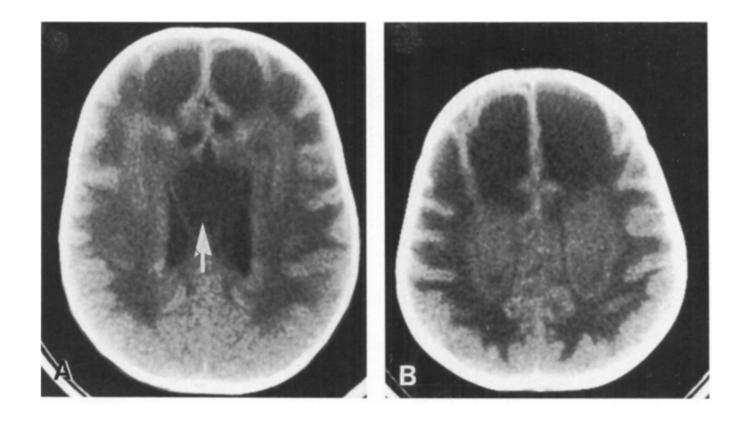
CASE STUDY OF A DISEASE "X"

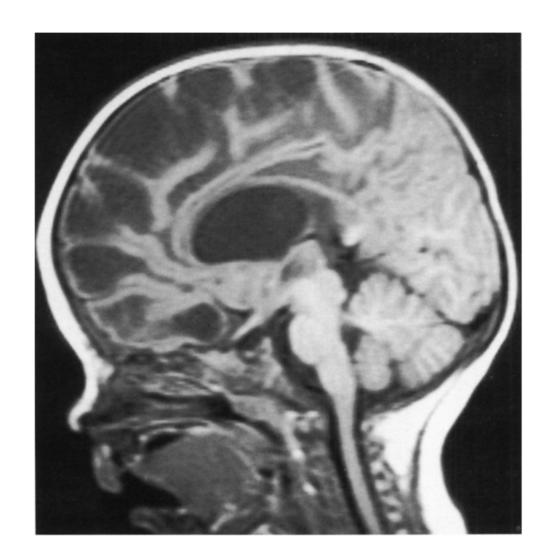
- J.N. was the first child of healthy parents
- Was normal for 2 months after birth except for a slightly large head circumference
- Her younger brother is normal and no disease history in the family

- At 3 months of age, 2 days after receiving a first diphtheria, pertussis, and tetanus (DPT) immunization, she developed stiffening spells and an abnormal cry
- Seizures few weeks later
- CT scan showed decreased density of the white matter
- Toxoplasmosis, rubella, cytomegalovirus, and herpes simplex tests were negative
- Later clinical seizures subsided, but motor delay remained

- At 8 months old happy child, but with spastic quadraparesis
- Head too large, veins dilated
- CT showed enlargement of ventricles, low cortical white matter

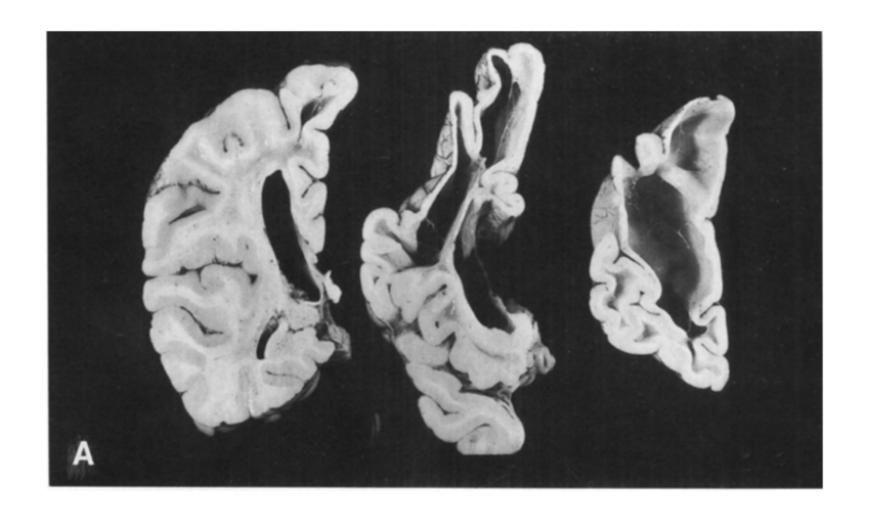


- MRI impairment of myelin in frontal and parietal cortex
- Only thin rim of frontal cortex remained

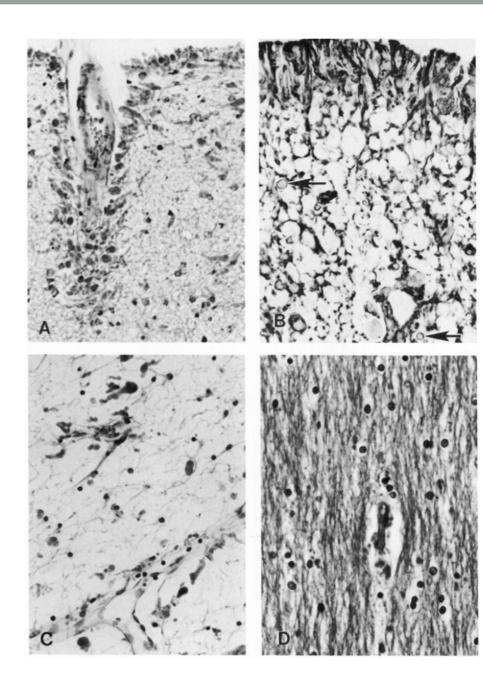


- For several years she was able move in a walker
- Actively played with social interaction
- Minimal language skills
- During last years all functions were compromised
- Died at 8 years

- Autopsy: huge reduction in cortex width, enlargement of ventricles
- Lysis of myelin and appearance of cavities

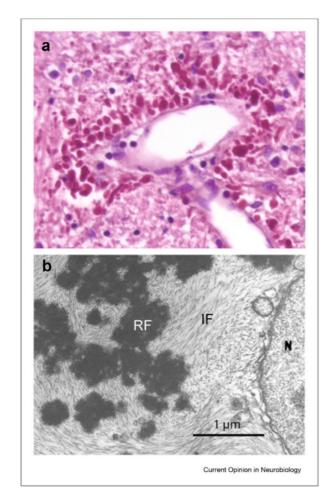


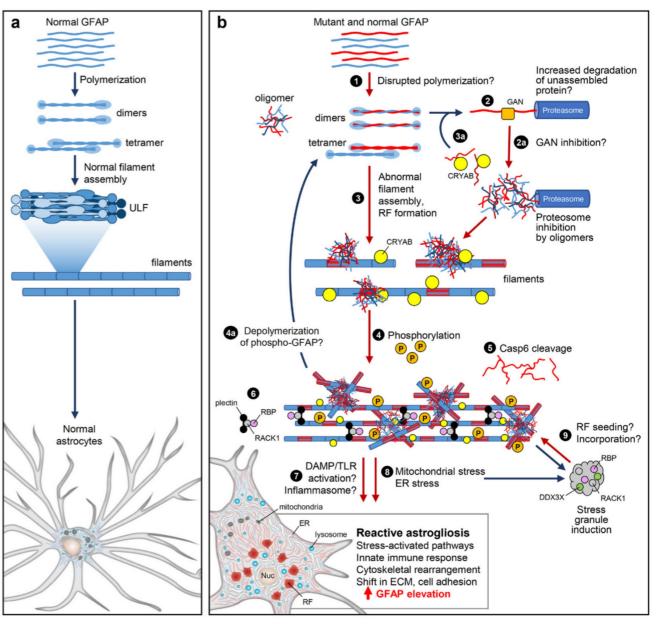
- GFAP staining
- A fibers around blood vessels in cortex
- B fibers in spinal cord
- C Demyelinated white matter in cortex depleated of axons
- D Preserved white matter in cortex contains fibers

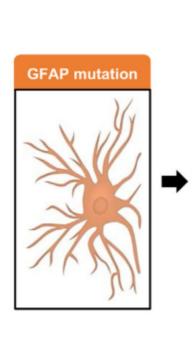


Alexander's Disease (AxD)

Rosenthal fibers – GFAP aggregates, characteristic of AxD:







Astrocyte response, function

Disrupted proteostasis

Protein aggregation Proteasome dysfunction Autophagy activation

Defective cellular transport

Lysosomes, ER distribution ATP release/ calcium signaling Mitochondria motility

Mitochondrial function

Altered energy supply/demand ROS production Antioxidant response

Reactive astrocyte response

Stress-activated pathways Immune signaling cascade Shift in ECM, cell adhesion GFAP elevation

Non-cell-autonomous effects

Disrupted support functions

Glutamate balance
Potassium balance
pH balance
Water and ion balance
Gap junction metabolite exchange
Energy supply

Immune response

Cytokine/chemokine release Microglia reactivity Infiltrating T-cells, others? Crosstalk

Development/maintenance

Oligodendrocyte maturation Myelination Synapse formation? Synapse maturation? Neurotoxicity (ROS, NO, glutamate)

CNS function

Seizures

Reduced glutamate uptake Altered GABA receptors/pathways

Hypo-/de-myelination

Oligodendrocyte support
Altered connectivity (gap junctions)
Altered ECM, cell adhesion, stiffness
Cytokines, chemokines signaling
Energy demands

Motor and Cognitive deficits

White matter pathology Long range & local circuits? Synapse development/function Neurodegeneration

Autonomic dysfunction

Brainstem, spinal cord atrophy Central pattern generators?

Current Opinion in Neurobiology

No treatment

Short interfering oligonucleotides (siRNA) – to target GFAP mRNA, decrease level of GFAP protein – prospective option