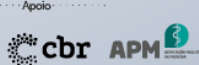


European Course on Pediatric Neuroradiology in Latin America (ECPNR-LATAM)

spr.org.br



3rd Cycle - Module 1
de 1^o a 4 de outubro

Local: Sede da APM
Associação Paulista de Medicina
São Paulo - Brasil

Neurodegenerative disorders.

Basal ganglia disorders in pediatric age

(at least those entities which usually affect mostly the basal ganglia)

Andrea Righini M.D.

Pediatric Radiology and Neuroradiology Department
Children's Hospital V. Buzzi, Milan, Italy

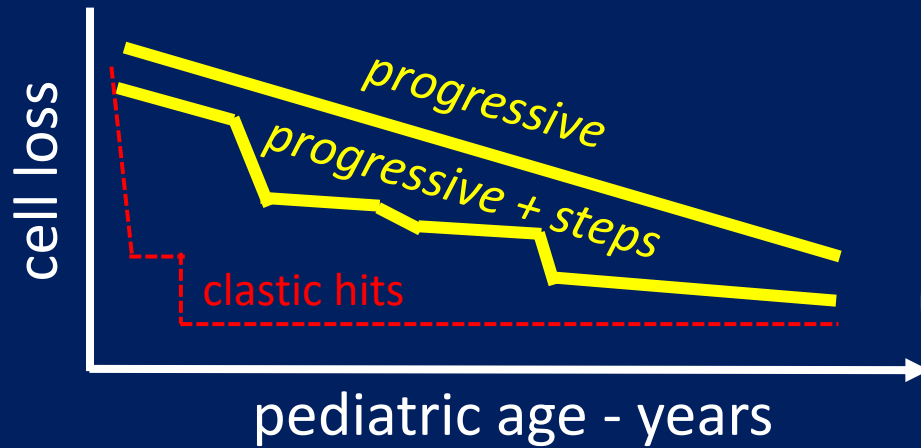
andrea.righini@asst-fbf-sacco.it

No conflict of interest to disclose

GENERAL CONCEPTS

- HIGH CLINICAL AND IMAGING VARIABILITY: very hard to set-up frameworks and determine sharp borders.
- Mostly unspecific MRI patterns, very few pathognomonic
- Often associated with anomalies of other regions
- Various literature attempts to grouping based on features of BG involvement: putamen, pallidus, thalamus...

BG degeneration concept



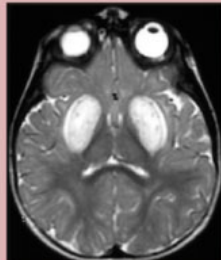
LARGE OVERLAP

- **Primitive degeneration** (*usually genetic*)
- Metabolic-toxic effect and progressive atrophy-necrosis
- Acute metabolic, infective, ischemic lesions and atrophy-necrosis sequelae

must read paper

CHILDHOOD ONSET BILATERAL BASAL GANGLIA CHANGES DISORDERS CLUSTER INTO FOUR MAJOR MRI PATTERNS

Cluster 1: Bilateral putaminal T2-Weighted hyperintensities

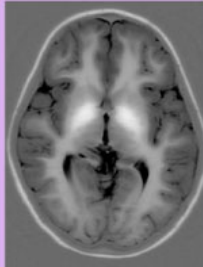


SLC19A3 associated biotin-thiamine responsive basal ganglia disorder

**CEREBRAL PALSY
MEGDEL
AMINOACIDOPATHIES
MYELINOLYSIS
ENCEPHALITIS....**

MANGANESE

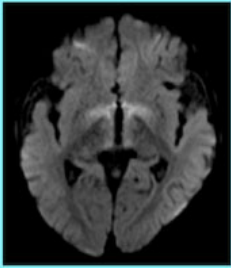
Cluster 4 - T1-Weighted hyperintensities in the basal ganglia



Hypermanganesemia with dystonia (SLC39A14)

**T1-hyper pallidus:
«accumulation»**

Cluster 3: T2-Weighted Hyperintensities in the globus pallidus, brainstem and cerebellum with diffusion restriction

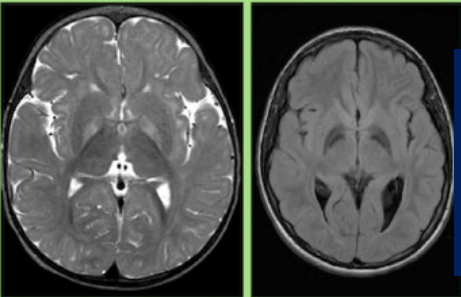


Vigabatrin toxicity

**VIGABATRIN
KRABBE**

**KERNICTERUS
METHYLMALONIC ACIDEMIA
PYRUVATE
DEHYDROGENASE
KEARNS SAYRE
BRAIN IRON**

Cluster 2: T2-Weighted hyperintensities or increased susceptibility in bilateral globus pallidus



Kernicterus Mitochondrial membrane protein associated Neurodegeneration (MPAN)

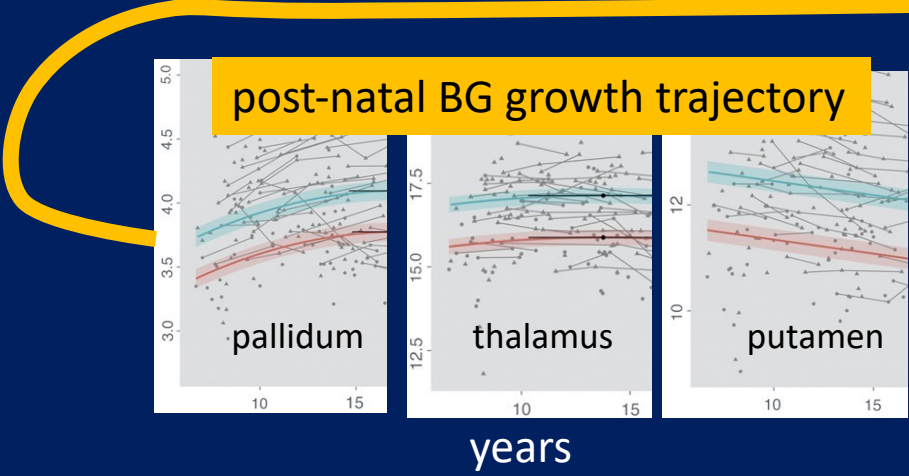
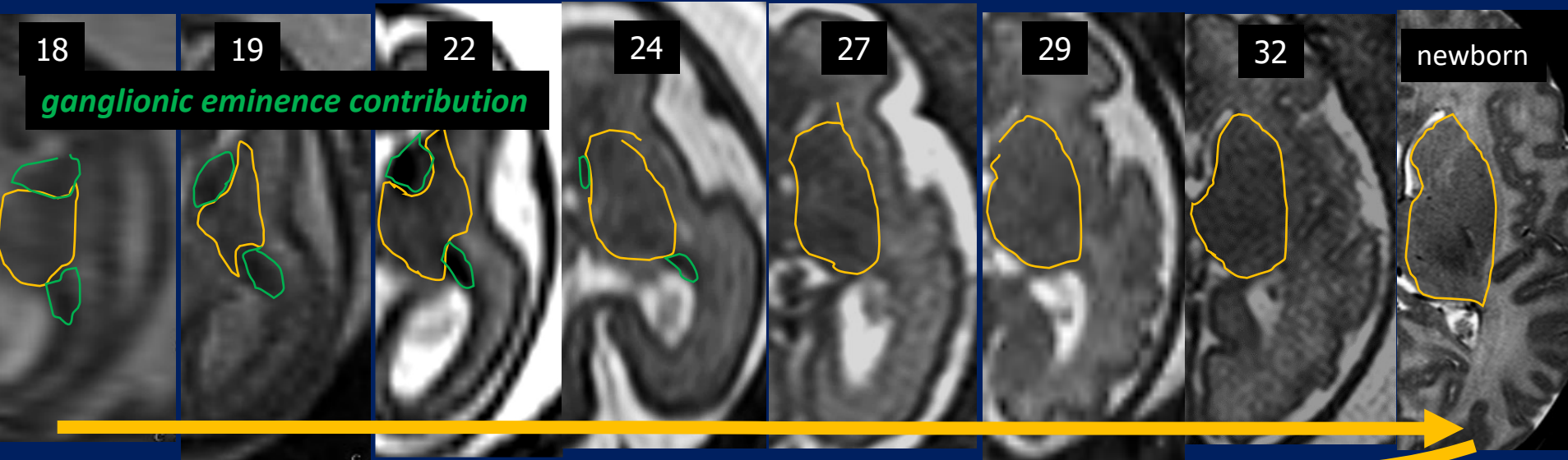
**Pallidus SWI +++
«BAD IRON»

but also T2-hyper**

T2-hyper putamen

T2-hyper pallidus

prenatal BG development

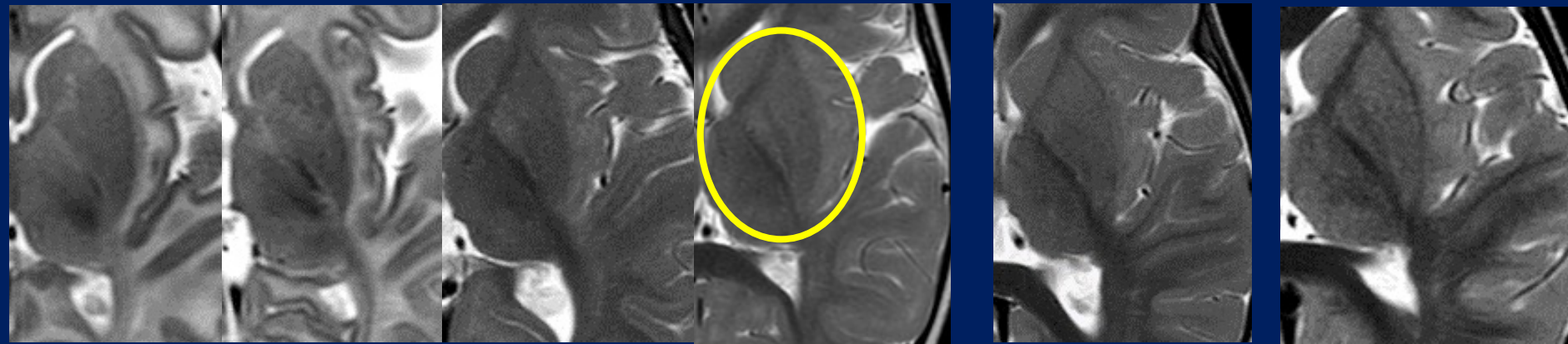


Neuroimage 2014. Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24
Lara Wierenga et Al..

Normal BG evolution (T2W)

1.5T

higher contrast resolution



newborn

3m

10m

15m

18m

2yrs

3yrs



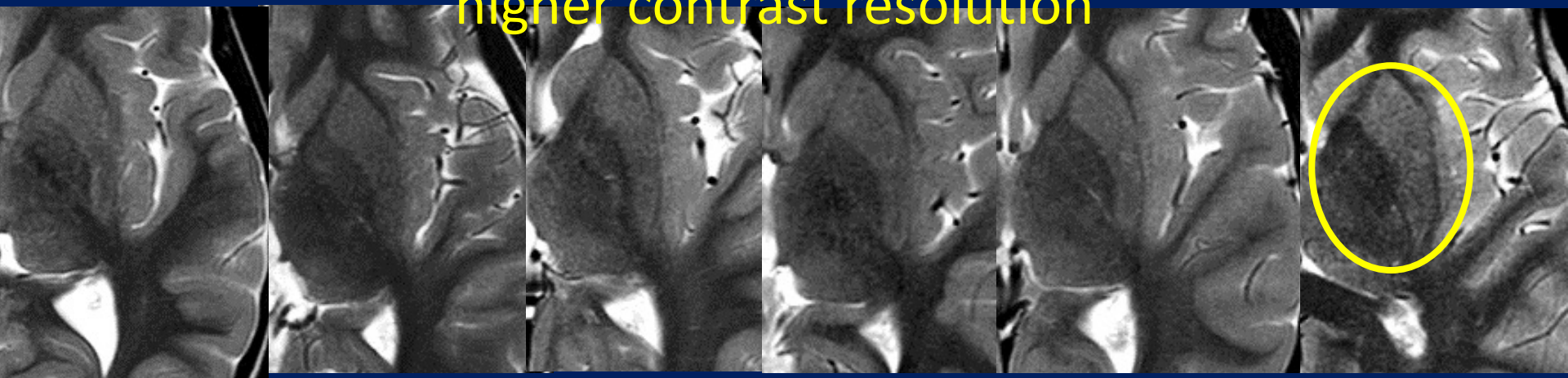
3T

higher spatial resolution

1.5T

Normal BG evolution (T2W)

higher contrast resolution



4yrs

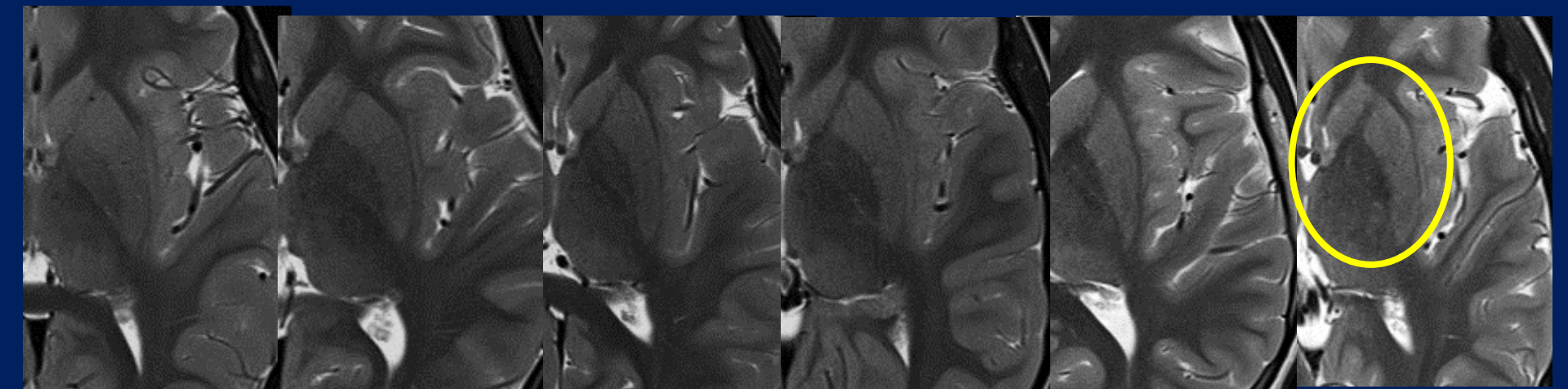
6yrs

7yrs

9yrs

10yrs

12 yrs

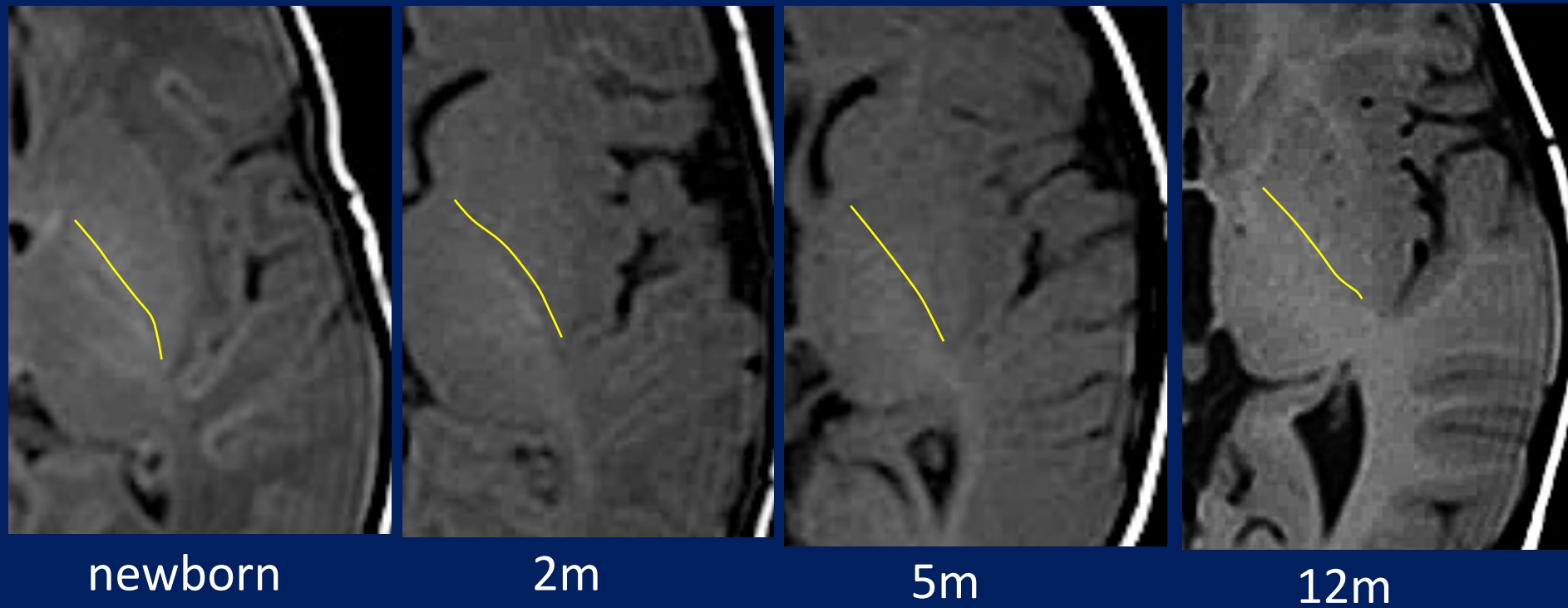


3T

higher spatial resolution

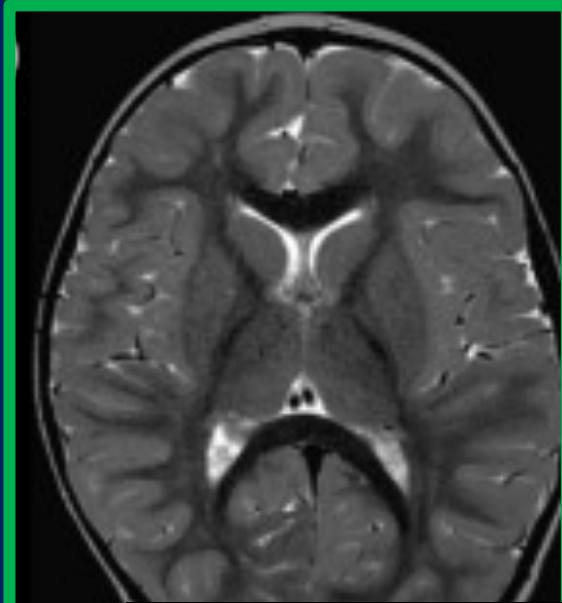
Normal BG evolution (T1-W)

1.5T

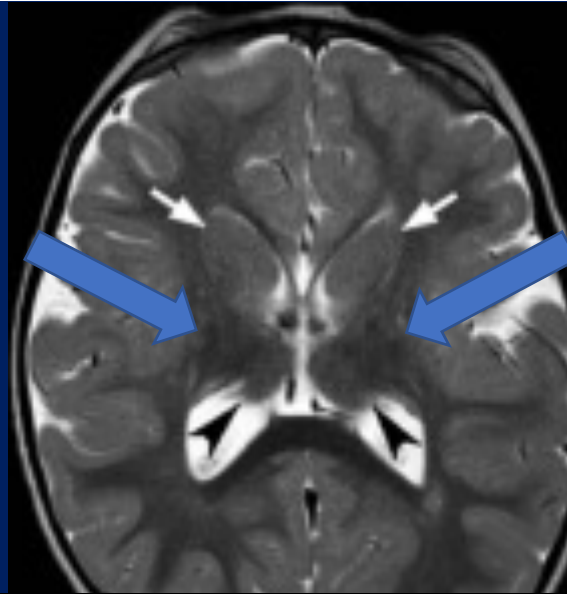


To start...BG (putamen and pallidus) CANNOT even develop at all

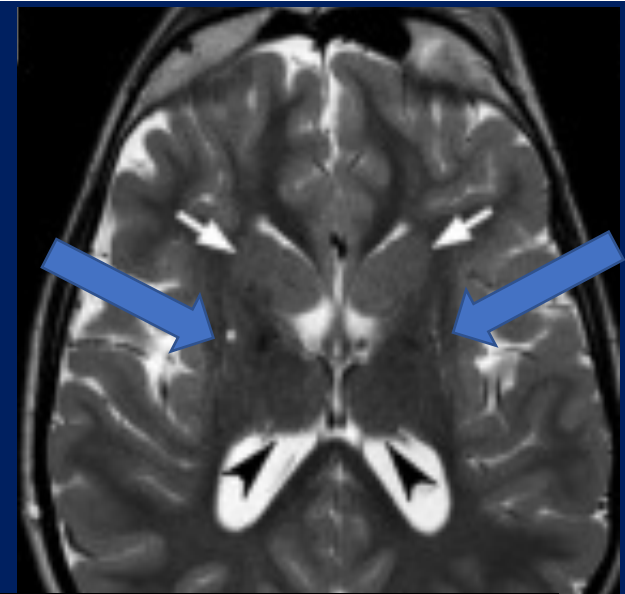
Brain. 2019; 142(10): 2965–2978. **Agnesis of the putamen and globus pallidus caused by recessive mutations in the homeobox gene *GSX2***. Roberta De Mori, Mariasavina Severino et Al..



control



patient 1



patient 2

GSX2-mutated patients presented agnesis or dysgenesis of the structures derived from lateral and median ganglionic eminences, including putamina, globi pallidi, caudate nuclei and olfactory bulbs.

Table 2. Basal ganglia neuroimaging abnormalities in neurometabolic diseases [10].

Disease	Thalamus	Pallidum	Putamen
Respiratory chain disorders	+	+	+
Biotin-thiamine-responsive basal ganglia disease			+
Pyruvate dehydrogenase deficiency	+	+	+
Coenzyme Q10 deficiency			+
Mitochondrial thiamine pyrophosphate transporter			+
Cerebrotendinous xanthomatosis		+	
Alpha-methylacyl-CoA racemase deficiency	+		
GM1 gangliosidosis			+
Fabry disease	+		
Methylmalonic aciduria		+	
Succinic semialdehyde dehydrogenase deficiency		+	
Urea cycle disorders		+	
Glutaric aciduria type 1			+
Wilson disease	+	+	+
Aceruloplasminemia	+	+	+
Neuroferritinopathy		+	+
Pantothenate kinase-associated neurodegeneration		+	
Infantile neuroaxonal dystrophy		+	
Hypermanganemia		+	

**NEURO
DEGEN
diseases**

>all BG

>putamen

>all BG

>putamen

>pallidum

>pallidum

>pallidum

>putamen

>putamen

>all BG

>pall+putam

>pallidum

>pallidum

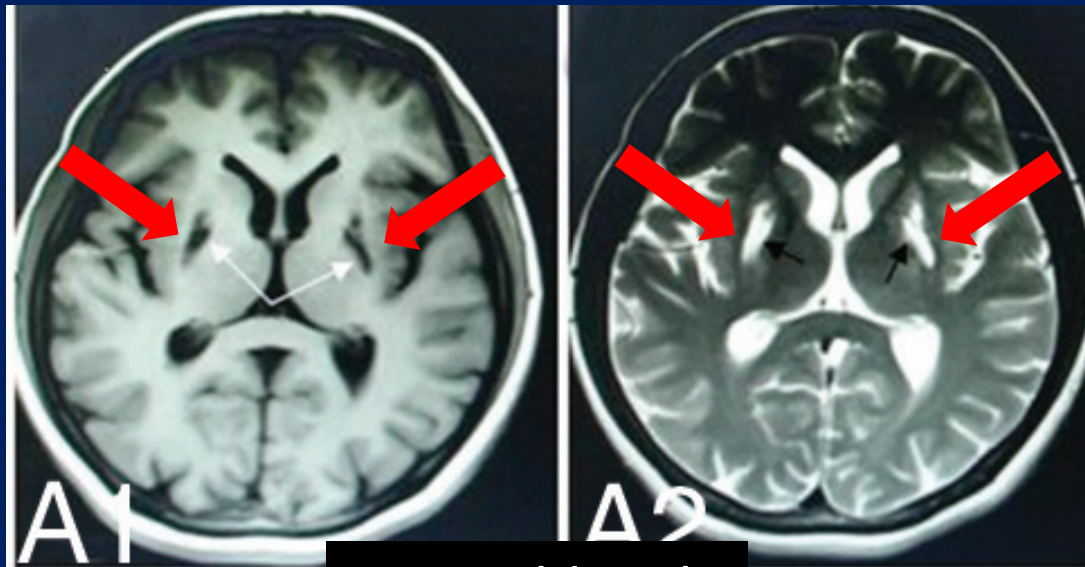
>pallidum

Wilson disease

MR Imaging of the Brain in Neurologic Wilson Disease.

X.-E. Yu, S. Gao, R.-M. Yang and Y.-Z. Han

AJNR Am J Neuroradiol 40:178–83 Jan 2019



14yrs old male

Pediatric Wilson Disease:
Putamen mainly affected

Table 2: Correlations between age of onset and region-specific brain damage in neurologic WD*

Age of Onset (yr)	No. of Cases	Putamen	Globus Pallidus	Caudate Nucleus	Thalamus	Midbrain	Pons	Cerebellum	Frontal Lobe	Temporal Lobe	Parietal Lobe	Corpus Callosum
Younger than 10	25	25 (100)										
10–14	112	107 (95.5)		31 (27.7)	47 (42.0)	52 (46.4)	74 (66.1)	2 (1.8)	3 (2.7)	2 (1.8)	3 (2.7)	8 (7.1)

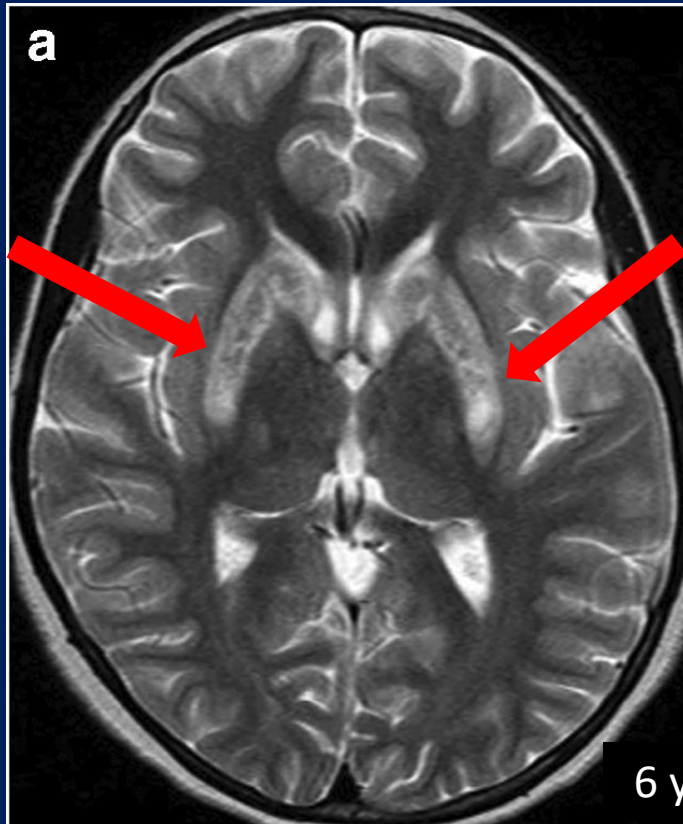
Wilson disease

Bilateral lesions of the basal ganglia and thalami (central grey matter)—pictorial review

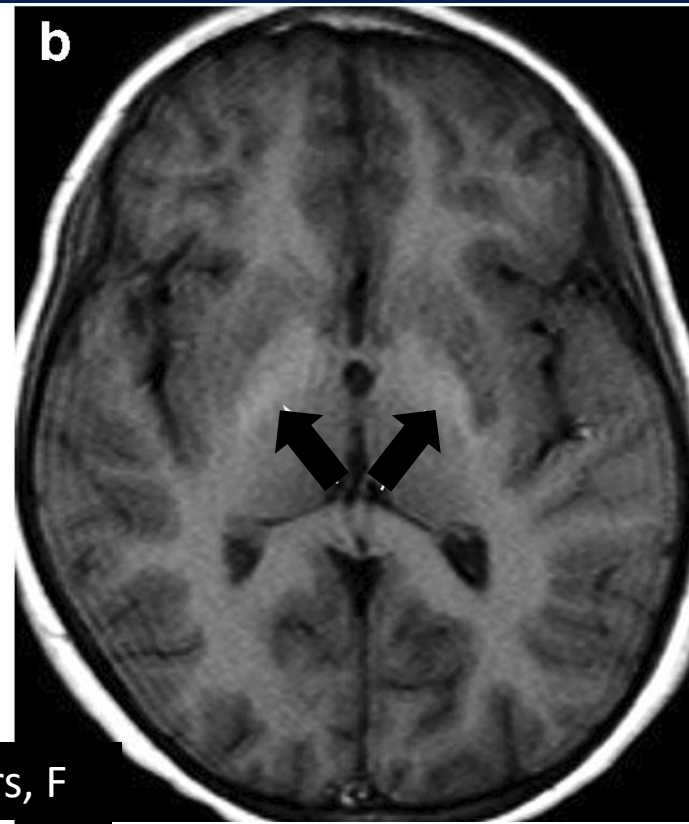
update

Neuroradiology (2020)

Sofie Van Cauter^{1,2}  • Mariasavina Severino³ • Rosamaria Ammendola³ • Brecht Van Berkel^{1,2} • Hrvoje Vavro⁴ • Luc van den Hauwe^{5,6} • Zoran Rumboldt^{7,8}



putamen degeneration/necrosis



pallidum mild T1 hyperintensity

PRKRA related dystonia and BG degeneration-(rare variant)



putamen mainly affected: progressive

PRKRA: autosomal recessive disorder combining generalized dystonia and parkinsonism.

Mov Disord 2021

PRKRA-Related Disorders: Bilateral Striatal Degeneration in Addition to DYT16 Spectrum

Silvia Masnada, Davide Tonduti, et Al.

Pathophysiology:

PRKRA involves an interferon inducible RNA activator of protein kinase PKR influencing cell differentiation and apoptosis

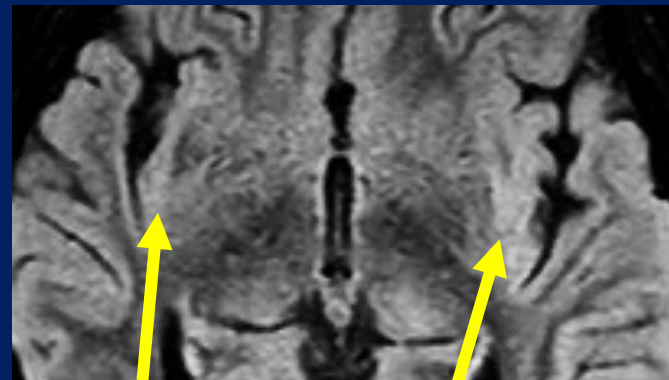
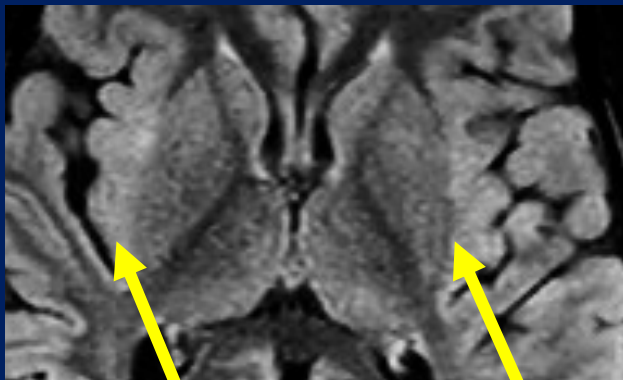
Acute infantile form with hypotonia, pyramidal sign, bradikinesia, motor regression

FIRES (*FEBRILE INFECTION-RELATED EPILEPSY SYNDROME*)

Stefano Meletti et al., Neurology 2015

Clastrum damage and refractory status epilepticus following febrile illness

“After a few days acute repeated seizures (focal motor/myoclonic events with alternating side involvement and subsequent generalization)”



bilateral claustrum lesion (*partially reversible?..*)

Cockayne syndrome

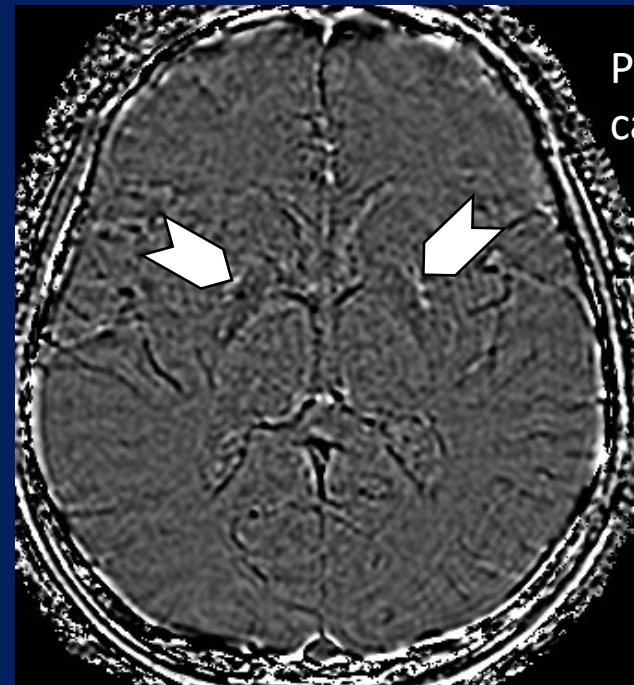
*Mutations in ERCC6 or ERCC8
gene-proteins involved in DNA repair:*
progressive neurodegeneration, accumulation
oxidative DNA lesions in postmitotic neurons,
leading to apoptosis.

*Nature 2000
DNA repair: The bases for
Cockayne syndrome
Philip C. Hanawalt*



BG atrophy
and abnormal signal

7yrs M



Pallidal
calcifications

SWI phase

Menkes disease

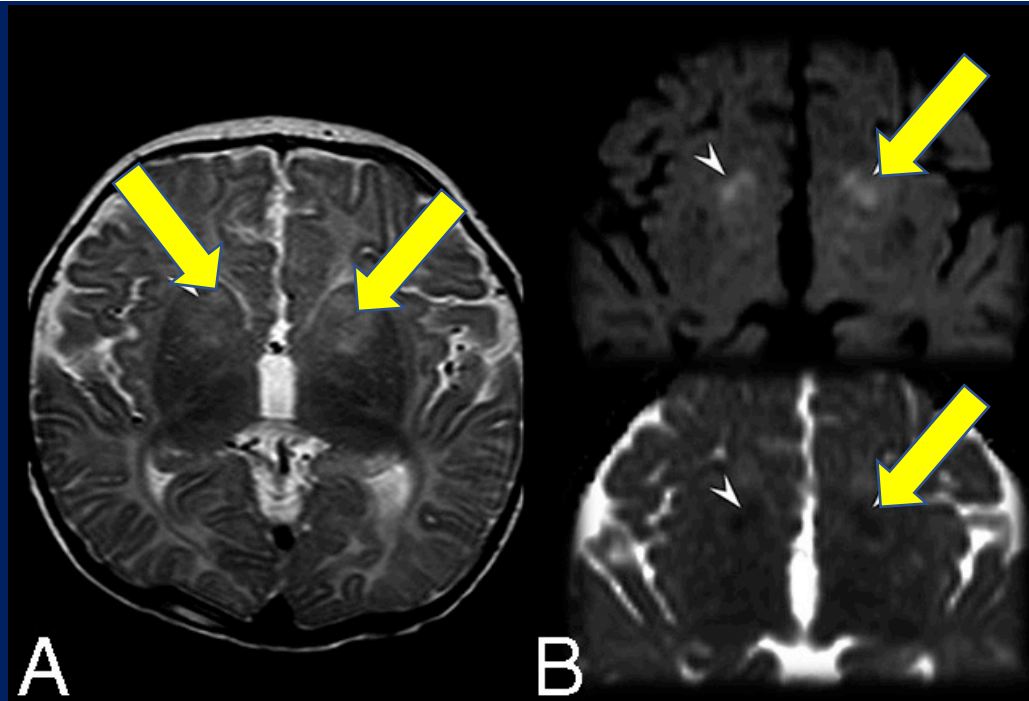
mutations *ATP7A* gene encoding copper-transporter P-type adenosine triphosphatase. Impaired absorption and cellular metabolism of copper

AJNR 2017

Neuroimaging Changes in Menkes Disease, Part 2

R. Manara et Al.

5m, M



BG involvement: caudate and putamen. Abnormalities may be transient in DWI; ischemic etiology?

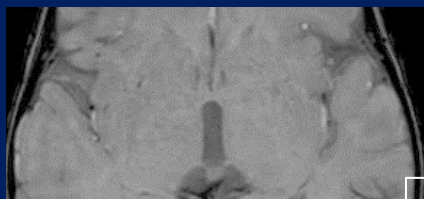
Brain iron and basal ganglia disorders in children

SWI: normal signal time-course, surrogate of iron accumulation assessment

before 4 yrs of age BG should be NO dark on SWI



newborn

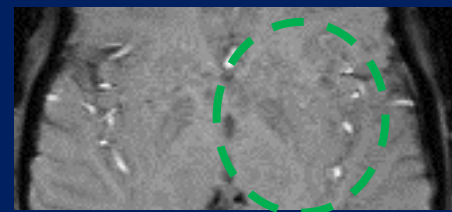


1yrs

3T



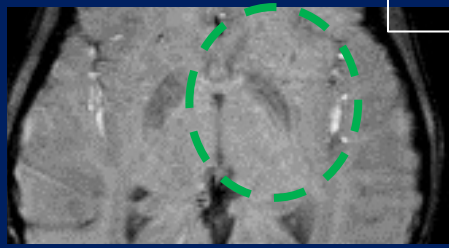
3yrs



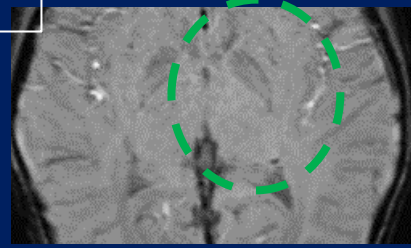
5yrs



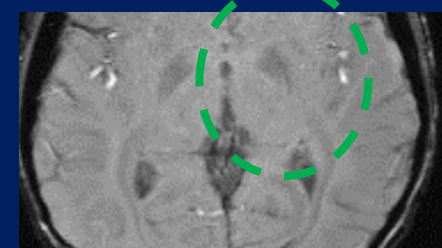
6yrs



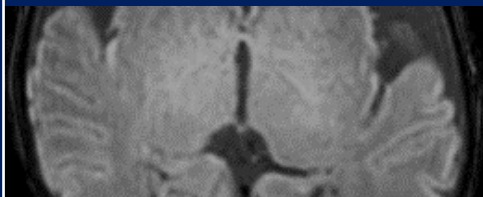
8yrs



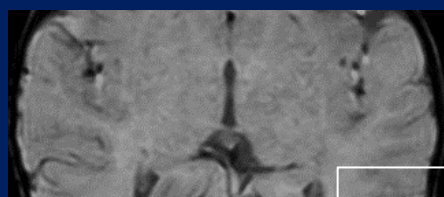
9yrs



10yrs

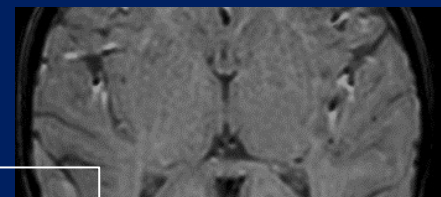


newborn

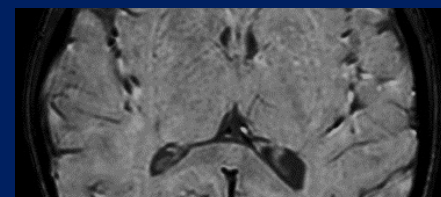


1yrs

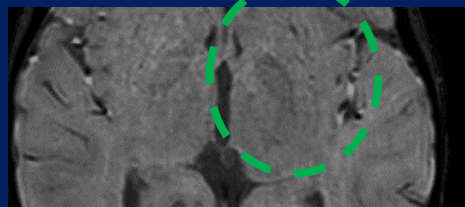
1.5T



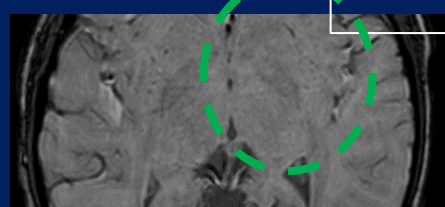
3yrs



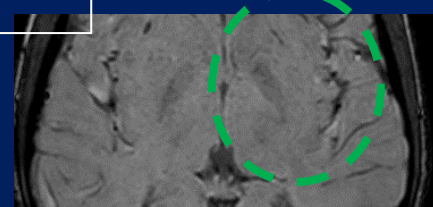
5yrs



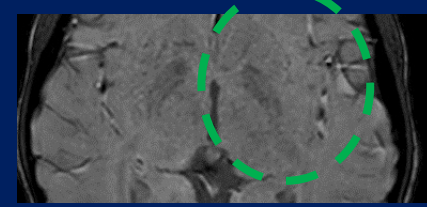
6yrs



8yrs



9yrs



10yrs

Neurodegeneration with brain iron accumulation (NBIA).

Heterogeneous group caused by defects in proteins with even NO DIRECT role in iron homeostasis.

All proteins are important for mitochondrial function.

Only two have a known role in iron homeostasis:

- ferritin light chain
- ceruloplasmin

Neurodegeneration with brain iron accumulation (NBIA).

The four most common:

1 - **PKAN** pantothenate kinase-associated neurodegeneration due to mutations in PANK2

On T2-weighted images “eye of tiger” sign

2 - **PLAN** phospholipase A2-associated neurodegeneration caused by mutation in PLA2G6

Cerebellar atrophy and optic nerve atrophy.

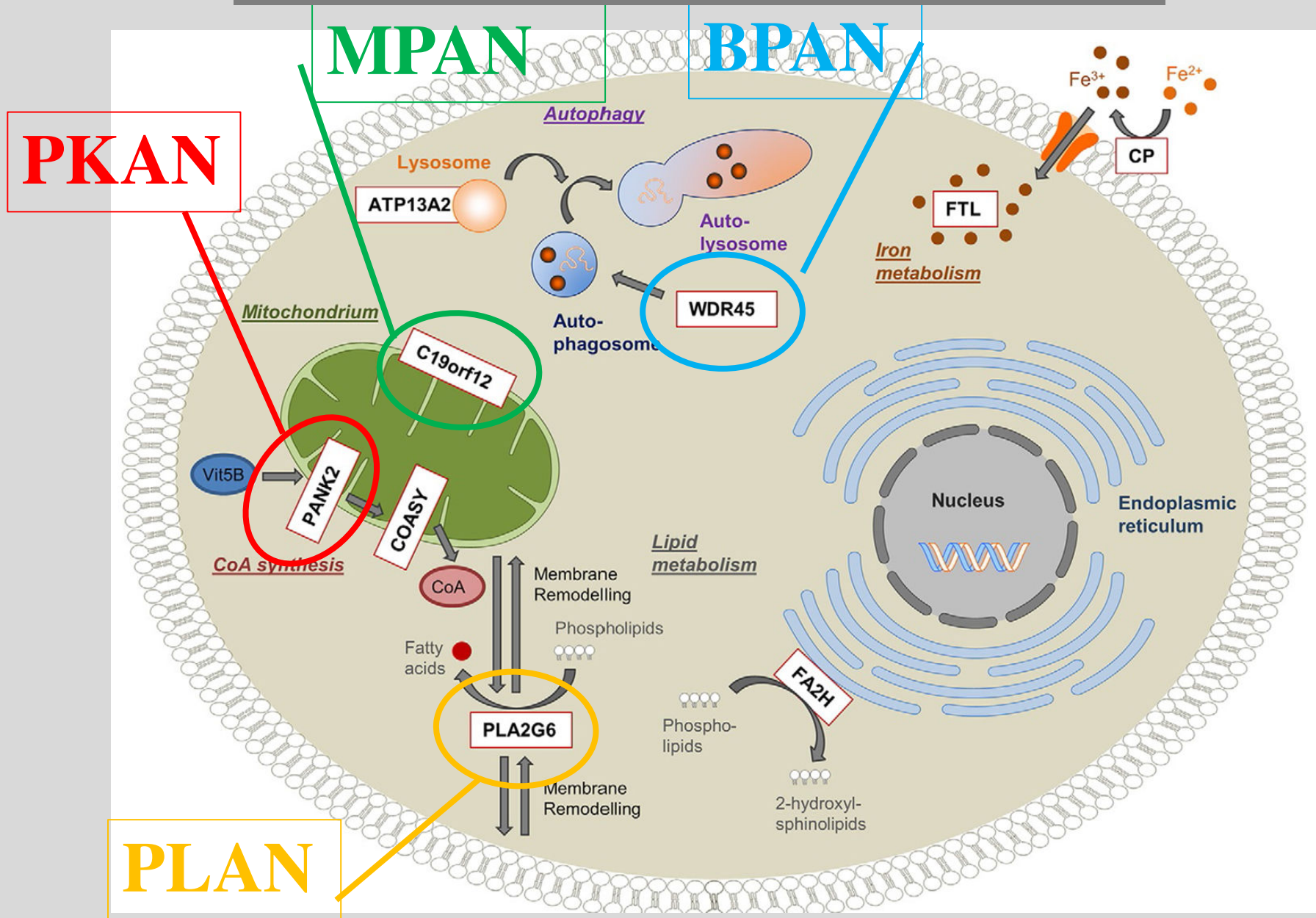
3 - **MPAN** mitochondrial membrane protein-associated neurodegeneration from mutations in C19orf12,

T2-hyperintense line of the medial medullary lamina between the lateral and medial parts of pallidus

4 - **BPAN** beta-propeller protein-associated neurodegeneration due to mutations in WDR45 encoding a putative autophagy protein

On T1-weighted images a hyperintense “halo” in the substantia nigra and cerebral peduncles

Neurodegeneration with brain iron accumulation (NBIA).



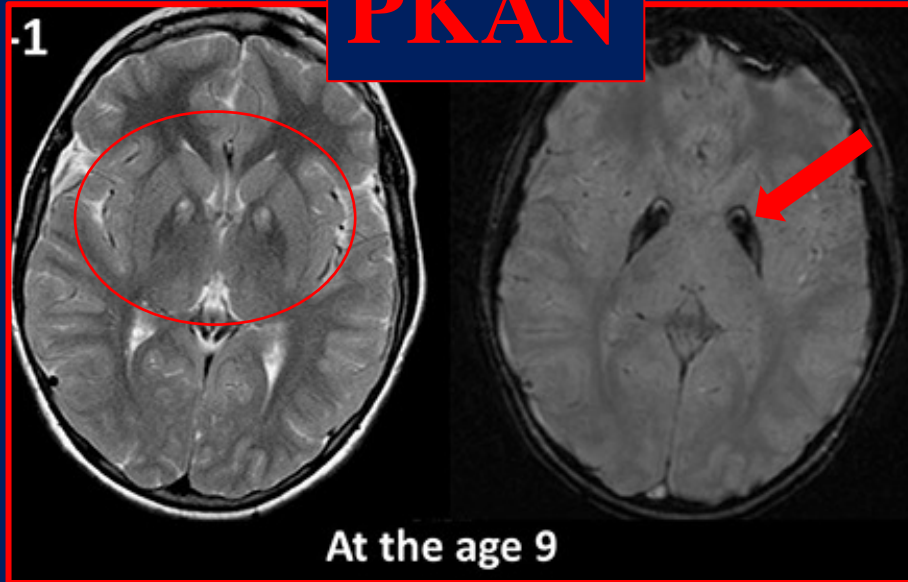
must read paper

Brain MRI Pattern Recognition in Neurodegeneration With Brain Iron Accumulation

Jae-Hyeok Lee et Al

Front. Neurol. 2020

PKAN



“eye of the tiger” sign on T2WI: central spot of hyperintensity (gliosis, edema) surrounded by hypointensity due to iron accumulation in pallidus

AJNR 2018. Looking Deep into the Eye-of-the-Tiger in Pantothenate Kinase–Associated Neurodegeneration
J.-H. Lee, Susan J. Hayflick et Al.



Suggestive but **NOT** pathognomonic, not so frequent in children



must read paper

Brain MRI Pattern Recognition in Neurodegeneration With Brain Iron Accumulation

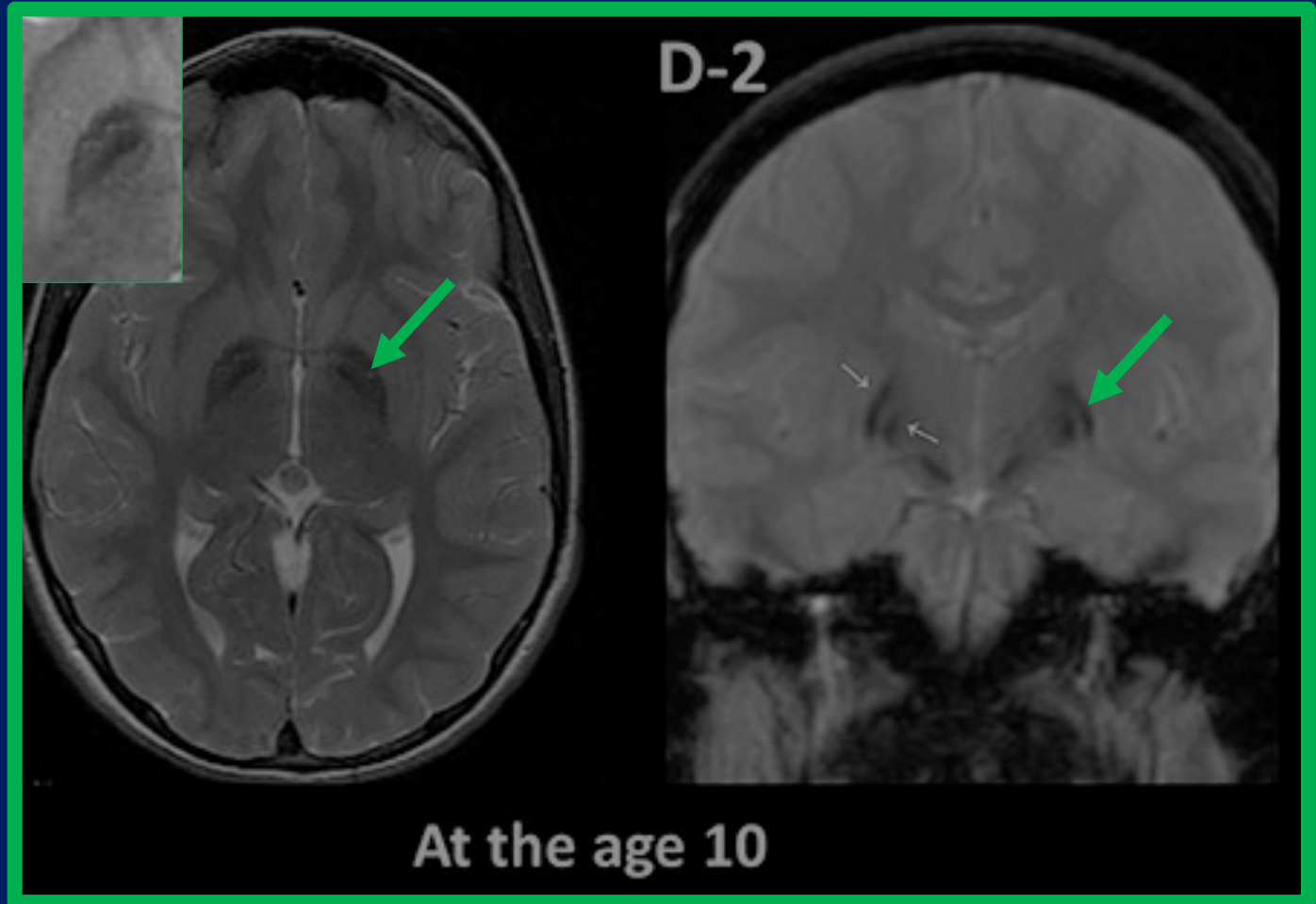
Jae-Hyeok Lee et Al

Front. Neurol. 2020

MPAN



T2-hyperintense line: medial medullary lamina between the lateral and medial pallidus



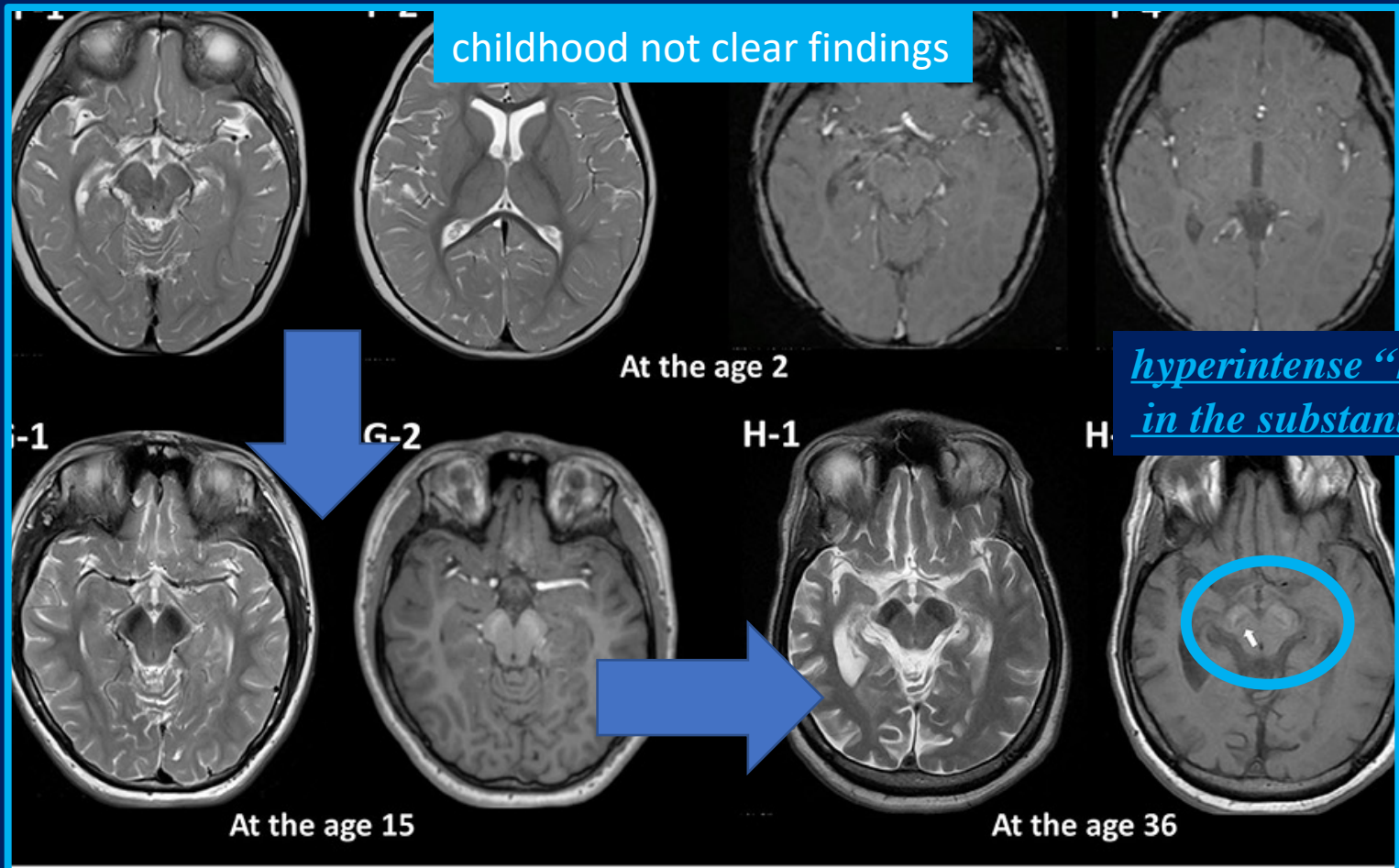
must read paper

Brain MRI Pattern Recognition in Neurodegeneration With Brain Iron Accumulation

Jae-Hyeok Lee et Al

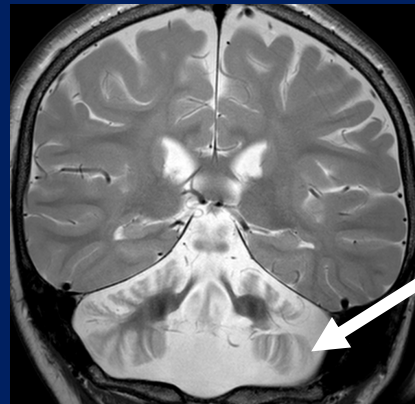
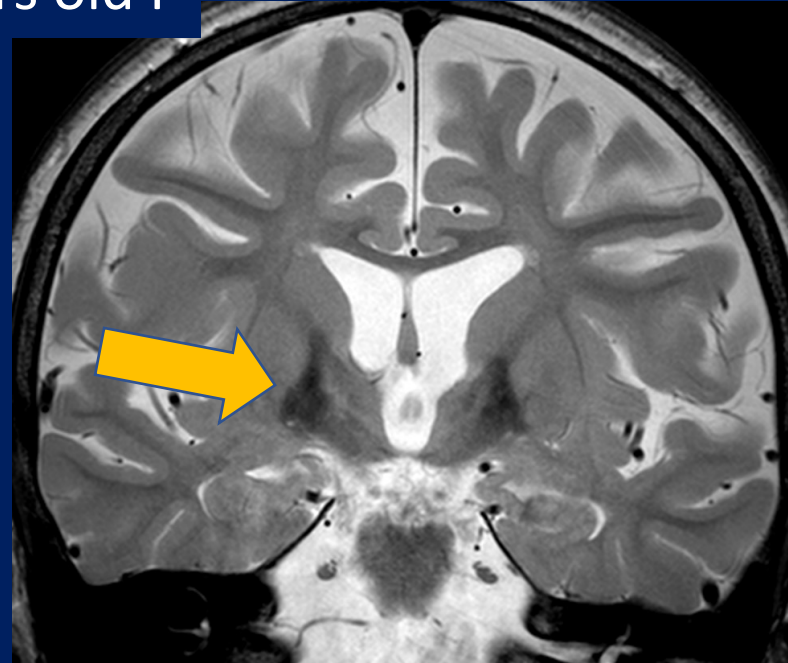
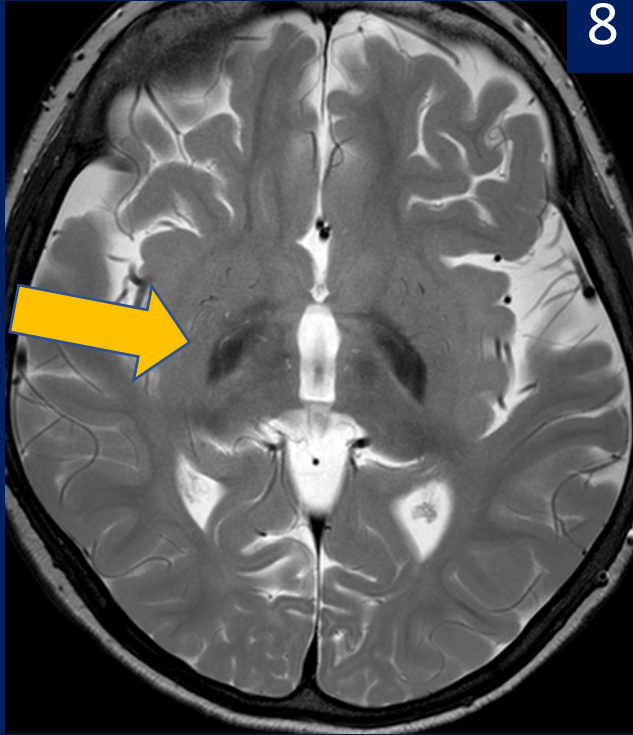
BPAN

Front. Neurol. 2020



PLAN phospholipase A2-associated neurodegeneration caused by mutation in PLA2G6

8 yrs old F



*cerebellar atrophy
and optic nerve
atrophy.*

Neurodegeneration with brain iron accumulation

SUSAN J. HAYFLICK et Al.

Two NBIA disorders set apart: genes that encode iron homeostatic proteins, ceruloplasmin and ferritin

Different from other NBIA's : extensive accumulation of iron in regions that are normally iron-rich: caudate, putamen, thalamus, dentate, and red nucleus, in addition to the globus pallidus and substantia nigra.

- Aceruloplasminemia
- Neuroferritinopathy

usually no MRI sign at pediatric age

Aceruloplasminemia: T2-HYPO in dentate, SN, pallidus, putamen, caudate, NO CAVITATIONS

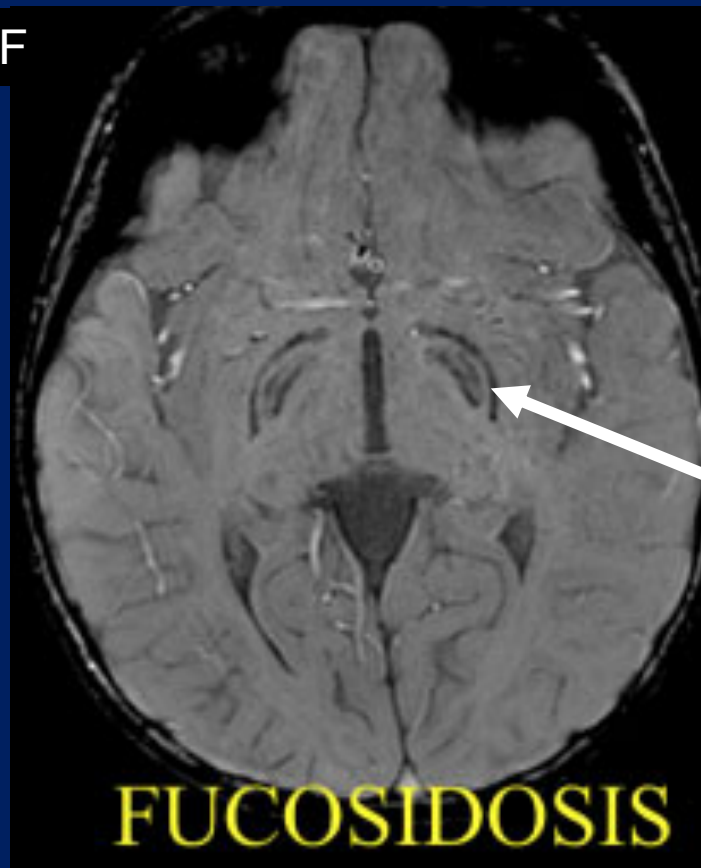
Neuroferritinopathy: T2-HYPO in dentate, SN, pallidus, putamen, caudate, WITH OFTEN CAVITATIONS

'NBIA mimics' such as alpha mannosidosis, fucosidosis, gangliosidoses, mucopolidosis type IV.

BRAIN COMMUNICATIONS 2020

Magnetic resonance imaging pattern recognition in childhood bilateral basal ganglia disorders. Shekeeb SM et Al.

2 yrs F



sparing of the internal medullary and accessory lamina

'NBIA mimics'

infantile neuroaxonal dystrophy

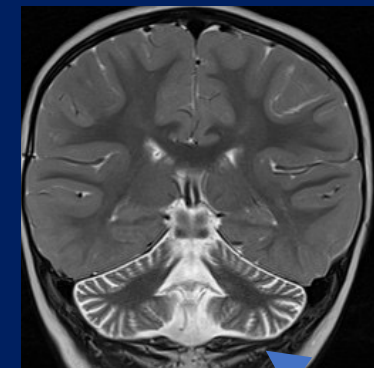
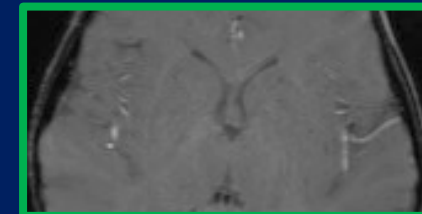
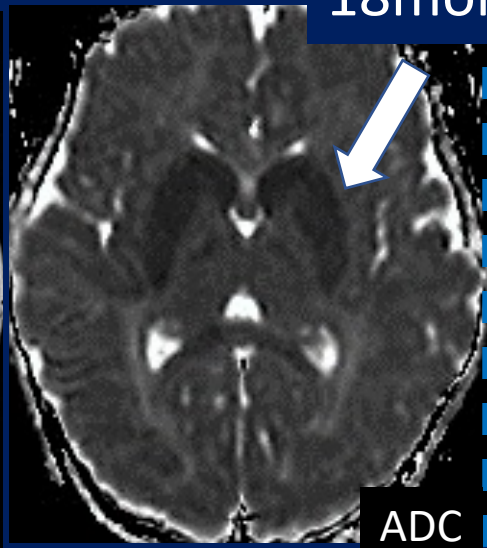
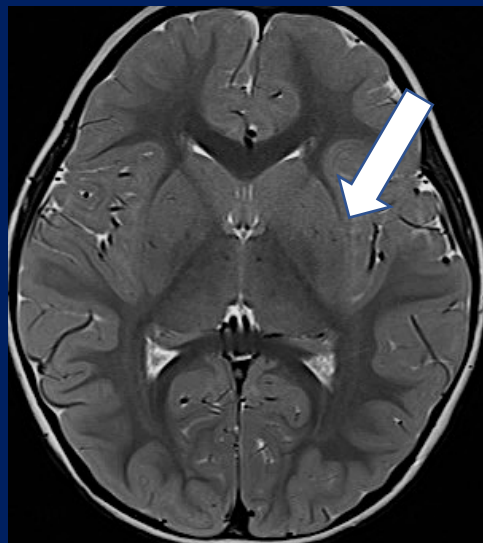
Special early case:

More aggressive form with acute-subacute putamen and caudate involvement too



18months M

pallidus IRON accumulation



control

Cerebellar cortex atrophy

more classic findings

'NBIA mimics'

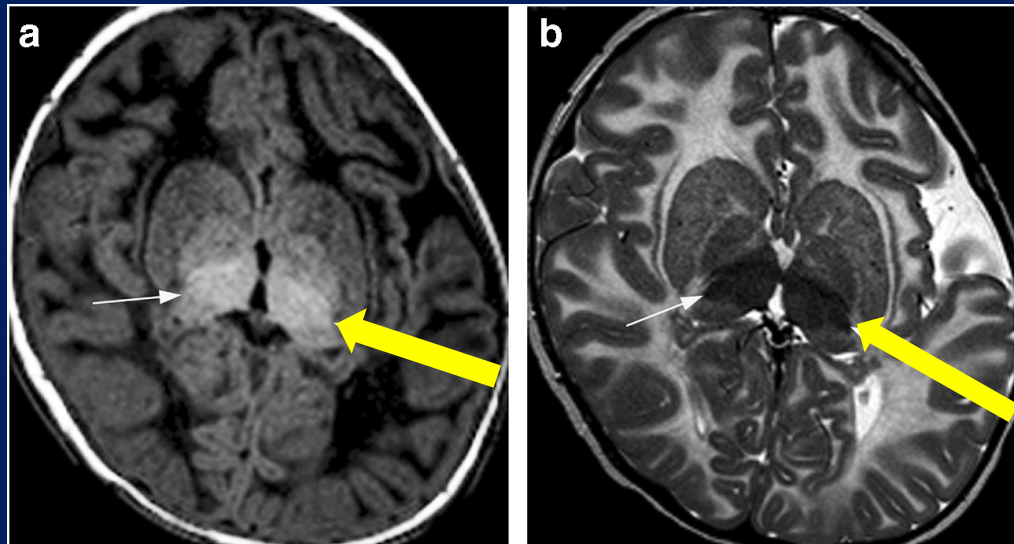
Gangliosidosis GM1 (Tay-Sachs) and GM2 (Sandhoff)

- **Lysosomal storage disorders** recessive and caused by lysosomal enzyme deficiency.
- Strictly metabolic disorder, however time-course «DEGENERATIVE»-like
- Infantile, juvenile and adult forms.
- symmetric **high-T1W** and **low-T2W** signal in thalami

Bilateral lesions of the basal ganglia and thalami (central grey matter)—pictorial review Neuroradiology (2020)

Sofie Van Cauter^{1,2} · Mariasavina Severino³ · Rosamaria Ammendola³ · Brecht Van Berkel^{1,2} · Hrvoje Vavro
Luc van den Hauwe^{5,6} · Zoran Rumboldt^{7,8}

17m F,
Infantile form
GM1



**BG degeneration in cell energy
homeostasis failure**

Leigh syndrome (subacute necrotizing encephalopathy)

Heterogeneous group of neurodegenerative disorders: clinical, neuroimaging and genetic variability.

Often **symmetric involvement** of basal ganglia, midbrain, dentate nuclei

CAUSES:

mutations in mitochondrial or nuclear DNA for:

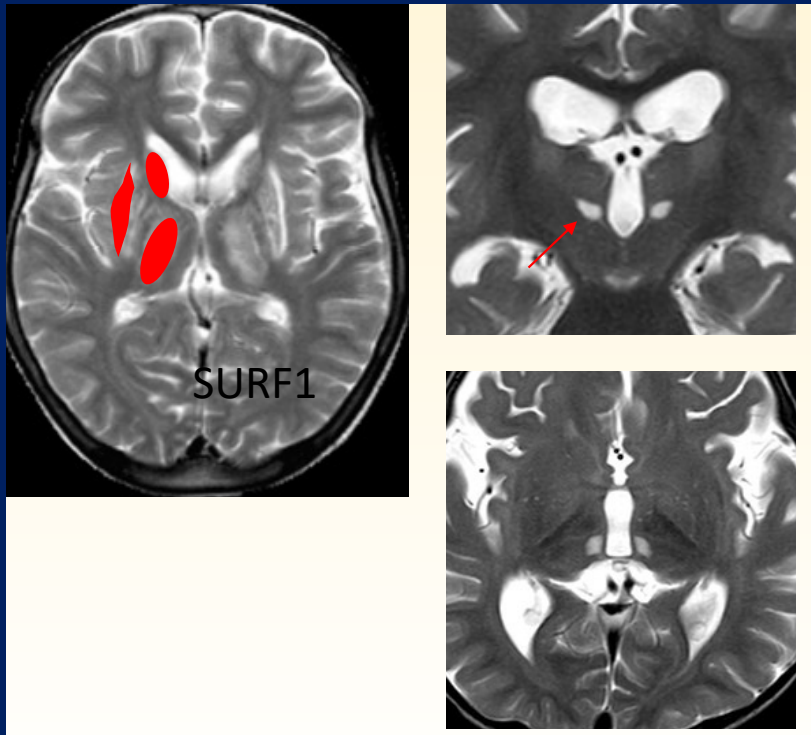
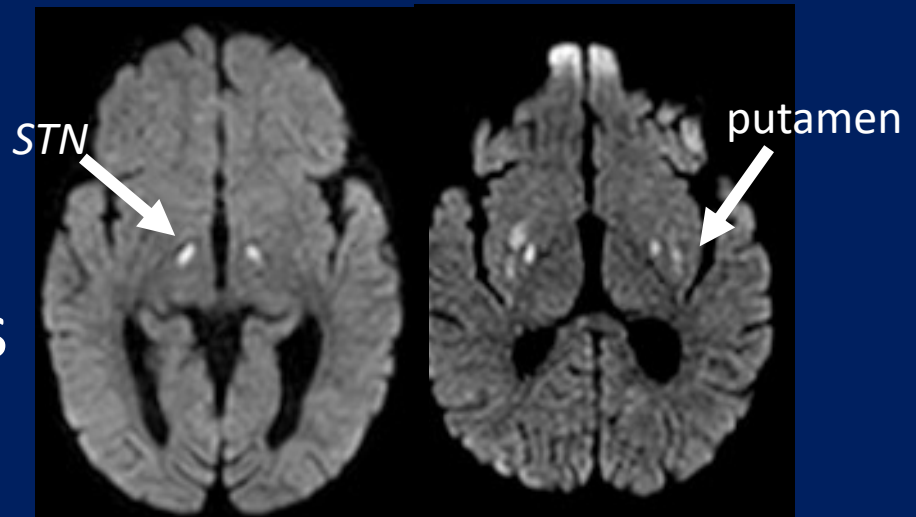
- proteins of respiratory chain complexes I (*NDUF1*), II, III, IV (*SURF1*), V
- mitochondrial tRNA,
- pyruvate dehydrogenase complex (PDHc)
- coenzyme Q10.

Others related to mitochondrial diseases:

- Valine catabolism pathway (ECHS1)
- Tiamine deficiency (SLC2)

Leigh syndrome

Subacute lesions
and ongoing necrosis
in bilateral subthalamus
and putamen.



Necrotic (cavitations)
sequelae STN,
putamen, thalamus,
bilaterally

Fahr disease and differentials

Primary familial brain calcifications:

autosomal dominant neurodegenerative disease with abnormal *calcium deposits* in the basal ganglia and other regions.

- Rare onset in childhood.

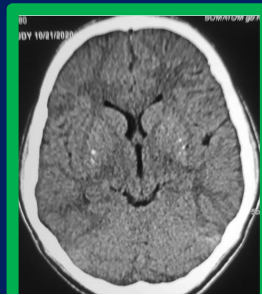
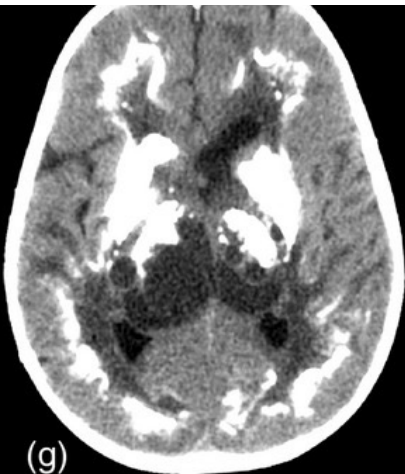
- Calcifications in BG, thalami, dentate nuclei, and WM.

- **Differential issue:** exclude metabolic disorders, various forms of hypoparathyroidism: most common cause of calcifications, also Aicardi-Goutières (AGS).

Intracranial calcification in childhood: a review of aetiologies and recognizable phenotypes JH

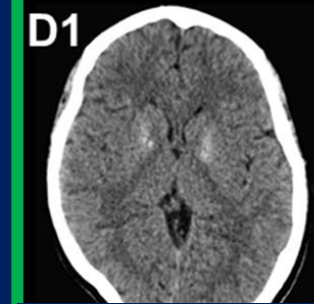
Livingston et Al. 2014

DD

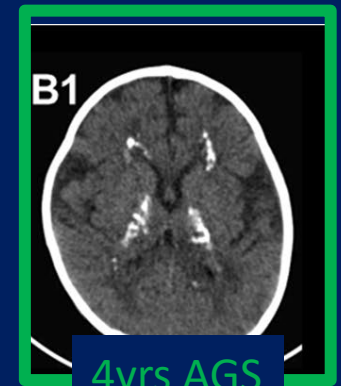


Ped. Neurol. 2023.

Mineralizing Lenticulostriate Vasculopathy: An Emerging Risk Factor for Basal Ganglia Stroke After Minor Head Trauma in Young Children Jatinder Singh Goraya



hypoparathyry

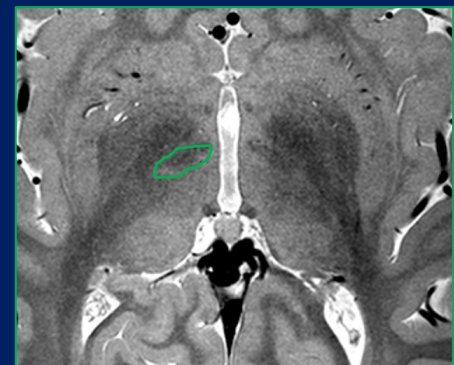
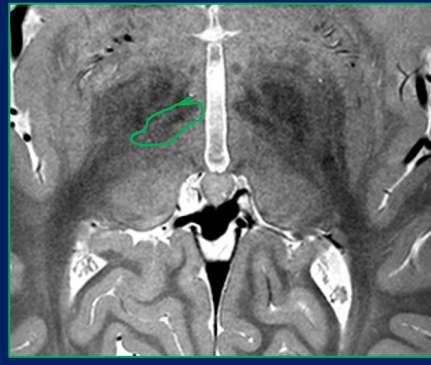
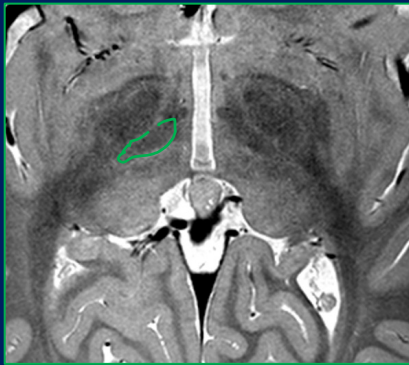


4yrs AGS

Neurol. Sci 2021 **How to look for intracranial calcification in children with neurological disorders: CT, MRI, or both of them?** Davide Tondui et Al

SUBTHALAMUS (STN) -1

Not strictly BG but very close functionally and anatomically

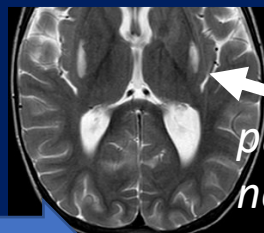
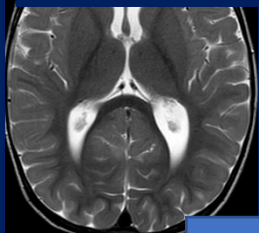


in plane res. 0.2 mm²

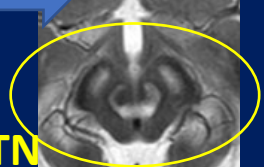
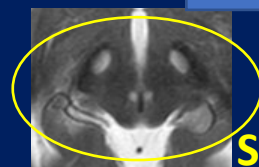
Some among more frequent entities involving STN as multiple-subacute or chronic lesions

mitochondr. disease

14 to 21 months



putamen
necrosis/degen.

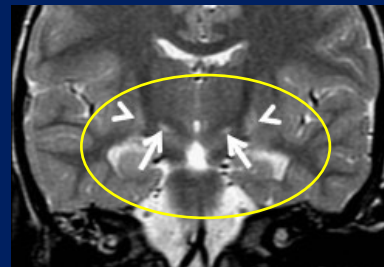


STN

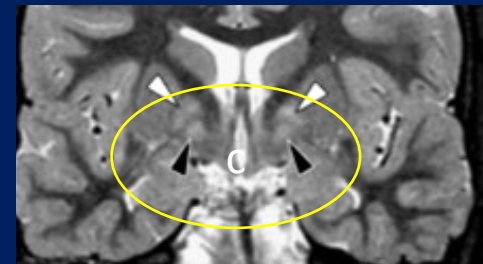
European Journal of Paediatric Neurology 2014

Subthalamic nucleus involvement in children: a neuroimaging pattern-recognition approach

Thangamadhan Bosemani et AL.



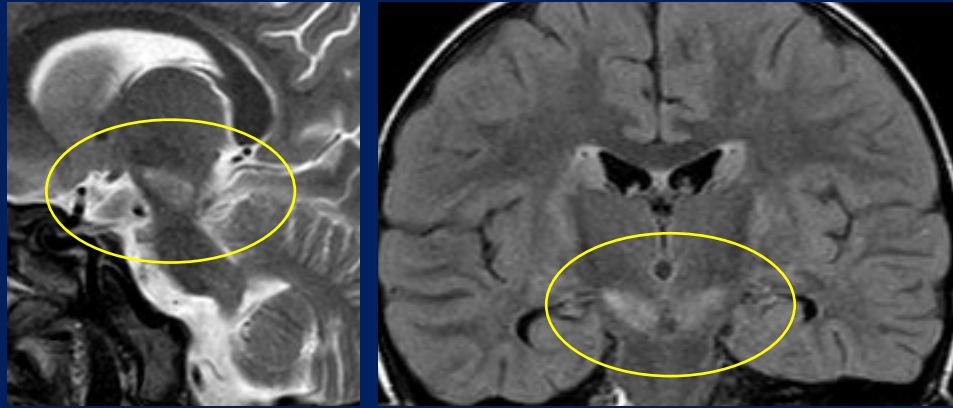
kernicterus



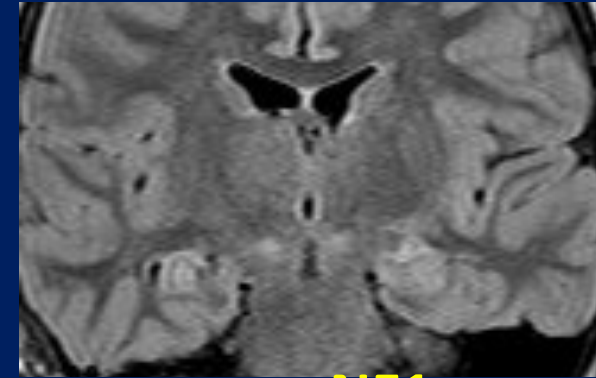
succinic semialdehyde
dehydrogen. deficit
(SSADHD)

SUBTHALAMUS (STN) - 2

Some among more frequent entities involving STN as multiple-subacute or chronic lesions



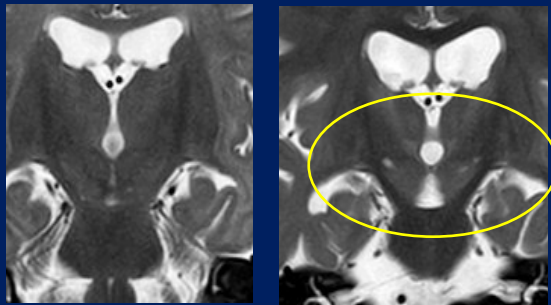
4 yrs old, **viral encephalitis** sequelae



10yrs, **NF1**

IF2AK2 mutat. implicated in early dystonia

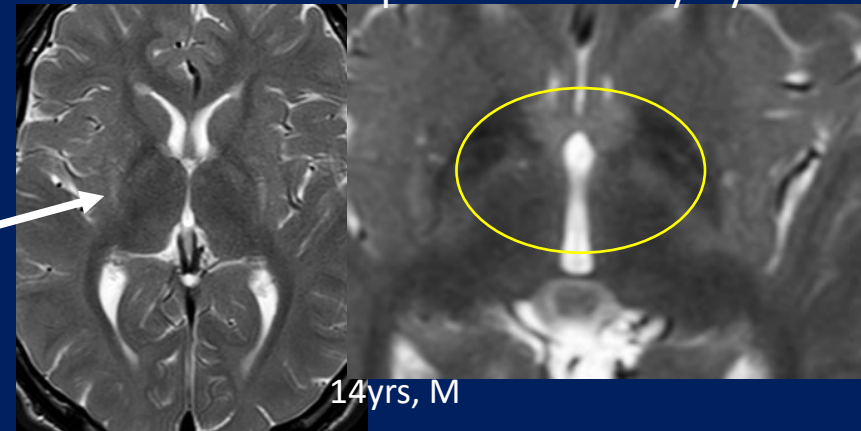
mitochondr. diseases



4m

15m

putamen
degen



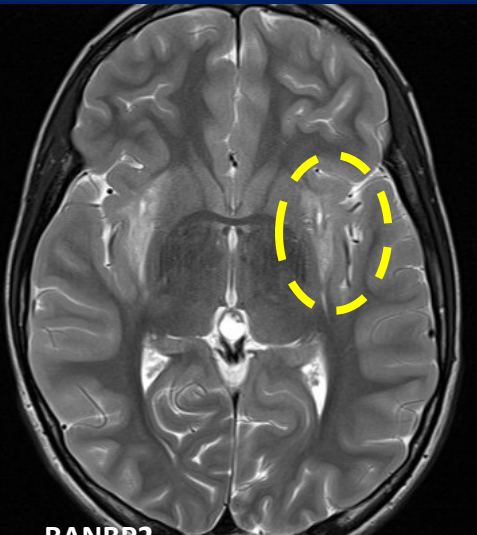
14yrs, M

translation initiation factor 2 alpha (eIF2 α), which contributes to the cellular stress response.

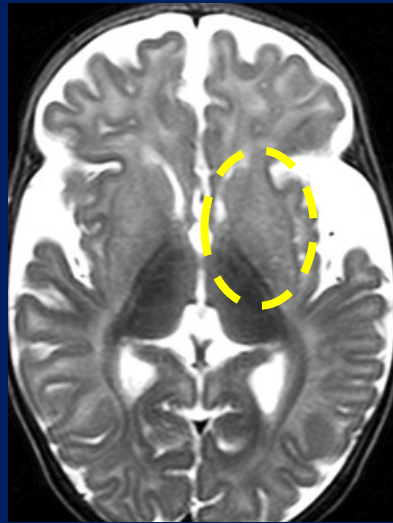
DIFFERENTIAL DIAGNOSIS A1

Acquired –metabolic or clastic disorders mimicking MRI features of neurodegenerative disorders and easily differentiated only when occur with **ACUTE** clinical features

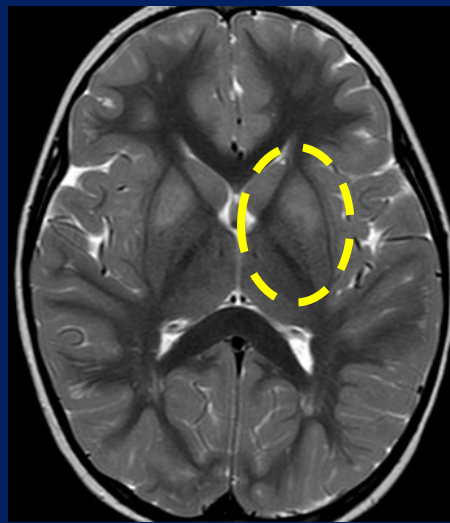
Prevalent bilat. putaminal-caudate involvement



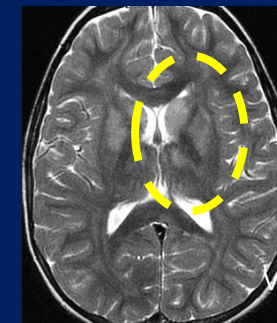
RANBP2
(RAN Binding Protein 2)
Familial acute necrotizing
encephalopathy



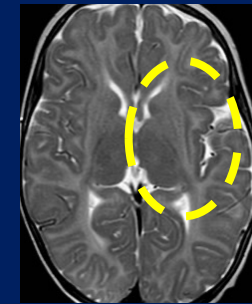
Glutaric aciduria type 1
5 months



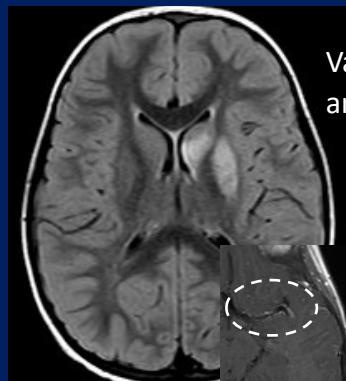
L2-hydroxyglutaric aciduria
4yrs



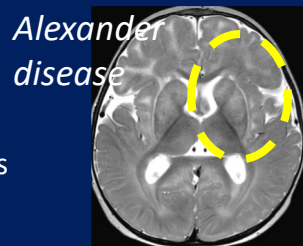
viral encephalitis



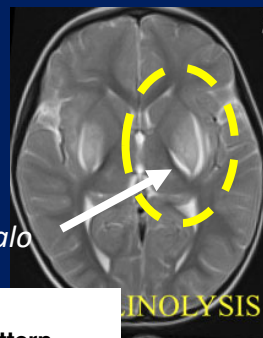
8 months M
HBC



Varicella
arthritis



Alexander
disease



halo

INOLYSIS

BRAIN COMMUNICATIONS 2020
Magnetic resonance imaging pattern
recognition in childhood bilateral basal
ganglia disorders. Shekeeb SM et Al.

Curr Neurol Neurosci Rep
2016
Neurological Disorders
Associated with Striatal
Lesions: Classification and
Diagnostic Approach
Davide Tonduti et Al.

biotine- thiamine
responsive
BG disease
(subacute)
SLC19A3
gene variants



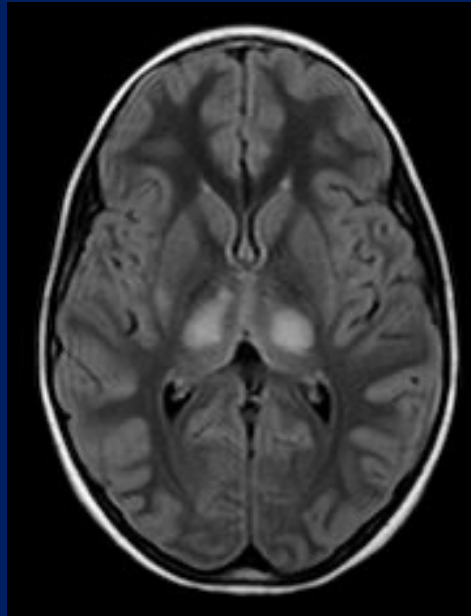
therapy

Alfadhel et al. Orphanet Journal
of Rare Diseases 2013,

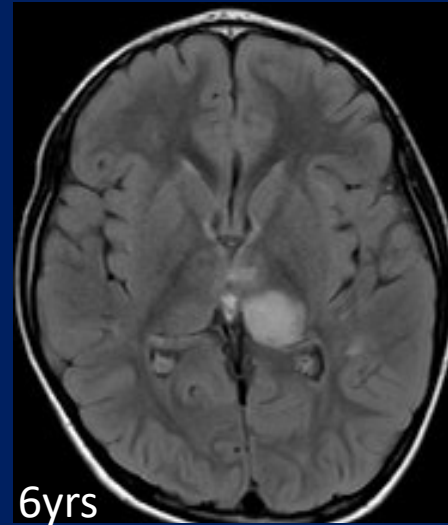
DIFFERENTIAL DIAGNOSIS A2

Acquired –metabolic disorders mimicking MRI features as neurodegenerative disorders and easily differentiated only when present with **ACUTE** clinical features

Prevalent thalamic involvement



Hemolytic Uremic Syndrome
(shiga, shigalike toxins)
E Coli O157:H7



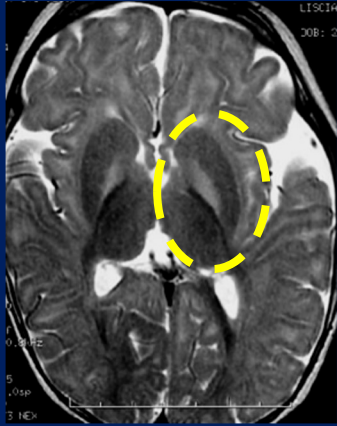
ADEM

DIFFERENTIAL DIAGNOSIS A3

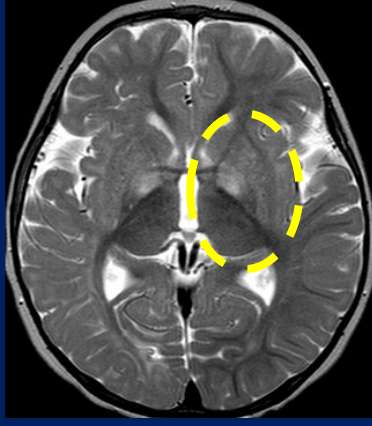
Acquired/metabolic disorders mimicking MRI features similar to neurodegenerative disorders
And easily differentiated only when **ACUTE** clinical features

Prevalent bilat. pallidal involvement

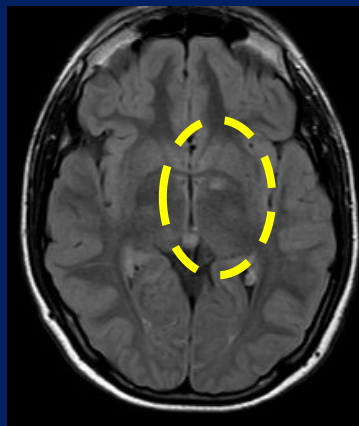
-----NOT so acute-----



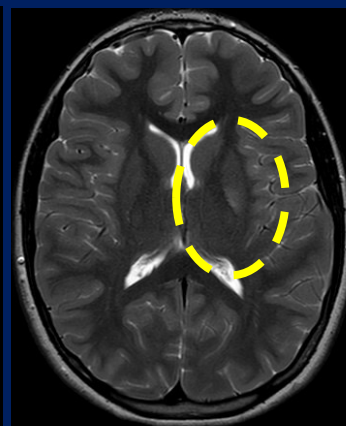
6 months
sequelae
of neonatal
Bilirubinemia
(*kernicterus*)



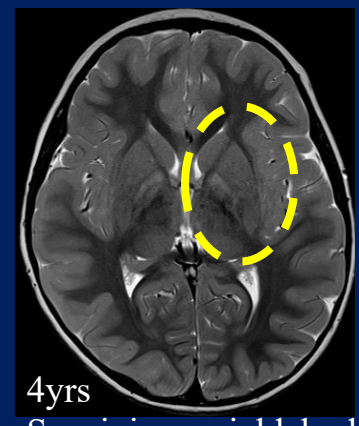
15 months
ECHS1 Mitochondrial
fatty acid oxidation
disorders associated
with short-chain enoyl-
CoA hydratase deficiency



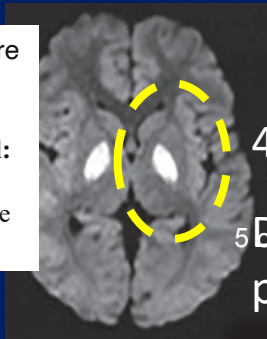
11yrs
NF1



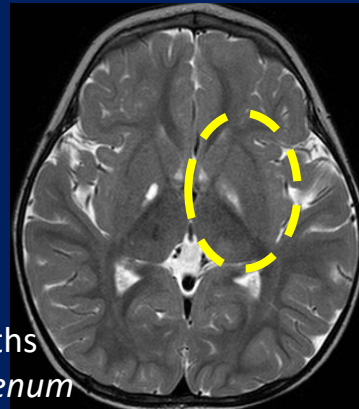
12 yrs (GH deficit)
?Incidentalomas?



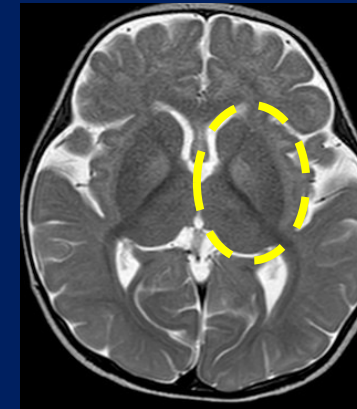
4yrs
Succinic-semialdehyde
dehydrogenase deficiency



4yrs F
5
Disulfiram
poisoning



19 months
molybdenum
cofactor deficiency-milder form



18 months
Vigabartin
toxicity

Indian J Critical Care
Medicine 2020,
Acute Disulfiram
Poisoning in a Child:
A Case Report and
Review of Literature
Kapil Bhalla et Al.

THANKS!