Dystonia & Dyskinesia: Cause & Clinical Presentation

가톨릭의대 성빈센트병원
홍 보 영

Contents

abnormal, uncontrolled, involuntary movement

can affect one body part, or it can spread over the entire body

Hyperkinetic: excessive involuntary movement

Hypokinetic: slow or absent(akinesia) or difficulty in initiating

Dyskinesia

sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both

typically patterned, twisting, and may be tremulous

often initiated or worsened by voluntary action and associated with overflow muscle activation

Dystonia

HISTORICAL REVIEW

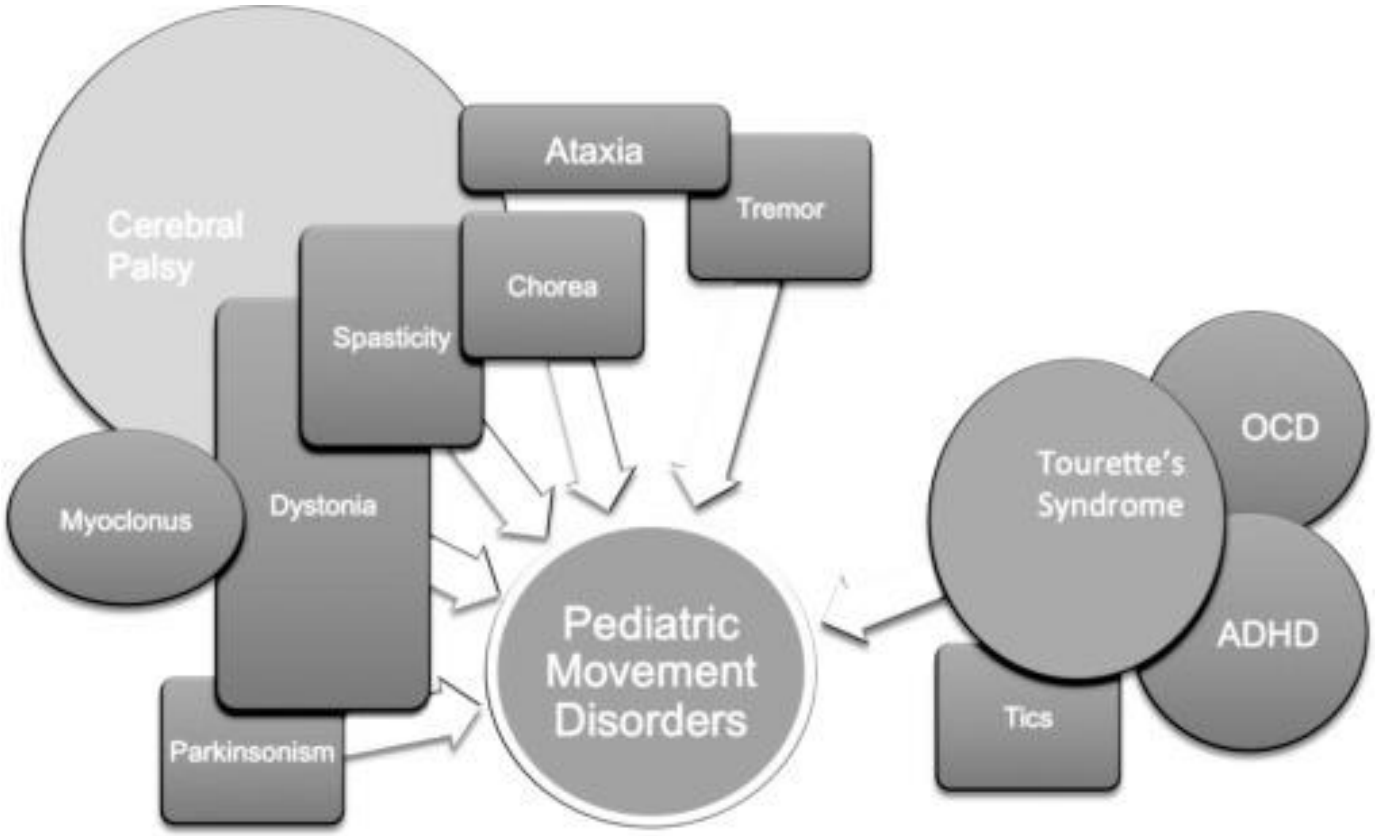
Translation of Oppenheim's 1911 Paper on Dystonia

Christine Klein, MD,[1]* and Stanley Fahn, MD[2]*

[1]University of Lübeck, Lübeck, Germany
[2]Columbia University Medical Center, New York, New York, USA

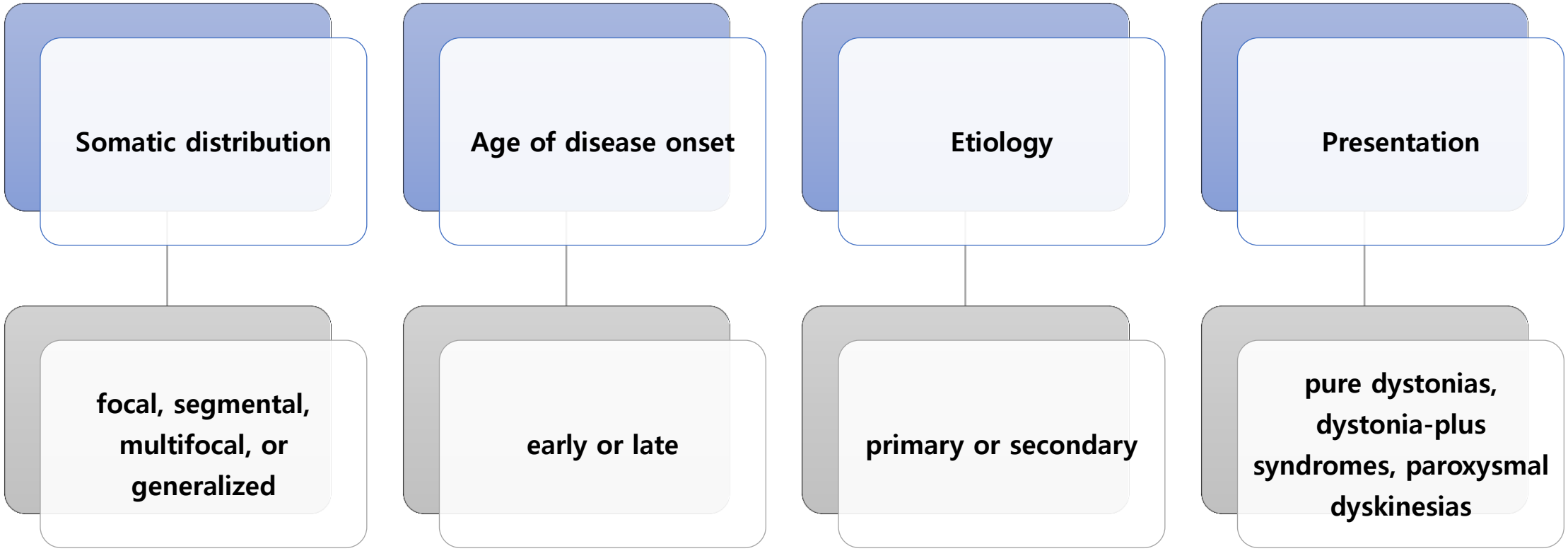
- Hermann Oppenheim (January 1, 1858 - May 5, 1919)
- Lehrbuch der Nervenkrank-heiten fur Arzte und Studierende (Textbook of Nervous Diseases for Physicians and Students), written in German, 5th edition, 1911
- *dystonia musculorum deformans*

Movement Disorders in Children



Management of Pediatric Movement Disorders: Present and Future. ***Seminars in Pediatric Neurology 2018***

Dystonia



Classification of Dystonia

Causes of acquired dystonia

Perinatal brain injury
Delayed-onset dystonia
Dystonic cerebral palsy
Cerebrovascular
Ischemia
Hemorrhage
Arteriovenous malformation and aneurysm
Brain injury
Head trauma
Brain surgery (including stereotactic ablations)
Electrical injury
Drug
Anticonvulsants
Calcium channel blockers
Dopamine agonists
Levodopa
Neuroleptics/antiemetics (dopamine receptor blocking drugs) including metoclopramide

Infection
Encephalitis lethargica
Human immunodeficiency virus (HIV) infection
Subacute sclerosing panencephalitis
Syphilis
Tuberculosis
Viral encephalitis
Neoplastic
Brain tumor
Paraneoplastic encephalitis
Toxic
3-nitropropionic acid
Carbon disulfide
Cobalt
Cyanide
Disulfiram
Manganese
Methanol
Psychogenic (functional)

Data from Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28:863.

Human Genome Organization (HUGO) Nomenclature

Monogenic forms of hereditary dystonia. Modified from Brüggemann and Klein (2010).

Type	Clinical presentation	Inheritance	Gene location	Gene	Protein	Protein function
DYT1	Childhood-onset generalized TD	AD	9q	*TORIA*	torsinA	Protein interactions in NE and ER (AAA + ATPase)
DYT3	X-linked dystonia parkinsonism; "lubag"	XR	Xq	*TAF1/DYT3*	TAF	transcription factor
DYT5a/DYT14[a]	Dopa-responsive dystonia; Segawa syndrome	AD	14q	*GCH1*	GTP cyclo-hydrolase	Biopterin biosynthetic enzyme
DYT5b	Dopa-responsive dystonia; Segawa syndrome	AR	11p	*TH*	tyrosine hydroxylase	dopa-biosynthetic enzyme
DYT6	Adolescent-onset TD of mixed type	AD	8p	*THAP1*	THAP1	zinc finger transcription factor
DYT7	Adult-onset focal TD	AD	18p	–	–	
DYT8	Paroxysmal nonkinesigenic dyskinesia	AD	2q	*PNKD1/MR1*	myofibrillogenesis regulator-1	unknown
DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity	AD	1p	–	–	–
DYT10	Paroxysmal kinesigenic choreoathetosis	AD	16p-q	–	–	–
DYT11	Myoclonus-dystonia	AD	7q	*SGCE*	epsilon-sarcoglycan	Dystrophin-glycoprotein complexes
DYT12	Rapid-onset dystonia-parkinsonism	AD	19q	*ATP1A3*	Na+/K + ATPase α subunit	ion transporter
DYT13	Multifocal/segmental dystonia	AD	1p	–	–	–
DYT15	Myoclonus-dystonia	AD	18p	–	–	–
DYT16	Young-onset dystonia-(parkinsonism)	AR	2p	*PRKRA*	PACT	stress response protein
DYT17	AR primary TD	AR	20pq	–	–	–
DYT18	Paroxysmal exertion-induced dyskinesia 2	AD	1p	*SLC2A1*	GLUT1	glucose transporter
DYT19	Episodic kinesigenic dyskinesia 2	AD	16q	–	–	–
DYT20	Paroxysmal nonkinesigenic dyskinesia 2	AD	2q	–	–	–

AD autosomal dominant, AR autosomal recessive, OMIN online mendelian inheritance in man, TD torsion dystonia, XR X-linked recessive.

[a] DYT14 recently was redefined as DYT5 (Wider et al., 2008).

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Inherited forms of dystonia

	Usual onset	Locus symbol	Gene locus	Gene symbol
Autosomal dominant				
Dystonia is the presenting or predominant manifestation				
Early-onset generalized dystonia (DYT-TOR1A)	Childhood-adolescence	DYT1	9q34	TOR1A
Dopa-responsive dystonia; Segawa syndrome (DYT-GCH1)	Childhood	DYT5a	14q22	GCH1
Adolescent-onset dystonia of mixed type (DYT-THAP1)	Adolescence	DYT6	8p11.21	THAP1
Cranial-cervical dystonia (DYT-GNAL)	Adulthood	DYT25	18p11.21	GNAL
Dystonia is an associated or secondary feature				
Paroxysmal nonkinesigenic dyskinesia 1 (DYT-MR1)	Adolescent-adult	DYT8	2q35	MR1
Episodic (paroxysmal) kinesigenic dyskinesia 1 (DYT-PRRT2)	Childhood-adolescence	DYT10	16p11.2	PRRT2
Myoclonus-dystonia (DYT-SGCE)	Childhood-adolescent	DYT11	7q	SGCE
Rapid-onset dystonia-parkinsonism (DYT-ATP1A3)	Childhood-adulthood	DYT12	19q	ATP1A3
Paroxysmal exercise-induced dyskinesia (DYT-SLC2A1)	Childhood	DYT18	1p34.2	SLC2A1
Dentatorubral-pallidoluysian atrophy	Adulthood	N/A	12p13.31	ATN1
Friedreich ataxia	Adolescence-adulthood	N/A	9q21.11	FXN
Huntington disease	Adolescence-adulthood	N/A	4p16.3	HTT
Idiopathic basal ganglia calcification 1	Adulthood	N/A	8p11.21	SLC20A2
Neuroferritinopathy	Adulthood	NBIA3	19q13.33	FTL
Spinocerebellar ataxia 3 (Machado-Joseph disease)	Childhood-adulthood	SCA3	14q32.12	ATXN3
Spinocerebellar ataxia 17	Adulthood	SCA17	6q27	TBP

Autosomal recessive				
Dystonia is the presenting or predominant manifestation				
Dopa-responsive dystonia; Segawa syndrome (DYT-TH)	Infancy-childhood	DYT5b	11p15.5	TH
Dopa-responsive dystonia (DYT-SPR)	Infancy-childhood	N/A	2p14-p12	SPR
Dystonia is an associated or secondary feature				
Aromatic L-amino acid decarboxylase deficiency	Infancy	N/A	7p12.1	DDC (AADC)
Ataxia-telangiectasia	Childhood	N/A	11q22.3	ATM
Chorea-acanthocytosis	Adulthood	N/A	9q21	VPS13A
Fucosidosis	Infancy	N/A	1p36.11	FUCA1
Glutaric acidemia	Infancy	N/A	19p13.2	GCDH
Huntington disease-like 3	Childhood	HDL3	4p15.3	?
Infantile neuroaxonal dystrophy	Infancy	NBIA2a	22q13.1	PLA2G6
Juvenile parkinsonism	Adolescence-adulthood	PARK2	6q26	PRKN
Kufor-Rakeb syndrome	Childhood-adulthood	PARK9	1p36.13	ATP13A2
Methylmalonic aciduria	Infancy	N/A	6p12.3 2q23.2	MUT MMADHC
Niemann-Pick disease type C	Infancy-adulthood	N/A	18q11-q12 14q24.3	NPC1 NPC2 (HE)
Pantothenate kinase-associated neurodegeneration	Childhood	NBIA1	20p13	PANK2
Tay-Sachs disease	Infancy-adulthood	N/A	15q23	HEXA
Wilson disease	Childhood-adulthood	N/A	13q14.3	ATP7B
Woodhouse-Sakati syndrome	Adolescent	N/A	2q31.1	DCAF17
X-linked				
Dystonia is an associated or secondary feature				
X-linked dystonia-parkinsonism; Lubag (DYT-TAF1)	Adulthood	DYT3	XR	TAF1?
Lesch-Nyhan syndrome	Childhood	N/A	Xq26.2-q26.3	HPRT
Mohr-Tranebjaerg dystonia-deafness syndrome	Childhood-adulthood	N/A	Xq22.1	TIMM8A (DDP)
Pelizaeus-Merzbacher disease	Infancy	N/A	Xq22.2	PLP1
Rett syndrome	Infancy	N/A	Xq28	MECP2
Mitochondrial				
Dystonia is an associated or secondary feature				
Leber optic atrophy	Childhood-adolescence	N/A		Multiple mitochonridal-encoded genes
Leigh syndrome*	Infancy	N/A		Multiple nuclear and mitochondrial-encoded genes

begins distally (children) vs. cranial-cervical distribution (adults)

Early-onset generalized isolated dystonia (primary dystonia): may be sporadic or inherited

Primary Dystonia

Isolated Dystonias

Early-onset generalized isolated dystonia
: dystonia with focal-onset beginning in childhood that often progresses to generalized involvement; cases may be sporadic, fa milial, genetically defined or without known cause
Early-onset generalized dystonia (DYT-TOR1A)
Adolescent-onset dystonia of mixed type (DYT-THAP1)
Focal or segmental isolated dystonia with onset in adulthood
: focal or segmental isolated dystonias usually begin after age 30 years; most are sporadic without identifiable cause, and rarely progress to generalized dystonia, but can extend to contiguous body regions
Adult-onset segmental dystonia (DYT-GNAL)
Cervical dystonia
Blepharospasm
Writer's cramp
Oromandibular dystonia
Laryngeal dystonia (spasmodic dysphonia)
Limb dystonia
Other syndromes of late adult-onset focal isolated dystonia

Combined Dystonias

Dystonia-parkinsonism
combine dystonia and parkinsonian features, sometimes accompanied by pyramidal tract involvement, and/or nonmotor features, including cognitive decline; many are inherited
Dopa-responsive dystonia (DYT-GCH1, DYT-TH, and DYT-SPR)
Wilson disease
Early-onset parkinsonism (PARK-PARKIN)
Early-onset parkinsonism (PARK-PINK1)
Early-onset parkinsonism (PARK-DJ1)
X-linked dystonia-parkinsonism/Lubag (DYT-TAF1)
Rapid-onset dystonia-parkinsonism (DYT-ATP1A3)
Neurodegeneration with brain iron accumulation:
Pantothenate kinase-associated neurodegeneration (PANK2 gene)
Infantile neuroaxonal dystrophy (PLA2G6 gene)
Mitochondrial membrane protein-associated neurodegeneration (C19ORF12 gene)
Beta-propeller protein-associated neurodegeneration, also known as static encephalopathy of childhood with neurodegeneration in adulthood (WDR45 gene)
Fatty acid hydroxylase-associated neurodegeneration (FA2H gene)
Kufor-Rakeb syndrome (PARK-ATP13A2)
Neuroferritinopathy (FTL gene)
Aceruloplasminemia (ceruloplasmin gene)
Woodhouse-Sakati syndrome (DCAF17 gene)

Combined Dystonias

Myoclonus-dystonia : combination of dystonia and myoclonus; dystonia may be mild, and myoclonus generally predominates
Myoclonus-dystonia (DYT-SGCE)
Paroxysmal dyskinesia with dystonia : episodes of spontaneous or induced dyskinesia with dystonia
Paroxysmal nonkinesigenic dyskinesia (DYT-MR1)
Paroxysmal kinesigenic choreoathetosis (DYT-PRRT2)
Paroxysmal exertion-induced dyskinesia (DYT-SLC2A1)

Short communication

Classification of dystonia in childhood

1) Clinical Characteristics
2) Aetiology

Daniel E. Lumsden [a, *], Hortensia Gimeno [a, b], Jean-Pierre Lin [a]

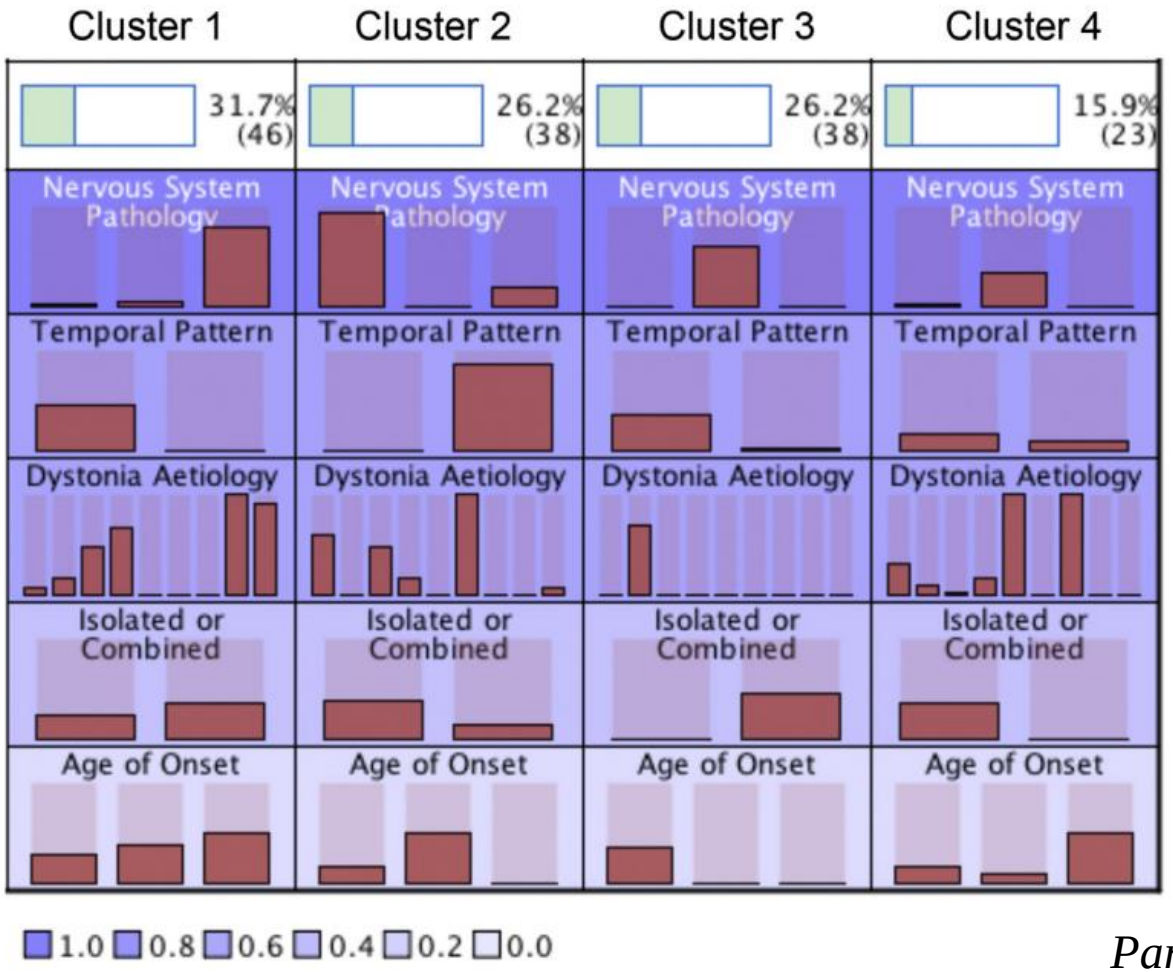
[a] Complex Motor Disorders Service, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK
[b] Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

A B S T R A C T

Objective: The most recent international consensus update on dystonia classification proposed a system based on 2 axes, clinical characteristics and aetiology. We aimed to apply this system to Children and Young People (CAYP) selected for movement disorder surgery, and determine if meaningful groupings of cases could be extracted.
Methods: The 2013 Consensus Committee classification system for dystonia was retrospectively applied to 145 CAYP with dystonic movement disorders. Two-step cluster analysis was applied to the resulting categorisations to identify groupings of CAYP with similar characteristics.
Results: Classification resulted in a total of 43 unique groupings of categorisation. Cluster analysis detected 4 main clusters of CAYP, comparable to previously used patient groupings.
Conclusions: The 2013 consensus update on dystonia classification can be applied to CAYP with dystonia. The large number of categories provides a wealth of information for the clinician, and also facilitates data driven grouping into clinically meaningful subgroups.

Characteristics of Cluster identified by cluster analysis process.

Cluster number	Cluster size (n)	Characteristics of cluster
1	48	Predominantly no evidence of degeneration or structural lesion, static disease course, mixed autosomal dominant/x-linked/idiopathic-familial inheritance, predominantly combined dystonia, mixed age of onset
2	38	Predominantly evidence of degeneration, progressive dystonia course, mixed autosomal recessive/x-linked inheritance, isolated dystonia and onset <12 years
3	38	Predominantly evidence of structural lesion, static dystonia course, acquired perinatal brain injury, combined dystonia, and onset <2 year
4	23	Predominantly evidence of structural lesion, static dystonia course, mixed acquired infection/vascular, isolated dystonia, onset >12 years



Nervous System Pathology (Evidence of degeneration, evidence of structural lesion, no evidence of degeneration or structural lesion), Temporal Pattern (static, progressive), Cause of dystonia (autosomal recessive, Perinatal brain injury, idiopathic-sporadic, Idiopathic-familial, Vascular, Mitochondrial, infection, x-linked and Autosomal dominant), Isolated or Combined (Isolated, combined), Age of Onset (<2 years, 3-12 years, 13-20 years). Rows are ordered from top to bottom in descending order of importance to the model prediction.

Parkinsonism and Related Disorders 33 (2016) 138-141

DYT1 dystonia (Oppenheim's dystonia)

- m/c cause of generalized dystonia in young patients
- AD, mutation in the TOR1A (DYT1) gene that encodes the protein torsinA, an ATP-binding protein in the 9q34 locus
- onset: the first decade of life
- Unilateral dystonia of the foot → gradual spreading of the movement disorder with involvement of the contralateral lower limb, trunk and even upper limbs, neck and face

Dopa-responsive dystonia (Segawa's disease)

- AD/AR, female>male
- DYT5 dystonia (GCH1, TH)
- Unusual form of inherited progressive dystonia
- Diurnal variation
- Usually starts in the legs and becomes generalized
- Dystonia-plus conditions: hyperreflexia, rigidity, tremor, and other parkinsonian features, and less commonly, cerebellar signs
- Remarkable response to low-dose L-dopa

Pathophysiology of Dystonia

Primary dystonia

- basal ganglia and related thalamocortical network

Secondary dystonia

- basal ganglia and thalamus
- occasionally, parietal cortex, cerebellum, brainstem, upper spinal cord

Lancet 2014; 384: 532–44

Studies using Neuroimaging

- Lesion studies
- [18F]-fluorodeoxyglucose-PET studies
- PET studies of blood flow
- fMRI studies
- DTI and tractography
- Quantitative structural imaging

Fluorodeoxyglucose PET studies of dystonia

Type of dystonia	Cases/controls	Regions affected				Source
		BG	CRB	CTX	Other	
Blepharospasm	6/6		Verm (↑)		Pons (↑)	(Hutchinson et al., 2000)
Blepharospasm	11/11	Caud (↑)	Hem (↓)	Cing (↑) Temp (↑)	Thal (↓)	(Kerrison et al., 2003)
Blepharospasm	25/38				Thal (↑) Pons (↑)	(Suzuki et al., 2007)
Blepharospasm	22/44				Thal (↑) Mid (↓)	(Emoto et al., 2010)
Cervical dystonia[a]	13/11					(Stoessl et al., 1986)
Cervical dystonia	10/15	Put (↑)	Hem (↑)	PreM (↑)	Thal (↑)	(Galardi et al., 1996)
Cervical dystonia	10/10	Put (↑)				(Magyar-Lehman et al., 1997)
DOPA-responsive dystonia	7/14	Put (↓)	Verm (↑)	SMA (↑) PreM (↓)	Mid (↑)	(Asanuma et al., 2005b)
DYT1 dystonia	10/14	Put (↑)	Hem (↑)	SMA (↑)	Thal (↑) Mid (↑)	(Eidelberg et al., 1998)
DYT1 dystonia[b]	7/14	Put (↑)	Hem (↑)	SMA (↑)		(Eidelberg et al., 1998)
DYT1 dystonia	23/11	Put (↑)	Hem (↑)			(Carbon et al., 2004b)
DYT6 dystonia	13/11	Put (↓)		Cing (↑) Temp (↑)		(Carbon et al., 2004b)
Mixed dystonias[c]	8/8					(Otsuka et al., 1992)
Mixed dystonias[c]	15/31	Caud (↓) Put (↓)	Hem (↑)	FC (↓) PreF (↓)	BS (↑)	(Karbe et al., 1992)
Mixed dystonias[c]	11/11	Put (↑)		PreM (↑) SMA (↑)	Mid (↑) Pons (↑)	(Eidelberg et al., 1995)

Fluorodeoxyglucose PET studies of dystonia are listed according to type of dystonia. Arrows indicate increased (↑) or decreased (↓) tracer uptake. Studies that compared multiple types of dystonia with a single control group are listed according to type of dystonia rather than as a combined group. Studies reporting only abnormal relationships among regions rather than absolute changes are not listed. Abbreviations: BS (brainstem), Caud (caudate) Cing (cingulate gyrus), FC (frontal cortex), Hem (cerebellar hemisphere), Mid (midbrain), PreF (prefrontal cortex), PreM (premotor cortex), PM (primary motor cortex), PS (primary sensory cortex), Put (putamen), STL (superior temporal lobe), SMA (supplementary motor area), Temp (temporal cortex), Verm (cerebellar vermis).

[a] No abnormalities were identified in any region, but there was an abnormal relationship between putamen and thalamus.

[b] Unaffected DYT1 mutation carriers were compared with controls.

[c] These studies included a mixture of generalized and focal idiopathic dystonias.

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DTI studies of dystonia

Type of dystonia	Cases/Controls	Primary measure	Regions affected				Source
			BG	CRB	CTX	Other	
Blepharospasm[a]	18/35	FA MD					(Fabbrini et al., 2008)[b]
Cervical dystonia	15/10	FA MD	Put (↑) Caud (↓) GP (↓) Put (↓)		CC (↓)		(Colosimo et al., 2005)[b]
Cervical dystonia[c]	7/7	FA MD	Caud (↑) GP (↑) Put (↑)		PreF (↓)	Thal (↓)	(Bonilha et al., 2007)
Cervical dystonia	16/35	FA MD	Put (↑) Caud (↓) Put (↓)		CC (↓) PreF (↑) SMA (↑)		(Fabbrini et al., 2008)[b]
DYT1 dystonia[d]	12/17	FA			SMC (↓)		(Carbon et al., 2004a)
DYT1 and DYT6 dystonias	7/8	FA		SSP (↓)	SMC (↓)		(Carbon et al., 2008b)
DYT1 and DYT6 dystonias[e]	20/8	Tractography		CRB-Thal (↓)	Thal-CTX (↓)		(Argyelan et al., 2009)
Spasmodic dysphonia	20/20	FA			IC (↓)	Thal (↑)	(Simonyan et al., 2008)
		MD	Put (↑)	MCP (↑)	CBT (↑) CP (↑) IC (↑)	Thal (↑)	
Writer's cramp	26/26	FA			IC (↑)		(Delmaire et al., 2009)

Diffusion tensor imaging (DTI) studies of primary dystonias are shown according to type of dystonia. Studies comparing multiple types of dystonia with a single control group or employing multiple methods are listed according to different types of dystonia and method rather than as combined groups. Arrows indicate increased (↑) or decreased (↓) changes in the measurement variable of fractional anisotropy (FA) or mean diffusivity (MD). FA and MD normally are closely related but opposing measures, but differences in sensitivity sometimes yield different results. All reported results are shown, although those for gray matter should be viewed with caution. Abbreviations: Caud (caudate), CP (cerebral peduncle), GP (globus pallidus), IC (internal capsule), MCP (middle cerebellar peduncle), PreF (prefrontal cortex), Put (putamen), SMC (sensorimotor cortex), SCP (superior cerebellar peduncle), SMA (supplementary motor area).

[a] No abnormalities were found.
[b] These studies involved overlapping cohorts of the same patients.
[c] All patients had cervical dystonia but 2 had generalized dystonia and 1 had spasmodic dysphonia.
[d] Comparison combined symptomatic and non-symptomatic patients versus normal controls.
[e] Reduced probability of connections calculated using probabilistic DTI fiber tracking between the cerebellum, thalamus and cerebral cortex.

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Neuroimaging

A group of brain regions not a single brain region

Uncertainties regarding whether abnormalities other than the visible ones are responsible for the disorder

Lack of consistency

Functional imaging: initial sx. vs. downstream consequences

Physiology

Loss of inhibition

Impaired sensorimotor integration

Maladaptive neural plasticity

Chorea

Chorea: ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments

Ballism (ballismus): "as chorea that affects proximal joints such as shoulder or hip," leading to "large amplitude movements of the limbs, sometimes with a flinging or flailing quality"; it is usually unilateral (hemiballismus) and often results from a lesion in the contralateral subthalamic nucleus and adjacent structures.

Chorea, Ballismus

Etiology of chorea

1. Developmental/aging choreas
Physiological chorea of infancy
Cerebral palsy - anoxic, kernicterus
Minimal cerebral dysfunction
Buccal-oral-lingual dyskinesia and edentulous orodyskinesia in elderly
Senile chorea (probably several causes)
2. Hereditary choreas
Huntington's disease
Benign hereditary chorea
Neuroacanthocytosis
Other CNS "degenerations": OPCAs, Azorean disease, ataxia telangiectasia, tuberous sclerosis, Hallervorden-Spatz, Dentato-rubral-pallido-luysian atrophy (DRPLA), familial calcification of basal ganglia, others
Neurometabolic disorders: Wilson disease, Lesch Nyhan, lysosomal storage disorders, amino acid disorders, Leigh, porphyria
3. Drug induced
Neuroleptics (tardive dyskinesia), antiparkinsonian drugs, amphetamines, tricyclics, oralcontraceptives, anticonvulsants, anticholinergics, others
4. Toxins

5. Metabolic
Hyperthyroidism
Hypoparathyroidism (various types)
Pregnancy (Chorea Gravidarum)
Hyper and hyponatremia, hypomagnesemia, hypocalcemia
Hypo and hyperglycemia (latter may cause hemichorea, hemiballism)
Acquired hepatocerebral degeneration
Nutritional (eg, beriberi, pellagra, B12 deficiency in infants)
6. Infectious
Sydenham's chorea
Encephalitis lethargica
Various other infections and postinfectious encephalitides, including Creutzfeldt-Jakob disease
7. Immunological
SLE (including ANF negative cases with lupus anticoagulant)
Henoch-Schonlein
Others rarely: Sarcoid, MS, Behcet's, polyarteritis nodosa, myeloproliferative disorder
8. Vascular (often hemichorea)
Infarction
Hemorrhage
AVM
Polycythemia rubra vera
Migraine
9. Tumors
10.Trauma
Including subdural and epidural hematoma
11. Miscellaneous
Including paroxysmal choreoathetosis

)ata from Jankovic, J, Lang, AE. Classification of movement disorders. In: Germano, IM, (Ed), Surgical Treatment of Movement Disorders, The American Association of Neurological Surgeons (AANS), Lebanon, NH, 1998. p.3.

Graphic 79166 Version 1.0

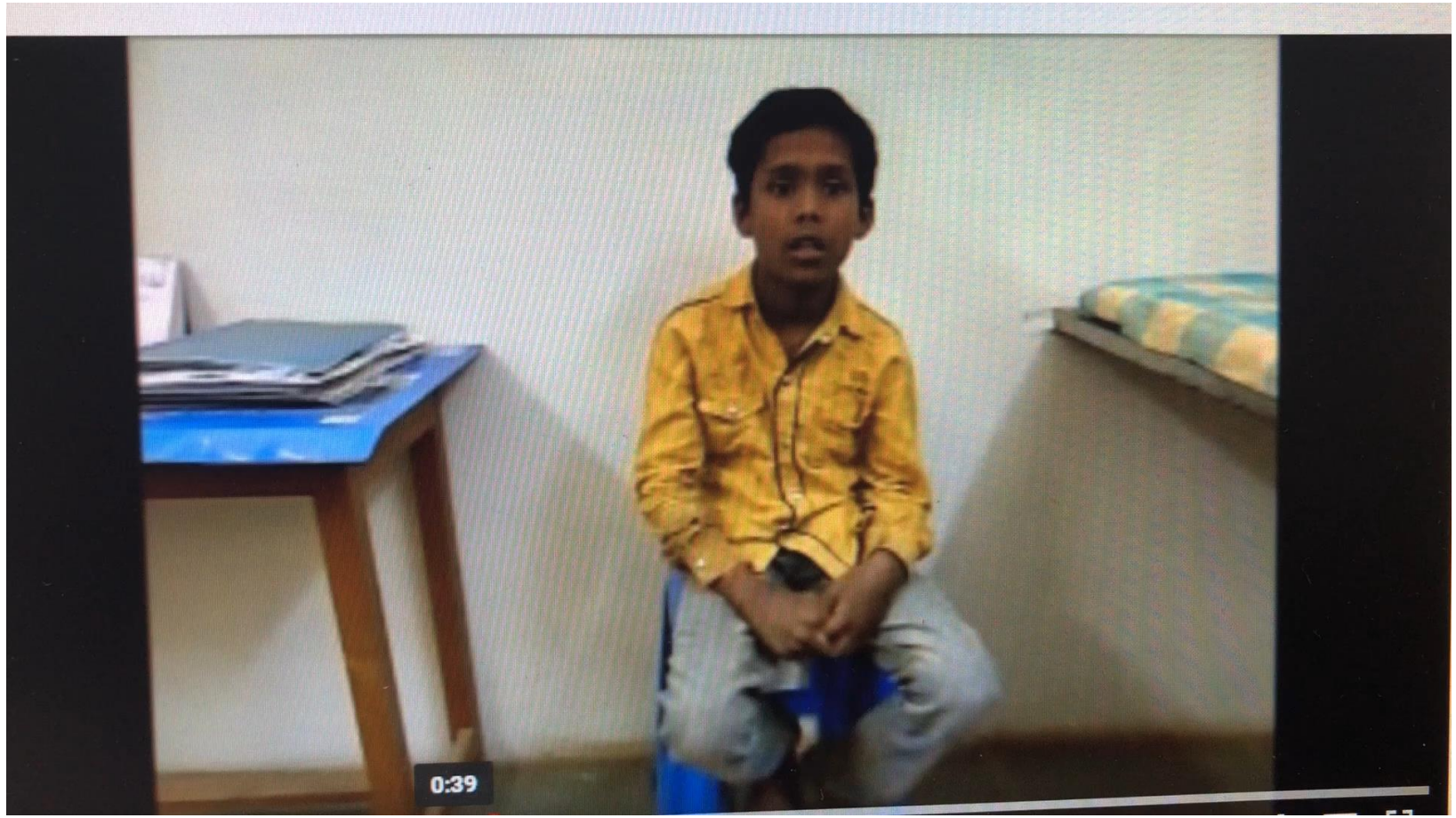
Chorea

Sydenham chorea

- clinical manifestations of acute rheumatic fever
- m/c form of acquired chorea in childhood (between 5 and 13 years of age)
- Girl>boy
- 8 months after the infection
- antibodies induced by β-hemolytic streptocci
- Other motor and non-motor features (20%): decreased muscle tone, vocalizations, emotional lability, obsessions and compulsions, attention deficit and hyperactivity, carditis, and others
- typically improves gradually (mean duration of 12 to 15 weeks)

Post-pump chorea

- 10 % (0.6 to 18 %)
- Risk factors: more time on pump, deeper hypothermia (<36 degrees), and circulatory arrest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27m/M

Wolf–Hirschhorn syndrome

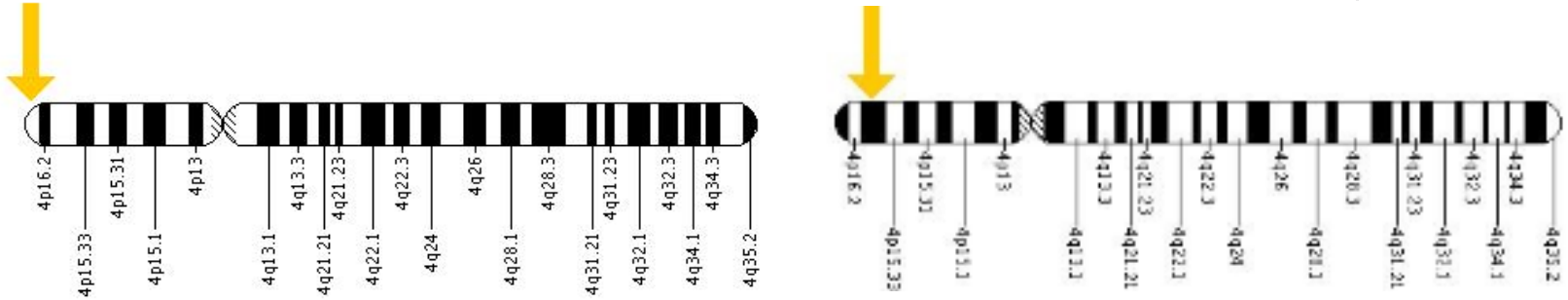
- 4p16.3 (*WHSC1, WHSC2)*
- 87% *de novo* deletion/13% inherited

- aortic valve stenosis, op. (+), ballooning (+)
- febrile seizure (+)

Deletion of Huntington's disease-linked G8 (D4S10) locus in Wolf–Hirschhorn syndrome

James F. Gusella*, Rudolph E. Tanzi*, Patricia I. Bader†, Mary C. Phelan‡, Roger Stevenson‡, Michael R. Hayden§, Karen J. Hofman‖, Anne G. Faryniarz* & Kerin Gibbons*

* Neurogenetics Laboratory, Massachusetts General Hospital, Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA
† Parkview Memorial Hospital, Fort Wayne, Indiana 46805, USA
‡ Greenwood Genetics Center, Greenwood, South Carolina 29646, USA
§ Clinical Genetics Unit, University of British Columbia, Vancouver, British Columbia, Canada V6H 3V5
‖ The Kennedy Institute, Johns Hopkins Hospital, Baltimore, Maryland 21205, USA



Hereditary Chorea

Huntington's disease

- childhood or juvenile form of HD (the Westphall variant): rigid-akinetic syndrome

Benign hereditary chorea (brain-thyroid-lung syndrome)

- AD, mutation in the TITF1/NKX2-1 gene (chromosome 14q13), which codes for a transcription factor essential for the organogenesis of the lung, thyroid, and basal ganglia
- ADCY5 gene (negative for NKX2-1 gene)
- thyroid disease, pulmonary disease (NKX2-1 gene)
- onset in infancy with marked hypotonia followed by generalized chorea
- delayed in motor and walking milestones
- myoclonus, upper limb dystonia, and motor and vocal tics
- Chorea: nonprogressive and often lessens over time or resolves by early adulthood
- Cognitive and behavioral disturbances: learning difficulty, ADHD
- growth hormone deficiency, pes cavus, kyphosis, duplex kidney anomaly, and obsessive-compulsive disorder

Hereditary Chorea

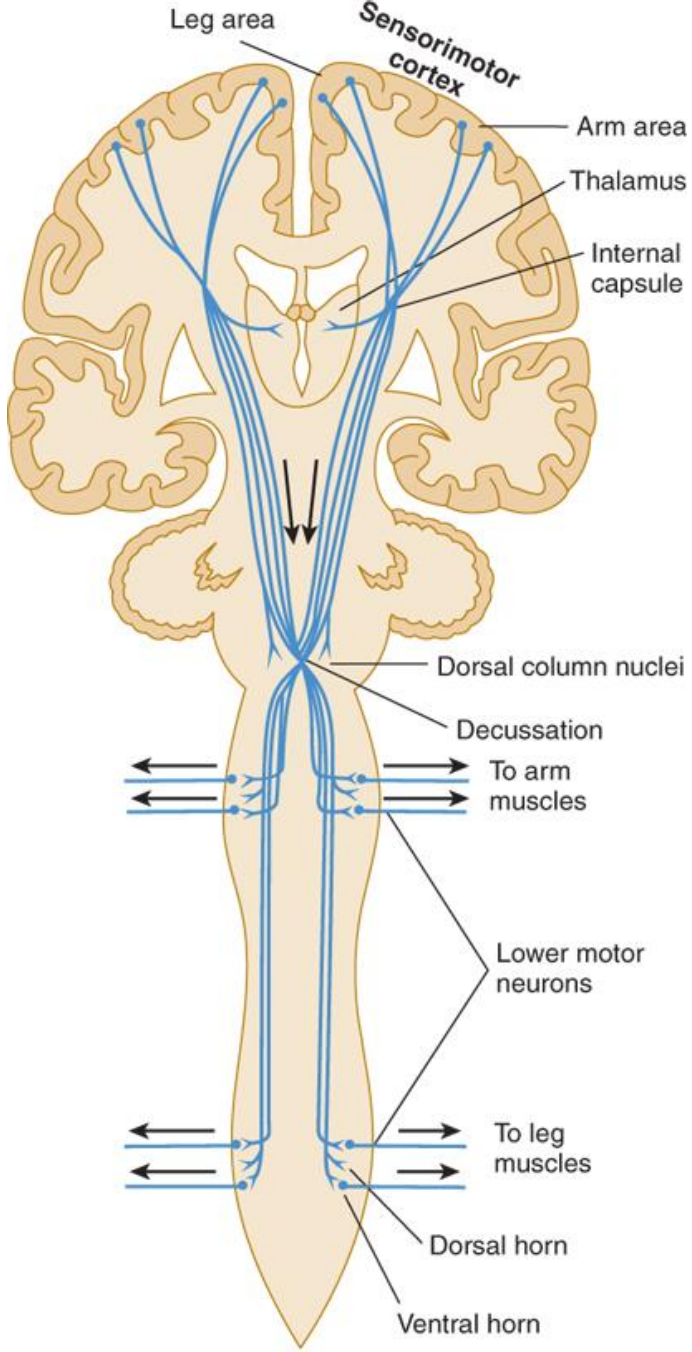
Lesch-Nyhan syndrome

- XR, mutations in the gene coding for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT)
- delayed developmental milestones, intellectual disability (mental retardation), and extrapyramidal and pyramidal motor symptoms; they also develop self-mutilating behavior
- hypotonia (3-6 months of age) → involuntary movements, predominantly dystonia (6-24 months)

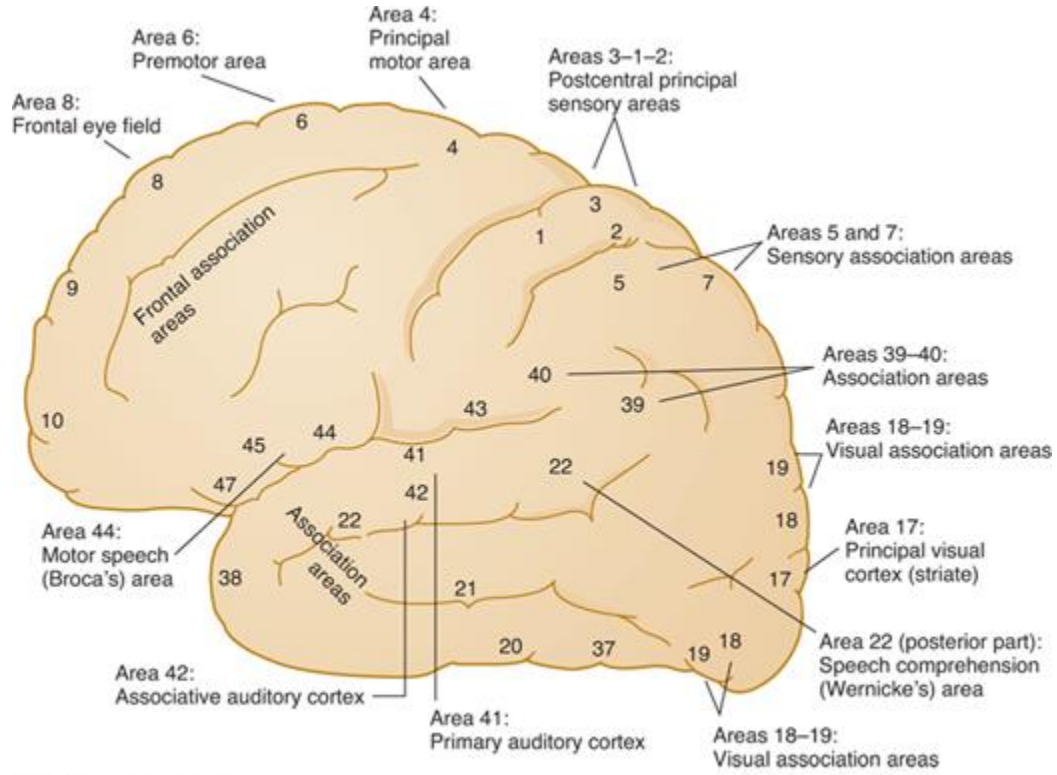
Functional Neuroanatomy

Major motor systems

- Corticospinal and Corticobulbar tracts from sensorimotor cortex
  - 55% originate in the frontal lobe (areas 4 and 6) → motor fx
  - 35% arise from areas 3, 1, and 2 in the postcentral gyrus of the parietal lobe → modulation
  - 10% of the fibers originate in other frontal or parietal areas



Source: Stephen G. Waxman
Clinical Neuroanatomy, Twenty-Eighth Edition
www.accessmedicine.com



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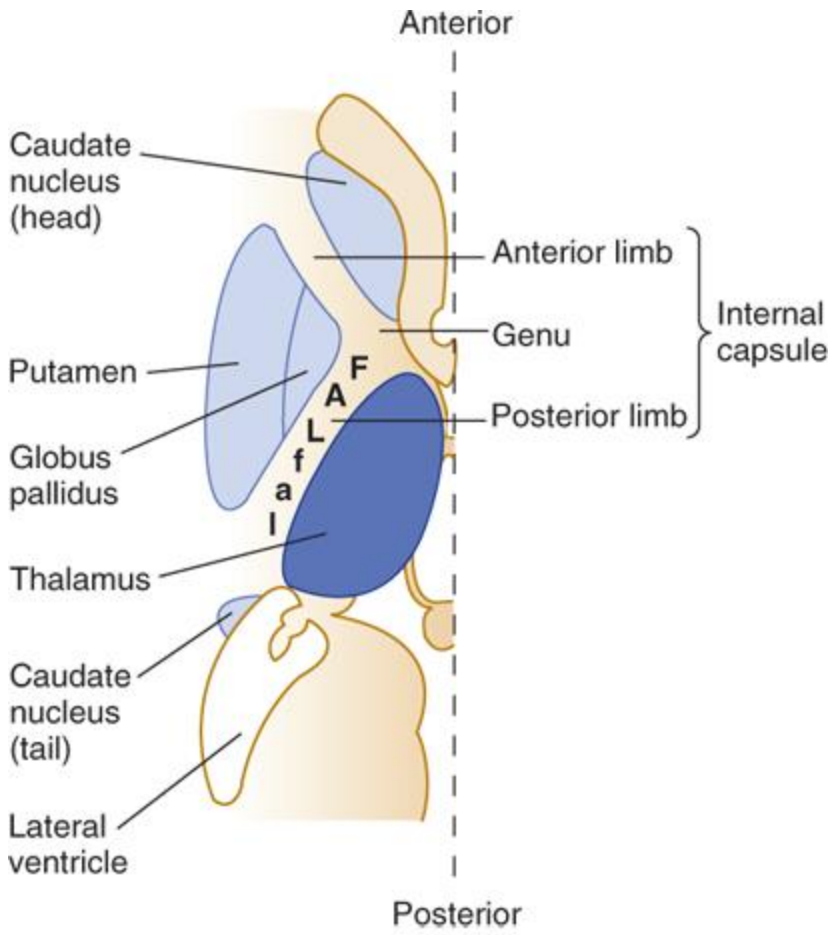
Internal capsule

- crucial band of myelinated fibers :corticobulbar and corticospinal tracts.

- Descending motor fibers for the face, arm, and leg (F, A, L) run in front of ascending sensory fibers (f, a, l) PL in the posterior limb of the internal capsule.

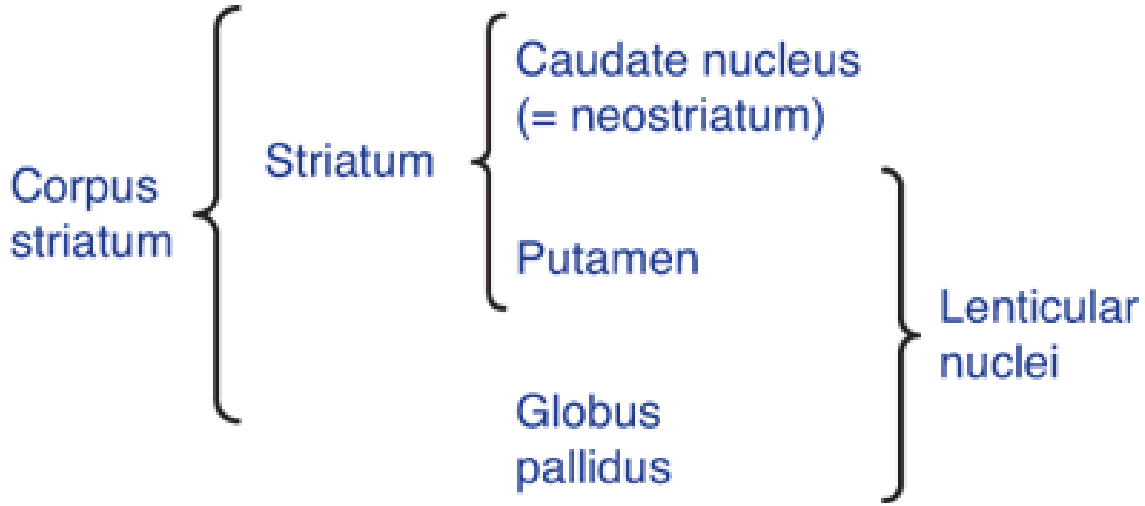


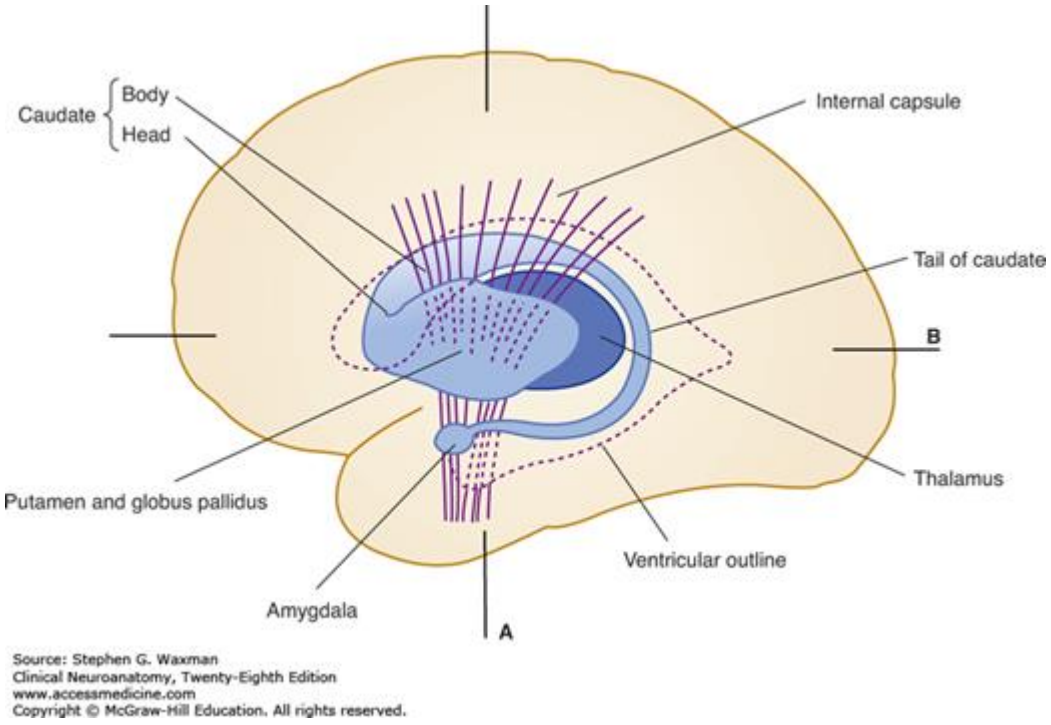
Internal capsule

- **Anterior limb**
  - thalamocortical fibers
  - corticothalamic fibers
  - frontopontine tracts
  - fibers from the caudate nucleus to the putamen
- **Posterior limb**
  - major ascending and descending pathways
  - corticobulbar tracts
  - corticospinal tracts
  - corticorubral fibers

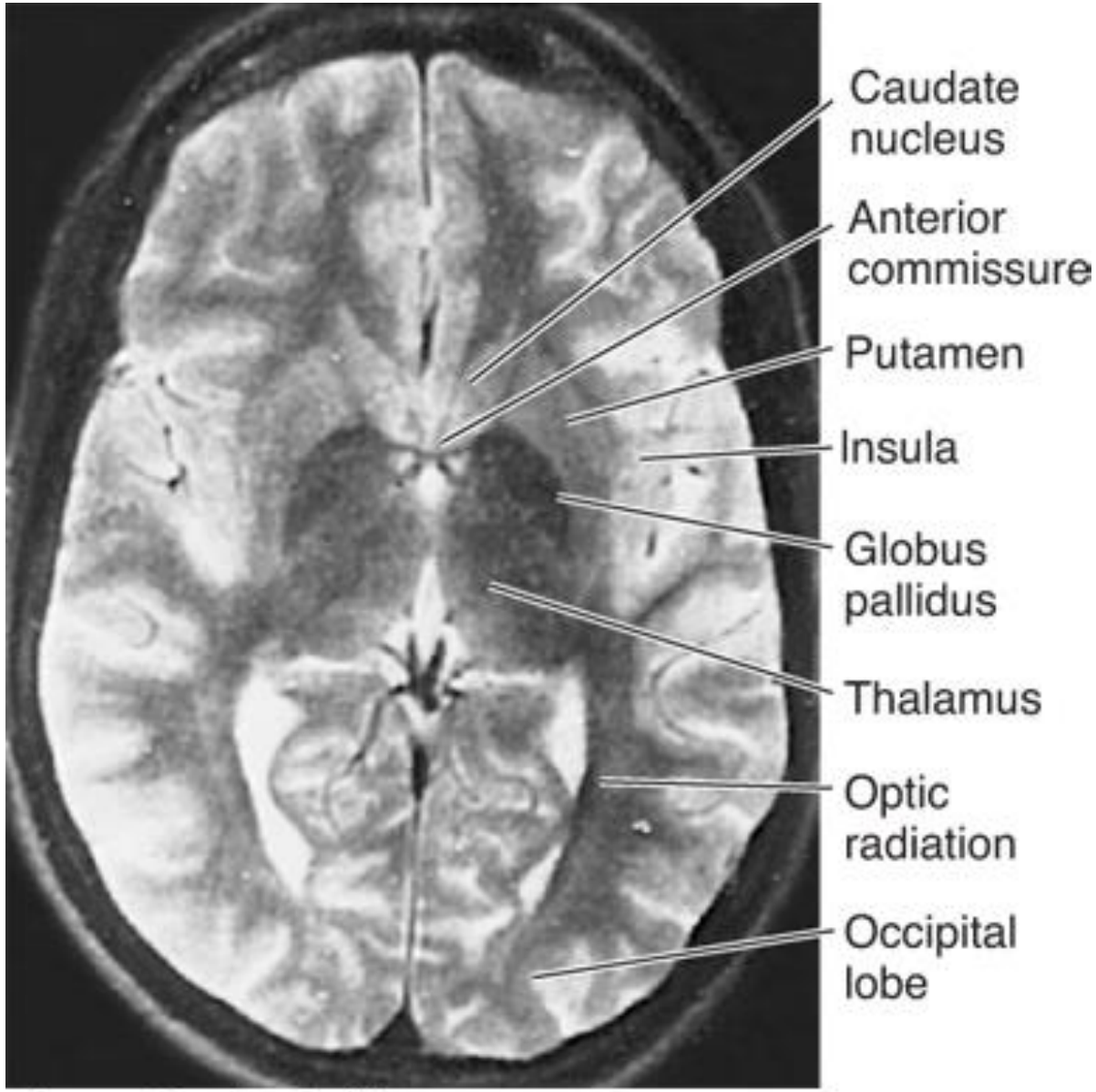
Basal Ganglia

- essential functional role in motor control
- **caudate nucleus**, **putamen**, **globus pallidus**





Major nuclei of the basal ganglia.



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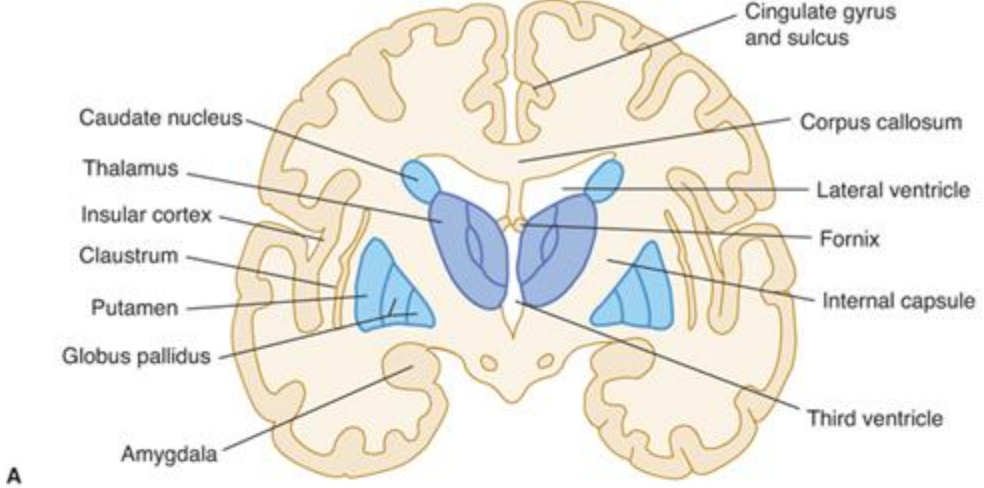
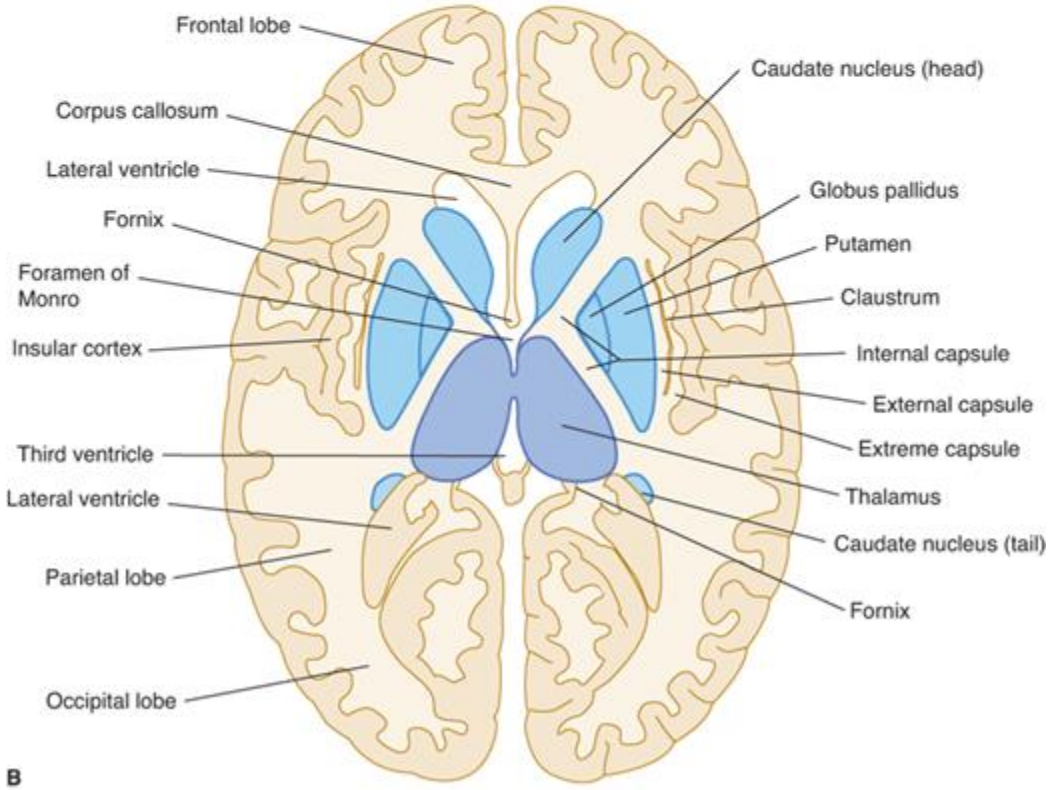


A



B

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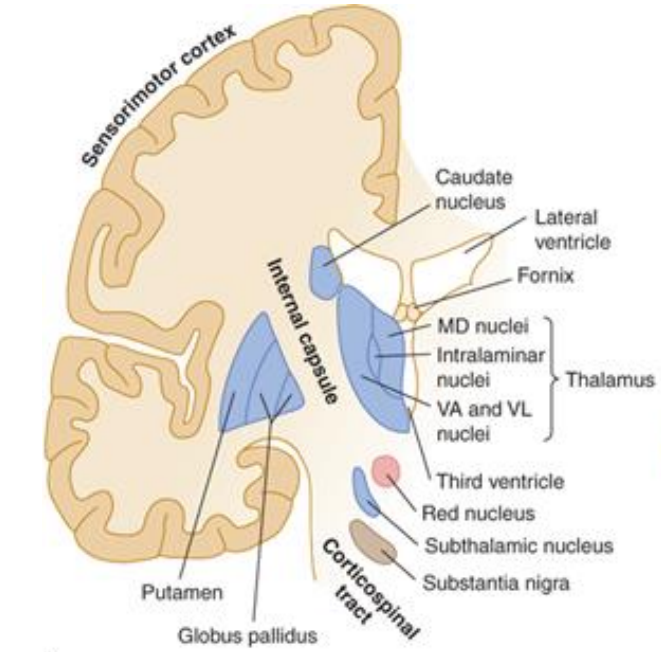
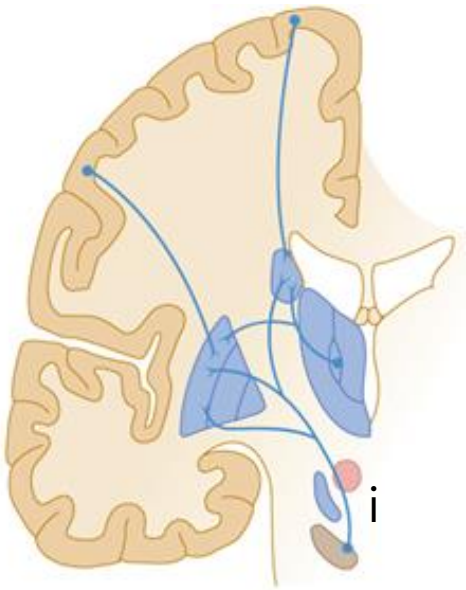
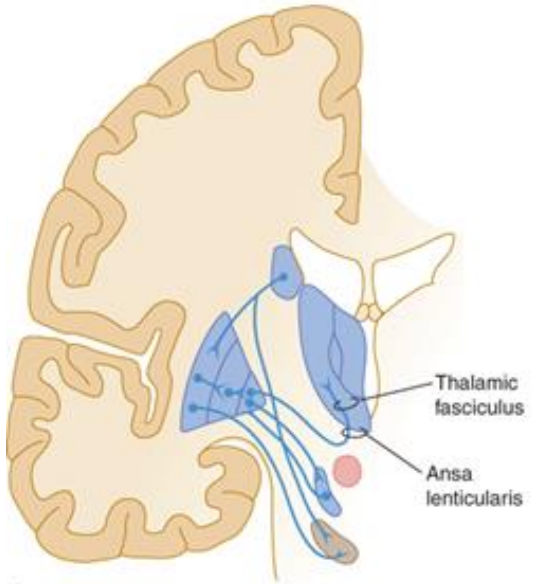
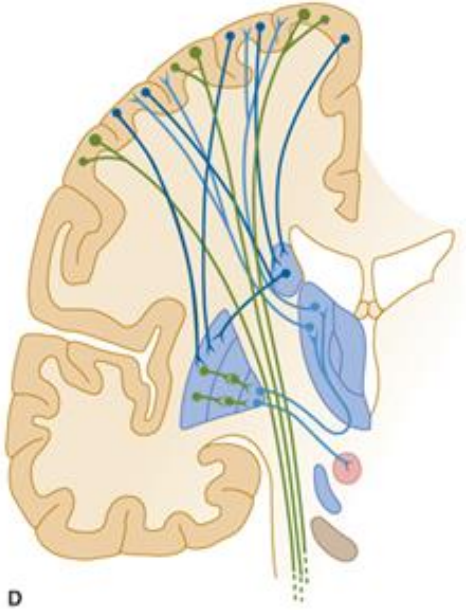
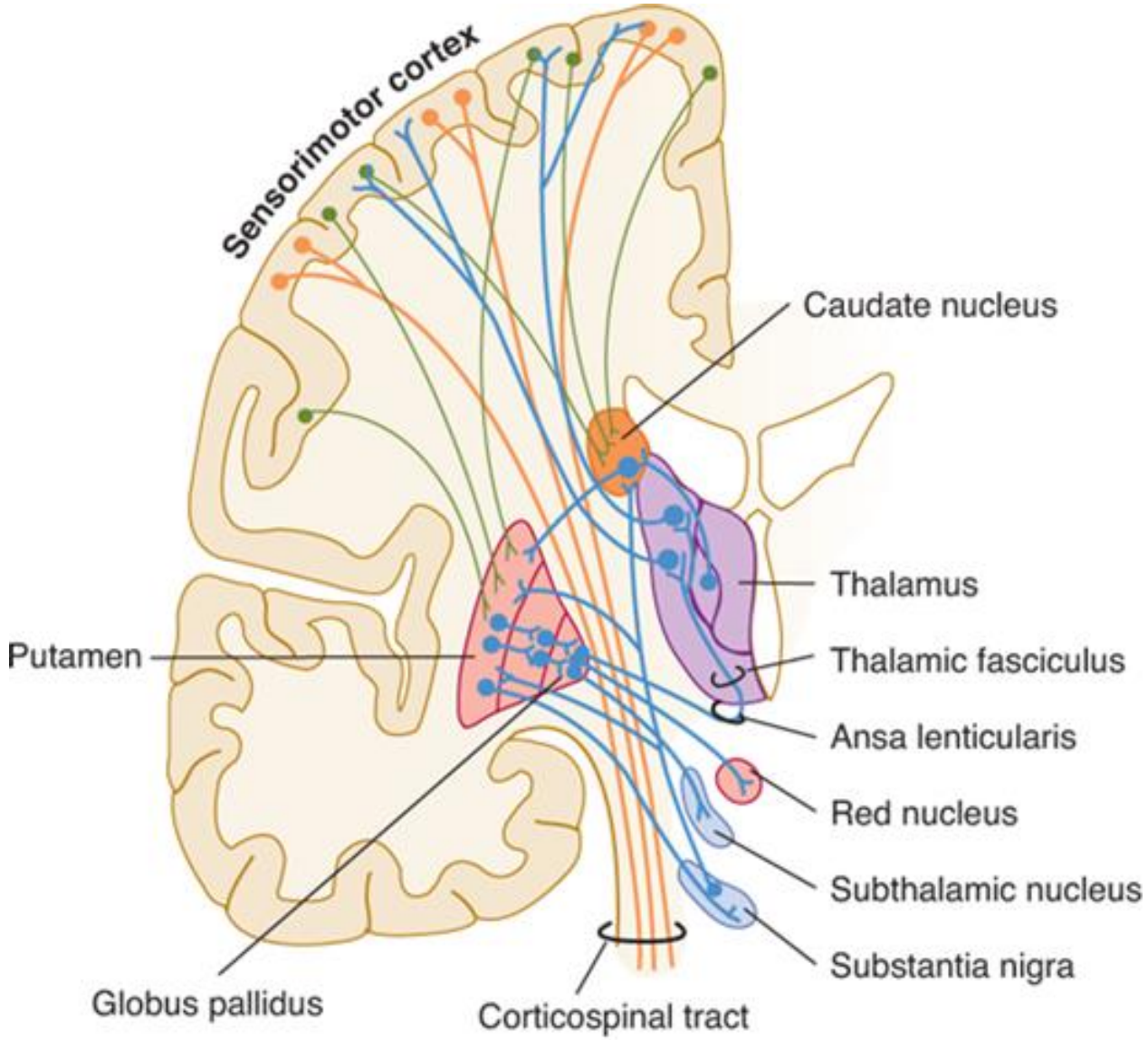










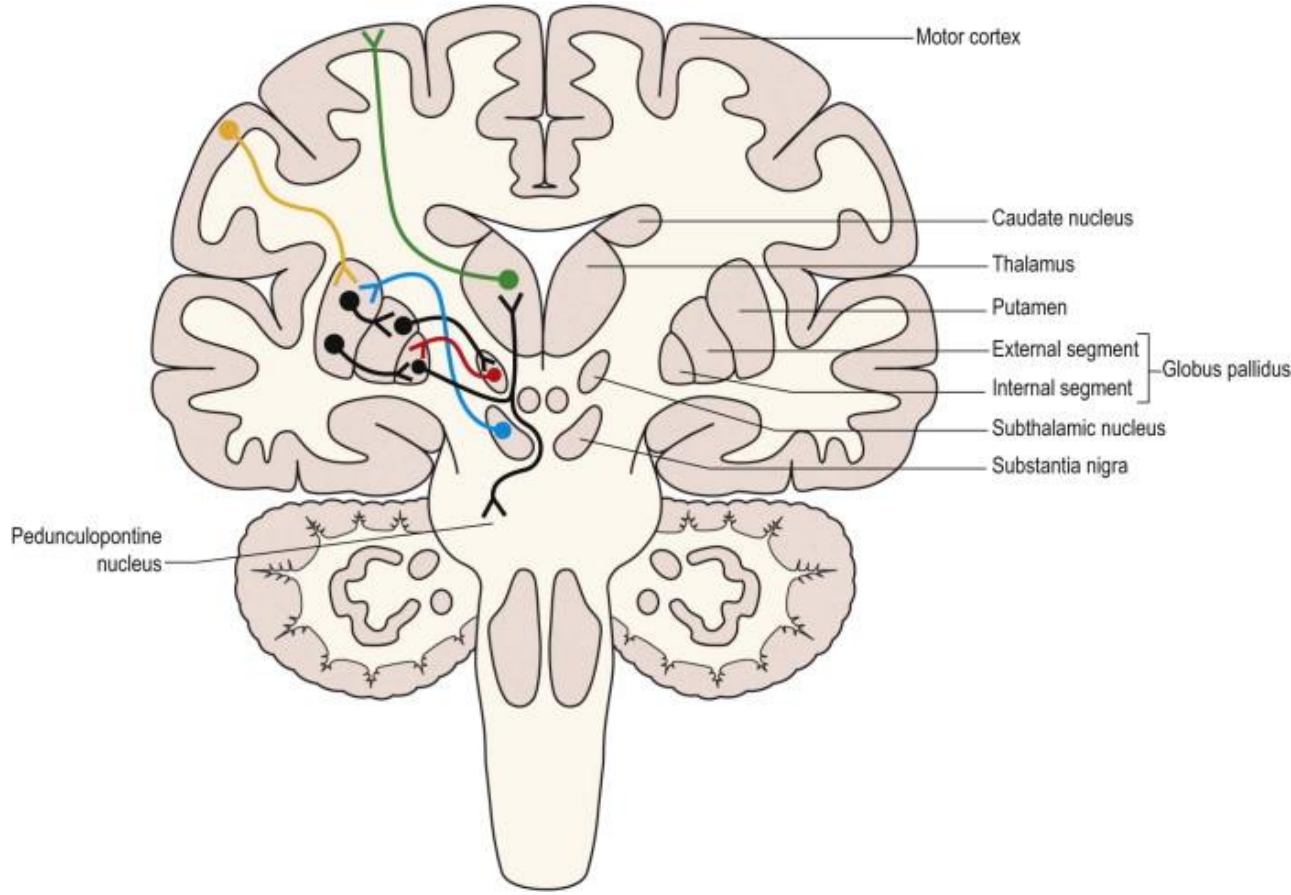
connections.

Striatal afferents

- Corticostriatal fibres
  - Frontal motor → putamen
  - More anterior frontal and other association cortices → caudate nucleus
  - Excitatory, glutamic acid
- Thalamostriatal projection
  - Intralaminar nuclei (centromedian and parafascicular nuclei) of the ipsilateral thalamus
- Nigrostriatal projection
  - Ipsilateral **substantia nigra (pars compacta)** of the midbrain tegmentum
  - Monoamine dopamine (both excitatory and inhibitory)
  - From raphe nuclei (serotonin)

Striatal efferents

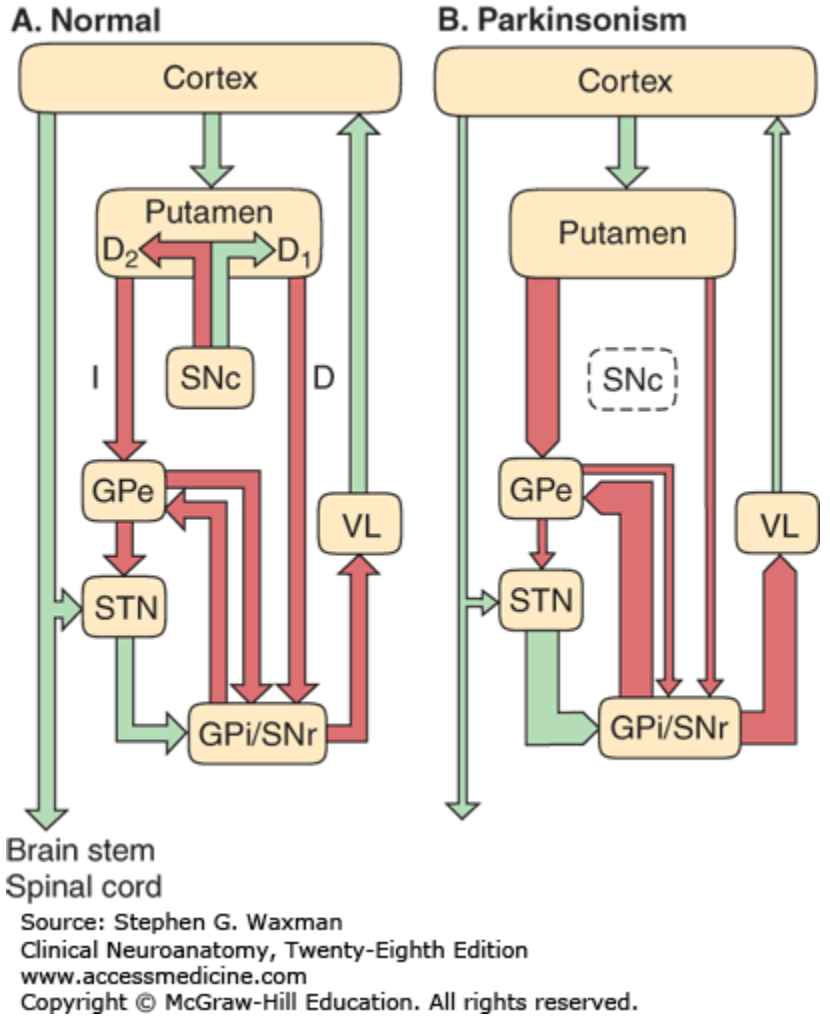
- Striatopallidal fibers
  - Globus pallidus
  - GABA
- Striatonigral fibers
  - Substantia nigra(pars reticulata)
  - GABA



- Globus pallidus(internal), substantia nigra: substance P, dynorphin
- Globus pallidus(external): met-enkephalin

Cortex → striatum → substantia nigra → thalamus → cortex

- Excitatory synaptic cortex directed to the putamen
- putamen also receives projections from the SNc
- Direct pathway (monosynaptic inhibitory projections to GPi/SNr) → enhance motor activity
- Indirect pathway (polysynaptic connections, through GPe and STN) → suppression of motor activity
- Outputs from GPi/SNr project toward the ventrolateral nuclear group of the thalamus (VL), and the VL in turn projects back to the cortex
- Most of the intrinsic connections within the BG, and the GPi/SNr projections: inhibitory (GABA-ergic), except for the projection between STN and GPi/SNr

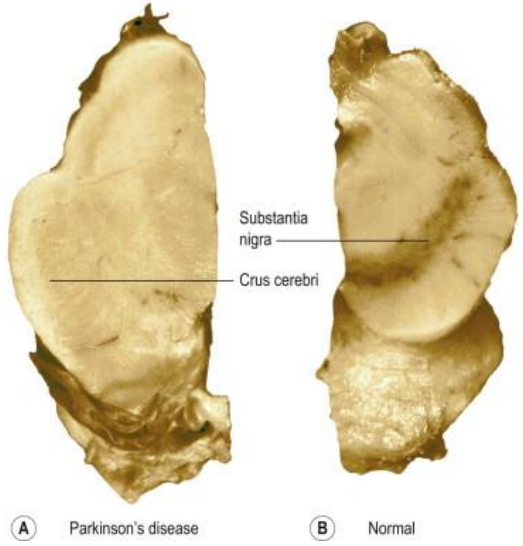


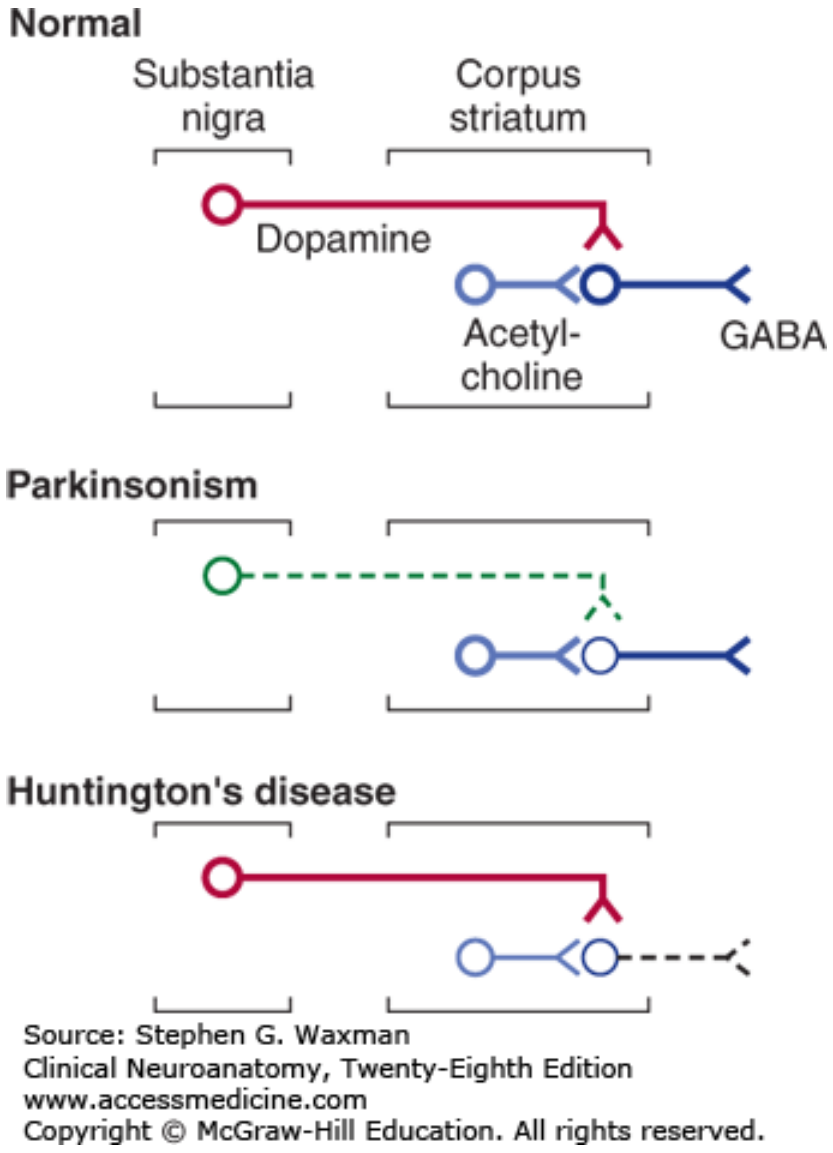
Defects in function of the BG

- Changes in muscle tone
- **Akinesia:** poverty of voluntary movement
- **Bradykinesia:** abnormally slow movements
- **Dyskinesia:** involuntary, abnormal movement
- **Tremors**
- **Athetosis:** slow, writhing movements of the extremities and neck musculature
- **Chorea:** quick, repeated, involuntary movements of the distal extremity muscles, face, and tongue, often associated with lesions of the corpus striatum

- **Huntington's Disease**
  - loss of neurons in the caudate and putamen
  - Loss of GABA-ergic (inhibitory) neurons in the striatum → chorea

- **Parkinson's Disease**
  - loss of pigmented (dopaminergic) neurons in the substantia nigra





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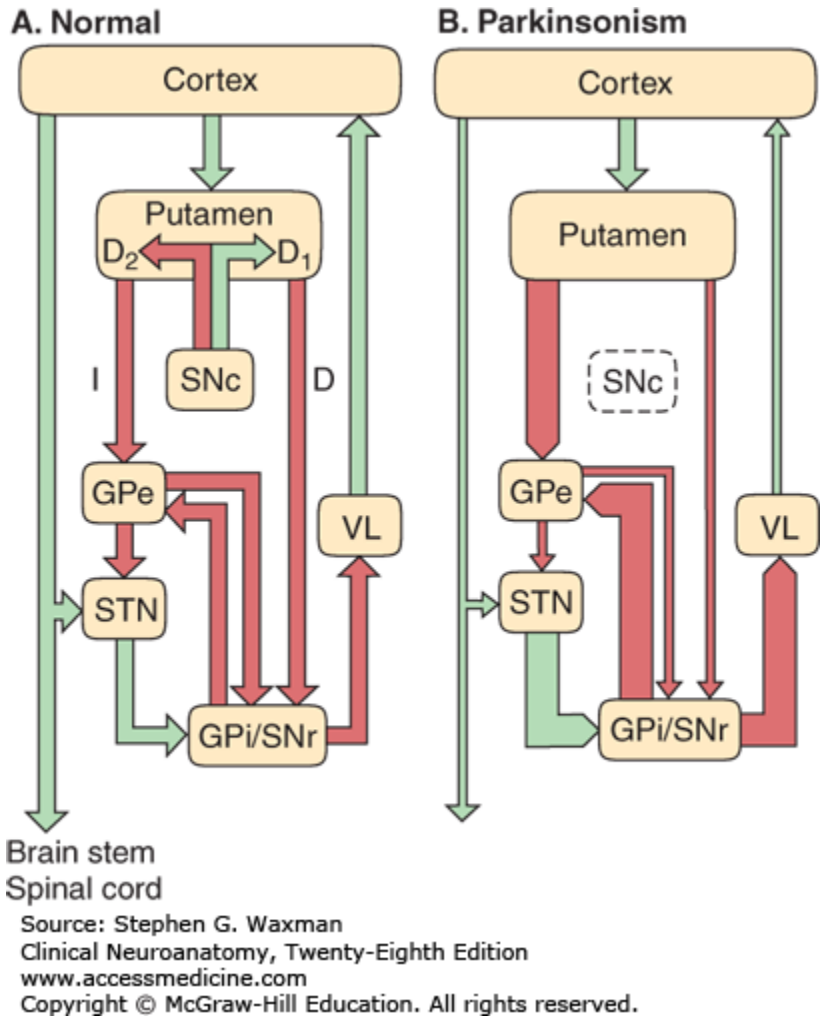
- Chorea : degeneration of the ‘indirect’ pathway in the basal ganglia with relative preservation of the ‘direct’ pathway, early in the disease

- Wilson’s disease: putamen, frontal lobes
- Hemiballism: STN



Subcortical descending systems

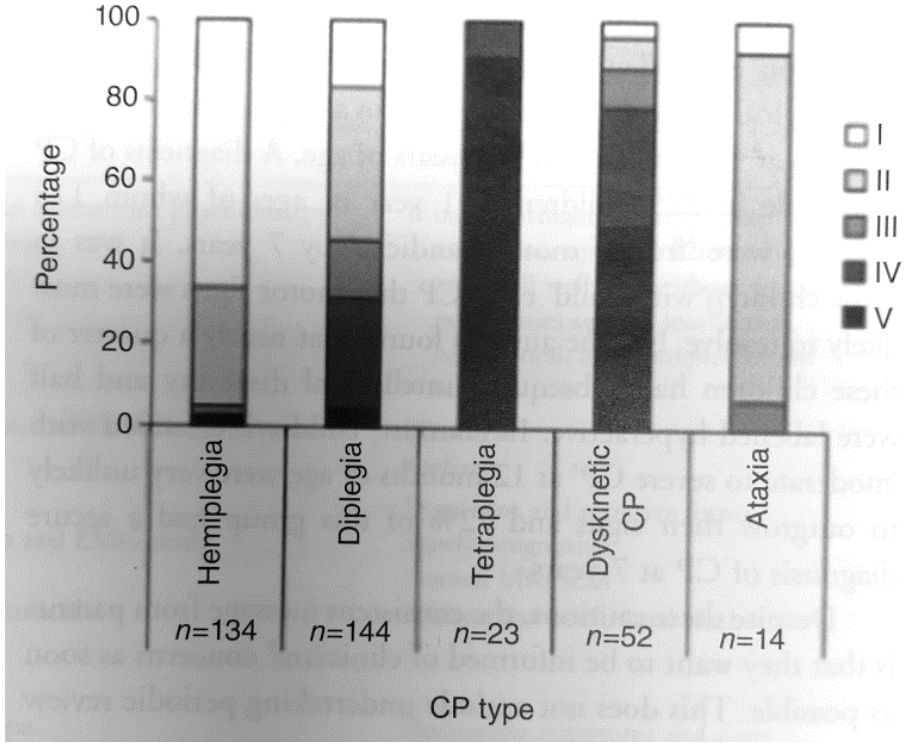
- Rubrospinal tract
  - contralateral deep cerebellar nuclei, motor cortex(bilateral) → Red nucleus → interneurons in the spinal cord
  - Flexor muscle tone control
  - Hand and finger movement
- Reticulospinal tract
  - Sensorimotor cortex → reticular formation → interneurons in the spinal cord, gamma motor neurons
- Vestibulopspinal tract
  - Vestibular nerve and cerebellum → 4 vestibular nuclei (crossed and uncrossed fibers to anterior horn neurons in the spinal cord)
  - Interneurons to alpha and gamma motor neurons, extensor muscles
  - Important role in maintaining an erect posture
- Tectospinal tract
  - Superior colliculus → cross the midbrain (red nucleus) → medial longitudinal fasciculus (medulla)
  - Control reflex movements of the upper trunk, neck, and eyes in response to visual stimuli

Dyskinetic Cerebral Palsy

Dyskinetic cerebral palsy (extrapyramidal)

- 10% of CP
- Predominantly term infants
- Abnormal movements or postures that result from defective coordination of movement and/or regulation of muscle tone

- 70% of dyskinetic CP: severe gross motor difficulties (GMFCS levels IV or V)
- Severe speech difficulties



Forms of dyskinetic CP

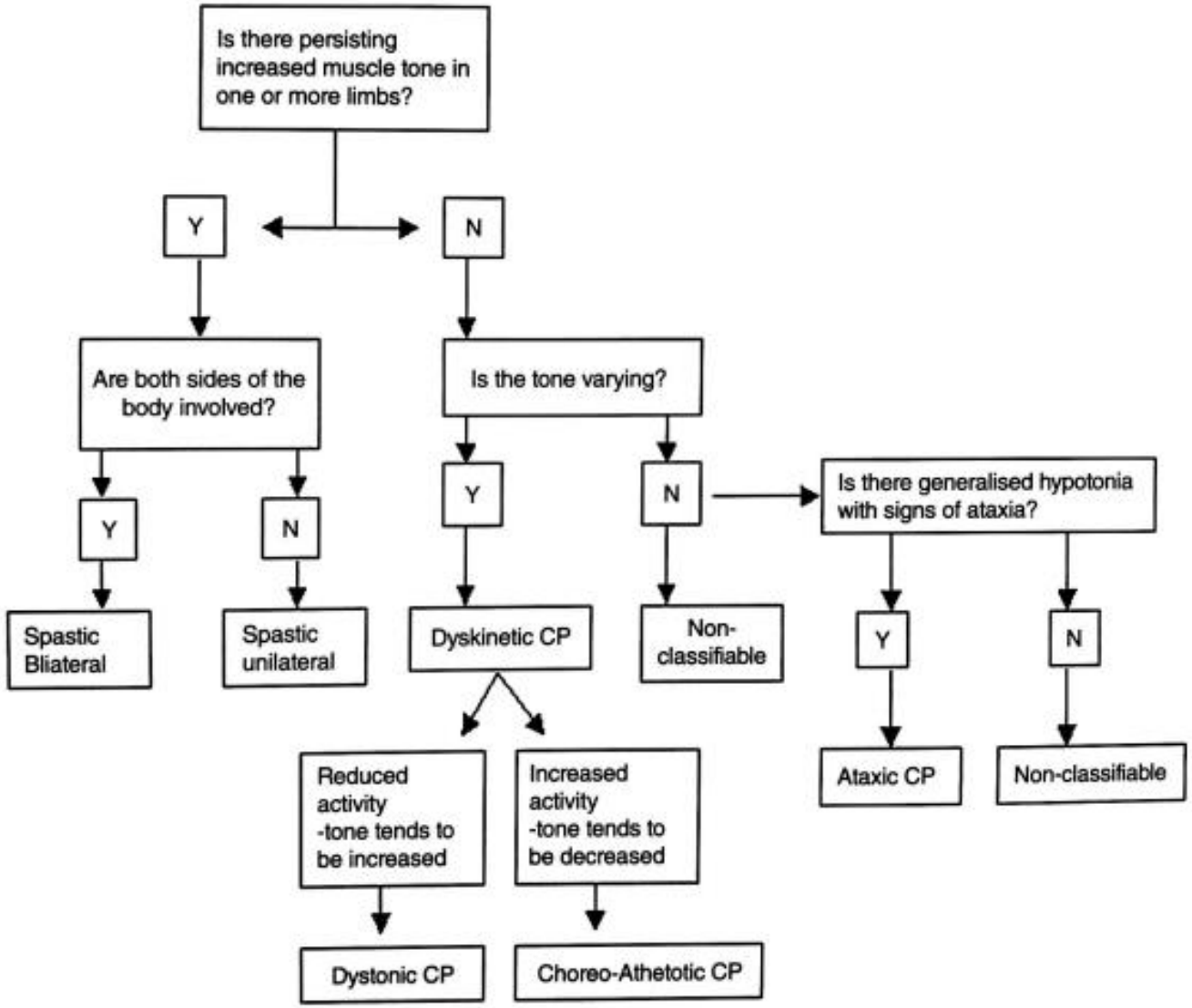
Dystonic CP (10%)	Slow sustained tonic contractions of limbs or axial musculature Provoked by emotion and effort and associated with persisting primitive reflexes (ATNR)
Choreoathetosis CP (5%)	Movements are purposeless and involuntary and may comprise movements that are slow, writhing, and distal, or choreic movements that are jerky and more proximal

Differential Diagnosis

Cerebral palsy is a diagnosis of exclusion

Typical symptoms and signs of CP (eg, early hypotonia, spasticity, and dystonia and/or choreoathetosis) may be present in other conditions

Decision tree for classification of CP



Hypertonia Assessment Tool (HAT)

HAT ITEM	SCORING GUIDELINES (0=negative or 1=positive)	SCORE 0=negative 1=positive *(circle score)*	TYPE OF HYPERTONIA
1. Increased involuntary movements/postures of the designated limb with tactile stimulus of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
2. Increased involuntary movements/postures with purposeful movements of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
3. Velocity dependent resistance to stretch	0= No increased resistance noticed during fast stretch compared to slow stretch	0	SPASTICITY
	1= Increased resistance noticed during fast stretch compared to slow stretch	1	
4. Presence of a spastic catch	0= No spastic catch noted	0	SPASTICITY
	1= Spastic catch noted	1	
5. Equal resistance to passive stretch during bi-directional movement of a joint	0= Equal resistance not noted with bi-directional movement	0	RIGIDITY
	1= Equal resistance noted with bi-directional movement	1	
6. Increased tone with movement of another body part	0= No increased tone noted with purposeful movement	0	DYSTONIA
	1= Greater tone noted with purposeful movement	1	
7. Maintenance of limb position after passive movement	0= Limb returns (partially or fully) to original position	0	RIGIDITY
	1= Limb remains in final position of stretch	1	

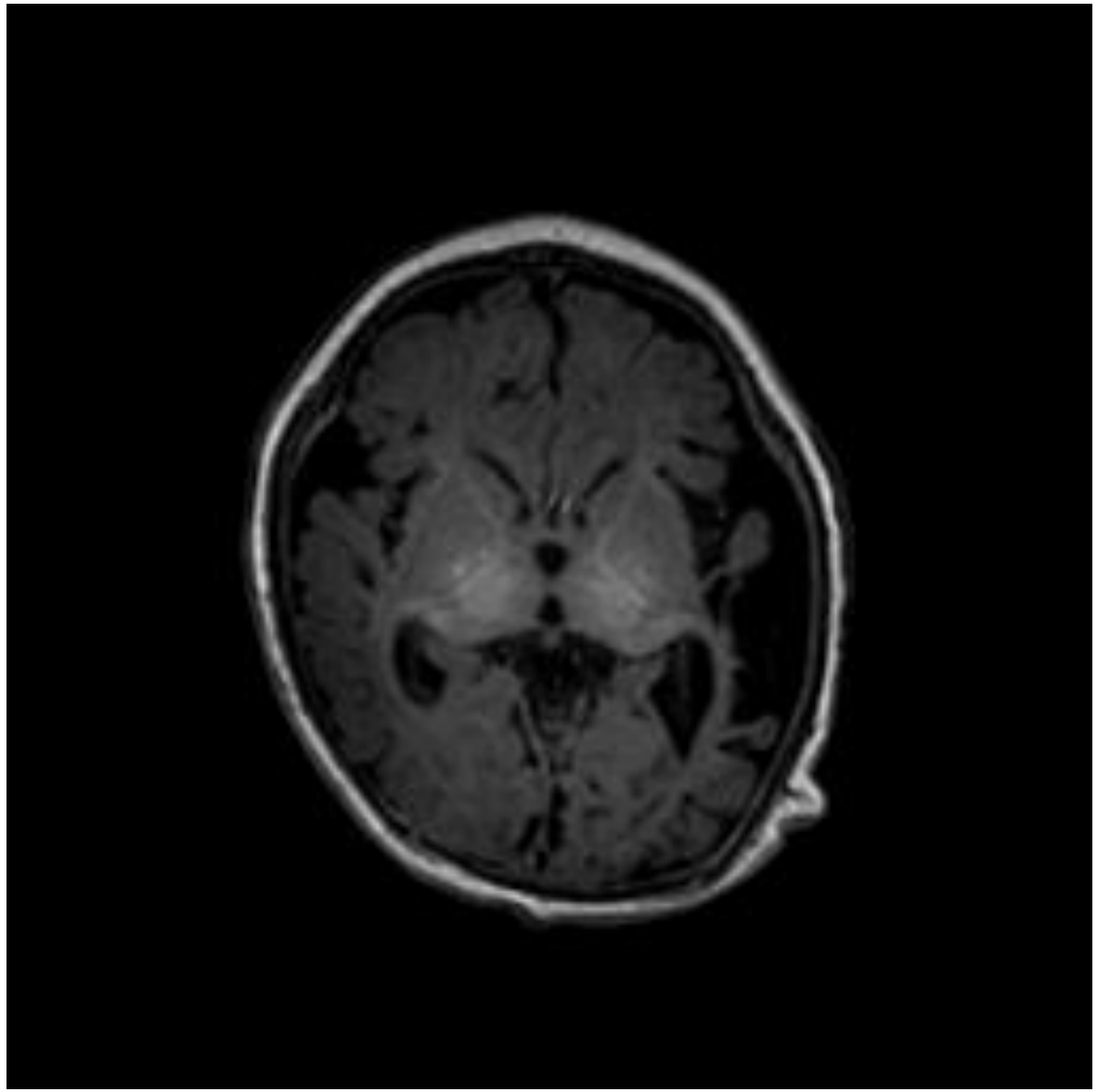
http://www.hollandbloorview.ca/research/scientistprofiles/fehlings.php

Causes of dyskinetic subtypes

- Most cases are caused by severe perinatal asphyxia resulting in injury to the **thalamus**, **basal ganglia**, hippocampus, reticular formation, and/or cerebellum
- Severe hyperbilirubinemia (kernicterus) can cause choreoathetotic CP

description of the brain abnormalities. So far, no study has systematically assessed the relationship between the clinical characteristics of dystonia and choreoathetosis and the underlying brain lesion, such as in the basal ganglia and thalamus.

5m/M, FT, meconium aspiration




MICRALITE

Common clinical features

- In early infancy
  - Reduced spontaneous movement
  - Hypotonia at rest, variable tone with movement or emotion
  - Oromotor incoordination
  - Persistence of primitive reflexes
  - Involuntary grimacing
  - Drooling
  - Delayed psychomotor development
  - Head can be persistently turned

Common clinical features

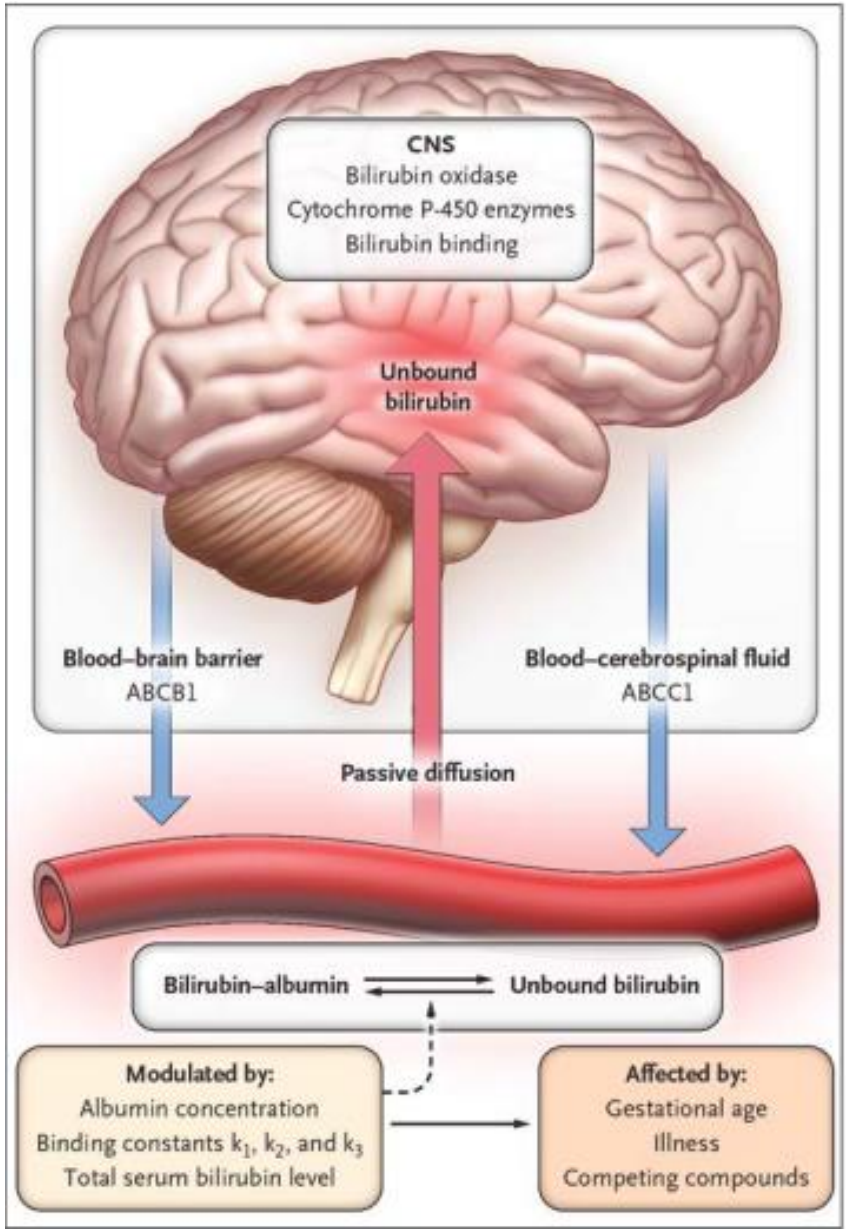
- Age two to three years
  - Involuntary movements are apparent
  - Abnormal posturing:
    - Extension patterns in the supine position
    - Flexion with shoulder retraction in the prone position
    - Head usually is persistently turned to one side

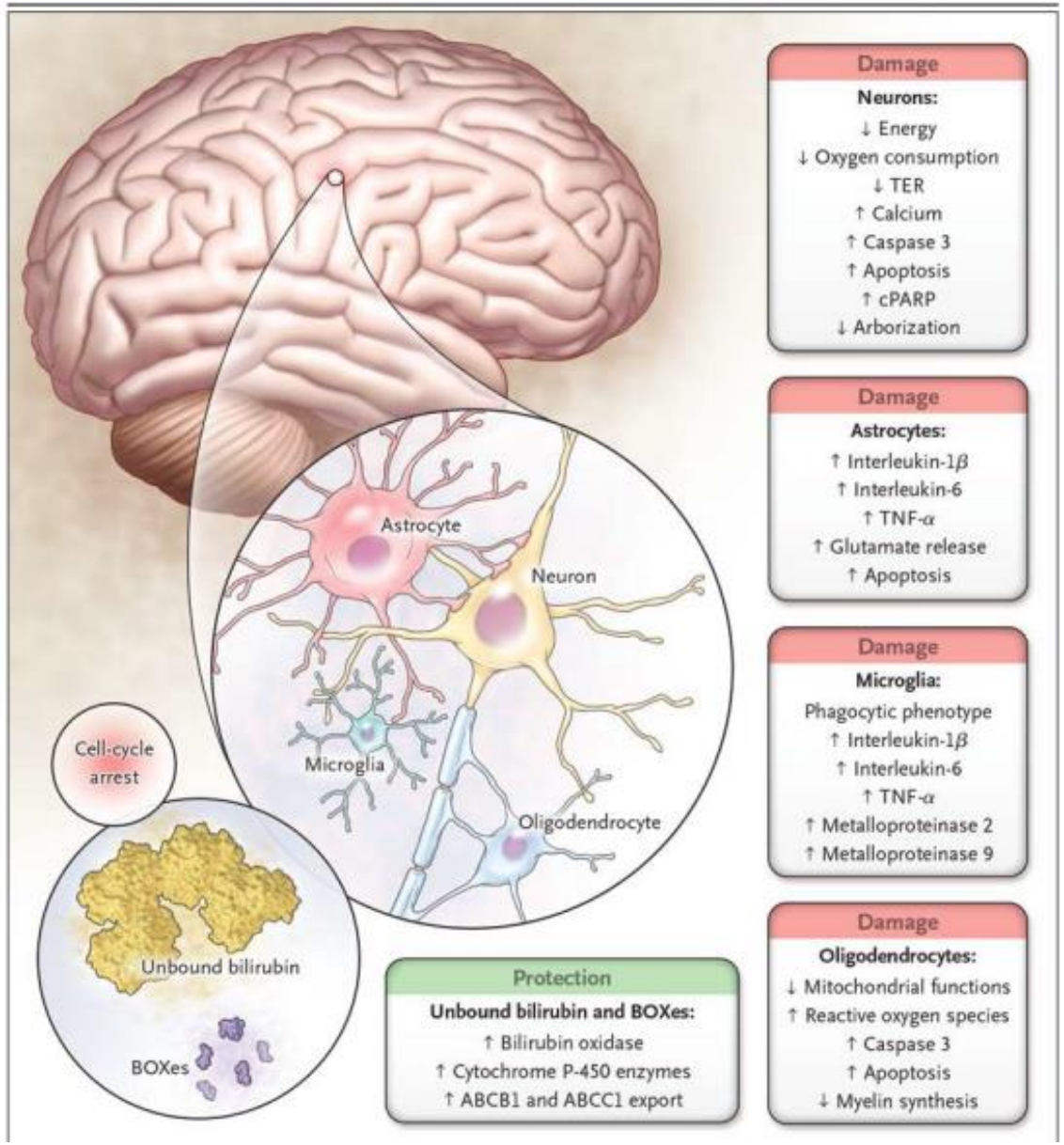
Common clinical features

- Children >5 years old
  - Involuntary movements
  - Contractures are not common but may evolve later in life
  - Variable degree of dysarthria and intellectual disability

Kernicterus

- severe hyperbilirubinemia
  - alloimmune hemolytic disease due to ABO incompatibility or other red blood cell antibodies
  - G6PD (glucose-6-phosphate dehydrogenase) deficiency
  - sepsis
- permanent neurologic sequelae of bilirubin-induced neurotoxicity (BIND) that manifests itself as a type of CP characterized by choreoathetosis, with gaze abnormalities and sensorineural hearing loss
- unconjugated bilirubin enters the brain and causes focal necrosis of neurons and glia
- basal ganglia and the brainstem nuclei for oculomotor and auditory function





N Engl J Med 2013;369:2021-30

Major risk factors for severe hyperbilirubinemia in infants

- Predischarge TB or TcB level in the high-risk zone
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCOc
- Gestational age 35 to 36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- East Asian race

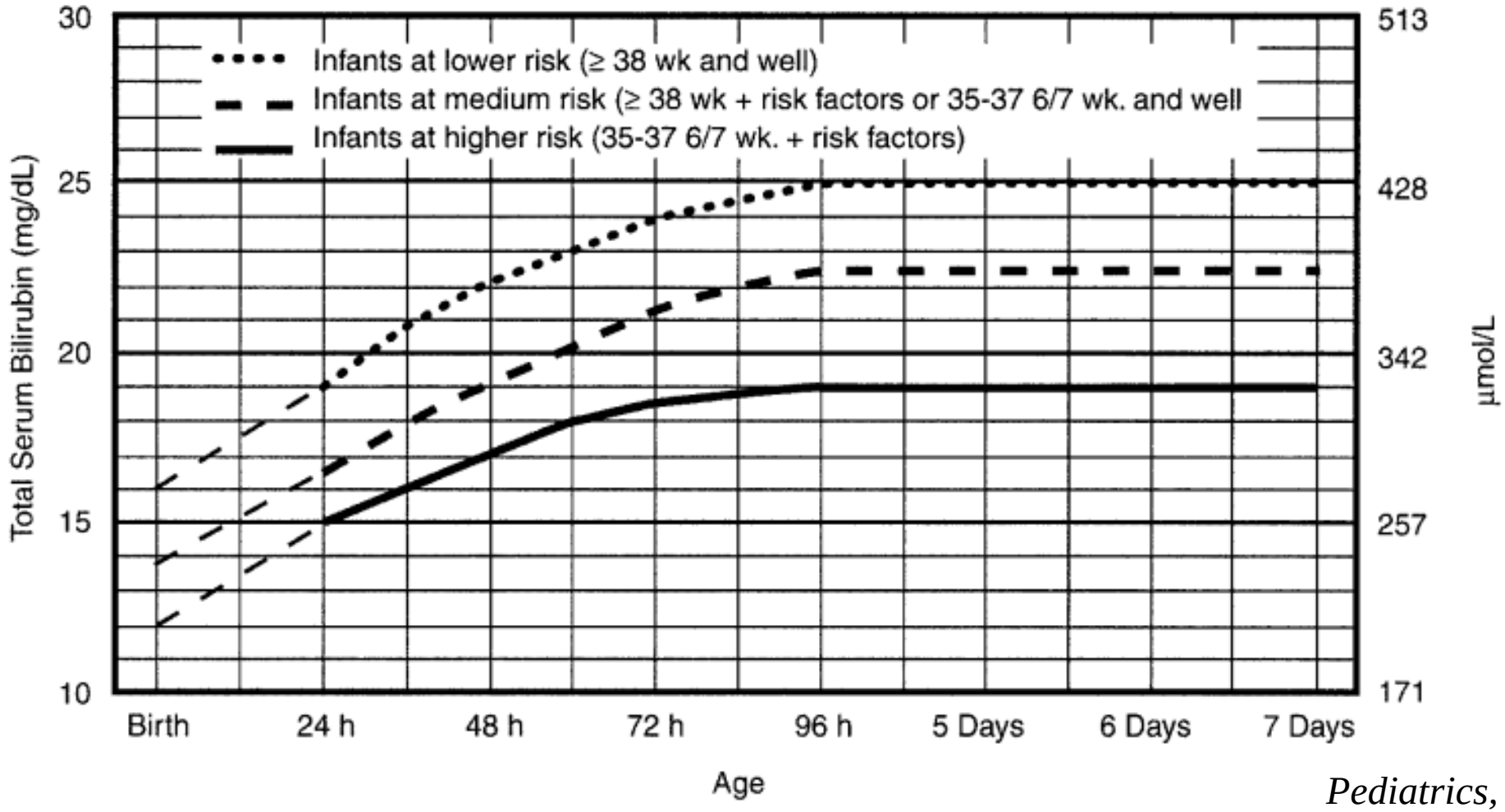
Pediatrics, Vol. 114, 297-316

6개월 여아

- 39+0 wks - 2640g - NSD - 8/9 → 전원
- ABO incompatibility → exchange transfusion
- 산모 혈액형 O+, 환아 혈액형 B+
- Small for gestational age
- Coomb's test (direct): positive, (indirect): negative
- Initial serum TB 12.90 (생후 4시간), exchange T/F 직전 serum 13.50
- Initial reticulocyte count 21.37
- AABR Pass

- prone to supine (+/+)
- 내원 전일 supine to prone
- Creeping (-)
- supine 자세에서 등으로 이동
- Fisting (+/+)
- Thumb in palm (+/+)
- Reaching : not very well
- Grasp: clumsy, ulnar side grasp

Guidelines for exchange transfusion in infants 35 or more weeks' gestation



Pediatrics, Vol. 114, 297-316

11m, creeping (+), sit up (-)

Assessment

Assessment of movements

History:
birth, development, medication, toxin, trauma, family history

Observation:
duration, speed, amplitude, smoothness, and repeatability

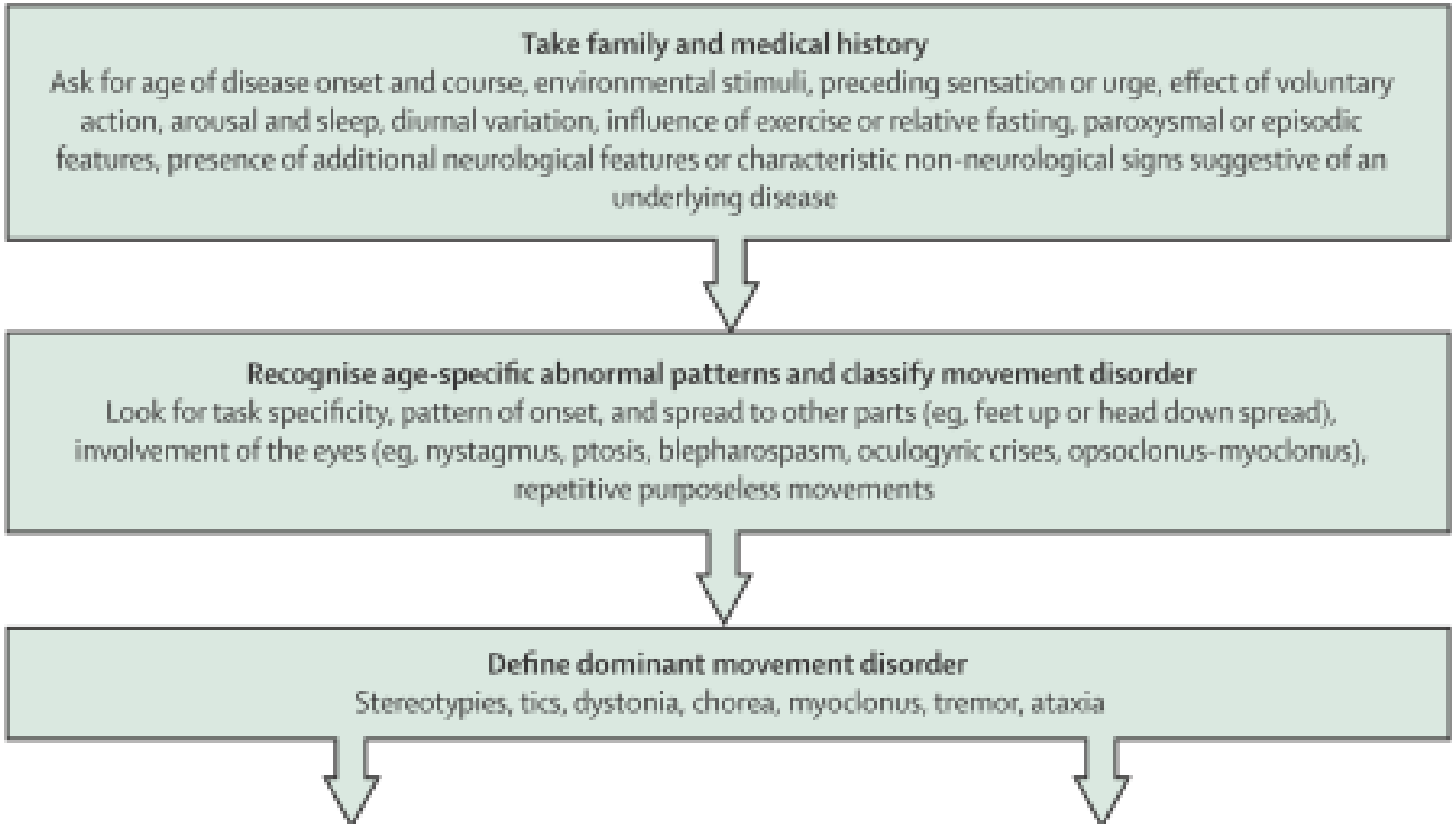
Muscle tone

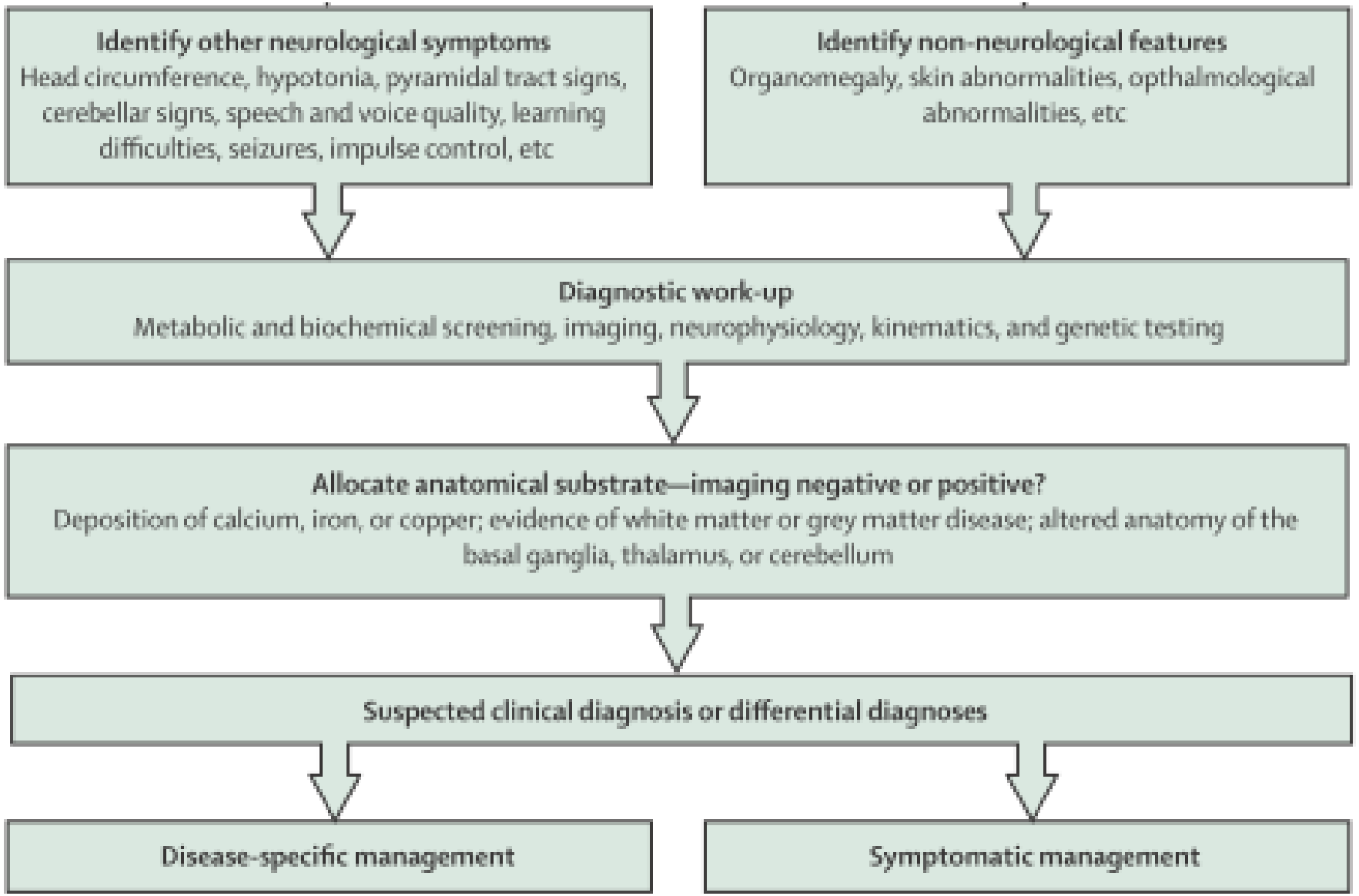
Intellectual function

Cognition in childhood dystonia: a systematic review

MARAIKE A COENEN | HENDRIEKJE EGGINK | MARINA A TIJSSEN | JACOBA M SPIKMAN

	Primary dystonia		Secondary dystonia due to CP		Secondary dystonia due to IEM
Intelligence	X		X		X
Working memory		X	X		X
Visual memory	X		X		X
Verbal memory	X		X		X
Information processing speed		X	X		
Visuospatial functions				X	
Social cognition			X		
	Normal	Mild deficits		Impaired	


Take family and medical history
Ask for age of disease onset and course, environmental stimuli, preceding sensation or urge, effect of voluntary action, arousal and sleep, diurnal variation, influence of exercise or relative fasting, paroxysmal or episodic features, presence of additional neurological features or characteristic non-neurological signs suggestive of an underlying disease
Recognise age-specific abnormal patterns and classify movement disorder
Look for task specificity, pattern of onset, and spread to other parts (eg, feet up or head down spread), involvement of the eyes (eg, nystagmus, ptosis, blepharospasm, oculogyric crises, opsoclonus-myoclonus), repetitive purposeless movements
Define dominant movement disorder
Stereotypies, tics, dystonia, chorea, myoclonus, tremor, ataxia



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