Centre de référence
Maladies Rares

LEUKO
FRANCE
« leucodystrophies »

European
Reference
Network
for rare or low prevalence
complex diseases

Network
Neurological Diseases
(ERN-RND)

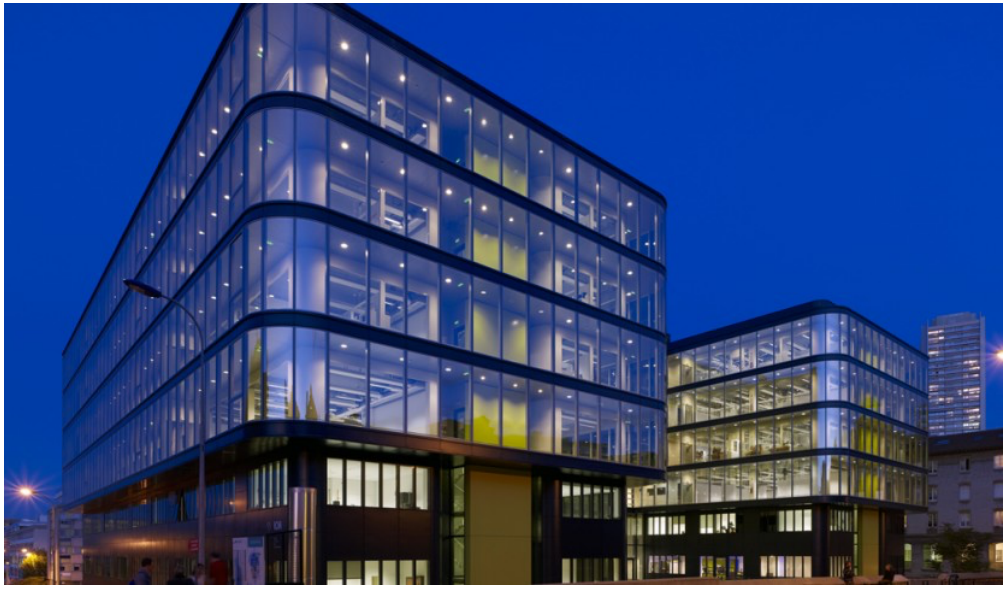
SORBONNE
UNIVERSITÉ
CRÉATEURS DE FUTURS
DEPUIS 1257

Adult leukodystrophies
Early symptoms of late-onset leukodystrophies

Fanny Mochel

Reference Center for Adult Neurometabolic Diseases and Leukodystrophies

La Pitié-Salpêtrière University Hospital, Paris, France



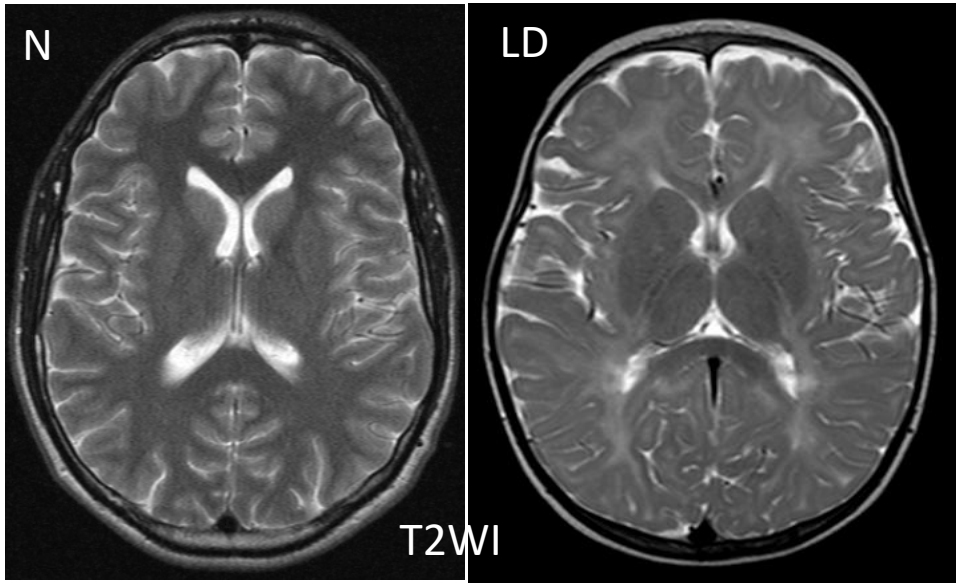
Learning objectives

- When to think about a leukodystrophy (LD) in adult patients?
- What are the clinical presentations of adult-onset LD?
- What are the first-line plasma biomarkers in adult-onset LD?
- What are the main treatments of adult-onset LD?

Leukodystrophies

MRI analysis: T2

T2 hyper intensity in the affected white matter is present



T1 signal may be variable

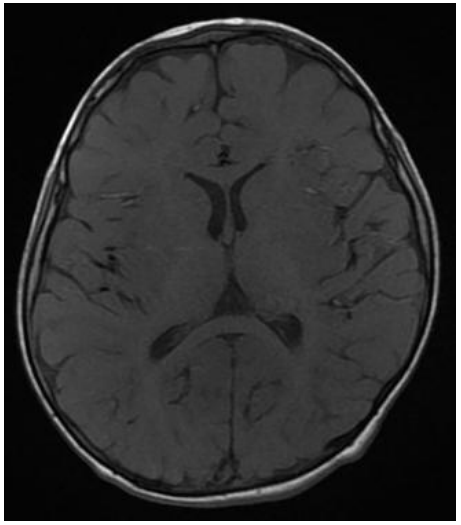
Diagnosis, prognosis, and treatment of leukodystrophies

Marjo S van der Knaap, Raphael Schiffmann, Fanny Mochel, Nicole I Wolf

THE LANCET
Neurology

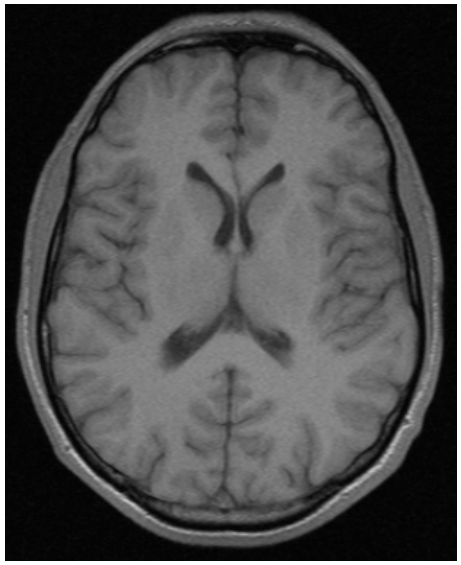
MRI analysis: T1

Hypomyelinating
Abnormal myelin formation



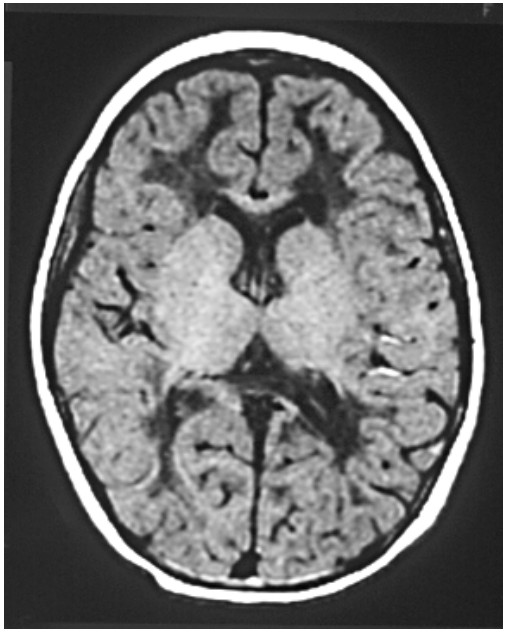
isosignal WM/GM
Or mild hypersignal

Normal
Full maturation



Hypersignal WM/GM

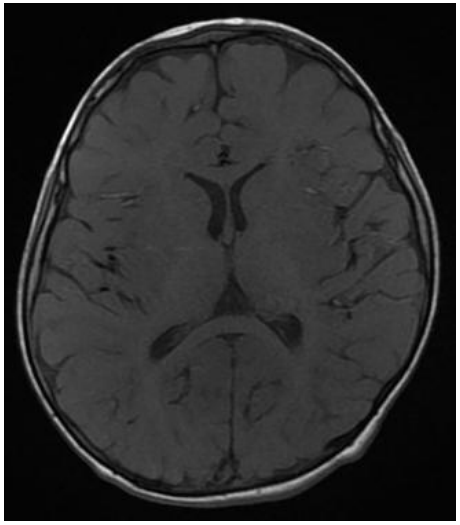
Demyelinating
Myelin destruction



hyposignal WM/GM

Leukodystrophies

Hypomyelinating
Abnormal myelin formation



isosignal WM/GM
Or mild hypersignal

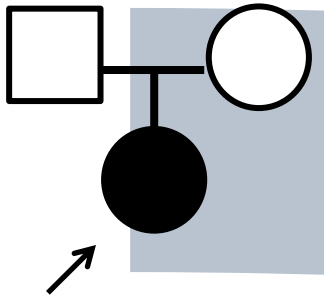
EDITORIAL

european journal of neurology
the official journal of the european academy of neurology

Eur J Neurol. 2021;00:1–2.

Hypomyelinating leukodystrophies in adults

PLP1
GJA1
GJC2
POLR3A
TUBB4A



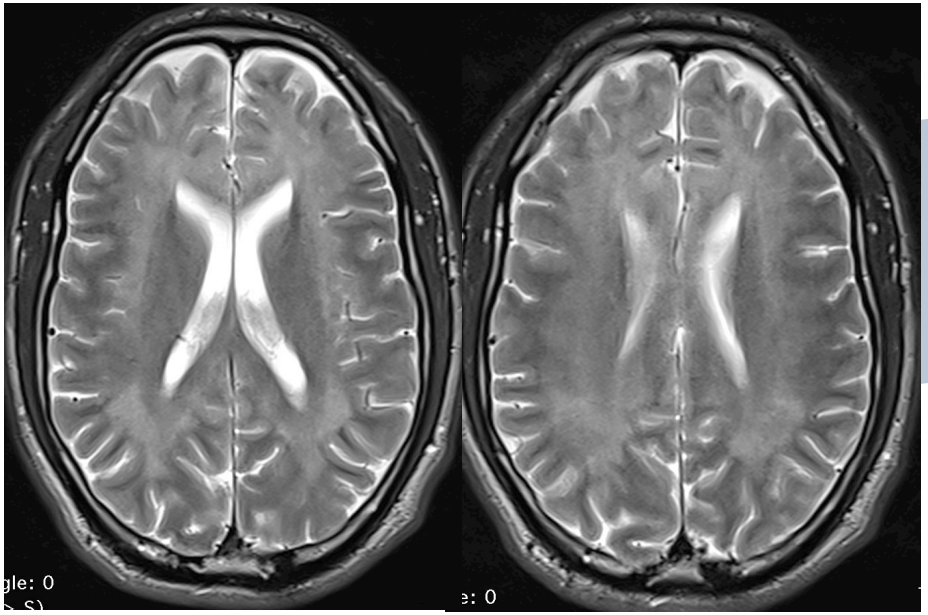
Primary amenorrhea

Adolescence

Hypogonadotropic hypogonadism

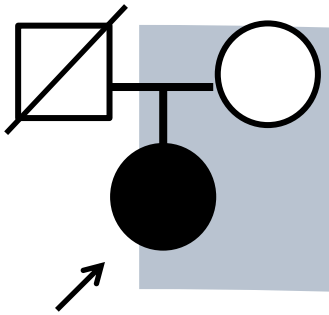
15 years

POLR3A



Partial seizures

19 years



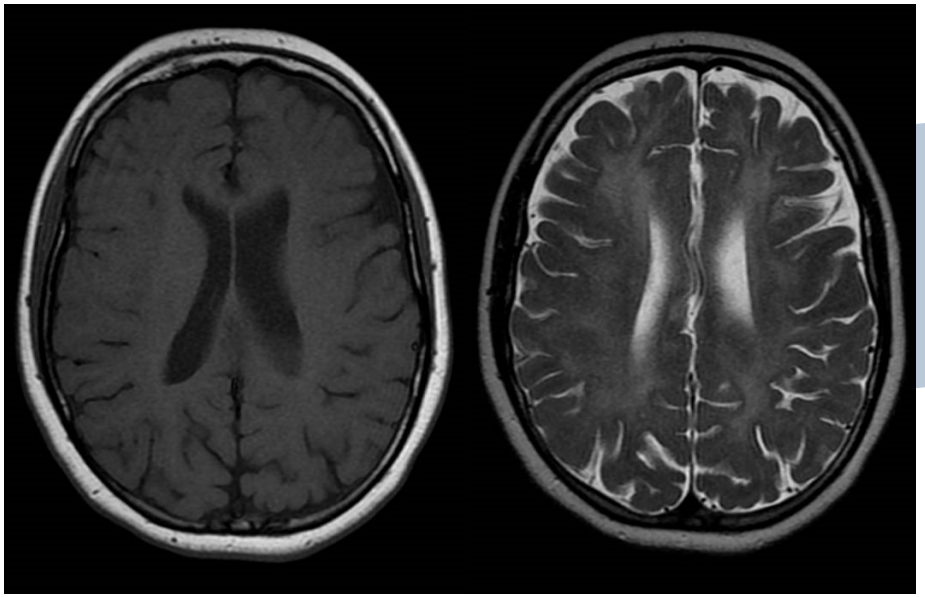
Mild
urgencies

17 years

Spastic
gait

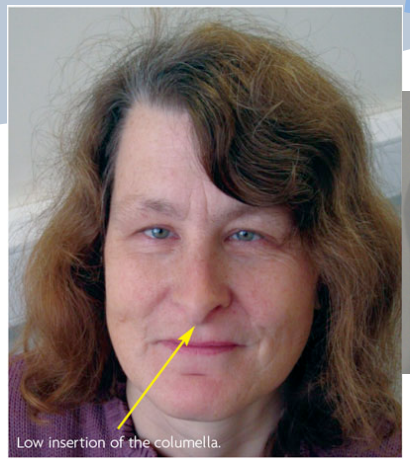
30 years

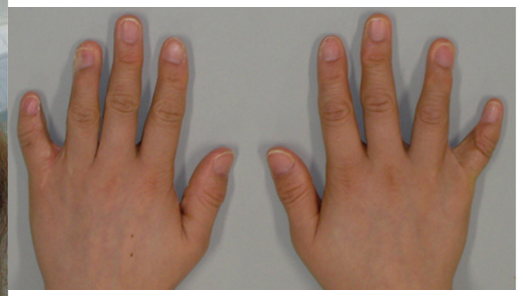
GJA1



Spastic paraplegia
Severe neurogenic bladder

49 years

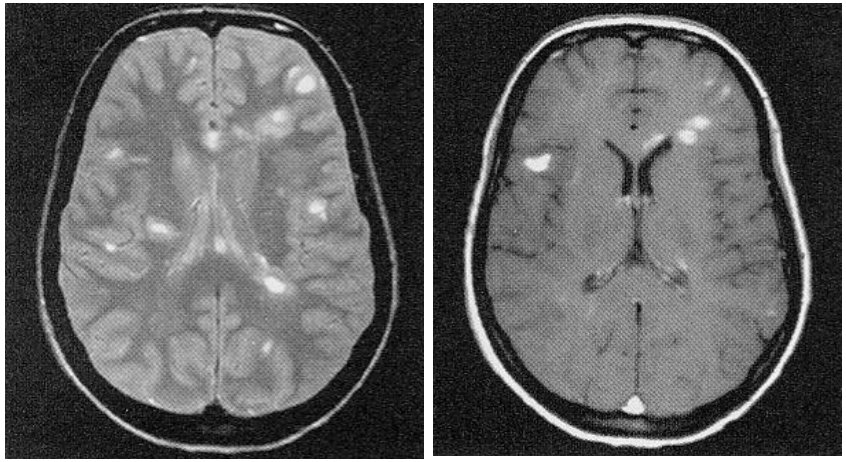




Demyelinating leukodystrophies

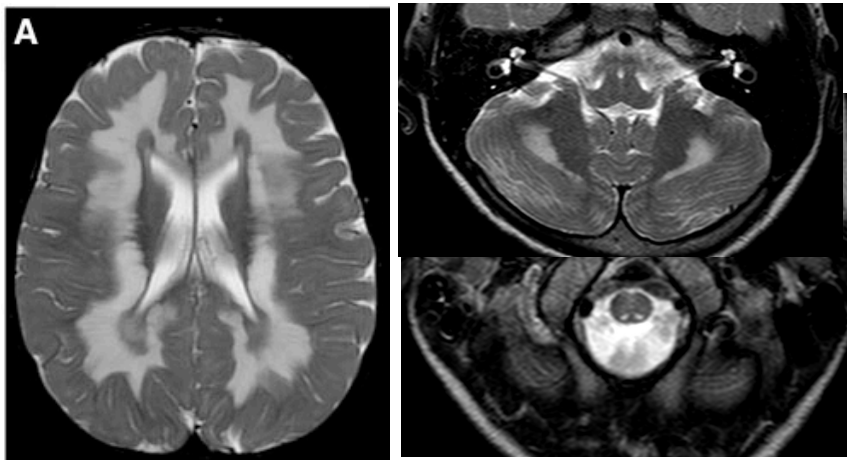
Acquired

- ***Asymmetric distribution***
- ***Gadolinium enhancement***
- ***Rapid increase***
- ***Different ages***



Genetic

- *Symmetric distribution*
- *Confluent or fascicular*



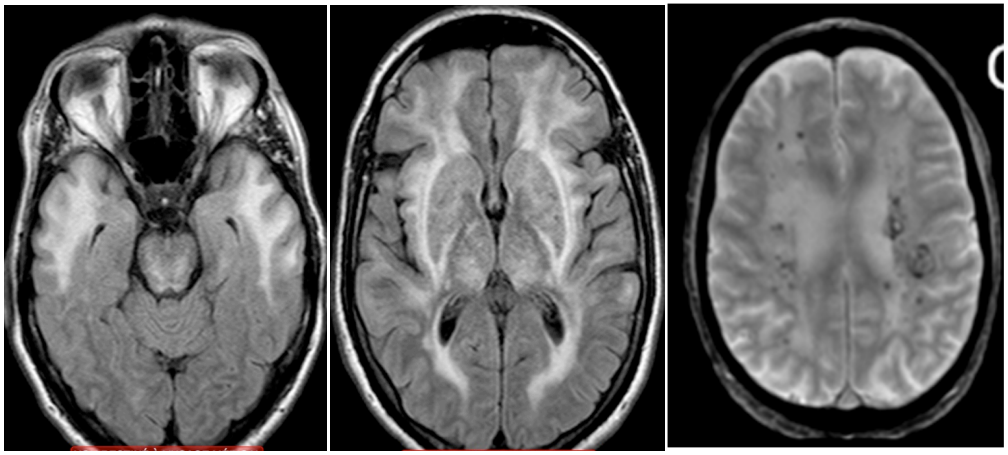
Demyelinating leukodystrophies - Genetic

Vascular

Calcifications

L with Calcifications and Cysts (LCC)
Aicardi Goutieres Syndrome

Without calcifications



-Brainstem
-Temporal lobes

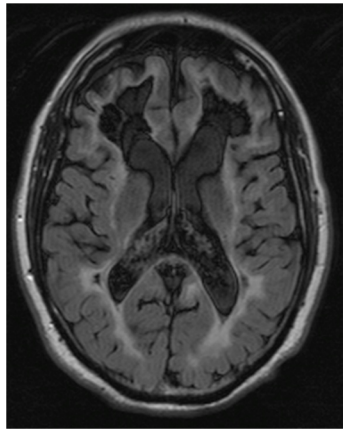
-External capsules
-Deep grey matter

Gradient echo
Sequence
Microbleeds

CADASIL *Notch3-ColIVA1 et A2*

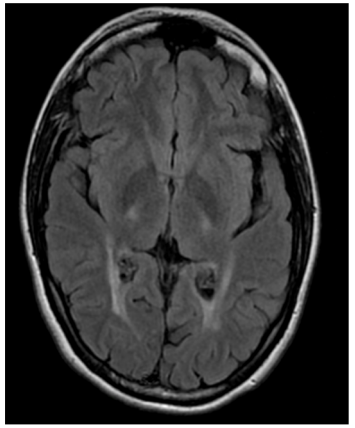
Non vascular

Swelling cavitating



Astrocytic dysfonction

Other



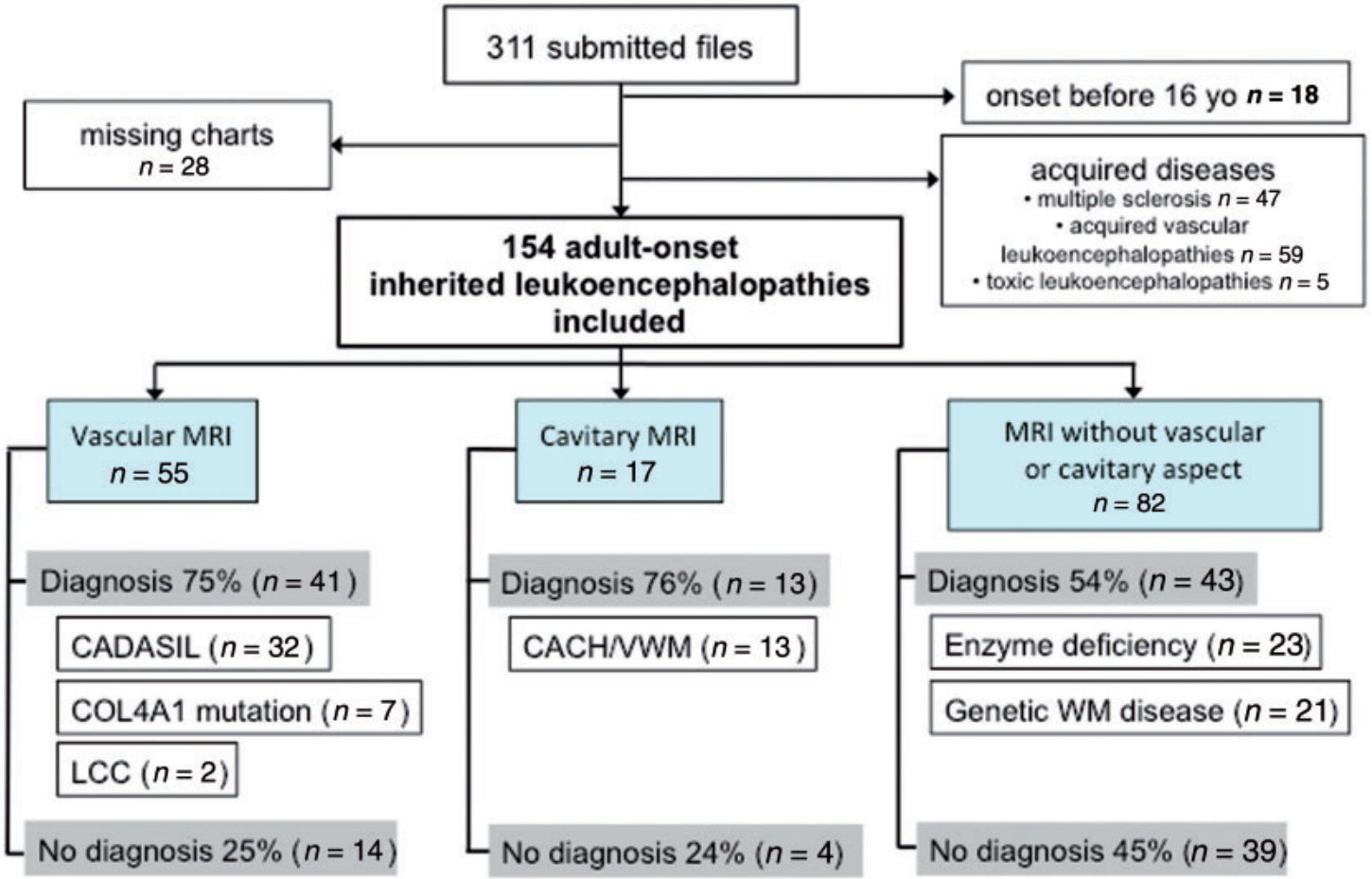
Metabolic screening

doi:10.1093/brain/awu353 BRAIN 2015: 138; 284–292 | 284

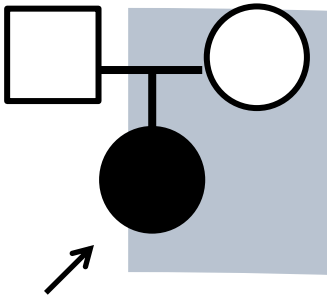
BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Adult-onset genetic leukoencephalopathies: A MRI pattern-based approach in a comprehensive study of 154 patients



Ayrignac et al, Brain 2015



Mild school difficulties

Adolescence

Premature ovarian failure

28 years

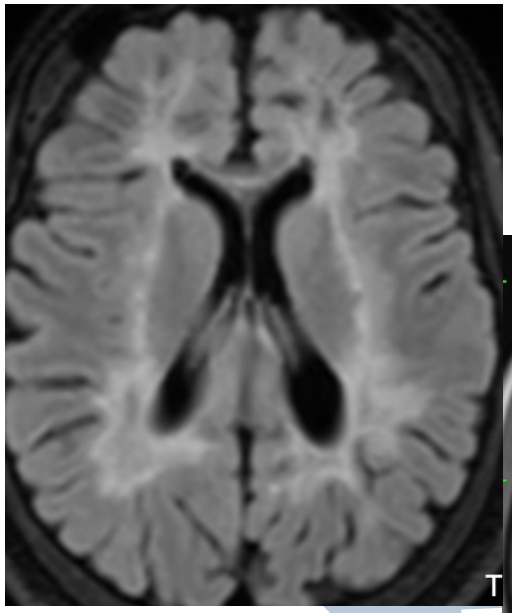
EIF2B3

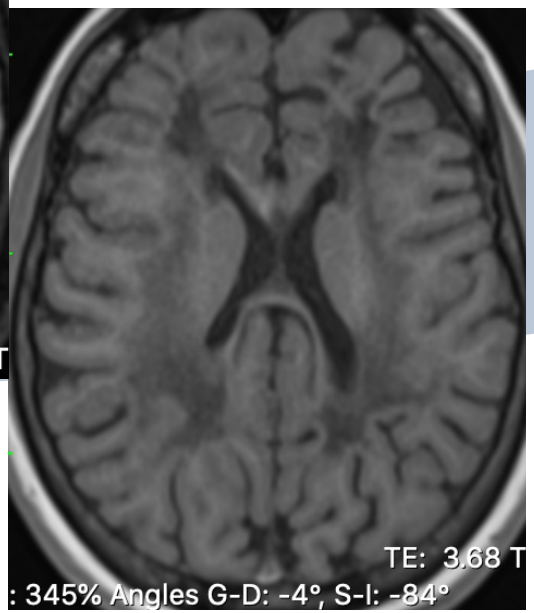
Neurogenic bladder

31 years

Cognitive decline
Propioceptive ataxia

35 years





What are the first-line plasma biomarkers in adult-onset leukodystrophy?

1. Vitamin E
2. Very long chain fatty acids, phytanic & pristanic acids
3. Homocystein
4. Lysosphingomyelin
5. Cholestanol

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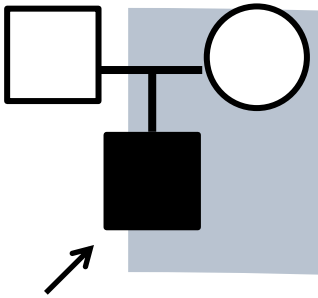
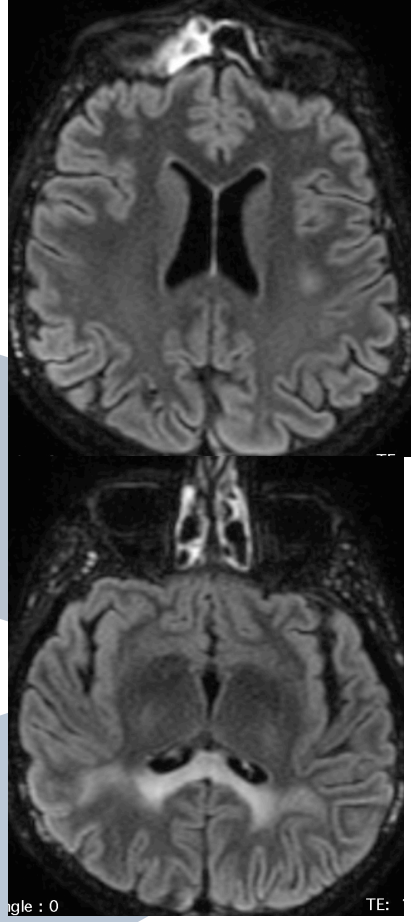


Gait difficulties
Falls

40 years

Progressive
spastic paraplegia

43 years



In a 44-year old man with VLCFA elevation, what is your next urgent course of action?

1. Measure fasting cortisol & ACTH
2. Perform nerve conduction studies
3. Address for genetic counseling
4. Assess urinary function
5. Perform brain MRI

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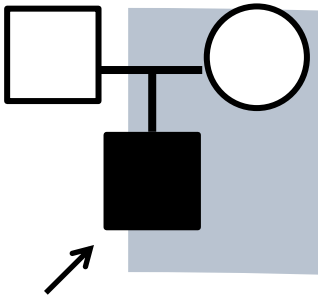

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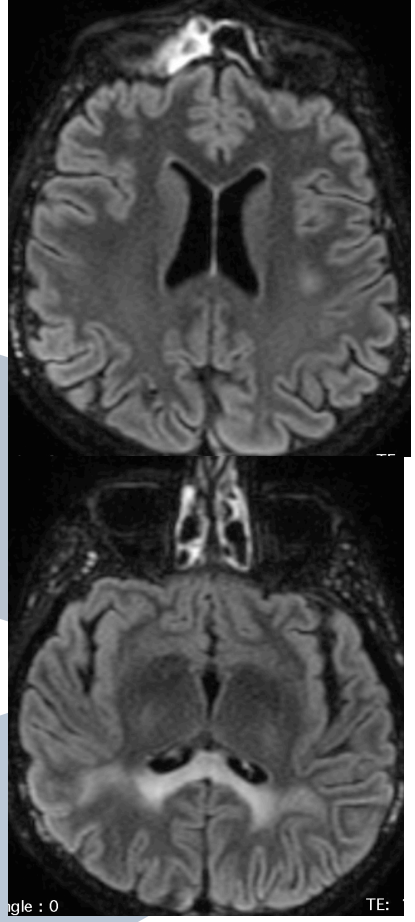

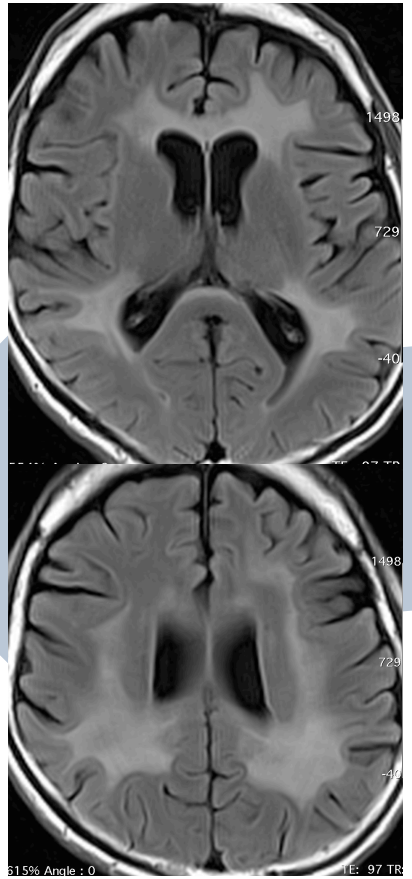

Rapid
cognitive decline

44 years

Which of the following statement(s) is (are) true in X-linked ALD?

1. Cerebral ALD affects about 20% of men with *ABCD1* variants.
2. Women shall be monitored for cerebral ALD by brain MRI.
3. In men, cerebral ALD can occur till about 50 years of age.
4. Hematopoietic stem cell transplant (HSCT) can only be performed with a (non-*ABCD1* variant carrier) haploidentical related donor.
5. HSCT does not protect from myelopathy.

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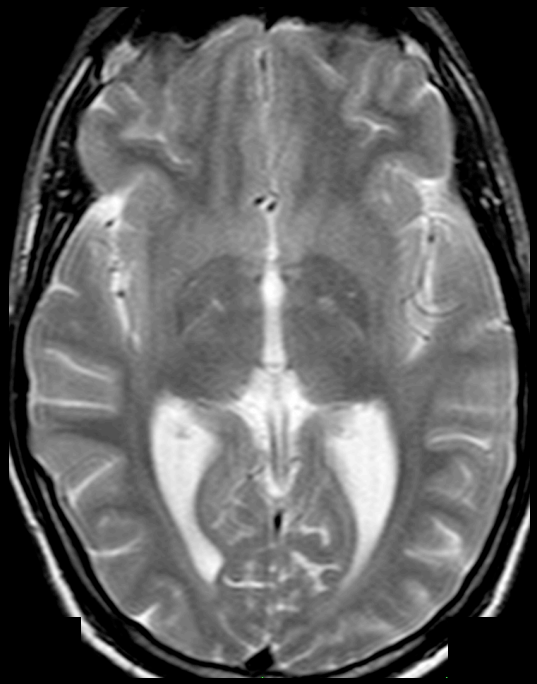
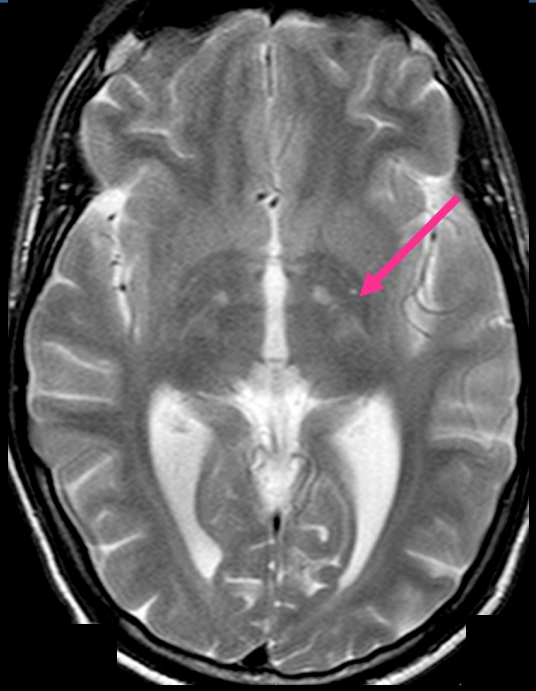
2015



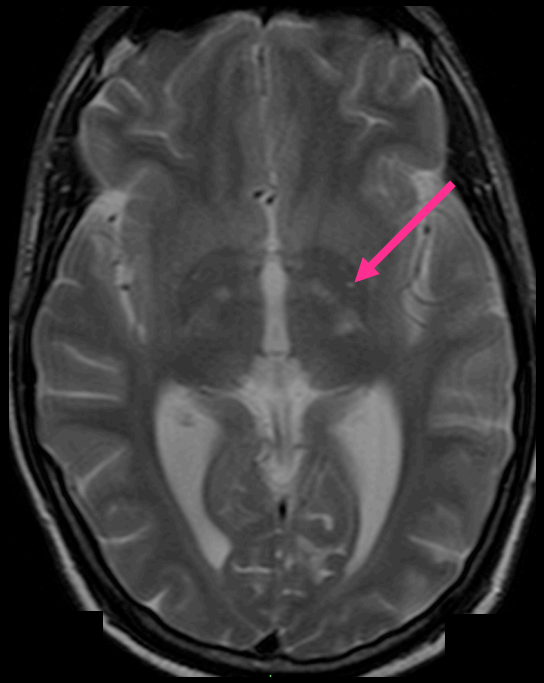


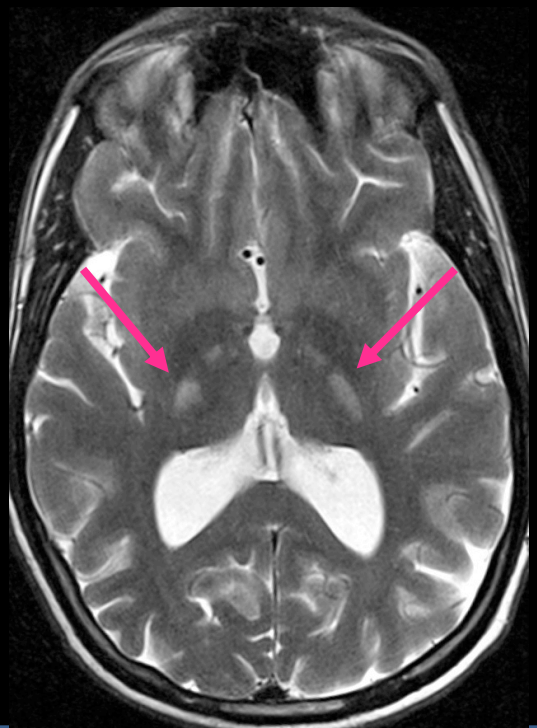
2018

Sudden career change

2019

Depression

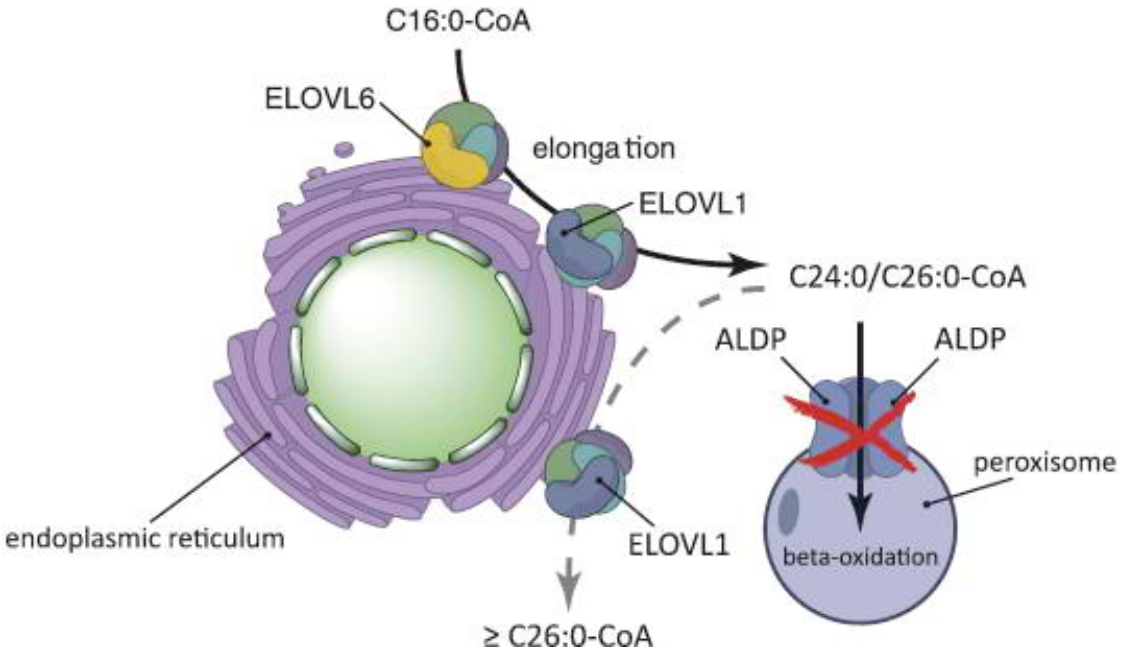




2020

Rapid motor & cognitive decline

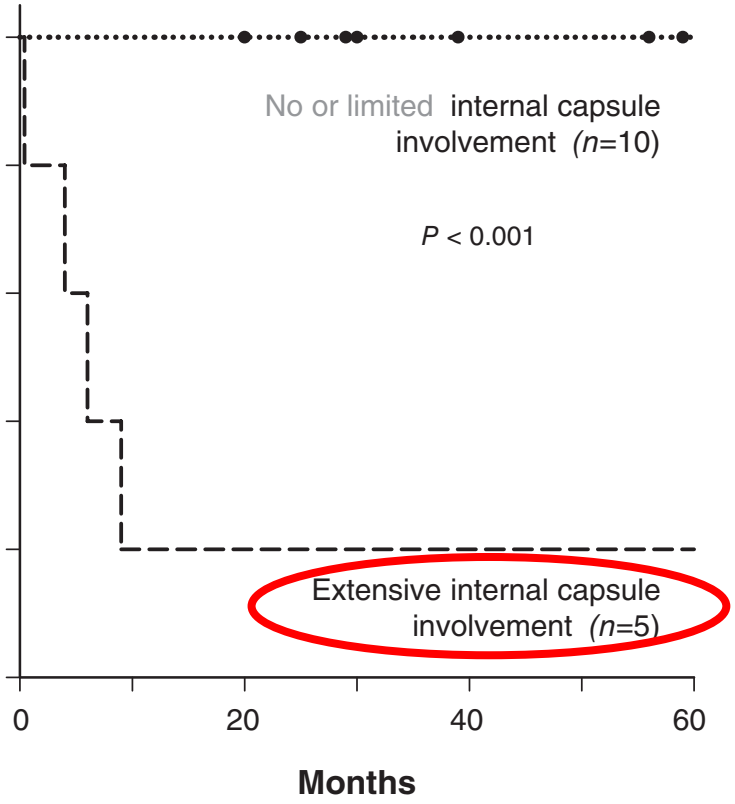
Adrenoleukodystrophy & very long chain fatty acids



- X-linked disease
- Adult cerebral form: 20-50% over 10 years
- Adrenocortical insufficiency – 80% (10% symptomatic)
- Early inflammatory phase: Hematopoietic stem cell transplantation

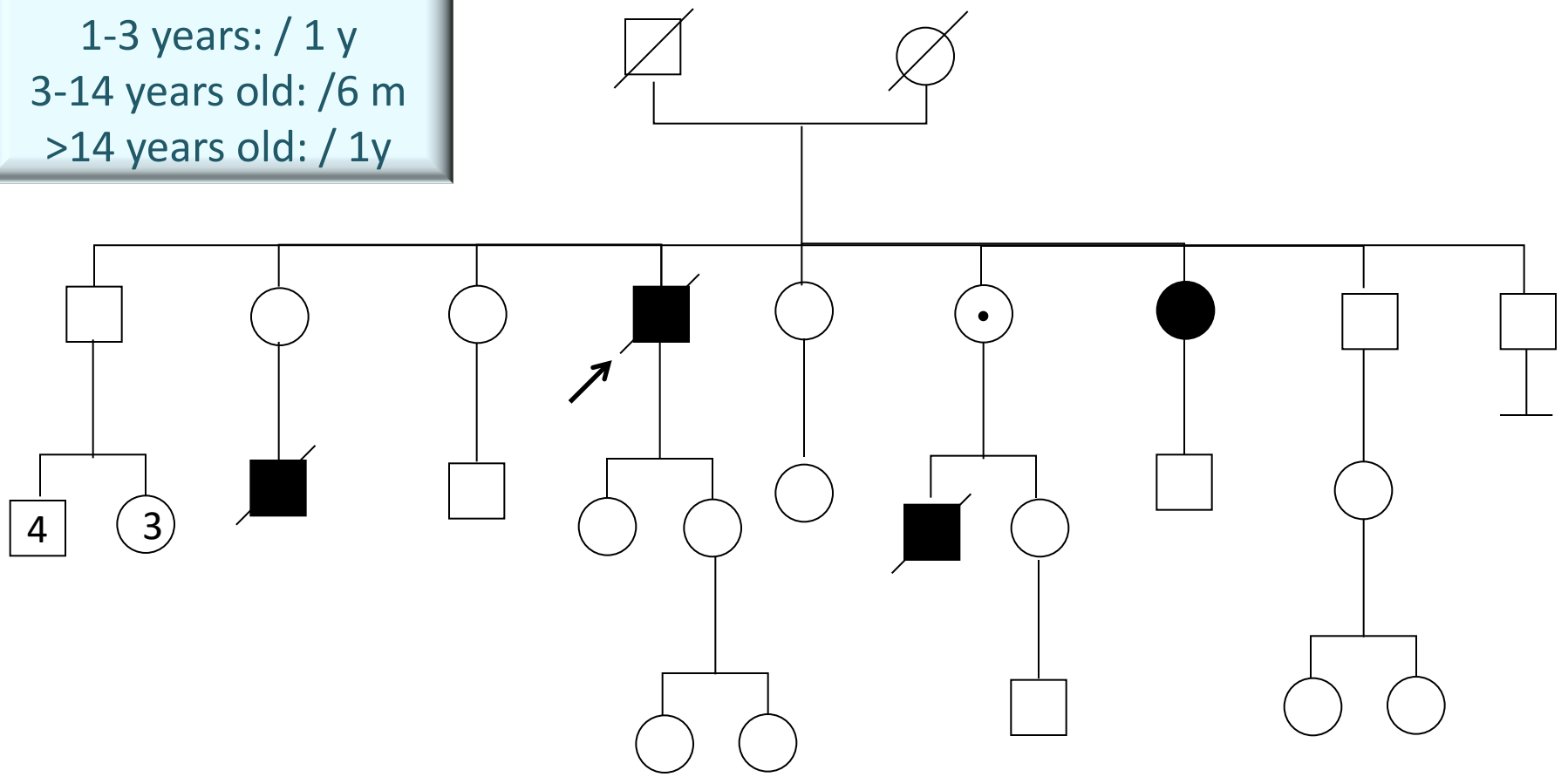
Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy

Nils Waldhüter[1] | Wolfgang Köhler[2] | Philipp G. Hemmati[1] | Christian Jehn[1] | Rudolf Peceny[3] | Giang L. Vuong[1] | Renate Arnold[1] | Jörn-Sven Kühl[4]



A family story…

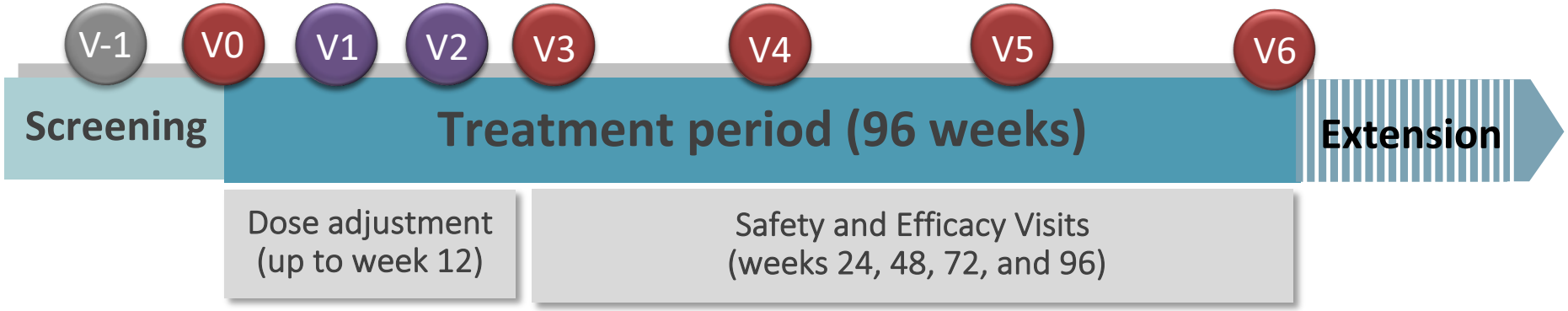
MRI
1-3 years: / 1 y
3-14 years old: /6 m
>14 years old: / 1y



minoryx therapeutics

ADVANCE

A Clinical Study in AMN



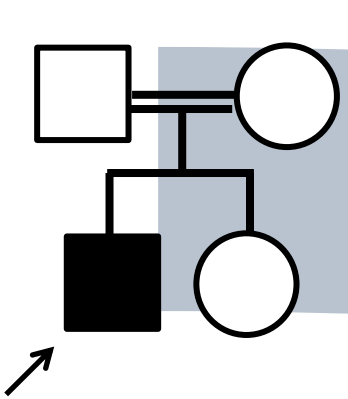
Daily dose of Leriglitazone or placebo (2:1 ratio)
116 patients randomized (10 countries) / 96 completed

The primary endpoint, change from Baseline in 6MWT, was not met. However a statistical and clinically meaningful difference was observed in early symptomatic patients.

Body Sway. Patients treated with leriglitazone showed statistically significant differences vs. Placebo on various parameters and conditions including "eyes closed, feet together" and "eyes closed, feet apart".

EDSS and SSPROM. Leriglitazone also consistently showed favorable trends when compared to placebo. Again, these beneficial effects on myelopathy symptoms were more prominent in patients with more recent onset of symptoms.

Progressive cALD reported by sites	Leriglitazone	Placebo	p-value
Total (% of randomized)	0 / 77 (0%)	6 / 39 (15.4%)	**0.001**



Right hemiparesis
Rapidly progressive

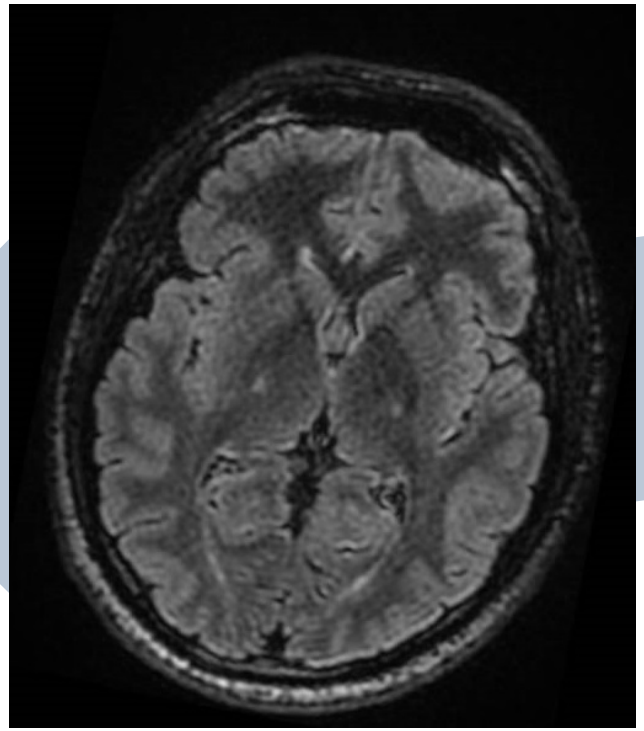
24 years

Left hemiparesis
Rapidly progressive
Inflammatory CSF

27 years

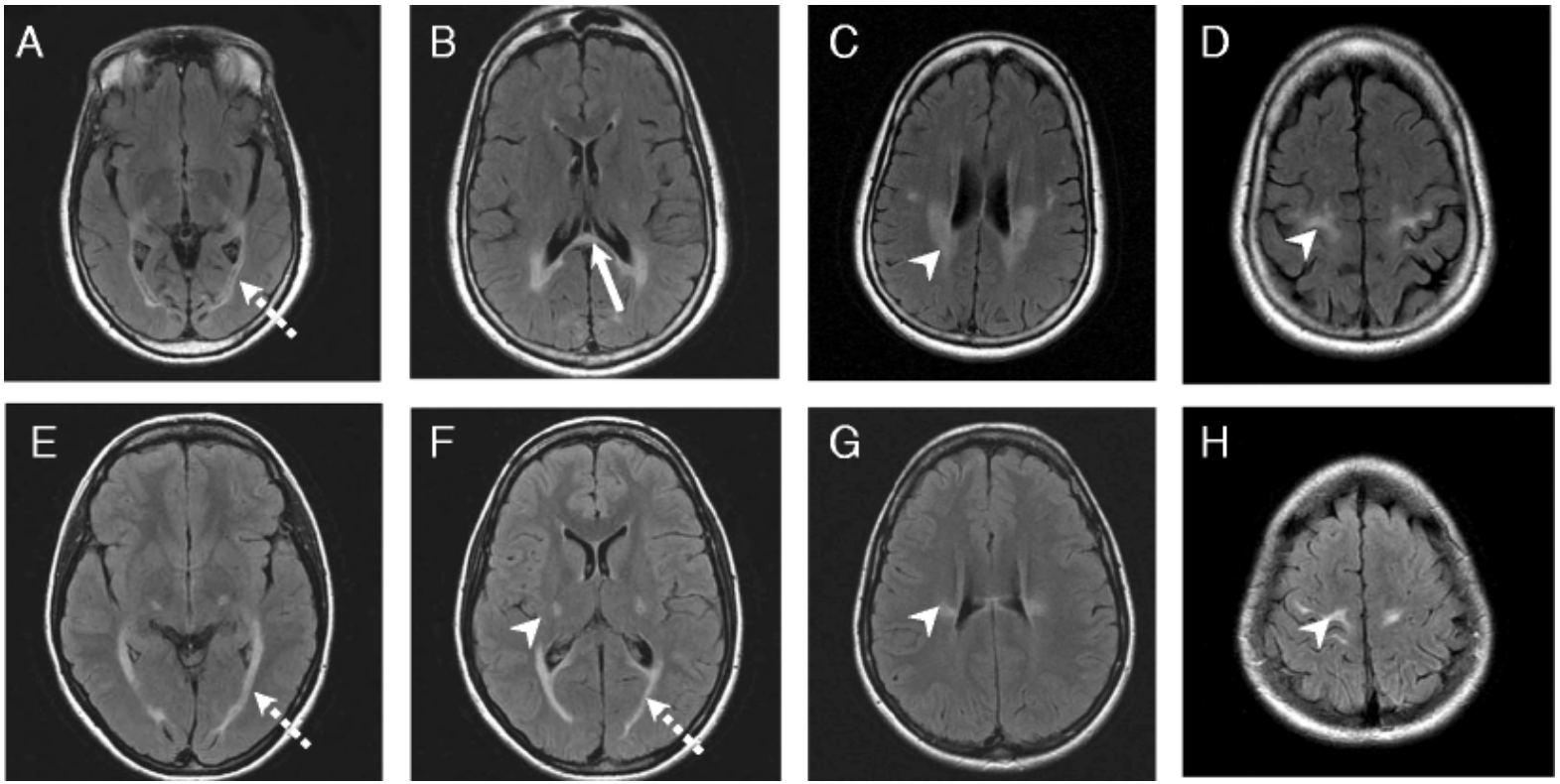
Tetrapyramidal Sd
EDSS 7

28 years



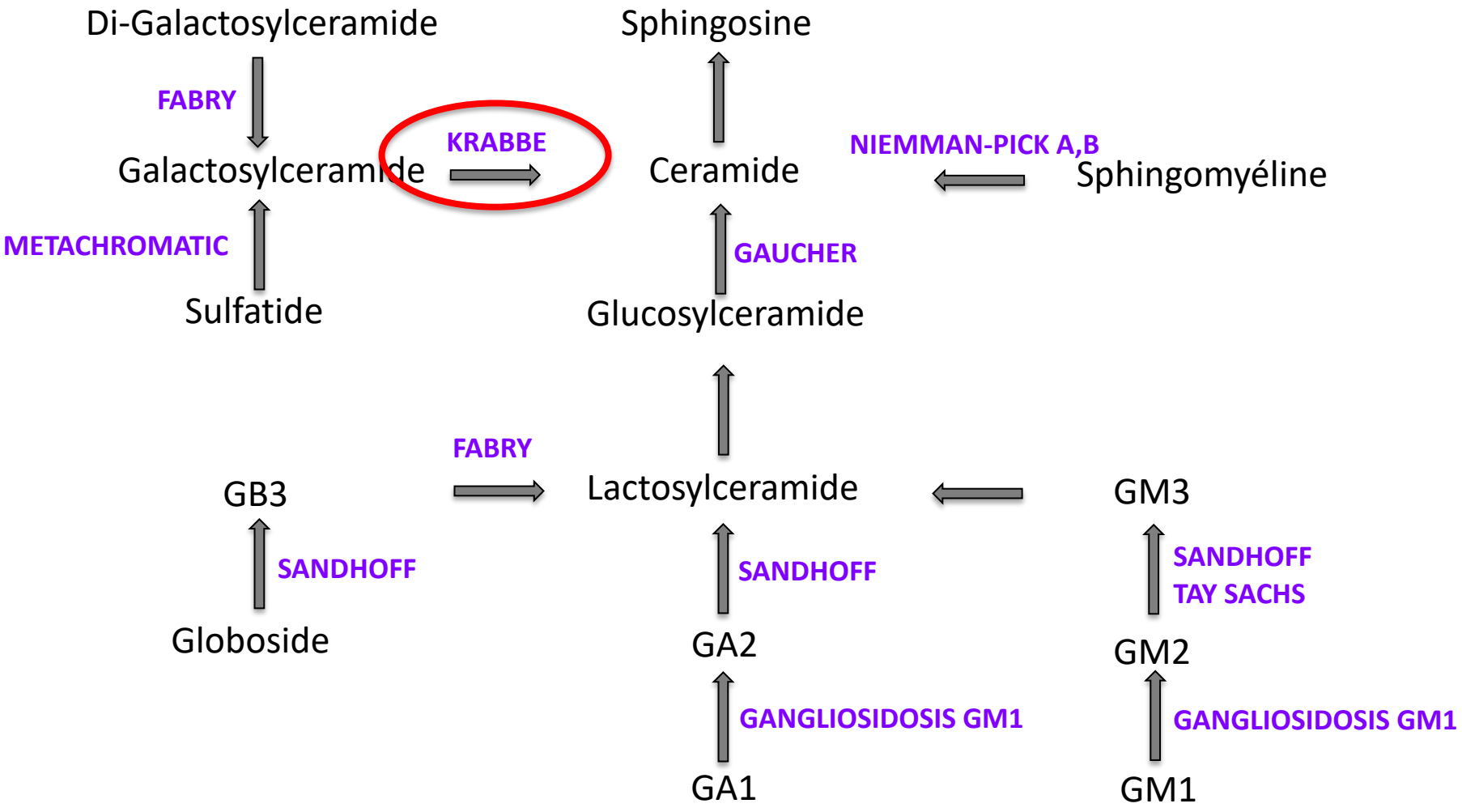
Krabbe disease (galactocerebrosidase deficiency)

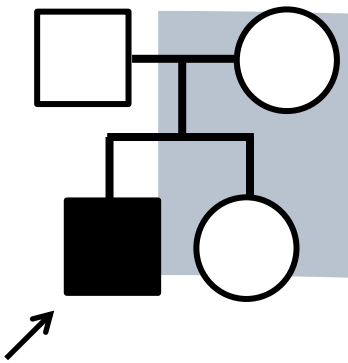
- 41 patients, 4-66 years old
- Spastic paraplegia > neuropathy > cerebellar ataxia
- Cognitive decline, optic atrophy (15%)



Debs et al, JIMD 2012

Sphingolipids metabolism





Break from the family

"Black out"

34 years

Lives on the street

Seizures

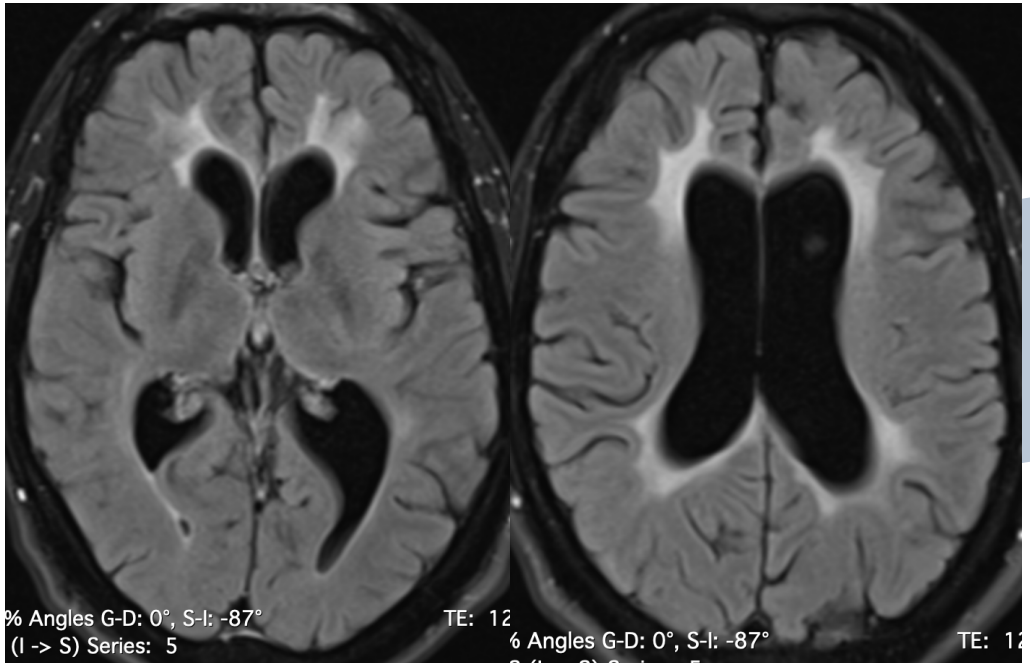
Psychosis

41 years

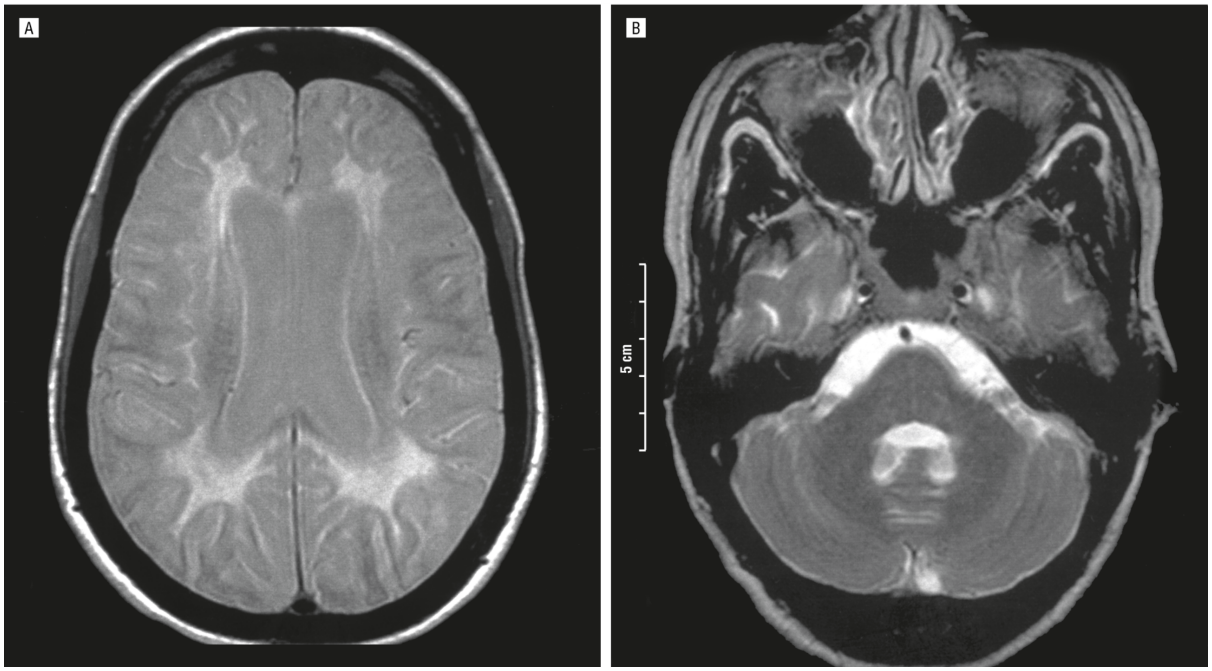
Schizophrenia

Frontal syndrome

42 years



Metachromatic leukodystrophy (arylsulfatase A deficiency)

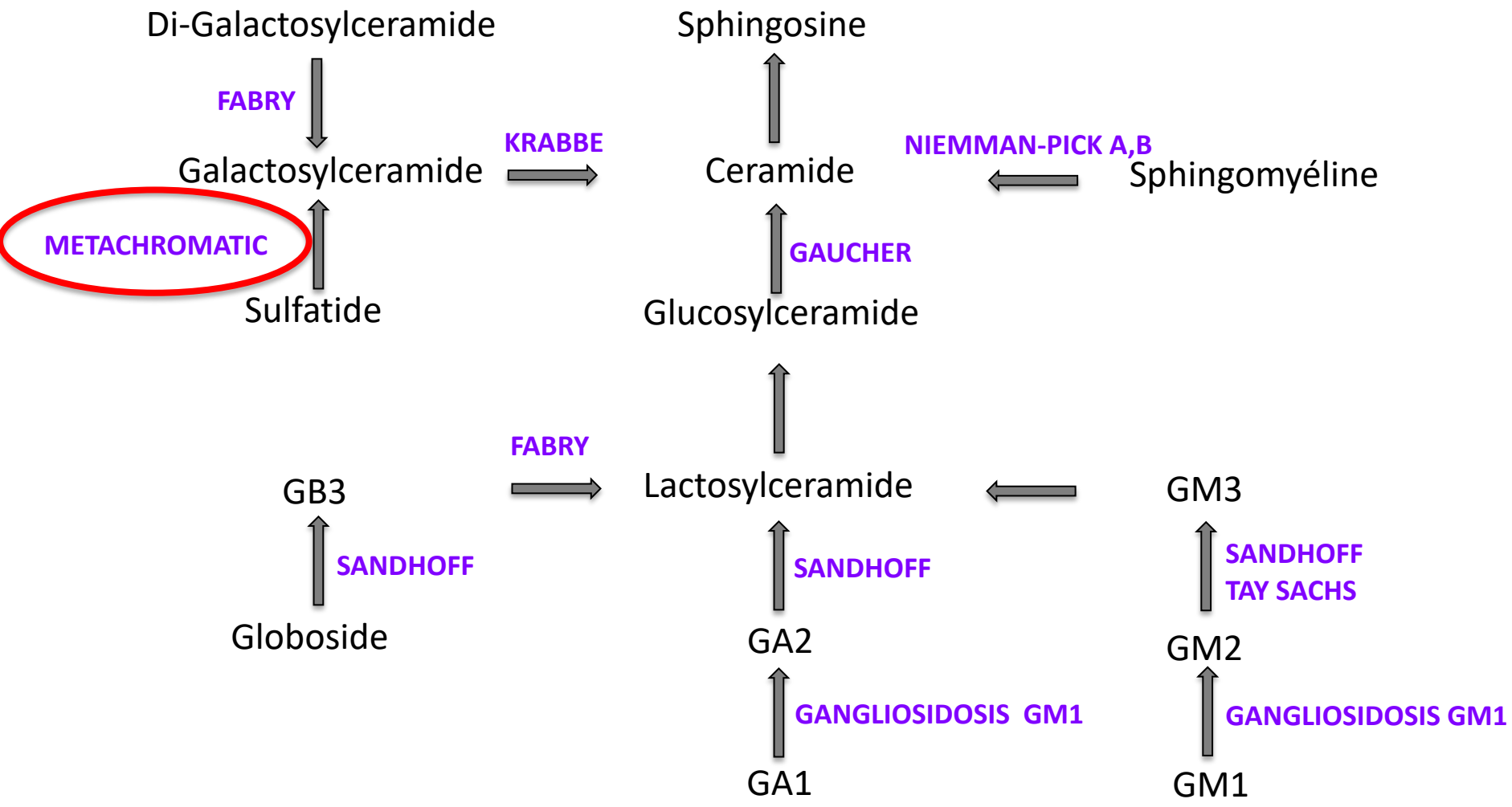


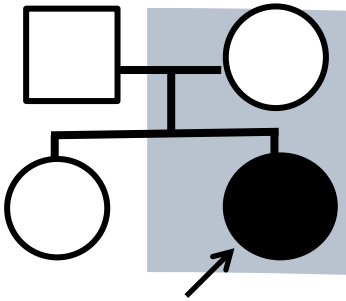
- 42 patients, 10-60 years old
- Genotype-phenotype correlation

Spastic paraplegia & ataxia / Fronto-temporal dementia

Rauschka et al, Ann Neurol 2006

Sphingolipids metabolism





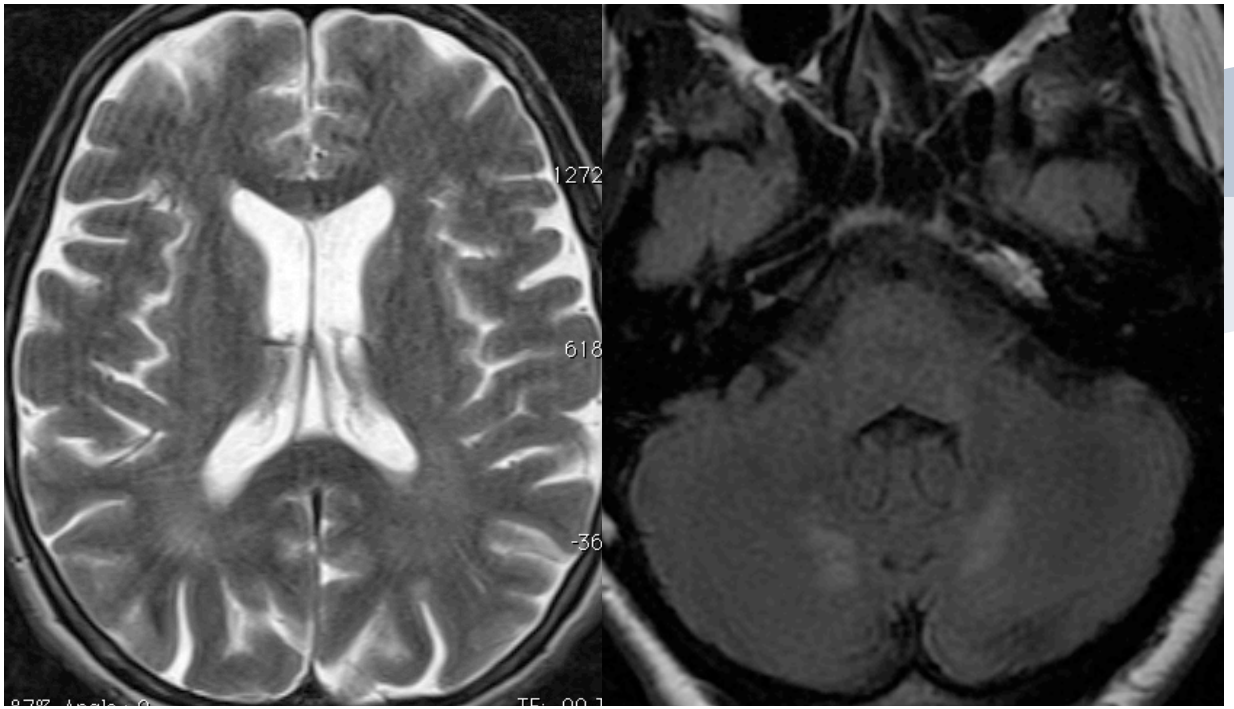
Psychotic symptoms
Hallucinations

15 years

Bilateral cataract

18 years

CYP27A1
(XCT)



22 years

Spastic paraplegia
Weight loss

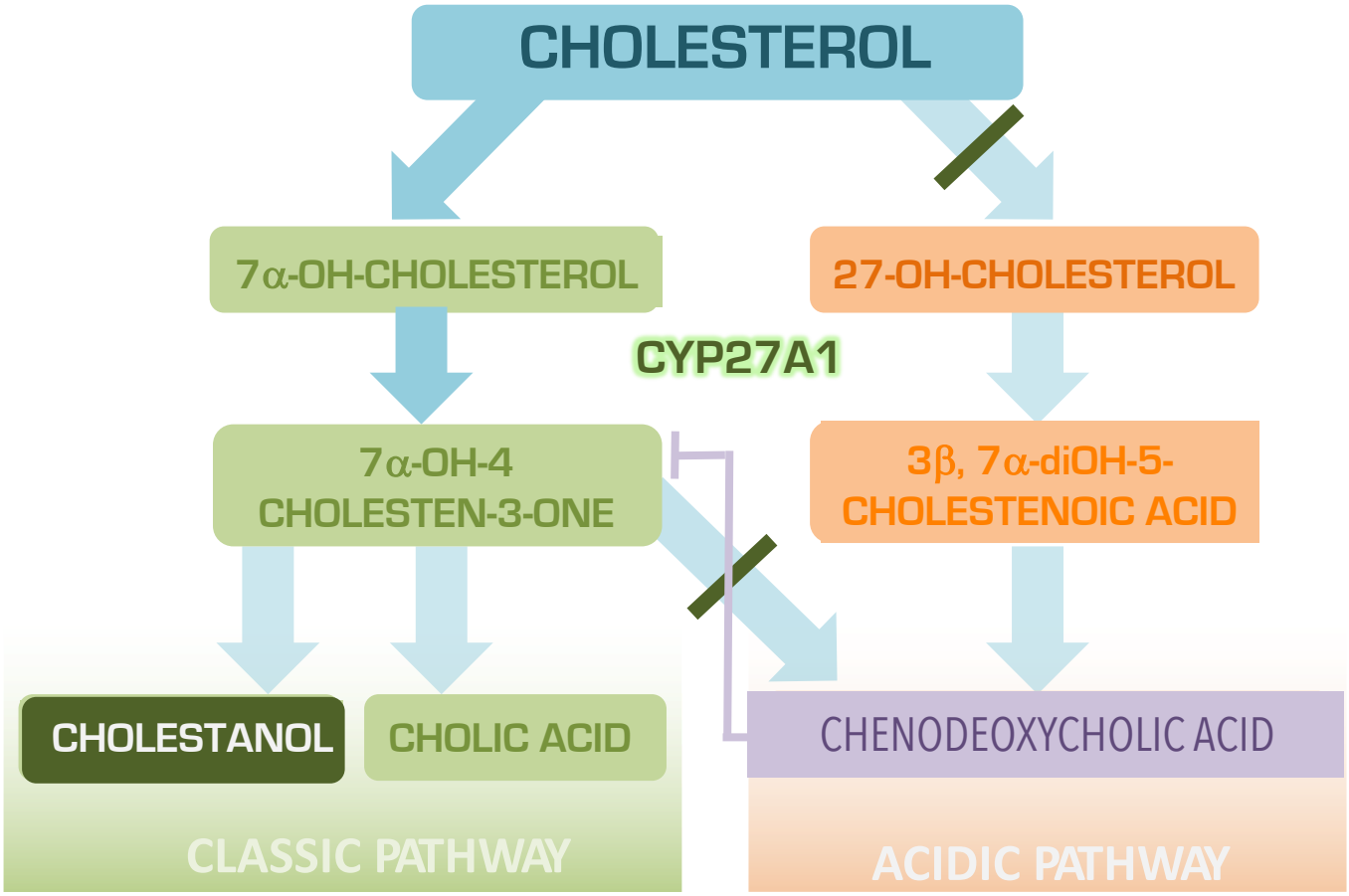
How would you treat this patient?

1. Cholic acid
2. Chenodeoxycholic acid
3. LDL apheresis
4. Cholic acid + atorvastatin
5. Chenodeoxycholic acid + atorvastatin

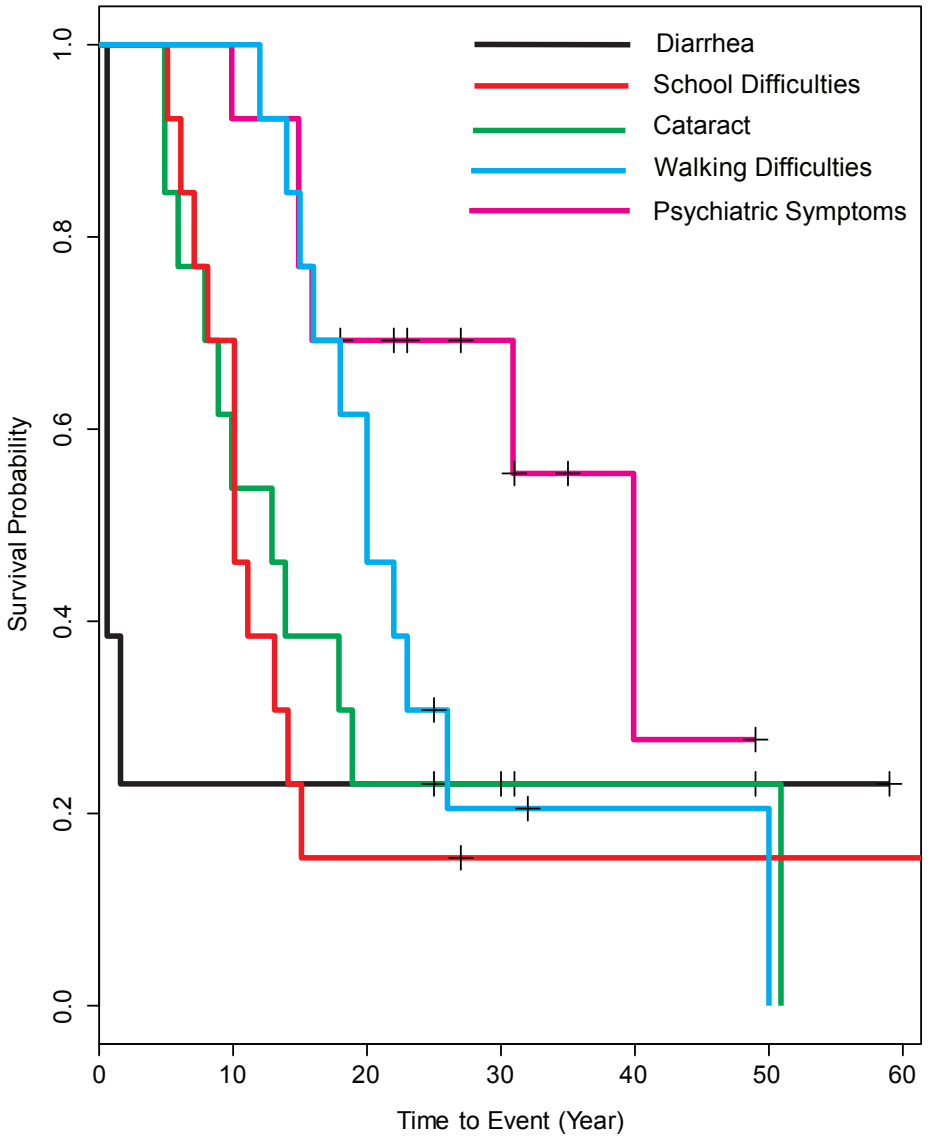
How would you treat this patient?

1. Cholic acid
2. Chenodeoxycholic acid
3. LDL apheresis
4. Cholic acid + atorvastatin
5. Chenodeoxycholic acid + atorvastatin

Cerebrotendinous xanthomatosis



Therapeutic window in CTX



Degos *et al. Orphanet Journal of Rare Diseases* (2016) 11:41
DOI 10.1186/s13023-016-0419-x

Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

Natural history of cerebrotendinous xanthomatosis: a paediatric disease diagnosed in adulthood

Therapeutic window in CTX

2021

Expert opinion on diagnosing, treating and managing patients with cerebrotendinous xanthomatosis (CTX): a modified Delphi study

Bianca M. L. Stelten[1*], Maria Teresa Dotti[2], Aad Verrips[3], Bülent Elibol[4], Tzipora C. Falik-Zaccai[5,6], Kate Hanman[7], Andrea Mignarri[8], Belina Sithole[9], Robert D. Steiner[10,11], Surabhi Verma[12], Gilad Yahalom[13,14], Tanyel Zubarioglu[15], Fanny Mochel[16] and Antonio Federico[17]

2019

Long-term treatment effect in cerebrotendinous xanthomatosis depends on age at treatment start

Bianca M.L. Stelten, MD, Hidde H. Huidekoper, MD, PhD, Bart P.C. van de Warrenburg, MD, PhD, Eva H. Brilstra, MD, PhD, Carla E.M. Hollak, MD, PhD, Harm.R. Haak, MD, PhD, Leo A.J. Kluijtmans, PhD, Ron A. Wevers, PhD, and Aad Verrips, MD, PhD

Correspondence
Dr. Stelten
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2018

Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes

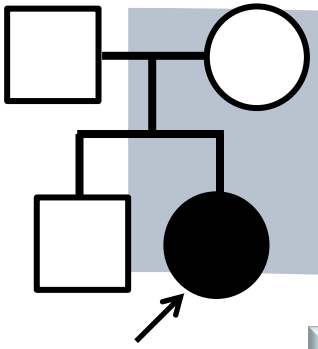
Maria del Mar Amador[1] · Marion Masingue[1] · Rabab Debs[1,2] · Foudil Lamari[3,4,5] · Vincent Perlbarg[6,7,8] · Emmanuel Roze[1,4,6] · Bertrand Degos[9,10] · Fanny Mochel[4,5,6,11,12]

< 25 years of age

2013

Neurological Outcome in Cerebrotendinous Xanthomatosis Treated With Chenodeoxycholic Acid: Early Versus Late Diagnosis

Gilad Yahalom, MD,† Rakefet Tsabari, MD,†‡ Noa Molshatzki, MSc,‡ Lilach Ephraty, MD,*† Hofit Cohen, MD,§|| and Sharon Hassin-Baer, MD*†||*



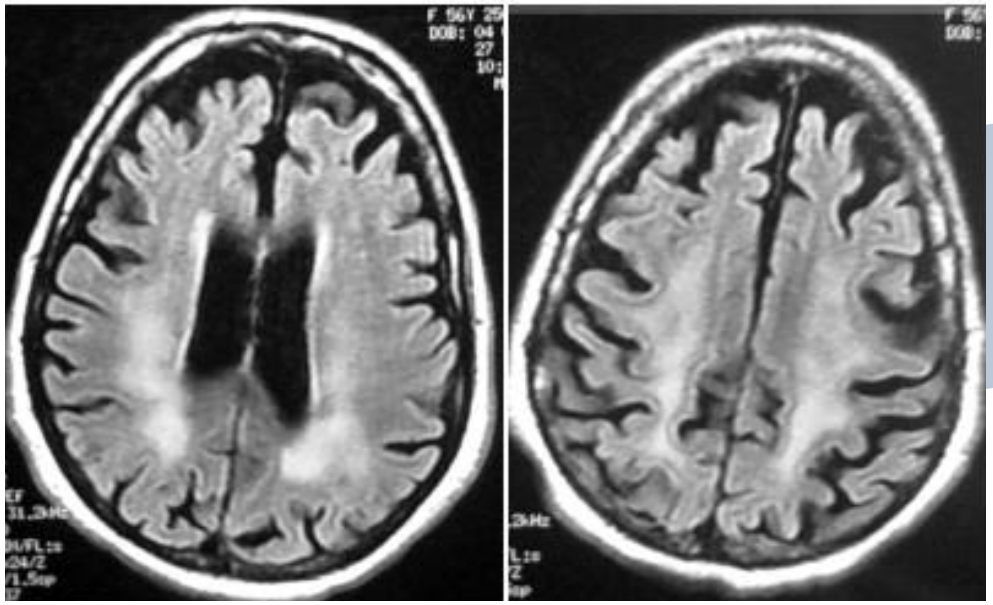
Depression
Suicidal attention

50 years

Psychosis
(visual hallucinations)

53 years

MTHFR



Acute paraplegia
Coma

56 years

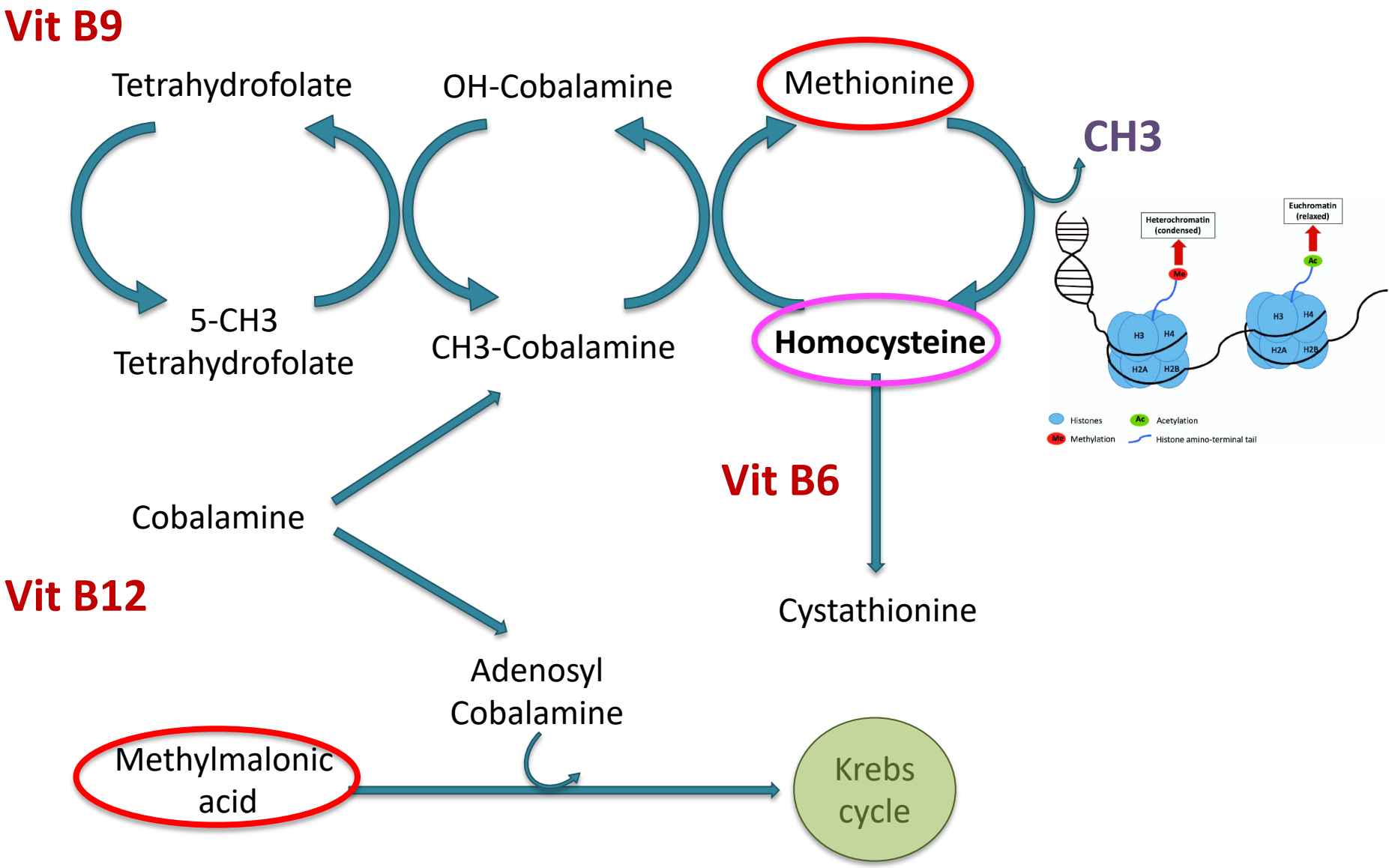
How would you treat this patient?

1. Vitamin B12
2. Folic acid
3. Low-protein diet
4. Betaine
5. Anticoagulants

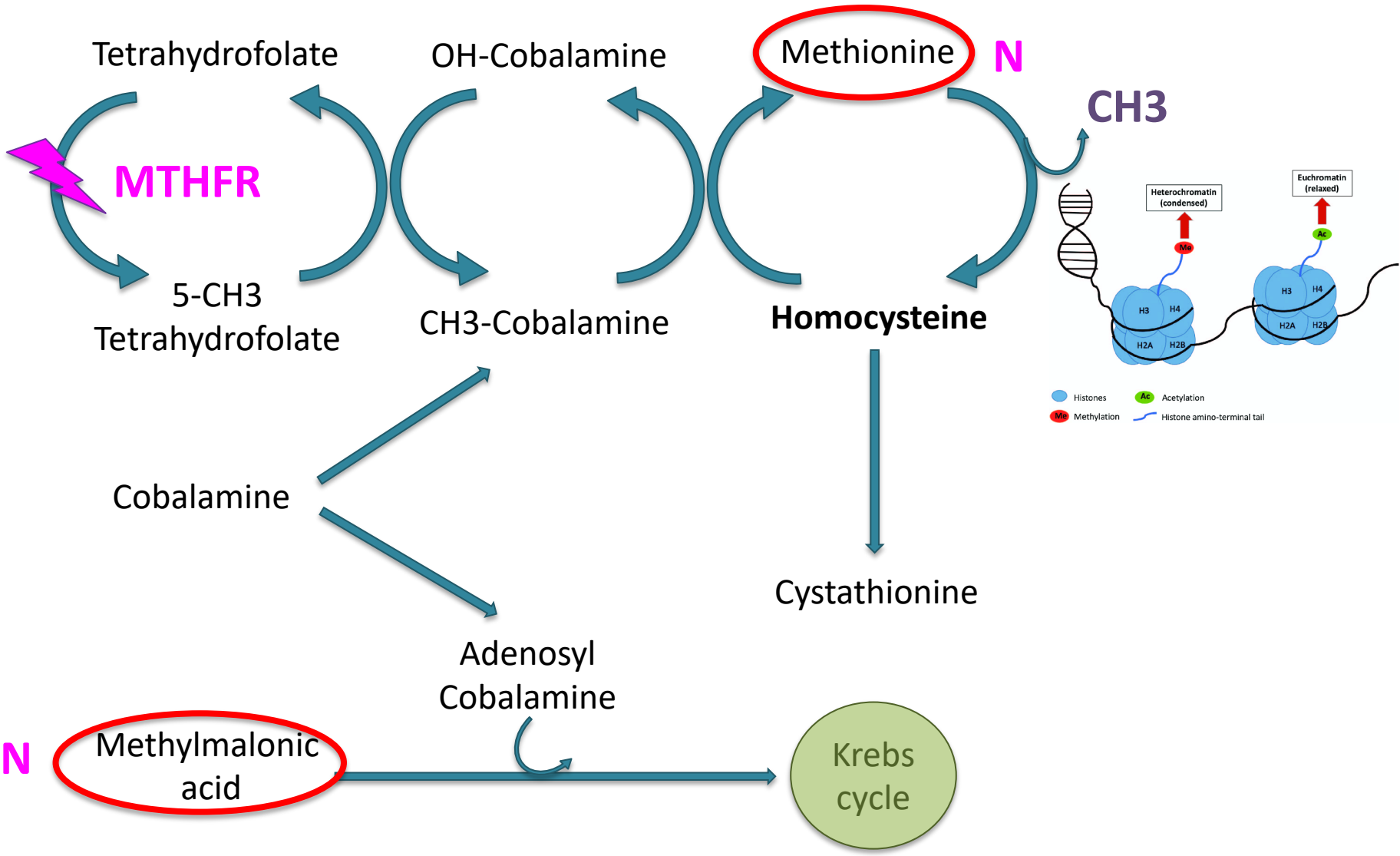
How would you treat this patient?

1. Vitamin B12
2. Folic acid
3. Low-protein diet
4. Betaine
5. Anticoagulants

MTHFR deficiency and homocystein remethylation



MTHFR deficiency



Treatment

Vit B9

Tetrahydrofolate

OH-Cobalamine

Methionine

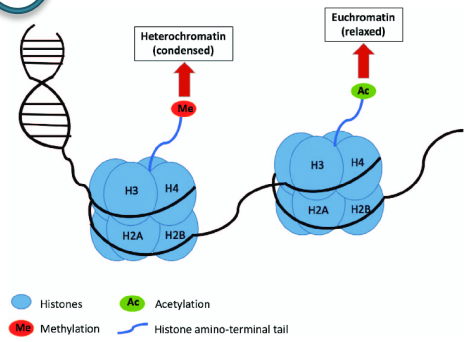
CH3

Betaine

5-CH3
Tetrahydrofolate

CH3-Cobalamine

Homocysteine



Cobalamine

Vit B12

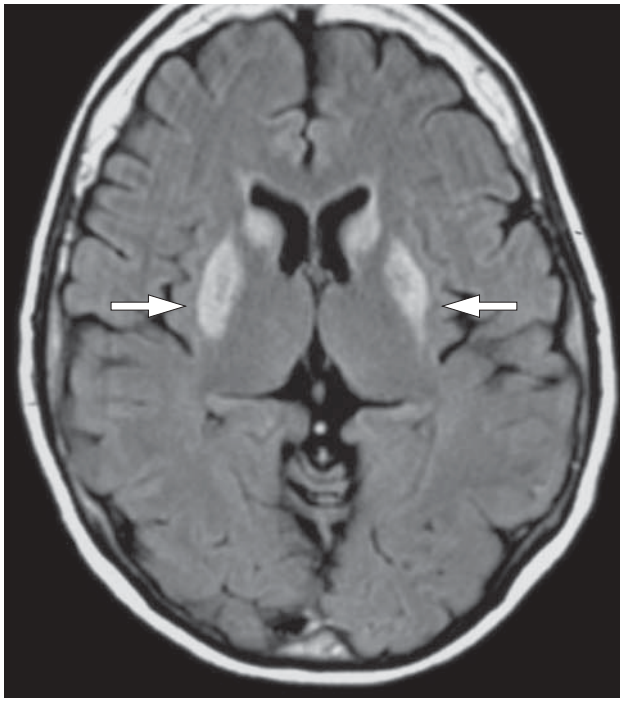
Cystathionine

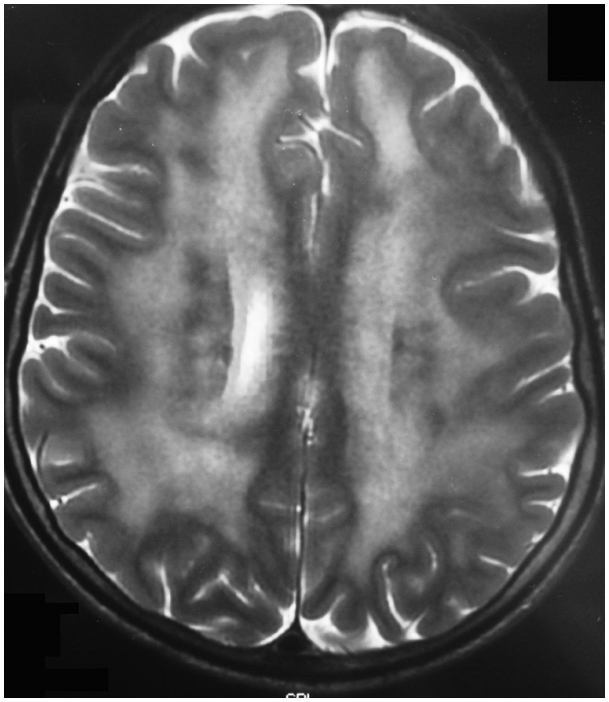
Adenosyl
Cobalamine

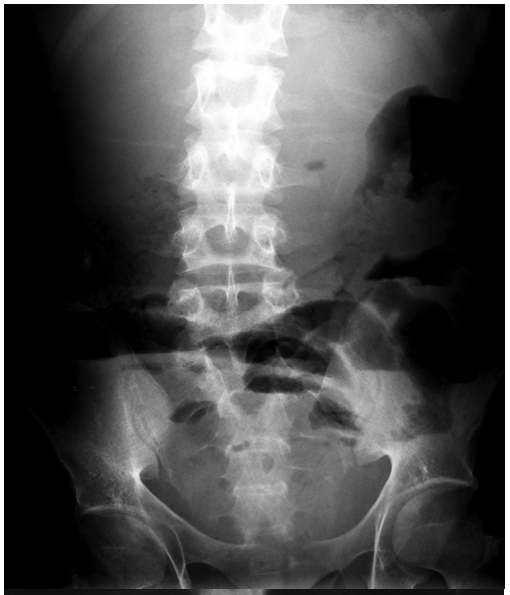
Methylmalonic
acid

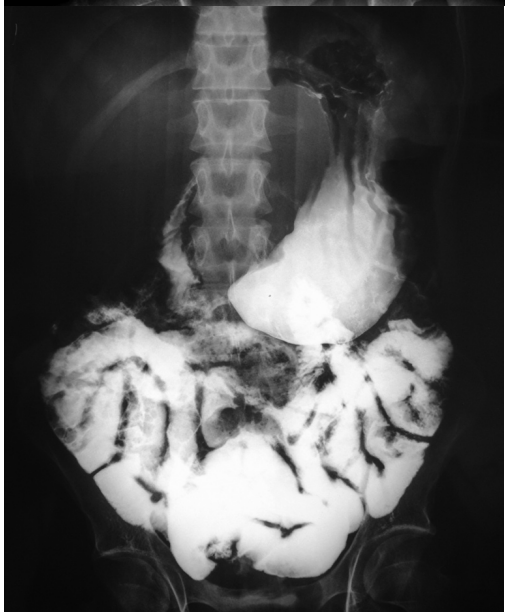
Krebs
cycle

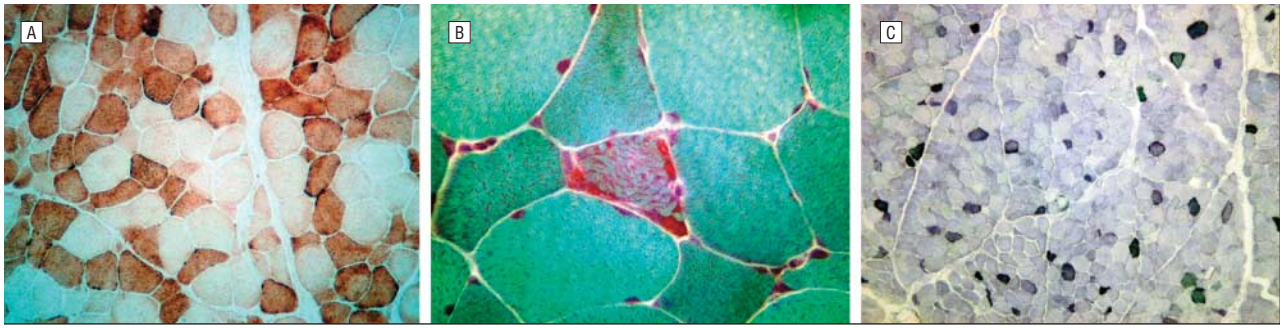
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE, thymidine phosphorylase)









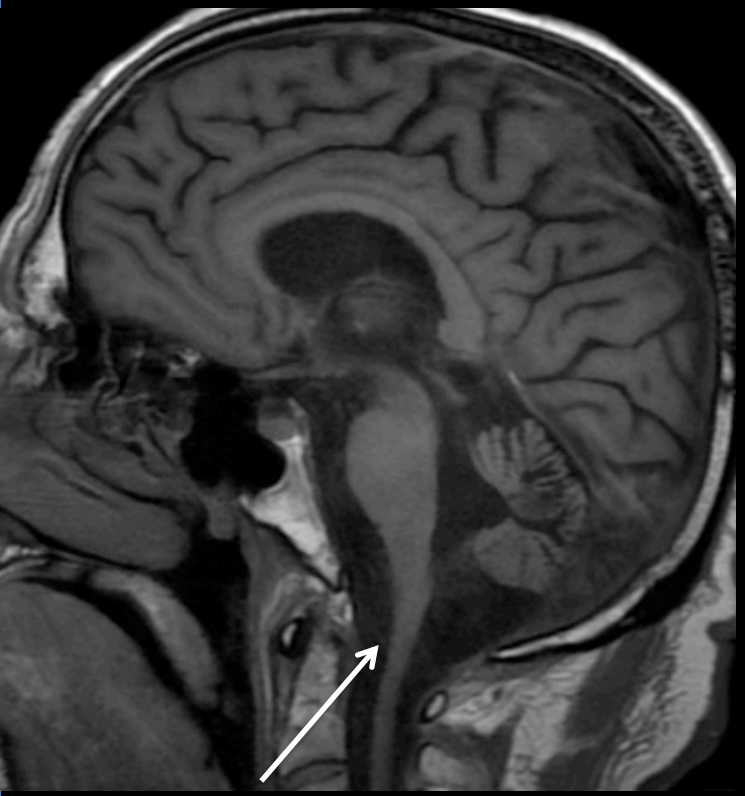


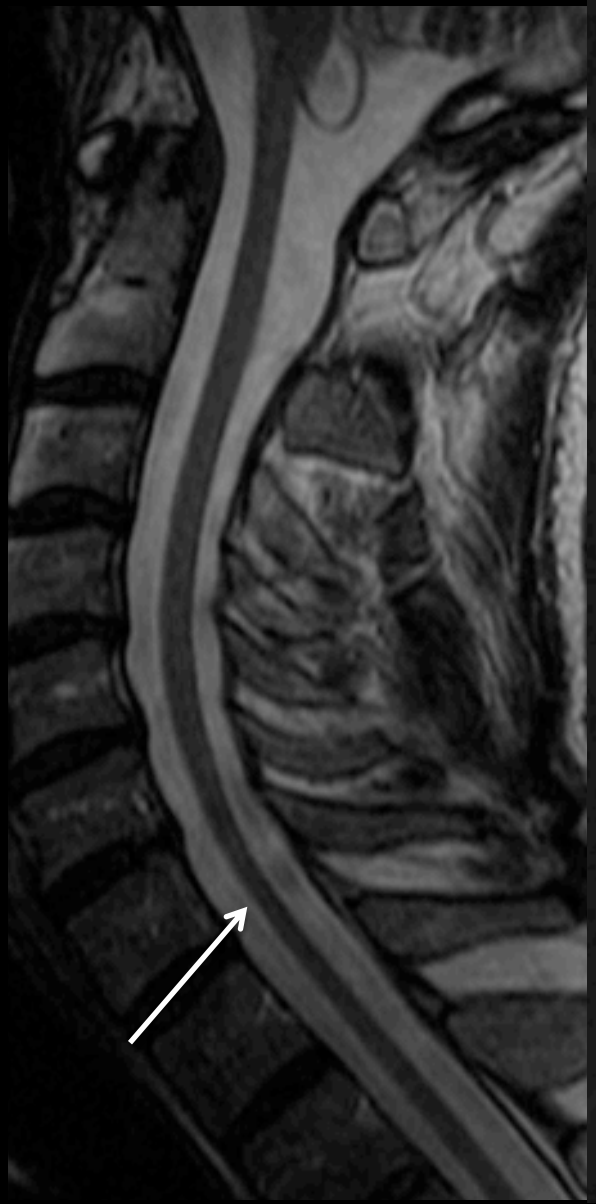
Liver transplantation

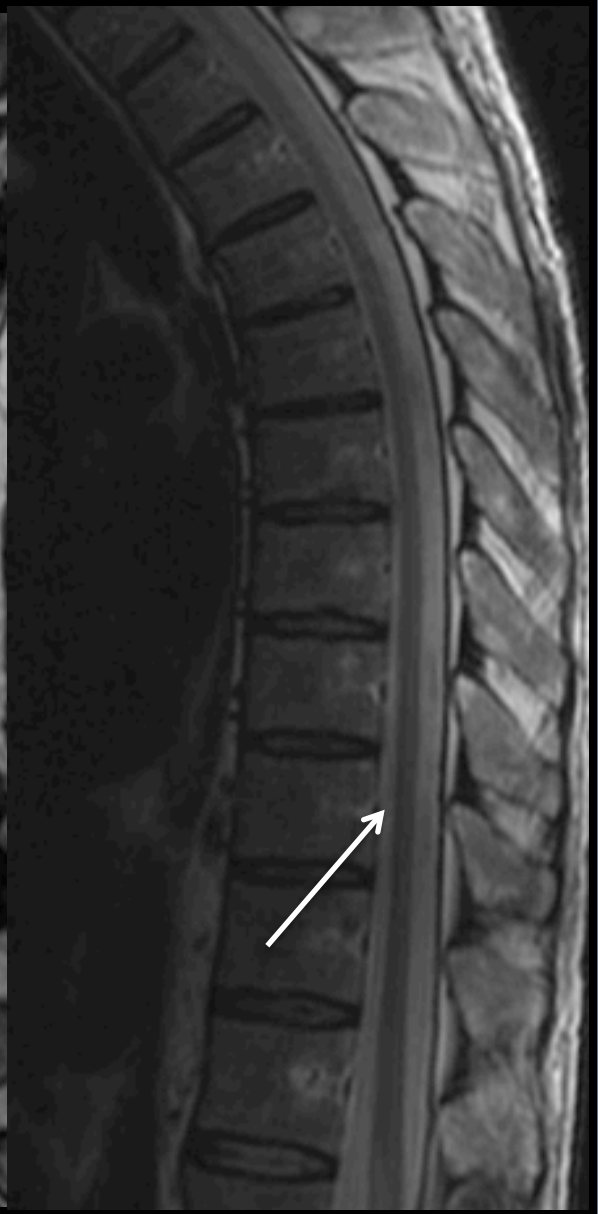
Leukodystrophy &… biomarkers

Ophthalmology, Audiometry, Other		Biomarkers
	Sterols	
delay, **cataract**, spasticity, ataxia, psychosis	**CTX**	Cholestanol
	Lysosome	
spasticity, ataxia, psychosis	**MLD**	Arylsulfatase A
spasticity, ataxia, **optic atrophy**	**Krabbe**	Galactocerebrosidase
delay, **deafness**, **bone**, ataxia, psychosis	**α-mannosidosis**	α-mannosidosis
	Peroxisome	
spasticity, **adrenal insufficiency**	**ALD**	VLCFA
spasticity, ataxia, **deafness**, **retinopathy**	**PBD**	Phytanic, pristanic acids
	Hcy methylation	
delay, spasticity, neuropathy, **epilepsy**	**MTHFR**	Homocystein
	Mitochondria	
PEO, **intestinal pseudo-obstruction**	**MNGIE**	Lactate

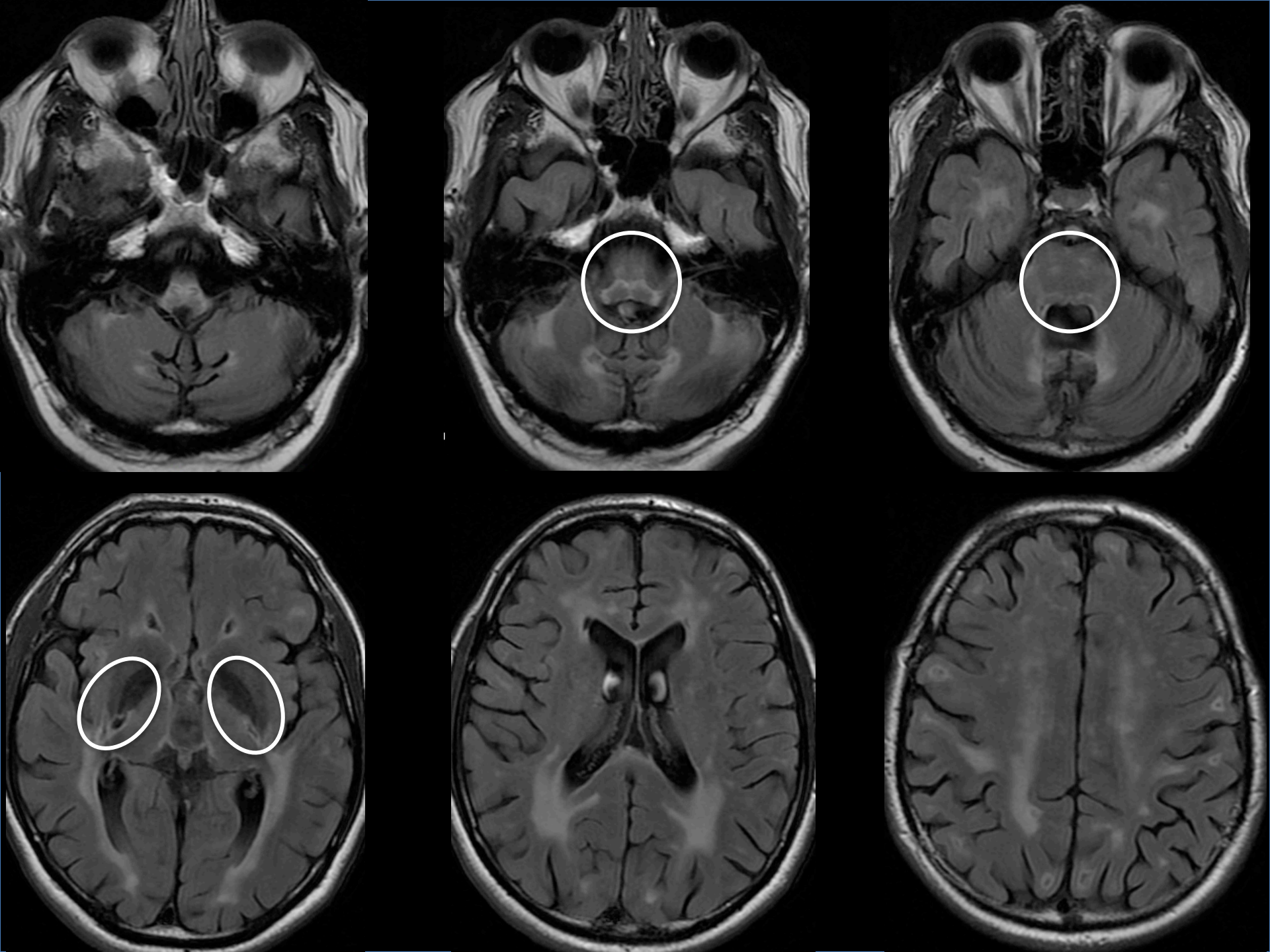
Peripheral (demyelinating) neuropathy



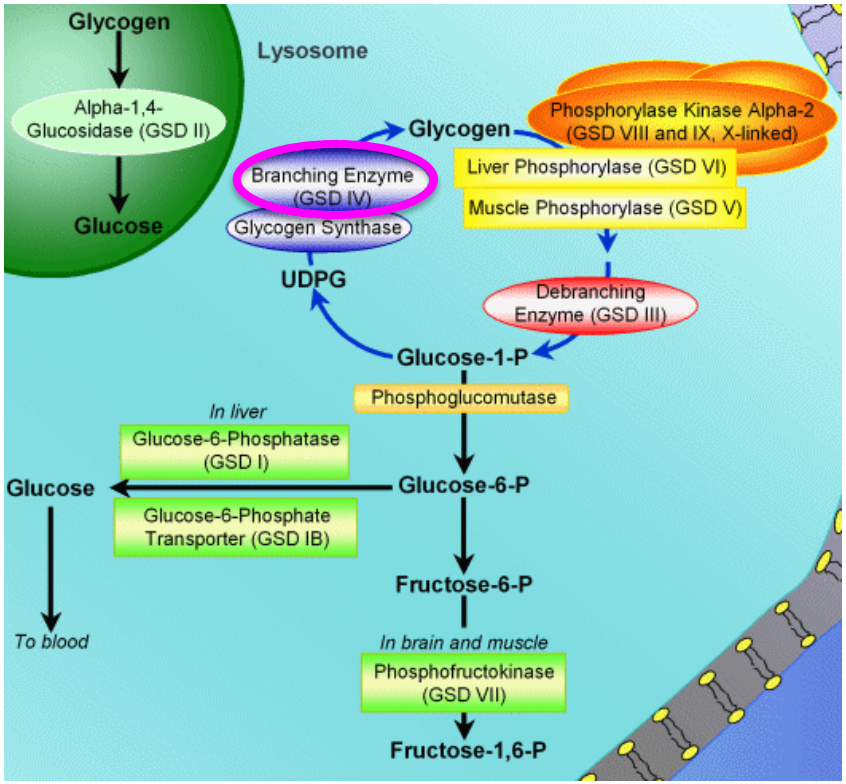


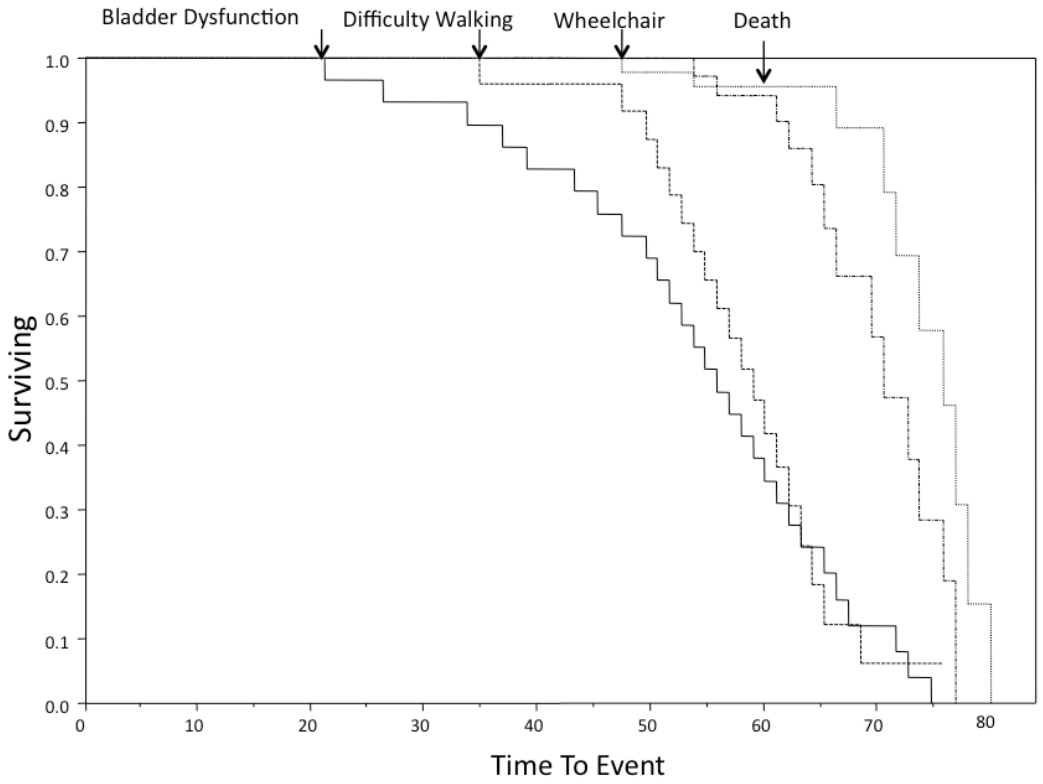


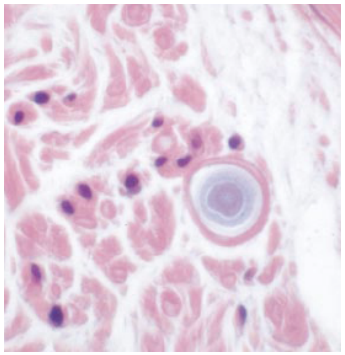
Mochel et al, Ann Neurol 2012



Glycogen branching enzyme

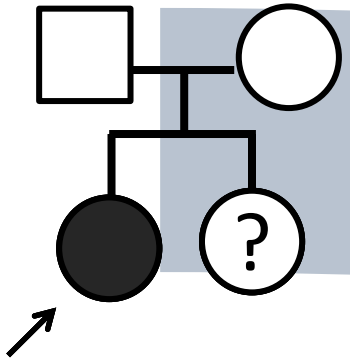






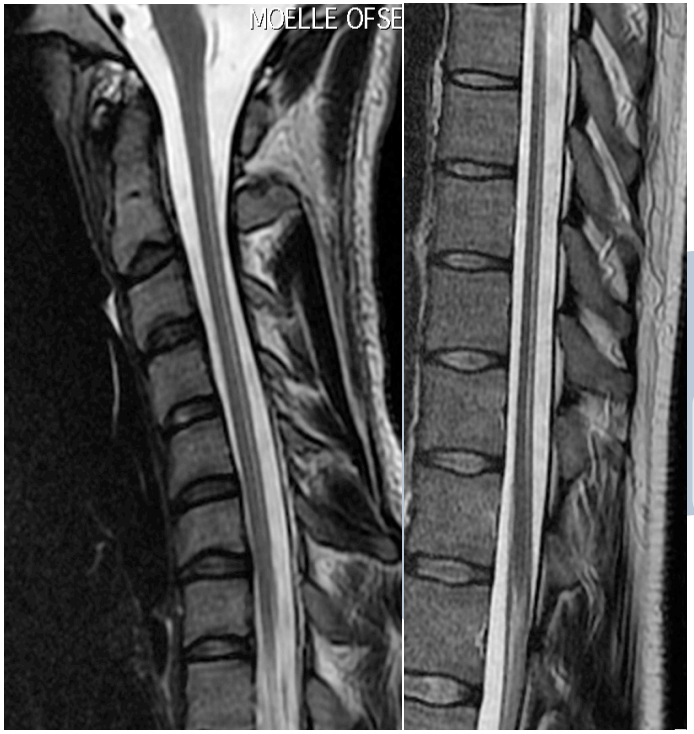
Adult Polyglucosan Body Disease

Mochel et al, Ann Neurol 2012



Depression
Psychosis

Adolescence



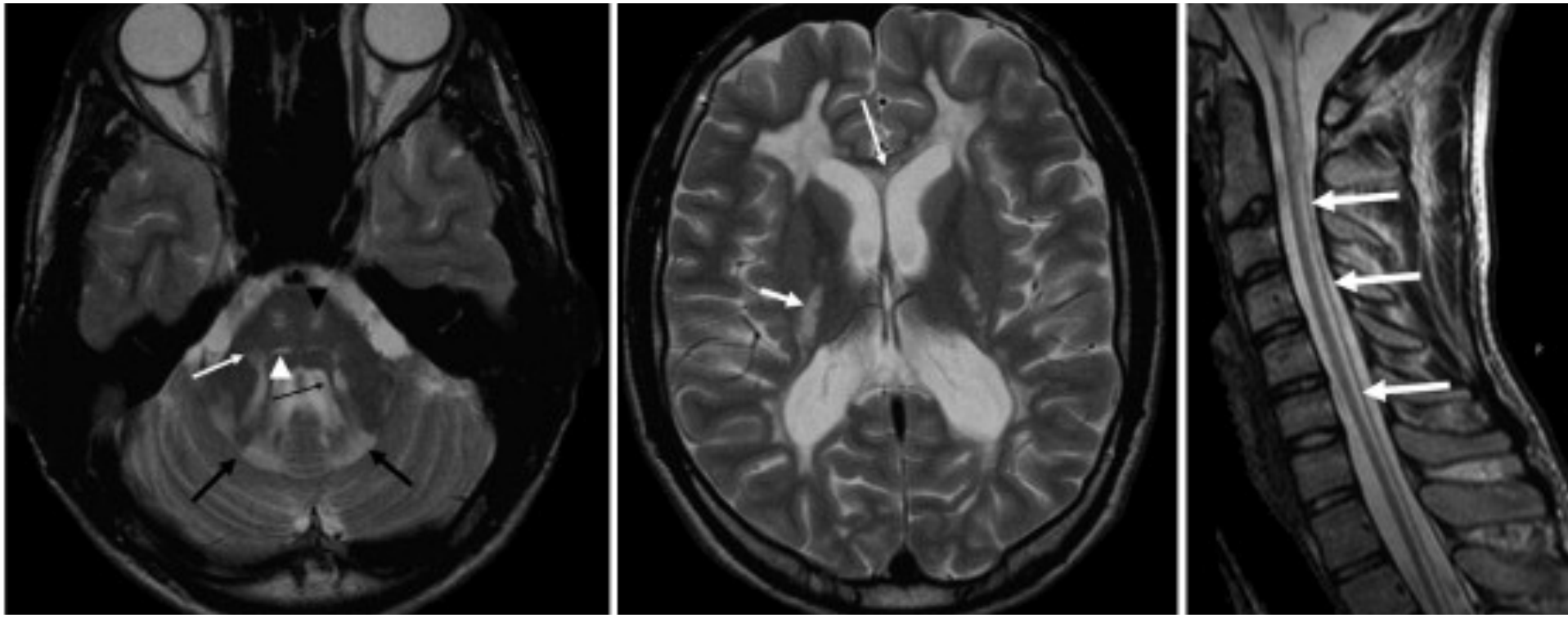
Motor deterioration
with NLP change

26 years

35 years

2nd episode of motor
deterioration with NLP change

LBSL: DARS2 mutations



Differential diagnosis: LMNB1 dup, Alexander disease

Myelitis and/or optic neuropathy

Family

Negative history

Narrative

Over 2 weeks: spastic tetraparesis

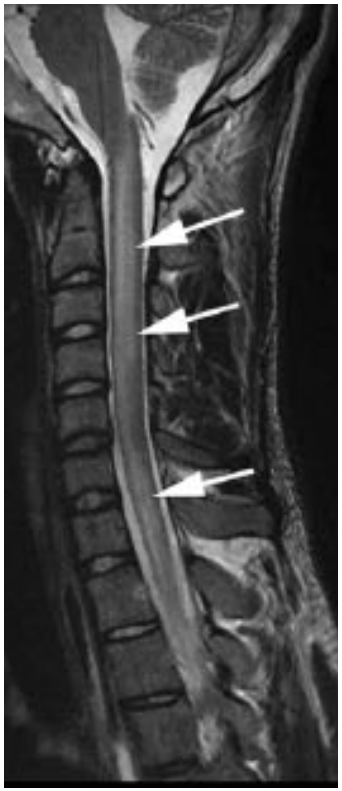
Decreased visual acuity

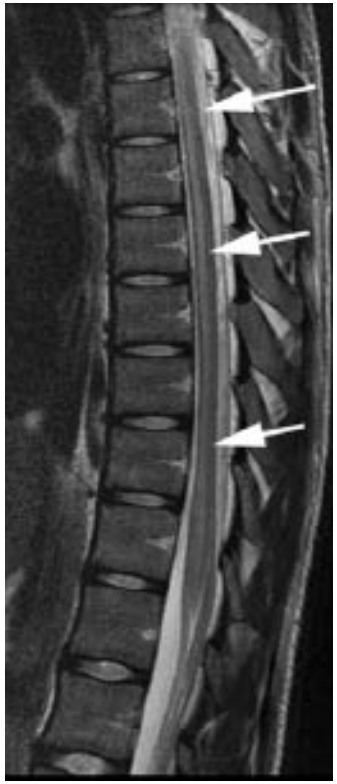
Bedridden and nearly blind

Investigation

Bilateral optic neuropathy

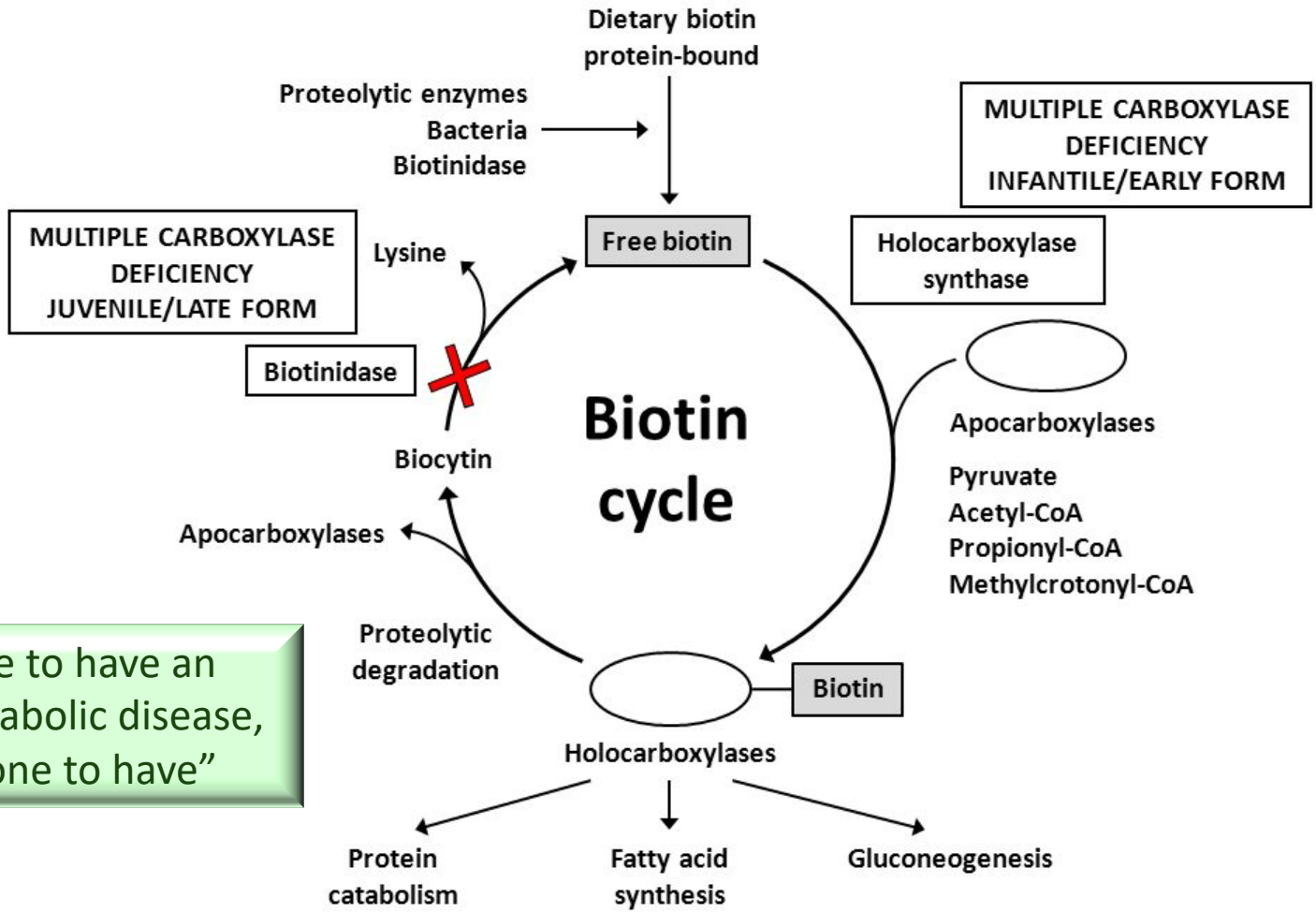
Oligoclonal bands



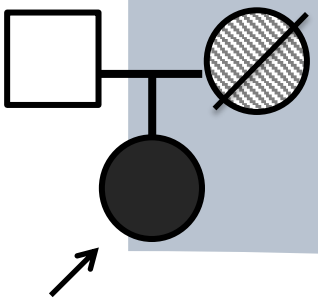


Bottin et al, Mult Scl 2015

Biotinidase deficiency



"If you have to have an inherited metabolic disease, this is the one to have"

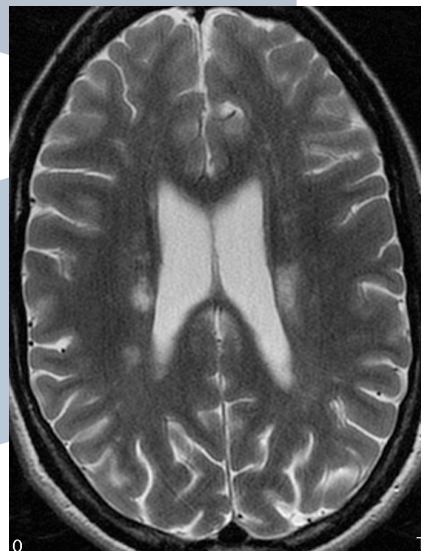


Mild head trauma
Stiffness right leg

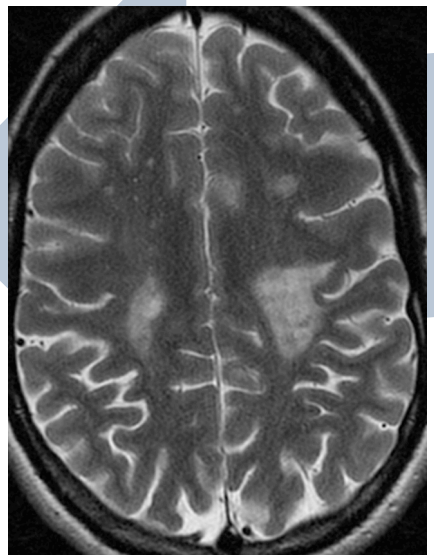
32 years

Rapid
spastic paraplegia

33 years

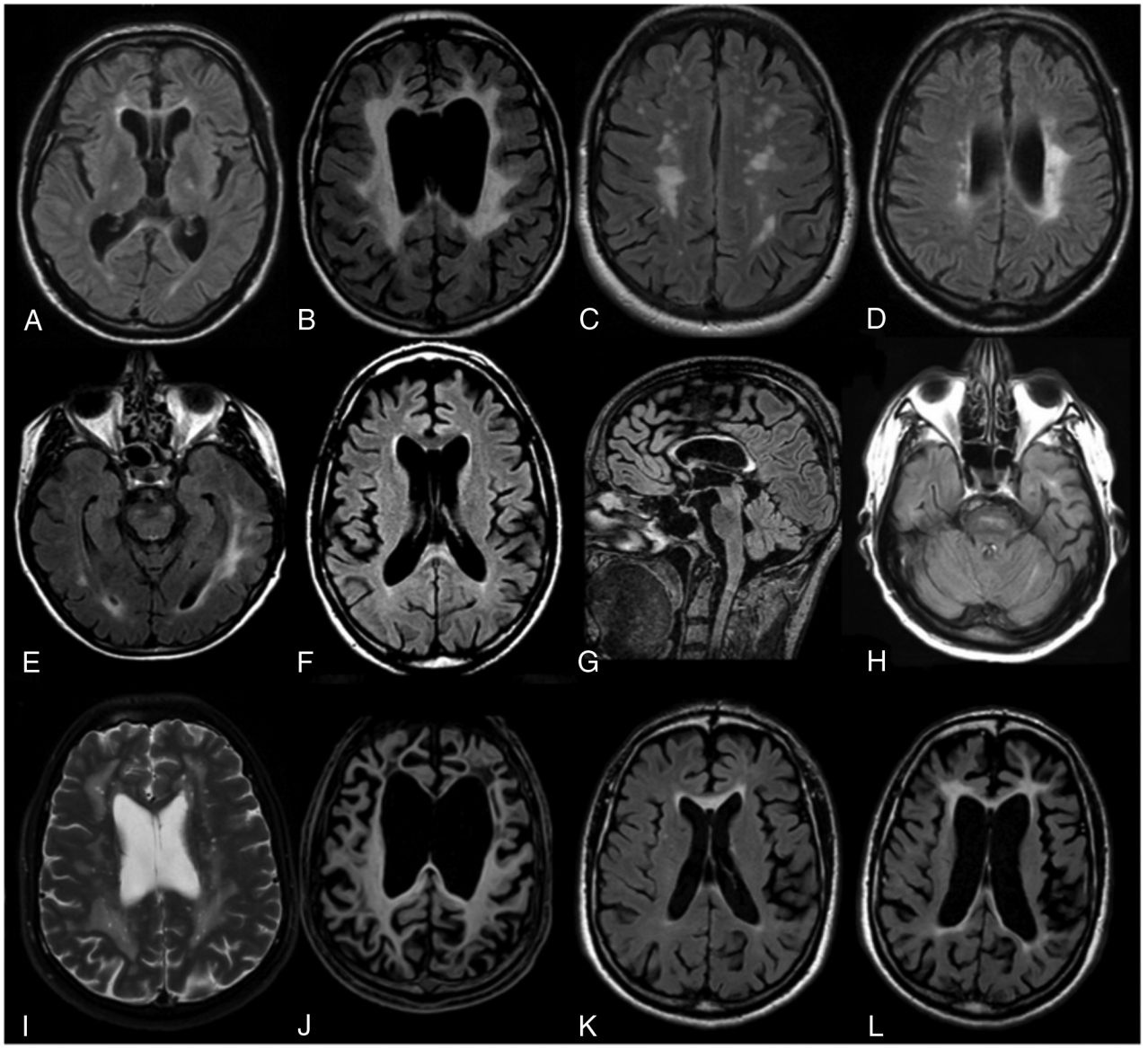


Need a walker
Only a few steps



CSF1R-related leukodystrophy

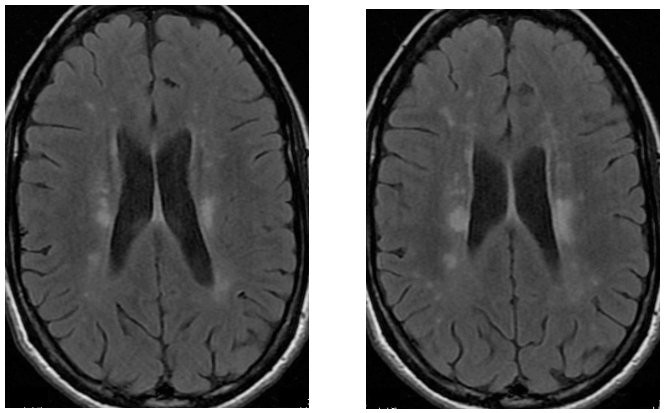
Family history
No Gd enhancement
No spinal lesions
Normal CSF

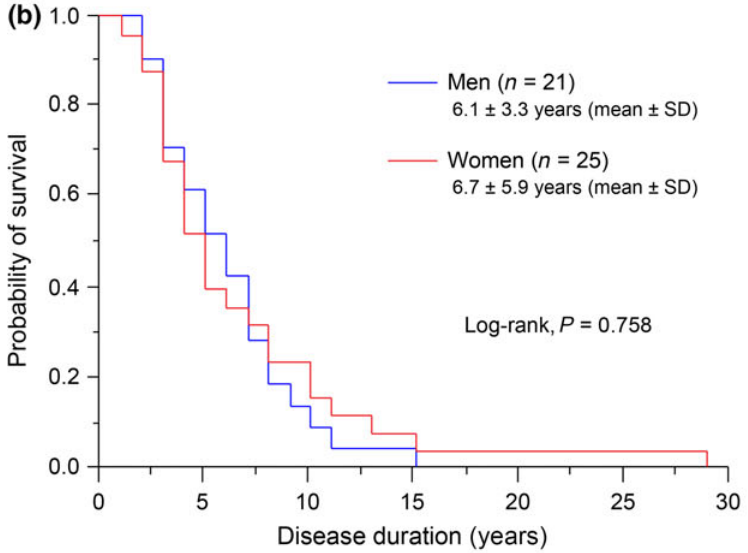


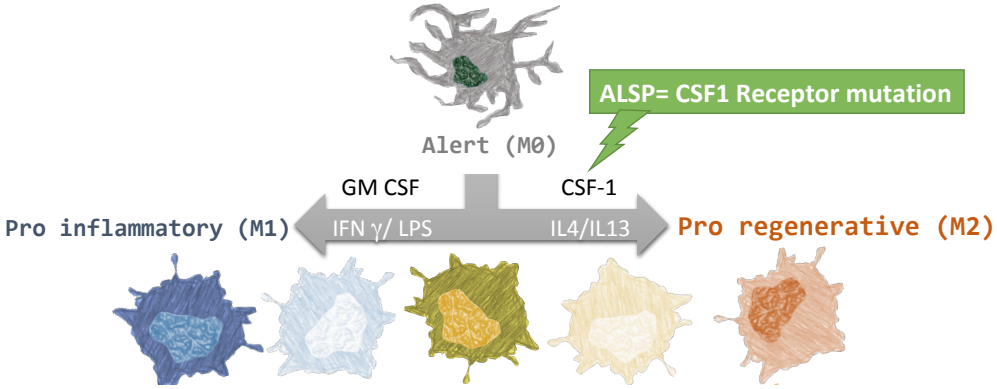
Codjia et al, AJNR 2018

CSF1R –related ALSP

Mimicks severe forms of multiple sclerosis

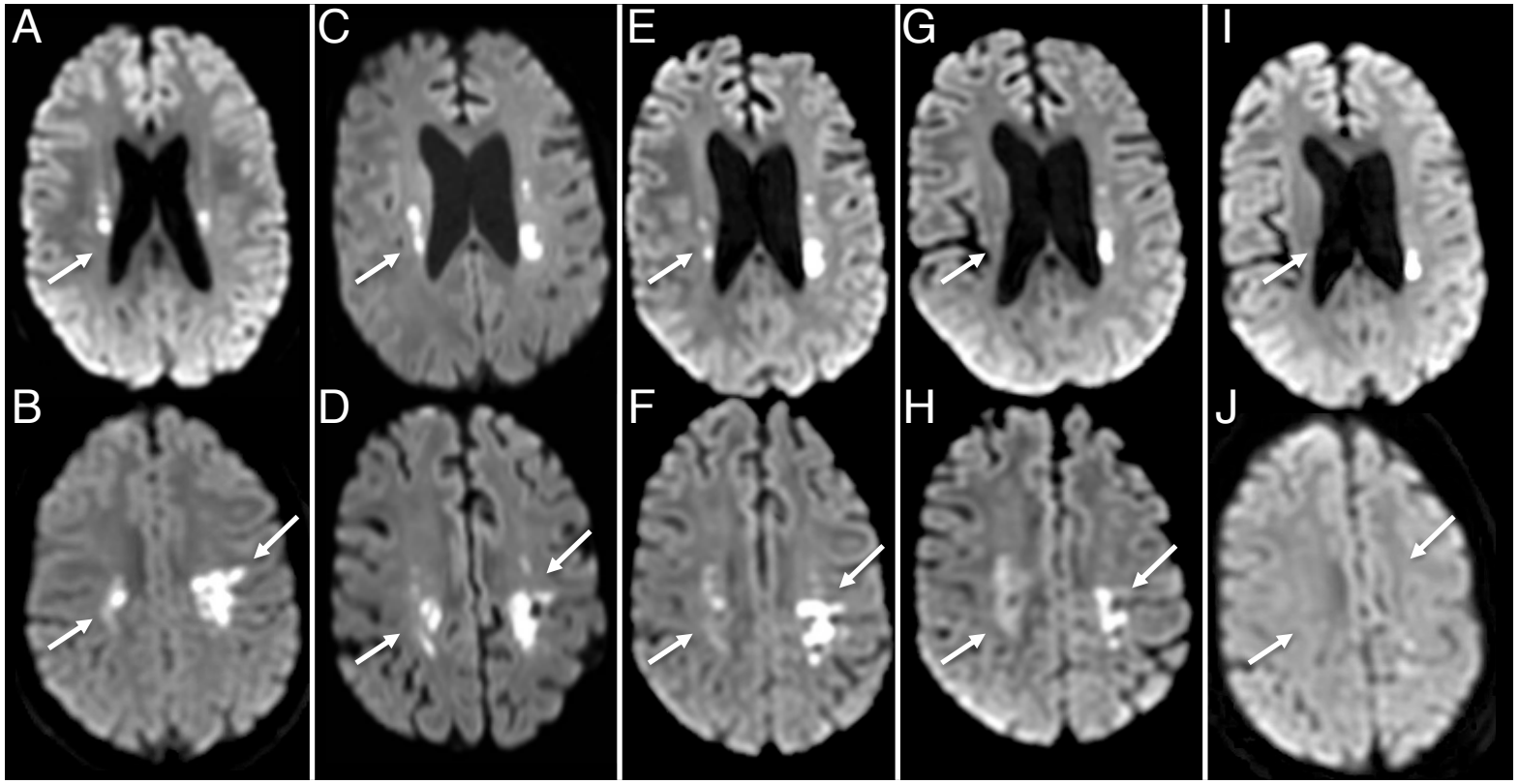




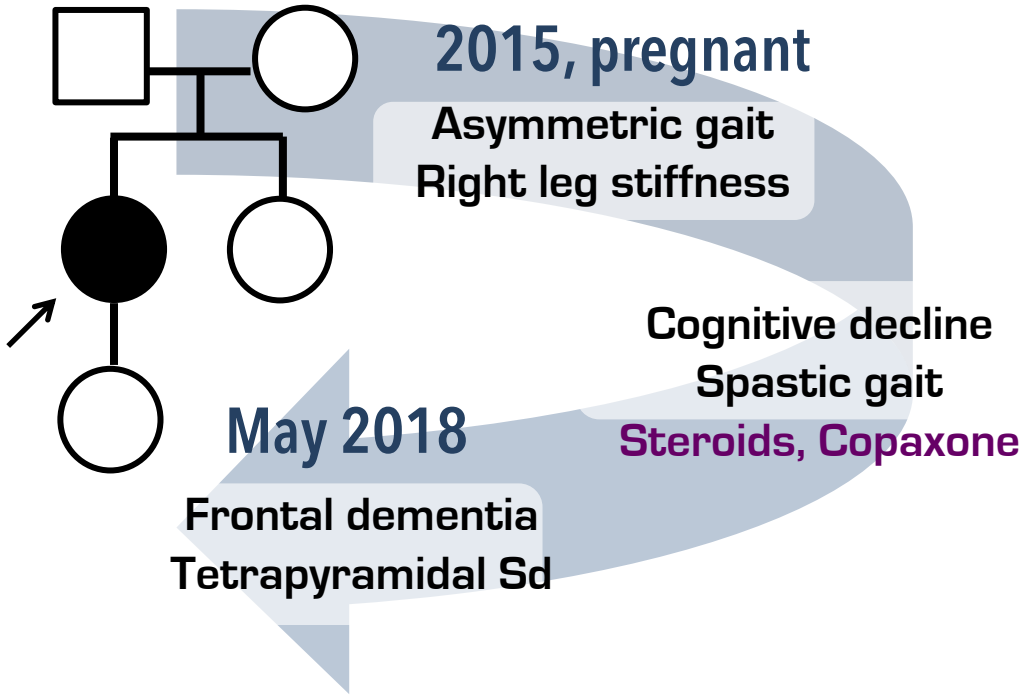


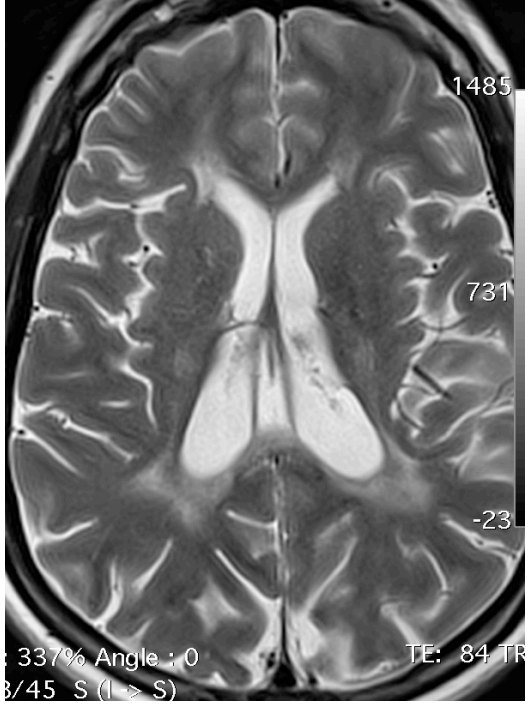
Hematopoietic Stem Cell Transplantation

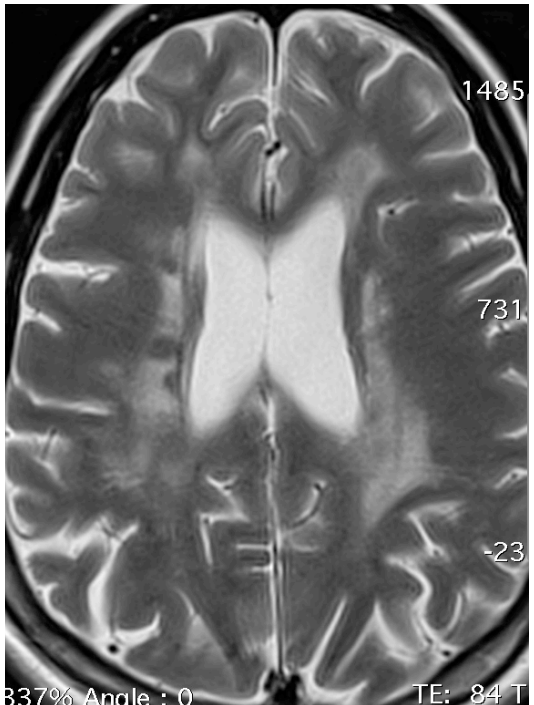
HSCT in CSF1R-ALSP



Mochel, Delorme, JNNP 2019


2015, pregnant
Asymmetric gait
Right leg stiffness
Cognitive decline
Spastic gait
Steroids, Copaxone
May 2018
Frontal dementia
Tetrapyramidal Sd


1485
731
-23
337% Angle : 0
3/45 S (I -> S)
TE: 84 TR


1485
731
-23
337% Angle : 0
TE: 84 T

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

- Think Leukodystrophy – it is not just MS…
- T1-weighted images, sensory evoked potentials, nerve conduction studies
- Think Biomarkers – it is not just NGS
- Think Treatments

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Centre de référence
Maladies Rares

« leucodystrophies »

Odile Boespflug-Tanguy
Caroline Sevin
Xavier Ayrignac
Clarisse Carra-Dallière
Pierre Labauge

Raphael Schiffmann
Marjo van der Knaap
Nicole Wolff