Complex Movement Disordersrelated to Genetic Disorders

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How to approach in complex movement disorders

- What is the phenomenology?
  - ► Hypokinesia
    - Parkinsonism; Akinesia/Bradykinesia, Rigidity
    - Dystonia
    - Stiffness
  - ► Hyperkinesia
    - Chorea
    - Dystonia
    - Tremor, Myoclonus
    - Akathisia
    - Ataxia/Asynergia/Dysmetria
    - Ballism

How to approach in complex movement disorders

- Which diseases can causes these phenomenology?
  - ► metabolic disorders
  - ► structural lesions
  - ► genetic disorders
  - ► drug-induced / tardive syndromes
  - ► psychogenic
- Features supporting genetic disorders
  - Family history : inheritance pattern
  - early onset
  - typical clinical or laboratory features

Cases with Video Clip

- Case 1
  - 55/F
  - chorea, dystonia, ataxia and cognitive impairment
  - Family history of gait disturbance and dementia
- Case 2
  - 22/F
  - seizure, myoclonus, ataxia, chorea and cognitive impairment
  - Family history of seizure, gait disturbance and dementia
- Case 3
  - 26/M
  - dystonia, parkinsonism and behavioral problem
  - liver cirrhosis
- Case 4
  - 38/F
  - myoclonus and dystonia
  - Family history of tremor and gait disturbance

Combinations of varieties of movements

- Psychogenic movement disorders
- Tardive syndromes
- Neuroacathocytosis
- Wilson disease
- Huntington disease
- Dentatorubral-pallidoluysian atrophy (DRPLA)
- Dystonia plus syndrome

Fahn S, Jankovic J, Hallet M. Principles and Practice of Movement Disorders, 2nd ed.

Clinical and Genetic Heterogeneity

- Clinical heterogeneity
  - A disorder can present various clinical phenotype.
- Genetic heterogeneity
  - A certain clinical picture can be caused by various mutations.
  - Genetic test according to specific syndrome

DRPLA

- Autosomal dominant neurodegenerative disease
  - CAG repeat expansion on chr 12p13.31
- Wide range of clinical manifestations
  - cerebellar ataxia, myoclonus, choreoathetosis
  - epilepsy
  - dementia
- Different manifestations depending on age at onset
  - early onset (before 20): PME phenotype
    mental retardation, epilepsy and myoclonus
  - late onset (after 20): non PME phenotype
    ataxia, chreoathetosis, dementia and personality change

Wilson disease

- Autosomal recessive systemic disorder
  - ATP7B gene on chr 13q14.3
- Inability to excrete copper to an adequate extent
- Neurologic manifestations
  - dystonia, chorea, tremor, parkinsonism, ataxia
  - seizure, behavioral changes
- Hepatic manifestations
  - acute/chronic hepatitis, fulminant hepatitis, liver cirrhosis
- Other organs
  - Eye, heart, kidney, anemia, bone and joint, parathyroid, pancreas, spleen

Huntington disease

- Autosomal dominant neurodegenerative disease
  - CAG repeat expansion on chr 4p16.3
- Various motor, behavioral and cognitive manifestations
  - chorea, dystonia, parkinsonism and cerebellar ataxia
  - anxiety, depression, aggressive/violent behavior, psychosis
  - inattention, memory deficit and subcortical dementia
- Different manifestations depending on age at onset
  - juvenile HD (before 20): akinetic rigid type
    prominent rigidity, dystonia, seizures and minimal chorea
    psychomotor regression

Myoclonus-dystonia

- Autosomal dominant dystonia-plus syndrome
  - SGCE gene mutation in chr 7q21
  - Maternal imprinting: markedly reduced penetrance from the affected mother
- Alcohol-responsive lightning-like jerks and dystonia
  - upper part of body affected, legs usually spared
  - childhood, adolescent and adult onset
  - slowly progressive and tends to plateau
- Psychiatric problems
  - obsessive-compulsive disorder
  - substance abuse (alcohol dependence)
  - anxiety/panic/phobic disorders, depression and psychosis

Genetic chorea syndromes

Condition/acronym	Mode of inheritance	Locus	Gene/protein	Main clinical features
HD	Autosomal dominant	4p	*IT15/huntingtin*	Chorea, personality changes, dementia
DRPLA	Autosomal dominant	12p	*Atrophin-1*	Progressive myoclonus, epilepsy or ataxia, chorea, dementia
HDL1	Autosomal dominant	20p	*PRNP*	Dementia, myoclonus, ataxia
HDL2	Autosomal dominant	16q	*Junctophilin-3 (JPH3)*	Cognitive deficits, chorea, dystonia in patients of African descent
HDL3	Autosomal recessive	4p	NK	Parkinsonism, dystonia, chorea, ataxia, dementia (single family)
HDL4/SCA17	Autosomal dominant	6q	*TATA-binding protein (TBP)*	Ataxia or Huntington phenocopy
Neuroferritinopathy	Autosomal dominant	19q	*FTL*	Chorea, dystonia, oromandibular involvement, parkinsonism
Benign hereditary chorea	Autosomal dominant	14q	*TITF-1*	Nonprogressive chorea, thyroid, pulmonary abnormalities
Aceruloplasminemia	Autosomal dominant	3q	*Ceruloplasmin gene*	Chorea
Pantothenate kinase-associated neurodegeneration (PKAN)	Autosomal recessive	20p	*PANK2*	Dysarthria, dystonia, corticospinal tract signs, neurobehavioral and cognitive problems
Neuroacanthocytosis	Autosomal recessive	9q	*CHAC/VPS13A*	Facial hyperkinesias, dysarthria, dysphagia, chorea, and less often dystonia, psychopathology and cognitive changes, muscle wasting and weakness
McLeod syndrome	X-linked	Xp21	*XK*	Chorea, parkinsonism, dystonia, psychiatric; seizures, neuropathy, cardiomyopathy, hepatosplenomegaly

Genetic forms of dystonia

Acronym	Mode of inheritance	Locus	Gene/protein	Main clinical features	OMIM #
DYT1	Autosomal dominant	9q	*TorsinA*	Young-onset primary generalized dystonia	128100
DYT2	Autosomal recessive	NK	NK	Recessive young-onset primary dystonia in a single Spanish gypsy family	224500
DYT3	X-linked	Xq13	*TAF1*	Dystonia-parkinsonism with poor response to levodopa in mainly male patients from the Filipino island of Panay	314250
DYT4	Autosomal dominant	NK	NK	Laryngeal dystonia (whispering dysphonia) a limb dystonia in a single Australian family	128101
DYT5a (DRD)	Autosomal dominant	14q	*GCH1*	Dystonia with onset in the legs and diurnal fluctuation of symptoms and worsening after exercise (Segawa's disease)	128230
DYT5b	Autosomal recessive	11b	*TH*	Dopa-responsive dystonia parkinsonism	605407
DYT6	Autosomal dominant	8p	*THAP1*	Adolescent primary craniocervical and limb dystonia	602629
DYT7	Autosomal dominant	18p	NK	Single (?) German family with primary craniocervical dystonia	602124
DYT8	Autosomal dominant	2q	*MR-1*	Attacks of dystonia and chorea precipitated by coffee, alcohol, and fatigue (paroxysmal nonkinesigenic dyskinesia; PNKD)	118800
DYT9	Autosomal dominant	1p	*SLC2A1*/GLUT1	Episodic chorea and ataxia with progressive interictal spasticity (paroxysmal exercise-induced dyskinesia; PED)	601042
DYT10	Autosomal dominant	16p	NK	Episodes of chorea and dystonia precipitated by sudden movement (paroxysmal kinesigenic Dyskinesia; PKD)	128200
DYT11	Autosomal dominant	7q, 11q	*ε-sarcoglycan*	Myoclonus and dystonia	159900
DYT12	Autosomal dominant	19q	*ATP1A3*	Rapid development of severe dystonia-parkinsonism with prominent bulbar features	128235
DYT13	Autosomal dominant	1p	NK	Single Italian family with primary craniocervical dystonia	607671
DYT14 (see DYT5a)	Autosomal dominant	14q	N/A	N/A	607195
DYT15	Autosomal dominant	18p	NK	Myoclonus and dystonia	607488
DYT16	Autosomal recessive	2q	*PRKRA*	Young-onset torsion dystonia, parkinsonism in some	612067
DYT17	Autosomal recessive	20p	NK	Young-onset focal and torsion dystonia, dysphonia (single Lebanese family)	612406
DYT18 (see DYT9)	Autosomal dominant	1p	*SLC2A1*/GLUT1	Paroxysmal exercise-induced dyskinesia	612126
DYT19/EKD2	Autosomal dominant	16q	NK	Episodic kinesigenic dyskinesia	611031
DYT20	Autosomal dominant	2q	NK	Paroxysmal nonkinesigenic dyskinesia type 2	611147

Monogenic forms of parkinsonism

Acronym	Mode of inheritance	Locus	Gene/protein	Main clinical features
PARK1/ PARK4	Autosomal dominant	4q	*SNCA (α-synuclein)*	Early-onset parkinsonism (~ 40 years), dementia, reduced life span
PARK5	Autosomal dominant	4p	*UCHL1 (ubiquitin carboxy-terminal hydrolase 1)*	Classical parkinsonism
PARK8	Autosomal dominant	12q	*LRRK2 (leucine-rich repeat kinase 2)*	Classical parkinsonism
PARK13	Probably autosomal dominant	2p	*Omi/HtrA2*	Classical parkinsonism
PARK2	Autosomal recessive	6q	*Parkin*	Early onset (~30-40 years), rarely juvenile, slow disease progression, exquisite response to L-dopa
PARK6	Autosomal recessive	1p	*PINK1 (PTEN-induced putative kinase 1)*	Early onset (~ 30–40 years), rarely juvenile, slow disease progression, exquisite response to L-dopa, frequently psychiatric features
PARK7	Autosomal recessive	1p	*DJ-1*	Early onset (~ 30–40 years), rarely juvenile
PARK9	Autosomal recessive	1p	*ATP13A2*	Juvenile or early-onset, dementia, spasticity, supranuclear gaze palsy; classical early-onset parkinsonism in carriers of heterozygous mutations
PARK14	Autosomal recessive	22q	*PLA2G6*	Early-onset pyramidal-extrapyramdial syndrome; Early-onset form: infantile neuroaxonal dystrophy; MRI with or without iron deposition

Clues to the SCAs

Age at onset	Young adult: SCA1, 2, 3, 21
	Older adult: SCA6
	Childhood onset: SCA2, 7, 13, 25, 27, DRPLA
Prominent anticipation	SCA7, DRPLA
Upper motor neuron signs	SCA1, 3, 7,12
	Some in SCA6, 8
	Rare in SCA2
Slow saccades	Early, prominent: SCA2, 7
	Late: SCA1, 3, 28
	Rare: SCA6
Extrapyramidal signs	Early chorea: DRPLA
	Akinetic-rigid, Parkinson: SCA2, 3, 12, 21
Generalized areflexia	SCA2, 4, 19, 21, 22
	Late: SCA3
	Rare: SCA1
Visual loss	SCA7
Dementia	Prominent: SCA17, DRPLA
	Early: SCA2, 7
	Otherwise: rare
Myoclonus	DRPLA, SCA2, 14, 19
Tremor	SCA2, 8, 12, 15, 16, 19, 27
Seizures	SCA10

Take home message

- Definition of movement phenomenology
- Clues to genetic disorders
  - family history and onset age
  - typical clinical feature of specific genetic disorders
- Clinical and genetic heterogeneity