Cerebral Palsy Mimics

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Cerebral palsy

Neurologist

- Old disease; 19th century disease
- Common(1-5;1000) WW, 10-1000 in SA
- Easily diagnosed by a general pediatrician or even a GP

Neurology fellow

- Boring
- No much new knowledge

Both

List of medications
Lots of papers work;
What is done is done(The insult is permanent)

Objectives

To provide an overview of the impact and genetics of the Cerebral palsy mimics

To provide a practical diagnostic approach to a child with motor delay early in life with features suggestive of CP.

To summarize some of the common metabolic and genetic conditions, that may be misdiagnosed as CP.

Facts at the time of genetic era &precision medicine

❑ 20% of CP cases has no clear underlying aetiology(Insult); ***Cryptogenic CP***

Mimics or Masqueraders; CP phenotypic features and has underlying genetic and metabolic cause

Types of genetic testing; CA, CMA, FISH, Methylation studies, WES, WGS, Mitochondrial genome analysis

Whole exome sequencing (WES);

-Typical and Atypical around 30%

-Atypical cerebral palsy(Cryptogenic); Yield was variable and found to 30-82%

-(Dyskinetic 50%, 91;100% Ataxic& combined ataxic/hypotonic

-Yield increase with comorbidities

- 1/3 of patients who has a diagnosis of CP has Mimics, Masqueraders

Importance of accurate diagnosis

- Genetic/ metabolic disorders might have specific disease-modifying treatment

In a systematic review, at least 54 treatable inborn errors of metabolism mimicking CP(diagnosed based on genetic not metabolic testing)

- Delineate the prognosis
- Genetic counselling
- Medicolegal implications

When to suspects?

History

Examination

MRI

Red flags

History

- Absence of risk factors
- Positive family history of CP
- Fluctuation in motor symptoms
- Paroxysmal symptoms in relation to time of day, diet/fasting, or activity
- Progressive neurological symptoms
- Regression of milestones

Examination

- ✓Dysmorphic features
- ✓Isolated motor dysfunction such as isolated ataxia or isolated hypotonia without dystonia or spasticity
- ✓Rigidity
- ✓Paraplegia
- ✓Peripheral nervous system abnormalities: absent reflexes, evolving sensory signs
- ✓Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)
- ✓Optic atrophy/retinopathy

Neuroimaging

- ❑Normal neuroimaging
- ❑Nonspecific abnormalities
- ❑Imaging abnormalities that are inconsistent/ not concordant with clinical history
- ❑Imaging characteristic of a particular genetic disorder
- ❑Isolated globus pallidus involvement

Differential diagnosis of Cerebral Palsy mimics

Disorders with prominent spasticity	Disorders with prominent dyskinesia	Disorders with prominent ataxia
- Hereditary spastic paraglegias	- Dopa-responsive dystonia	- Glucose transporter deficiency type 1
- Arginase deficiency	- Sepiapterin reductase deficiency	- Ataxia telangiectasia
- COL4A1-Related spastic CP	- Glutaric aciduria type 1	- Pelizaeus-Merzbacher disease
- Biotinidase deficiency	- Glucose transporter deficiency type 1	- Hereditary ataxias
- Aicardi-Goutières syndrome	- Neurodegeneration with brain iron accumulation	- Joubert syndrome
- Sulfite oxidase deficiency/ Molybdenum cofactor deficiency[22]	- Cerebral creatine deficiency syndrome	- Mitochondrial cytopathies (mainly 8993 mutation)[42]
- Leukodystrophies, such as metachromatic leukodystrophy,[23] adrenoleukodystrophy,[24] Sjo Larsson syndrome[25]	- Lesch Nyhan syndrome	- Pontocerebellar hypoplasia[36]
	- Cerebral folate deficiency	- Cockayne syndrome[43]
	- ADCY5-related dyskinesia PCDH12-related dyskinesia[34]	- Niemann-Pick disease type C[44]
	- NKX2-1 related ataxic dyskinetic CP[35]	- Angelman syndrome[12]
	- TSEN54 Gene-related pontocerebellar hypoplasia type 2[36]	- Gangliosidosis type 1 , juvenile and adult forms[45]
		- Non-ketotic hyperglycinemia[3]
		- Maple syrup urine disease[3]
		- NKX2-1 related ataxic dyskinetic CP[35]

CP- cerebral palsy

Approach to a child with developmental delay; CP phenotype

1. History

- Detailed antenatal, perinatal and postnatal history
- Apgar scoring
- Cord PH
- Onset/ progression/ regression
- Family history

Identify Red flags

No further testing

Suggestive of typical CP(No red flags/ concordant MRI)

2. Examination

- Head C at birth and chart following
- dysmorphism
- Examination

Identify Red flags

3. Differential diagnosis

Other diagnosis CP or MIMICs?

-Spastic
-Dyskinetic
-Ataxic

4. Brain Imaging

Identify Red flags

5. Genetic/ Metabolic testing

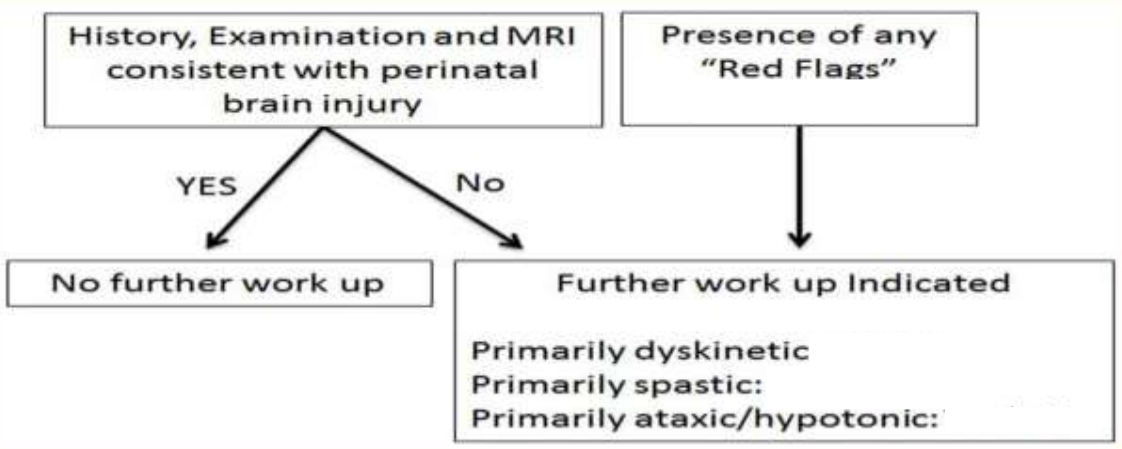
Non-specific → NGS(Panel/ WES)

Suggestive of specific syndrome → Targeted mutation

MRI brain

- Gold standard and the most important first line investigation
- +/_ add spine MRI if clinically indicated
- Re-Imaging if the there is clinical progression in symptoms or signs
- Brain MRI is normal in 15% of established CP patients
- Nonspecific findings in clinica18%.

Diagnostic Evaluation of the Child with Cerebral Palsy



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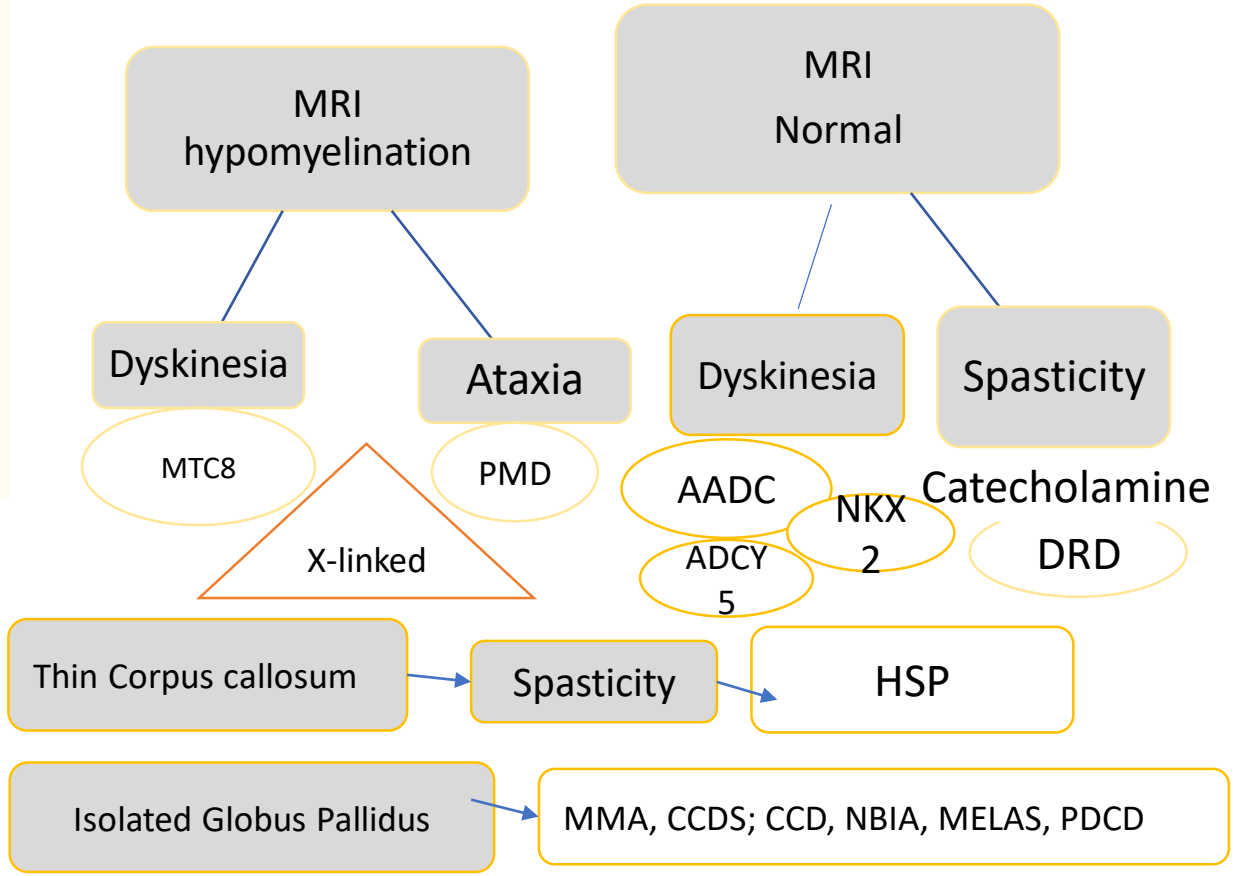
CP- cerebral palsy



Genetic/metabolic testing

Scenario 1

Features are suggestive of specific syndrome

Targeted gene/ biomarker analysis

Scenario 2

Features are non-specific/ normal /non-concordance

- ❑ Ammonia
- ❑ Lactate
- ❑ Amino acids/ Organic acid
- ❑ Acyl carnitine profile
- ❑ VLCFA
- ❑ Uric acid
- ❑ Thyroid function
- ❑ CK
- ❑ Alpha fetoprotein
- ❑ CSF lactate/ glucose/ Glycine, neurotransmitters
- ❑ Enzymes assay

Genetics testing

Genetic testing

- **Clear syndrome** **Single-gene testing;** detects small intragenic deletions/insertions and missense, nonsense, and splice site variants
- **Clear isolated abnormalities; dyskinesia, ataxia, spasticity; Panel / dyskinesia panel, ataxia panel, CP panel**
- ***Atypical phenotypic features*** ***comprehensive genomic testing; WES***

If exome sequencing is not diagnostic and particularly when evidence supports autosomal dominant inheritanc

– ***Exome array*** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis

-**WGS**

-If mitochondrial inheritance is suspected; mitochondrial genome assessment

Limitations

Exon or whole-gene deletions/duplications are not detected.

pathogenic variants in genes that do not explain the underlying phenotype

Doesn't detect (multi)exon deletions or duplications

Doesn't include MG

Invitae Cerebral Palsy Spectrum Disorders Panel

☑ Primary panel (425 genes)

ABAT	ABCD1	ACADM	ACADVL	ACAT1	ACBD5	ACOX1	ACTB
ADAR	ADCY5	ADD3	ADNP	ADSL	AFG3L2	AGAP1	AHDC1
AHI1	AKT3	ALDH18A1	ALDH3A2	ALDH5A1	ALDH7A1	ALG13	ALG3
ALS2	AMACR	AMPD2	AMT	ANO3	AP4B1	AP4E1	AP4M1
AP4S1	AP5Z1	APTX	ARG1	ARHGEF9	ARL6IP1	ARSA	ARX
ASL	ASNS	ASPA	ASS1	ASXL1	ATAD1	ATL1	ATM
ATP13A2	ATP1A3	ATP7A	ATP7B	ATP8A2	ATRX	AUH	AUTS2
B4GALNT1	BCAP31	BCKDHA	BCKDHB	BICD2	BSCL2	BTD	C12orf65
C19orf12	CACNA1A	CACNA1G	CAMTA1	CAPN1	CASK	CBS	CCDC88C
CCT5	CDKL5	CEP290	CHD8	CHRNA1	CIZ1	CLN2 (TPP1)	CLN3
CLN5	CLN6	CLN8	CLTC	COASY	COL4A1	COL4A2	COL6A3
COQ2	COQ4	COQ6	COQ7	COQ8A	COQ9	CPS1	CPT1C
CREBBP	CTBP1	CTNNB1	CTSD	CYP27A1	CYP2U1	CYP7B1	DARS
DARS2	DBH	DBT	DCAF17	DDC	DDHD1	DDHD2	DDX3X
DGKZ	DHDDS	DHFR	DLAT	DLD	DMD	DNAJC12	DNM2
DPAGT1	DYNC1H1	DYRK1A	EEF2	EHMT1	EIF2B1	EIF2B2	EIF2B3
EIF2B4	EIF2B5	ELOVL4	ELOVL5	ENTPD1	EPHA4	ERCC6	ERCC8
ERLIN1	ERLIN2	ETFA	ETFB	ETFDH	ETHE1	EXOSC3	FA2H
FAM126A	FARS2	FAT2	FGF12	FGF14	FH	FOLR1	FOXG1
FRRS1L	FTL	FUCA1	GABRA2	GAD1	GALC	GAMT	GATM
GBA	GBA2	GCDH	GCH1	GFAP	GJC2	GLB1	GLDC
GLRA1	GLRB	GM2A	GNAL	GNAO1	GNB1	GNS	GPHN
GPR88	GRID2	GRIN1	GRIN2B	GRM1	HACE1	HESX1	HEXA
HEXB	HGSNAT	HLCS	HMGCL	HPCA	HPRT1	HSD17B10	HSD17B4
HSPD1	IBA57	IFIH1	IQSEC2	IREB2	ITPA	ITPR1	KANK1
KAT6A	KCNA2	KCNC3	KCNJ6	KCNMA1	KCNQ2	KCNT1	KCTD17
KCTD7	KDM5C	KIDINS220	KIF1A	KIF1C	KIF5A	KMT2A	KMT2B
KMT2C	L1CAM	L2HGDH	LAMA2	LIAS	LMBRD1	MAG	MAOA
MAP2K1	MARS2	MAST1	MCCC1	MCCC2	MCEE	MECP2	MECR
MFSD8	MICU1	MLYCD	MMAA	MMAB	MMACHC	MMADHC	MOCS1
MOCS2	MOCS3	MPC1	MTHFR	MTOR	MTPAP	MTR	MTRR
MTTP	MUT	NAA10	NAA35	NAGLU	NAGS	NBAS	NGLY1
NIPA1	NKX2-1	NPC1	NPC2	NPHP1	NT5C2	NUS1	OTC
PAFAH1B1	PAH	PAK3	PALM	PANK2	PCBD1	PCCA	PCCB
PCDH12	PDE10A	PDE2A	PDHA1	PDHB	PDHX	PDP1	PDSS1
PDSS2	PDYN	PEX1	PEX10	PEX11B	PEX12	PEX13	PEX14

INVITAE

Individuals Providers

PRKRA	PROSC	PRRT2	PRUNE1	PSAT1	PSPH	PTPN11	PTS
PURA	QDPR	RAB3GAP1	RAB3GAP2	RANBP2	REEP1	REEP2	RHOBTB2
RNASEH2A	RNASEH2B	RNASEH2C	RNASET2	RTN2	SACS	SAMHD1	SATB2
SCN1A	SCN2A	SCN3A	SCN8A	SETD5	SGCE	SGSH	SHH
SIL1	SIX3	SLC16A2	SLC17A5	SLC18A2	SLC19A3	SLC1A4	SLC25A15
SLC25A22	SLC2A1	SLC30A10	SLC33A1	SLC39A14	SLC6A19	SLC6A3	SLC6A5
SLC6A8	SON	SPART	SPAST	SPATA5	SPG11	SPG21	SPG7
SPR	SPTAN1	SPTBN2	SQSTM1	ST3GAL5	STAMBP	STUB1	STXBP1
SUCLA2	SUCLG1	SUOX	SURF1	SYNGAP1	TAF1	TANGO2	TBC1D24
TBCK	TBL1XR1	TCF4	TECPR2	TFG	TGIF1	TGM6	TH
THAP1	TMEM240	TMEM67	TOR1A	TREX1	TRPC3	TSEN54	TTBK2
TTPA	TUBA1A	TUBB2A	TUBB2B	TUBB3	TUBB4A	UBE3A	UCHL1
VAC14	VAMP1	VPS13A	VPS13D	VPS37A	WARS2	WASHC5	WDR45
WDR62	ZBTB18	ZC4H2	ZEB2	ZFR	ZFYVE26	ZIC1	ZIC2
ZIC4							

3mL whole blood in a purple-top EDTA tube (K2EDTA or K3EDTA)

ALTERNATE SPECIMENS:
Saliva, assisted saliva, buccal swab and gDNA

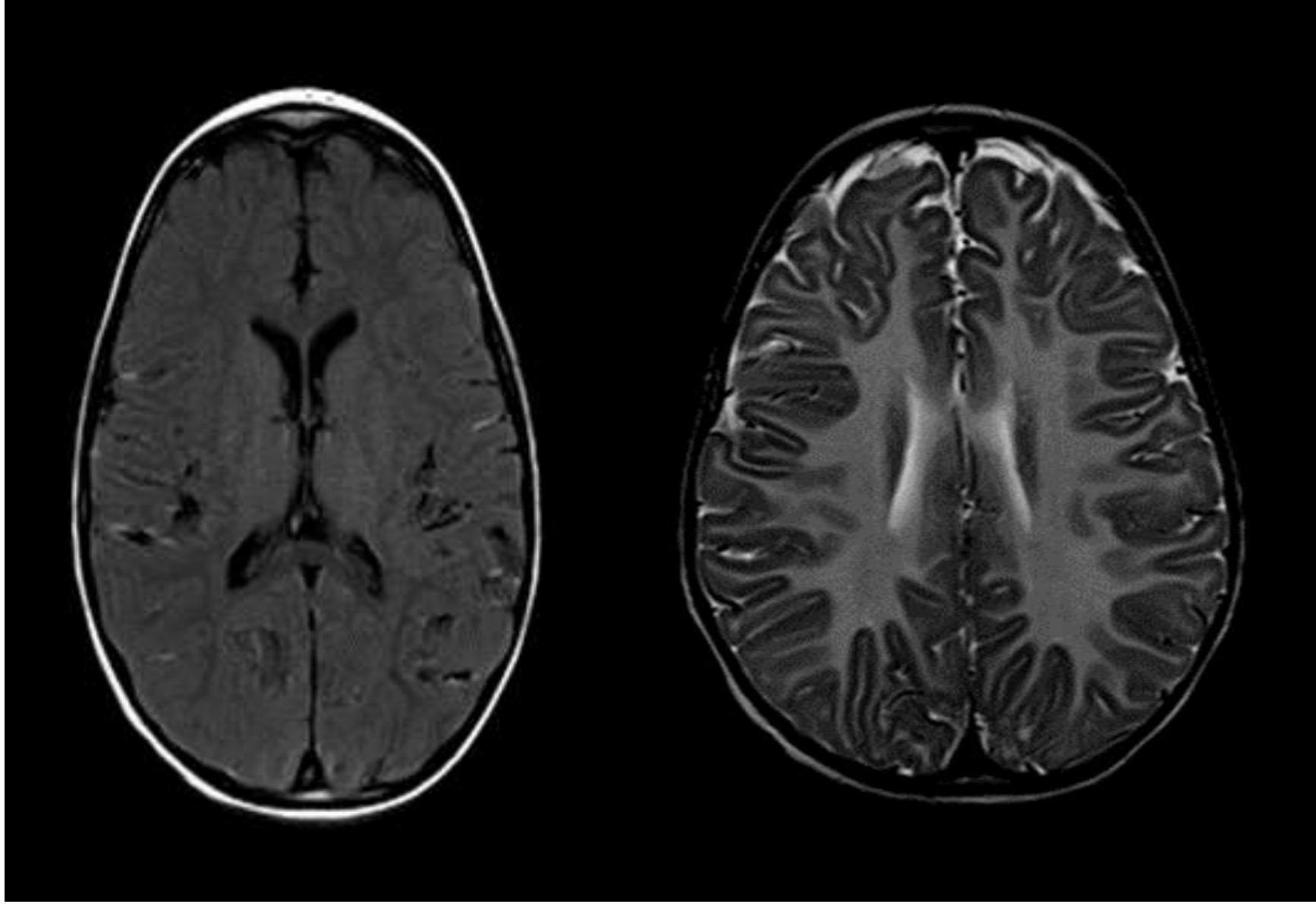
Mitochondrial inheritance and repeat expansions are not evaluated by this panel.

Scenario 1

Case 1

An 18 month-old male presented with global developmental delay, hypotonia, mixed-type ataxic/dystonic/spastic CP and rotary nystagmus.

Term, no pregnancy or delivery complications



Features are suggestive of specific syndrome ⟷ Targeted gene/ biomarker analysis

This picture is highly suggestive of PLP1-related hypomyelination disorders.

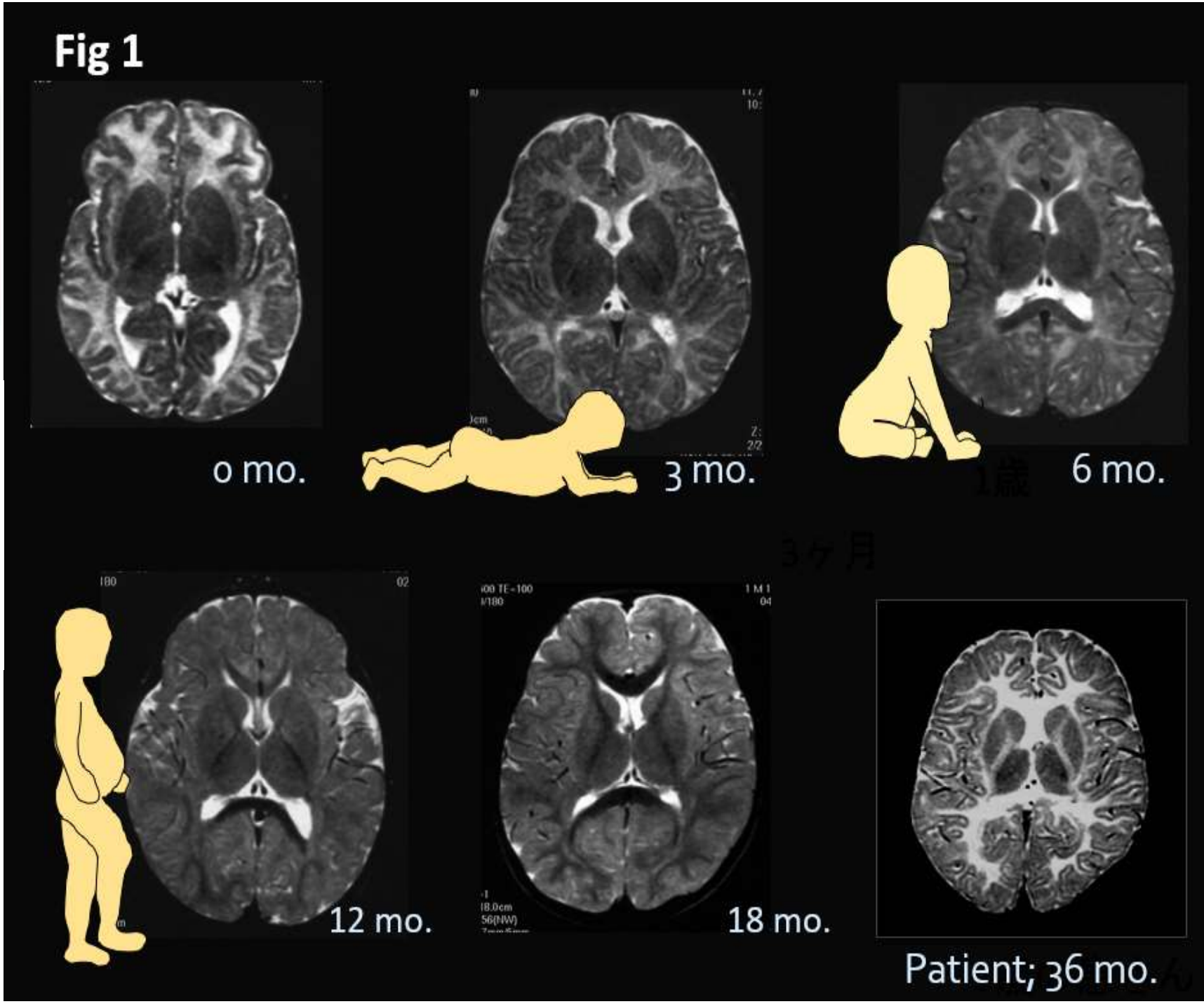
RESULT: POSITIVE

One Pathogenic variant identified in PLP1. PLP1 is associated with X-linked hereditary spastic paraplegia and Pelizaeus-Merzbacher disease .

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PLP1	Gain (Entire coding sequence)	copy number = 2	PATHOGENIC

Pelizaeus-Merzbacher disease (PMD)

PLP-1(proteolipid protein 1) mutation



Diagnostic Evaluation of the Child with Cerebral Palsy

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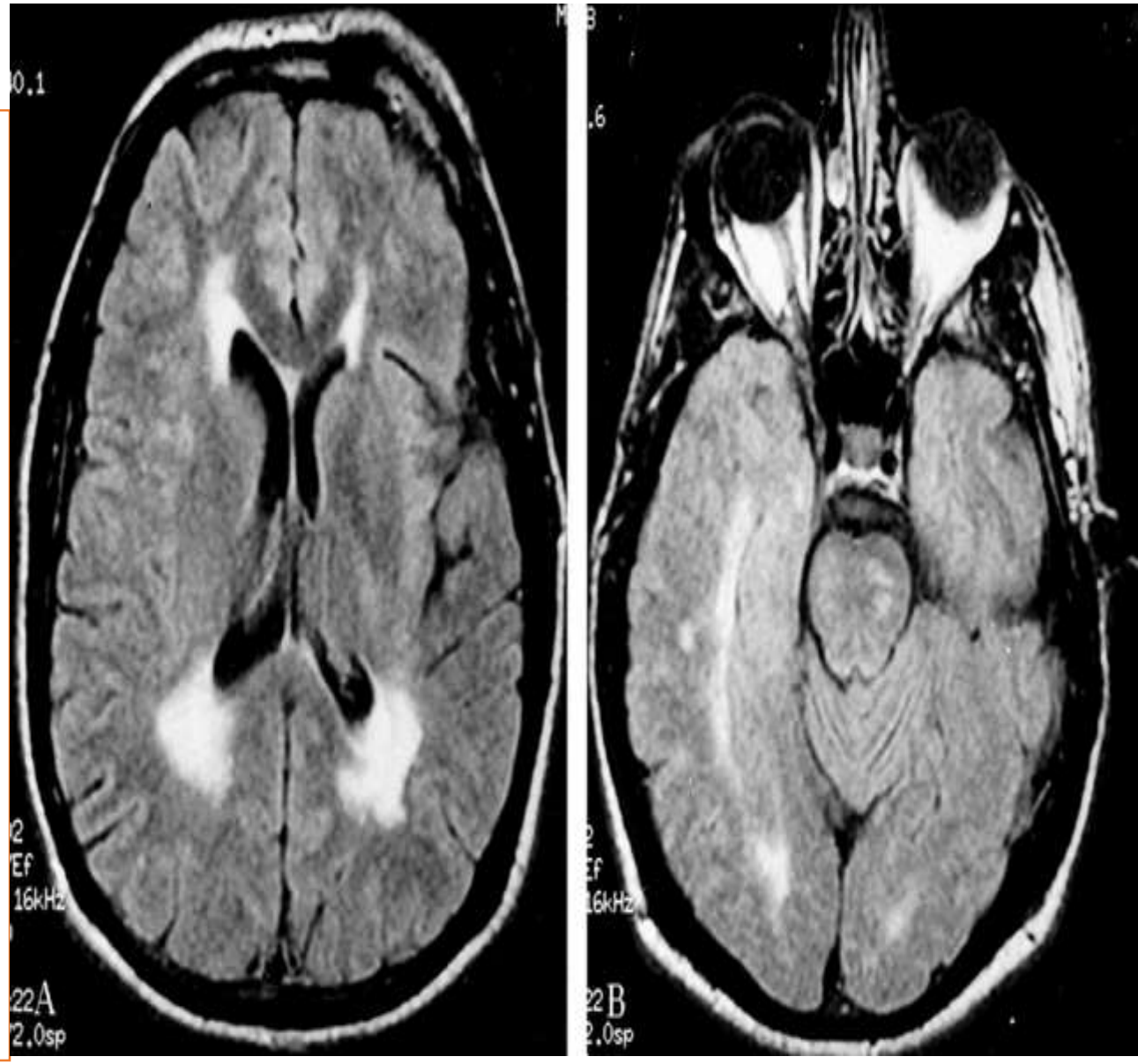
CP- cerebral palsy

Case NO 2

- 9-year-old male was born at term following an unremarkable pregnancy and delivery.
- Developmental delay early onset.
- 2 years of age exhibited features suggestive of spastic diplegia, dysarthria and dystonic posturing
- On subsequent follow ups he noted to have progressive difficulty ambulation attributed to contractures
- Parental consanguinity; non- affected.
- Brain CT was done upon presentation (2 years) normal



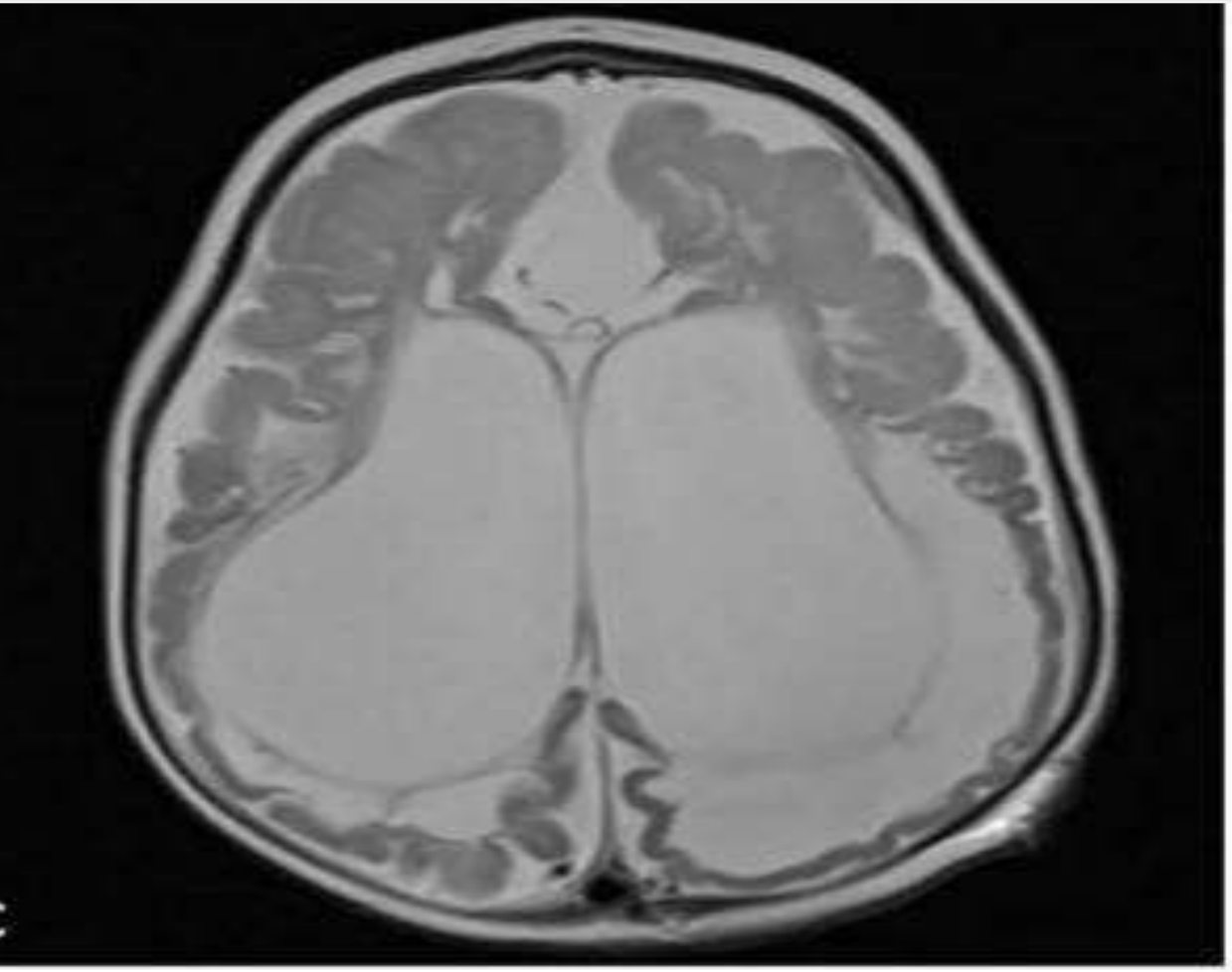
Labelled as having a spastic Diplegic CP

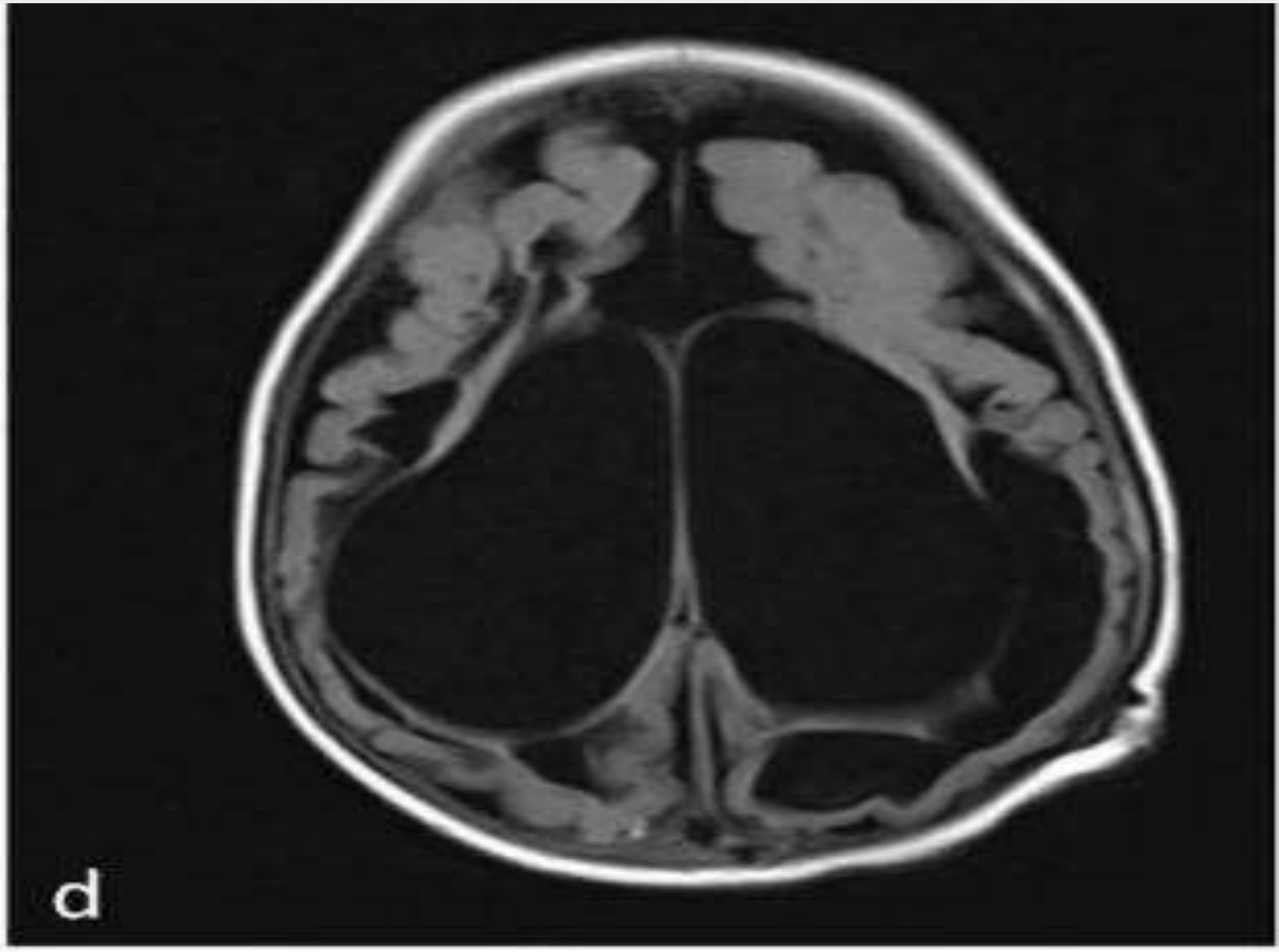
Infantile-Onset Hereditary Spastic Paraplegia

SPG3A due to mutation in the ALS2 gene

Case 3

- 2-year-old boy, presented with spastic quadriplegia and Global delay
- He was born at term; history of prolong labour by mother but normal Apagr scores on the records
- He has seizures which started since neonatal periods day 15(neonatal hypoxic-ischemic)
- He has feeding difficulties
- Hypertonia, spasticity and hyperreflexia
- *A diagnosis of cerebral palsy was made based on the history of prolong labour and typical MRI findings of HIE.*

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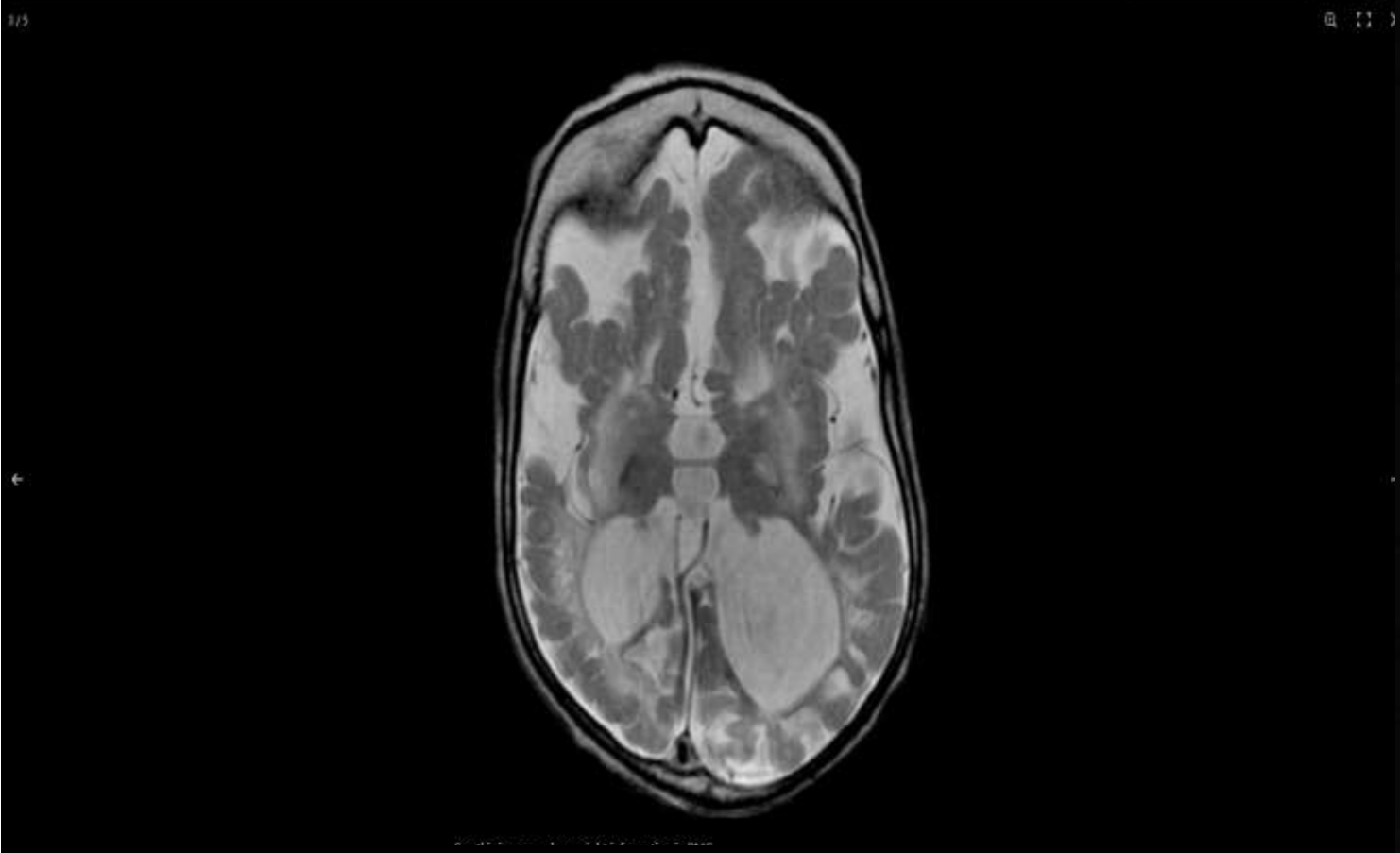
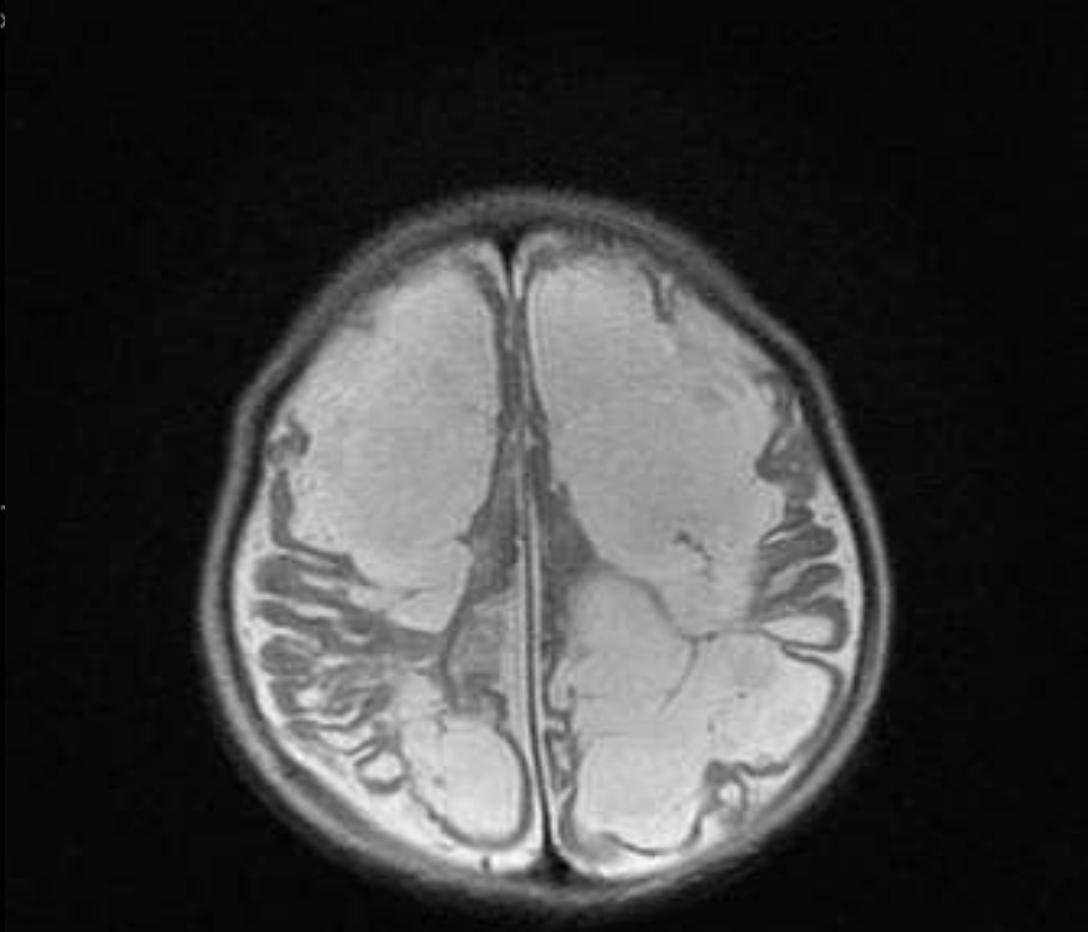


MCD



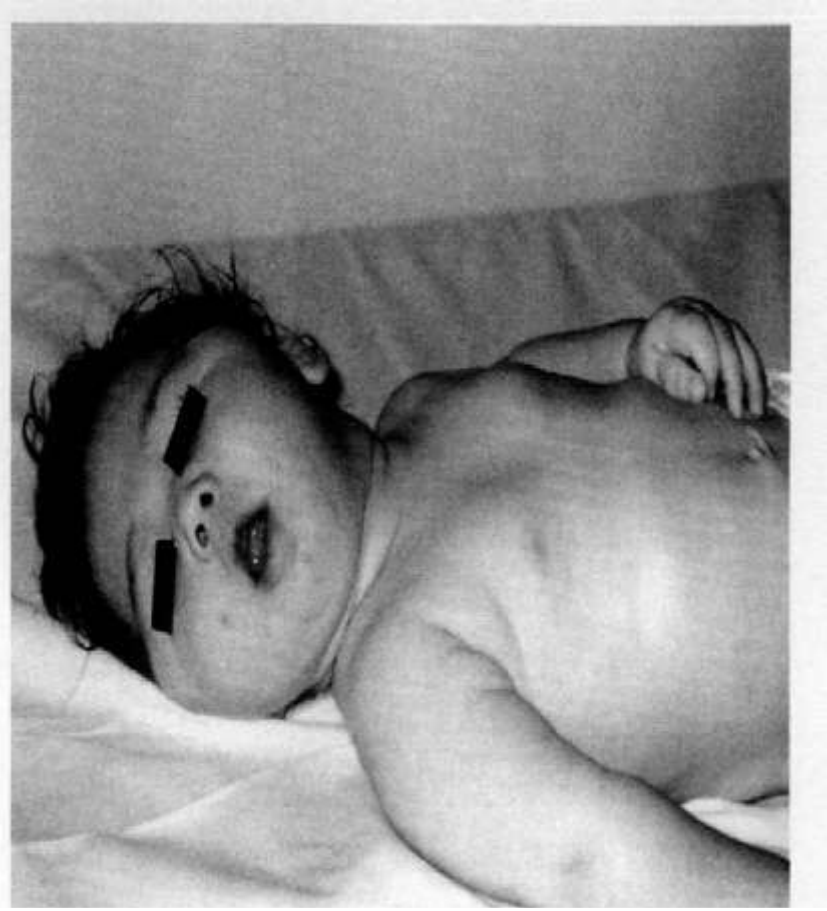
Cystic PVL

Molybdenum cofactor deficiency (MCD)

- AR
- Co factor for xanthine dehydrogenase and Sulphite oxidase
- The major clinical findings are severe neonatal seizures, feeding difficulties, and a progressive neurologic deficit.
- Microcephaly
- Dysmorphism
- Progressive reduction in serum uric acid.
- *Decrease in urinary uric acid*
- *Increase sulfite in the urine*
- *MCOS1&2 mutation*

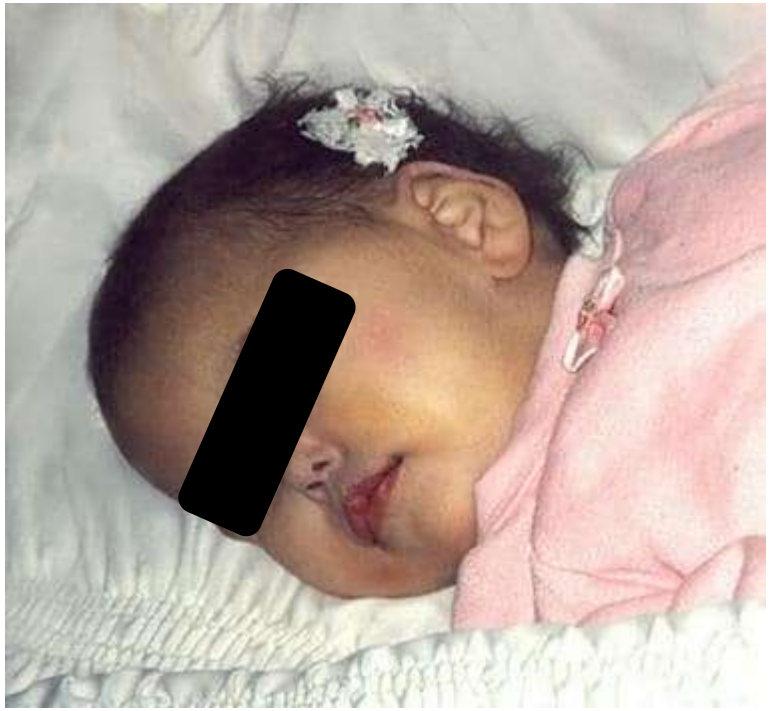
Management

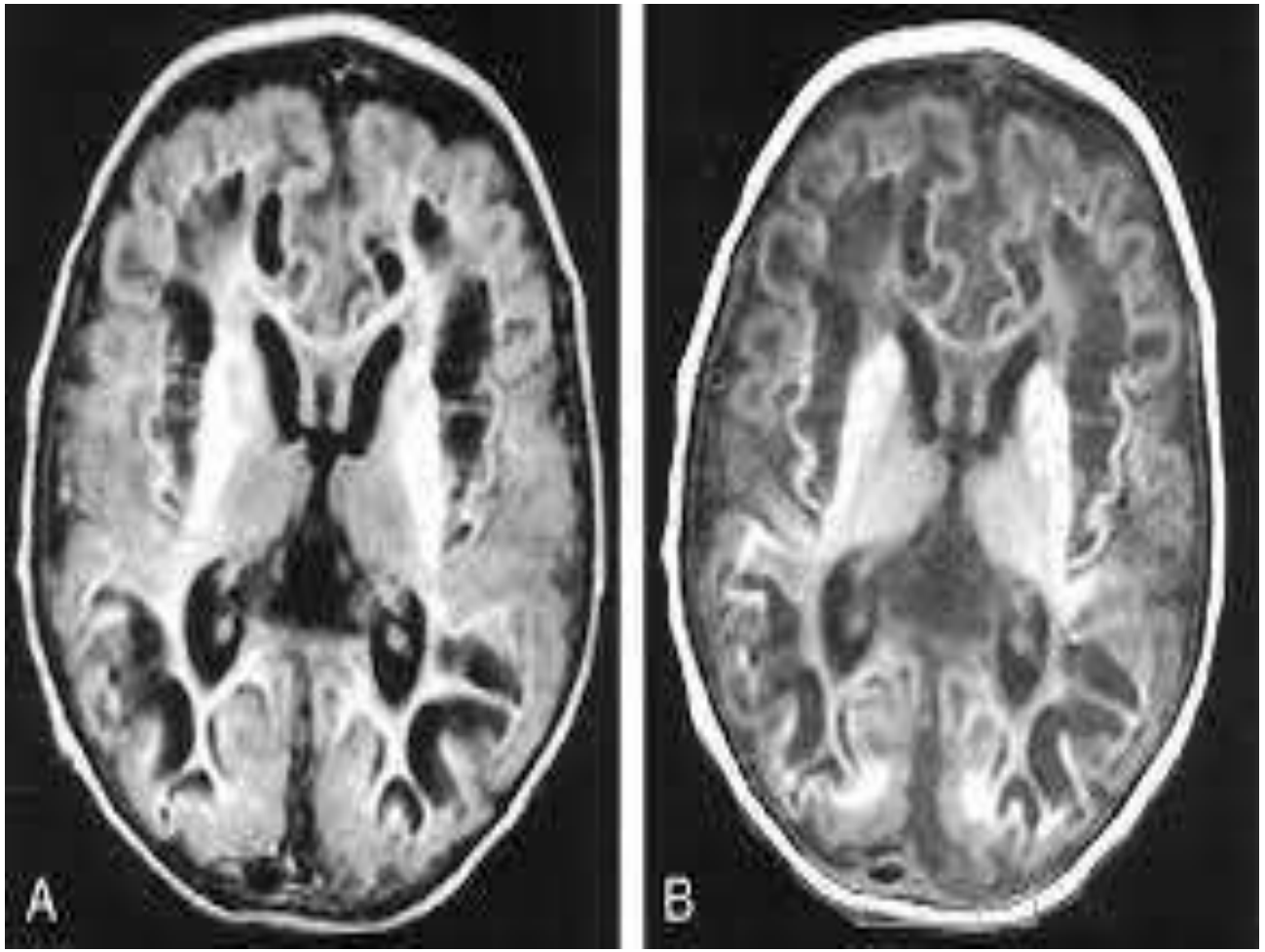
- Seizures management
- Restriction of Sulphur-containing amino acids
- Cyclic pyranopterin infusion
- Thiamine supplement

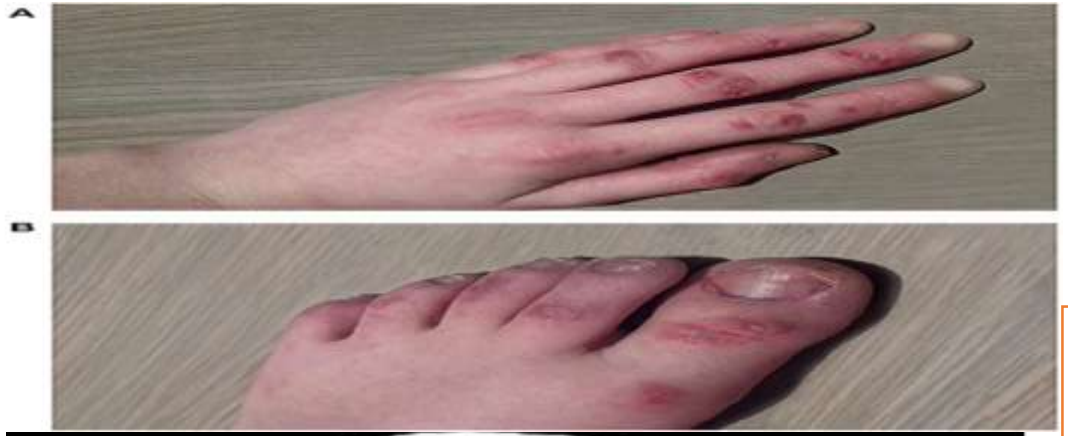


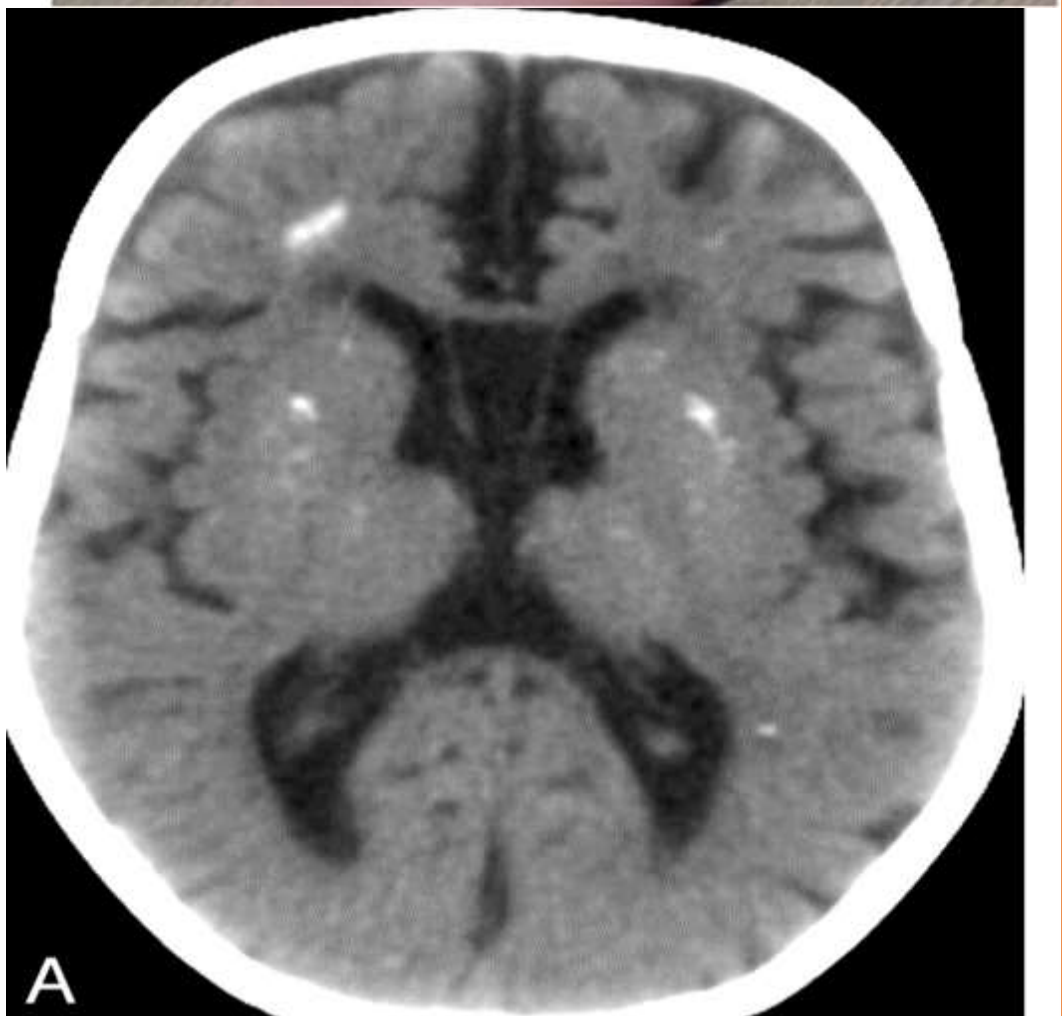
Sulphite Oxidase Def

- Positive urine sulphite reaction
- Ectopia lenses
- Dysmorphism
- *SUOX MCOS1&2 mutation*





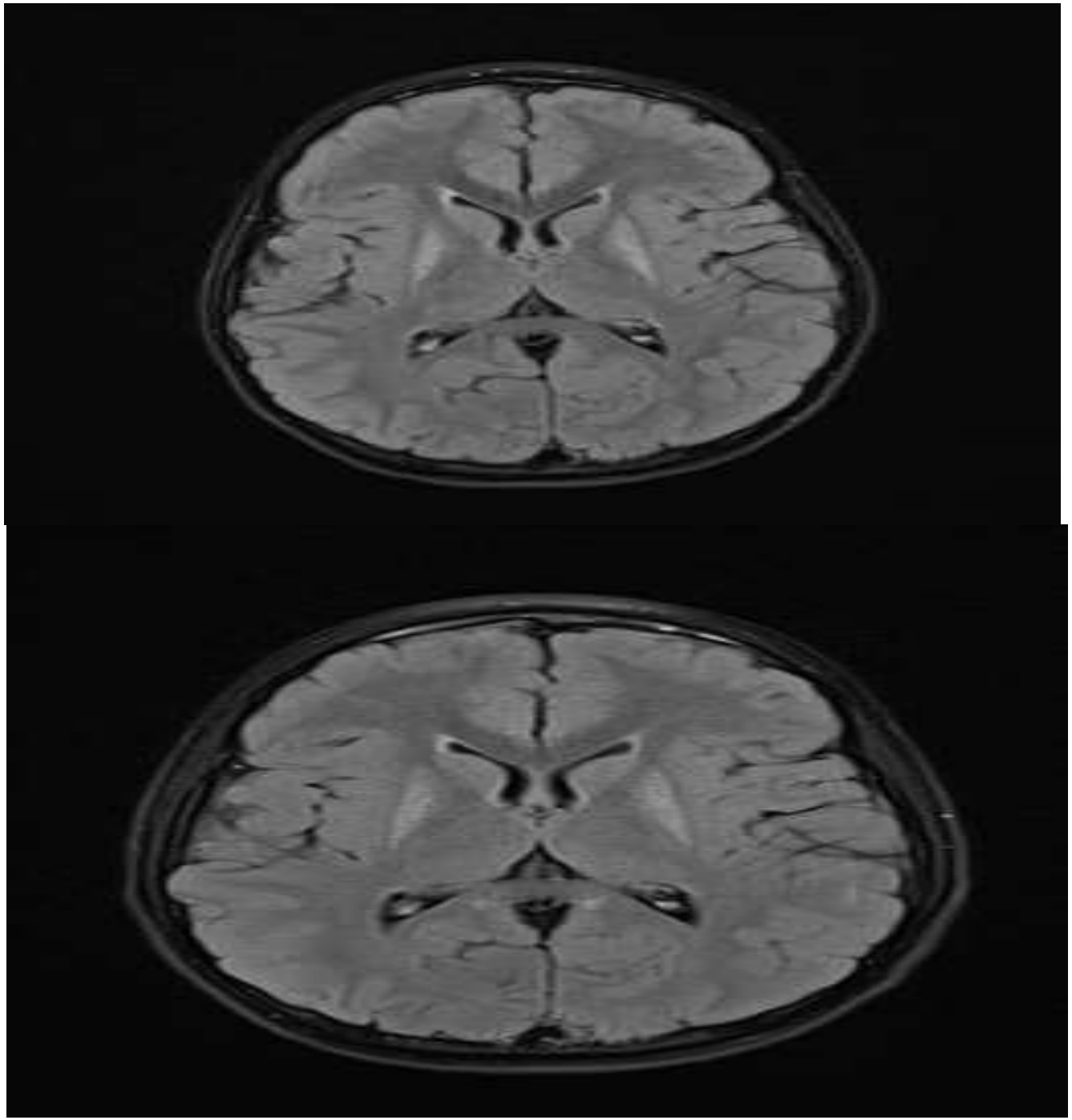




case 4

- 9-year-girl DD noted at the age of 10 months after febrile illness
- No perinatal history of note.
- Parents are first-degree cousins.
- Her mother had two early miscarriages.
- Examination: a quadriplegia of mixed spasticity and dyskinesia was noted, more pronounced on the right side of her body.
- Mild intellectual disability and speech deficit were observed.
- During winter, she developed skin lesions on her feet which were initially attributed to pressure lesions from splints.

- *Diagnosed as CP of mixed spastic and dyskinetic type due TORCH infection*



INVITAE DIAGNOSTIC TESTING RESULTS

Reason for testing Diagnostic test for a personal history of disease	**Test performed** Sequence analysis and deletion/duplication testing of the 265 genes listed in the Genes Analyzed section. Invitae Cerebral Palsy Spectrum Disorders Panel

RESULT: POSITIVE

One Pathogenic variant and one Variant of Uncertain Significance identified in ADAR. ADAR is associated with autosomal dominant dyschromatosis symmetrica hereditaria and autosomal recessive Aicardi Goutieres syndrome.
Additional Variant(s) of Uncertain Significance identified.

Aicardi-Goutières syndrome ;ACS

- Usually mis-diagnosed as congenital infection Pseudo-TORCH s
- Aicardi-Goutières syndrome is a genetically inherited autoimmune-mediated encephalopathy
- Type 1 interferonopathies; interferon-mediated antiviral response is usually triggered by viral infections.
- Neurological manifestation of the infantile form usually appear in early infancy, with progressive microcephaly, spasticity, dystonia, and severe psychomotor retardation.
- Phenotypic variability ; mild spasticity ⟷ classical infantile form
- Progression is variables from fulminant , slowing progressive to even static.
- Non-neurological features include hepatosplenomegaly, elevated hepatic transaminases and thrombocytopenia and chilblain lesions
- CSF high WBC , high interferon , negative serologic screen for prenatal infections
- Imaging Cerebral calcifications and white matter abnormalities.
- Genetic heterogeneity is common with mutations identified in the following genes: TREX1(AGS1), RNASEH2A(AGS4), RNASEH2B(AGS2) and RNASEH2C(AGS3),SAMHD1(AGS5), ADAR(AGS6) & IFIH1(ACS7)

BRIEF RESEARCH REPORT article
Front. Neurol., 22 April 2021 | https://doi.org/10.3389/fneur.2021.617813

Genetic Testing Contributes to Diagnosis in Cerebral Palsy: Aicardi-Goutières Syndrome as an Example

Diane Beysen[1†], Chania De Cordt[2†], Charlotte Dielman[3], Benson Ogunjimi[2,4,5], Julie Dandelooy[6], Edwin Reyniers[7], Katrien Janssens[8] and Marije M.E. Meuwissen[7,8*]

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confirmed diagnosis of Aicardi-Goutières syndrome (AGS); phenotypes ranged from clearly suggestive for the disorder to non-specific findings like spastic diplegia/quadriplegia, developmental delay and non-pathognomonic brain MRI findings.

- Findings suggest that AGS may be a rather common cause of CP, that frequently remains undiagnosed without additional genetic testing.
- The diagnosis of AGS must be considered in cases with spastic CP, even in the absence of characteristic brain abnormalities.
- A genetic diagnosis of AGS may have significant therapeutic consequences, as targeted therapies are being developed for type 1 interferonopathies; (AGS).

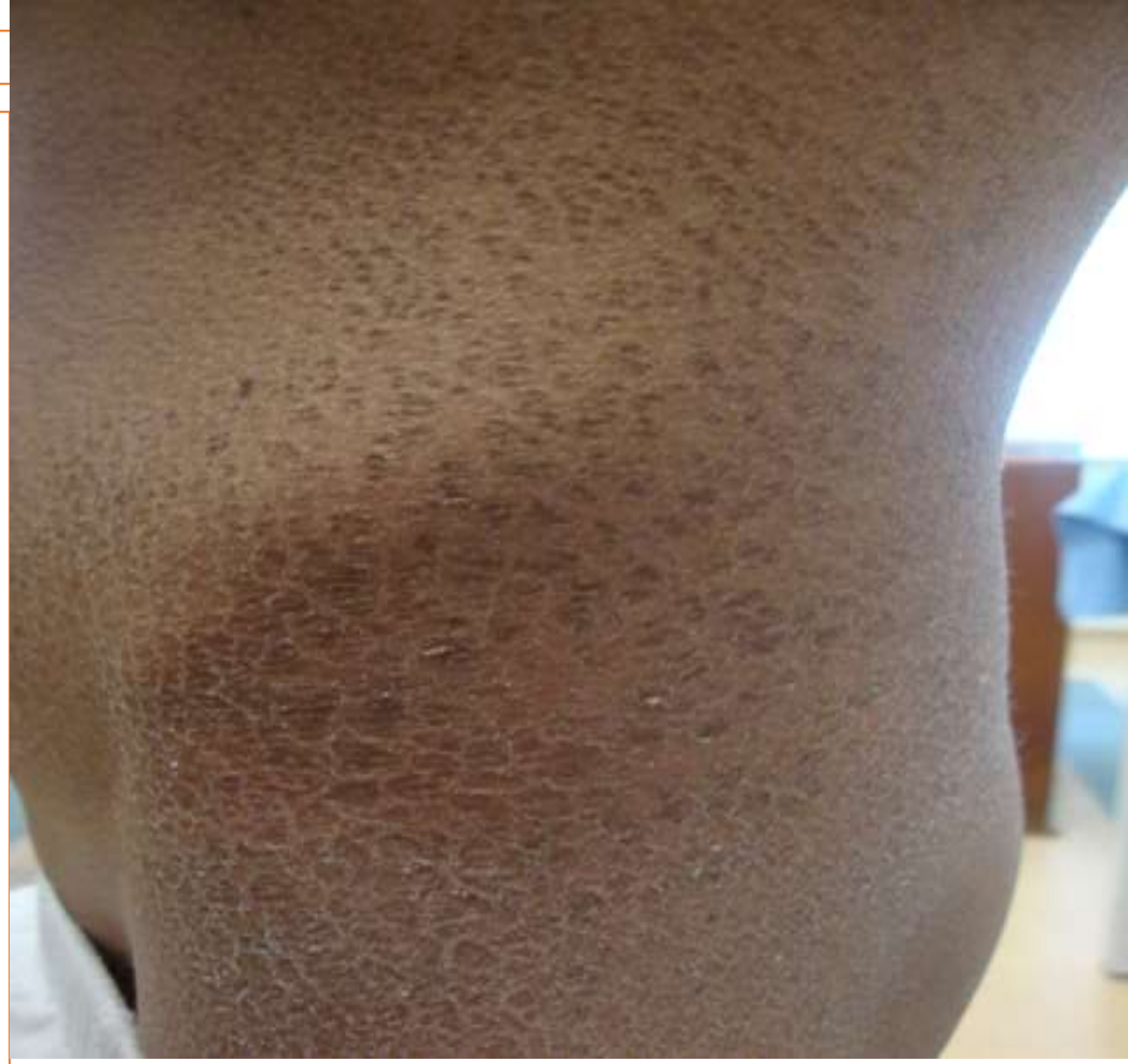
	Case 1	Case 2	Case 3
Affected gene	*SAMHD1*	*RNASEH2B*	*RNASEH2B*
Pathogenic variant	c.109G>T (p.Glu37*)(HET)/deletion exon 5 (HET)	c.529G>A (p.Ala177Thr)(HOM)	c.529G>A (p.Ala177Thr)(HOM)
Sex	F	F	F
History of consanguinity	–	+	–
Age at last examination	12 y, 1 m	15 y, 8 m	3 y, 6 m
Age at presentation	1 y, 10 m	8 y, 8 m	2 y, 1 m
Age at diagnosis	10 y, 3 m	14 y, 9 m	3 y, 2 m
Motor delay	+	+	+
Speech delay	+	+	–
Intellectual disability	+	+	+
Seizures	–	–	?
Chiblain lesions	+	+	–
Head circumference (cm)	46.5 (p20)	52 (p50)	48.3 (p50)
Neurological findings	Spastic diplegia ADHD	Spastic and dyskinetic quadriplegia	Spastic diplegia
Ophthalmological findings	–	–	–
Other findings	Eczema	–	–
Brain MRI	Bilateral white matter abnormalities, parietal cortical atrophy and signs of Moyamoya disease	Posterior thinning corpus callosum	Periventricular microcysts and white matter abnormalities

HET, heterozygous; HOM, homozygous; F, female; y, years; m, months.

Case 5

- 13-year-old male
- He was born in 32th-week of gestation with 2,400 grams birth weight
- learning difficulties.
- Global delay; head control at 7 months, walked at 22 months
- Wt. and Ht. are both below the 5th centile ; normocephalic
- His speech was not fully comprehensible.
- CNs: Normal
- Muscle tone increased in both LLs
- DTR 3+
- Planter response was extensor
- Walking on his Tip toes; diplegic gait
- Dryness and peeling of the skin were prominent on in trunk and legs
- Brain MRI was done at the age of 2 years and was

He was diagnosed as spastic diplegic cerebral palsy due to prematurity .



Sjogren Larson syndrome

Diagnostic Evaluation of the Child with Cerebral Palsy

Disorders with prominent spasticity	Disorders with prominent dyskinesia	Disorders with prominent ataxia
- Hereditary spastic paraglegias - Arginase deficiency - COL4A1-Related spastic CP - Biotinidase deficiency - Aicardi-Goutières syndrome - Sulfite oxidase deficiency/ Molybdenum cofactor deficiency[22] - Leukodystrophies, such as metachromatic leukodystrophy,[23] adrenoleukodystrophy,[24] Sjo Larsson syndrome[25]	- Dopa-responsive dystonia - Sepiapterin reductase deficiency - Glutaric aciduria type 1 - Glucose transporter deficiency type 1 - Neurodegeneration with brain iron accumulation - Cerebral creatine deficiency syndrome - Lesch Nyhan syndrome - Cerebral folate deficiency - ADCY5-related dyskinesia PCDH12-related dyskinesia[34] - NKX2-1 related ataxic dyskinetic - TSEN54 Gene-related pontocerebellar hypoplasia type 2[36]	- Glucose transporter deficiency type 1 - Ataxia telangiectasia - Pelizaeus-Merzbacher disease - Hereditary ataxias - Joubert syndrome - Mitochondrial cytopathies (mainly 8993 mutation)[42] - Pontocerebellar hypoplasia[36] - Cockayne syndrome[43] - Niemann-Pick disease type C[44] - Angelman syndrome[12] - Gangliosidosis type 1 , juvenile and adult forms[45] - Non-ketotic hyperglycinemia[3] - Maple syrup urine disease[3] - NKX2-1 related ataxic dyskinetic CP[35]

CP- cerebral palsy

case 6

- A five year-old female born at term with no perinatal risk factors, presented during late infancy with tip toeing
- Noted to have abnormal posturing
- Examination showed spasticity and hyperreflexia more pronounced over the lower limbs

Diagnosis of “spastic diplegia”

After treatment
with L Dopa

Dopa-Responsive dystonia

- Commonly misdiagnosed as CP.
- Metabolic disorder of the dopamine synthetic pathway.
- Genetic AD(commonest), AR
- Diurnal fluctuation and improvement with rest or sleep.
- Brisk deep-tendon reflexes in the legs, ankle clonus, striatal toe may be present

- CSF neuro-transmitters concentration biopterin(BP) and NP(neopterin) Both are low in GTPCH1-deficient DRD
- confirmation Genetic testing

Treatment: Levodopa

GTPCH1-deficient DRD, DYT5a

- Commonest form of Dopa responsive dystonia 80%
- Typical age around 6Y
- Childhood with gait disorder due to foot dystonia Initial symptoms are often gait difficulties attributable to flexion-inversion (equinovarus posture) of the foot
- Normal intellectual and cognitive function, no sensory, autonomic or cerebellar signs .

Tyrosine Hydroxylase Deficiency DY5b

Clinical Phenotype	Severity	Age at Onset	Effect of Levodopa
TH-deficient dopa-responsive dystonia	Mild	12 mos-12 yrs	Dramatic & sustained
TH-deficient infantile parkinsonism with motor delay	Severe	3-12 mos	Incomplete [1]
TH-deficient progressive infantile encephalopathy	Very severe	<3-6 mos	Little to none [2]

TH-deficient myoclonus-dystonia DY511

DD, hypotonia, developmental motor delay, generalized dystonia, and prominent myoclonic jerks in infancy.

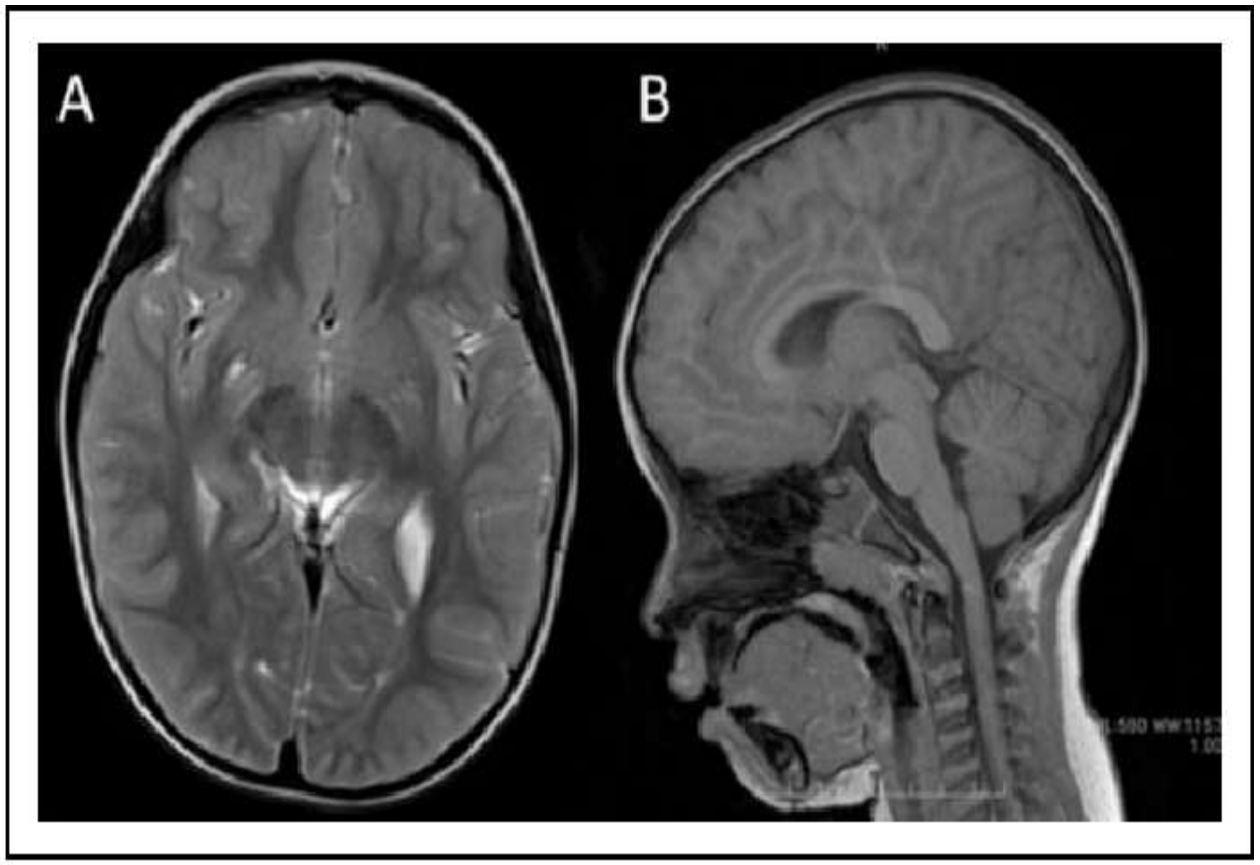
Sepiapterin Reductase Deficiency

Clinical features in the majority of affected individuals include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises; symptoms show diurnal fluctuation and sleep benefit.

Case NO 7

- 4-year-old girl, born near term , her neonatal period was respiratory distress that's needed CPAP
- Noticed to have neonatal hypotonia, motor developmental delay, generalized dyskinesia and mild motor delay late infancy
- Currently, she is ambulatory with frequent falls.
- Her testing showed low thyroid hormones.
- MRI brain was normal

Diagnosed as having dyskinetic-ataxiac CP with hypothyroidism



Progression----------

- ✓ She was seen by a neurologist who diagnosed here as Dopa-responsive dystonia
- ✓ She showed good response to L-dopa in with improvement in ambulation and decrease in abnormal movements.

Would you offer further work up???

Why??

NKX2-1-Related Disorders; case NO 7

(TITF1 gene thyroid transcription factor 1 gene (*TITF-1*),

Brain-lung-thyroid syndrome

- NKX2-1-related disorders range from **Benign Hereditary Chorea** (BHC) to choreoathetosis, congenital hypothyroidism, and neonatal respiratory distress
- AD with variable expression
- Delayed motor development, hypotonia followed by the movements disorder
- Chorea generally begins in early infancy or about age one year (most commonly) or in late childhood or adolescence, and progresses into the second decade after which it remains static or (rarely) remits.
- SNHL, joint hypermobility
- Pulmonary disease, the second most common manifestation, can include respiratory distress syndrome in neonates, interstitial lung disease in young children, and pulmonary fibrosis in older persons.
- The risk for pulmonary carcinoma is increased in young adults
- Responds to high dose of L- Dopa

- A six year-old male presented with DD, hypotonia, movements disorder; dystonic posturing, oculogyric crises, and autonomic changes
- Combined neurotransmitters def(Ser, Dop, NE, E)

❖ Brain MRI showed only minimal prominence of frontal horns

Aromatic Acid Decarboxylase (AADC) Deficiency
DDC gene mutation.

AADC activity assays/ CSF metabolite +Genetic mutation

- ✓ Pyridoxine/ Pyridoxal phosphate (PLP)(Co-factor)
- ✓ Folinic acid (If low CSF 5-MTHF levels)
  Pramipexole(dopamine agonist)

Dramatic improvement in speech, gait, hand use

Subset showed response to Dopa.

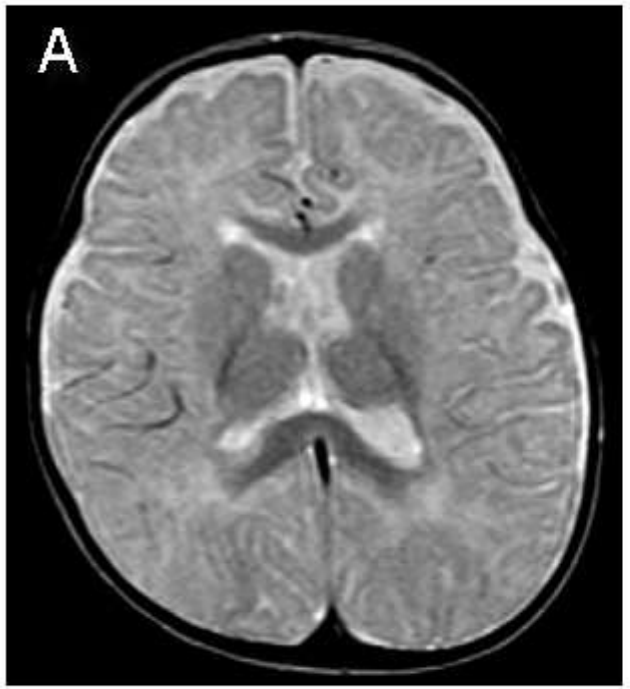
Gene therapy in Phase 2

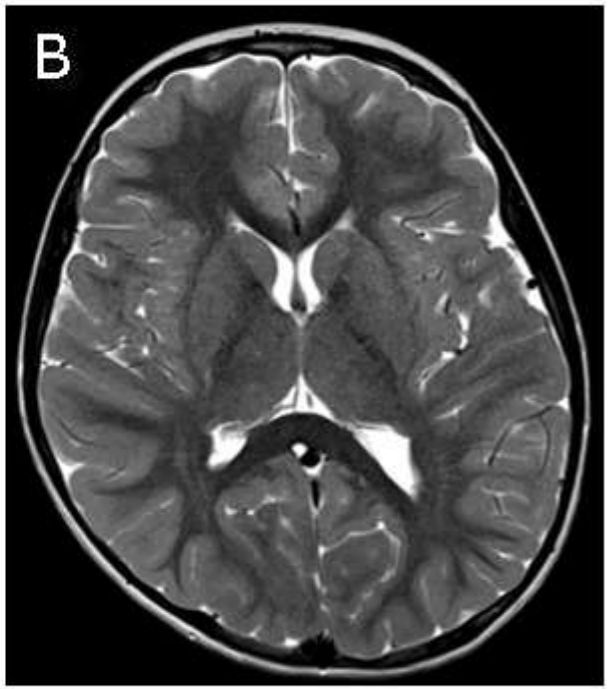
Review | Open Access | Published: 18 January 2017

Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency

Case NO 8

- A boy presented at 2 years with profound global developmental delay, hypotonia, intermittent dystonic posturing, and subtle dysmorphic facial features.
- Pregnancy and delivery were uncomplicated.
- Examination showed as mixed spasticity, hypotonia, and dyskinesia.
- Serum thyroid T3 levels were high at 3.66 ng/mL (0.94 – 2.69 ng/mL), T4 low at 0.5 ng/dL (4.5 – 12.5 ng/dL), and thyroid stimulating hormone within the normal range
- Therapy with thyroid hormone has not been successful.





Age of 12 months

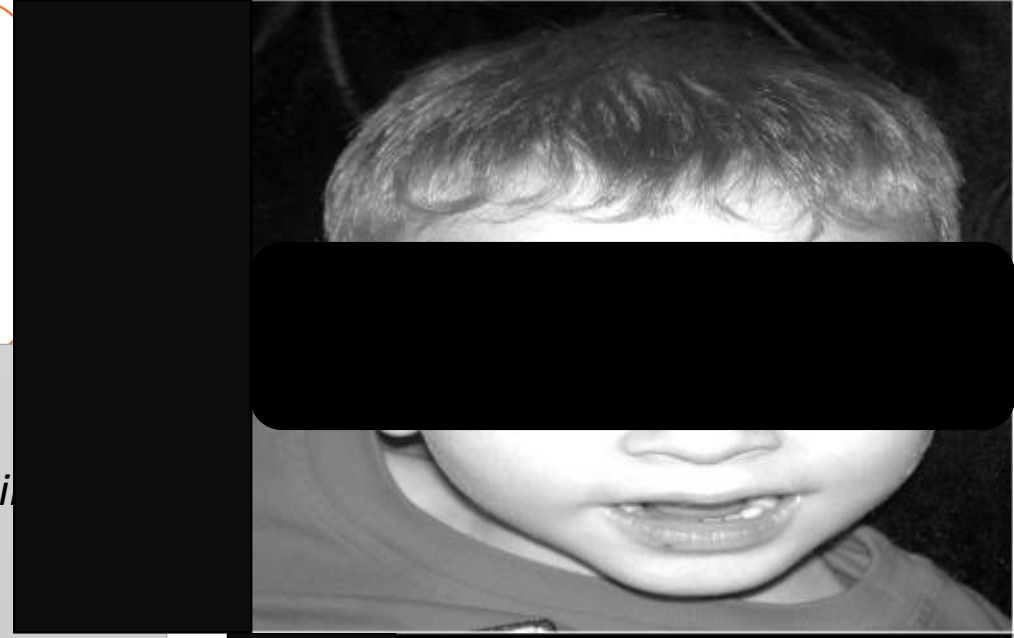
At 7-year

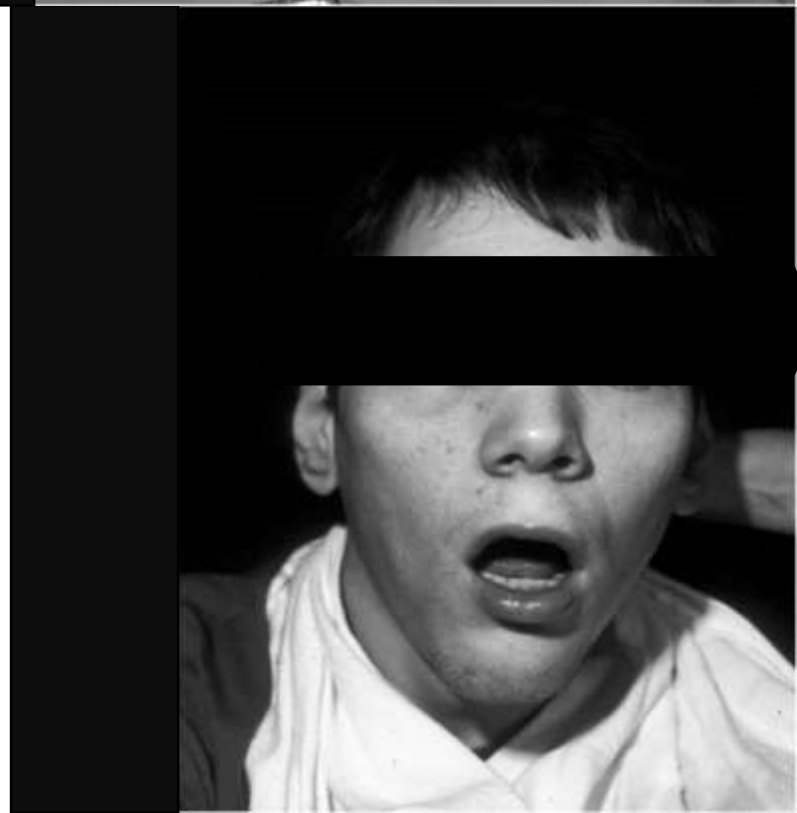
Monocarboxylate Transporter 8 Deficiency (MCT 8)

Allan-Herndon-Dudley syndrome (AHDS)

- X-linked condition; SLC16A2 mutations
- *Thyroid hormone transporter monocarboxylate transporter 8 (MCT8) result i*

  MCT8 deficiency.
- Congenital hypotonia(100%) that progresses to spasticity with severe psychomotor delays. LD (100%)
- Seizure is common and usually refractory to treatment
- Muscular atrophy of trunk and limbs
- Some have a distinctly myopathic face, which tends to worsened with age
- *Patients have elevated serum levels of free T(3), low to below normal serum levels of free T(4), and levels of thyroid stimulating hormone that are within the normal range.*
- *Treatment NA.*
- *Phase 2 TRIAC*





Case NO 9

- 8-year-old boy, with no perinatal history of note.
- Noted to have global delay and hypotonia since early infancy.
- Noted to have abnormal movements that’s involve the face and limbs more during sleep, the tends to have exacerbations.
- No response to anti-dystonia medications
- Brain MRI Normal

Diagnosed as having dyskinetic CP

ADCY5-related dyskinesia; Infantile form

- A significant genetic cause of early-onset non-progressive hyperkinetic movement disorders(AD)
- ADCY5 gene encodes a specific adenylyl cyclase 5(ATP → cAMP)
- Onset -6 months of age in a patient known to have hypotonia or motor delay.
- The movement disorder, in form of dystonia(prominent feature), chorea or choreoathetosis, episodic and sleep-related.
- The facial movements are typically periorbital and perioral.
- Dyskinesia may exacerbate upon awakening, falling asleep or during intercurrent illnesses for few minutes up to days.
- Some has long periods (days to weeks) of remission
- Hyperreflexia of the lower limbs, hypotonia and intermittent head or limb tremors
- Normal cognitive function or mild intellectual disability
- Normal Brain MRI.

The exacerbation of dyskinesia in relation to sleep should prompt consideration of an underlying ADCY5 mutation.

Treatment of Manifestations Acetazolamide
May respond to caffeine

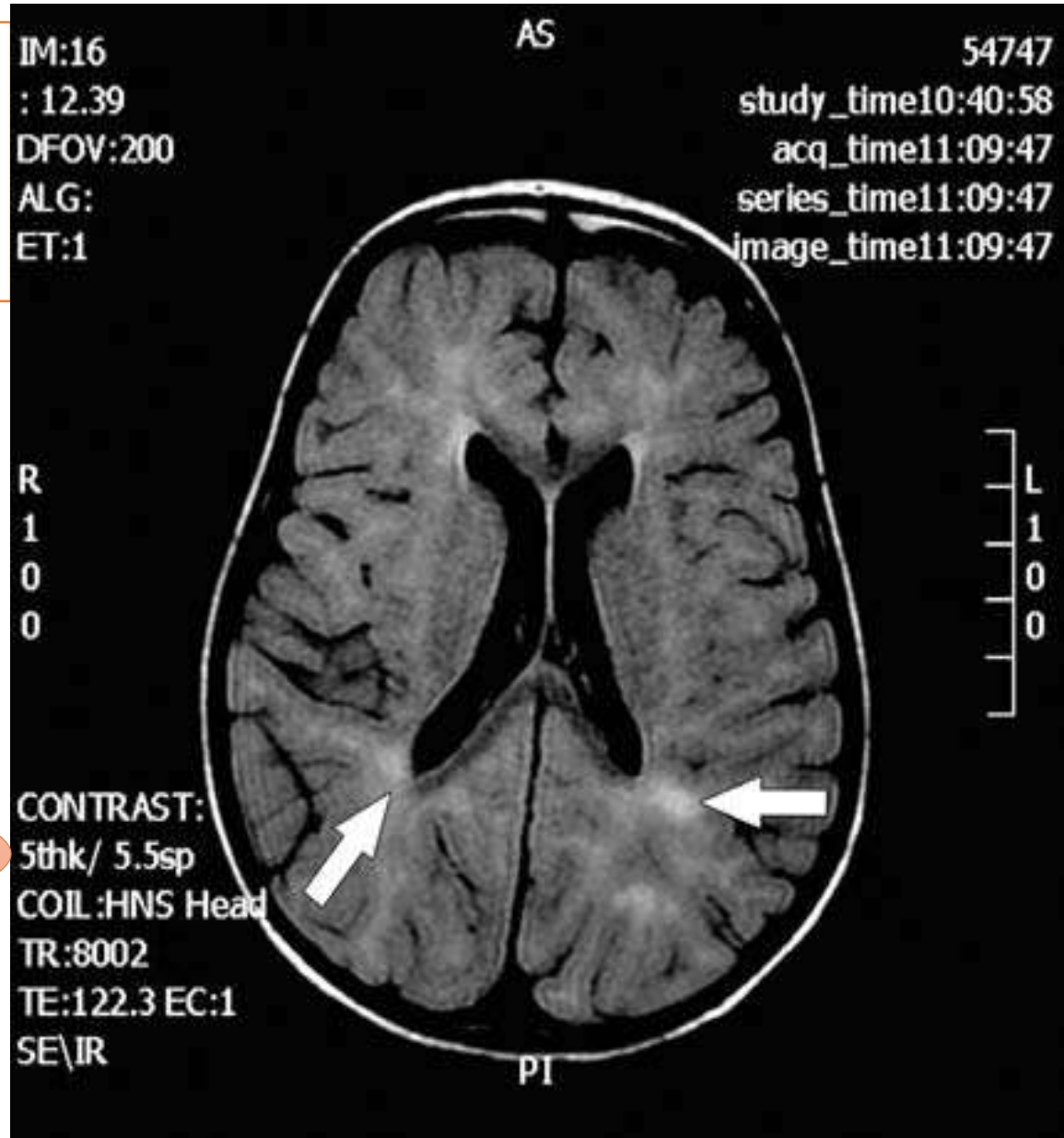
- A four-year-old female presented with infantile-onset epilepsy, truncal hypotonia, dystonia, spasticity, intellectual disability and intermittent worsening of dyskinesia associated with fatigue.
- Examination showed spastic diplegia

CSF glucose 40 mg/dL, compared with blood glucose of 86 mg/dL.

Epilepsy panel showed mutation in the SLC2A1 gene

Glucose Transporter Type 1 (Glut1) Deficiency—

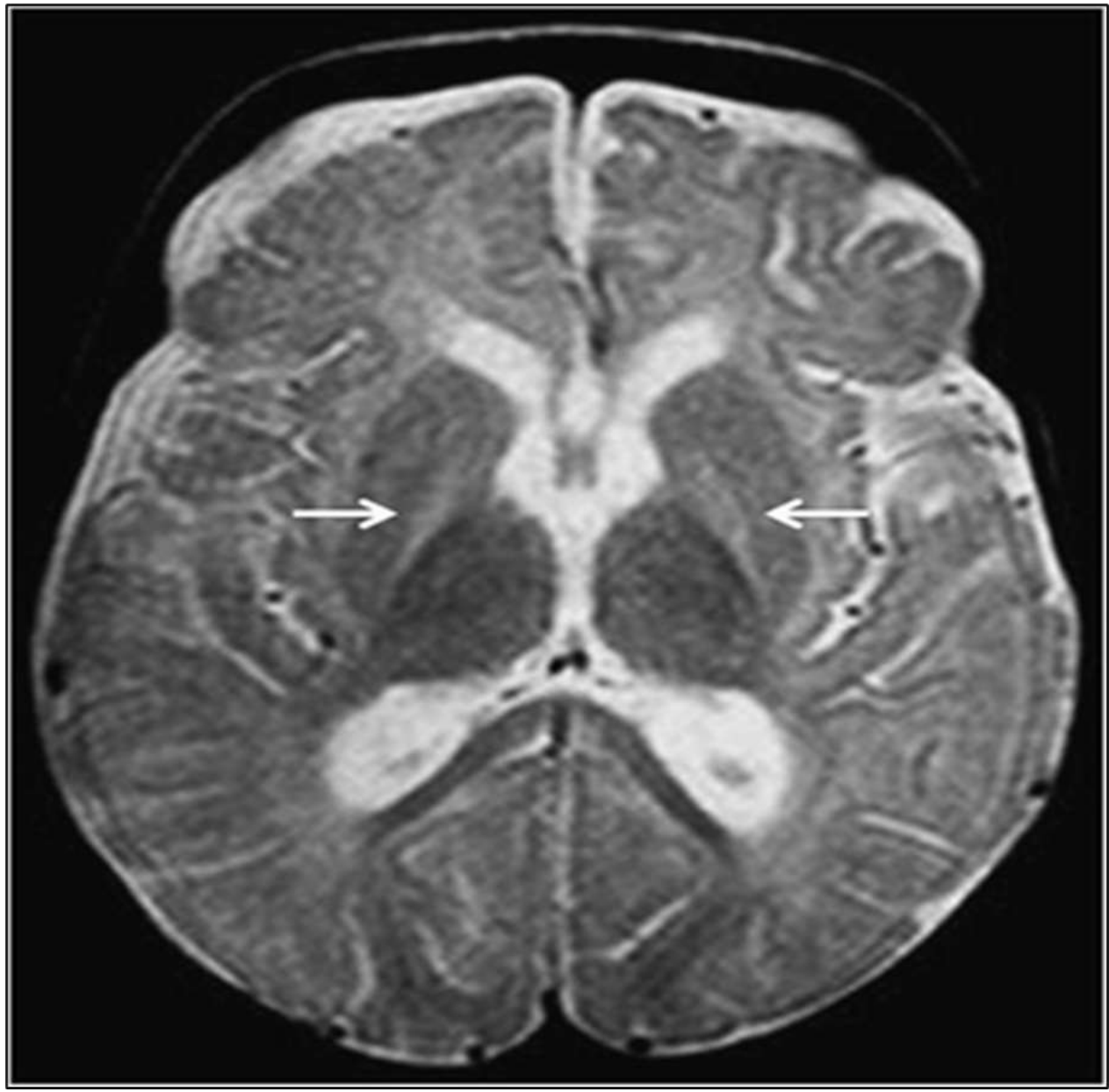
ketogenic diet



- A 14-year-old boy presented with history of prematurity born at 30-weeks. hospitalization in the neonatal intensive care, no reported hyperbilirubinemia .

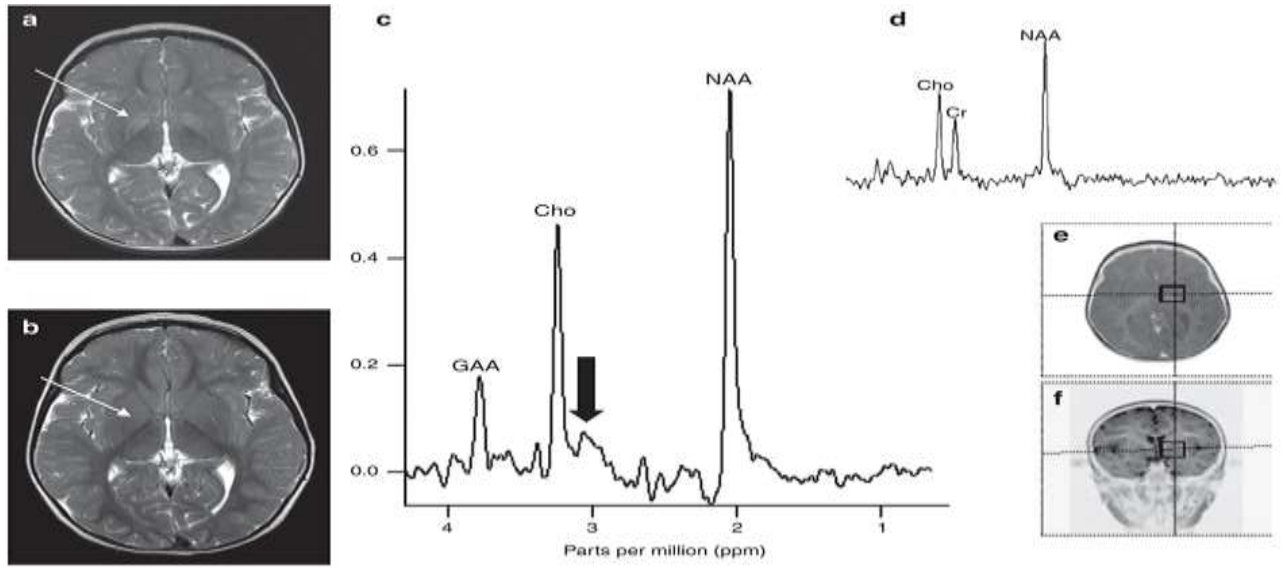
- He has severe dystonia, and ***diagnosed as severe infantile onset dystonic cerebral palsy due to prematurity.***

- The family history was significant for a maternal history of ocular migraine headaches and a maternal aunt with intractable epilepsy.
- A case confirmed as MELAS

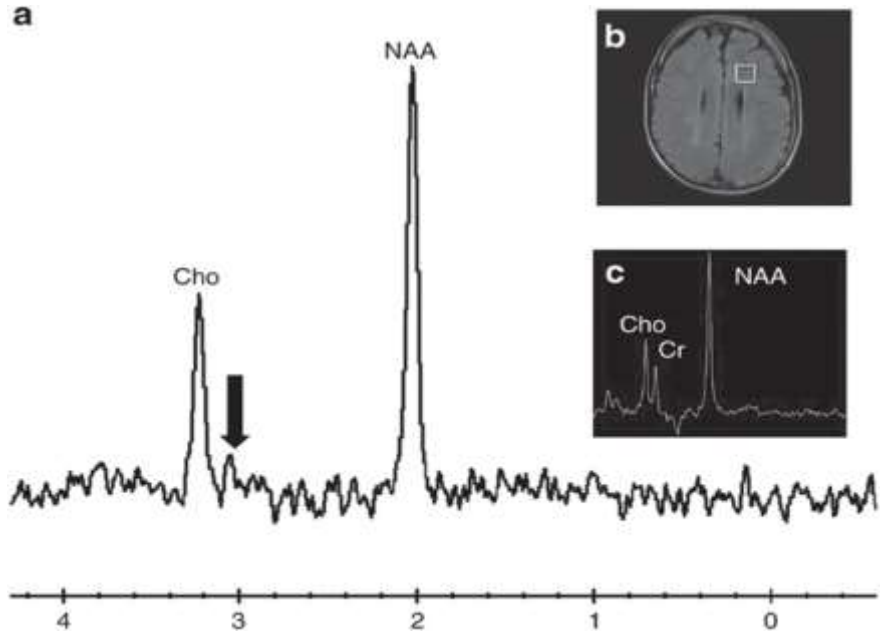


Cerebral creatine deficiency syndromes (CCDS)

- Cerebral creatine deficiency syndromes are a group of the creatine synthesis and transport with 3 recognized syndromes: arginine, glycine amidino transferase(AGAT). Guanidinoacetate methyltransferase (GAMT) def, transporter
- Patients typically present with an intellectual disability, severe speech delay, seizures, ataxia dystonia and/or chorea.
- Low Creatine in urine, elevated GAA
- The brain MRI is usually nonspecific; may cause GP hyper-intensities
- Treatment with oral creatine(not usually effective in CTD)



	AGAT	GAMT	CTD
Blood creatine	Low	Low	Normal
Blood creatinine	Low	Low	Normal
Blood GAA	Low	High	Normal
Urine creatine	Low	Low	Normal to high
Urine creatinine	Low	Low	Normal
Urine GAA	Low	High	Normal



Diagnostic Evaluation of the Child with Cerebral Palsy

Disorders with prominent spasticity	Disorders with prominent dyskinesia	Disorders with prominent ataxia
- Hereditary spastic paraglegias - Arginase deficiency - COL4A1-Related spastic CP - Biotinidase deficiency - Aicardi-Goutières syndrome - Sulfite oxidase deficiency/ Molybdenum cofactor deficiency[22] - Leukodystrophies, such as metachromatic leukodystrophy,[23] adrenoleukodystrophy,[24] Sjo Larsson syndrome[25]	- Dopa-responsive dystonia - Sepiapterin reductase deficiency - Glutaric aciduria type 1 - Glucose transporter deficiency type 1 - Neurodegeneration with brain iron accumulation - Cerebral creatine deficiency syndrome - Lesch Nyhan syndrome - Cerebral folate deficiency - ADCY5-related dyskinesia PCDH12-related dyskinesia[34] - NKX2-1 related ataxic dyskinetic - TSEN54 Gene-related pontocerebellar hypoplasia type 2[36]	- Glucose transporter deficiency type 1 - Ataxia telangiectasia - Pelizaeus-Merzbacher disease - Hereditary ataxias - Joubert syndrome - Mitochondrial cytopathies (mainly 8993 mutation)[42] - Pontocerebellar hypoplasia[36] - Cockayne syndrome[43] - Niemann-Pick disease type C[44] - Angelman syndrome[12] - Gangliosidosis type 1 , juvenile and adult forms[45] - Non-ketotic hyperglycinemia[3] - Maple syrup urine disease[3] - NKX2-1 related ataxic dyskinetic CP[35]

CP- cerebral palsy

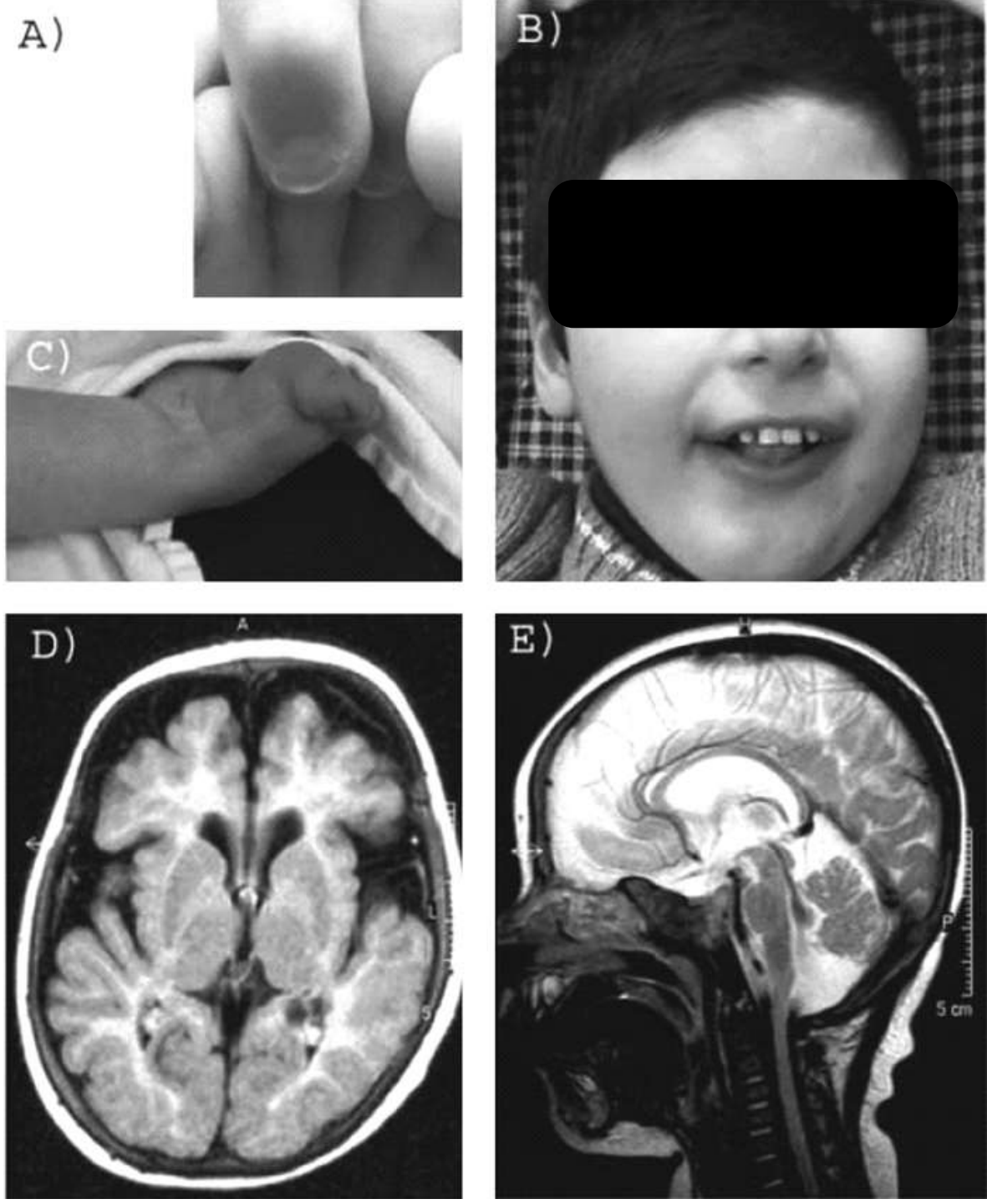
A 17-month-old male was born at term gestation.

He presented with dysmorphic facial features, sacral dimple, hypospadias, pes planus, developmental delay, and subacute onset of falls secondary to an unsteady gait

Congenital Disorders of Glycosylation

MR-imaging typically shows a small hypoplastic cerebellum, including the vermis and both hemispheres

- Transferrin affinity chromatography by mass spectrometry showed an unusual glycoform variant
- Genetic testing:



Angelman syndrome

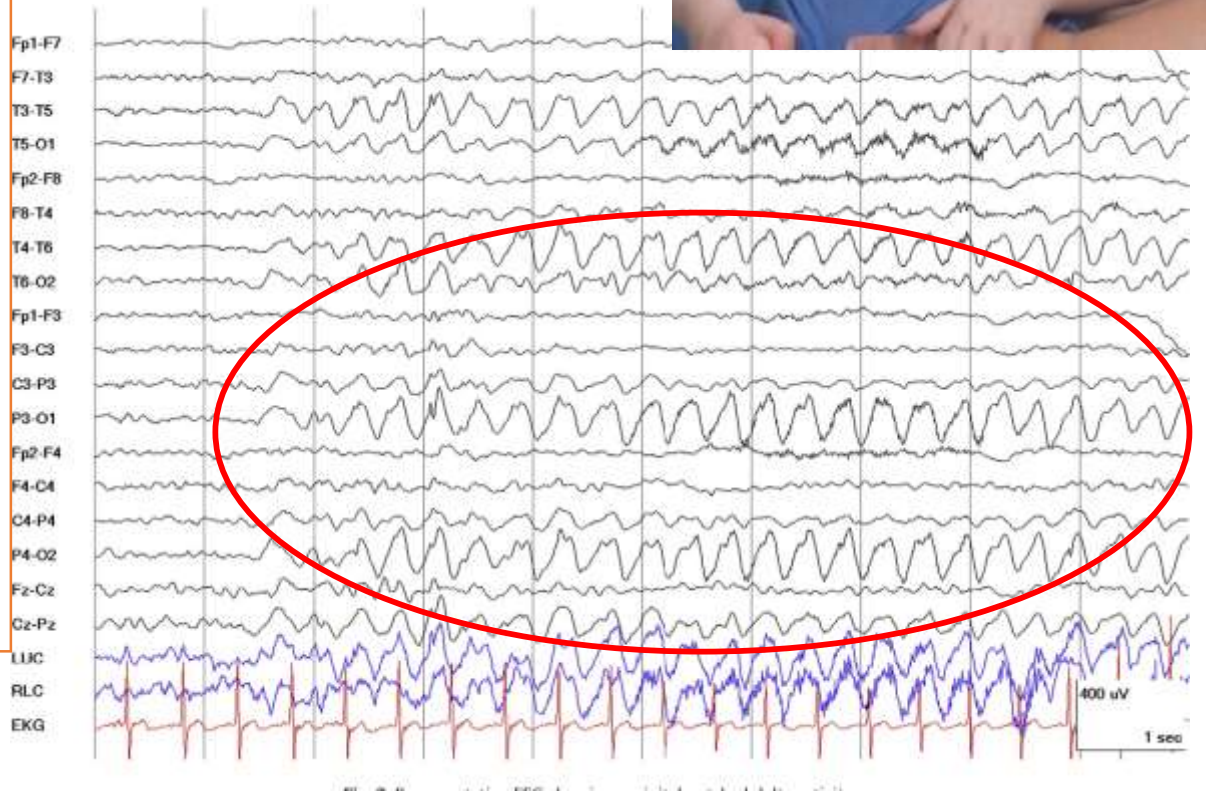
- 6-year-old boy, DD .
- He was born at term with no reported postnatal complications

- Seizures-started to have frequent limbs jerk and prolong staring since infantile period; MRS
- Infantile onset spasticity in lower extremities, truncal ataxia and intellectual disability. Feeding difficulties, microcephaly and GDD.

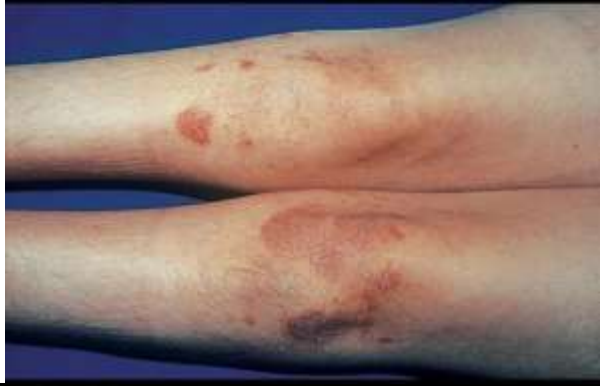
At one year of age he was diagnosed with ataxic CP. Language impairment was profound.

Brain MRI; mild loss of brain volume

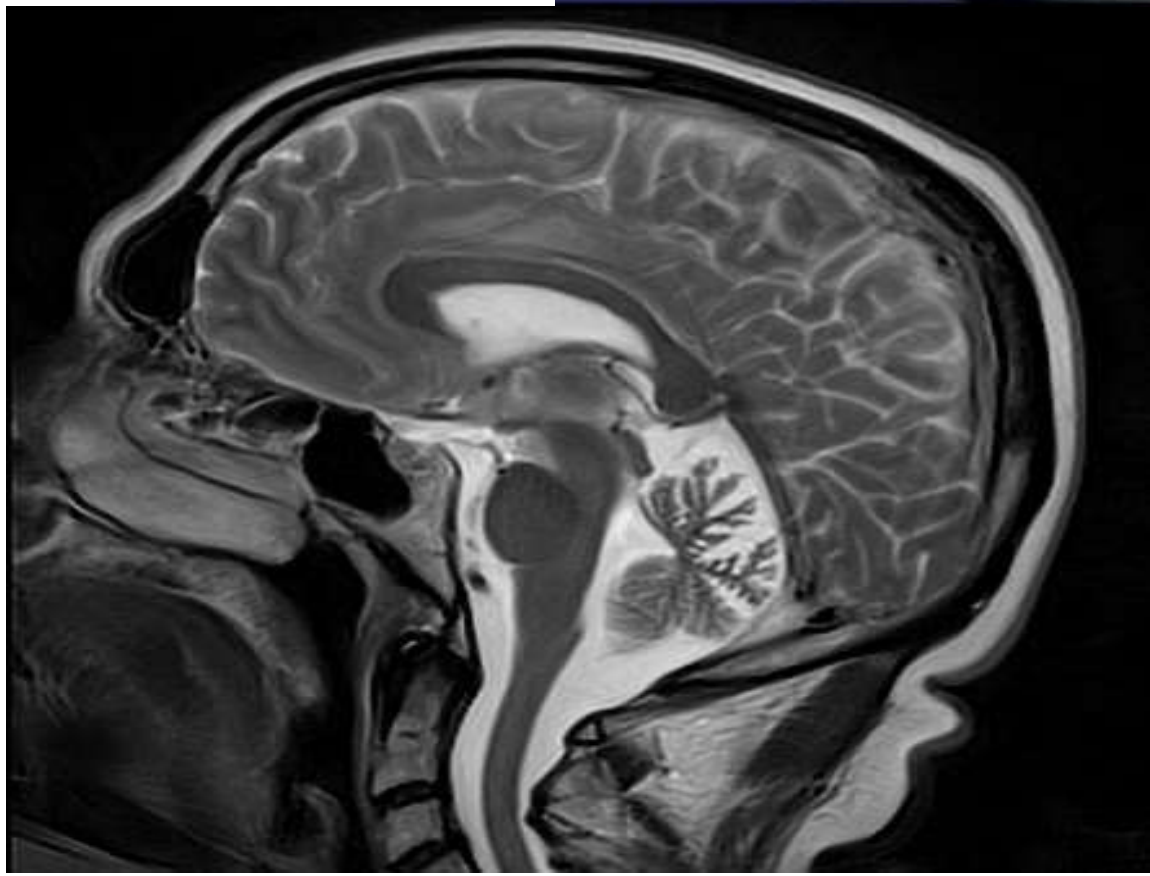
Diagnosed as Ataxic CP



Ataxia telangiectasia



- AR
- Mutations in the ATM gene.
- Multisystem neurodegenerative and immunodeficiency disorder.
- Progressive cerebellar ataxia,
- Oculomotor apraxia, oculocutaneous telangiectasia, sinopulmonary infections
- Radiosensitivity, early aging, and increased incidence of cancer



Key points

- ✓ Careful clinical history taking.
- ✓ Skin rashes in CP might be an important clinical feature.
- ✓ Clinical examination alone is often insufficient for identification of an aetiology of CP.
- ✓ low serum levels of uric acid may provide diagnostic clues in patients with cerebral palsy of undetermined cause.
- ✓ Urine sulphite in case of HIE pictures in MRI with no clear HIE injury
- ✓ Thyroid dysfunction in boys with CP-mimic
- ✓ Ophthalmology assessment and follow ups is to be included in assessment of any child who presented with GDD.
- ✓ Every genetic test has it is own limitations
- ✓ In patient with dyskinesia or spastic diplegia of unknown aetiology, a trial of L-Dopa points toward this diagnosis and merits further diagnostic assessment.
- ✓ CP is best considered a descriptive, rather than a diagnostic label, better to be consider as a syndrome with an underlying primary aetiology that has to be looked for in every case.

That’s why I chose to present this topic.

- CP is an old clinical descriptive term however, etiological diagnosis of CP is an area of ongoing discoveries
- That CP is not easy to diagnose since accurate diagnosis can be challenging to even an experience neurologist
- The topic is not boring, and the knowledge is diverse
- Someone can argue that regardless of the knowledge the disease is unfixable ; the answer will be having an accurate diagnosis can alter the outcome, prevent further damage , and in some cases ‘’reversed’’ the presumed insult