Chorea, Ballism, Athetosis

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Chorea

Chorea (L.; Gr. c*horeia* = dance) is a hyperkinetic movement disorder, characterized by involuntary continuous, abrupt, rapid, brief, jerky, irregular movements that flow randomly from one body part to another.

Chorea worsens with stress and may affect fine and gross motor function, activities of daily living, gait and balance, eventually impacting on the quality of life, resulting in markedly increased morbidity and mortality.

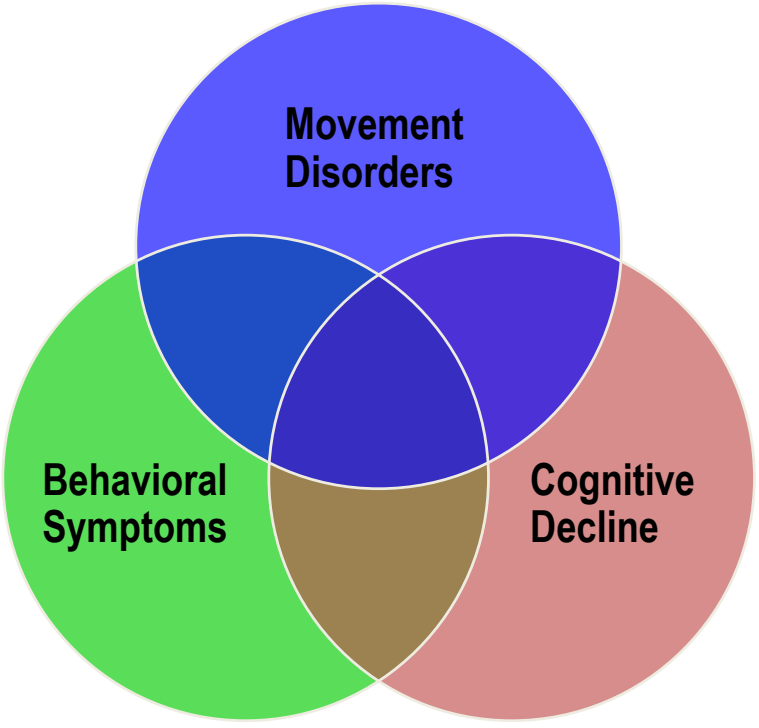
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Chorea: Associated Features

- Parakinesia (semipurposeful camouflage)
- Irregular narrowing of palpebral fissures and frontalis contractions (especially in HD)
- Motor impersistence ("darting tongue", "milkmaid's grip")
- "Hung-up" and "pendular" reflexes
- Irregular ("dance-like") gait

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Huntington Disease



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Differential Diagnosis of Chorea

Inherited Choreas

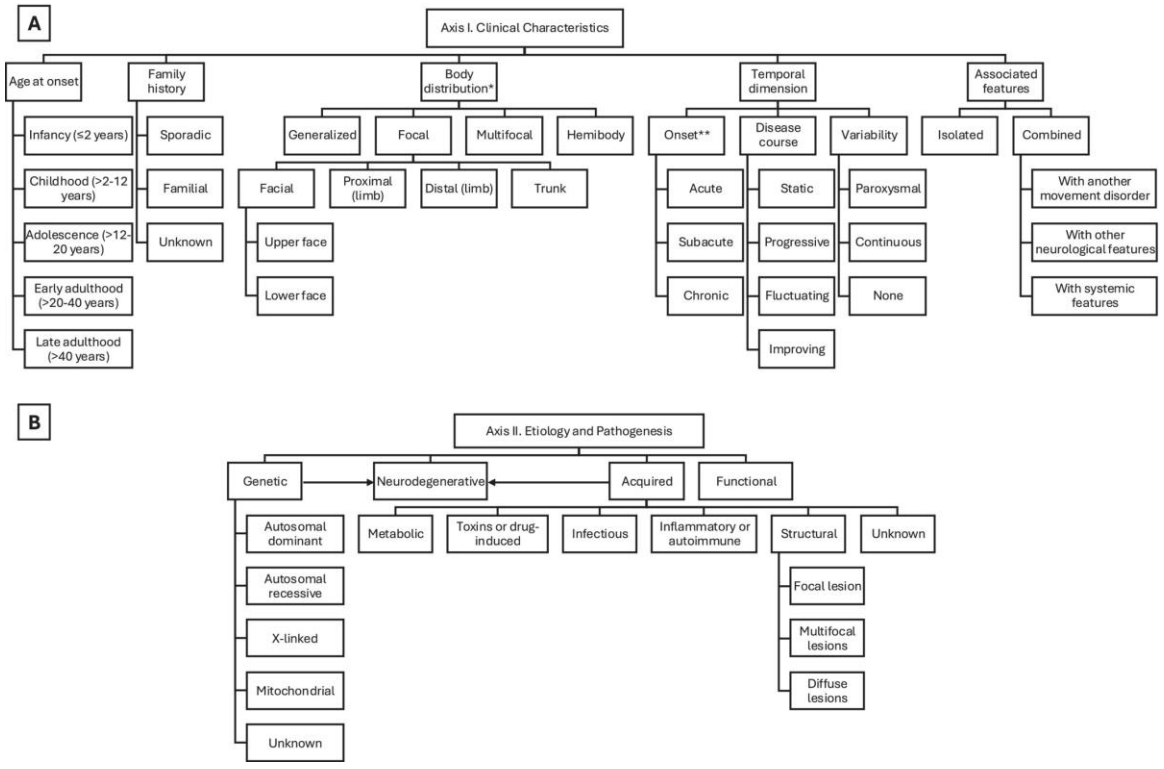
- HD (*HTT*)
- HDL1 (*PRNP*), HDL2 (*JPH3*)
- DRPLA (*JNK*)
- Neuroacanthocytosis (*VPS13A*)
- McLeod (*HK*)
- Brain-Lung-Thyroid (*NKX2-1*)
- *ADCY5*-Related movement disorder
- *C9orf72* expansion
- NBIAs: PKAN, neuroferritinopathy, aceruloplasminemia, infantile neuroaxonal dystrophy (PLA2G6); mitochondrial membrane protein-associated neurodegeneration (MPAN; *C19orf12*)
- Wilson disease
- Ataxia-chorea: SCA 1,2,3,8,17; Friedreich's ataxia, AOA, AT
- Mitochondrial disorders
- Other genetic choreas: *GNAO1, FOXG1, PDE10A, PDE2A, OPA3, PCCA/PCCB, FITM2, TWNK, TANGO2, ATP1A2 and 3, HPCA, RFC1, PURA, AIFM1, Notch3*

Sporadic/Secondary Choreas

- Static encephalopathy - CP
- Sydenham chorea
- Other autoimmune choreas (SLE, APS, NMDAR encephalitis, paraneoplastic syndromes, etc)
- Vascular chorea, polycythemia, moyamoya (genetic component)
- Creutzfeldt-Jakob Disease
- Hyperthyroidism
- AIDS
- Tardive dyskinesia
- Metabolic encephalopathy
  - Hepatolenticular degeneration
  - Non-ketotic hyperglycemia
  - Hypoglycemia
  - Renal failure
  - Ketogenic diet
- Functional (psychogenic) chorea

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Proposed axis-based classification system for chorea according to clinical characteristics (A, axis I) and etiology and pathogenesis (B, axis II)



Patino et al. Mov Disord Clin Pract 2026;13:1187-91

Phenocopies of HD

- **HDL1 – seizures, psychiatric features**
  - **AD, *prion protein, PRNP*; 20p12**
    Xiang et al. Am J Hum Genet 1998;63:1431
- **HDL2 – no seizures, blacks of South African origin**
  - **AD, *junctophilin, JPH3;* 16q24.3**
    Margolis et al. Ann Neurol 2001;50:373
- **HDL3 (?) – onset 3-4 years, intellectual deficit, dysarthria, dystonia, spasticity, ataxia, Saudi Arabia (1 family)**
  - **AR, 4p16.3 (?)**
    Kambouris et al. Am J Hum Genet 2000;66:445
- **HDL4 (?) = SCA17, markedly heterogeneous presentation**
  - **AD, *TATA-Box binding protein (TBP)*, CAA/CAG, 6q27**

HDL2

- Onset in the 3rd or 4th decade
- Death in 15-25 years
- African (South African founder effect) >>> Hispanic
- Early behavioral changes (social interactions)
- Progressive dementia
- Chorea
- Dystonia
- Parkinsonism
- Weight loss
- Acanthocytosis (?)
- CTG/CAG trinucleotide repeat expansion within the *junctophilin-3* (*JPH3*) gene on chromosome 16q24.3 (NL repeat length: 6-27 CTG/CAG triplets, HDL2: 41-58)

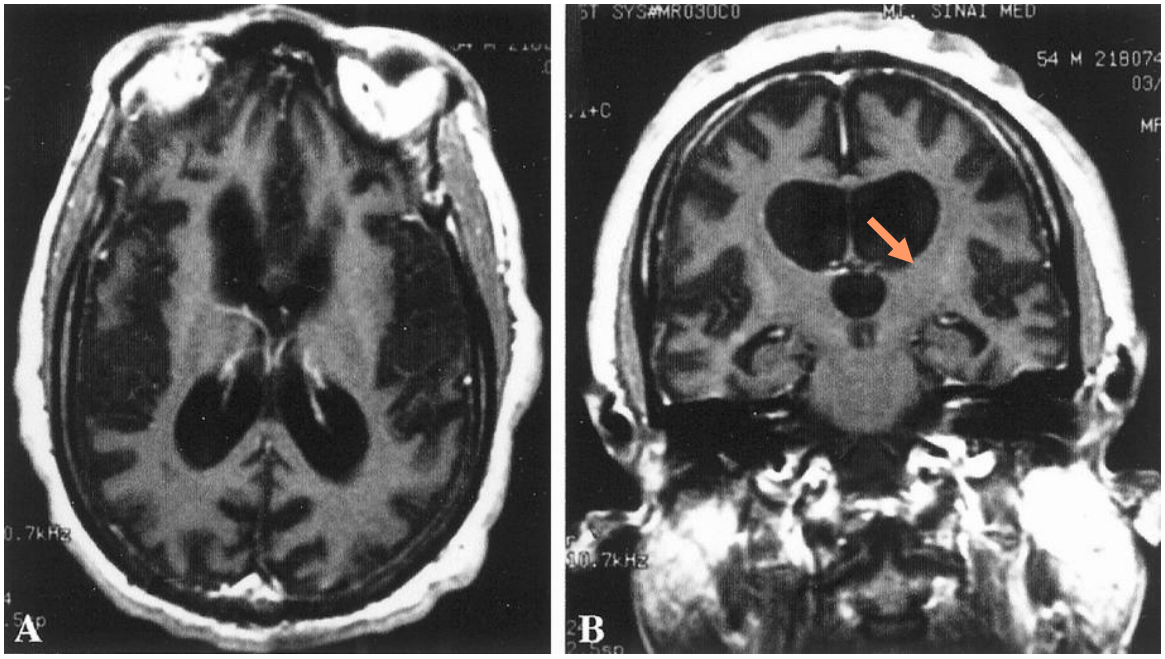
HDL2: 56 y/o initially diagnosed with HD, had 22 year hx of progressive changes in memory and personality, involuntary movements, and pseudobulbar affect.
Autopsy: severe striatal atrophy with neuronal loss and gliosis, intranuclear inclusions in the cortex, SN, and thalamus



Walker RH, Jankovic J, O'Hearn E, Margolis RL. Mov Disord 2003;18:1527-30

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HDL2
Marked Atrophy of Cerebral Cortex and Striatum



Walker RH, Jankovic J, O'Hearn E, Margolis RL. Mov Disord 2003;18:1527-30

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Dentatorubral-Pallidoluysian Atrophy (DRPLA)

- Particularly prevalent in Japan, also UK, US (Haw River syndrome)



- Age at onset: 30 (1^{st} – 7^{th} decade)
- Neuropathology: dentate, red and STN nuclei, GPe > striatum, SN, inf. olive, Purkinje cells, thalamus, lat. corticospinal tract, widespread demyelination and deposition of lipofuscin, intranuclear inclusions
- Mutation: Unstable CAG expansion (>35) in the *ATN1* gene on chromosome 12p13.31 coding for c-Jun NH(2)-terminal kinase

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Dentatorubral-Pallidoluysian Atrophy (DRPLA)

Early Onset	Late onset
<20	>20
Mild-moderate	Moderate-severe
Myoclonus	Ataxia (severe)
Epilepsy	Choreoathetosis
Intellectual impairment	Dystonia
	Rest and postural tremor
	Parkinsonism
	Dementia
	MRI - white matter changes
62 – 79 CAG repeats	54 – 67 CAG repeats

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DRPLA

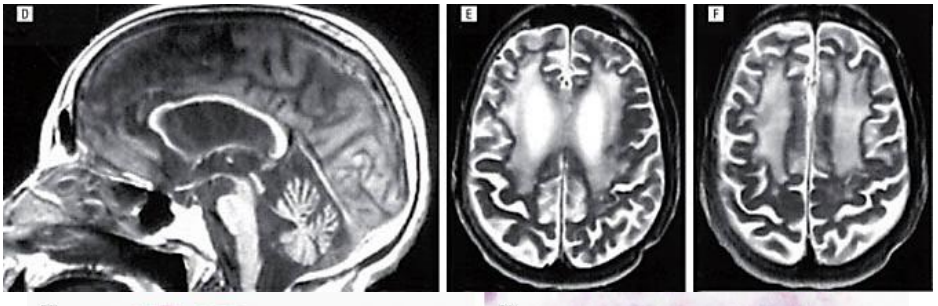
41 y/o presented at age 28 with writer's cramp; later developed chorea, anxiety, and dementia. Her mother and younger brother died of the same disease and another brother was in a NH with the diagnosis of "Huntington disease".

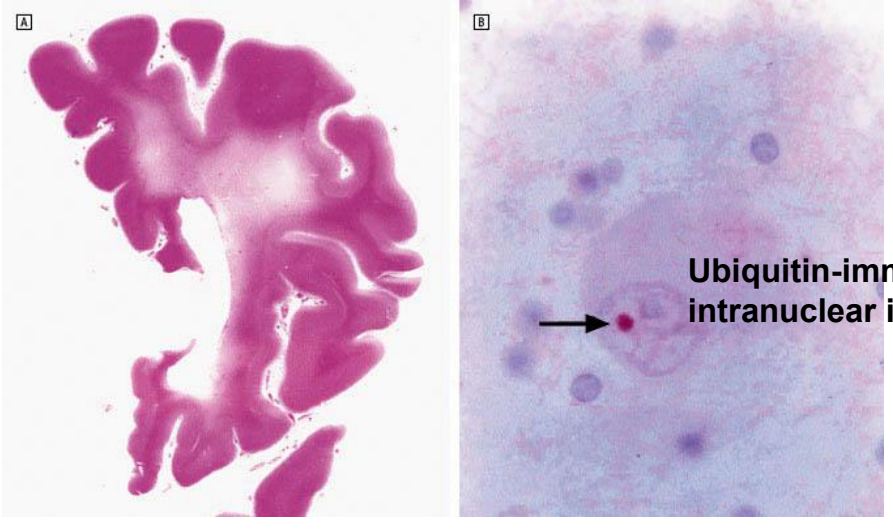


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DRPLA

62 y/o woman with severe cerebral white matter changes





Ubiquitin-immunoreactive intranuclear inclusion

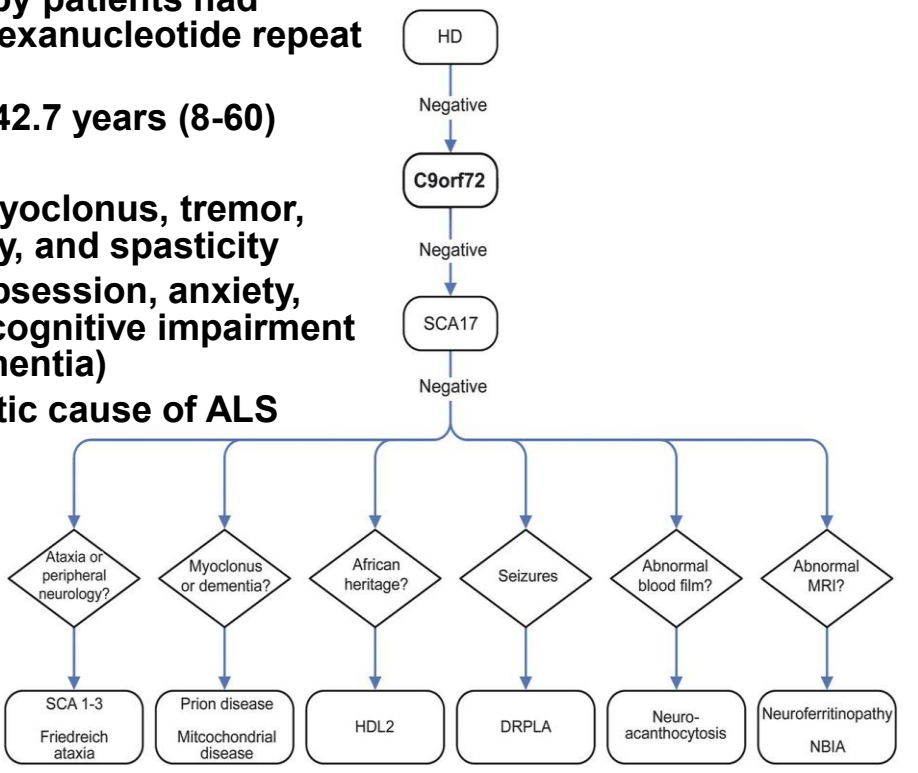
Munoz et al. Arch Neurol 2004;61:946-9

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C9orf72 expansions - the most common genetic cause of Huntington disease phenocopies.

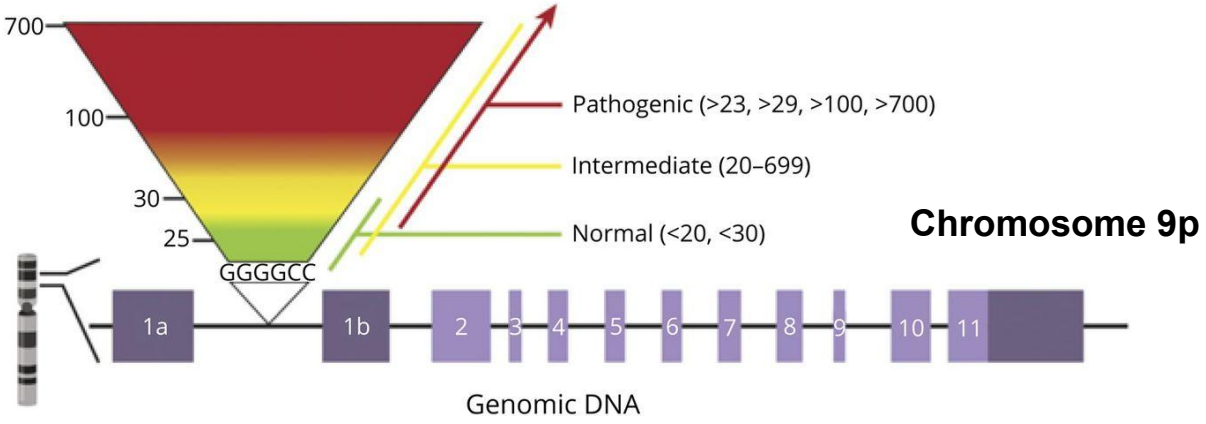
Hensman Moss et al. Neurology 2014;82:292-9

- **10/514 HD phenocopy patients had C9orf72 GGGGCC hexanucleotide repeat expansion**
- **Mean age at onset: 42.7 years (8-60)**
- **70% had FHx, AD**
- **Dystonia, chorea, myoclonus, tremor, bradykinesia, rigidity, and spasticity**
- **Early depression, obsession, anxiety, apathy, psychosis, cognitive impairment (frontotemporal dementia)**
- **Most common genetic cause of ALS**



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Clinical Spectrum of *C9ORF72*-Related Disorders

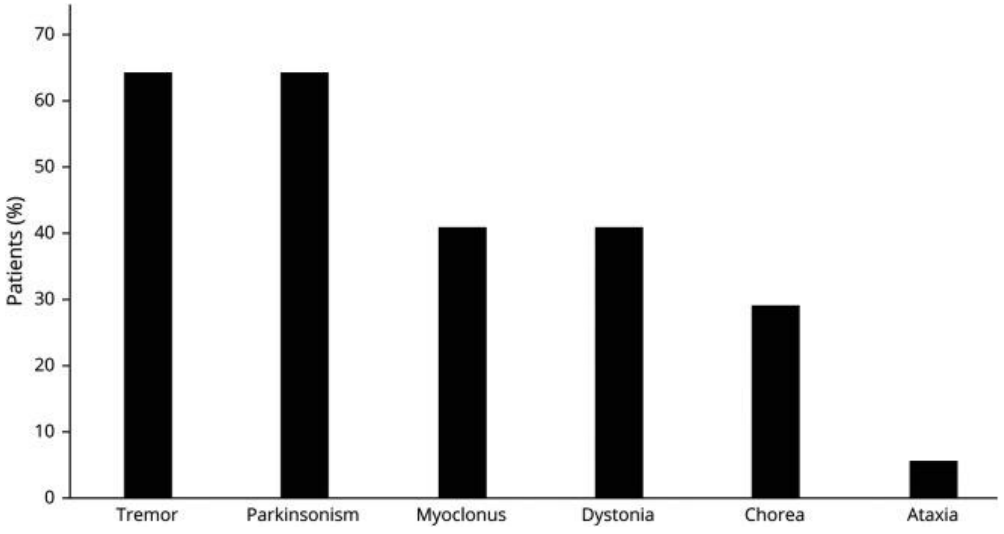


- **Since its discovery in 2011, a pathogenic hexanucleotide repeat expansion in the *C9ORF72* gene was found to be the leading genetic cause of ALS, FTD, and HDL.**
- **It also causes a variety of psychiatric and movement disorders, including clinically typical PD and atypical parkinsonism, etc.**
- **The repeat expansion causes both loss of function and gain of function (toxicity) with aggregation of TAR DNA-binding protein 43 (TDP-43).**

Breevoort et al. Neurol Genet 2022;8:e670

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Distribution of Movement Disorders in Patients With Hexanucleotide Repeat Expansions in *C9orf72*



ET-like tremor, parkinsonism, distal myoclonus, chorea with orofacial involvement, and cervical dystonia in the context of familial neurodegenerative conditions should prompt molecular genetic testing of the *C9orf72* gene.

Estevez-Fraga et al. Neurol Genet 2021;7:e575

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Neuroacanthocytosis

“Neuroacanthocytosis”, coined in 1985 to replace Levine-Critchley syndrome and choreoacanthocytosis and to draw attention to the heterogenous presentation with a variety of hyperkinetic and hypokinetic movement disorders in addition to other neurological deficits and abnormal laboratory findings.

Jankovic J, Killian JM, Spitz MC. Neuroacanthocytosis syndrome and choreo-acanthocytosis (Levine-Critchley syndrome). Neurology 1985;35:1679

Familial tic disorder, parkinsonism, motor neuron disease, and acanthocytosis: A new syndrome

Spitz MC, Jankovic J, Killian JM. Neurology 1985;35:366-370

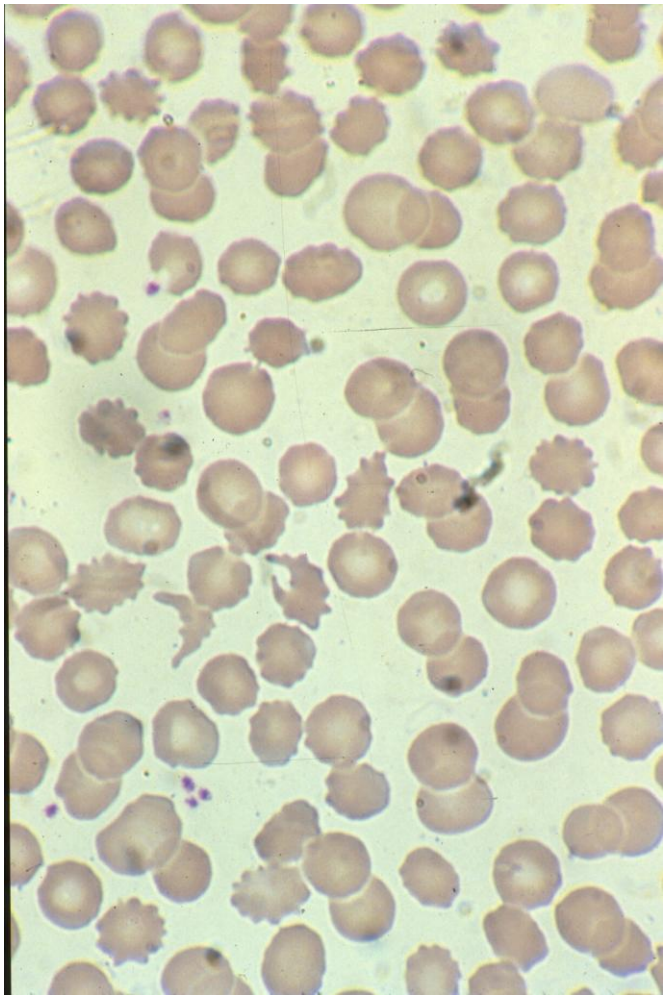
We report two brothers who were of consanguineous parents and who displayed a unique association of motor and vocal tics, parkinsonism, distal muscular atrophy and acanthocytosis. In the older brother, leg weakness and muscle wasting started at age 13, and he became wheelchair bound at 40. Electrophysiologic studies and muscle biopsy confirmed diffuse denervation. Involuntary vocalizations and facial tics began at age 36, but within 5 years the tics were replaced by progressive parkinsonism with supranuclear ophthalmoparesis. CSF studies implied impaired central dopamine and serotonin turnover. In the younger brother, orofacial tics started at age 36, vocalizations and fasciculations in the legs began 1 year later, and parkinsonian findings were present at age 40. This is the first report of an association of Tourettism, parkinsonism, motor neuron disease and acanthocytosis occurring as an autosomal recessive syndrome.

Suggested the term neuroacanthocystosis.

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Neuroacanthocytosis

- Onset: 20-40 yrs
- Autosomal recessive
- Chorea, dystonia, tics, parkinsonism, ophthalmoparesis
- Oro-buccal lingual dyskinesia (eating dystonia)
- Behavioral changes, dementia, OCD
- Seizures
- Peripheral neuropathy and myopathy
- Self-mutilation (lip-tongue biting)
- Absent tendon reflexes
- Elevated creatine kinase, liver function tests
- Hepatosplenomegaly



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Neuroacanthocytosis



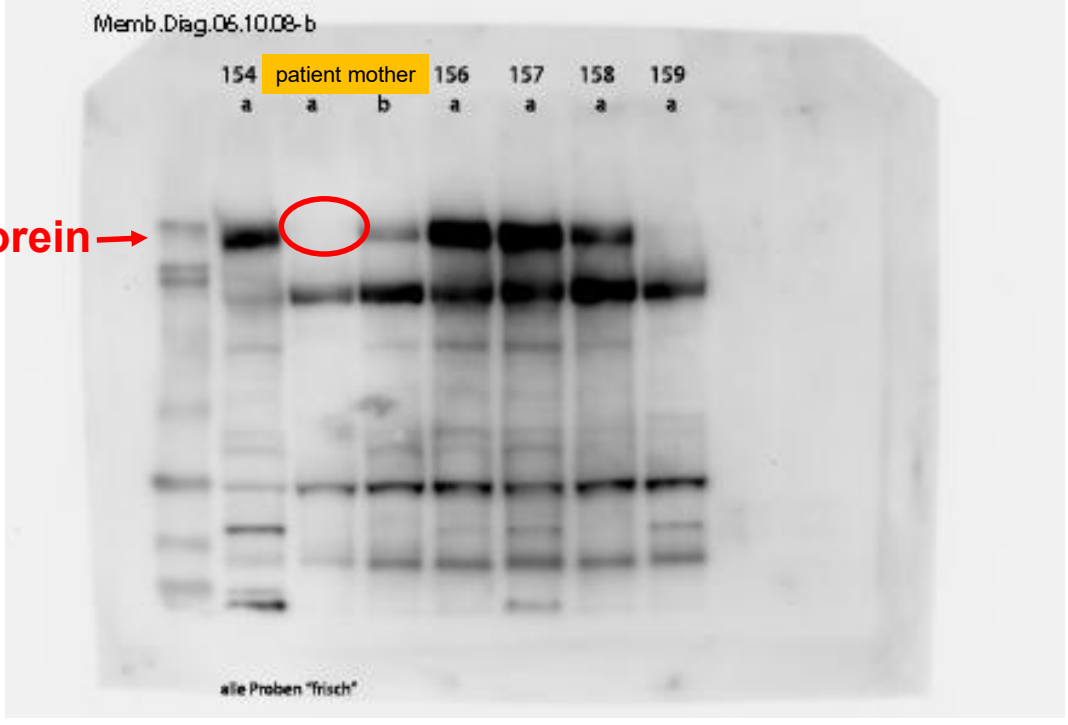
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Neuroacanthocytosis

- **Autosomal recessive (CHOR-VPS13A, OMIM 605978) disease caused by biallelic mutations in *VPS13A*, resulting in reduced or absent levels of its protein product vacuolar protein sorting 13 homolog A, VPS13A (chorein); large protein (3,174 AAs)**
- ***VPS13A* gene (9q21, 73 exons) ~100 different mutations (testing available via Invitae and Fulgent Genetics)**
- **VPS13A protein, chorein, localized between the ER and mitochondria; facilitates lipid transport**
- **Absence of expression of chorein (Western blot) in RBC membrane is strongly suggestive of a diagnosis of neuroacanthocytosis (www.naadvocacy.org)**

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Neuroacanthocytosis
Absence of Chorein (Western Blot)



Performed by Dr Benedikt Bader, Munich

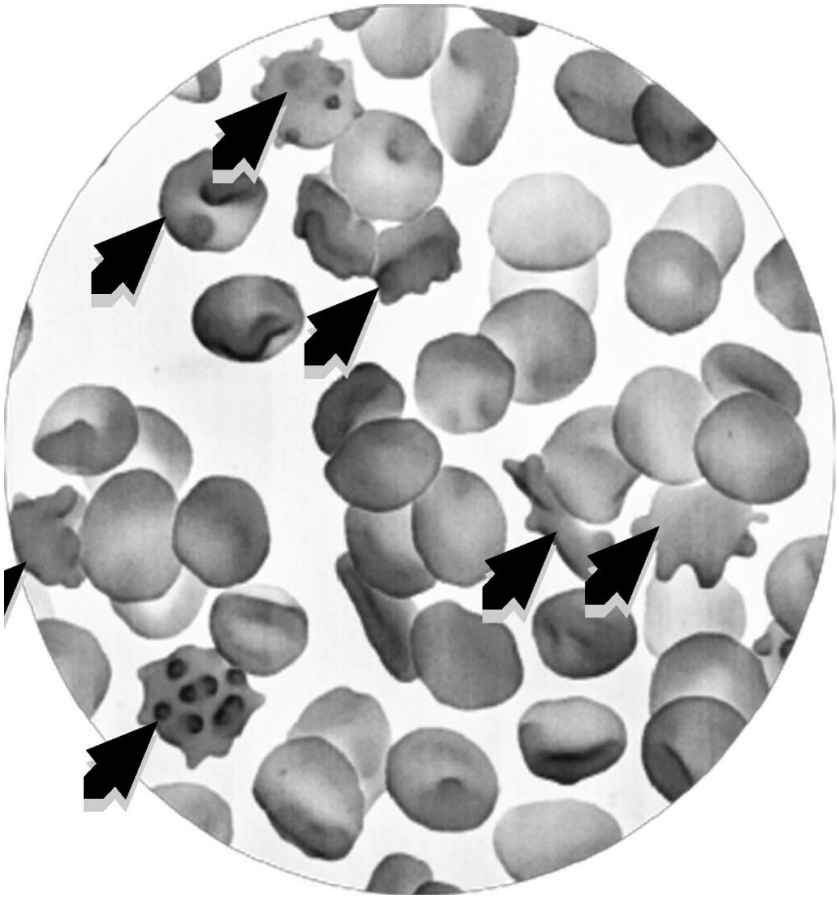
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Neuroacanthocytosis

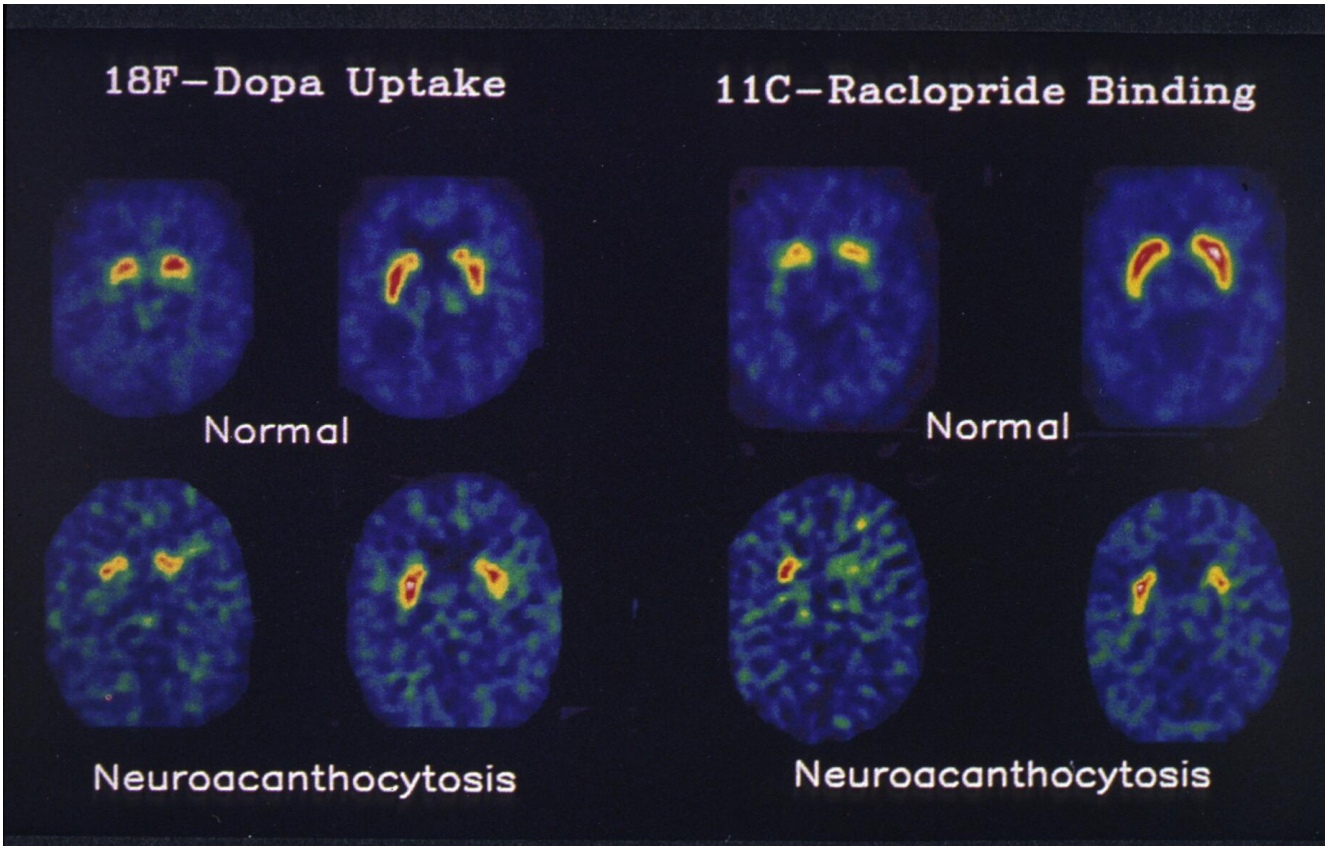
Laboratory Findings

- Acanthocytosis and echinocytosis; increased yield with dilution in saline, in vitro aging, contact with glass, and scanning EM; no longer necessary for diagnosis
- ↑ palmitic acid and ↓ stearic acid in RBCs
- ↑ CK
- EMG/NCV consistent with distal axonal sensorimotor polyneuropathy with dying-back
- PET
  - ↓ Caudate metabolism and striatal blood flow
  - ↓ {^{18}F} Dopa uptake in posterior putamen
  - ↓ {^{11}F} raclopride in caudate > putamen

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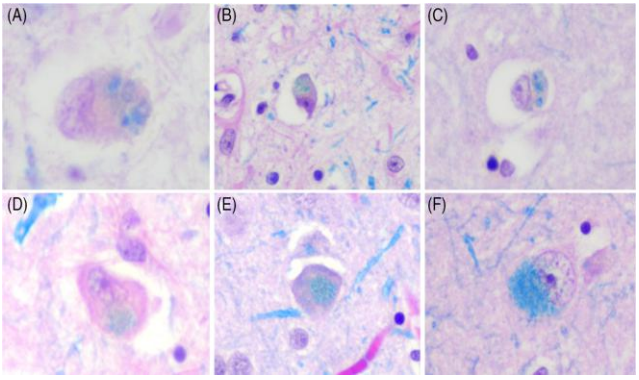
Brooks et al. Ann Neurol 1991;30:166-71

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Neuroacanthocytosis

Pathology and Neurochemistry

- Neuronal loss and gliosis in the striatum (caudate>putamen), sparing the GP and SN
- Striatal calcifications
- Axonal neuropathy of large myelinated fibers
- Luxol fast blue (LFB)-positive intracytoplasmic accumulations with variable patterns of granular lipid inclusions in the striatum and amygdala



Ditzel et al. Mov Disord 2023;38:2163-72

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Neuroacanthocytosis Syndromes

Characteristic	Chorea-Acanthocytosis	McLeod Syndrome
Gene	*VPS13A*	*XK*
Protein	Chorein	XK
Inheritance	Autosomal recessive	X-linked
Acanthocytes	+++	+++
Cellular compartment	Cytoplasm	Membrane
Membrane proteins affected	Band3/adducin, actin junctional complex	Band3/4.1R complex, actin junctional complex
Red blood cell phenotype	Unaffected	Weak Kell antigens, Kx antigen absent
Serum creatine kinase level, U/L	300-3000	300-3000
Neuroimaging	Striatal atrophy	Striatal atrophy
Age of onset, y	20-30	25-60
Chorea	+++	+++
Other movement disorders	Feeding and gait dystonia, tongue and lip biting, parkinsonism	Vocalizations, parkinsonism
Seizures	Generalized, partial-complex	Generalized
Neuromuscular manifestations	Areflexia, weakness, atrophy	Areflexia, weakness, atrophy
Cardiac manifestations	None	Atrial fibrilliation, malignant arythmias, dilative cardiomyopathy

Roulis et al. JAMA Neurol 2018;75:1554-62

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Parkinsonism and Related Disorders 64 (2019) 293–299

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Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

McLeod syndrome: Five new pedigrees with novel mutations

J. Weaver[a,*], H. Sarva[a], D. Barone[a], S. Bobker[a], K. Bushara[b,c], A. Hiller[d], M. Ishii[a], J. Jankovic[e], S. Lakhani[a], K. Niotis[a], D.W. Scharre[f], P. Tuite[b], A. Stutz[b], C.M. Westhoff[g], R.H. Walker[h,i]

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Neuroacanthocytosis
hyperCKemia
Obstructive sleep apnea

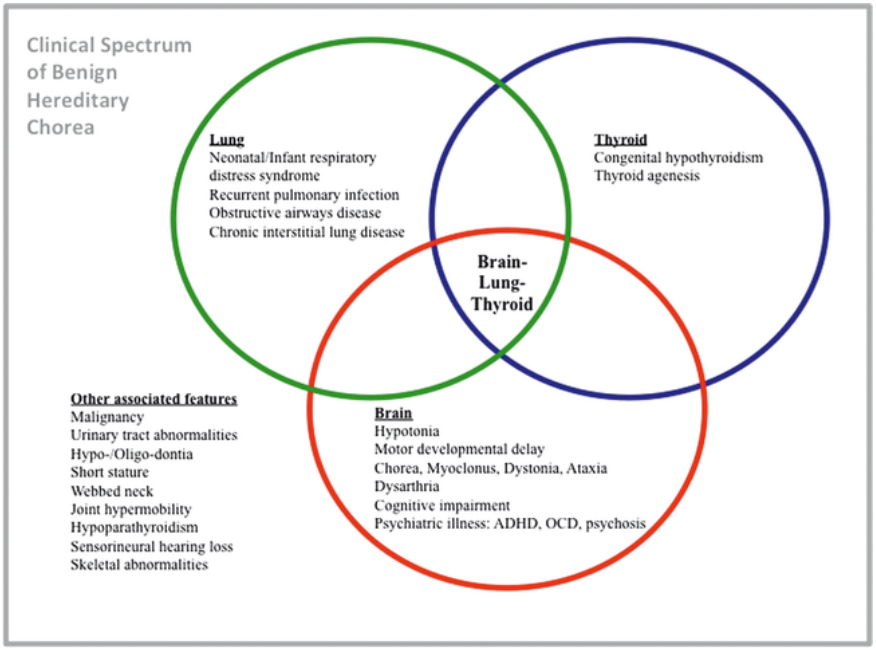
ABSTRACT

Objective: To present five new McLeod Syndrome (MLS) pedigrees with novel *XK* gene mutations, review the literature of this disorder, and discuss the typical and atypical clinical features noted with these new mutations.
Methods: This is a multi-center retrospective review of five MLS cases with novel gene mutations. Genotypic and phenotypic information has been obtained from each center.
Results: Five novel mutations are reported in this Case series. New clinical findings include prolonged asymptomatic elevated creatine kinase (CK) levels, vocal tics, presence of obstructive sleep apnea (OSA), and one patient of Vietnamese ethnicity.
Conclusions: We expand on the clinical and genetic spectrum of MLS demonstrating the clinical variability of MLS.

Brain-Lung-Thyroid (BLT) Syndrome
"Benign Hereditary Chorea"

- **Onset in early childhood; progresses until 2nd decade → static or spontaneously improves**
- **Intellectual impairment but no dementia**
- **MRI usually normal, but may show hypoplastic pallidum, lack of differentiation of medial and lateral components, and bilateral signal hyperintensities on T2-weighted images**
- **No pathological changes, but may have reduced number of striatal and neocortical interneurons**
- **Autosomal dominant – due to mutation in the thyroid transcription factor *NKX2-1* gene on chr 14q13.1–q21.1 (formerly *TITF1*)**
- ***NKX2-1* gene mutations should be considered in patients with chorea, growth hormone deficiency, pes cavus, kyphosis, duplex kidney, chronic lung disease, and congenital hypothyroidism**
- **May improve with levodopa, methylphenidate or VMAT2 inhibitors**
  Nou-Fontanet et al. Eur J Neurol 2023;30:3928-48

BLT (Brain-Lung-Thyroid) Syndrome



Peall KJ, Kurian MA. Tremor Other Hyperkinet Mov 2015;5:314

Patel NJ, Jankovic J. NKX2-1-Related Disorders. Updated 2023]. In: Adam et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. http://www.ncbi.nlm.nih.gov/books/NBK185066/

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Is Benign Hereditary Chorea Really Benign? Brain-Lung-Thyroid Syndrome Caused by *NKX2-1* Mutations.

Parnes M, Bashir H, Jankovic J. Mov Disord Clin Pract 2018;6:34-9

- **Since its localization to the *NKX2-1* gene in 2002, the phenotype of the disorder historically called "benign hereditary chorea" has been expanding beyond chorea.**
- **5 patients (3 females), ages 2-31 years, with confirmed pathogenic variants in *NKX2-1*.**
- **All patients exhibited chorea, gross motor delay, and gait impairment. Other symptoms included neonatal respiratory failure (n=4), cognitive deficits (n=3), hypothyroidism (n=4), joint laxity (n=2), myoclonus (n=1), hypotonia (n=3) and seizures (n=1). Chorea often proved refractory to medical therapies.**
- **Conclusion: The phenotype associated with pathogenic variants in *NKX2-1* frequently includes disabling and often medically-refractory neurologic and non-neurologic abnormalities.**

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Clinical characterization of individuals with *NKX2-1*-related disorders (*NKX2-1*-RD)

- **N=68 (37 F; median age 16 yrs, range 2-60 yrs)**
- **Neurodevelopmental delay 94%**
- **Movement disorders: Chorea 92.7%, hypotonia 57.4%, dystonia 46.3%, gait abnormalities 34.3%, myoclonus 32.8%, dysarthria 14.9%, tremor 9.0%; frequent falls 61%**
- **Neonatal respiratory distress syndrome 35.5%, respiratory symptoms 57.6%**
- **Hypothyroidism 82%**
- **Psychiatric comorbidity (>1/3): ADHD, anxiety and depression**

Nou-Fontanet et al. Mov Disord 2026;41:889-900

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31 y/o with *NKX2-1* mutation and chorea. History of respiratory failure after birth and ongoing thyroid dysfunction. Delayed motor milestones. Initially, chorea well controlled with TBZ but worsened after pregnancy with marked deterioration of gait requiring walker. She subsequently improved with levodopa. Her daughter also had respiratory failure at birth, generalized chorea and ataxia.



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Gain-of-Function *ADCY5* Mutations in Familial Dyskinesia with Facial Myokymia

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Objective: To identify the cause of childhood onset involuntary paroxysmal choreiform and dystonic movements in 2 unrelated sporadic cases and to investigate the functional effect of missense mutations in adenylyl cyclase 5 (*ADCY5*) in sporadic and inherited cases of autosomal dominant familial dyskinesia with facial myokymia (FDFM).
Methods: Whole exome sequencing was performed on 2 parent–child trios. The effect of mutations in *ADCY5* was studied by measurement of cyclic adenosine monophosphate (cAMP) accumulation under stimulatory and inhibitory conditions.
Results: The same de novo mutation (c.1252C>T, p.R418W) in *ADCY5* was found in both studied cases. An inherited missense mutation (c.2176G>A, p.A726T) in *ADCY5* was previously reported in a family with FDFM. The significant phenotypic overlap with FDFM was recognized in both cases only after discovery of the molecular link. The inherited mutation in the FDFM family and the recurrent de novo mutation affect residues in different protein domains, the first cytoplasmic domain and the first membrane-spanning domain, respectively. Functional studies revealed a statistically significant increase in β-receptor agonist-stimulated intracellular cAMP consistent with an increase in adenylyl cyclase activity for both mutants relative to wild-type protein, indicative of a gain-of-function effect.
Interpretation: FDFM is likely caused by gain-of-function mutations in different domains of ADCY5—the first definitive link between adenylyl cyclase mutation and human disease. We have illustrated the power of hypothesis-free exome sequencing in establishing diagnoses in rare disorders with complex and variable phenotype. Mutations in *ADCY5* should be considered in patients with undiagnosed complex movement disorders even in the absence of a family history.

ANN NEUROL 2014;75:542–549

ADCY5-Related Movement Disorder

- Autosomal dominant or recessive disorder caused by mutations in the *ADCY5* gene (3p21-3q21.9) that codes for adenyl cyclase 5, a striatal-specific enzyme that converts ATP into cAMP.
- The original family was described as "familial dyskinesia and facial myokymia", but subsequent reports have de-emphasized facial myokymia and focused on a combination of initially paroxysmal and progressive chorea, dystonia, myoclonus, tremor, spasticity in the legs, and axial hypotonia (in the neck and trunk).
- Fluctuating but non-progressive course with episodic, paroxysmal, exacerbations upon awakening, triggered by sleep, intercurrent illnesses, excitement, or stress; attacks may resemble medial frontal lobe seizures (EEG is usually normal).
- Additional features: language delay, "myopathic facial appearance", heart failure, often misdiagnosed as "cerebral palsy" or "functional".
- No effective pharmacologic treatment, but the following may provide some relief: caffeine, theophylline, clonazepam, clobazam, tetrabenazine, acetazolamide, and GPi DBS.

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ADCY5-related movement disorders: Frequency, disease course and phenotypic variability in a cohort of paediatric patients

Miryam Carecchio [a, b, c, 1], Niccolò E. Mencacci [d, e, *, 1], Alessandro Iodice [f], Roser Pons [g], Celeste Panteghini [a], Giovanna Zorzi [b], Federica Zibordi [b], Anastasios Bonakis [h], Argyris Dinopoulos [i], Joseph Jankovic [j], Leonidas Stefanis [h], Kailash P. Bhatia [k], Valentina Monti [a], Lea R'Bibo [d], Liana Veneziano [l], Barbara Garavaglia [a], Carlo Fusco [f], Nicholas Wood [d], Maria Stamelou [m, h, 2], Nardo Nardocci [b, 2]

CONCLUSION: Mutations in *ADCY5* are responsible for a hyperkinetic movement disorder that can be preceded by episodic attacks before the movement disorder becomes persistent and is frequently misdiagnosed as dyskinetic cerebral palsy. A residual degree of neck hypotonia and a myopathy-like facial appearance are frequently observed in patients with *ADCY5* mutations.

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ADCY5-related movement disorders

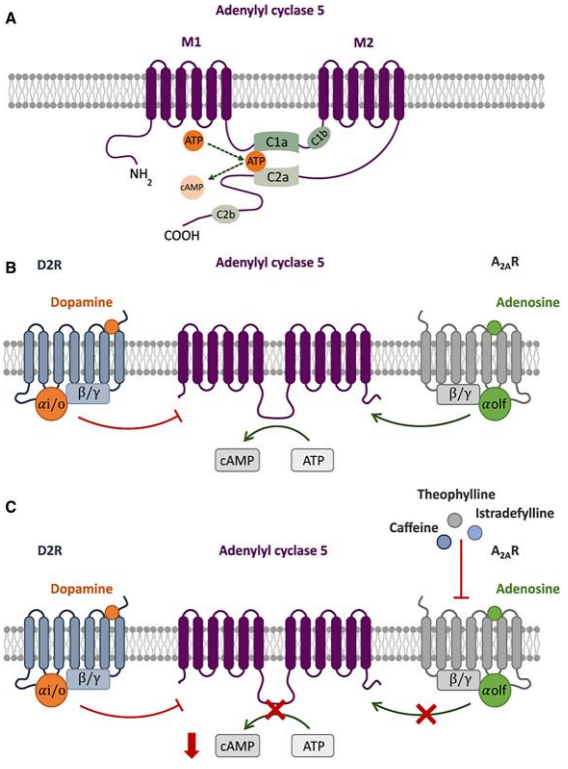
Carecchio et al. Parkinsonism Relat Disord 2017;41:37-43

Patient #	ADCY5 mutation	Gender	Family history	AAO (MD)	Current age	Additional signs at onset	MD at onset	Current MD	Nocturnal paroxysms	Diurnal paroxysms	Paroxysmal episodes amelioration	Motor delay
Pt 1	c.1252 C>T; p. R418W	F	N	1.5	15	Axial hypotonia	Paroxysmal dystonic episodes	Chorea, dystonia	Y	Y	Y	Y
Pt 2	c.1253 G>A; p.R418Q	M	N	1	18	Spastic gait	Paroxysmal dystonic episodes	Myoclonus, dystonia	Y	Y	Y	Y
Pt 3	c.1252 C>G; p.R418G	M	Y	1	3	Axial hypotonia	Chorea, dystonia	Chorea, dystonia	N	N	NA	Y
Pt 4	c.1252 C>G; p.R418G	M	Y	3	47	UK	Chorea	Chorea, dystonia	Y	Y	N	Y
Pt 5	c.1252 C>T; p. R418W	F	N	3 mo	35	Axial hypotonia	Chorea	Chorea, dystonia	Y	Y	Y	Y
Pt 6	c.1252 C>T; p. R418W	M	N	2	5	Axial hypotonia	Paroxysmal dystonic episodes	Chorea, dystonia	N	Y	N	Y

Additional Features: **language delay, myopathic facial appearance, exacerbation during sleep (no EEG correlate), variable course (spontaneous improvement), often misdiagnosed as cerebral palsy**

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Adenyl Cyclase Protein



- Most *ADCY5* mutations result in a gain-of-function response with increased binding of ATP and increased levels of cAMP.
- The phenotype is affected by the location of the mutations within the protein.
- Mutations in the C1a domain seem to have a more severe presentation, with 78% having onset in infancy, 71% nocturnal movements, 79% paroxysmal worsening, 86% axial hypotonia, 43% painful dystonia, 71% facial movements, and 36% brisk reflexes.
- Mutations in the M1 and M2 domain have been associated with a spastic paraparesis phenotype.

Menon et al. Mov Disord Clin Pract 2023;10:1048-59

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ADCY5-Related Movement Disorder
Generalized chorea, loss of balance, intermittent hypotonia associated with paroxysmal falls



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6 y/o girl with prior diagnosis of dyskinetic cerebral palsy, global developmental delay with moderate intellectual disability. WES revealed a mutation in *ADCY5* gene. MRI brain was normal.



Courtesy M. Parnes, MD

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Efficacy of Caffeine in ADCY5-Related Dyskinesia: A Retrospective Study.

Méneret et al. Mov Disord 2022;37:1294-8

- **A worldwide retrospective study in 30 patients with a proven *ADCY5* mutation.**
- **26 (87%) reported an improvement in overall movement disorders of 40% or more and thus were considered to be caffeine responders.**
- **Theophylline (5-20 mg/kg/day; 400 mg/day of slow-release theophylline) may be more effective than caffeine (60 to 800 mg/day).**

- **Caffeine, theophylline, and istradefylline reduce cAMP by inhibiting the A2A receptor.**
  Tänzler et al. PLoS One 2023;18:e0282593



GNAO1-Related Movement Disorders

- AD inheritance;*GNAO1* encodes the alpha subunit of guanine nucleotide binding protein; mutations result in gain-of-function abnormalities related to the control of cAMP levels affecting neurotransmitter release
- Severe early-onset hyperkinetic syndrome, with prominent chorea, orofacial dyskinesia, dystonia (arousal opisthotonos)
- Fluctuates, with critical and life-threatening exacerbations, such as status dystonicus
- The presence of chorea appears to be predictive of a higher risk of movement disorder emergency - may require DBS

Schirinzi et al. Parkinsonism Relat Disord 2019;61:19-25

Sex	
Female	27(58.7%)
Male	19(41.3%)
Movement disorders features	
Age in months at MD onset† [mean(median)±SD]	24.2(17) ± 23.3
Chorea	27(58.7%)
Dystonia	30(65.2%)
Dyskinesia	29(63%)
MD emergencies	21(45.7%)
Need for intensive care hospitalization	19(41.3%)
Surgical treatment	10(21.7%)
Neuroimaging Features	
Cortical atrophy	21(45.7%)
White matter abnormalities	18(39.1%)
Basal ganglia abnormalities	3(6.5%)
Epileptic features	
Epilepsy	22(47.8%)
Epileptic encephalopathy	9(19.6%)‡
Age in months at epilepsy onset [mean(median)±SD]	28.9(3)±43.6
Total seizure control	10(45.4%)
Partial seizure control	1(4.5%)
Intractable seizures	5(22.7%)
No data	6(27.2%)
Follow up data	
Death	4(8.7%)
Age in years at exitus [mean(median)±SD]	4.8(4) ±3.8
Age in years at last follow up [mean(median)±SD]	6.9(5) ±4.8

Clinical characteristics of *GNAO1* patients

GNAO1 patients N = 157 (%)	
Sex	
Female	89/157 (56.68%)
Male	67/157 (42.67%)
Mean age (last follow-up) [mean ± SD]	11 y (±1–66 y)
Developmental delay	139/157 (88.5%)
Hypotonia	115/157(73.2%)
Movement Disorder	139/157 (88.5%)
Age at MD onset [mean]	51 months
Dystonia	107/157 (68.2%)
Chorea	68/157 (43.3%)
Dyskinesia	56/157 (36.6%)
Parkinsonism	20/157 (12.73%)
Ocular abnormalities	10/157 (6.36%)
Periodic exacerbations	62/157 (39.5%)
Status dystonicus - need for ICU	46/157 (29.29%)
Surgery	35/157 (22.29%)
Epilepsy	75/157 (47.77%)
Feeding difficulties	44/157 (28.0%)
Dysmorphic features	16/157 (10.2%)
Neuroimaging abnormalities	62/157 (39.49%)
Cortical atrophy	40/157 (25.47%)
White matter abnormalities	21/157 (13.37%)
Basal ganglia abnormalities	15/157 (9.55%)
Follow up data: deceased patients	14/157 (8.9%)

Novelli et al. Parkinsonism Relat Disord 2023;111:105405

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Genotype-phenotype correlation and treatment effects in young patients with *GNAO1*-associated disorders.

Thiel et al. J Neurol Neurosurg Psychiatry 2023;94:806-15

- **Symptom onset within the first months of life, with central hypotonia or seizures.**
- **Within the first year of life, nearly all patients developed a movement disorder comprising dystonia (84%) and choreoathetosis (52%); 12 (48%) suffered life-threatening hyperkinetic crises; 15 (60%) had epilepsy with poor treatment response.**
- **9(38%) patients were treated with bilateral GPi DBS which reduced hyperkinetic symptoms and prevented further hyperkinetic crises.**
- **Conclusion: The broad clinical spectrum and genetic findings expand the phenotypical spectrum of *GNAO1*-associated disorder. No specific overall genotype-phenotype correlation was identified. DBS is a useful treatment option in this disorder.**

Dystonia may respond to levodopa.
Vasconcellos et al. Tremor Other Hyperkinet Mov 2023;13:11

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*GNAO1-A*ssociated chorea

3 y/o girl with developmental delay, seizures, chorea exacerbated during febrile illness; markedly improved after GPi DBS



Courtesy M. Parnes, MD

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Neurodegeneration with Brain Iron Accumulation

NBIA	Inheritance	Clinical Features
NBIA/DYT-PANK2	AR	Pantothenate kinase-associated neurodegeneration (PKAN) (NBIA1): dystonia, spasticity, parkinsonism, cognitive decline, eye-of-a-tiger sign
NBIA/DYT/PARK-PLA2G6	AR	PLA2G6-associated neurodegeneration (PLAN) (NBIA2/PARK14): dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood), LB pathology, infantile neuroaxonal dystrophy
NBIA/CHOREA-FTL	AD	Neuroferritinopathy (NBIA3): dystonia, chorea, parkinsonism, oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritin
NBIA/MPAN C19orf12	AR/AD	Mitochondrial membrane protein associated neurodegeneration (MPAN) (NBIA4): dystonia, levodopa-responsive parkinsonism, tremor, gait impairment, optic nerve atrophy, axonal motor neuropathy; Lewy body pathology
NBIA/PARK-WDR45	X-Linked	Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome) (NBIA5): parkinsonism, dystonia, stereotypies, developmental delay, intellectual disability, behavioral symptoms, autism, seizures, spasticity
NBIA/DYT/PARK-CP	AR	Aceruloplasminemia; dystonia, chorea, parkinsonism, tremors, ataxia; cognitive decline, behavioral symptoms, diabetes mellitus, retinal degeneration, anemia, liver iron storage
HSP/NBIA-FA2H	AR	Fatty acid hydroxylase-associated neurodegeneration (FAHN); spasticity, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizures (SPG35)

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Neurodegeneration with Brain Iron Accumulation (NBIA) (PKAN secondary to *PANK2* mutation)



Eye-of-a-tiger Sign

Sethi et al.
Ann Neurol1988;24:692-4

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Profile

Kapil Sethi: all about water buffaloes and refusing to be boring



Published Online
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S1474-4422(17)30466-0

You may know him as Professor Emeritus of Neurology at the Medical College of Georgia, Augusta University (Augusta, GA, USA), as director of the College's Movement Disorders Program (1985–2016), or perhaps as director of its National Parkinson's Foundation Center of Excellence (2000–2009). You may know him from the many (many) clinical trials on Parkinson's disease, restless legs syndrome, and other movement disorders with which he has been involved. Many of you will know him best as your teacher—the expert in movement disorders who tried to make your medical training more meaningful, more relevant, and whenever possible, more fun. His own primary school teachers back in the Punjabi town of Sultanpur, however, knew him as the little rascal who used to run away from school and who had to be dragged back to class (yes, truly held on jute mats under a shade tree). While he tells me his story, I wonder if what I write should be a tribute to him or to those teachers, whose brilliant educational diagnosis and application of the right treatment planted the seed that grew into those different Kapils we know today.

"I hated didactic teaching and was bored stiff", he remembers. "After leading school prayer at 9 am I used to quickly run away to play with boys who never did any schooling. We would jump on the backs of water buffaloes and bathe in the stream nearby to cool off. I have vivid memories of the schoolteacher sending half the class to find me, and of the bigger boys who brought me back, kicking and screaming. The teachers soon discovered that the only way to keep me in school was for me to teach a junior class and sometimes even my own. I guess that set the stage for the rest of my life."

To stop his own medical students from running away, Kapil has championed the idea of patient-centred, problem-based learning. "It's about starting with a patient's problem and learning backwards", he explains. "In traditional medical teaching, students don't see a patient for at least two years, but as soon as they get into a clinical rotation their eyes light up! They realise that everything they learnt for those two years was for a reason, but they also know that that time was SO boring! But does it have to be so? In our movement disorder program we have students from the first year seeing patients, at least on videos. They want to be doctors, and this way they see the problems that people have. We then help them try to come to a diagnosis and choose treatment options. The book learning on disease mechanisms, patient management, the equations, etc. comes later and is integrated into this clinical experience, making that learning more meaningful." His own teachers at the DAV College, Jalandhar (Punjab, India), where Kapil did his undergraduate studies, didn't use those techniques, "...and during my fist year I missed half the didactic classes and watched about 200 Bollywood movies instead", he recalls (perhaps not without a little shame).

But while Kapil is best known in different ways to different people, everybody knows him as the judge at Neurobowl, one of the most popular opening events at the annual American Academy of Neurology meetings. "Neurobowl was the brainchild, over 20 years ago, of Tom Swift, my Augusta colleague and mentor. We collect case examples of difficult and rare cases, and everyone tries to figure out what the patient may have and how to help. It's educational, it's training, and it's fun. Basically, it's how we teach in our movement disorder program." The International Parkinson and Movement Disorder Society now runs something similar at its meetings called the Video Challenge—and guess who is Co-Master of Ceremonies? Were it not for his father's insistance, however, he might never have sat in the judge's seat. "I wanted to be a singer when I was young, but my Dad thought I wouldn't make a very good living at it, and he had other ideas", he recalls. "Basically, he told me that I was going to be a doctor! I have, however, kept my interest in music and learned to play amateurish tabla and I still sing Hindi and Panjabi songs". In fact, he is a member of a band along with his daughter and son-in-law.

After Kapil's arrival in Georgia in 1983 following a two-year stint in the UK and seven years training in India (having graduated in medicine from the Christian Medical College in Ludhiana, Punjab), it was the same Tom Swift who suggested he develop an interest in movement disorders. "And after nine and a half years of residency, I was sick of being trained and re-trained", says Kapil, "so one fine morning I declared myself to be a movement disorders specialist. Now all I had to do was prove that I was not a fake!"

Just before our time winds up, Kapil mentions something that makes movement disorders seem the perfect career choice for someone who in his own words "hated didactic teaching". "With these disorders you always have to start with the patient," he insists. "It's about keen observation and coming to a diagnosis through that. You can't learn that from a book." It kind of sums him up. As I pack my recording equipment, my thoughts drift back to that empty jute mat under the shade tree, and I wonder what Kapil's primary school teachers would think of him now, and of their achievement: a professor of movement disorders made out of a little boy who, long ago, they understood how to make sit still.

Adrian Burton

Lancet Neurol 2018;17:583

Neuroferritinopathy:

Expanding the phenotype and geography

Ondo WG, Adam OR, Jankovic J, Chinnery P. Mov Disord 2010;25:2470-2

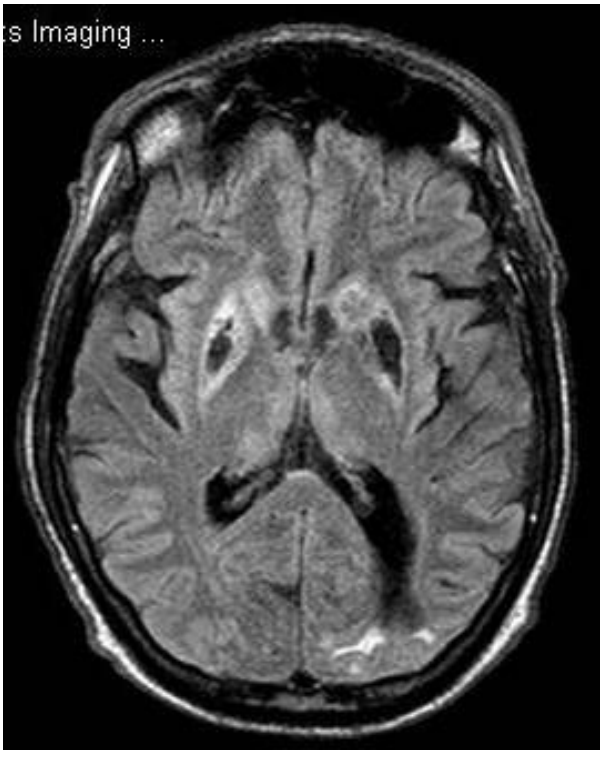
72 y/o with 22 yr hx of stereotypy, chorea, OMD, BG abnormalities, and c.460dupA *FTL* mutation (codes for ferritin light polypeptide).

49 y/o son with adult onset tics, chorea and similar MRI abnormalities. Improved with tetrabenazine.

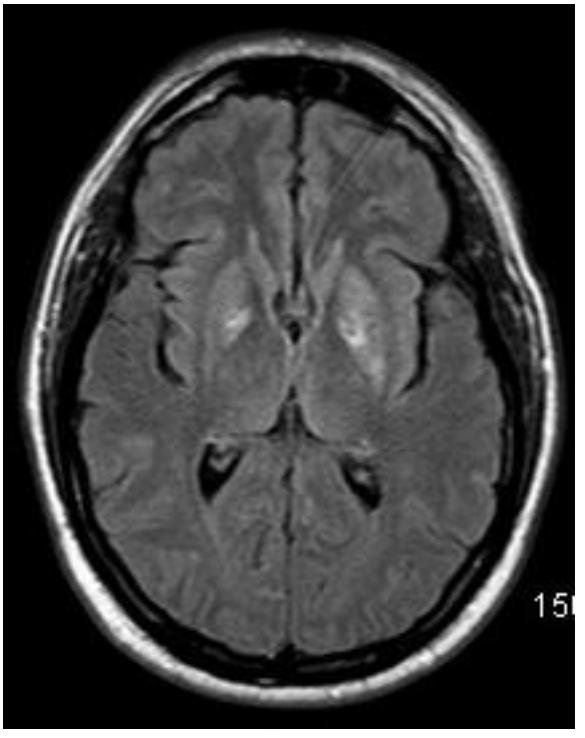


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MRI – Flair
72 y/o

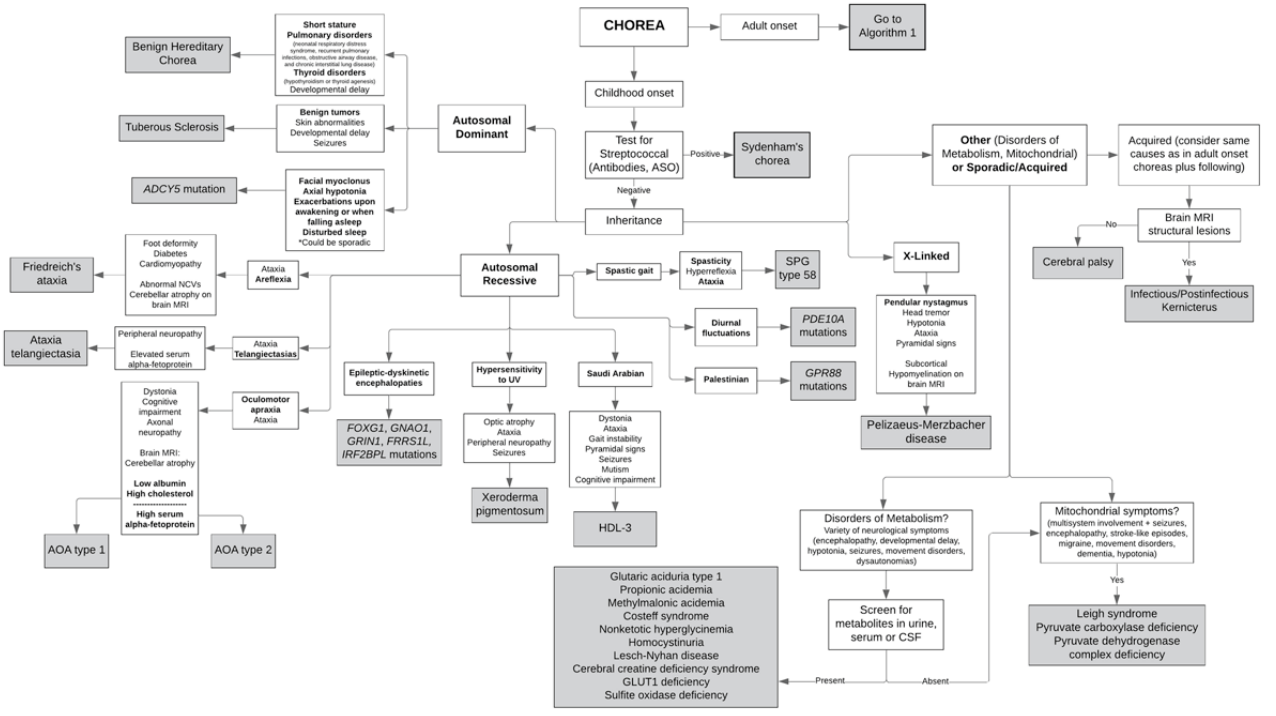


MRI – Flair
49 y/o son



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Early/childhood-onset choreas



Martinez-Ramirez et al. Tremor Other Hyperkinet Mov 2020;10:24



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Differential Diagnosis of Chorea

Inherited Choreas

- HD (*HTT*)
- HDL1 (*PRNP*), HDL2 (*JPH3*)
- DRPLA (*JNK*)
- Neuroacanthocytosis (*VPS13A*)
- McLeod (*HK*)
- Brain-Lung-Thyroid (*NKX2-1*)
- *ADCY5*-Related movement disorder
- *C9orf72* expansion
- NBIAs: PKAN, neuroferritinopathy, aceruloplasminemia, infantile neuroaxonal dystrophy (PLA2G6); mitochondrial membrane protein-associated neurodegeneration (MPAN; *C19orf12*)
- **Wilson disease**
- **Ataxia-chorea: SCA 1,2,3,8,17; Friedreich's ataxia, AOA, AT**
- **Mitochondrial disorders**
- **Other genetic choreas:** ***GNAO1, FOXG1, PDE10A, PDE2A, OPA3, PCCA/PCCB, FITM2, TWNK, TANGO2, ATP1A2 and 3, HPCA, RFC1, PURA, AIFM1, Notch3***

Sporadic/Secondary Choreas

- **Static encephalopathy - CP**
- **Sydenham chorea**
- **Other autoimmune choreas (SLE, APS, NMDAR encephalitis, paraneoplastic syndromes, etc)**
- **Vascular chorea, polycythemia, moyamoya (genetic component)**
- **Creutzfeldt-Jakob Disease**
- **Hyperthyroidism**
- **AIDS**
- **Tardive dyskinesia**
- **Metabolic encephalopathy**
  - **Hepatolenticular degeneration**
  - **Non-ketotic hyperglycemia**
  - **Hypoglycemia**
  - **Renal failure**
  - **Ketogenic diet**
- **Functional (psychogenic) chorea**

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Sydenham's Chorea
Clinical Features

- **In 1686 Thomas Sydenham, English physician, described chorea minor in a chapter "On Saint Vitus' dance"; Richard Bright, English physician, in 1831 noted that chorea was "intimately connected with rheumatism".**
- **Typical age at onset: 7-10, <30 years**
- **4-8 weeks after pharyngitis caused by group A β-hemolytic streptococcus (GABHS)**
- **70% cardiac (mitral valve) involvement, 30% arthritis**
- **Chorea in 26% of patients with rheumatic fever, in 20% the only finding**
- **Usually asymmetrical (20% - hemichorea)**
- **Individual contractions are slightly longer (>100 msec) compared to HD (50-100 msec), but both have reduced corticospinal excitability as demonstrated by TMS studies (possibly compensatory?)**
  (Hallett and Obeso. Mov Disord 2015;30:169-70; Khedr et al. Mov Disord 2015;30:259-62)

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Sydenham's Chorea
Clinical Features

- **Often associated with neuropsychiatric symptoms including ADD, obsessive compulsive behaviors (≤70%), personality changes, emotional lability, anxiety, age-regressed behaviors, and anorexia**
- **Other features: motor impersistence (tongue darting, milkmaid, and pronator sign), hypometric saccades, tics, clumsiness, dysarthria, and hypotonia (8% have "chorea paralytica" due to profound hypotonia)**
- **Usually spontaneously resolves in 3-4 months, but may persist in half of the patients during a 3-year follow up (OCD, ADD); some patients have residual cognitive deficits, impaired verbal fluency, psychiatric symptoms, and mild parkinsonism**
- **May recur during pregnancy ("chorea gravidarum")**
  - **15/20 (75%) patients developed chorea gravidarum**
  - **All patients with chorea gravidarum who were later treated with oral contraceptives developed recurrence of chorea**
    Maia et al. Parkinsonism Relat Disord 2012;18:458-61

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Sydenham's chorea



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Sydenham's Chorea
Diagnosis

- The combination of antistreptolysin (ASO), positive in only 10-30% of cases, and antideoxyribonuclease B (ADNaseB) antibodies has a high sensitivity and specificity (also antihyaluronidase and antistreptokinase antibodies)
- MRI is usually normal, but may show enlargement of the striatum and globus pallidus
- 18F-fluorodeoxyglucose PET scan – slightly increased metabolism

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Sydenham's Chorea
Pathogenesis

- **Molecular mimicry between GABHS and CNS antigens**
- **Antibodies from patients with SC bind to neuronal surface and also target neuronal tubulin**
- **Rats immunized with GABHS developed antibodies against D1 and D2 receptors and clinically showed compulsive–like behaviors** (Brimberg et al. Neuropsychopharmacology 2012;37:2076-87) **and passively-transferred serum obtained from GABHS-immunized mice caused behavioral disturbances** (Yaddanapudi et al. Mol Psychiatry 2010;15:712-26)
- **Antibodies targeting lysoganglioside of group A Streptococcus cross react with dopamine D1 and D2 receptors** (Cunningham. Microbiol Spectr 2019;7:4)

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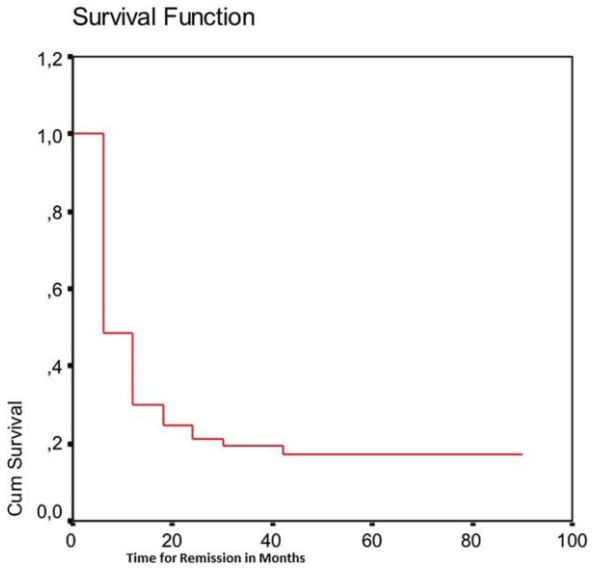
Sydenham's Chorea
Treatment

- **A 10-day course of oral penicillin or an IM injection of benzathine penicillin G at the time of diagnosis. Sulfa drugs are commonly used for those individuals with a penicillin allergy.**
  Oosterveer et al. Pediatr Neurol 2010;43:1-6
- **Penicillin prophylaxis is advisable in all patients for 5-10 years after rheumatic fever or carditis. WHO recommends 1.2 million units of penicillin G administered IM every 21 days.**
- **A DBPC study of prednisone (2 mg/kg/day for 4 weeks with a 25-day taper) showed beneficial effects on chorea and prognosis (remission), but relapses may still occur.**
  Paz et al. Pediatr Neurol 2006;34:264-9
- **IVIG (1 g/kg on 2 consecutive days), Plasmapheresis, Rituximab (?)**
- **Symptomatic treatment**
  - **VMAT2 inhibitors, valproic acid, and carbamazepine until the condition resolves spontaneously**

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Sydenham's Chorea
Prognosis

A Kaplan-Meyer curve of the time for remission of a cohort of 108 patients with Sydenham chorea prospectively followed



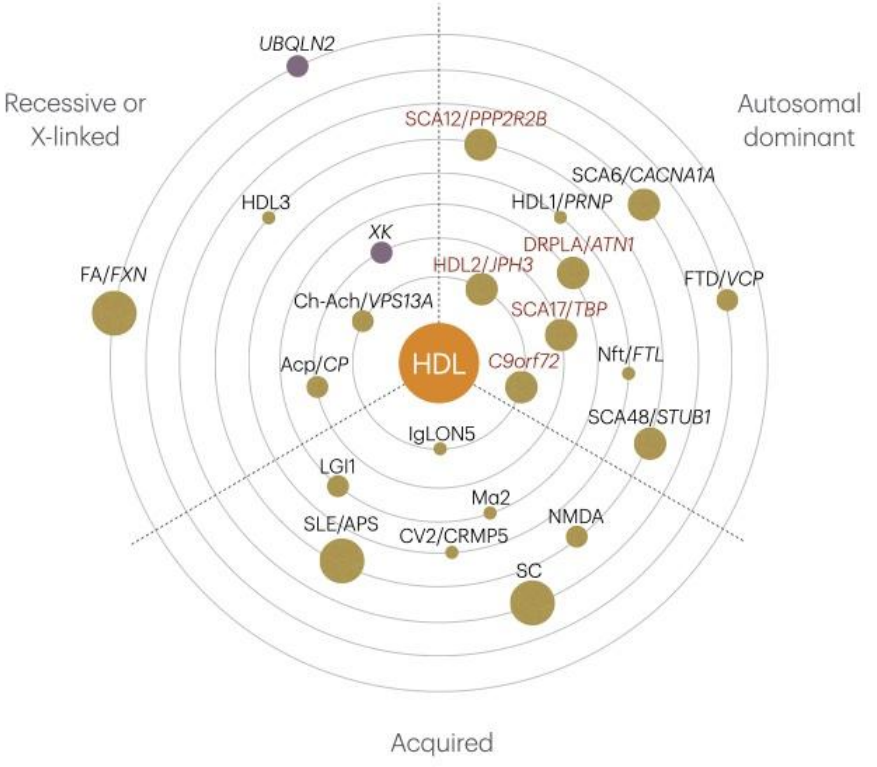
- **Self-limited condition with remission after a course of 8–9 months, but up to 50% of patients may remain with chorea after a follow-up of 2 years**
- **Despite regular use of secondary prophylaxis, recurrences are observed in up to 30% of patients (often without association with streptococcus infection or even anti-basal ganglia antibodies); chorea gravidarum**

Cardoso F. JNNP 2017;88:412-7

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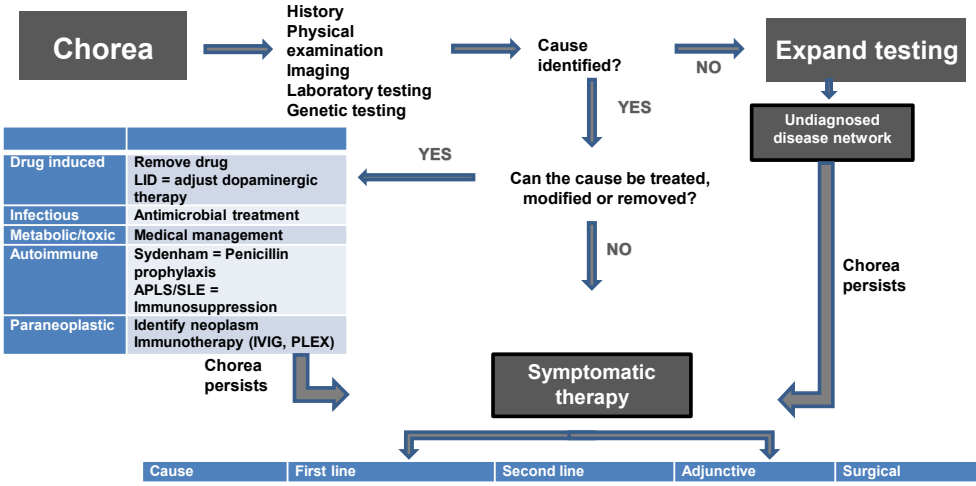
Non-Huntington's disease chorea: an expanding universe with acquired causes.

Cardoso et al. Brain 2026;149:1860-73



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Diagnostic and Therapeutic Approach to Chorea

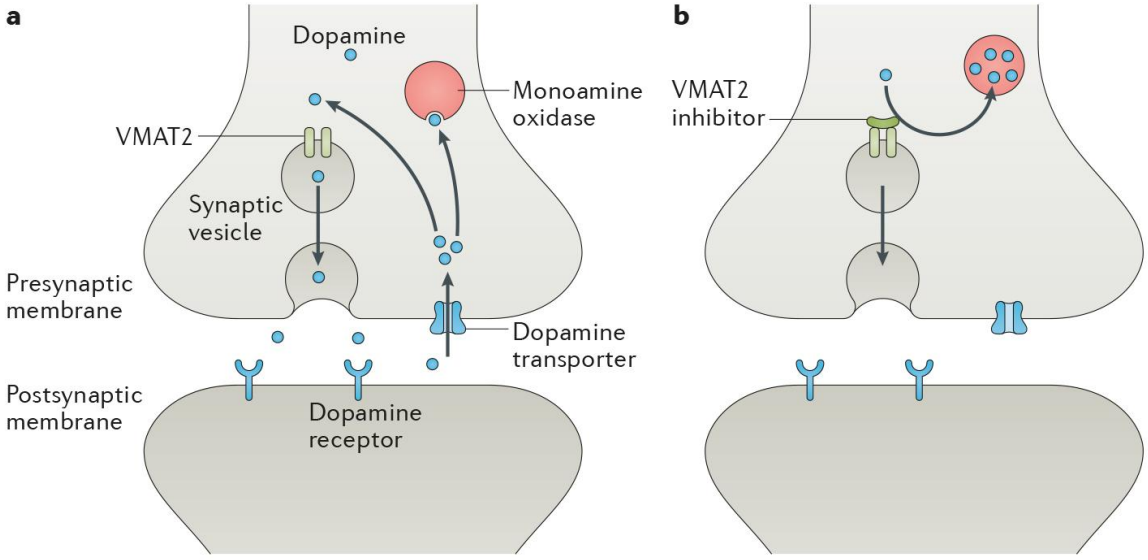


Cause	First line	Second line	Adjunctive	Surgical
Huntington's disease	Deutetrabenazine TBZ Antipsychotic - Tiapride (EU), olanzapine (UK)	Antipsychotic (olanzapine, quetiapine, other)	Amantadine Clonazepam Levetiracetam Other (cannabinoid etc.)	GPi Other targets under study
BLT	Levodopa	TBZ, anti-psychotic	-	-
Tardive Dyskinesia	Valbenazine, deutetrabenazine	TBZ, anti-epileptic	BoNT, clonazepam	GPi or STN
LID	Amantadine	Antipsychotic	Clonazepam	GPi or STN
PKD	CBZ, PHT	Other anti-epileptics	TBZ, levodopa	-
Sydenham's	VPA, CBZ (mild-moderate) Steroids (severe)	Antipsychotic Immunotherapy (IVIG, PLEX)	Clonazepam	-
Unspecified	Dopamine depleter	Antipsychotic	Several	Consider DBS, rTMS

APLS = antiphospholipid antibody syndrome, BLT = brain-lung-thyroid, BoNT = botulinum toxin, CBZ = carbamazepine, DBS = deep brain stimulation, EU = European Union, GPi = globus pallidus internus, IVIG = intravenous immunoglobulin, LID = levodopa-induced dyskinesia; PHT = phenytoin, PKD = paroxysmal kinesigenic dyskinesia, PLEX = plasma exchange/plasmapheresis, rTMS = repetitive transcranial magnetic stimulation, SLE = systemic lupus erythematosus, STN = subthalamic nucleus, TBZ = tetrabenazine, UK = United Kingdom, VPA = valproic acid.

Bashir H, Jankovic J. Expert Rev Neurother 2018;18:51-63

Mechanism of action of VMAT2 inhibitors



Vesicular membrane transporter type 2 (VMAT2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase.

VMAT2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase.

VMAT2 inhibitors do not cause tardive dyskinesia

Jankovic. Nature Reviews Neurology 2017;13:76-78

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Ballism

- Involuntary, flinging, coarse, random, continuous movement
- Predominantly proximal
- Usually unilateral (hemiballism), but may be bilateral (paraballism)
- More severe hemiballism tends to be associated with a lesion in the subthalamic nucleus
- May evolve into dystonia
- Often improves spontaneously
- Many locations and etiologies
- Usually associated with lesions, but not always (e.g. levodopa-induced dyskinesia)

Lesion-induced hemichorea-ballism: A systematic review of 586 cases

Elina Myller [a,b,*], Vilja Minkkinen [a], Elizabeth G. Ellis [a,c], Daniel T. Corp [a,c,d], Joseph Jankovic [e], Sanjay Pandey [f], Juho Joutsa [a,b]

Parkinsonism Relat Disord 2026

Lesion Location

Total number of cases, N	586
Basal ganglia, n (%)	343 (58.5%)
Subthalamic nucleus, n (%)	144 (24.6%)
Putamen, n (%)	108 (18.4%)
Caudate nucleus, n (%)	102 (17.4%)
Globus pallidus, n (%)	73 (12.5%)
Substantia nigra, n (%)	28 (4.8%)
"Basal ganglia", not specified, n (%)	27 (4.6%)
Thalamus, n (%)	158 (30.0%)
White matter, n (%)	152 (25.9%)
Cortex, n (%)	112 (19.1%)
Brainstem, n (%)	45 (7.7%)
Cerebellum, n (%)	14 (2.4%)
Extracerebral, n (%)	13 (2.2%)

STN involvement was reported in only 24.6% of patients, but it leads to a more severe disorder

Lesion Etiology

Total number of cases, N	586
Stroke, n (%)	477 (81.4%)
Infarction, n (%)	374 (63.8%)
Intracerebral hemorrhage, n (%)	95 (16.2%)
Hemorrhagic infarction, n (%)	8 (1.4%)
Other etiologies, n (%)	109 (18.6%)
Infection/abscess, n (%)	33 (5.6%)
Tumor, n (%)	32 (5.5%)
Inflammatory lesion, n (%)	13 (2.2%)
Malformation, n (%)	11 (1.9%)
Anoxic/hypoxic lesion, n (%)	9 (1.5%)
Traumatic contusion, n (%)	3 (0.5%)
Subdural hematoma, n (%)	2 (0.3%)
Other: cyst, central nervous system lupus, tuberous sclerosis, perivascular lesion, n (%)	6 (1.0%)

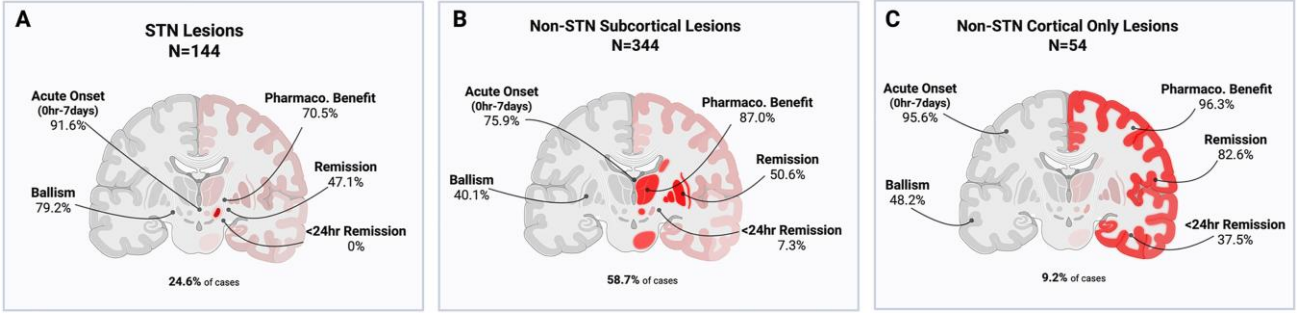
150

Lesion-induced hemichorea-ballism: A systematic review of 586 cases

Elina Myller [a,b,*], Vilja Minkkinen [a], Elizabeth G. Ellis [a,c], Daniel T. Corp [a,c,d], Joseph Jankovic [e], Sanjay Pandey [f], Juho Joutsa [a,b]

Parkinsonism Relat Disord 2026

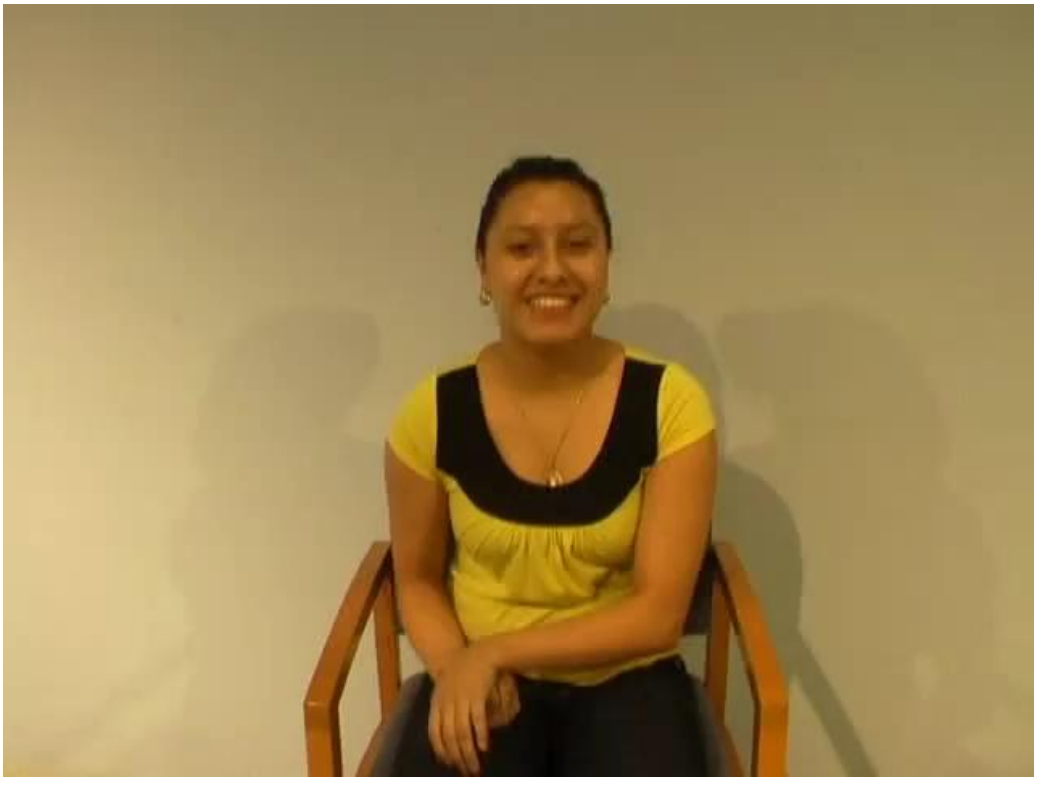
Differences in clinical characteristics and outcome according to the lesion locations



83.1 % had acute symptom-onset and 52.8 % of cases remitted. Cases with STN lesions more often showed ballism, had a shorter symptom latency, benefited less often from symptomatic pharmacotherapy, more often underwent functional neurosurgery, and showed a longer delay to remission, compared to cases with non-STN lesions (P < 0.05). Pure cortical lesions were associated with a more favorable prognosis.

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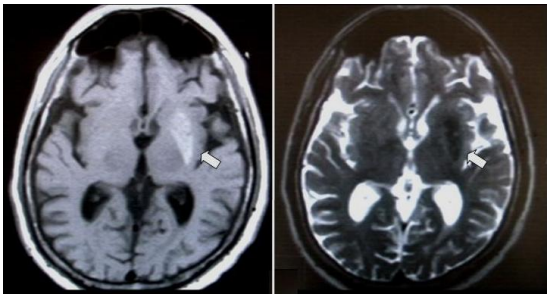
17 y/o with involuntary movement of RUE for 3 years
L STN-Midbrain AVM



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Hemiballism In Acute Hyperglycemia Without Ketosis





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Hyperglycemic chorea/ballism

- **Majority are women, >65 years of age**
- **Almost all patients have decompensated DM type 2 upon arrival to the ER; chorea usually develops within 1 month after an episode of hyperglycemia; may be the presenting feature of DM**
- **Majority have unilateral chorea/ballism**
- **Most common MRI finding was abnormalities of the contralateral basal ganglia; putamen T1-hyperintensity (often misdiagnosed as hemorrhage)**
- **After glucose correction, the chorea usually resolves within one week without recurrence**
- **Responsive to dopamine blocking or depleting agents**
- **Although rare, hyperglycemic chorea is usually reversible and should always be considered in cases of hemichorea/hemiballism**

Ryan et al. Parkinsonism Relat Disord 2018;48:97-100
Costa Hoffmeister et al. Arch Endocrinol Metab 2024;68:e220413

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Hemiballism: Prognosis and Treatment

- **Prognosis is usually good**
- **Some patients develop contralateral parkinsonism**
- **Therapy should preferentially target the etiology**
- **If the patient is disabled by the persistent hemiballism, drugs such as dopamine depleters may be tried**
- **GPi DBS**

  Masood et al. TOHM 2023;13:21

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Athetosis

- Writhing, random, movements (slow chorea)
- Induced by voluntary movement ("overflow")
- May co-exist with chorea (choreoathetosis) and dystonia
- Differentiate from pseudoathetosis (loss of proprioception)
- Cerebral palsy is the most common cause of childhood-onset athetosis

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Dyskinetic Cerebral Palsy

- **CP is a developmental, non-progressive disorder manifested by abnormal movements (chorea, athetosis, dystonia), spasticity and/or ataxia, accompanied by disturbances of cognition, behavior, communication, and other neurologic and musculoskeletal problems.**
- **CP is attributed to damage in the developing fetal or infant brain, such as perinatal hypoxia-ischemia, intracranial hemorrhage or cerebral infarction, neonatal hyperbilirubinemia (kernicterus), and brain maldevelopment.**
- **Prevalence: 1.7-3.1/1000 live births, higher in developing countries; the most common cause of disability in early childhood.**
- **Dyskinetic CP is the third most common form of CP (15%), after spastic (hemiplegic > quadriplegic > diplegic) and ataxic CP.**
- **Dystonia, choreoathetosis – exacerbated by action.**
- **Exclude CP mimickers, e.g. Dopa responsive dystonia (DRD), Sepiapterin reductase deficiency (SRD), Beta-propeller protein-associated neurodegeneration (BPAN); *NKX2-1, ADCY5, GNAO1, KANK1, FOXG1*-related disorders, Glut1 deficiency, Ataxia telangiectasia, Congenital disorders of glycosylation (CDG), Lesch-Nyhan, HSP, etc.**

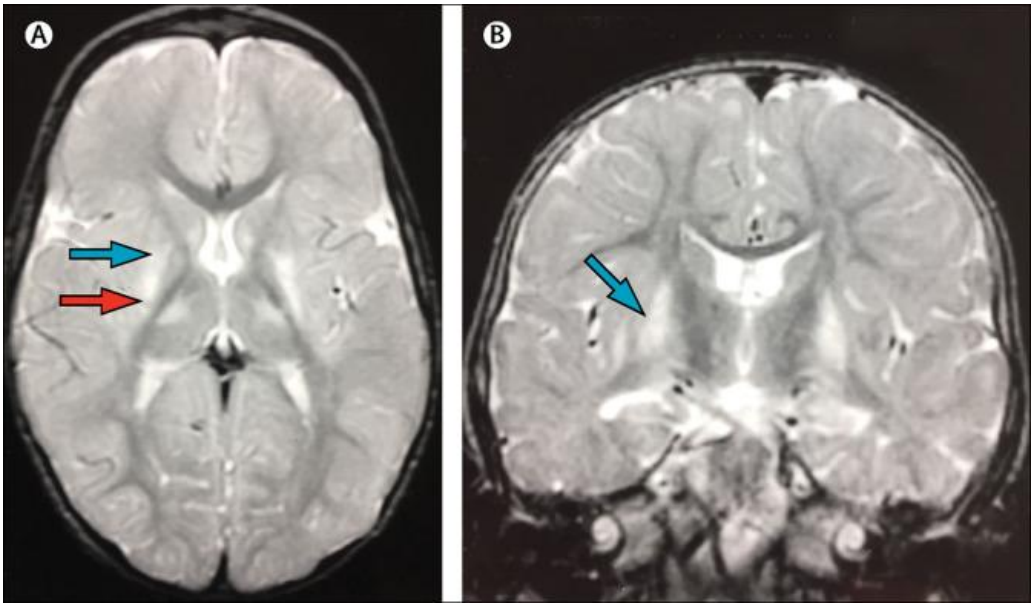
Monbaliu et al. Lancet Neurol 2017;16:741-9

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70% of CP patients have lesions in the BG or thalamus (10% have normal MRI)



T2-weighted MRI images of the transverse plane and coronal plane
bilateral focal hyperintensity in posterior putamen, mediolateral thalamus, and central region

Monbaliu et al. Lancet Neurol 2017;16:741-9

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Cerebral palsy
("Static Encephalopathy")

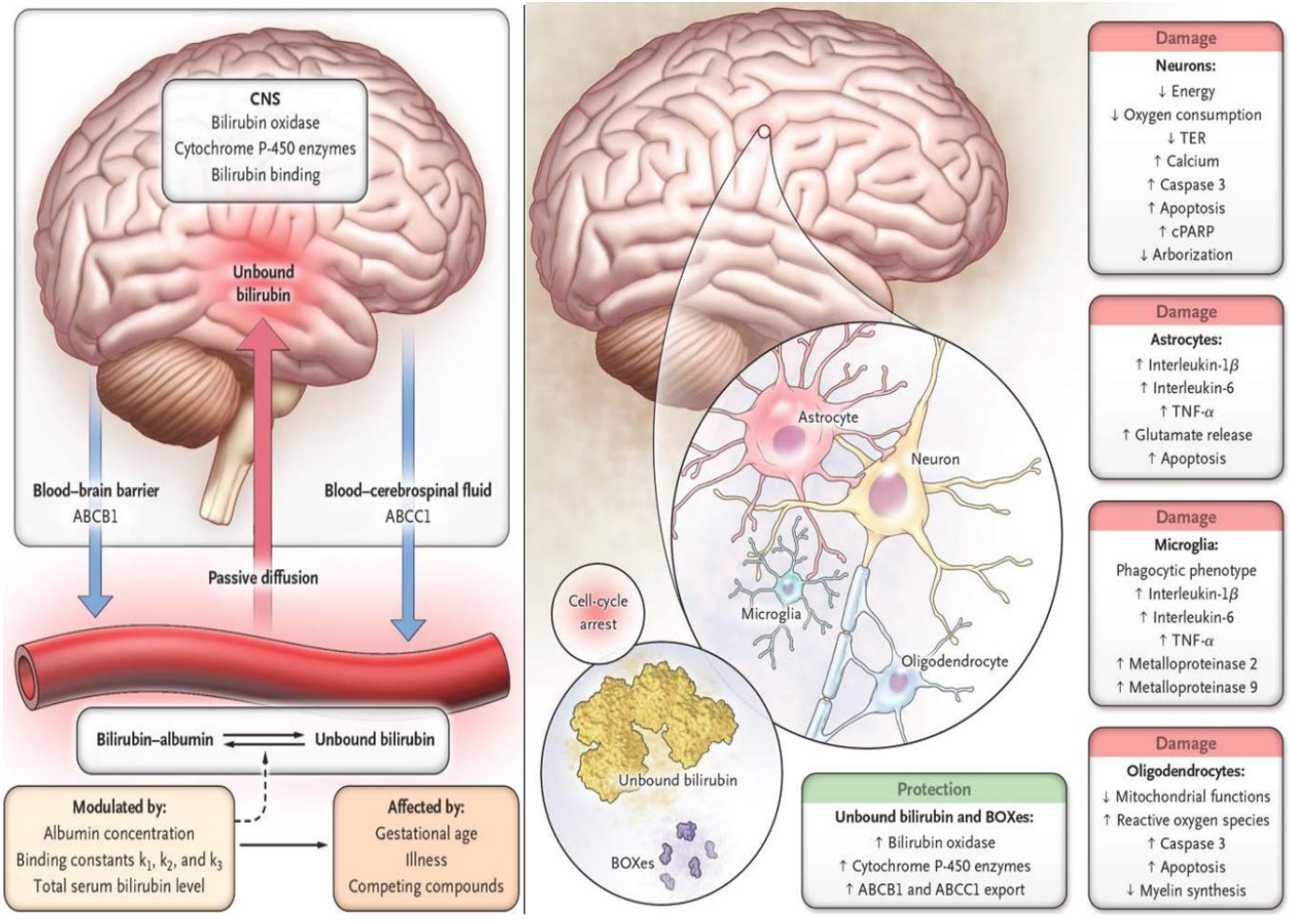
- **58 brains** (Tsusi et al. Neuropathology 1999;19:14-27)
  - **1. microgyria-pachygyria (N = 45)**
  - **2. thinned cerebral mantle (N = 10)**
  - **3. hydrocephalus (N = 3)**
- **Early macrophage reaction, cytokine production, coagulation necrosis, coupled with intrinsic vulnerability of the immature oligodendrocyte → periventricular leukomalacia**
  Kadhim et al. Neurology 2001;56:1278
- **Perinatal events are most important pathogenic determinants, but genetic factors are increasingly recognized (5-10% family history)**
- **Rarely delayed-onset and progressive**
  Scott and Jankovic. Neurology 1996;46:68-74 N = 53

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Bilirubin Encephalopathy:
Acute (kernicterus) and Chronic (post-kernicterus)

- Blood group incompatibility between the mother and the fetus → hemolysis → unconjugated bilirubin >20 mg/dL → CNS damage
- Affects 3% of neonates in developing countries (due to inability to measure total serum bilirubin, high prevalence of 6-phosphate dehydrogenase deficiency, Rh isoimmunization, and sepsis)
- Delayed developmental milestones
- Vertical ophthalmoparesis
- Deafness
- Dysplasia of the dental enamel
- May be delayed and progressive
- MRI - bilateral lesions of GP ± STN

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Watchko JF, Tiribelli C. N Engl J Med 2013;369:2021-30

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Kernicterus

7 y/o from Nigeria, product of second pregnancy, first pregnancy terminated in stillbirth, neonatal jaundice. Partial deafness, dental problems, mild oculomotor dysfunction



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Medical Treatment of Dyskinetic CP

	Mechanism of action	Dystonia	Chorea	Side-effects
Dopamine agonists (levodopa)[55]	Enhances the activity of dopamine	Used	..	Nausea, orthostatic hypotension, and constipation
Anticholinergic (trihexiphenidyl, benzatropine)[51,55]	Blocks acetylcholine muscarinic receptor	Used	..	Drowsiness, confusion, memory difficulty, blurred vision, hallucinations, urinary retention, and worsening chorea
Benzodiazepine receptor agonists (diazepam, clonazepam)[55,58]	Enhances GABA-A inhibition	Used	Used	Sedation, confusion, depression, ataxia, and dependence
GABA-B receptor agonist (baclofen)[51,55-57]	Enhances the activity of GABA-B receptor	Used	..	Worsening chorea, incontinence, sedation, dizziness, dry mouth, and increased blood glucose
Dopamine and serotonin antagonist (clozapine)[56]	Binds to serotonin and dopamine receptors and prevents release	Used	..	Decreased white blood cell count, sedation, hypotension, myocarditis, cardiomyopathy, drooling, arrhythmia, seizures, and diabetes mellitus
(tetrabenazine)[24,55,59] deutetrabenazine	resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine storage			anxiety, and akathisia
Monoamine depleters (reserpine)[51]	Blocks the vesicular monoamine transporter	..	Used	Nasal congestion, nausea, vomiting, weight gain, gastric intolerance, gastric ulceration, stomach cramps and diarrhoea, hypotension, bradycardia, and worsening of asthma
Voltage-gated sodium and calcium channel blocker (carbamazepine)[55]	Blocks voltage-sensitive sodium channels	Used	..	Decreased white blood cell count and platelets; increased risk of suicide
Calcium channel blocker (levetiracetam)[53,54]	Binds to a synaptic vesicle glycoprotein and inhibits presynaptic calcium channels, reducing neurotransmitter release and acting as a neuromodulator	..	Used	Somnolence, decreased energy, headache, dizziness, and (mild) ataxia
Muscle tone reducer (dantrolene)[59]	Reduces skeletal muscle tone at the muscle fibre level	Used	..	Speech and visual disturbances; depression and confusion; hallucinations; headache; insomnia and exacerbation or precipitation of seizures, and increased nervousness
Voltage-gated calcium channel blocker (gabapentin)[60]	Antagonises binding of thrombospondin to voltage-gated calcium channel a2d-1 receptors and inhibits synthesis of glutaminergic excitatory synapses	Used	..	Dizziness, drowsiness, sedation, fever, fatigue, viral infection, ataxia, and nystagmus

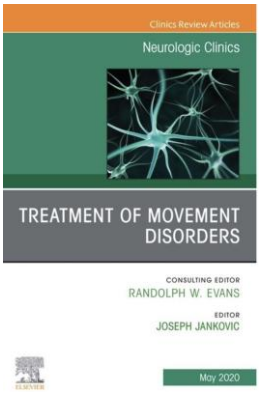
"Findings support the efficacy of tetrabenazine in children with dyskinetic CP"

Scalese et al. Front Neurol 2021;12:612429

Monbaliu et al. Lancet Neurol 2017;16:741-9

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Principles of Medical and Surgical Treatment of Cerebral Palsy



Eric M. Chin, MD[a,*], Hilary E. Gwynn, MD[a], Shenandoah Robinson, MD[b], Alexander H. Hoon Jr, MD, MPH[a]

Neurol Clin 2020;38:397-416

KEYWORDS

• Cerebral palsy • Movement disorders • Management principles • Complex care

KEY POINTS

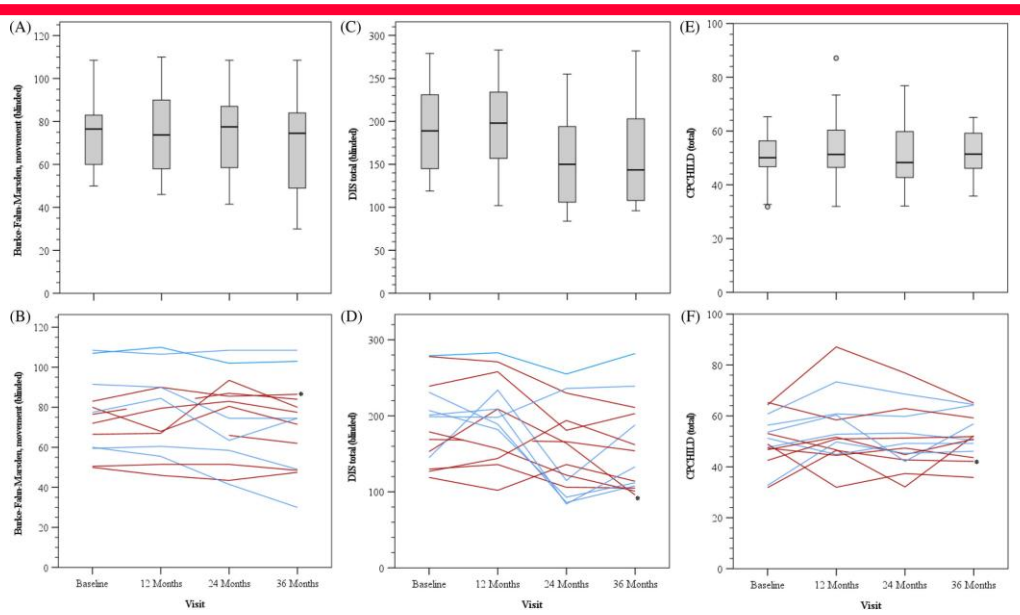
- In cases of cerebral palsy, early brain injury or dysgenesis results in a wide variety of movement disorders as well as associated nonmotor impairments.
- Successful management to optimize independence, participation, and quality of life requires individualized multidisciplinary care throughout the lifespan.
- Many symptomatic treatments of specific manifestations are available and widely used, including physical therapy, medications, and neurosurgical and orthopedic interventions. Most lack strong evidence of efficacy. For any intervention, open dialogue between patients, families, and providers regarding therapeutic options and expected benefits and potential side effects is essential.
- Modern imaging and genetic investigations have significantly advanced understanding of the causes and can improve treatment in some individual cases.
- It is important to identify comorbid medical, cognitive, and mental health disorders as these can contribute significantly to outcome.

Beketshi et al. Lancet Neurol 2023;22:229-43

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Long-Term Follow-Up of Pediatric Patients with Dyskinetic Cerebral Palsy and GPi DBS.

Koy et al. Mov Disord 2023;38:1736-42



Among the 14 patients who were assessed, there was a significant change in the (blinded) ratings of the total Dyskinesia Impairment Scale at 36 months; 12 serious AEs were documented.
Conclusion: DBS significantly improved dyskinesia, but other outcome parameters did not change significantly.

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JNS

CLINICAL ARTICLE

J Neurosurg 2023;139:605-14

Cerebellar deep brain stimulation for the treatment of movement disorders in cerebral palsy

*Iahn Cajigas, MD, PhD,[1] Melanie A. Morrison, PhD,[2] Marta San Luciano, MD,[3] and Philip A. Starr, MD, PhD[1]

Departments of [1]Neurological Surgery, [2]Radiology & Biomedical Imaging, and [3]Neurology, University of California, San Francisco, California

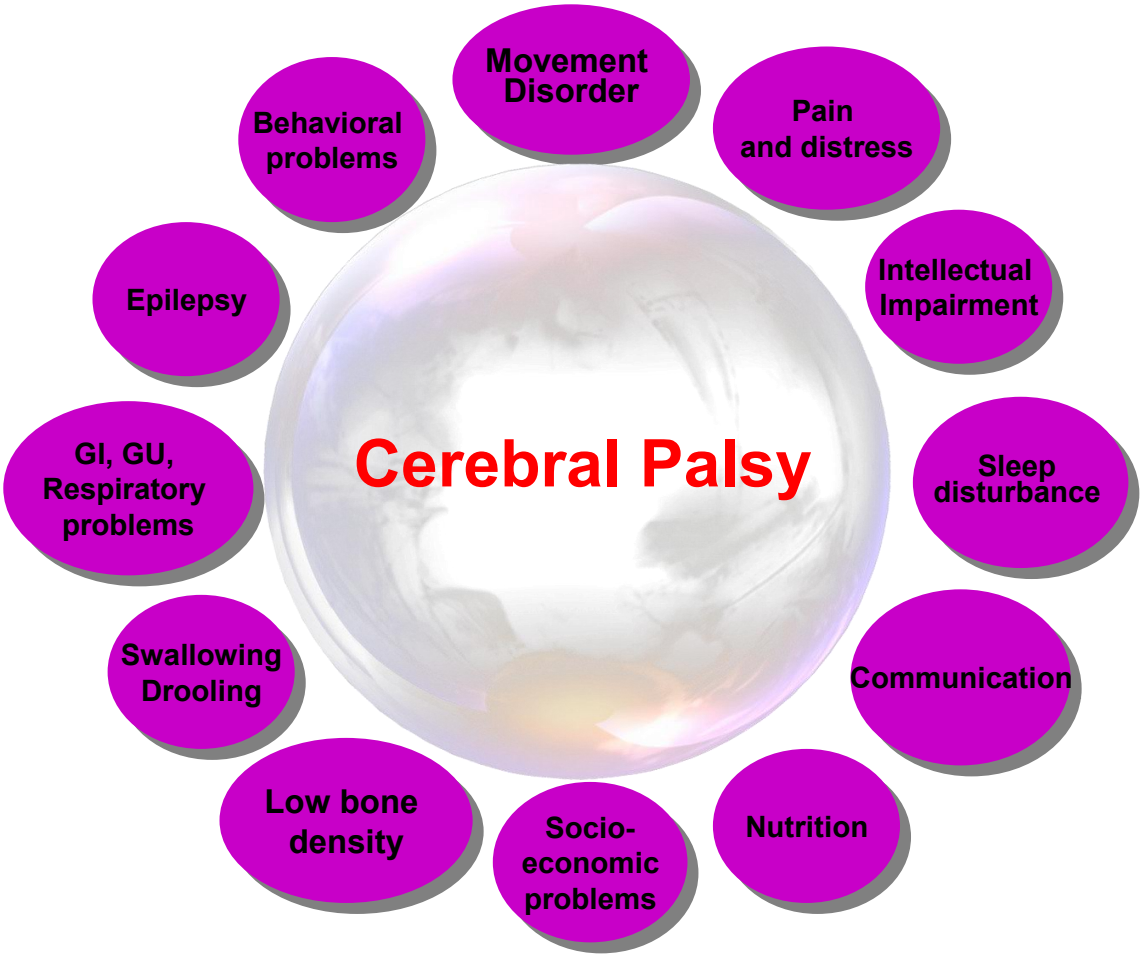
OBJECTIVE Cerebral palsy (CP) represents the most common childhood physical disability that encompasses disorders of movement and posture attributed to nonprogressive disturbances that occurred in the developmental fetal or infant brain. Dyskinetic CP (DCP), the second most common type of CP after spastic forms, refers to a subset of patients in whom dystonia and choreoathetosis are the predominant motor manifestations. Most children with CP have abnormal brain MRI studies indicative of cortical and deep gray matter damage consistent with hypoxic ischemic encephalopathy, which may preclude or suggest decreased efficacy of standard deep brain stimulation (DBS) targets. The cerebellum has been posited as an attractive target for treatment of DCP because it is frequently spared from hypoxic ischemic damage and has shown promise in alleviating patient symptoms both in early work in the 1970s and in more recent case series with DBS.

METHODS The authors performed bilateral cerebellar DBS implantation, targeting the dentate nucleus (DN) and cerebellar outflow pathway, in 3 patients with DCP. Leads were connected to a pulse generator that senses local field potentials during chronic continuous DBS. The authors report their surgical methods, examples of chronic cerebellar local field potential recordings, and preliminary clinical outcomes. Motor outcomes were assessed using the Burke-Fahn-Marsden Dystonia Rating Scale.

RESULTS Three patients 14–22 years old with DCP and MRI evidence of structural damage to the basal ganglia were offered cerebellar stimulation targeting the DN. All patients tolerated the procedure well and demonstrated improvement in subjective motor function as well as objective improvement in the Burke-Fahn-Marsden Dystonia Rating Scale movement subscale, although the range of responses was variable (19%–40%). Patients experienced subjective improvement in motor function including ease of hand movements and coordination, gait, head control, speech, decreased overflow, and diminished muscle tightness.

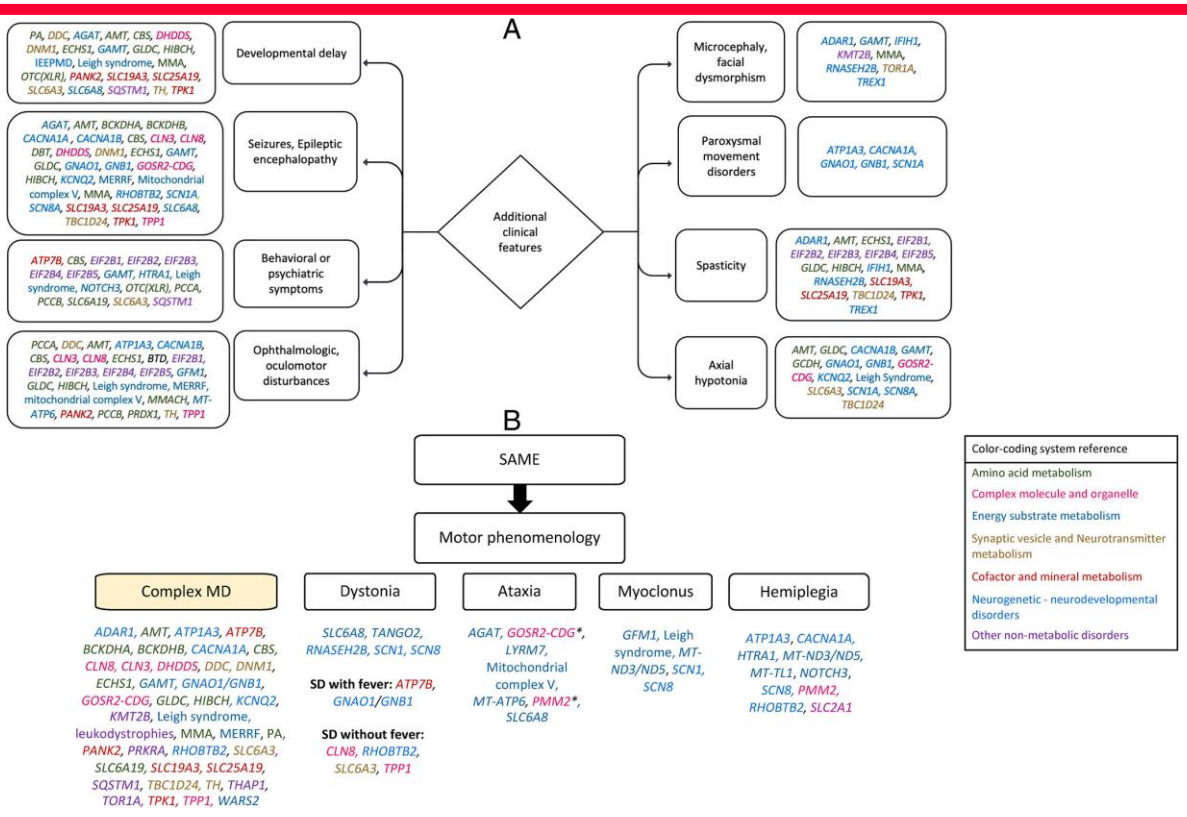
CONCLUSIONS DBS of the dentate nuclei in patients with DCP appears to be safe and shows preliminary evidence of clinical benefit. New chronic sensing technology may allow for determination of in vivo mechanisms of network disruption in DCP and allow for further understanding of the effects of neuromodulation on brain physiology. Larger studies with long-term follow up will be required to further elucidate the clinical benefits of this therapy. This report addresses a gap in the literature regarding the technical approach to image-based stereotactic targeting and chronic neural recording in the DN.

https://thejns.org/doi/abs/10.3171/2023.1.JNS222289


Cerebral Palsy
Movement Disorder
Pain and distress
Intellectual Impairment
Sleep disturbance
Communication
Nutrition
Socio-economic problems
Low bone density
Swallowing Drooling
GI, GU, Respiratory problems
Epilepsy
Behavioral problems

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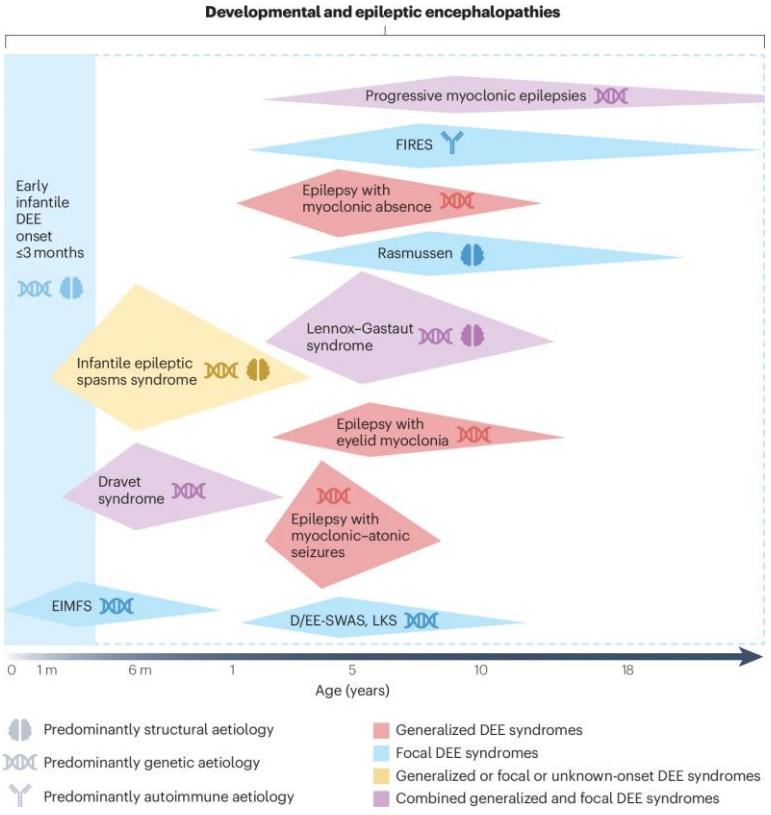
Severe Acute Motor Exacerbations (SAME) across Metabolic, Developmental and Genetic Disorders



Couto et al. Mov Disord 2024;39:1446-67

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Developmental and Epileptic Encephalopathy (DEE)



Schefffer et al. Nat Rev Dis Primers 2024;10:61

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Genetic and Metabolic Testing on Children with Developmental Delay

Diagnostic Test	Yield (%)
Chromosomal Microarray (CMA) - copy number variations (microdeletions and duplications), most chromosome number abnormalities (trisomy)	7.8-10.6
Karyotype studies	4-18.6
StFISH studies	0.5-7.4
Targeted genetic testing (*PTEN, AKT3 - macrocephaly*) **Ion channel genes** *(SCN1A, SCN2A, SCN8A, KCNQ2, KCNT)* **Other genes** (*GNAO1, STXBP1, FOXG1, CDKL5, KMT2B, SERAC1, CTNNB1)* **X-linked genetic testing** (*ARX, JARID1C, SLC6A8, FMR1, MeCP2*) **Whole-exome and –genome sequencing (WES, WGS)**	17-42 (<males)
Metabolic testing (inborn errors of metabolism – carbohydrate, amino acid, and lipid, global metabolics)	0.2-4.6

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Diagnostic Yield of Exome or Genome Sequencing in Cerebral Palsy Studies

EDITORIAL

All Patients With a Cerebral Palsy Diagnosis Merit Genomic Sequencing

Clare van Eyk, PhD; Suzanna C. MacLennan, MB, BS; Alastair H. MacLennan, AO, MB, ChB, MD

Cerebral palsy is a clinically diagnosed neurodevelopmental disorder with a broad phenotype. Until recently, cerebral palsy was often incorrectly assumed to be generally associated with birth asphyxia, birth trauma, or extreme prematurity. Most individuals with cerebral palsy have appropriately received neuroimaging.

Related article

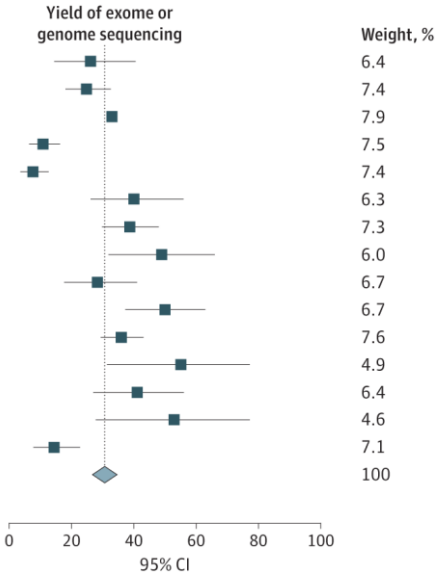
However, imaging alone will often not provide an accurate etiological diagnosis and may miss the presence of dual etiologies.[1] The meta-analysis by Gonzalez-Mantilla et al[2] reports on 13 studies totaling 2612 individuals with cerebral palsy and conservatively shows that the diagnostic yield of exome or genome sequencing was 31.1%. This is likely to be an underestimate, as not all studies cast a wider genetic net to look for copy number variation and many did not conduct parent-child trio analysis.

tively recent advent of genomic sequencing in cerebral palsy cohorts, novel gene-disease associations, along with systematic genomic sequencing, are likely to play a major role in increase in diagnostic yield, with more than one-third of all clinically unselected cerebral palsy cases likely to have an underlying monogenic cause.

The published meta-analysis[2] provides strong data to justify the cost of genomic sequencing. The diagnostic yield for cerebral palsy is similar to other neurodevelopmental disorders, such as developmental delay, intellectual disability, and autism spectrum disorder,[8] where genomic sequencing has been largely accepted as a first-tier test. Including genomic sequencing as a routine diagnostic test can circumvent lengthy, costly, and sometimes invasive clinical investigations to determine etiology where a clinical diagnosis of cerebral palsy has been made.

Estimates of the proportion of cases with clinically actionable findings in cerebral palsy cohorts vary from 12% to 30%.

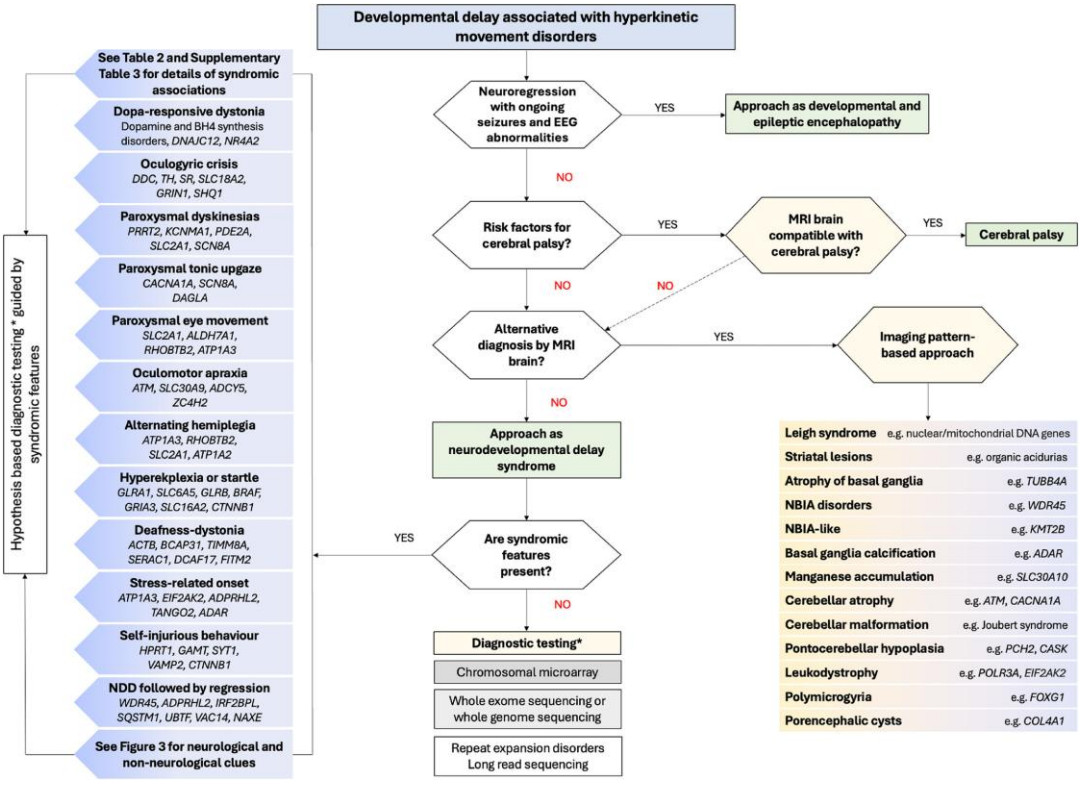
Van Eyk et al. JAMA Pediatr 2023;177:455-6



Diagnostic yield of ES or GS of 31.1%

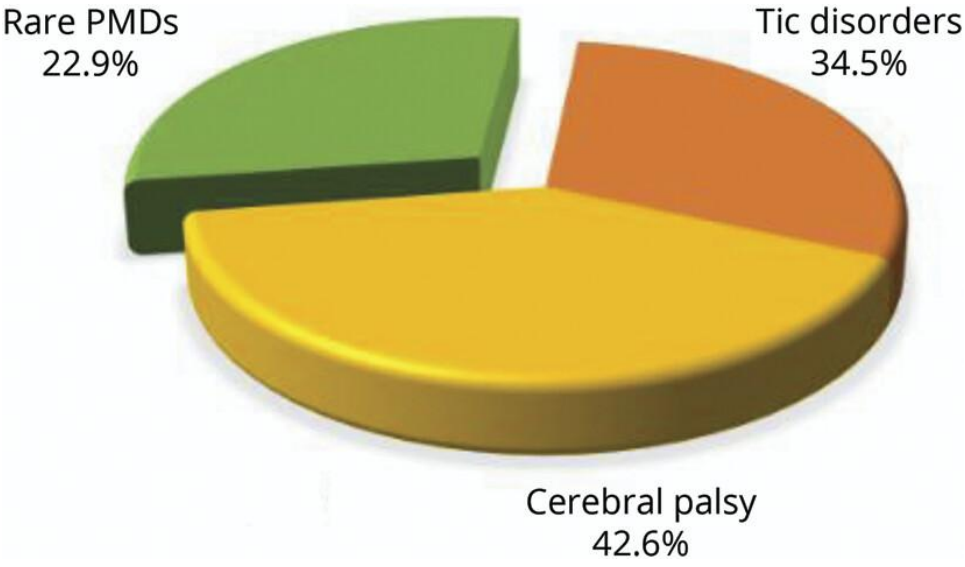
Gonzalez-Mantilla et al. JAMA Pediatr 2023;177:472-8

Proposed algorithm for the approach of developmental disorders associated with hyperkinetic movement disorders



Morales-Briceño et al. Mov Disord Clin Pract 2026

Cross-Section of Pediatric Movement Disorders Patient Cohorts Seen Over a 5-Year Period at an Academic Practice

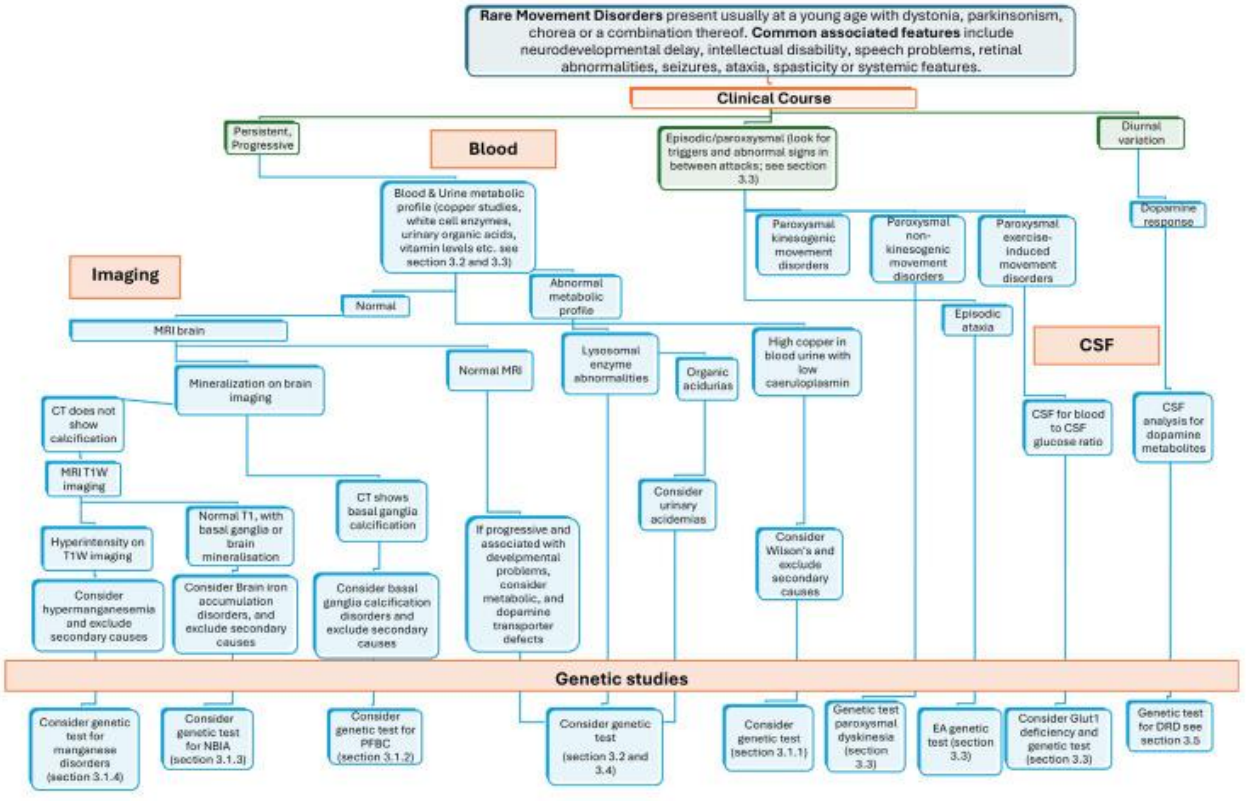


Rare diseases are very common

Kahlon et al. Neurology 2024;102:e208050

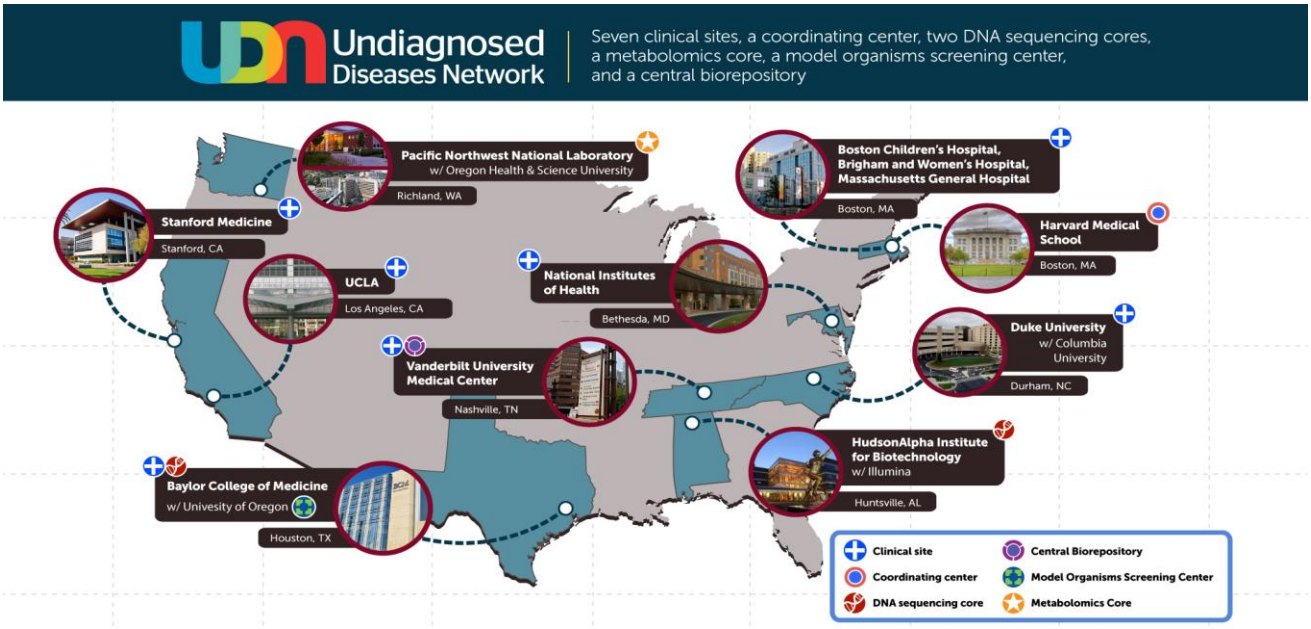
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A decision-tree linking clinical, genetic, and imaging testing to facilitate the recognition of RMDs



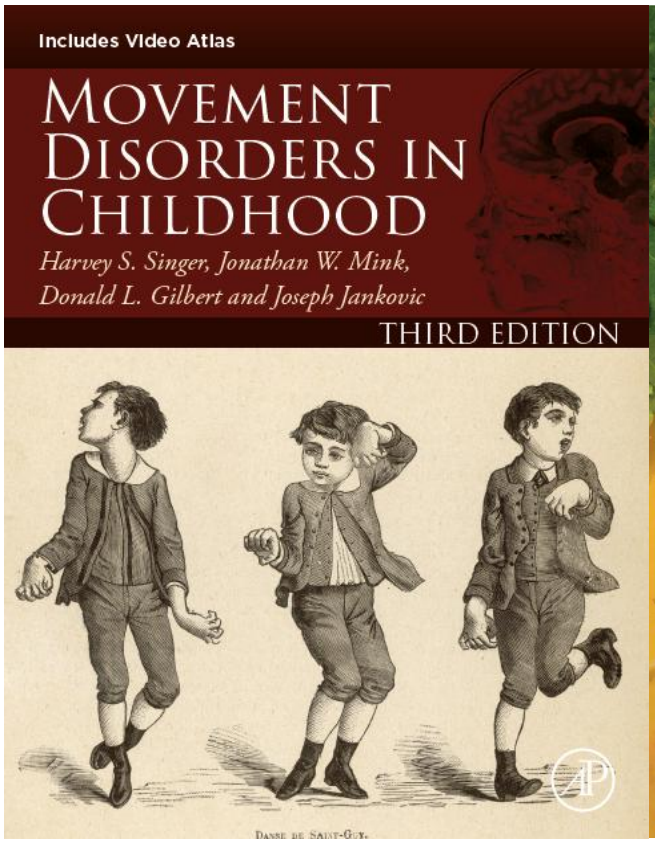
Jesuthasan et al. Int J Mol Sci 2025;26:6024

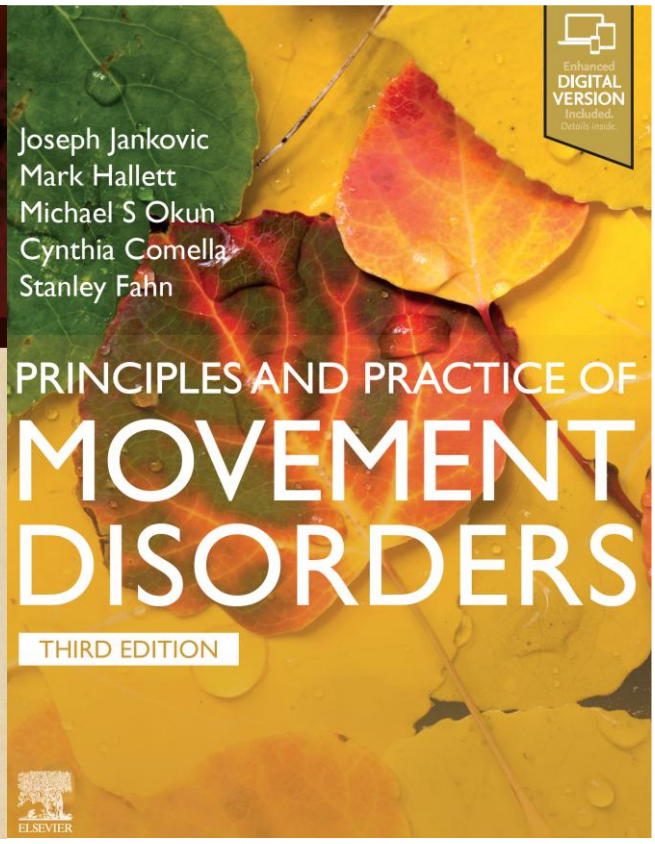
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For more information see:
https://rarediseases.org/rare-diseases/
or https://rarediseases.info.nih.gov/

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Includes Video Atlas
MOVEMENT DISORDERS IN CHILDHOOD
Harvey S. Singer, Jonathan W. Mink, Donald L. Gilbert and Joseph Jankovic
THIRD EDITION


Enhanced DIGITAL VERSION Included. Details inside.
Joseph Jankovic
Mark Hallett
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PRINCIPLES AND PRACTICE OF
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