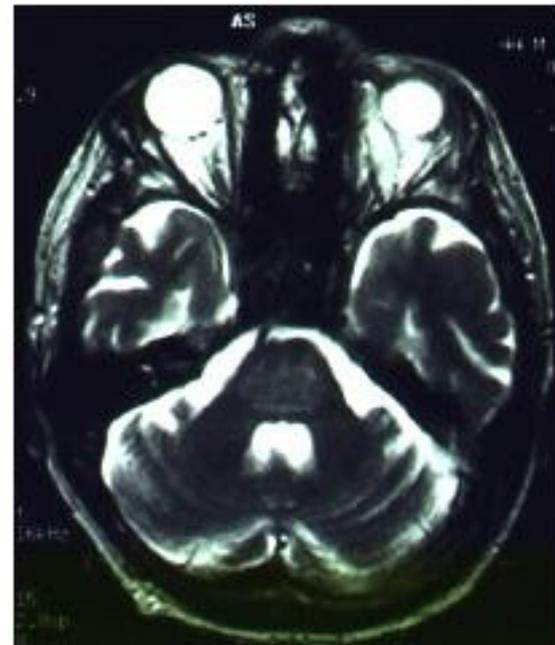
**.. typically from  $<110$  mmol/l or  $> 2$  mmol/l/hour**

**More likely with acute than chronic hyponatraemia**

***Flaccid* brain stem nuclear and long tract signs**

**Extrapontine features are common**

**Monophasic with full recovery is usual**



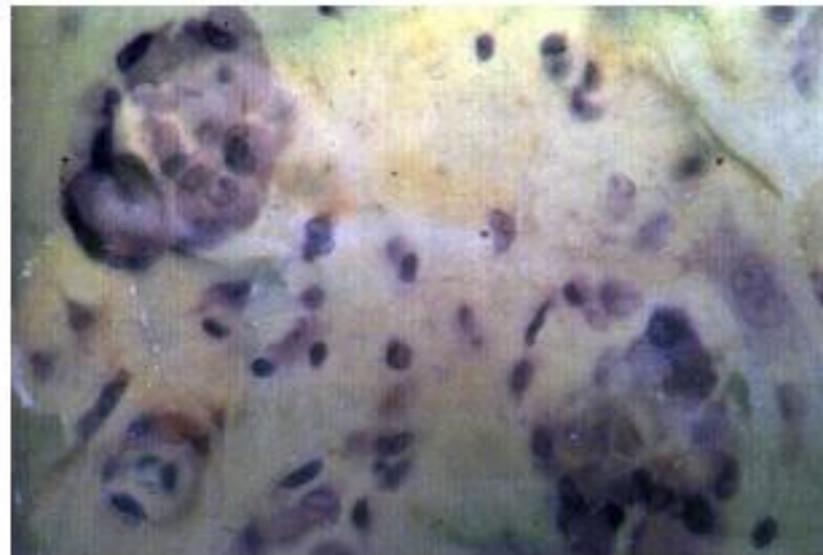
## Globoid cell leucodystrophy or Krabbe's disease

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**Accumulation of galatocerebroside in white matter multinucleate cells (and leucocytes or fibroblasts)**

**Childhood onset (infancy) but may be late onset developmental delay, epilepsy, corticospinal signs and optic atrophy + peripheral neuropathy**

**Defect is in alpha galatocerebrosidase encoded @ 14q21-q31**

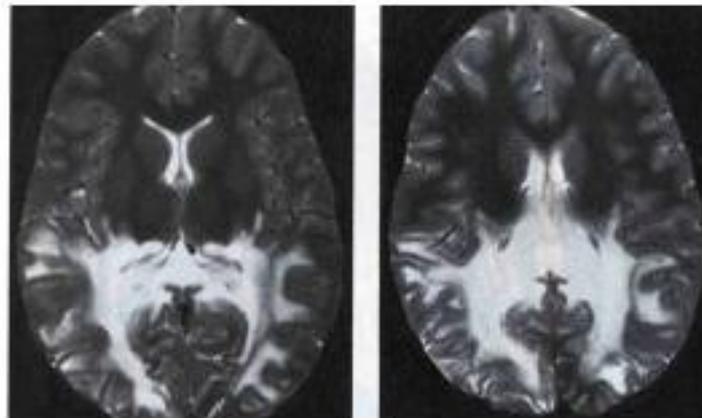


## Adrenoleukodystrophy

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Due to deposition of saturated fatty acids due to defective very-long chain fatty acid acyl-CoA synthetase activity failing to anchor VLCAs or translocate these into the peroxisome membrane  
Screening is for ratio of hexanoic : tetra / docosanoic acid in males, and *Lyonised* or homozygotic females

Autosomal recessive adrenoleucodystrophy and Zellweger's syndrome present in infant females with epilepsy, hypotonia, mental retardation, retinal degeneration and hepatic disease



## Metachromatic leucodystrophy

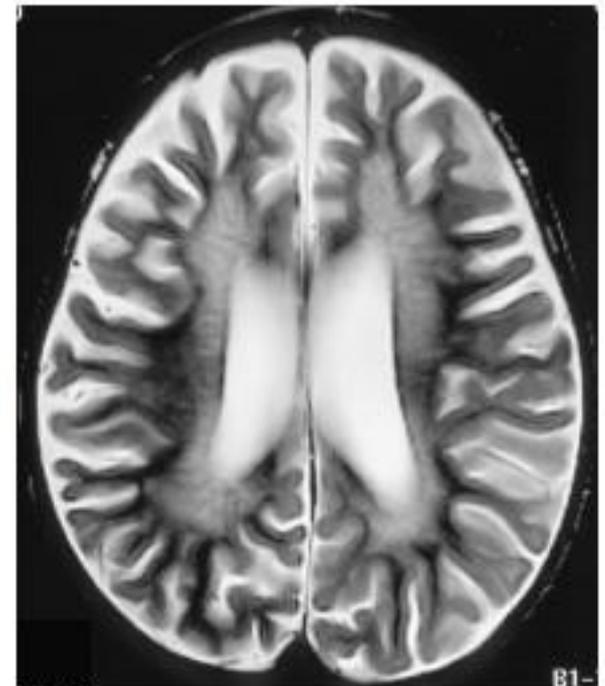
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**Ex-Diffuse Sclerosis based on metachromatic material in brain macrophages and peripheral nerve, detected as increased urinary metachromatic material and sulphatide due to deficiency of aryl-sulphatase A or its activator .. multiple sulphatase deficiency combines MLD with mucopolysaccharidosis**

**Painful neuropathy with demyelination and remyelination + non-inflammatory CNS demyelination with axon sparing causing corticospinal signs, dementia and optic atrophy**

**Phenotype depends on absolute deficiency of aryl-sulphatase .. age at onset varies from infancy to early adult life**

**Rx: dietary restriction of vitamin A and sulphur containing foodstuffs + bone marrow transplantation**



## Pelizaeus-Merzbacher disease

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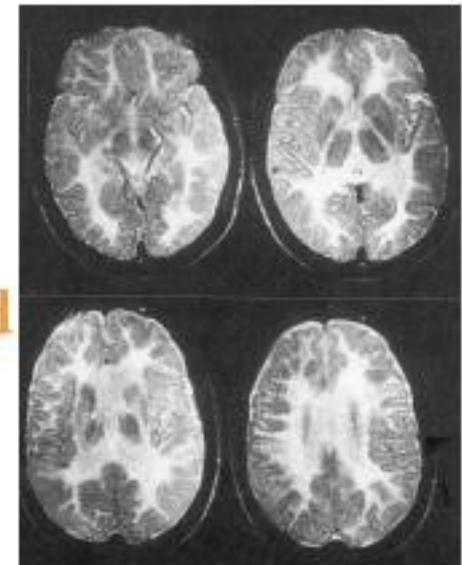
Childhood onset of motor and developmental delay with epilepsy ..

Three types distinguished by abnormal eye movements, movement disorders and laryngeal paralysis

Onset is usually in childhood but may be delayed into adult life

Defect is mutations (>30) of *plp* @ Xq21.1

PLP stabilises the lamellar structure of myelin .. mutations lead to oligodendrocyte loss and dysmyelination



## Progressive multifocal leucoencephalopathy

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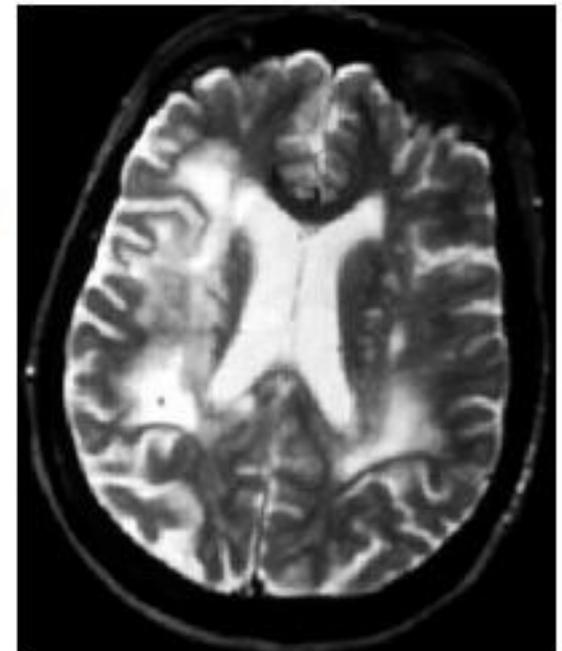
**Areas of confluent demyelination starting in but not confined to the posterior cerebral hemispheres**

Oligodendrocyte destruction by papovavirus infection - JC, BK and SV40 *viridae* inclusions  
Complicates chronic immune deficiency from reticulosis, chronic infection and immune therapies + HIV1 infection

Latent virus in renal tissue → brain

Presents as visual loss, epilepsy, corticospinal signs, cognitive impairment and coma

Usually fatal but may arrest with or without antiviral therapy or protease inhibitors



## .. and when in Rome ... Marchiafava Bignami disease

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The disease of Italian red wine  
Quoted in every textbook of neurology  
Never seen in clinical practice

... was it imaginary .. or has Italian  
wine improved?

