Movement disorders as clinical features of CDG

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CDG
Congenital Disorders of Glycosylation

Movement disorders

Abnormal and involuntary movements of parts of the body

Hyperkinetic Movements

- Dystonia
- Chorea
- Ballism
- Tremors
- Tics
- Myoclonus
- Athetosis
- Ataxia

More frequent in children, may occur in CDG

Hypokinetic Movements

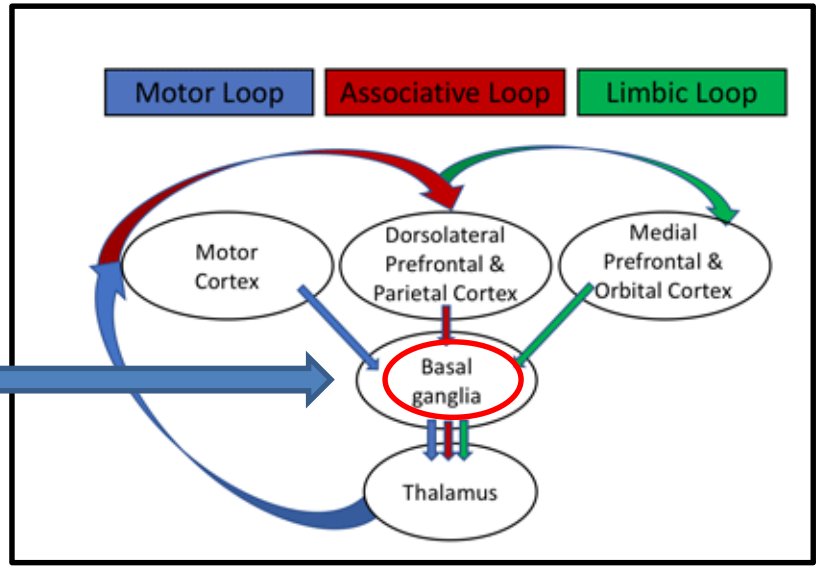
- Parkinsonism

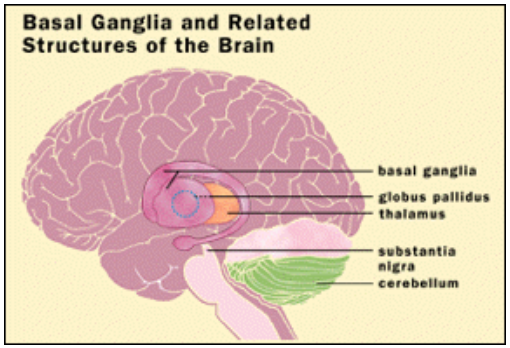
Uncommon in children

Pathophysiology

cortico-basal ganglia-thalamo-cortical pathways

Aberrant afferent inputs from the cerebellum





Modified from: Simonyan K. F1000Research 2019

Neurological Aspects of CDG

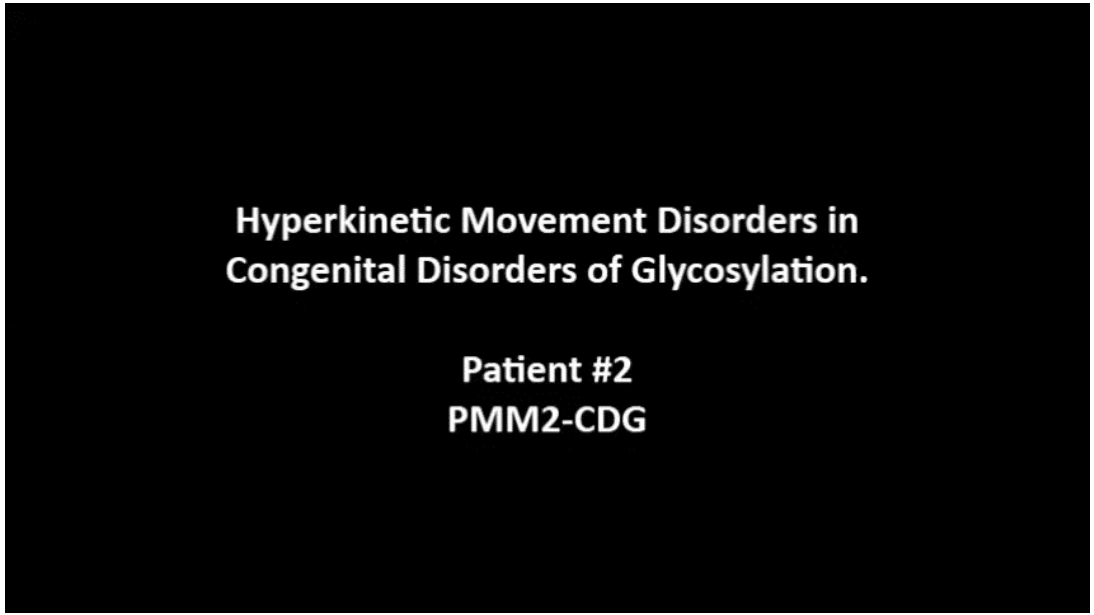
Freeze et al., Annu Rev Neurosci 2015; Barone et al., J Neurol 2015; Lam et al., Genet Med 2017; Altassan et al., J Inherit Metab Dis 2019

Cerebellar signs (i.e. PMM2-CDG).
Epilepsy: from pharmacologically manageable epilepsy to severe epileptic encephalopathies.
Developmental delay/Intellectual disability
Eyes: involuntary eyes movements, retinal dystrophy, optic neuropathy, cortical blindness
Neuropathy / Myopathy

Movement Disorders?

- PMM2-CDG: only few patients, focal dystonia (Altassan et al., J Inherit Metab Dis 2019)
- NGLY1-CDG: choreo-athetosis, dystonia, myoclonus, tremor (Lam et al., Genet Med 2017)

Our aim: clinical observation of dyskinesia in patients with CDG



Mostile G. et al., Eur J Neurol. 2019

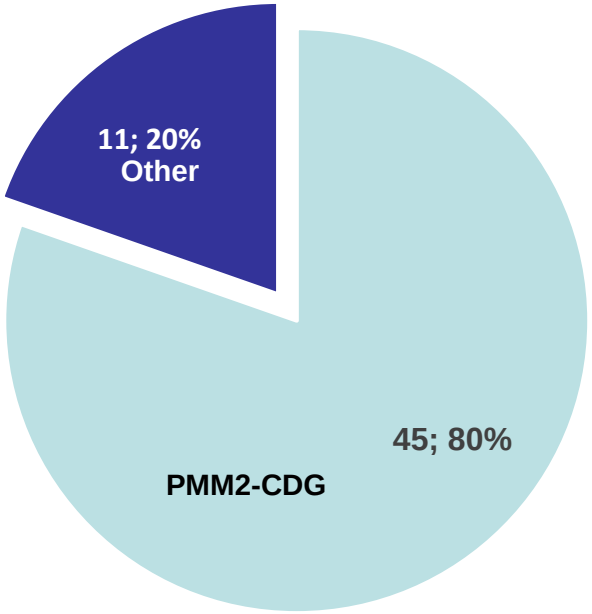
METHODS

- Subjects were identified from a cohort of patients with CDG who were referred to the University Hospital of Catania, Italy
- Case-only design study (January to December 2017)
- All patients with CDG observed during the study period were enrolled
- Patients were clinically examined and videotaped based on a standardized protocol

RESULTS

January to December 2017 N = 8

14% of subjects over the last 25 years



PMM2-CDG (N=4)

Ataxia, dystonia, choreo-athetosis

ALG6-CDG (N=1)

Epileptic encephalopathy, generalized hypotonia.

Choreo-athetosis, dystonia.

ALG8-CDG (N=1)

Epilepsy, ataxia. Chorea.

COG5-CDG (N=1)

Psychomotor disability, generalized hypotonia.

Complex stereotypies.

CDG-type Ix (N=1)

Intellectual disability. Stereotypies.

RESULTS

A variety of hyperkinetic movement disorders were observed

Dystonia and choreo-athetosis were the principal movement disorders in patients with PMM2-CDG.

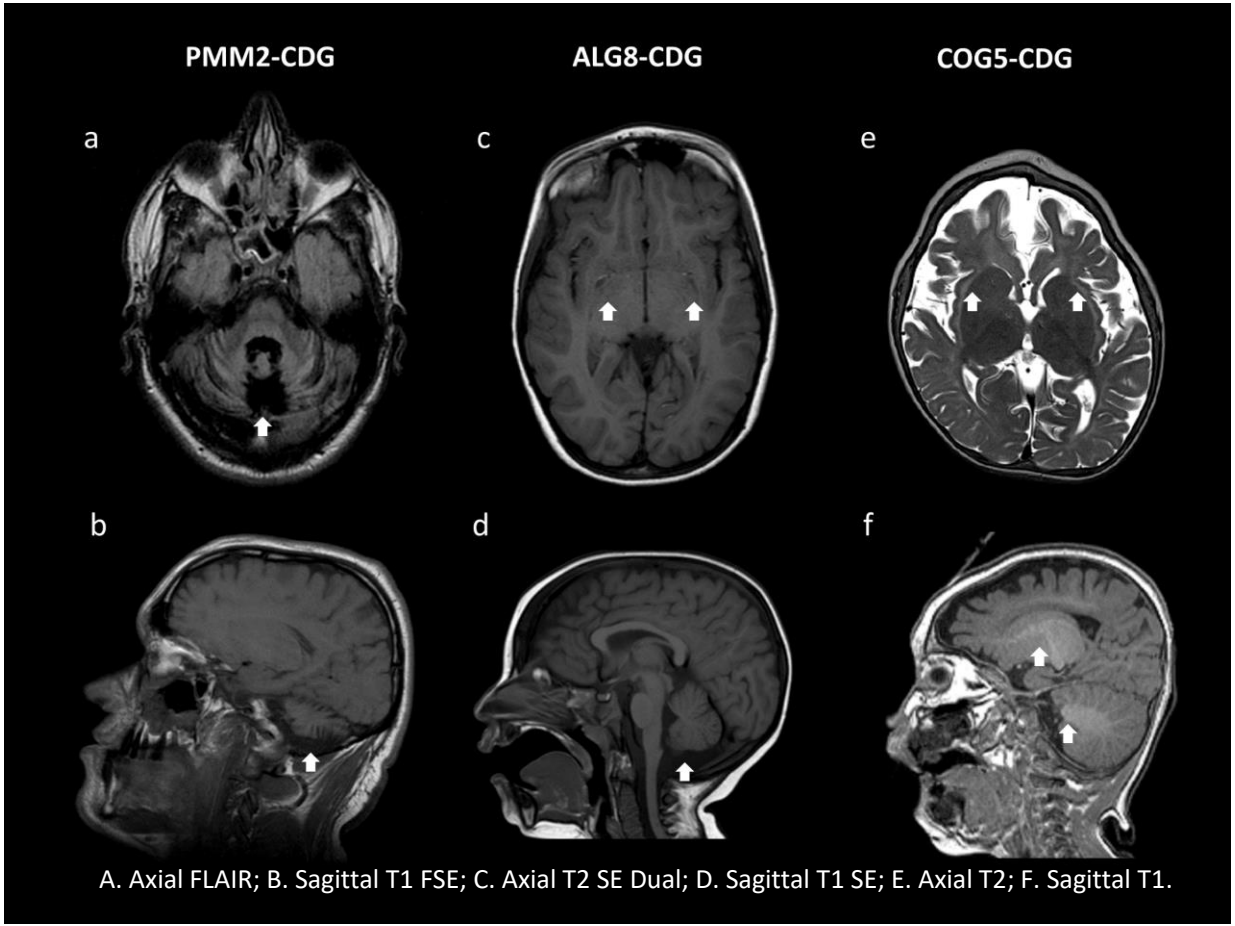
In patients affected by other CDG types, a wide range of movement disorders including chorea, dystonia and complex stereotypies were observed.

RESULTS

Main characteristics of hyperkinetic movement disorder in study patients with CDG

- Childhood onset
- Stability over time
- Generalized (younger subjects) to segmental/multifocal

Brain MRI in patients with CDG and movement disorders



A. Axial FLAIR; B. Sagittal T1 FSE; C. Axial T2 SE Dual; D. Sagittal T1 SE; E. Axial T2; F. Sagittal T1.

Movement Disorders reported in patients with CDG

Disorder (#OMIM)	Gene	Function	Movement disorder (reported cases)
N-linked pathway			
PMM2-CDG #212065	*PMM2*	Conversion of Man-6P to Ma-1P	Dystonia ($N = 3$) [17,19]; stereotypies ($N = 4$) [10,17,18]; tremor ($N = 2$) [18]
ALG6-CDG #603147	*ALG6*	Glucosyltransferase	Tremor ($N = 1$) [2,23]
DPAGT1-CDG #608093	*DPAGT1*	GlcNAc transferase	Tremor [13]
ALG13-CDG #300884	*ALG13*	GlcNAc transferase	Extrapyramidal signs [13]
MGAT2-CDG #212066	*MGAT2*	GlcNAc transferase II	Stereotypies ($N = 1$) [40]
DDOST-CDG #614507	*DDOST*	Subunit of the OST complex	Tremor [13]
N- and *O*-linked pathways			
TRAPPC11-CDG #614138	*TRAPPC11*	Transport protein particle complex 11	Chorea, tremor [2]
NGLY1 deficiency #615273	*NGLY1*	Deglycosylates *N*-glycoproteins via cleavage at the GlcNAc-asparagine linkage	Choreo-athetosis, dystonia, myoclonus, tremor ($N = 12$) [20]
GPI anchor synthesis			
Hyperphosphatasia intellectual disability syndrome #239300	*PIGV*	Mannosyltransferase	Athetosis, dystonia [13]
Autosomal recessive GPI anchor deficiency #614080	*PIGN*	GPI ethanolamine phosphate transferase	Tremor [13]; chorea ($N = 1$) [13,41]
Autosomal recessive GPI anchor deficiency #611655	*PGAP1*	Lipid remodeling steps of GPI anchor maturation	Stereotypies [2]
Other			
Amish infantile epilepsy or salt and pepper syndrome #609056	*ST3GAL5*	Sialyltransferase	Choreo-athetosis ($N = 1$) [2,13,42]; tremor [2]
Complex hereditary spastic paraplegia #609195	*B4GALNT1*	Galactosaminyltransferase 1	Dystonia [13]

Conclusions

All CDG patients evaluated during the observational period presented clinically detectable involuntary movements with more than one movement disorder, suggesting that the occurrence of hyperkinetic movement disorders in CDG may overall be underestimated

Relevance of these symptoms to CDG diagnosis

- Movement disorders should be added to the list of wide ranging neurological symptoms reported in CDG

- Movement disorders may be one of the presenting features of CDG and should be considered in differential diagnosis.

- **Key features for the diagnosis:** the combination of hyperkinetic movement disorders with developmental delay, dysmorphism with/without multisystemic involvement should prompt to consider a CDG diagnosis

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Hyperkinetic movement disorders in congenital disorders of glycosylation

EDITORIAL

Hyperkinetic movement disorders: expanding the phenotype of congenital disorders of glycosylation

S. Pandey and A. Chouksey, 2019

DOI: 0.1111/ene.14007

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