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Network Neuromuscular Diseases (ERN EURO-NMD)

Webinar

‘X-Linked adrenoleukodystrophy in children’

by Caroline Sevin,

Reference Center for Leukodystrophy, Institute for Brain and Spine, Paris, France

7. October 2021

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Learning objectives

By the end of this webinar you will be able to:

- Discuss the different phenotypes of X-linked Adrenoleukodytrophy
- Know how to diagnose and follow X-ALD children
- Evaluate the indications and limits for HSCT
- Understand why genetic counselling is so important in this disease
-

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Webinar outline

- Initial clinical case
- What is ALD and what are the different phenotypes
- What is the clinical and radiological course of CALD
- How to evaluate the severity or CALD
- What are the indications and results for HSCT in ALD
- Importance of family screening and monitoring of presymptomatic patients
- Final clinical case

Just start with a clinical case

6 years old boy

- Only child of non-consanguineous parents (French/Portuguese)
- No familial history
- Medical history
  - Asthma, Allergy
  - Normal psychomotor development
  - For 1 year:
    - Occasional enuresis
    - Several episodes with fever, vomiting, abdominal pain (duration <24 hours)
    - Recent attention deficit, writing a little less neat

When the story begins, it seems « banal » ...

- D0 in the evening: headache, asthenia
- D+1: fever 38.8 ° C
- D+1 in the evening : degradation -> emergency room
  - T ° = 39.2 ° C
  - hemodynamic shock requiring filling with physiological saline -> improvement
  - confusion, psychomotor agitation, signs of encephalitis
  - headache, photophobia
  - normal neurological examination otherwhise
  - tanned skin (ethnical)

Initial assessment

- Hb: 13.6, WBC: 11,300, CRP 186
- Na: 128; K 5.3; urea 14 mmol / l; creatinine 95 umol / l.
- CSF:
  - WBC 33; Glc 2.9 mm; Prot 0.57; sterile
  - PCR HSV, VZV, enteroV, mycoplasma: negative
- EEG: encephalitis-like, no seizures.
- Brain CT scan: normal
- Nasopharyngeal swab: positive for influenza B

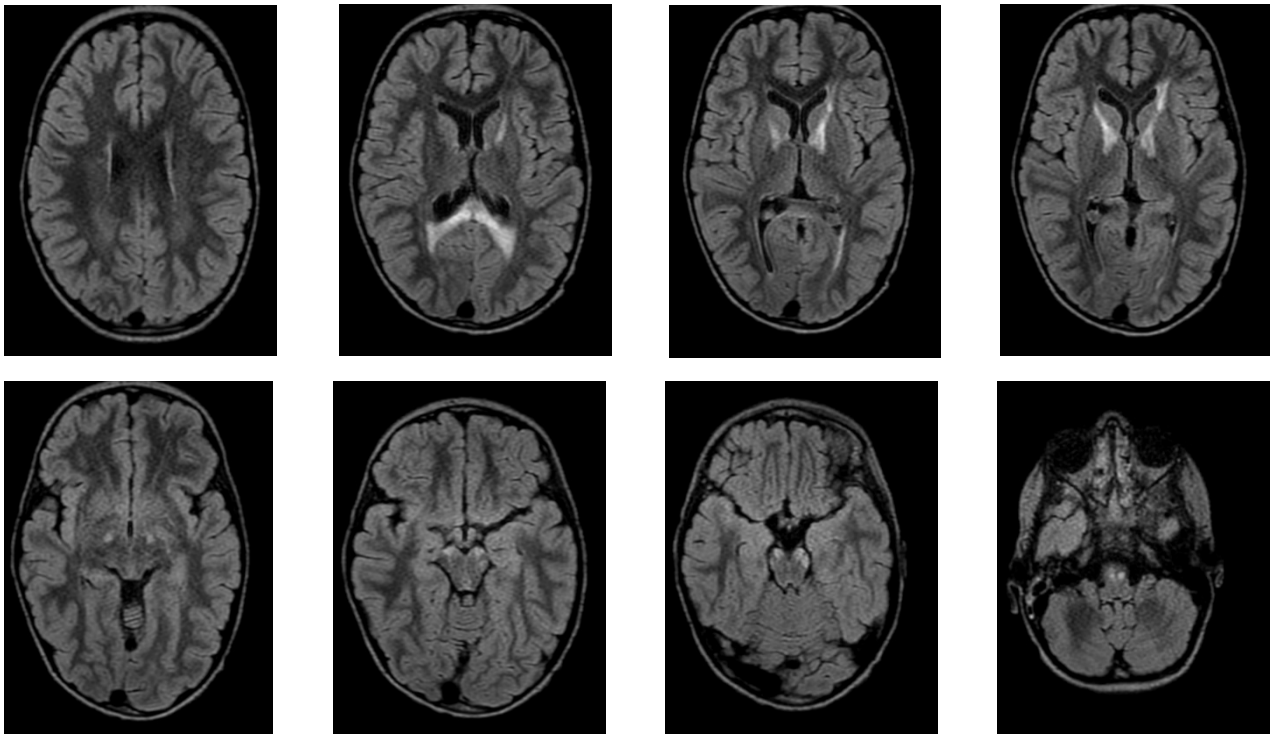
Influenza encephalitis

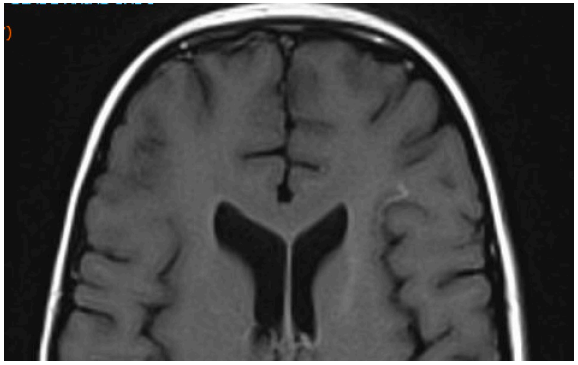
Rapid recovery

→ end of the story?

- IV rehydration -> normalisation of biological parameters
- normalisation of clinical signs in 3 days

Brain MRI…





Gadolinium enhancement

hyper Flair/T2 lesions (splenium, internal capsules, frontal WM, corticospinal tracts, auditory pathway)

What would you have done?

A) Discharge the boy from hospital, without particular recommendation, the diagnosis of influenza encephalitis is evident and the child has recovered

B) Try to better understand biological abnormalities (hyponatremia, hyperkaliemia)? -> perform other blood tests?

C) Do another lumbar puncture with aditionnal tests?

D) Consider genetic leukodystrophy?

E) I don’t know

Not a so « simple » case…

- **ACTH ↑↑ 6250 pg/ml**, cortisol ↓
- Renin ↑113 pg/ml
- …..Melanoderma
- ….. Recurrent abdominal pain episodes

ADRENAL INSUFFICIENCY

+ Leukodystrophy…

X-LINKED ADRENOLEUKODYSTROPHY

Very Long Chain Fatty Accids (VLCFA)

C26:0 = 2.5µmol/L (N< 1.06),

C24:0 = 86 µmol/L,

C22:0=64µmol/L,

C26:0/C22:0 = 0.039 (N < 0.019).

Take home messages

- Hyponatremia: always think to adrenal insufficiency
- Adrenal insufficiency in boys => ALD until proven otherwise
  - first cause of ALD in childhood (boys)
  - even if normal MRI
  - test AGTLC+++
- Beware of behavioral changes (ADHD) that occur "unexpectedly"
- Adrenoleukodytrophy = ”Urgent" diagnosis
  - adrenal insufficiency
  - treatment is possible for the brain disease but the window is narrow

What is X-linked Adrenoleukodystrophy (X-ALD)

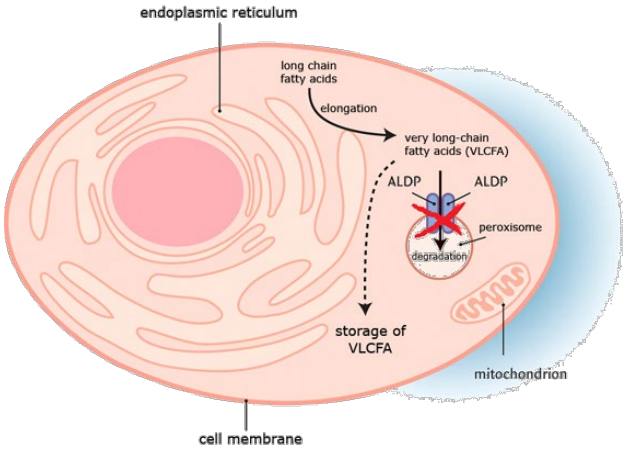
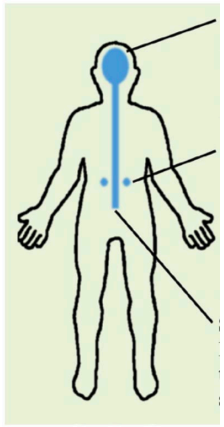
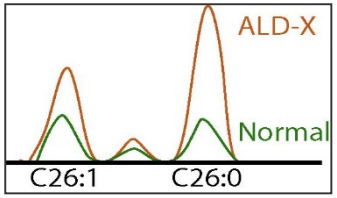


Image from: http://www.x-ald.nl/biochemistry-genetics/vlcfa/
Moser HW. *Brain* 1997;120:1485-1508.

- A progressive X-linked metabolic disease
- The first cause of leukodystrophies in childhood (1/17,000 births)
- Due to mutations in the *ABCD1 gene*
- leading to impaired expression of the peroxisomal half-transporter ALD protein (ALDP) involved in peroxisomal import of very long chain fatty acids (VLCFA)
- VLCFA accumulation primarily in adrenal and nervous system tissues

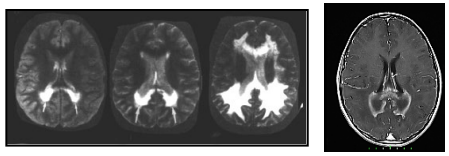


- **100% of males and 75-80% of heterozygous women accumulate VLCFA (diagnostic marker in the plasma)**
- **VLCFA levels are not correlated to the phenotype**



What are the different phenotypes of ALD?

- **Childhood Cerebral ALD = CCALD (3-12 years): 35-40%**



- **Adrenomyeloneuropathy = AMN (adult): 55%**
  - spastic paraparesis
  - sphincter disorders, sensory ataxia, PN involvement
  - adult males (100% penetrance> 55 years)
  - and heterozygous females (> 80%)
  - not lethal, but severe motor impairment
  - **and 30-50% of AMN patients will develop cerebral ALD (ACALD**)

- **Adrenal Insufficiency (10%) -> CCALD or AMN**

-> Continuum of severity

Asymptomatic → **Adrenal insufficiency** → **Adrenomyelo-neuropathy (AMN)** → **Cerebral ALD (CALD)**

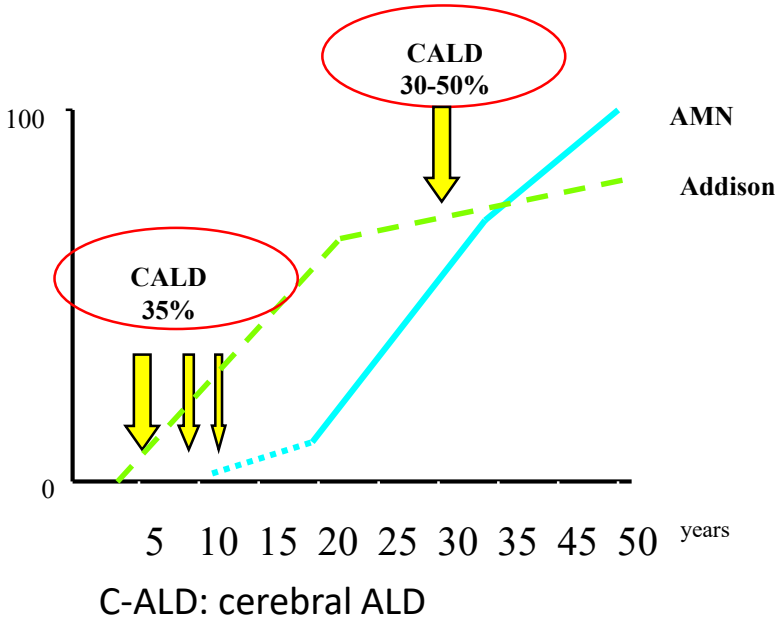
> 60% of male will develop cerebral ALD

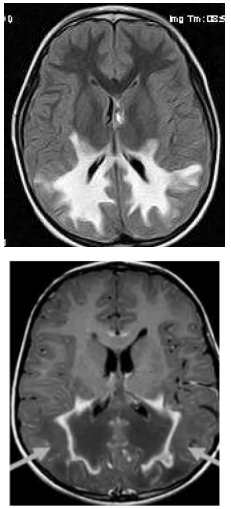
Women: no cerebral ALD (>1%), no adrenal insufficiency

ALD: one disease, two phenotypes?

Primary phenotype of ALD is an axonopathy of spinal cord (AMN)

With an additional risk to develop cerebral demyelinating disease





C-ALD: cerebral ALD

What is the clinical course of CALD?

Initial Symptoms

- Poor school performance
- Behavioral problems
- May be misdiagnosed as ADHD
- Insidous

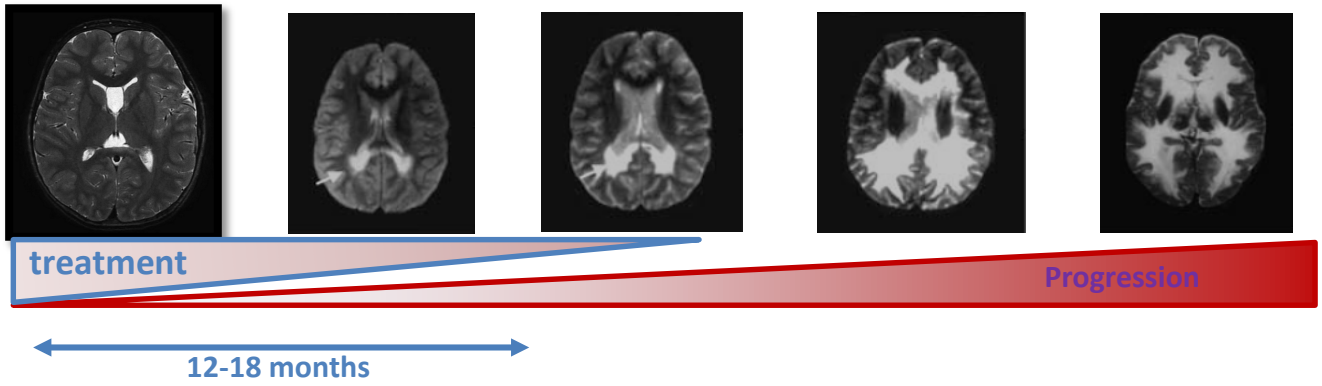
Moderate Disability

- Hearing impairment
- Aphasia/apraxia
- Vision impairment
- Swallowing dysfunction
- Walking/running difficulties
- Episodes of incontinence
- Seizures

Major Functional Disability

- Cortical blindness
- Loss of communication
- Tube feeding
- Wheelchair dependence
- No voluntary movement
- Total incontinence

Brain MRI

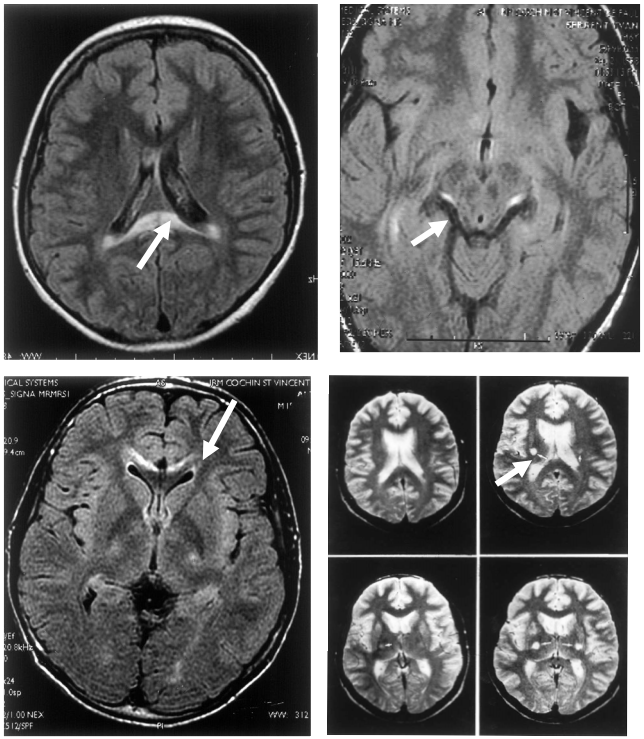


CALD: Initial sites of cerebral demyelination are always at the same location

Splenium or genu
of the corpus callosum

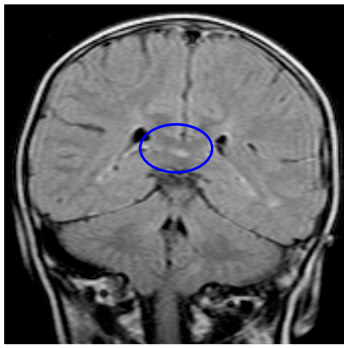
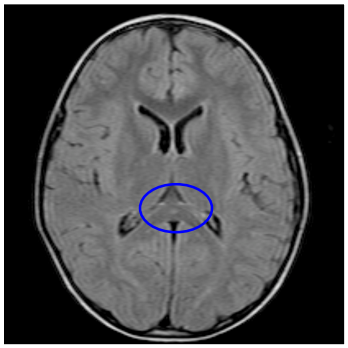
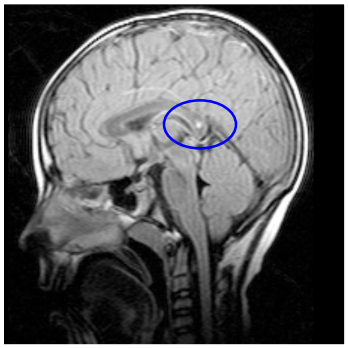
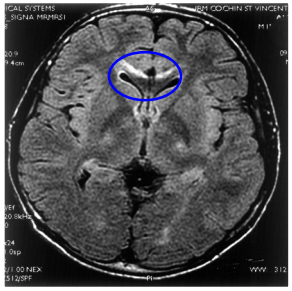
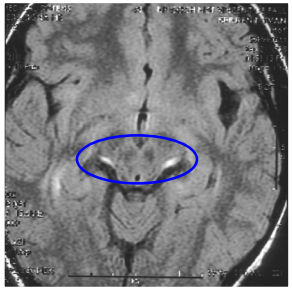
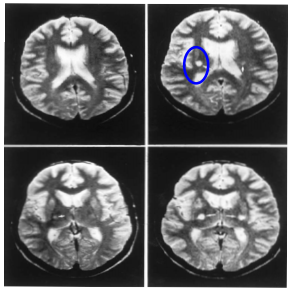
But also

- along pyramidal tracts
- auditive pathways
- anterior commissura
- ponto-cerebellar tracts



And therefore very easy to detect early onset of cerebral ALD

assuming you are looking at the right places…

How to evaluate the severity or CALD?

Neurologic Function Score (NFS, 0-25)

Major Functional Disabilities, MFD

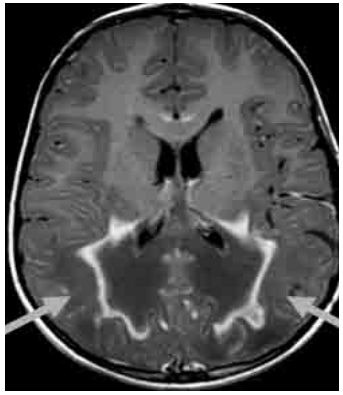
Component	Score
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment	1
Cortical blindness	2
Swallowing dysfunctions	2
Tube feeding	2
Running difficulties	1
Walking difficulties/ spasticity	1
Spastic gait (need assistance)	2
Wheelchair dependence	2
No voluntary movement	3
Episodes of incontinence	1
Total incontinence	2
Non-febrile seizures	1
Possible Total	25

Loes MRI severity score:

34-point severity scale for brain MRI findings, based on the location and extent of involvement, and on the presence of either focal or global atrophy

Gadolinium enhancement:

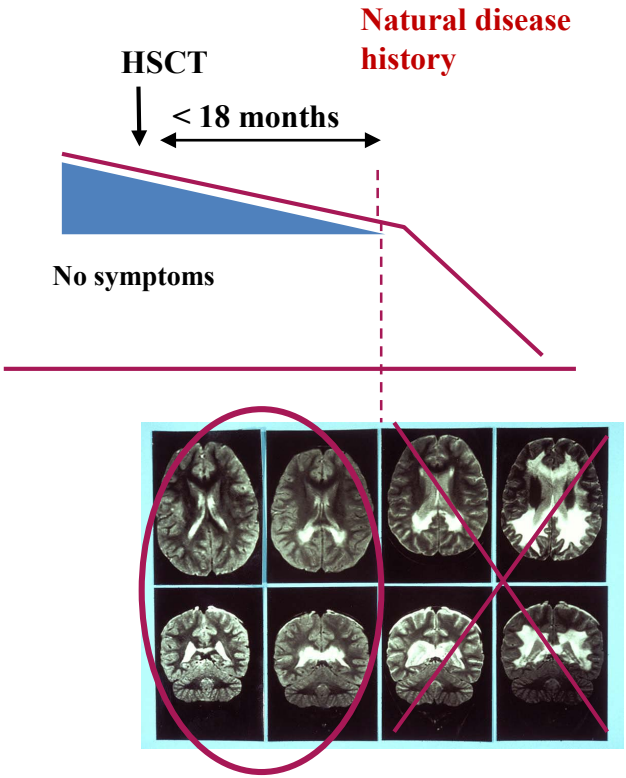
Indicator of active inflammation

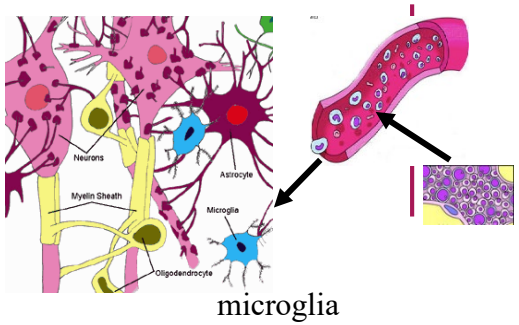


Hematopoietic stem cell transplant (HSCT) may arrest cerebral demyelination in CALD

… If performed early enough

- Minimal lesions on MRI (Loes score ≤ 9)
- Inflammation (taking gadolinium on MRI)
- No / (few) symptoms
- Benefits of MRI screening / monitoring
- Action period 12-18 months

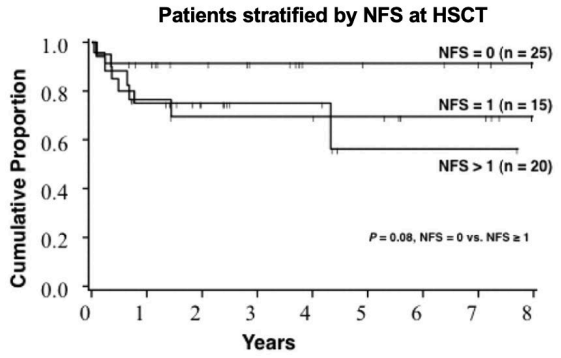


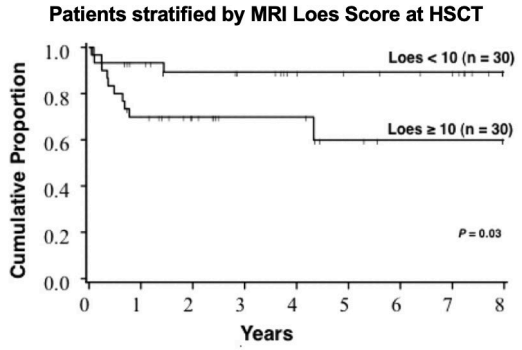


microglia

Benefits and risks of allo-HSCT

Significant improvement of survival without major functional disabilities





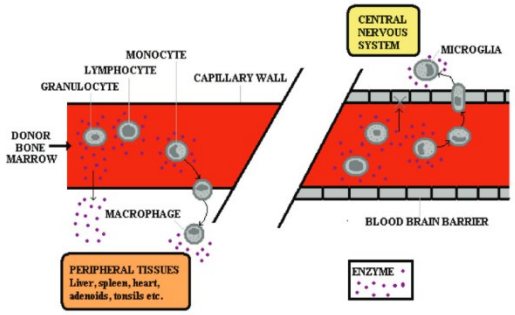
-> correlated to NFS and LS
-> the soonest is the better

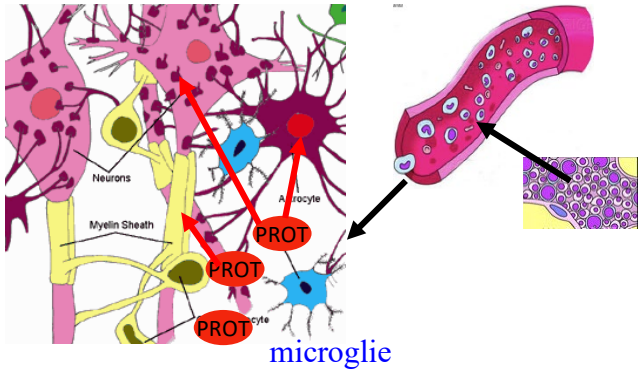
But HSCT complications, particularly if
- poorly matched donors
- advanced disease

- myeloablation
- graft failure
- acute/chronic GVHD
- related to required in the post-transplant immune suppression

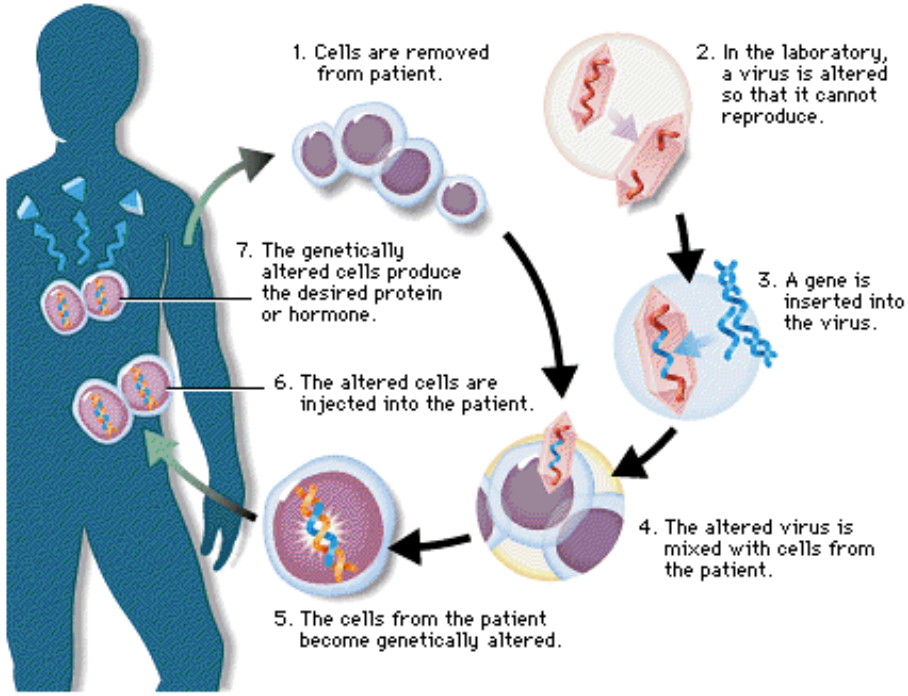
Full HLA donor match
is required for best outcomes

Ex vivo gene therapy: an alternative to allo-HSCT?





Conventional HSCT



Ex vivo gene therapy

- Autotransplantation of genetically corrected HSCs
- Lentiviral vector

Ex-vivo gene therapy for CCALD in children: clinical trial
(Bluebird Bio ALD102/104 studies, Skysona)

- Safety profile (N = 50 patients)
  - Myeloablative conditioning (same as for allograft)
  - N**o GVH,** early hematopoietic reconstitution
  - **2 MDS recently described**

- Stabilization of the progression of the neurological disease
  - Loes score,
  - NFS score,
  - occurrence of major functional disabilities

=> Overall: efficacy comparable to allo-HSCT transplantation

Ex-vivo gene therapy for CCALD in children: clinical trial

(Bluebird Bio ALD102/104 studies, Skysona)

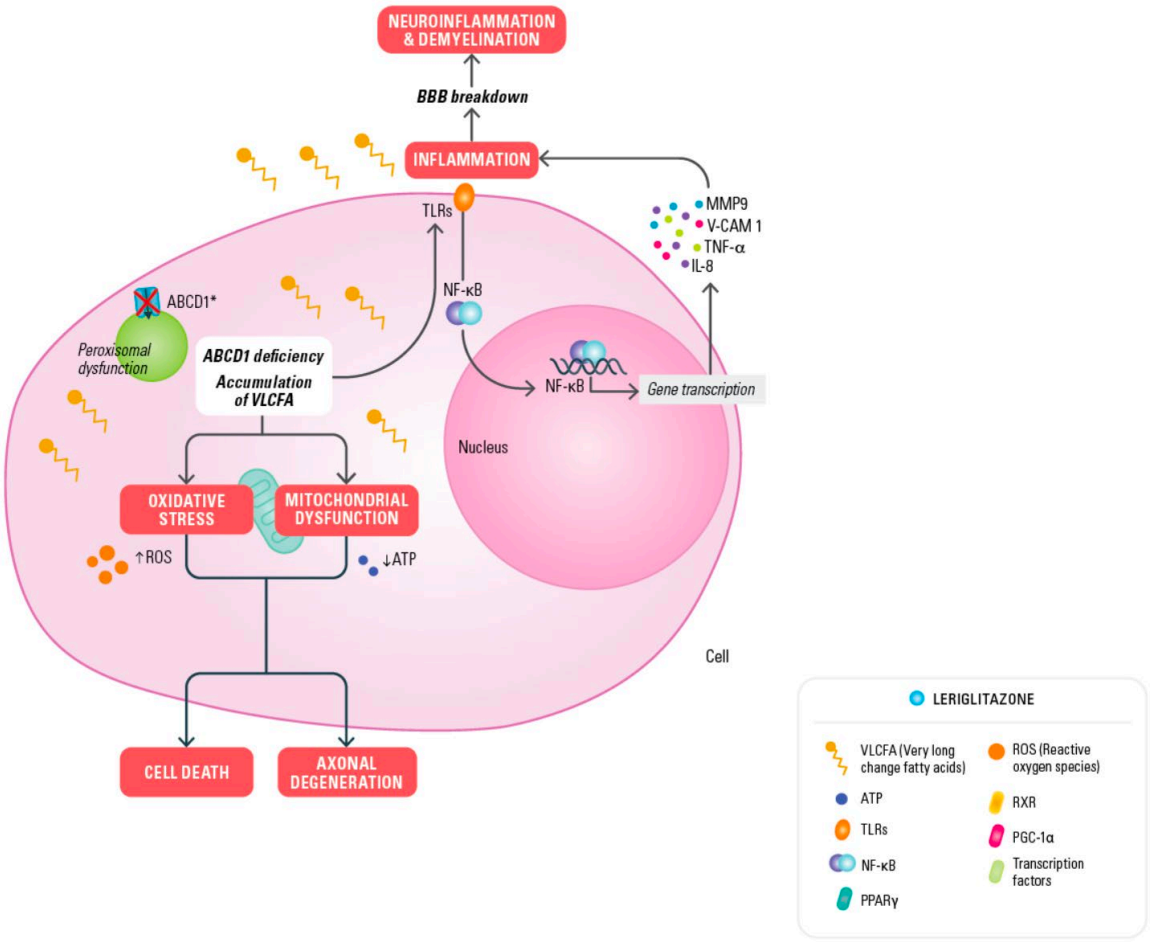
Alternative to allo-transplant?

- Yes if no match related donor
- No need to search for a donor -> faster
- Autotransplantation -> 100% matched donor
- No need for long-term immunosuppression (no GVH)
- Long-term results are to be evaluated
  - efficacy
  - insersional mutagenesis
- EMA marketing authorization of SKYSONA™ **(JUL 2021)**

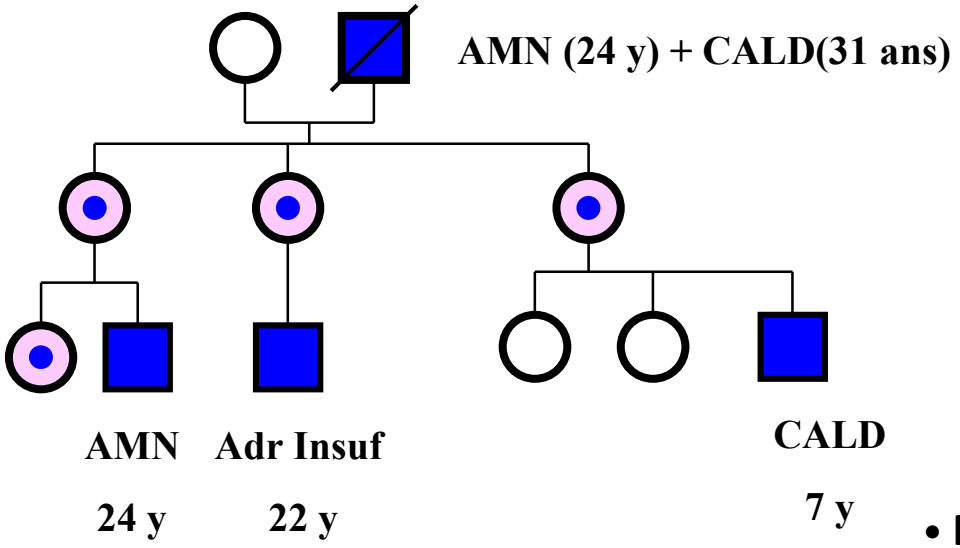
Leriglitazone (Min 102) in CCALD?
NEXUS trial, Minoryx Therapeutics

- PPAR-gamma agonist
- Derived from pioglitazone
- Better intracrebral penetration
- Oral administration
- Clinical trials in Friedreich, AMN

- **<u>NEXUS trial</u>**
  - Age <14 years
  - Loes score<10
  - Gad+ ou Gad-
  - MRI/3 mois
  - Prevention/attenuation of neuroinflammation?
  - Cliical effect



Phenotypic variability of ALD



Look at this family…
a typical family

- **No genotype / phenotype correlation**
- **No phenotypic biomarker**

- **Extensive family investigation**

- **Extensive folllow-up of boys (adrenal, IRM)**

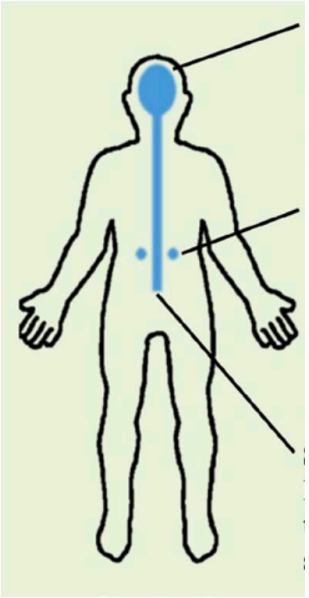
- >900 unique mutations

and variations in the *ABCD1* gene

- 4% de novo

Follow-up of children with ALD

- **Brain MRI:**
  - Every year from 1 to 3 years,
  - Every 6 months from 3 to 12 years
  - Then 1/year up to 55-60 years



- **Adrenal function every 3 to 6 months**

- **Adults: signs of AMN (men and women)**

Do and redo exhaustive family screening ++ to detect :

- heterozygous female (genetic counselling)
- asymptomatic ALD males (children or adults) likely to develop cerebral ALD
- asymptomatic patients with Addison

Newborn Screening?

Two words on the pathophysiology of ALD

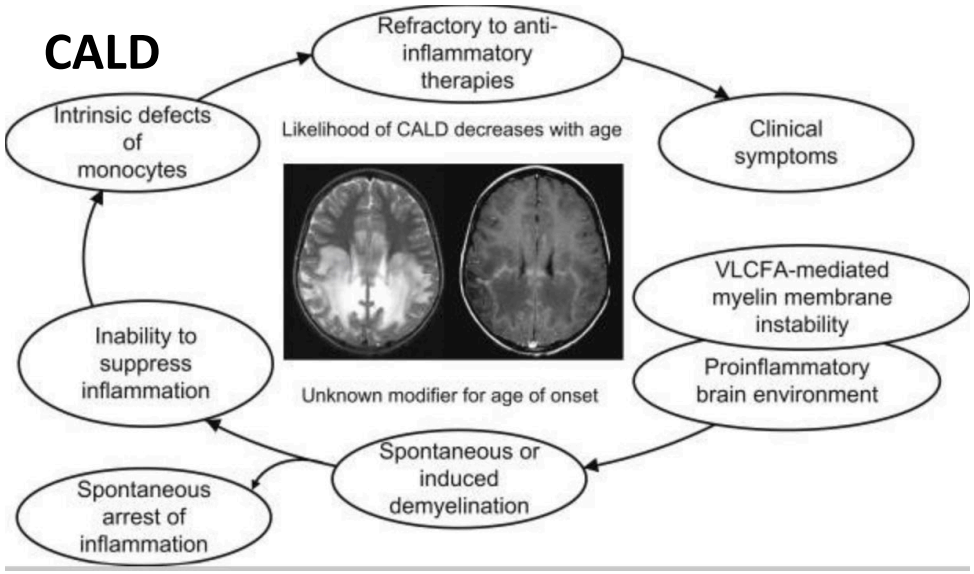
PATHOPHYSIOLOGY of X ALD

Neuroinflammation is a major hallmark of demyelination

Biochimie. 2014 Mar;98:135-42. doi: 10.1016/j.biochi.2013.11.023. Epub 2013 Dec 4.

Pathophysiology of X-linked adrenoleukodystrophy.

Berger J[1], Forss-Petter S[2], Eichler FS[3].



Impaired plasticity of macrophages in ALD??

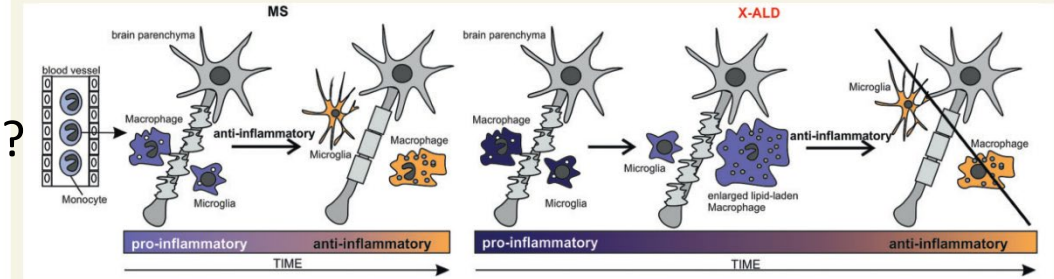


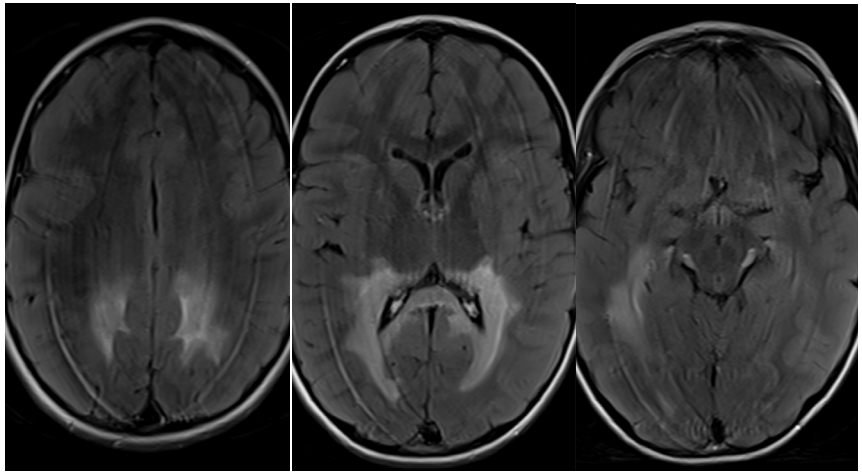
Figure 6 Hypothetical model of the progression of CALD when compared to multiple sclerosis. In CALD, a reinforced destruction of myelin occurs that could be caused by a reduced capacity of pro-inflammatory enlarged lipid-laden macrophages to clear the injured site and induce remyelination.

To conclude, another clinical case

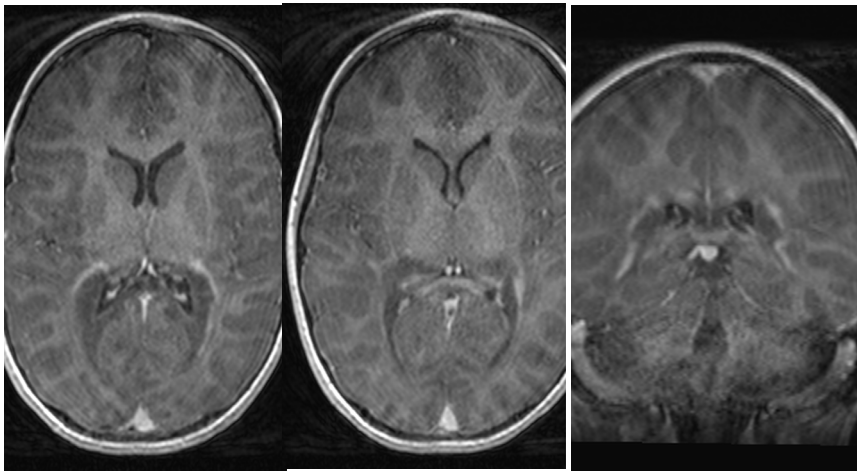
7 year-old boy

- Family history
  - maternal uncle -> spastic paraparesia (25y), diagnosis of multiple sclerosis
- Normal psychomotor development
- 7y: head injury, vomiting -> CT scan and MRI

FLAIR



T1 GAD



What is your diagnosis?

A)Intracerebral lesion following head injury

B)Multiple sclerosis(like his uncle)

C)Mitochondrial disease

D)Cerebral ALD

E)I don’t know

7 year-old boy: the true story

- Family history of ALD
  - maternal uncle -> spastic paraparesia (25y) -> diagnosis of AMN
  - patient's mother -> heterozygous for the ABCD1 mutation
  - no presymptomatic diagnosis was performed for the patient despite genetic counselling (bad counselling)

- Normal psychomotor development
- 6 y: attention deficiency
- 6y ½: decrease in school performance, visuo-spatial difficulties
- 7y: head injury, vomiting -> CT scan and MRI

DIAGNOSIS = ALD

Evolution

- HSCT (Loes score 10…)
- Deterioration following the transplant
  - visual impairment
  - attention deficit
- Negativation of gad enhancement 3 months post HSCT
- Progression of the demyelinating lesions up to 9 months post transplant

-> Was tranplanted too late
-> Geneticist should have proposed presymptomatic testing (VLCFA and ABCD1 mutation)

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NEXT Webinar- Focus: Neurorehabilitation

'Functional gait disorders: a sign-based approach'

by Jorik Nonnekes,

Radboud University Medical Centre, Department of Rehabilitation, Nijmegen, NL

12. October 2021