Spectrum of movement disorders in 18p deletion syndrome

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Abstract

Background

Deletion of the short arm of chromosome 18 leads to the 18p deletion syndrome. Clinical features include short stature, facial dysmorphism, mental retardation and several types of movement disorders.

Methods

The 18p deletion syndrome in our patient was diagnosed using karyotype analysis and confirmed by genome-wide single nucleotide polymorphism array. We have performed a literature search and summarized all previously reported patients with 18p deletion syndrome and movement disorders.

Results

We present a 41-year-old male patient with childhood-onset generalized dystonia. Dystonia is the most prevalent movement disorder in 18p deletion patients, with onset ranging from childhood to adulthood. Chorea, myoclonus, tremor, tics and ataxia have been reported in a minority of these patients.

Conclusion

Dystonia is commonly observed in 18p deletion syndrome. The variable size of the deletion on 18p is probably responsible for the broad phenotypic variability of movement disorders in this syndrome.

Introduction

Dystonia is a movement disorder characterized by involuntary sustained or intermittent muscle contractions, resulting in abnormal movements, which are often repetitive and may be accompanied by postures.[1] Several clinical features are important for the classification of dystonia: onset age, body distribution, temporal pattern, concomitant presence of other movement disorders and coexistence of other neurological symptoms. The etiology of dystonia can be either inherited or acquired. Deletion of the short arm of chromosome 18 is a rare chromosomal abnormality and occurs in approximately 1/50.000 live births.[2] The 18p deletion syndrome (18p- syndrome) was first described by de Grouchy in 1963.[3] The clinical features of the 18p- syndrome are variable and can include short stature, craniofacial dysmorphism (round face, dysplastic ears, wide mouth and dental abnormalities), abnormalities of the limbs, genitalia, brain, eyes, and heart as well as intellectual disability and several types of movement disorders. We present a patient with 18p- syndrome and generalized dystonia. Subsequently, we provide an overview of previously reported 18p- syndrome patients with movement disorders.

Methods

The 18p- syndrome was initially diagnosed in our patient using karyotype analysis in peripheral blood cells. Also, a SNP array (Illumina CytoSNP-12v2.1) was performed to delineate the deleted region on chromosome 18. Data analysis (CNV Webstore 2.0) resulted in a genome-wide resolution of approximately 180 kb.[4] The positions are relative to Genome Reference Consortium Human build 37 (GRCh37). We have conducted a literature review and have included previously reported patients with 18p- syndrome and movement disorders in publicly available databases (PubMed, Medline).

Results

We report a 41-year-old male patient with generalized dystonia and congenital intellectual disability. Truncal dystonia with mild kyphosis was observed at age 12. The gait impairment (dystonic gait) and truncal dystonia became more apparent around age 20, according to the parents. The cervical dystonia and upper limb dystonia had started insidiously around age 35. Exacerbation of dystonic symptoms during infectious episodes or secondary to other stressors was not documented in the medical files. The patient completed the Wechsler Intelligence Scale for Children-Revised (WISC-R, Wechsler, 1974) at age 11. He obtained a full IQ score of 52, with a verbal IQ score of 56 and a performance IQ score of 60. The patient underwent surgery for divergent strabismus in childhood. Orthognatic surgery was performed in adolescence.

Clinical examination revealed a short stature, bilateral mild ptosis, divergent strabismus and a round face with short philtrum. The speech was slightly dysarthric. An orofacial dystonia was present, with intermittent peri-oral dystonic movements and discrete blepharospasm. We could not elicit any cerebellar or pyramidal sign. Hypokinetic-rigid symptoms and myoclonus were absent. We observed a cervical dystonia, characterized by a rotation and laterocollis to the right side. Sensory tricks for the cervical dystonia were not detected during the examination. The patient was able to walk independently. The mobile dystonia in the trunk and in the limbs became more apparent, when he was walking. The cervical dystonia responded well to a symptomatic treatment with periodic botulinum toxin (onabotulinumtoxin A) injections. A brain computed tomography (CT) scan was unremarkable. Karyotype analysis in peripheral blood cells revealed a hemizygotic deletion of 18p. Molecular-genetic analysis identified a deletion of 18p11.32p11.21 (arr 18p11.32p11.21

(12842_14385836) x1), resulting in a monosomy 18p.

Clinical reports of movement disorders in 18p- patients are scarce. A literature search yielded 12 relevant publications. We have identified 16 patients with 18p- syndrome and movement disorders (Table 1). Dystonia was present in 15/16 patients.[5-16] Ataxia without any dystonic feature was observed in a single patient. Dystonia is clearly the most commonly reported movement disorder in patients with 18p- syndrome and can present as focal, segmental, multifocal or generalized dystonia. Myoclonus, chorea, tremor, tics and ataxia have also been reported in a minority of 18p- patients. The onset age of the movement disorder in 18p- syndrome is variable and ranges from childhood to age 38.

The size of the deletion of 18p in our patient is 14.39 Mb (maximal size) and the deleted region contains 66 protein-coding genes. Eleven genes (*TGIF1, SMCHD1, TUBB6, GNAL, LAMA1, PIEZO2, MC2R, LPIN2, NDUFV2, AFG3L2* and *APCDD1*) are associated with known diseases (Table 2).

Discussion

We have reported a patient with 18p- syndrome and childhood-onset generalized dystonia. A brain CT scan did not show any abnormalities. The patient refused to have brain magnetic resonance imaging performed. Therefore, we were not able to assess the presence of cerebral white matter T2-hyperintensities, which have been described in some 18p- syndrome patients.[5, 9, 10, 13] The prevalence of movement disorders in 18p- syndrome is probably underestimated due to the presence of important abnormalities in several organ systems in the majority of the patients (e.g. skeletal deformities, severe neurodevelopmental problems, genito-urinary abnormalities). One can assume that the focus of the medical care for these patients is therefore not immediately directed to the abnormal movements. In more than half of the reported patients, abnormal movements started in childhood or in adolescence. Possible dystonic features or other abnormal movements could have been missed in the initial clinical examination and follow-up in infancy or early childhood. Among the reported movement disorders in 18p- syndrome, dystonia was observed in 15/16 patients. The body distribution of dystonia showed a wide variability, although craniocervical dystonia was present in the majority of the patients. Myoclonus was reported in three patients.[7-9] Vertical supranuclear gaze palsy and mild appendicular ataxia were observed as additional symptoms in an adult 18p- syndrome patient with lower limb dystonia.[17] Ataxia was documented as main movement disorder in a 9-year old female patient with monosomy 18p.[12] Choreic movements or vocal tics were seen in combination with dystonia in a minority of the reported patients.[11, 14]

Several genes on the short arm of chromosome 18 could potentially be implicated in the pathogenesis of the abnormal movements in 18p- syndrome. Deletion of the *GNAL* (*guanine nucleotide-binding protein, alpha-activating activity polypeptide,*

olfactory type) gene, which is located on 18p11.21, is the molecular-genetic cause for dystonia in 18p- syndrome. Haploinsufficiency of *GNAL* was previously reported in several 18p- patients with dystonia.[5, 7-9, 11] Deletion of 18p is dominantly inherited, however *de novo* deletions are frequent.[2] Heterozygous mutations in *GNAL* were identified in 8 out of 39 dystonia families of mixed European origin with a predominant phenotype of cervical dystonia.[18] Mutations in *GNAL* were independently confirmed in an extended African-American pedigree and in three Caucasian pedigrees of isolated dystonia patients, also showing evidence for reduced penetrance.[19] DYT-GNAL (i.e. DYT25) mainly presents as an adult-onset isolated craniocervical dystonia. In several follow-up studies *GNAL* mutations were identified as rare cause of isolated craniocervical dystonia.[17, 20-22] A homozygous *GNAL* missense mutation was recently identified in two sisters with childhood-onset generalized dystonia and intellectual disability.[23] The phenotype in patients with bi-allelic *GNAL* mutations seems to be more severe than in heterozygous missense mutation carriers. The whole-gene deletion of one copy of the *GNAL* gene in 18p-syndrome can also lead to a similar phenotype with early-onset generalized dystonia and intellectual disability. The *GNAL* gene encodes the α subunit of a heterotrimeric G-protein ($G\alpha_{olf,}$) that is highly expressed in striatal neurons.[18] The $G\alpha_{olf}$ protein plays an important role in the coupling of dopamine D1 receptors and adenosine A2A receptors to downstream pathways (e.g. functional coupling to adenylyl cyclase).[24]

In conclusion, we have detected an important phenotypic variability in the movement disorders in 18p- syndrome patients. Dystonia was reported in almost all patients, however the severity, body distribution and onset age can be different. Deletion of the *GNAL* gene is probably responsible for the dystonia in 18 p- syndrome patients. Variation in the centromeric breakpoint could contribute to genetic heterogeneity in

18p- syndrome, leading to alterations in the phenotype. Further studies with extended patient cohorts and detailed mapping of the deleted 18p region are needed for the refinement of genotype-phenotype correlations in this rare syndrome. Earlier identification of dystonic features in 18p- syndrome is highly important in clinical practice. Prompt initiation of treatment for dystonia can then lead to a reduction of long-term neurological and non-neurological complications in patients with 18p- syndrome.

Author roles

(1) Research Project: A. Conception, B. Organization, C. Execution

(2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique

(3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

DC: 1A, 1B, 1C, 3A

BB: 1A, 1B, 1C, 3B

GVG: 1A, 1B, 1C, 3B

Disclosures

- **Ethical Compliance Statement**: The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The patient and his parents gave informed consent prior to inclusion in this report.
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Table 1: Overview of reported 18p deletion syndrome patients with movement disorders

Study	Year	Gender	Onset age (years)	Dystonia type	Distribution of dystonia	Associated neurological features
Crosiers et al.	2018	M	12	Generalized	F, C, UL, T, LL	
Kumar et al.[5]	2017	F	38	Multifocal	LL, F	Ataxia, vertical supranuclear gaze palsy
Hasi-Zogaj et al.[6]	2015	NA	childhood	N.A.	NA	
		NA	childhood	N.A.	NA	
Esposito et al.[7]	2013	F	adolescence	Multifocal	C, UL, LL	Myoclonus
Kowarik et al.[8]	2010	F	27	Generalized	B, T, UL, LL	Myoclonus
Postma et al.[9]	2009	F	30	Generalized	C, T, LL	Tremor, myoclonus
Graziadio et al.[10]	2009	F	childhood	Multifocal/generalized	B, C, T	
Nasir et al.[11]	2006	F	adolescence	Multifocal	B, C, UL	Vocal tics
Wester et al.[12]	2006	F	childhood	None	None	Ataxia
Klein et al.[13]	1999	F	12	Segmental	B, LF, C	
		F	15	Segmental/generalized	C, T, UL	
		M	17	Multifocal	B, LF, C, UL	
Awaad et al.[14]	1999	F	adolescence	Segmental/generalized	C, T, UL, LL	Chorea
Tezzon et al.[15]	1998	M	N.A.	Generalized	NA	Hypokinesia
Kakinuma et al.[16]	1994	N.A.	N.A.	Focal	NA	

Table 2 : Overview of protein-coding genes in the deleted region of the short arm of chromosome 18 in the presented patient. Only genes associated with known diseases are shown (data extracted from OMIM database in July 2018).

Gene	Gene description	Chromosomal location	Associated disease(s)
TGIF1	*TGFB induced factor homeobox 1*	18p11.31	Holoprosencephaly type 4
SMCHD1	*structural maintenance of chromosomes flexible hinge domain containing 1*	18p11.32	1) Facioscapulohumeral dystrophy type 2 2) Bosma arhinia microphtalmia syndrome
TUBB6	*tubulin beta 6 class V*	18p11.21	Congenital facial palsy with ptosis and velopharyngeal dysfunction
GNAL	*G protein subunit alpha L*	18p11.21	DYT25
LAMA1	*laminin subunit alpha 1*	18p11.31	Poretti-Boltshauser syndrome
PIEZO2	*piezo type mechanosensitive ion channel component 2*	18p11.22-p11.21	Arthrogryposis
MC2R	*melanocortin 2 receptor*	18p11.21	Glucocorticoid deficiency
LPIN2	*lipin 2*	18p11.31	Majeed syndrome
NDUFV2	*NADH:ubiquinone oxidoreductase core subunit V2*	18p11.22	Mitochondrial complex I deficiency
AFG3L2	*AFG3 like matrix AAA peptidase subunit 2*	18p11.21	1) Spinocerebellar ataxia 28 2) Spastic ataxia 5 (autosomal recessive)
APCDD1	*APC down-regulated 1*	18p11.22	Hypotrichosis