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

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG , Chorea and HD‘
13. October 2020

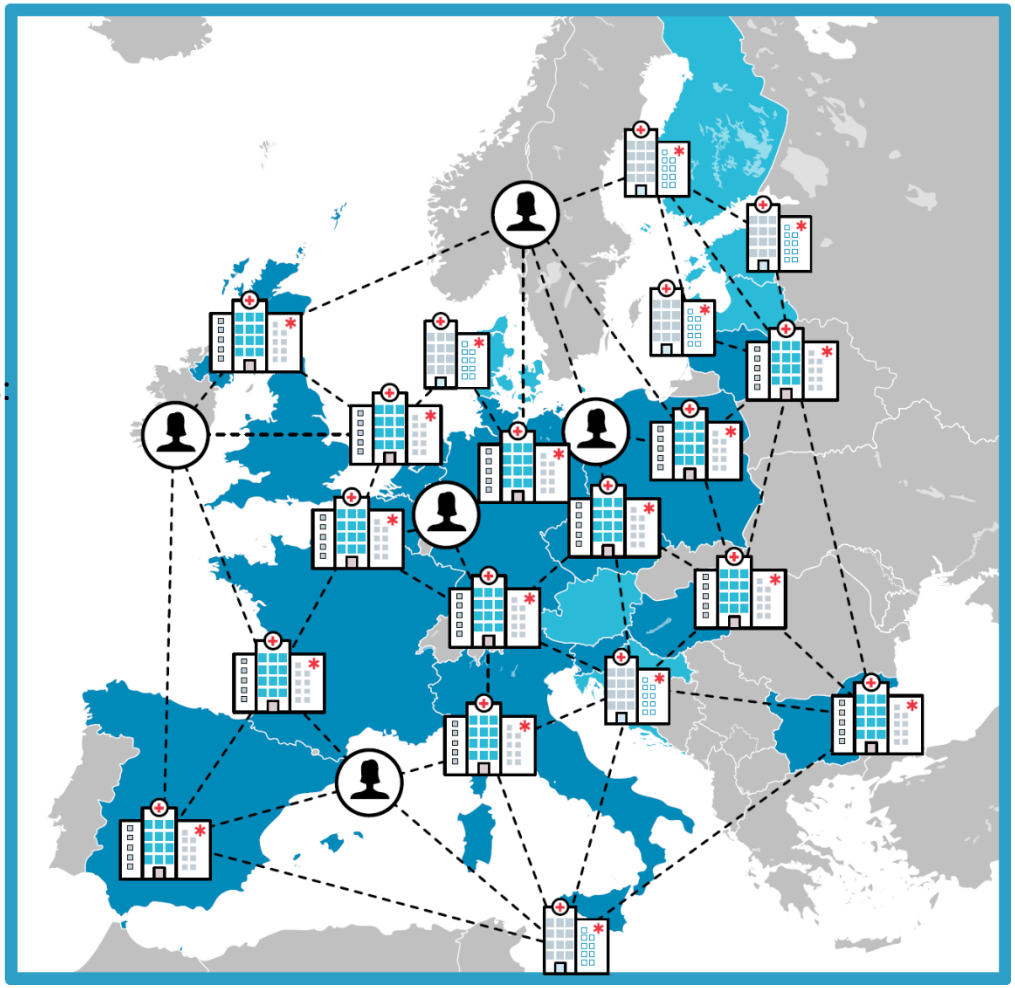
Joint webinar series

‘Diagnostic algorithm for childhood onset chorea‘ by Juan Dario Ortigoza-Escobar

Sant Joan de Déu Hospital, Barcelona, Spain

European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members**
- **Countries with Affiliated Partners**



ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

General information about the webinars

- Focus on : RARE neurological, neuromuscular and movement disorders
- 40-45min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- Further information: http://www.ern-rnd.eu/disease-knowledge-hub/ataxia/
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

ePAG: european Patient Advocacy Groups

Astri Arnesen

President of the European Huntigton Association

In ERN-RND Patient Advocate forthe DG ‘**Chorea and HD**‘

Speaker: Juan Dario Ortigoza-Escobar

Position: Consultant Child Neurologist, Head of Movement Disorders Unit

Affiliation (since 2017): Movement Disorders Unit, Pediatric Neurology Department, Hospital Sant Joan de Déu, Universidad de Barcelona

Training: Pediatric (Paraguay) and Pediatric (Barcelona) and Child Neurology (Barcelona)

Research focus: childhood onset movement disorders with special interest in choreas, thiamine responsive disorders and deep brain stimulation

What is your professional background?

a) Neurologist
b) Neuropediatrician
c) Neurology resident
d) Psychiatrist
e) Nurse
f) Physiotherapist
g) Geneticist
h) Patient or patient representative
i) Pediatrician
j) Other

Webinar outline

- Chorea
  - Definition, pathophysiology and physical examination
  - Diagnostic algorithm
    - Acquired causes
    - Genetic causes
      - Inborn errors of metabolism
      - Epileptic encephalopathies
      - Other genetic causes
  - Treatment

Learning objectives

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

- discuss the **clinical features** of chorea
- identify the commonest causes of **acquires and genetic chorea**
- recognize the sign as part of **inborn errors of metabolism** and **epileptic encephalopathies**
- **outline the genetic approximation** in a child with suspected genetic chorea

Definition

- **Chorea** consists of involuntary, continual, abrupt, rapid, brief, irregular movements that flow randomly from one body part to another
- Movements appear random due to variability in **timing, duration, direction, or anatomic location**
- Chorea can **partially** or temporarily be suppressed
- Chorea can involve trunk, neck, face, **tongue**, and **extremities**
- Chorea frequently can be camouflage by incorporating some of the movement into semipurposeful activities (**parakinesia**)
- The patients describe chorea as "***clumsiness***", "***motor impersistence***" or by reason of its effects "***frequent falling of objects from the hands***"

Sanger et al. Mov Disord. 2010 August 15; 25(11): 1538–1549.

Definition

- **Ballism** mainly affects proximal joints such as shoulder or hip leading to to large-amplitude movements of the limbs

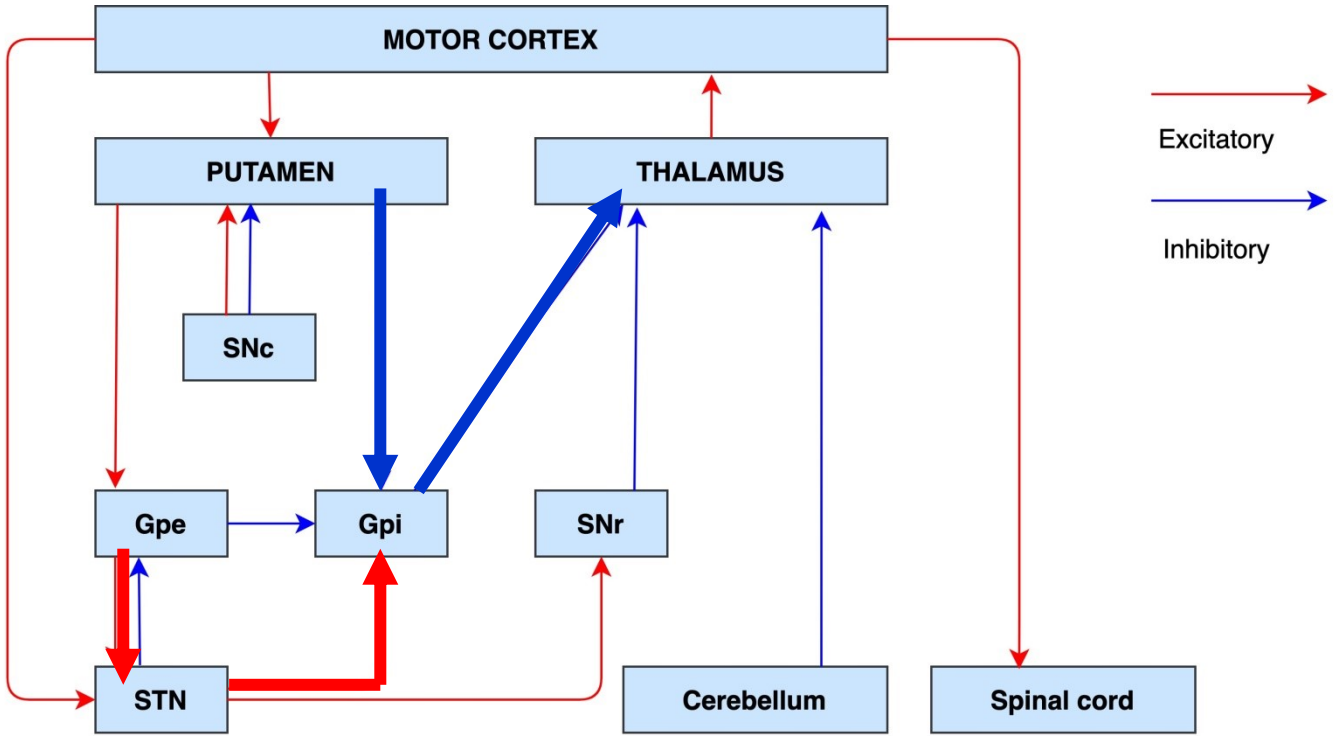
- **Athetosis** is a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture. Athetosis involves continuous smooth movements that appear random and are not composed of recognizable sub-movements or movement fragments

- **Chorea, athetosis and ballism** may overlap in the same patient and cannot be differentiate as mutually exclusive phenomena

Sanger et al. Mov Disord. 2010 August 15; 25(11): 1538–1549.

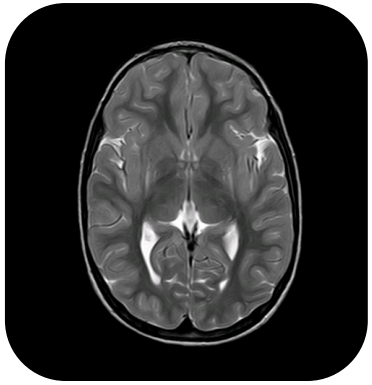
Pathophysiology of Chorea

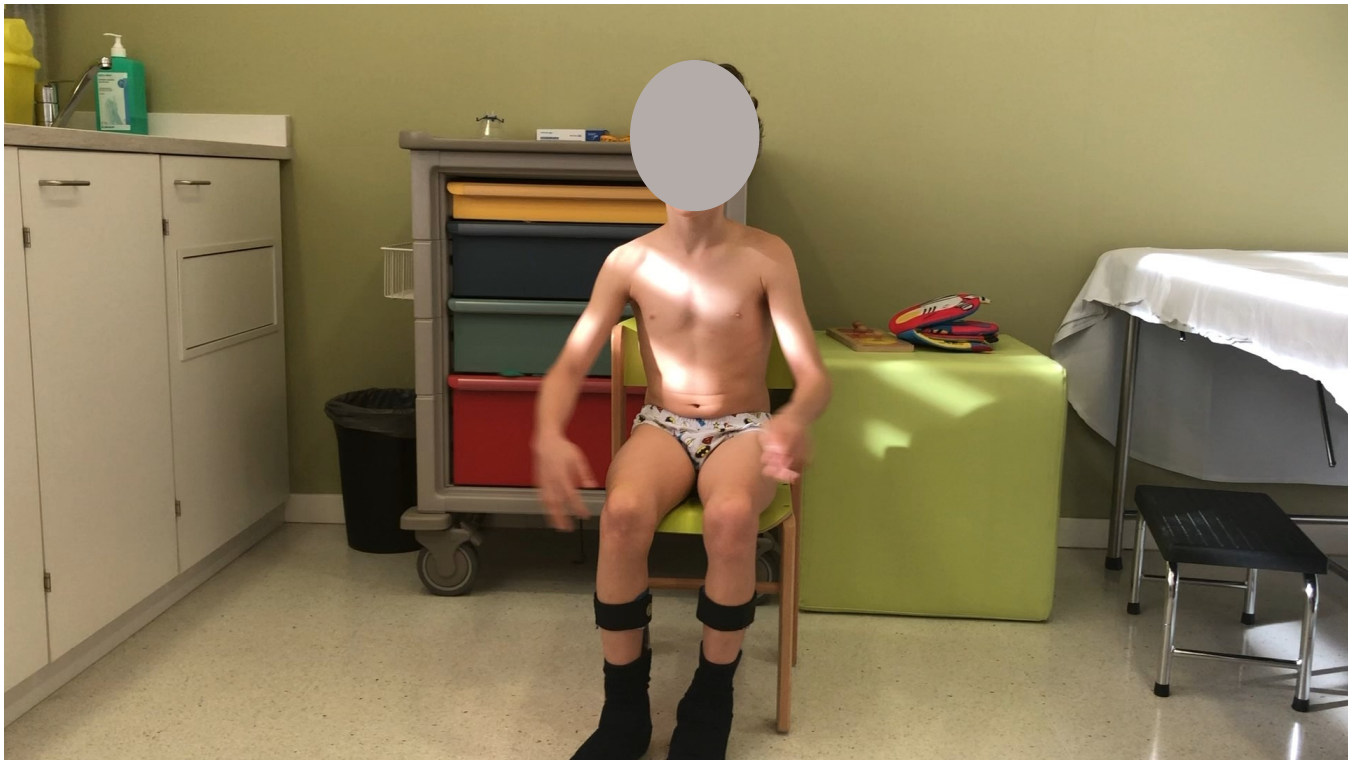
- Chorea is associated with disorders of the **cerebral cortex, basal ganglia, cerebellum,** and **thalamus.**



Physical examination

- **Spooning sign**
- Touchdown sign
- Darting tongue
- Milkmaid´s grip





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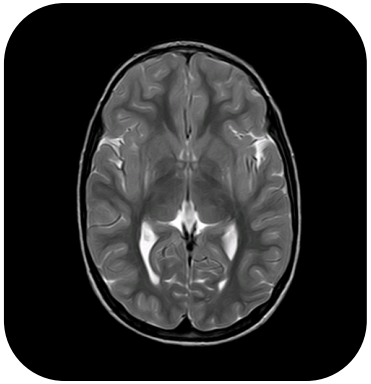

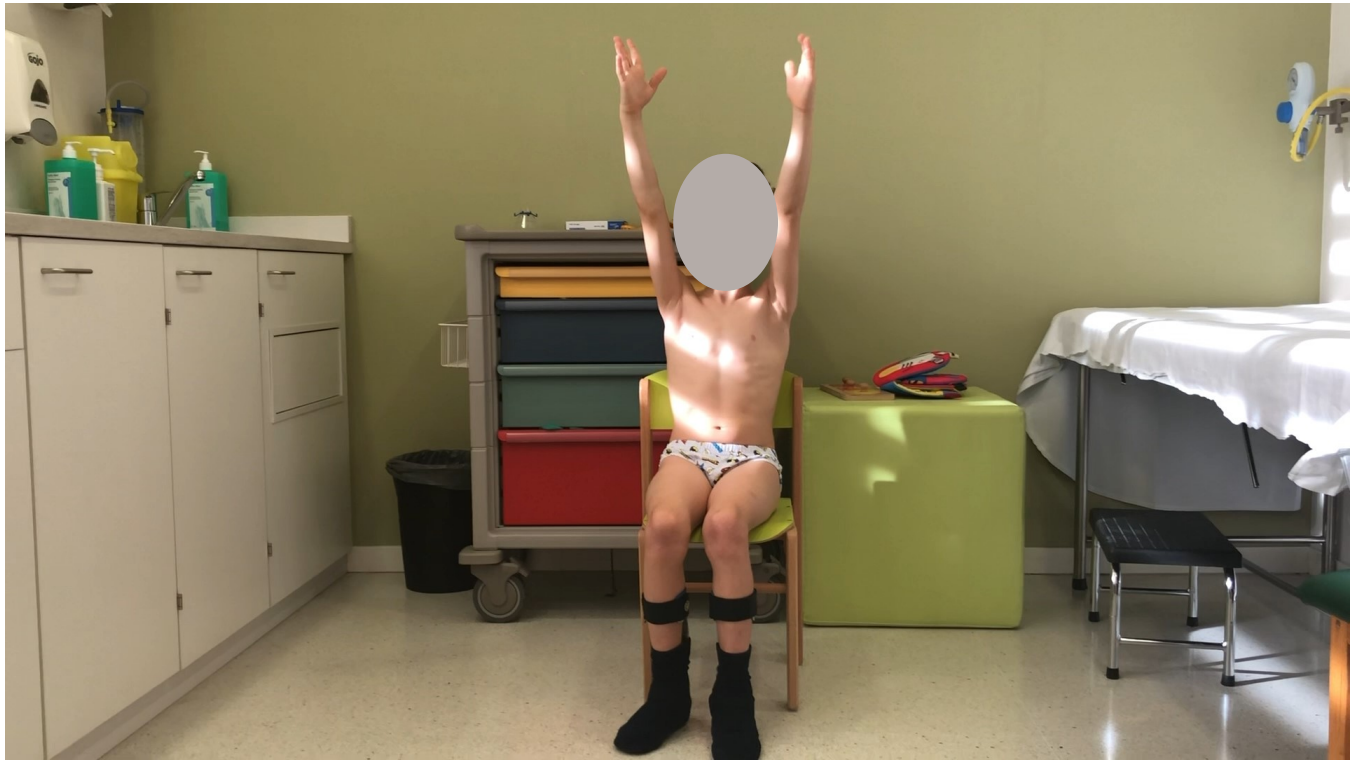

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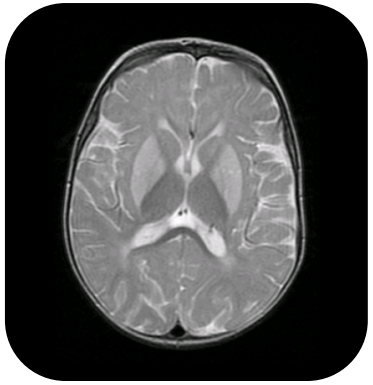

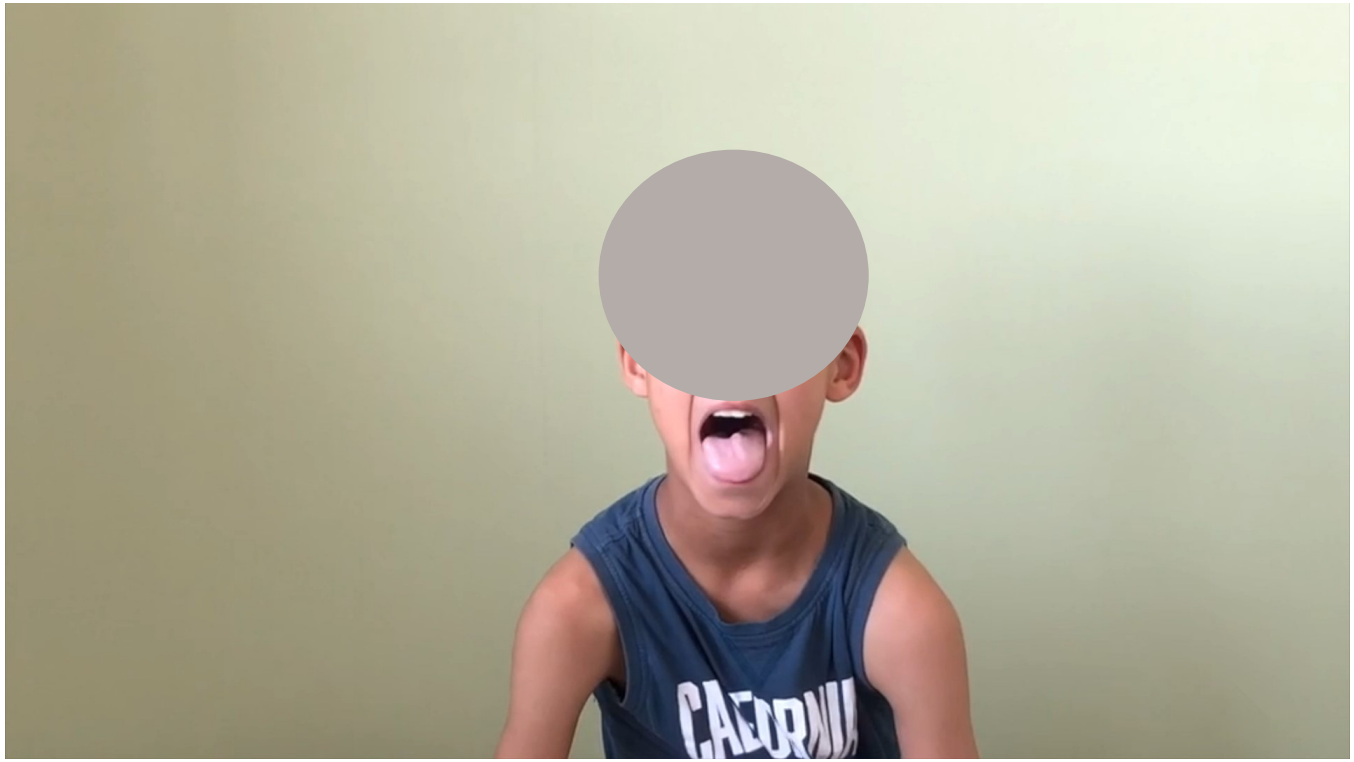

Duration – Paroxysmal chorea

Paroxysmal MD associated genes

ATP1A3
ATP1A2
ADCY5
CACNA1A
CACNB4
DLAT
GCH1
GNAO1
KCNA1
KCNMA1
KCNQ2
PDHA1
PNKD
PARKIN
PRRT2
SCN1A
SLC2A1
SLC1A3
SCN2A
SCN8A
SGCE
SLC2A1

VIP CLUES

Duration – Paroxysmal chorea

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VIP CLUES

ERN-RND and ERN-EuroNMD webinar: Paroxysmal dyskinesias: Giovanna Zorzi

12 May 2020, 2:00 pm–3:00 pm

Multiple choice questions – 1

- Which of the following is **NOT** a cause of hemichorea?

a) Hyperglycemia

b) Sydenham chorea

c) Varicella Zoster vasculopathy

d) Oral contraceptives

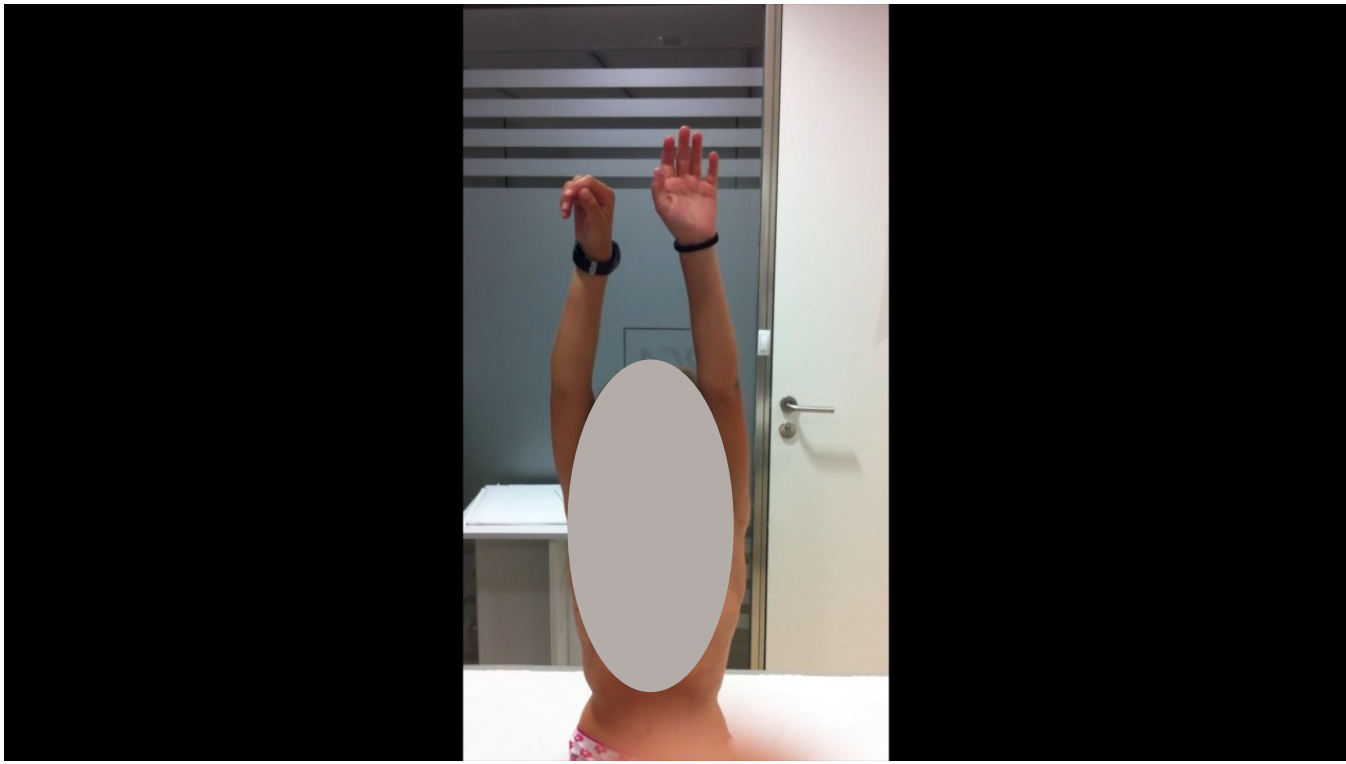
e) All of the above causes hemichorea

Distribution - focal / hemicorea

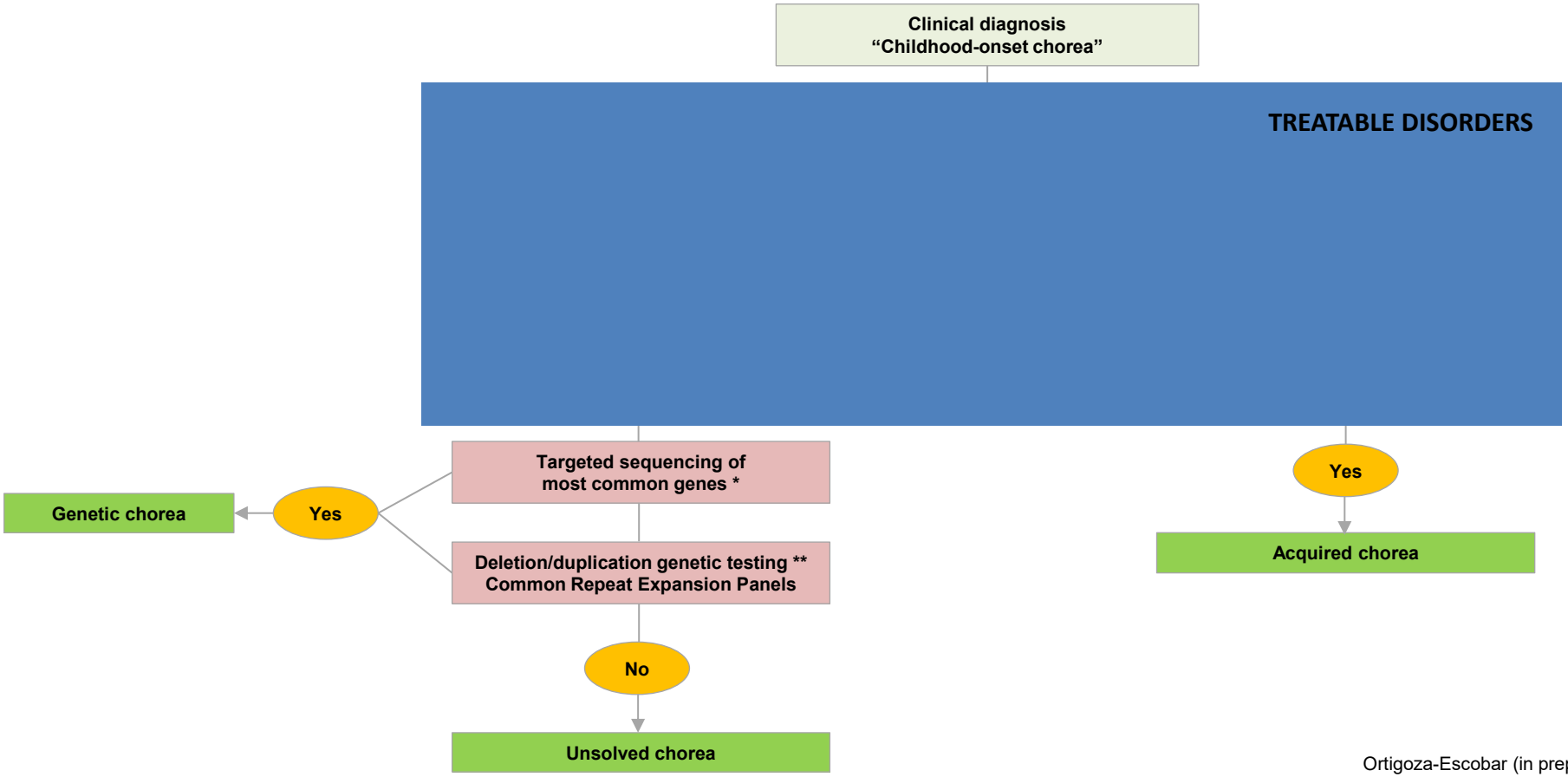
Hemichorea

Non-ketotic hyperglycemia
Sydenham chorea
Post-pump
Lupus/antiphospholipid
Churg-Strauss syndrome
antiNMDAr encephalitis
Tuberculosis
Enteric fever
Varicella Zoster vasculopathy
Mumps
Cerebral cysticercosis
Moya-Moya
Stroke
Cerebral vasculitis
Brainstem glioma
Basal ganglia/thalamic astrocitomas
Caudate cavernous angioma
Oral contraceptives
Wilson disease

VIP CLUES



Chorea



Ortigoza-Escobar (in preparation)

* Single gene targeted, multigene targeted (TruSightOne (analyses 63/77 chorea-related genes) or Expanded TruSightOne (analyses 72/77 chorea-related genes) sequencing), WES, WGS
** quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), ArrayCGH or gene-targeted microarray

Acquired Chorea

Chorea

Acquired chorea [5]

4 Structural / basal-ganglia lesions

Athetotic cerebral palsy
Bilirubin encephalopathy (kernicterus)
Extrapontine myelinosis
Mass lesions (tumors)
Malformation of cortical development (e.g.. holoprosencephaly, etc)
Post cardiac surgery
Vascular chorea (Moya Moya disease stroke)

3 Parainfectious and autoimmune

Acute necrotizing encephalitis
Antiphospholipid antibody syndrome
Chorea gravidum
NeuroBehçet disease
NMDAr encephalitis
Multiple sclerosis/**ADEM**
Paraneoplastic chorea
Postinfectious or postvaccinal
Sydenham's chorea
Systemic lupus erythematosus
CNS vasculitis

2 Infectious chorea

Bacterial endocarditis
Cysticercosis
Diphtheria
EBV/CMV infection
HSV encephalitis
HIV encephalopathy
Legionella
Lyme disease
Mycoplasma
Syphilis
Parvovirus B19
Scarlet fever
Toxoplasmosis
Viral encephalitis (mumps, measles, varicella)

3 Metabolic or toxic

Hepatic/renal failure
Hypocalcemia
Hypo/hyperglycemia (Diabetes-Related Chorea)
Hypo/hypernatremia
Hypoparathyroidism
Hyperthyroidism
Poisoning (Bismuth, carbon monoxide, manganese, methanol, mercury, organophosphate, thallium, toluene)
Vitamin B12 deficiency

1 Drug induced chorea

Dopamine receptor blocking agents
Phenothiazines
Butyrophenones
Benzamides
Antiparkinsonian drugs
L-dopa
Dopamine agonist
Anticholinergics
Antiepileptic drugs
Phenytoin
Carbamazepine
Valproic acid
Phenobarbital
Psychostimulants
Amphetamines
Cocaine
Calcium-channel blockers
Cinnarizine
Flunarizine
Verapamil
Others
Azithromycin
Baclofen
Cyclosporine
Digoxin
Lithium
SSRIs
Steroid/oral contraceptives
Theophylline
Tricyclic antidepressants

*** Laboratories studies:**

- CBC, ESR, CRP, glucose, blood gases, electrolytes, calcium, phosphate, PTH, TSH, FT4, T3, ALP, B12, ASLO, ANA, Anti-dsDNA, antiphospholipid antibodies, hCG pregnancy test
- LP: routine (protein, glucose, cell count/differential, GRAM staining, culture), IgG index, OCB, antineuronal antibodies (antiNMDAr, MOG, Anti-neurochondrin, LGI1, GABAB, Autoantibodies, etc).
- Consider 1) infectious testing, 2) prothrombotic risk factors testing (factor V Leyden, protein C, protein S, lipoprotein(a), antithrombin III, prothrombin gene mutation, homocysteine/MTHFR gene mutation and 3) heavy metal and drug screening based on clinical scenario

**** EKG**
***** MRI brain w/ and without gad**
****** Cardiac evaluation** if Sydenham's chorea is suspected

Ortigoza-Escobar (in preparation)

Structural basal-ganglia lesions

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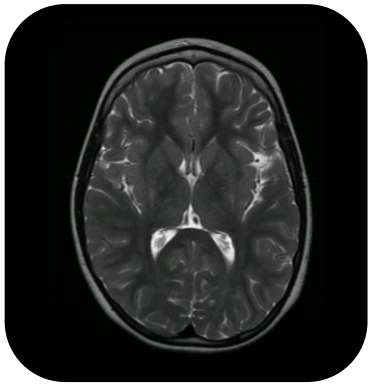

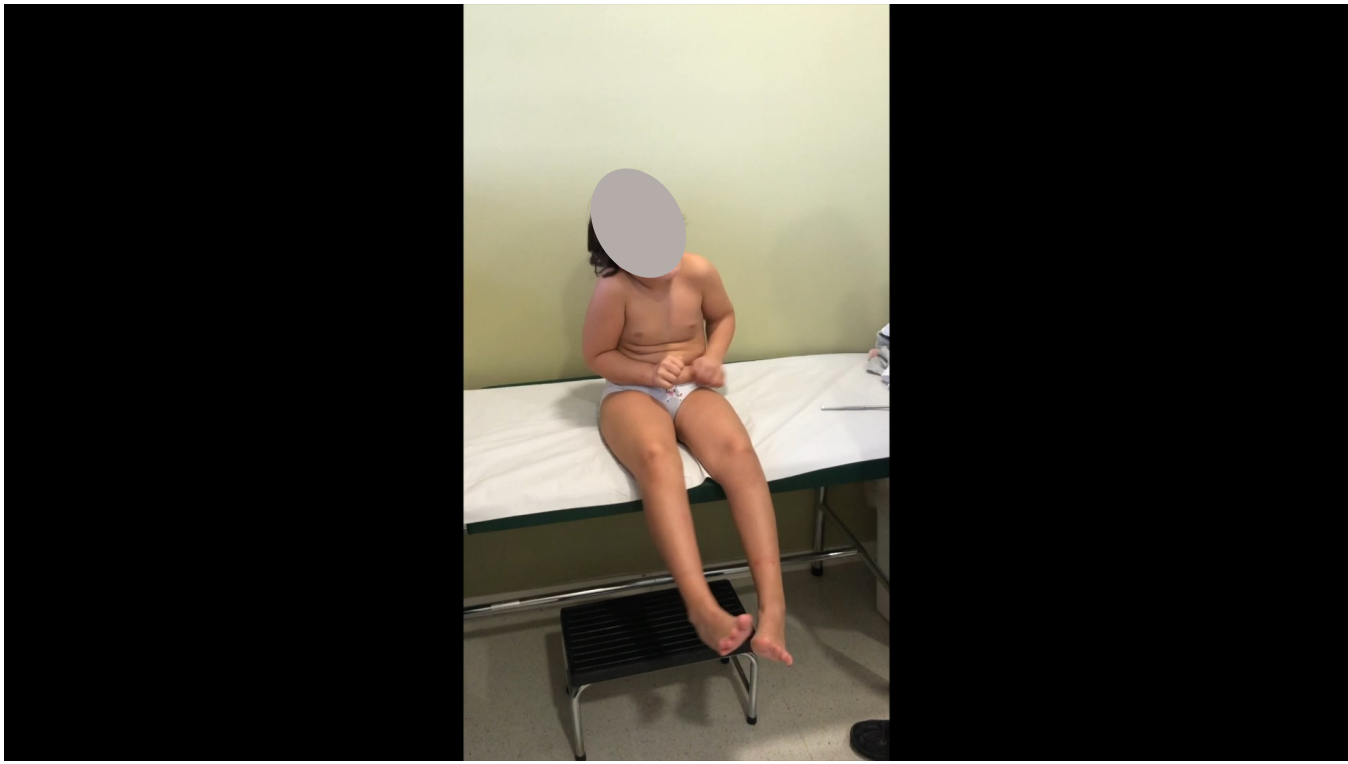

Dyskinetic CP accounts for about 2-5% of all CP cases.

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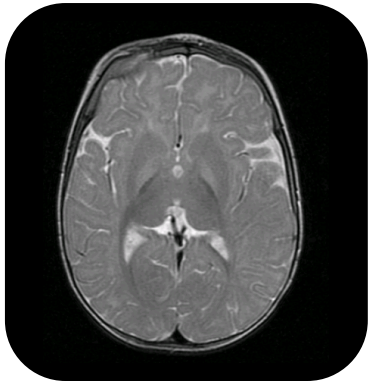

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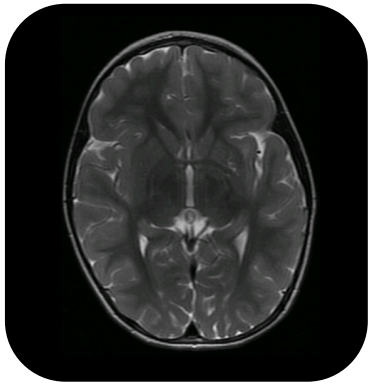

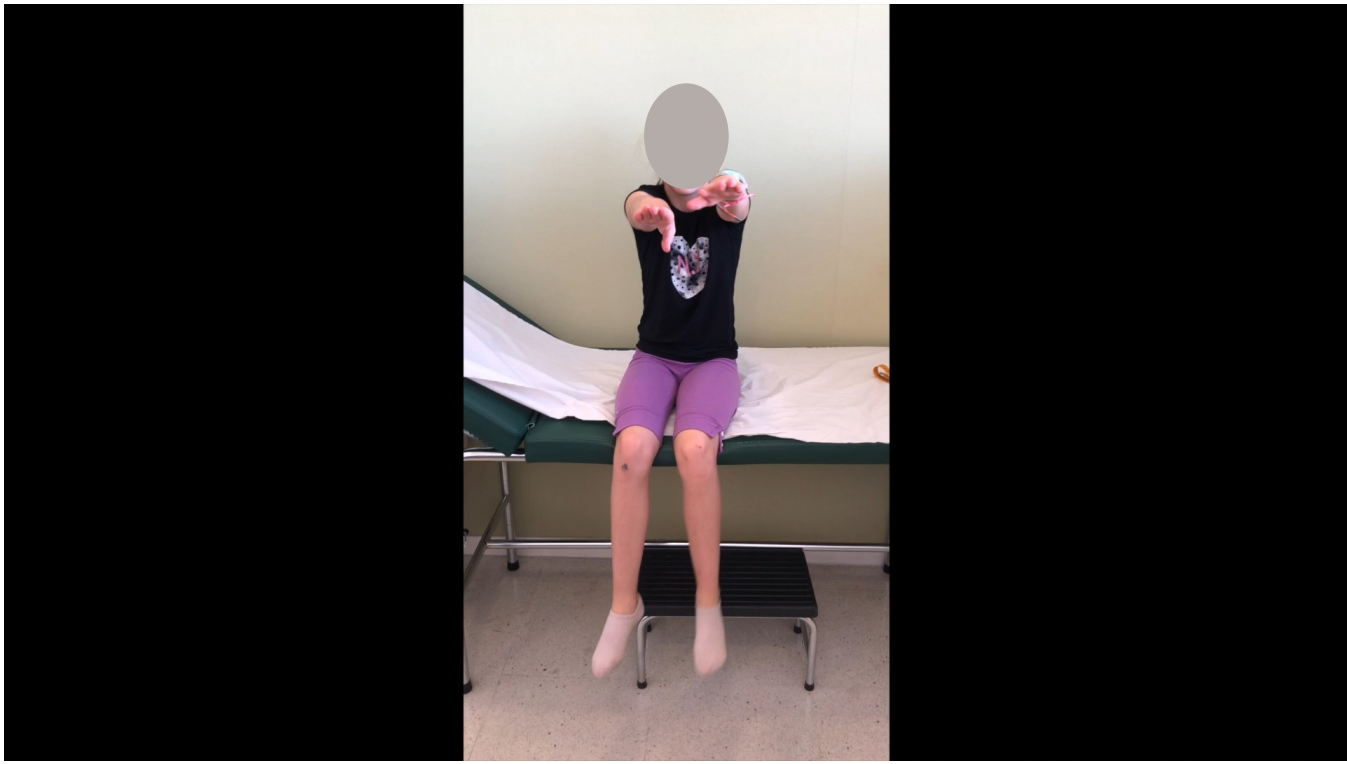

Parainfectious and autoimmune

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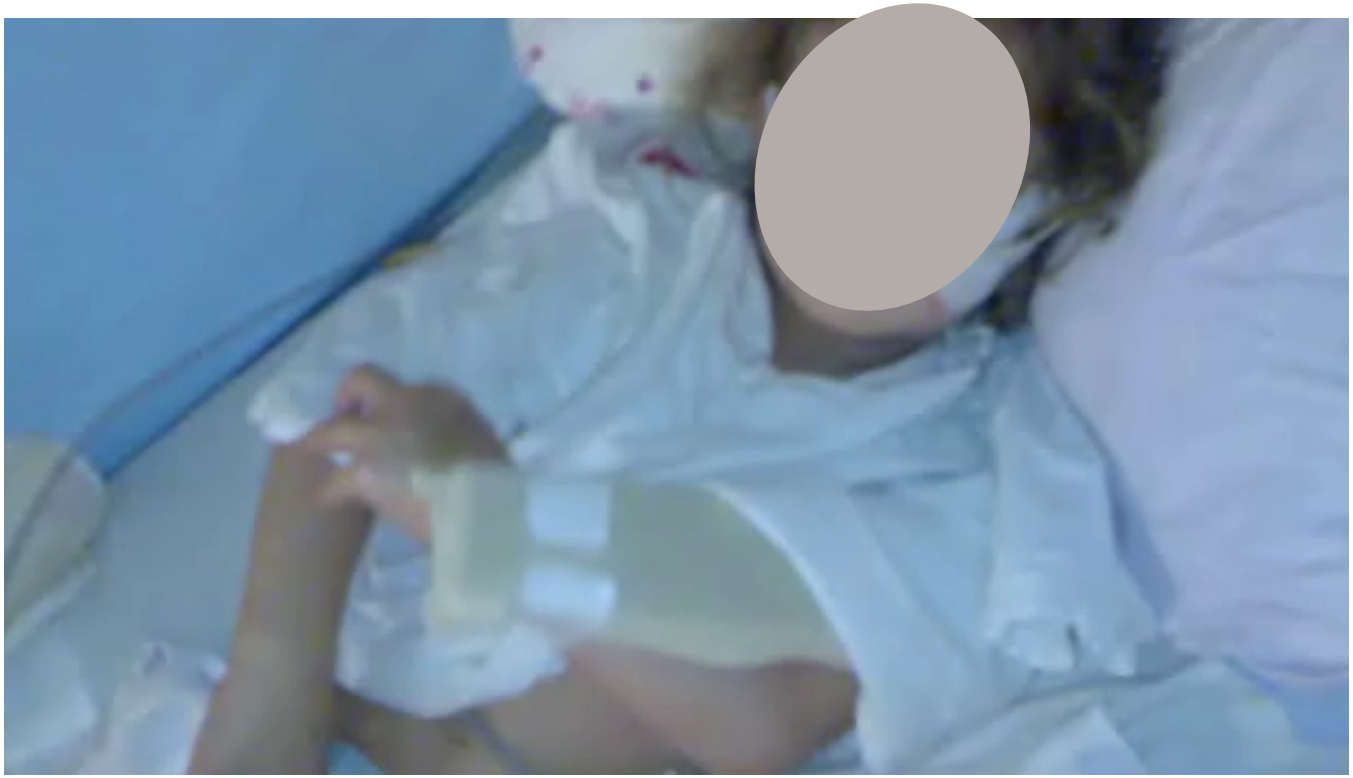
Antiphospholipid antibody syndrome
Chorea gravidum
NeuroBehçet disease
NMDAr and autoinmune encephalitis
ADEM
Paraneoplastic chorea
Postinfectious or postvaccinal
Sydenham's chorea
Systemic lupus erythematosus
CNS vasculitis



** Courtesy of Dr. Armangué*

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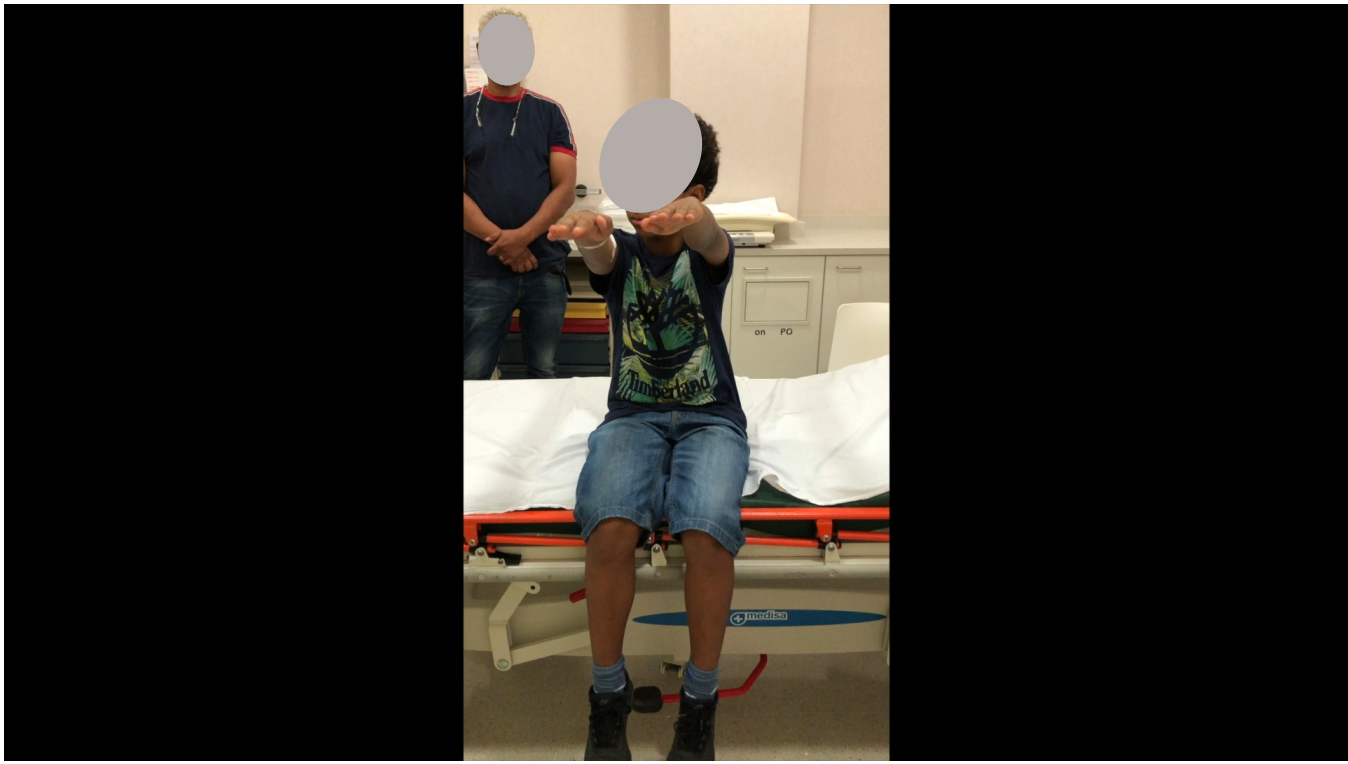

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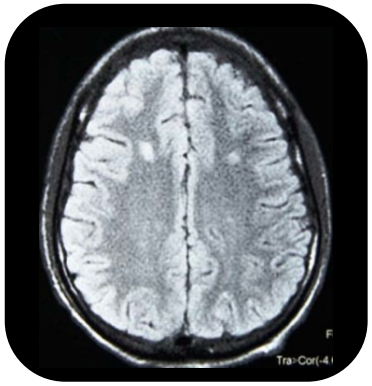

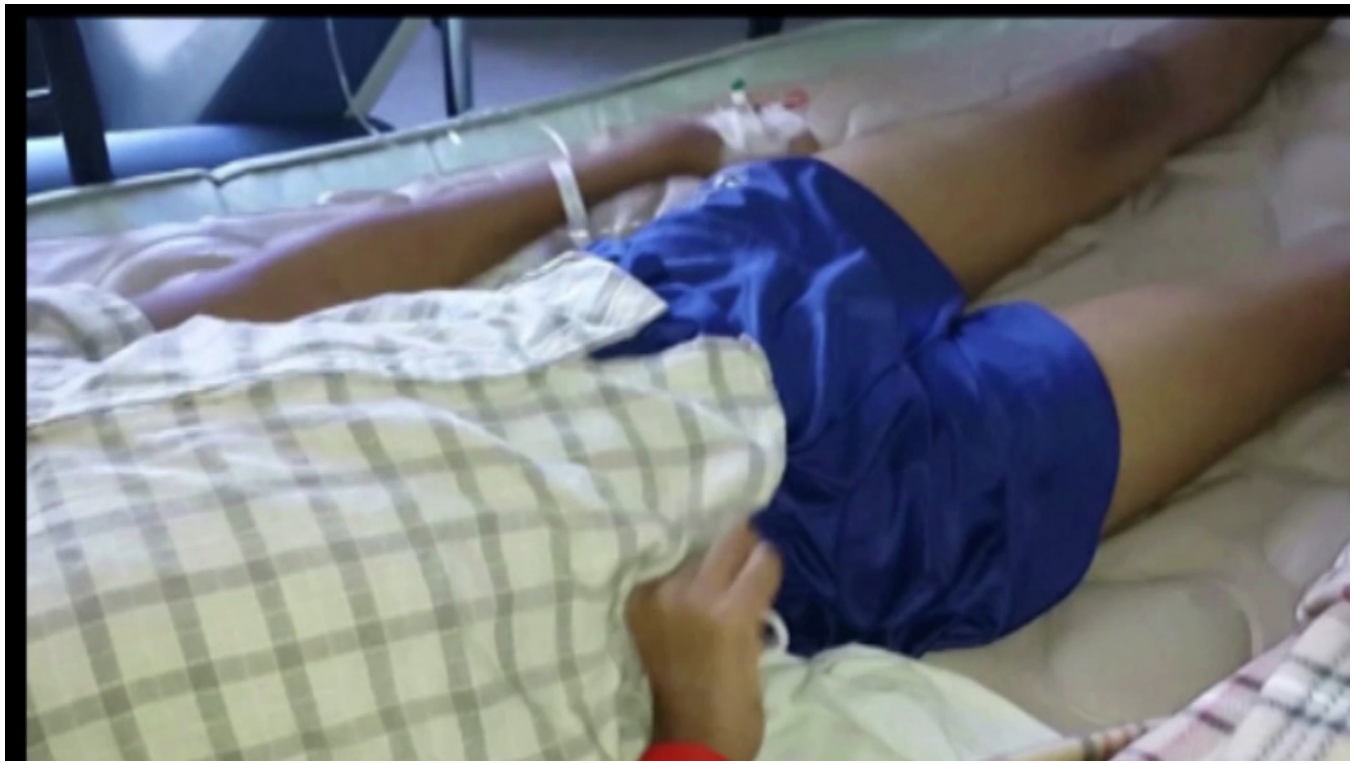

Ramcharan et al. BMJ Case Rep. 2015 May 7;2015:bcr2014209201.

Genetic Chorea

Chorea

Genetic chorea [4]

1 Epileptic encephalopathies

Epileptic encephalopathy, early infantile, 1 – *ARX*
Epileptic encephalopathy, early infantile – *SCN2A*, *KCNQ2*, Seizures, benign neonatal – *KCNQ2*, *KCNQ3*
Epileptic encephalopathy, early 29 – *AARS*
Epileptic encephalopathy, early 17 – *GNAO1*
.....

2 Inborn error of metabolism

Cerebral creatine deficiency - *SLC6A8*
HSD10 mitochondrial disease - *HSD17B10*
Lesch-Nyhan syndrome - *HPRT1*
Menkes disease – *ATP7A*
Methylmalonic acidemia and homocysteinemia, cblX type - *HCFC1*
Pyruvate dehydrogenase E1-alpha deficiency – *PDHA1*
Neurodegeneration with brain iron accumulation – *FTL, PLA2G6*
Optic atrophy 3 with cataract – *OPA3*
2,4-dienoyl-CoA reductase deficiency – *NADK2*
3-methylglutaconic aciduria, type III – *OPA3*
Aceruloplasminemia – *CP*
Aromatic L-amino acid decarboxylase deficiency – *DDC*
Xeroderma pigmentosum – *XPA, ERRC2* and *ERCC6*
Wilson disease – *ATP7B*
Sulfite oxidase deficiency – *SOUX*
Neurodegeneration with brain iron accumulation – *PANK2*
Parkinsonism-dystonia, infantile - *SLC6A3*
Metachromatic leukodystrophy - *ARSA*
Methylmalonic aciduria, mut(0) type – *MUT*
Mitochondrial DNA depletion - *FBXL4* and *POLG*
Multiple congenital anomalies-hypotonia-seizures syndrome 1 - *PIGN*
Combined oxidative phosphorylation deficiency 13 - *PNPT1*
Glutaric aciduria, type I - *GCDH*
Hyperphenylalaninemia, BH4-deficient – *QDPR* and *PTS*
Leukodystrophy, hypomyelinating and Spastic paraplegia – *GJB2, HSPD1*
Muscular dystrophy, limb-girdle, type 2S - *TRAPPC11*
Pyruvate dehydrogenase E2 deficiency – *DLAT*
Salt and pepper developmental regression syndrome - *ST3GAL5*
Dystonia, DOPA-responsive, with or without hyperphenylalaninemia – *GCH1*
Dystonia, DOPA-responsive, with or without hyperphenylalaninemia – *GCH1,SPR*
Myopathy with extrapyramidal signs – *MICU1*

3 Other choreas

Dystonia-Parkinsonism, X-linked – *TAF1*
McLeod syndrome - *XK*
Pelizaeus-Merzbacher disease and spastic paraplegia 2 – *PLP1*
Rett syndrome – *MECP2*
Alternating hemiplegia of childhood – *ATP1A3*, *ATP1A2*
Basal ganglia calcification, idiopathic – *XPR1*, *PDGFB*, *PDGFRB,* and *SLC20A2*
Chorea, benign hereditary - *NKX2-1*
Dyskinesia, familial, with facial myokymia – *ADCY5*
Episodic kinesigenic dyskinesia 1 – *PRRT2, SCN8A*
Spinocerebellar ataxia 1 - *ATXN1*
Spinocerebellar ataxia 7 - *ATXN7*
Paroxysmal nonkinesigenic dyskinesia 1 - *PNKD*
Rett syndrome, congenital variant – *FOXG1*
Ataxia-telangiectasia – *ATM*
Ataxia-telangiectasia-like disorder - *MRE11*
Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia - *APTX*
Choreoacanthocytosis - *VPS13A*
Congenital cataracts, facial dysmorphism, and neuropathy - *CTDP1*
Dyskinesia, limb and orofacial, infantile-onset – *PDE10A* and *PDE2A*
Woodhouse-Sakati syndrome - *DCAF17*
Sneddon syndrome – *CERC1*
Spinocerebellar ataxia, autosomal recessive 1 – *SETX*
Striatonigral degeneration, infantile – *NUP62*
Nasu-Hakola disease - *TREM2, TYROBP*
Pontocerebellar hypoplasia – *TSEN2, TSEN34* and *CHMP1A*
Dentatorubro-pallidoluysian atrophy - *ATN1*
Huntington disease – *HTT*
Spinocerebellar ataxia 17 - *TBP*

Ortigoza-Escobar (in preparation)

Chorea

Genetic chorea [4]

Autosomal dominant
Alternating hemiplegia of childhood – *ATP1A3*, *ATP1A2*
Basal ganglia calcification, idiopathic – *XPR1*, *PDGFB* , *PDGFRB*, and *SLC20A2*
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Seizures, benign neonatal – *KCNQ2*, *KCNQ3*
Spinocerebellar ataxia 1 - *ATXN1*
Spinocerebellar ataxia 7 - *ATXN7*
Spinocerebellar ataxia 17 - *TBP*

Autosomal recessive
2,4-dienoyl-CoA reductase deficiency – *NADK2*
3-methylglutaconic aciduria, type III – *OPA3*
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Spinocerebellar ataxia, autosomal recessive 1 – *SETX*
Striatonigral degeneration, infantile – *NUP62*
Sulfite oxidase deficiency – *SOUX*
Woodhouse-Sakati syndrome - *DCAF17*
Xeroderma pigmentosum – *XPA, ERRC2* and *ERCC6*
Wilson disease – *ATP7B*

X-linked
Cerebral creatine deficiency - *SLC6A8*
Epileptic encephalopathy, early infantile, 1 - *ARX*
Dystonia-Parkinsonism, X-linked – *TAF1*
HSD10 mitochondrial disease - *HSD17B10*
Lesch-Nyhan syndrome - *HPRT1*
McLeod syndrome - *XK*
Menkes disease – *ATP7A*
Methylmalonic acidemia and homocysteinemia, cblX type - *HCFC1*
Pelizaeus-Merzbacher disease and spastic paraplegia 2 – *PLP1*
Pyruvate dehydrogenase E1-alpha deficiency – *PDHA1*
Rett syndrome – *MECP2*

* HTT - Consensus holds that asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing. Individuals younger than 18 years of age who are symptomatic usually benefit from having a specific diagnosis established/ ** The genes in shadow font are caused by Repeat Expansion

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Genetic chorea [4]

[1] History and Physical examination

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Neurological symptoms

- Ataxia: *APTX, ARSA, ATM, ATN1, ATP1A3, ATXN1, ATXN7, FBXL4, GCH1, HTT, MECP2, MICU1, MRE11, PLA2G6, POLG, OPA3, PLP1, SETX, TBP*
- Behavioral abnormality/Autism spectrum disorder: *ADA2, ADCY5, ARSA, ATN1, ATP1A3, ATP7A, ATP7B, CERC1, CP, DECAF17, DDC, DELAT, ERC2, ERC6, FOXG1, FTL, GCDH, GCH1, HSD17B10, HTT, KCNQ2, KCNQ3, MECP2, NKX2-1, PANK2, PDGFB, PDGFRB, PDE10A, PLA2G6, POLG, PRRT2, PTS, QDPR, SCN2A, SCN8A, TBP, TREM2, TYROBP, VPS13A, XPA, XPR1*
- Developmental regression: *ADA2, ARX, ATP7A, ERCC2, FOXG1, FTL, GCDH, HTT, MECP2, NUP62, POLG, PLA2G6, SCN2A, SCN8A, ST3GAL5, TREM2, VPS13A, XPA*
- Diminished or absent deep tendon stretch reflexes: *AARS, ARSA, ATP7A, ERRC2, ERCC6, PIGN, SETX, XPA*
- Dystonia – parkinsonism: *AARS, ADCY5, APTX, ARSA, ATM, ATP1A2, ATP1A3, ATP7B, CP, DCAF17, DDC, DLAT, FBXL4, FOXG1, FTL, GCDH, GCH1, GNAO1, GCDH, HCFC1, HPRT1, KCNQ2, MECP2, MICU1, MUT, NDK2, NKX2-1, NUP62, PDGFB, PDGFRB, PDHA1, PLA2G6, PLP1, PRRT2, PTS, SETX, SLC6A3, SPR, SUOX, TAF1 (Philippines), TBP, TSEN2, TSEN34, VPS13A*
- Hypotonia: *ADCY5, ARSA, ARX, ATP7A, DDC, FBXL4, FOXG1, HCFC1, HPRT1, HSD17B10, HSPD1, MECP2, NADK2, PDE10A, PLP1, PIGN, SLC6A3, SLC6A8, SCN2A, SCN8A, SPR, SUOX*
- Infantile spasms: *ARX, KCNQ2, SCN2A, SCN8A*
- Intellectual disability: *ARSA, ARX, ATN1, ATXN7, ATP1A2, ATP1A3, ATP7A, ATP7B, DCAF17, DLAT, ERRC2, ERCC6, FOXG1, FTL, GNAO1, HCFC1, HPRT1, HSD17B10, HSPD1, KCNQ2, KCNQ3, MECP2, MICU1, MUT, NXK2-1, NUP62, OPA3, PDE10A, PDHA1, PIGN, PLA2G6, PLP1, PRRT2, SCN8A, SPR, TBP, TRAPPC11, SCN8A, SLC6A8, SOUX, XPA*
- Microcephaly: *AARS, ARX, ATP7A, ERRC2, ERCC6, FBXLA, FOXG1, HCFC1, MECP2, MICU1, MRE11, NADK2, PDGFB, PDGFRB, PDHA1, PLP1, POLG, SCN8A, SOUX, ST3GAL5, XPA, XPR1*
- Myoclonus: *ARX, ATN1, ATM, KCNQ2, KCNQ3, POLG, PRRT2, TAF1 (Philippines), TYROBP,*
- Myopathy: *POLG, VPS13A, XK*
- Paroxysmal chorea: *ADCY5, ATP1A3, ATP1A2, PKND, PRRT2, SCN8A*
- Peripheral neuropathy: *ADA2, AARS, APTX, ARSA, ATM, ATP7A, ATP7B, ATXN1, ERRC2, ERCC6, GJB2, KCNQ2, KCNQ3, MICU1, OPA3, PLP1, POLG, PRRT2, SCL2A1, SCN2A, SCN8A, SETX, XPA, VPS13A*
- Pyramidal signs: *ARSA, ATN1, ATP1A3, ATXN1, ATXN7, DDC, FTL, GCDH, GCH1, GJB2, HPRT1, HSPD1, HSD17B10, TBP, MECP2, NDK2, OPA3, PANK2, PDGFB, PDGFRB, PLA2G6, PLP1, SCL6A8, SPR, SETX, ST3GAL5, TAF1*
- Seizures: ADA2, *ARSA, ARX, ATM, ATN1, ATP1A3, ATP7A, CERC1, ERRC2, ERCC6, FBXL4, FOXG1, GJB2, GNAO1, HCFC1, HSD17B10, HSPD1, HTT, KCNQ2, KCNQ3, MECP2, MUT, NDK2, PDGFB, PDGFRB, PIGN, PLA2G6, POLG, PRRT2, SCN2A, SCN8A, SLC2A1, SLC6A8, ST3GAL5, SOUX, TBP, TYROBP, VPS13A, XPA, XPR1, XK*
- Self-mutilation: *HPRT1,SLC6A8, VPS13A*
- Tremor: *ADA2, ADCY5, APTX, ATM, ATP7B, ATXN7, CP, ERRC6, FTL, GCH1, GJB2, MECP2, MICU1, OPA3, PDE10A, PDGFB, PDGFRB, PIGN, PLA2G6, PLP1, POLG, SCN2A, SETX, SLC20A2, SPR, SLC6A3, TAF1 (Philippines), TRAPCC11, VPS13C*

Skin manifestations

- Alopecia: *DCAF17*
- Skin abnormalities: *ADA2, ATP7A, ARX, ATM, CERC1, ERRC2, ERRC6, GJB2, KCNQ2, MECP2, MRE11, PANK2, PDGFB, PDGFRB, SCN2A, SETX, SLC2A1, ST3GAL5 , SUOX, TRAPPC11, XPA, XPR1*
- Sun sensitivity: *ERRC2, ERCC6, SCN2A, XPA*

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Genetic chorea [4]

[1] History and Physical examination

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Chorea

Eye abnormalities

- Cataracts: *CTDP1, ERCC2, ERCC6, FBXL4, FTL, POLG, OPA3, TRAPPC11, VPS13A, XPA*
- Ectopia lentis: *SOUX*
- Eye movement abnormalities, including nystagmus: *AARS, APTX, ARX, ATM, ATN1, ATP1A2, ATP1A3, ATXN1, ATXN7, DLAT, ERCC2, ERRC6, FBXL4, HSPD1, MICU1, MRE11, NDK2, NUP62, OPA3, PDHA1, PDGFRB, PIGN, PLA2G6, PLP1, POLG, PRRT2, SCN8A, SETX, SLC2A1, SLC6A3, ST3GAL5, VPS13A*
- Optic atrophy: *ADA2, ARSA, ARX, ATXN1, ATXN7, ATP1A3, ERCC2, ERCC6, FTL, GJB2, HSD17B10, MICU1, MUT, NUP62, OPA3, PANK2, PLA2G6, PLP1, POLG, ST3GAL5, XPA*
- Retinopathy: *ATXN7*, ERCC2, *HSD17B10, OPA3*
- Kayser-Fleischer rings: *ATP7B*

Others

- Anemia: *ADA2, ATP7B, CP, HPRT1, MUT, OPA3*
- Bone cysts *PDGFRB, TREM2, TYROBP*
- Cardiomyopathy/congestive heart failure: *ADCY5, FBXL4, HSD17B10, MUT, POLG, VPS13A, XK*
- Dysmorphic features: *ARX, ATP7A, DCAF17, ERRC2, ERCC6, HCFC1, NKX2-1, PDHA1, PIGN, SLC6A8, ST3GAL5, SOUX, XPA*
- Hearing impairment: *AARS, ATP1A2, ATP1A3, DCAF17, ERRC2, ERCC6, GJB2, HSD17B10, PLA2G6, POLG, PRRT2, TRAPCC11, XPA*
- Hypogonadism: *ATM*, *DCAF17, ERCC2, ERRC6, POLG, XPA*
- Hypospadias: *ARX, FBXL4, HCFC1, MECP2, PIGN*

Multiple choice questions – 2

Which biochemical alteration guides the diagnosis of **benign hereditary chorea (*NKX2-1*)**?

a) Acanthocytosis

b) Immunoglobulin deficiency

c) Hypothyroidism

d) Hypoalbuminemia

e) Hyperuricemia

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Genetic chorea [4]

[2] Laboratories studies

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BLOOD

- Acanthocytosis: *PANK2, VPS13A, XK*
- Immunoglobulin deficiency: *ADA2, ATM, ERRC2,*
- Lymphopenia *ATM*
- Increased creatinquinase: *FBXL4, MICU1, PLA2G6, POLG, SETX, TRAPPC11, VPS13A, XK*
- Increased transaminases: *ADA2, ATM, ATP7B, FBXL4, POLG, TRAPPC11, VPS13A*
- Increased alpha-fetoprotein: *ATM, SETX*
- Lactic acidemia: *DLAT, FBXL4, HSD17B10, HSPD1, MUT, NADK2, PNPT1 , PDHA1, POLG*
- Hyperammonemia: *FBXL4, MUT*
- Low insulin-like growth factor 1 (IGF-1): *DCAF17*
- Hypothyroidism: *CP, DCAF17, NKX2-1*
- Hypoalbuminemia: *APTX*
- Hyperuricemia: *HPRT1*
- Reduced total homocysteine: *SUOX*
- Increased total homocysteine: *HCFC1*
- *CP:* Not detectable serum ceruloplasmin, serum copper concentration <10 µg/dL, serum iron concentration < 45 µg/dL, serum ferritin concentration is 850-4000 ng/mL and plasma ceruloplasmin ferroxidase activity is not detectable.
- *ATP7A*: low copper 0-55 µg/dL and low ceruloplasmin 10-160 mg/L
- *ATP7B*: serum ceruloplasmin < 20 mg/dl,
- *NDK2*: elevated plasma C10:2-carnitine, hyperlysinemia
- Hyperphenylalaninemia: *PTS, QDPR*

CSF

- *Increased lactate: DLAT, FBXL4, HSPD1, NDK2, PDHA1, PNPT1, POLG*
- *DDC:* normal CSF pterins profile, reduced HVA, 5-HIAA and MHPG, increased OMD and levodopa
- *GCH1*: normal or reduced CSF pterins, normal Phe, normal or reduced HVA and 5-HIAA
- *HCFC1:* elevated glycine and methylmalonic acid
- *NDK2*: elevated lysine
- *PTS:* increased Phe, increased neopterin, decreased biopterin, HVA and 5-HIAA
- *QDPR:* increased Phe, normal neopterin, increased biopterin, decreased HVA, 5-HIAA and folate
- *SLC6A3:* Raised HVA, normal 5-HIAA, HVA:5-HIAA ratio >4.0, normal CSF pterins
- *SPR*: low HVA and 5-HIAA and high levels of biopterin and dihydrobiopterin with the presence of sepiapterin

URINE

- *ATP7B*: 24-h urine Cu> 40 mcg
- GCSH: increased 3-hydroxy glutaric acid and glutaric acid
- *HCFC1, HSPD1, MUT*: increased urinary methylmalonic acid
- *HPRT1:* Urate/creatinine ratio > 2.0
- *HSD17B10*: elevation of 2-methyl-3-hydroxybutyrate and tiglylglycine
- *NDK2*: elevated lysine
- *OPA3*: Increased urinary excretion of 3-methylglutaconate and 3-methylglutaric acid.
- *SLC6A8* Males: Guanidinoacetate normal, Creatine normal to elevated and Creatine/creatinine ratio elevated
  Females Guanidinoacetate normal Creatine normal to elevated Creatine/creatinine ratio normal to mildly elevated
- SUOX: Urinary sulfite identified on a dipstick screening test. Elevated urinary thiosulfate and S-sulfocysteine and low urinary organic sulfate.

Chorea

Genetic chorea [4]

[3] MRI

Basal ganglia abnormalities

Iron deposition: *CP, DCAF17, FTL, PANK2, PL2G6*

Caudate atrophy: *HPRT1, HTT, TREM2, TYROBP, VPS13A*

Hypoplastic globus pallidus *NKX2-1*

Hyperintensity: *ATP7B, DLAT, FBXL4, FTL, GCDH, KCNQ2, MICU1, MUT, NADK2, NDK2, NUP62, PDE10A, PDHA1, PNPT1, POLG, SCN2A, SCN8A, XK*

Calcification

ATP7A, ERRC2, ERCC6, PDGFB, PDGFRB, PTS, QDPR, SLC20A2, SOUX, XPA, XPR1

White matter abnormalities

Hypomyelination/defective myelination - *AARS, ARX, ATP7A, CTDP1, DDC, FBXL4, FOXG1, GNAO1, HCFC1, SCN2A, PLP1, PNPT1, PTS*

Leukoencephalopathy / Unspecific periventricular gliosis - *ARSA, ATM, CTDP1, DCAF17, DDC, FBXL4, GJB2, HSPD1, NADK2, POLG, PTS, QDPR, SCN2A, SLC6A8, ST3GAL5, TREM2, TYROBP*

MR Spectroscopy

Lactate peak – *DLAT, FBXL4, HSD17B10, PNPT1, PDHA1, POLG*
Cerebral creatine deficiency - *SLC6A8*
Abnormal white matter N-acetyl aspartate (NAA) levels – *PLP1, MECP2, HSPD1*
Elevated citrate, glycine and creatine *AARS*

Normal

ADCY5, ATP1A3, ATP1A2, KCNQ3, DDC, GCH1, PDE2A, PKND, SLC6A3, SPR, TAF1 , TRAPPC11

Others

Arachnoid cysts: *FBXL4*

Brain atrophy: *AARS, ARX, ATRX, ATXN7, ATN1, CTDP1, DDC, ERRC2, ERRC6, FBXL4, FOXG1, GJB2, GNAO1, HPRT1, HSD17B10, HTT, KCNQ2, MECP2, NADK2, PDHA1, PIGN, POLG, SCN8A, ST3GAL5, TBP, TYROBP, VPS13A, XPA*

Cerebellar atrophy: *APTX, ATM, ATXN1, ATXN7, CTDP1, ERRCC6, HTT, MECP2, MRE11, OPA3, PIGN, PLA2G6, POLG, SCN2A, SCN8A, SETX, TBP*

Hypoxic-ischemic encephalopathy-like, including cystic leukomalacia: *SOUX*

Ischemic lesions: *CERC1, FBXL4*

Malformation of cortical development: *ARX*

Pontocerebellar atrophy - *ATXN1, ATN1, CHMP1A, HSPD1, SETX, TSEN2, TSEN34*

Sella turca cysts *NKX2-1*

Spinal cord atrophy – *CTDP1*

Thin corpus callosum - *ARX, AARS, CTDP1, FBXL4, FOXG1, GJB2, GNAO1, KCNQ2, MECP2, SCN8A, TYROBP*

Vascular tortuosity - *ATP7A*

Ventricular enlargement – *AARS*, ARX, *ATP7A, ERRC2, ERCC6, FOXG1, HTT, MECP2, NADK2, PDGFB, PDGFRB, PDHA1, PIGN, TSEN2, TYROBP, SLC6A8, SLC20A2, VPS13A, XPA, XPR1, XK*

Genetic Chorea

Epileptic encephalopathies

Chorea and Early Infantile Epileptic Encephalopathies (EIEE)

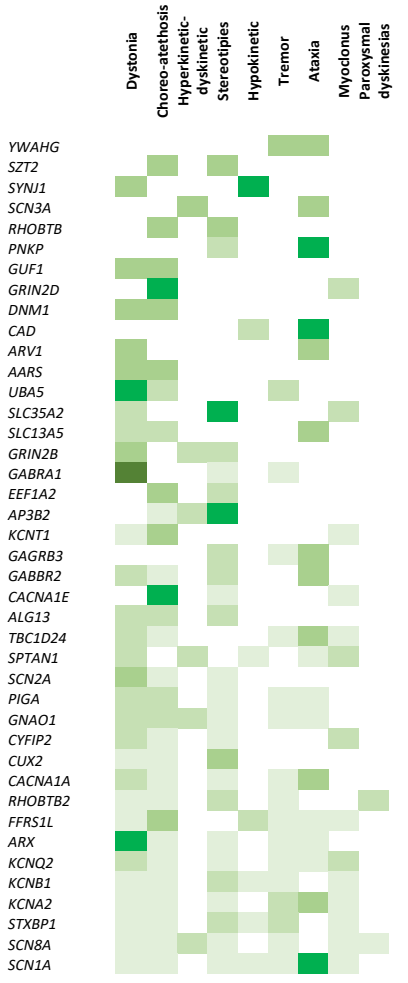


Figure 2. Distribution of movement disorders by gene and frequency. Genes with only one type of isolated movement disorders were not included: 1) dystonia (*PARS2* and *SLC25A22*), 2) choreoathetosis (*ITPA* and *NTRK2*), 3) hyperkinetic (*SLC1A2*), 4) stereotypies (*CDKL5,DOK7, HNRNPU, PLCB1* and *SIK1*), 5) ataxia (*ARHGEF9, FGF12, HCN1, PCHDH19* and *SCN1B*) and 6) myoclonus (*TRAK1*). The following genes without movement disorders were not included: *ADAM22, CNPY3, CPXL1, DENND5A, GAGRB1, GLS, KCNT2, MDH12, NECAP1, PHACTR1, PIGP, PIGQ, RNF13, SLC12A5, SLC25A12, ST3GAL3, WWOX.*

Martinez-Esteve Melnikova A, Bonino M et al., (in preparation)

- 1713 out of 14462 articles reviewed
- 77 OMIM genes for EIEE
- Data of 2200 patients (age at seizure onset:media±SD:0,87±2,03 years, age range: neonatal period-18 years old) were included
- 724/2200 (32%) of the patients presented MD
- **16%** patients presented choreoathetosis

Chorea and EIEE associated genes

AARS, ***ALG13****, AP3B2, ARX, CACNA1A, CACNA1E, CUX2, CYFIP2, DNM1, EEF1A2, FFRS1L, GABBR2, GABRA1, GNAO1, GRIN2D, GUF1, ITPA, KCNA2, KCNB1, KCNQ2, KCNT1, NTRK2,* ***PIGA,*** *RHOBTB2, SCN1A, SCN2A, SCN8A, SLC13A5, STXBP1, SZT2, TBC1D24*

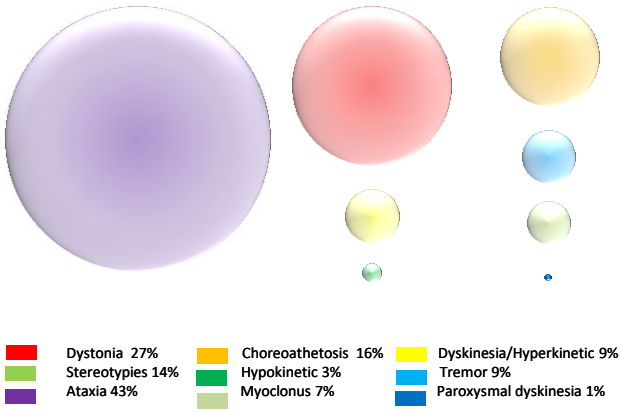
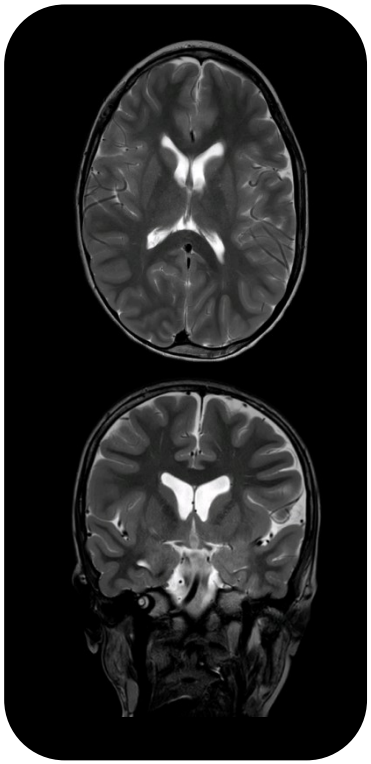
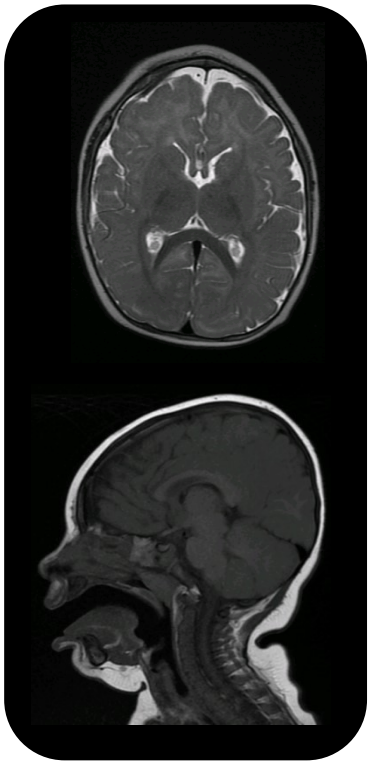


Figure 1. Distribution of movement disorders in 724 patients with EIEE

Chorea and Early Infantile Epileptic Encephalopathies (EIEE)



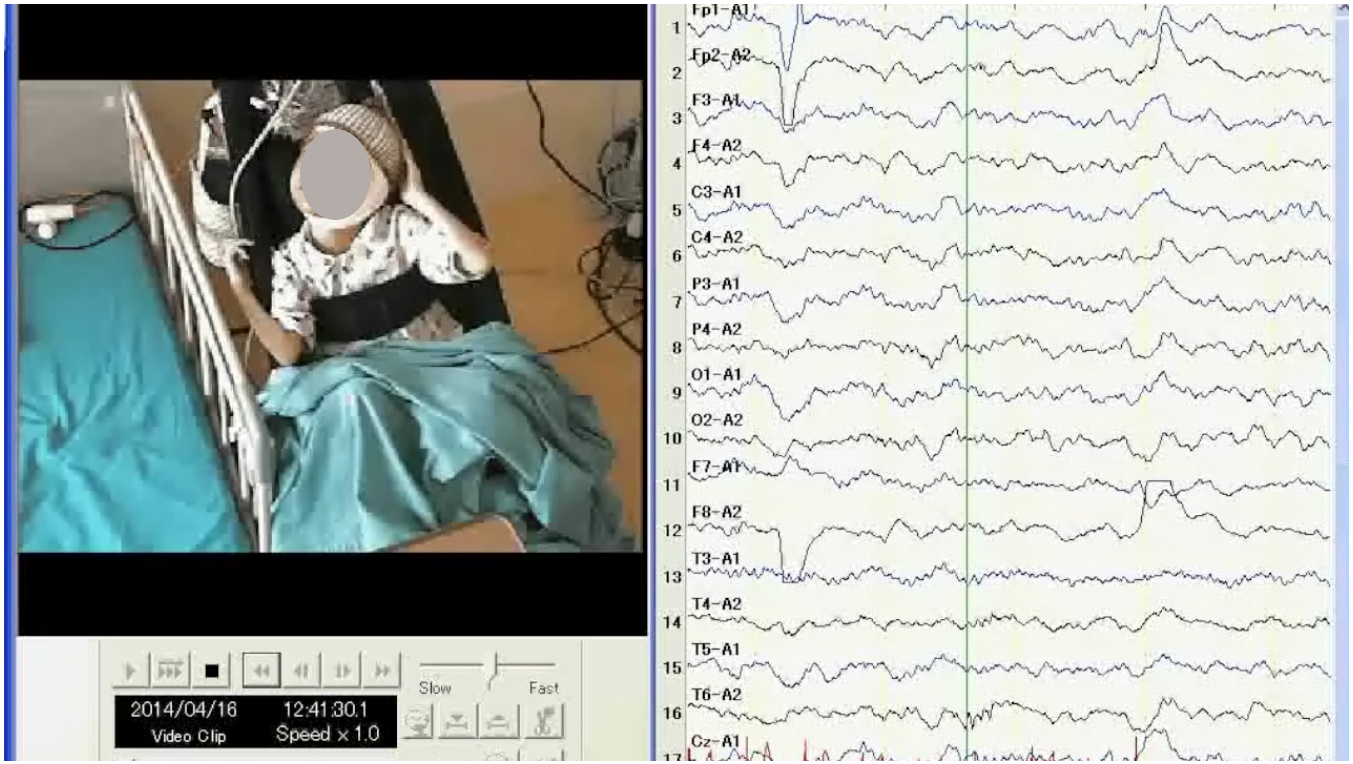
Chorea and Early Infantile Epileptic Encephalopathies (EIEE)



Chorea and Early Infantile Epileptic Encephalopathies (EIEE)

Helbig et al. Am J Hum Genet. 2018 Nov 1;103(5):666-678.

Chorea and Early Infantile Epileptic Encephalopathies (EIEE)



Ohba et al. Epilepsia, 56(6):841–848, 2015

Multiple choice questions – 3

In which of the following IEMs, chorea **is not a common symptom**?

a) Disorders of purine and pyrimidine metabolism
b) Disorders of monoamine metabolism
c) Disorders of copper metabolism
d) Disorders of peroxisomes
e) Congenital disorders of glycosylation

Genetic Chorea

Inborn error of metabolism

Chorea and IEMs

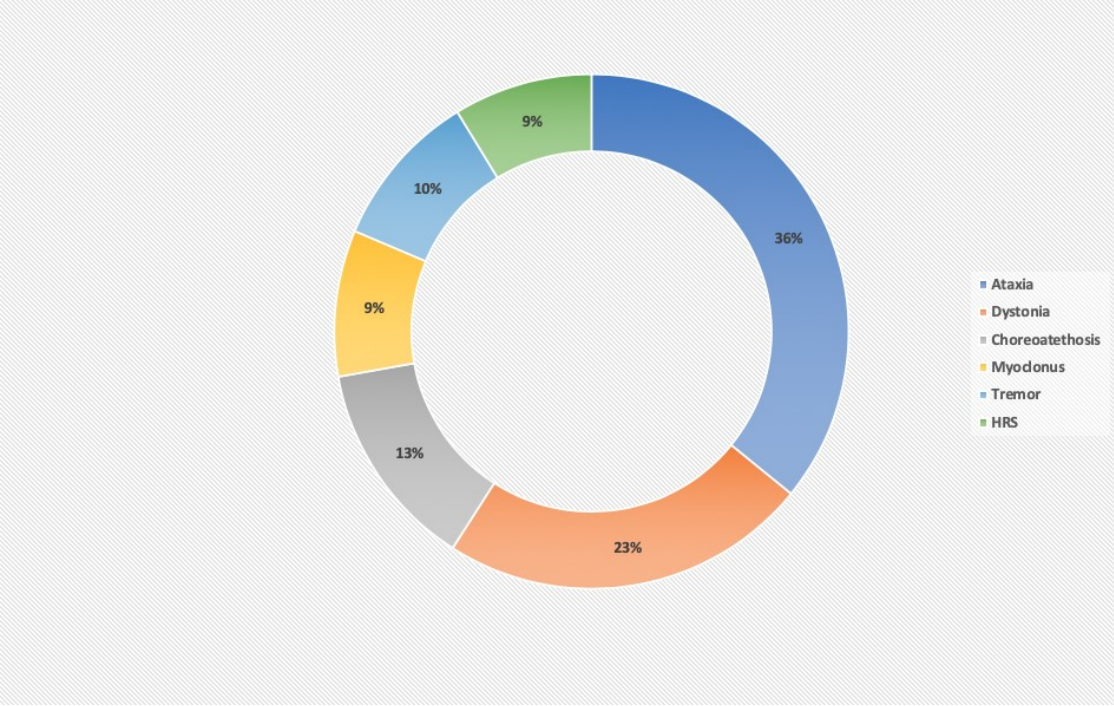
231 IEMs presenting with MD

MD in the context of IEMs are generally a **combination** of different MD

MD can be part of a more **diffuse clinical picture**

There are only a few studies that make an comprehensive description of the MD in the IEMs

Six-step algorithm proposed

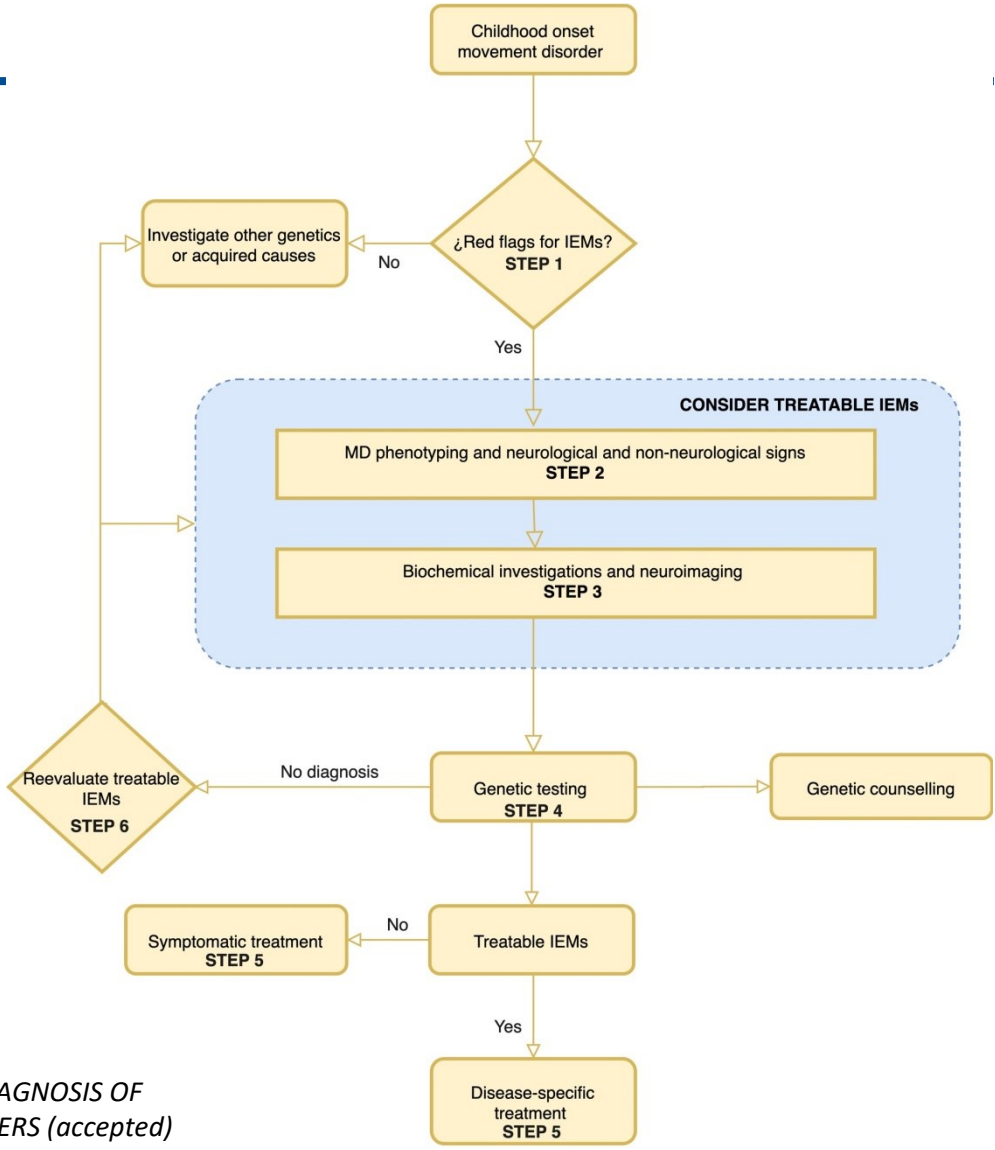


Ortigoza-Escobar et al., A PROPOSED DIAGNOSTIC ALGORITHM FOR THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM PRESENTING WITH MOVEMENT DISORDERS (accepted)

Chorea and IEMs

Red flags for IEMs presenting with MD

- **Diffuse clinical picture with several neurological and non-neurological signs**
- **Combination of different MD** (ataxia plus dystonia, dystonia plus parkinsonism, chorea plus dystonia and myoclonus with any other MD or neurological or non-neurological signs, other than seizures),
- **Acute or subacute onset**, remarkably if the onset is associated with encephalopathy/coma or if onset is precipitated by a concurrent febrile illness, starvation, physical exhaustion or after a high-protein ingestion,
- **Insidious onset in a patient with multiple previous non-systemic manifestations**,
- **Consanguinity** and/or recessive or X-linked inheritance pattern,
- Distinct **neuroradiological findings** for instance basal ganglia abnormalities, white matter involvement (hypomyelination/leukoencephalopathy) or cerebellar atrophy,
- **Atypical or progressively abnormal MD** that fails to respond to standard treatment,
- **MD that are not explained by classical etiologies** (e.g. structural brain lesion, infectious/para infectious or autoimmune disorders, toxic or drug induced MD and other well-known genetic or neurodegenerative MD, etc.)



Ortigoza-Escobar et al., A PROPOSED DIAGNOSTIC ALGORITHM FOR THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM PRESENTING WITH MOVEMENT DISORDERS (accepted)

Chorea and IEMs

IEMs presenting with Chorea

Hypoxanthine guanine phosphoribosyltransferase deficiency
Guanidinoacetate methyltransferase deficiency
Creatine transporter deficiency
Aromatic L-amino acid decarboxylase deficiency
Dopamine transporter deficiency
6-Pyruvoyl-tetrahydropterin synthase deficiency
Sepiapterin reductase deficiency
Dihydropteridine reductase deficiency
Propionic acidemia
Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency
Glutaric aciduria type 1
Glycine encephalopathy due to glycine decarboxylase deficiency
Glycine encephalopathy due to aminomethyltransferase deficiency
cblX disease
Hereditary folate malabsorption
Classic galactosemia
Folate receptor alpha deficiency
Molybdenum cofactor deficiency
Wilson disease
Aceruloplasminemia
Glucose transporter 1 deficiency
Pyruvate dehydrogenase complex deficiency
Beta-ketothiolase deficiency
Cerebrotendinous xanthomatosis
CLN2 disease

Minimal biochemical investigation in IEMs presenting with Chorea

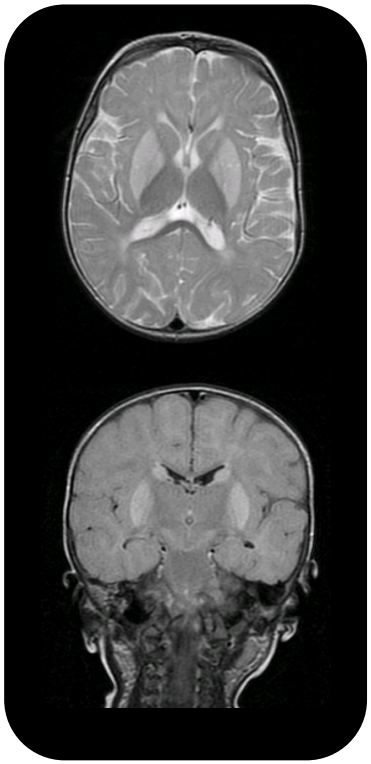
Blood: 1st Tier: blood count, ASAT/ALAT, glucose, lactate, pyruvate, uric acid, creatine, guanidino compounds, prolactin, amino acids, pterins, purine, total homocysteine, copper, ceruloplasmin, acylcarnitines, methylmalonic acid, folate, sterols, acetoacetate. 2nd Tier: Galactose-1-P, GALT enzyme activity, TPP1 enzyme activity

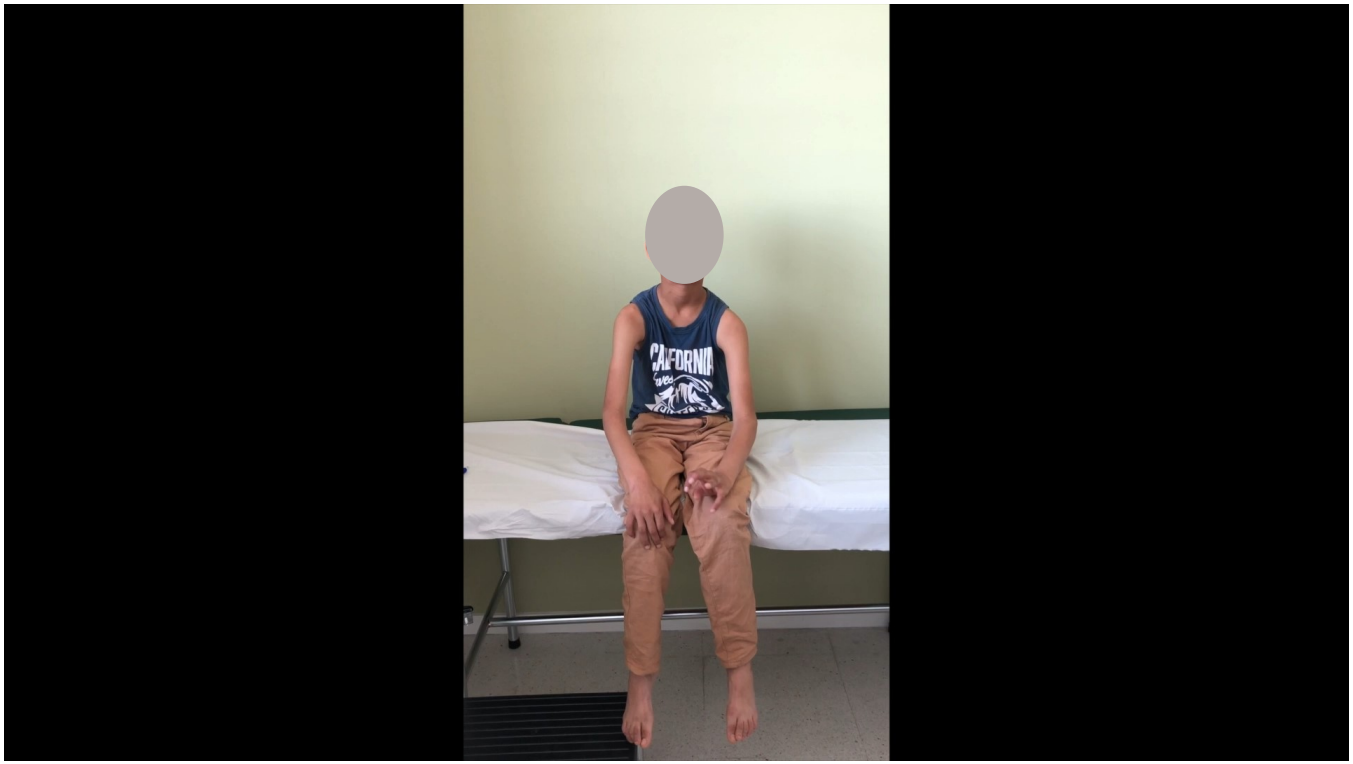
Urine: 1st Tier: glucose, lactate, purine and pyrimidines, guanidino compounds, pterins, organic acids, sulfites, copper, acetoacetate

CSF: 2nd Tier: amino acids, neurotransmitters, pterins, 5-Methyl-THF, pipecolic acid

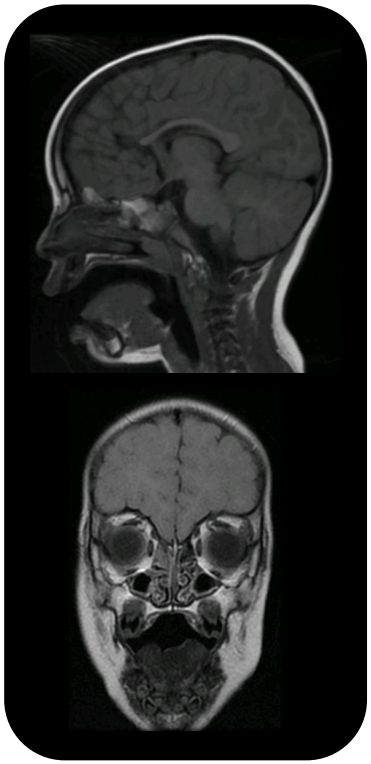
Ortigoza-Escobar et al., A PROPOSED DIAGNOSTIC ALGORITHM FOR THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM PRESENTING WITH MOVEMENT DISORDERS (accepted)

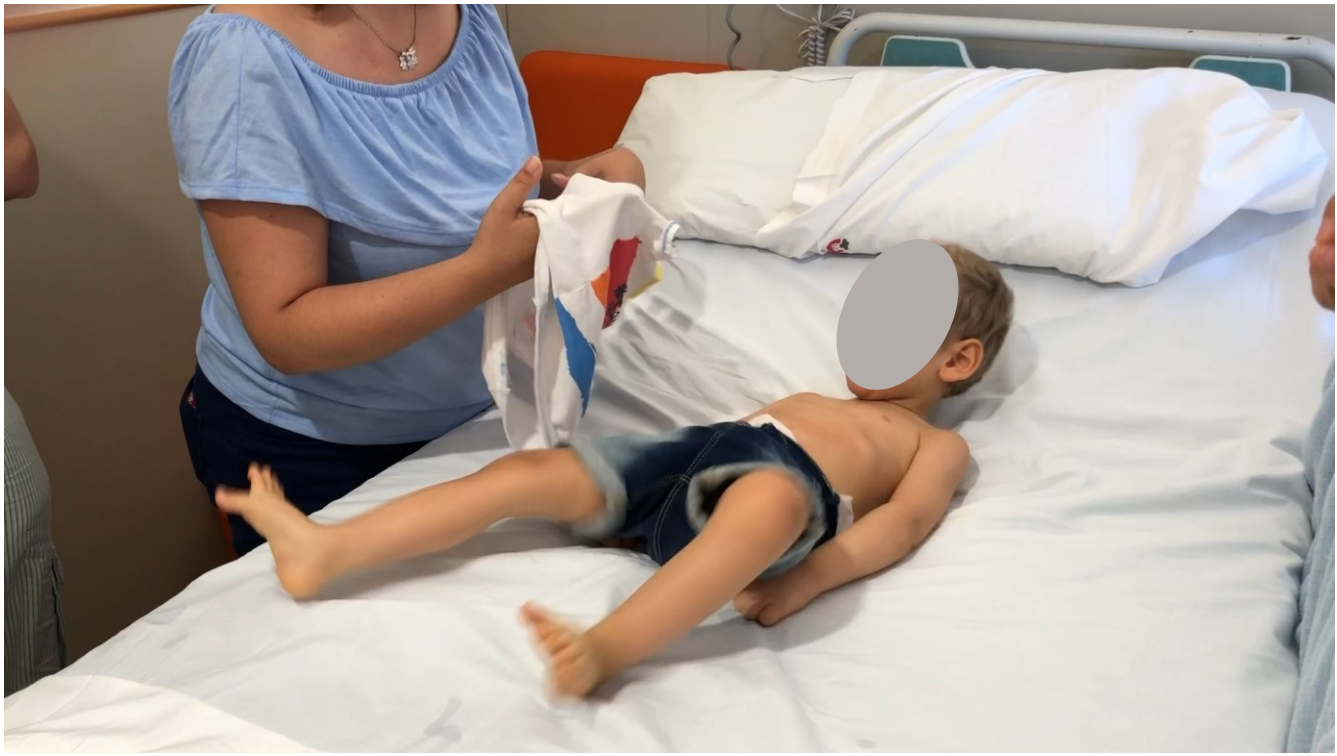
Chorea and IEMs



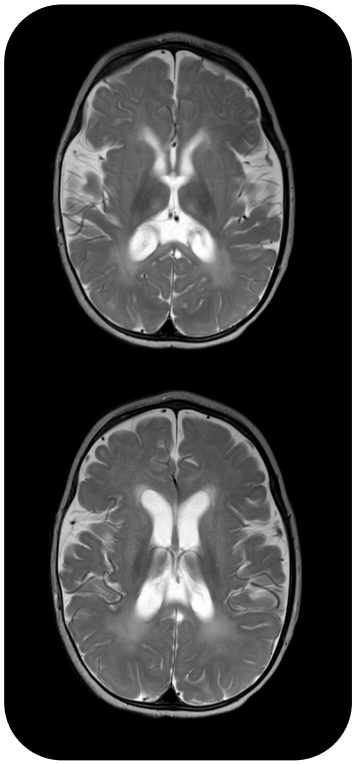


Chorea and IEMs





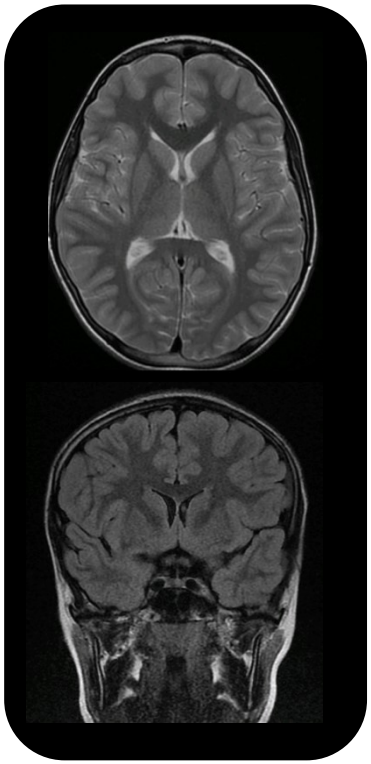
Chorea and IEMs



Genetic Chorea

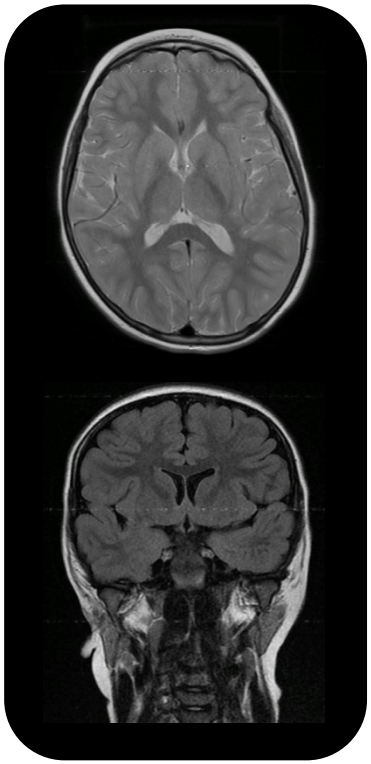
Other choreas

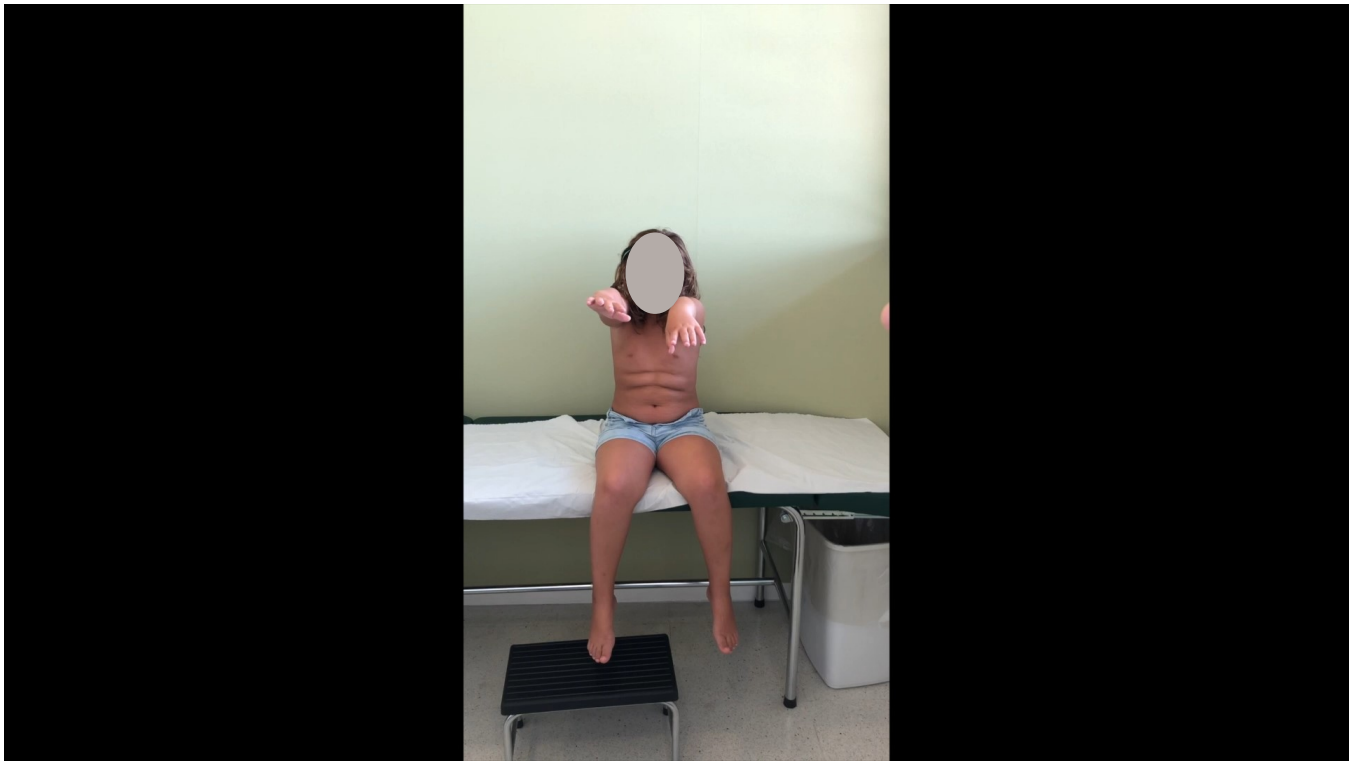
Genetic chorea



NKX2-1
ADCY5
PDE10A
PDE2A

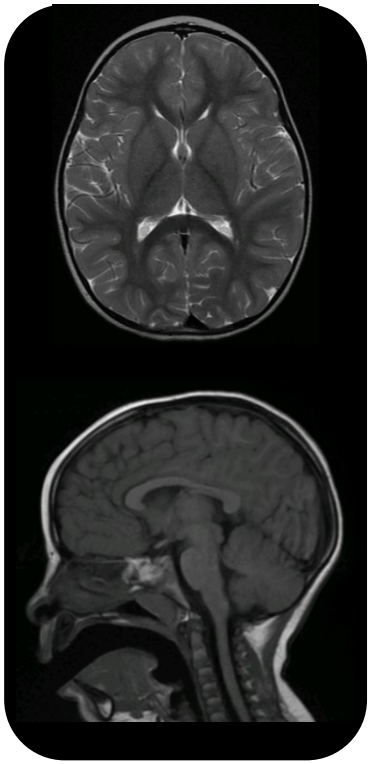
Genetic chorea





NKX2-1
ADCY5
PDE10A
PDE2A

Genetic chorea



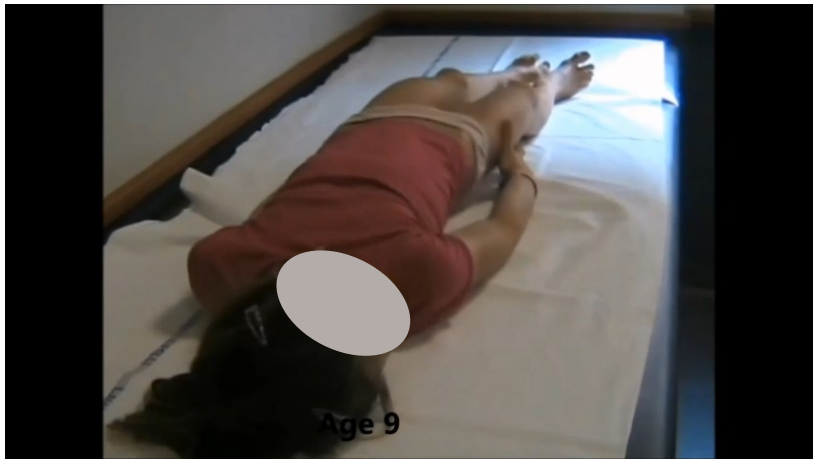
NKX2-1
ADCY5
PDE10A
PDE2A

[redacted]

[redacted]

Genetic chorea

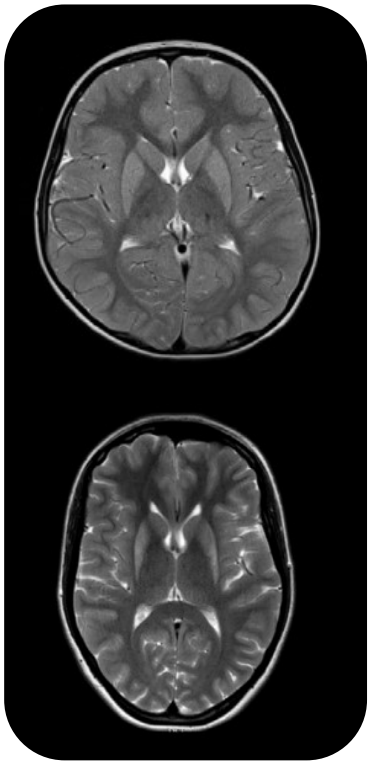
Friedman et al. Mov Disord. 2016 Jan;31(1):147-8.



Carecchio et al. Parkinsonism Relat Disord. 2017 Aug;41:37-43.

NKX2-1
ADCY5
PDE10A
PDE2A

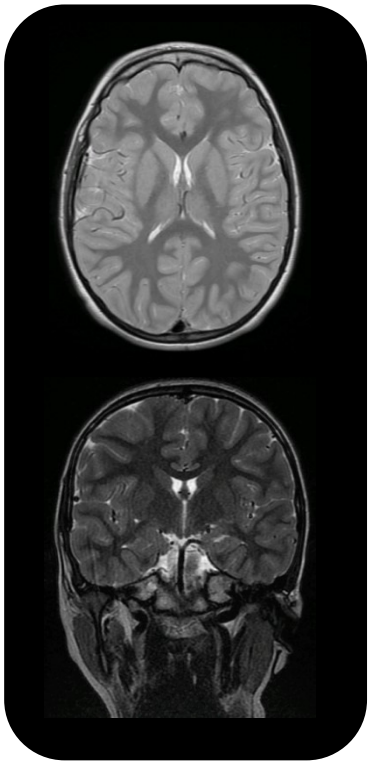
Genetic chorea

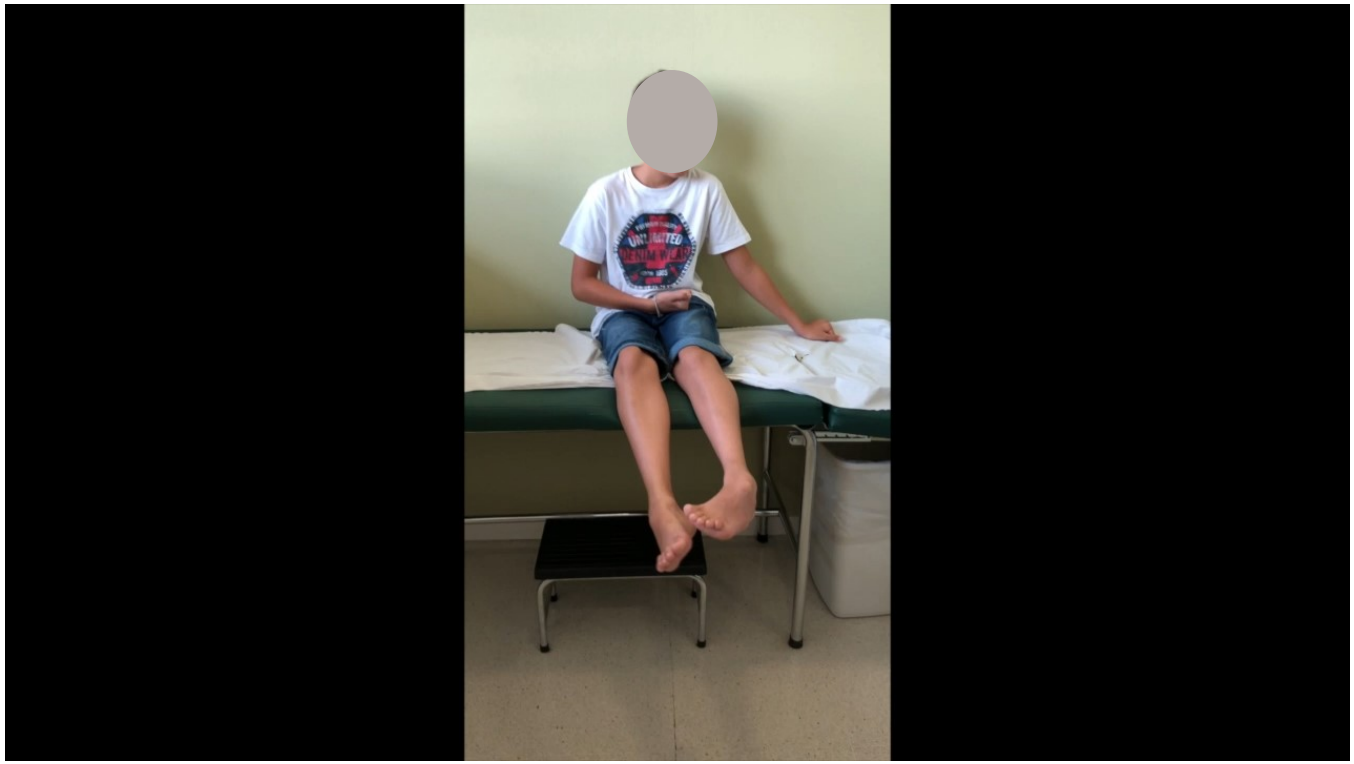


NKX2-1
ADCY5
PDE10A
PDE2A

Diggle et al. Am J Hum Genet. 2016 Apr 7;98(4):735-43.

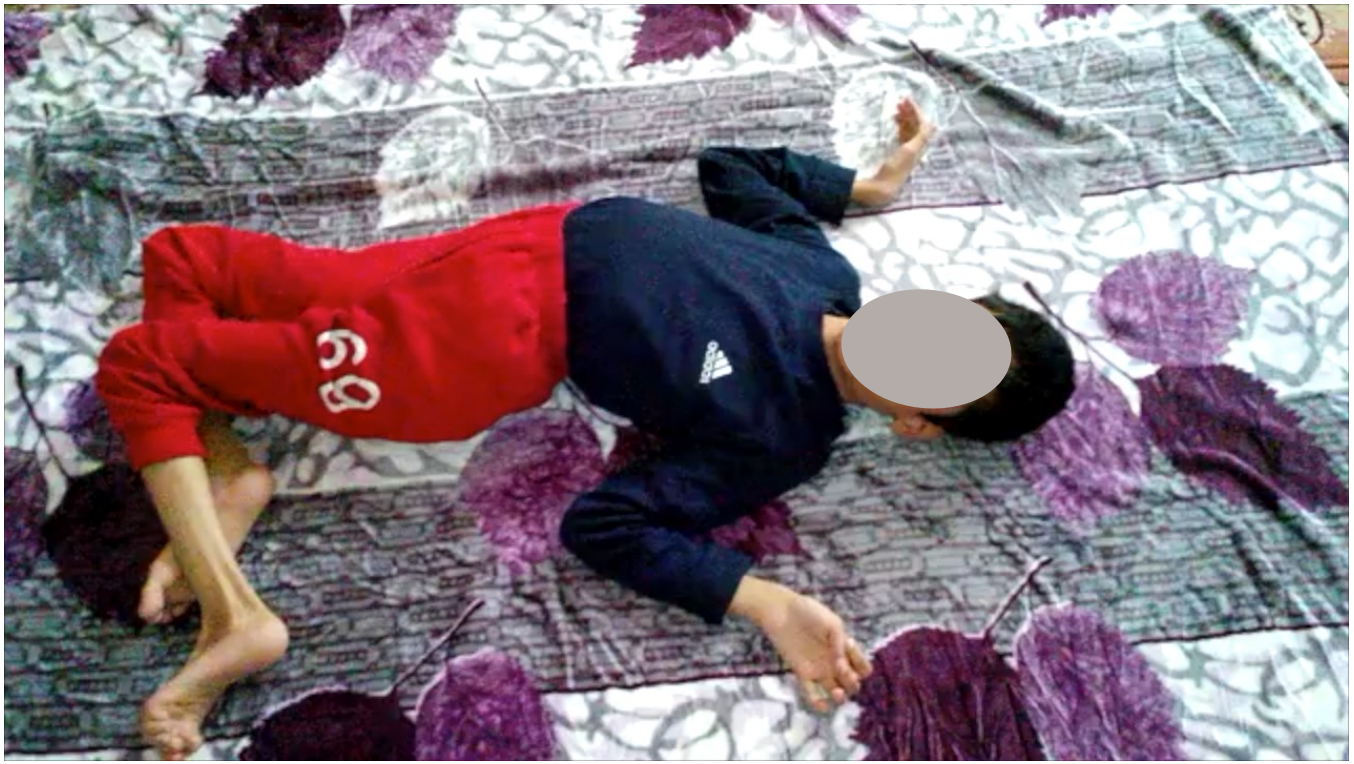
Genetic chorea





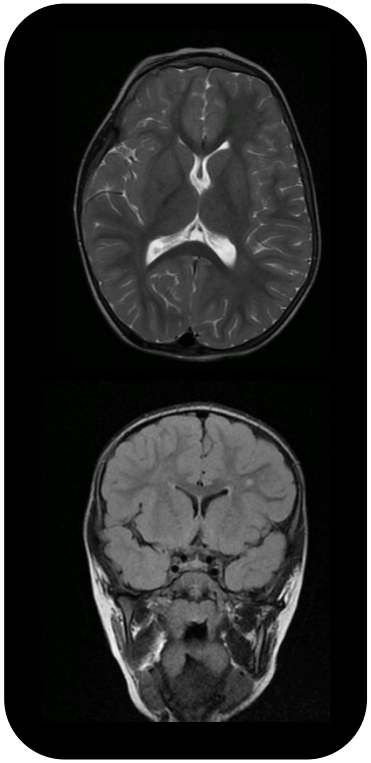
NKX2-1
ADCY5
PDE10A
PDE2A

Genetic chorea

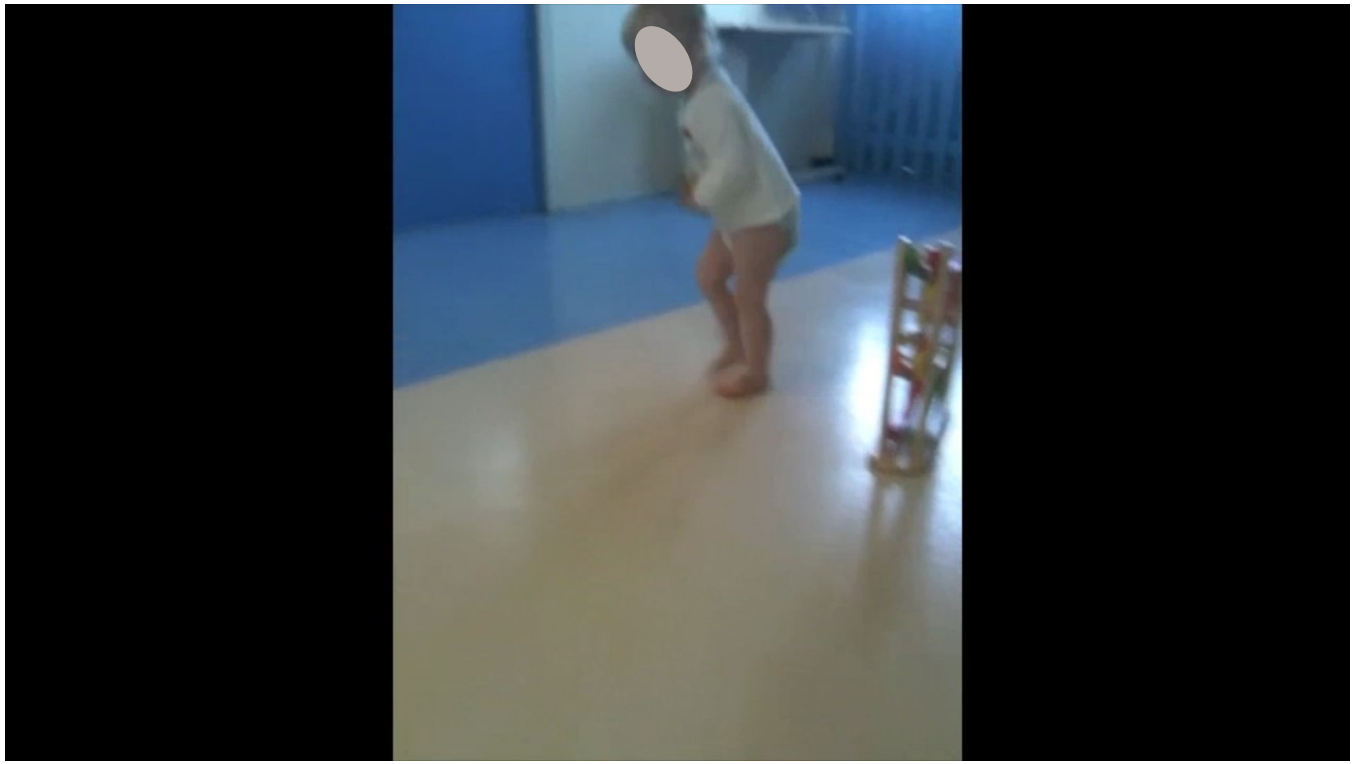


McMillian et al. Orphanet J Rare Dis. 2018 May 31;13(1):86.

Genetic chorea



Genetic chorea

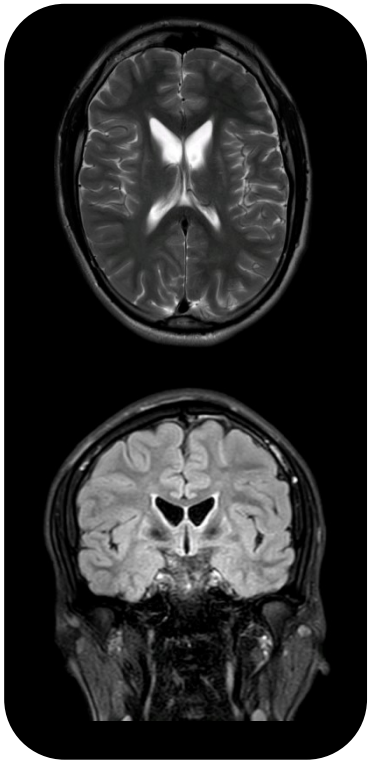


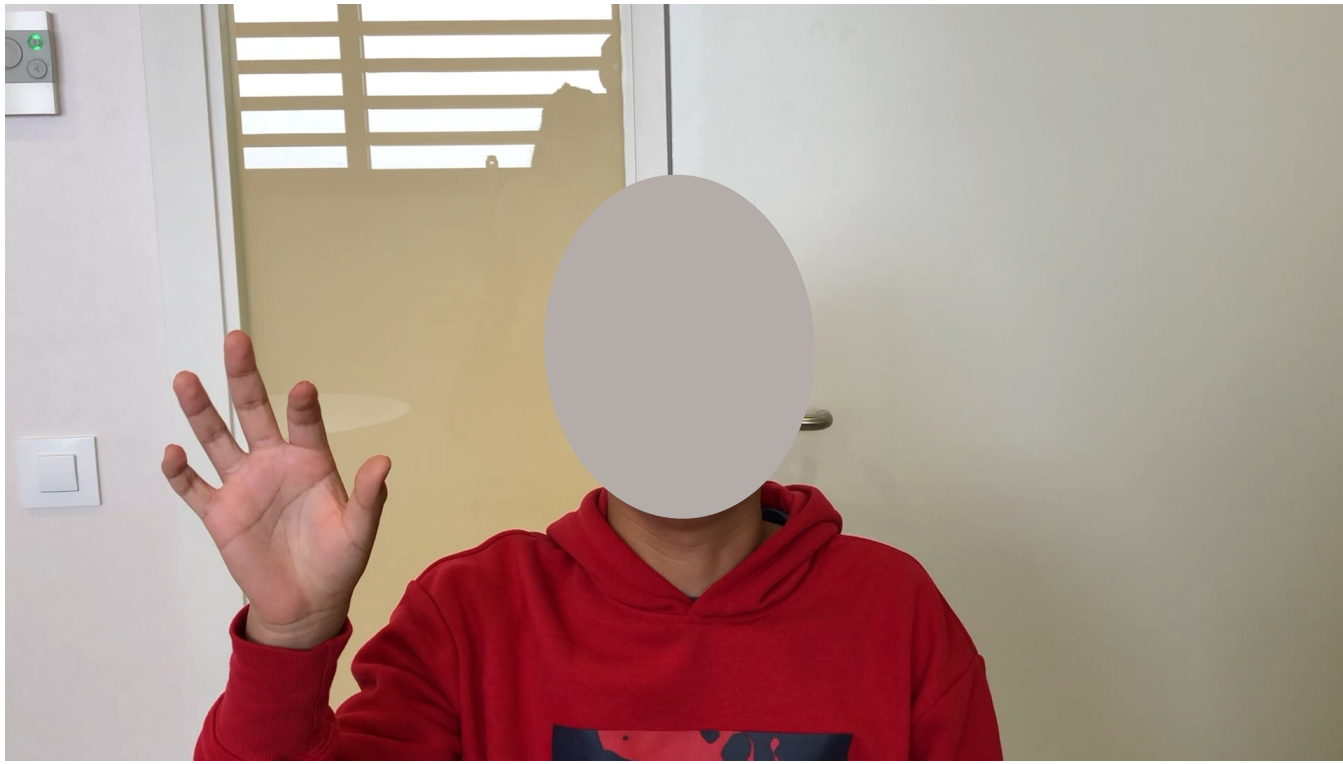
Thompson et al. Mov Disord Clin Pract. 2014 Jun 11;1(3):249-251.

Genetic Chorea

Chorea not chorea and unsolved choreas

Not to forget … CHOREA NOT CHOREA



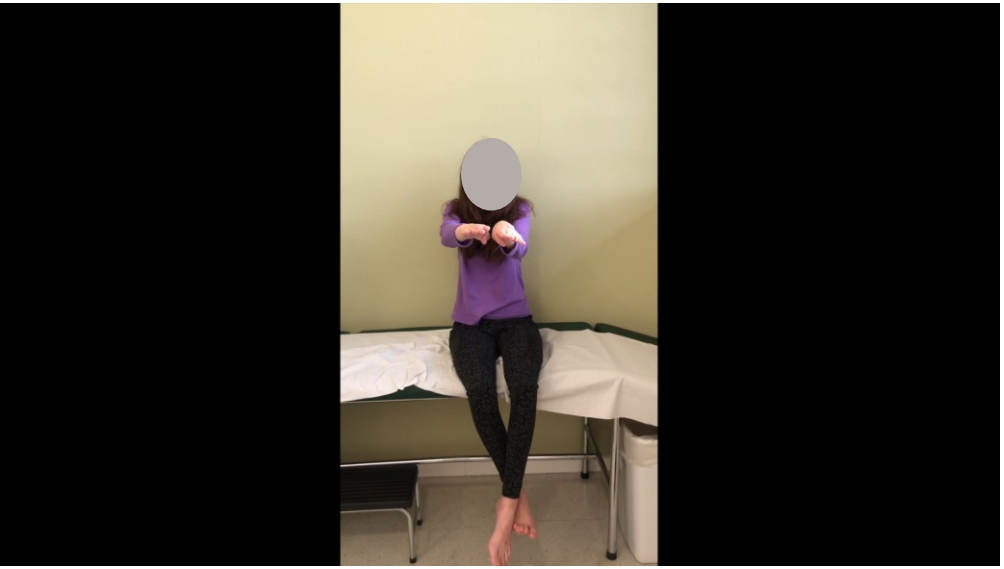


PAST WEBINAR - 15 September 2020

A challenge in neurogenetics: Huntington disease in kids

Ferdinando Squitieri

Not to forget … UNSOLVED CHOREA



UNSOLVED CASES*

Definition: Rare disease cases with an inconclusive exome/genome

Number: 19,000 unsolved exomes/genomes

Main activities: Perform standardised collation and re-analysis

**in collaboration with all ERNs, Undiagnosed Disease Initiatives and further associated partners*

1

SPECIFIC ERN COHORTS

Definition: Disease group specific cohorts from four core ERNs (exome available)

Number: a) 2,000 WGS for more complete (non-)coding sequence & CNV/SVs etc.;
b) 500 long-read WGS;
c) >2,000 cases novel omics approaches

Main activities: Conduct „beyond the exome" approaches

2

ULTRA RARE RARE DISEASES

Definition: Phenotypically most special/ remarkable patients with a rare disease without an exome

Number: 1,200 exomes (300 per core ERN)

Main activities: Carry out phenotype jamborees and exome analysis

3

THE UNSOLVABLES

Definition: Highly recognisable clinically defined diseases / syndromes for which no disease gene was identified yet despite WES/WGS and considerable research invested

Number: 120 syndromes/ diseases

Main activities: apply all -omics tools to ‚crack' the „Unsolvables"

4

Key Points /Conclusions

- Chorea in children has a wide variety of etiologies, including acquired and genetic causes
- Type of onset and age of onset allow us to differentiate between genetic and acquired chorea
- MRI is essential in the study of a patient with chorea
- Algorithm available at

http://www.ern-rnd.eu/wp-content/uploads/2019/10/Diagnostic-flowchart-for-Childhood-onset-Chorea.pdf

- Identifying the cause is important in order to provide appropriate treatment and prognosis

Thank you to all the patients and families …

Co-financed by the Connecting Europe Facility of the European Union

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

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Chorea and HD'
13. October 2020

European Reference Network | Neurological Diseases (ERN-RND)

This webinar has been supported by ERN-RND , which is partly co-funded by the European Union within the framework of the Third Health Programme "ERN-2016 - Framework Partnership Agreement 2017-2021."

Joint webinar series

THANK YOU

Next Webinar: **‚Clinical practice recommendations for physical therapy for Huntington's disease' by Bernhard Landwehrmeyer**

20. October 2020, 15-16h CET