

A case with 18p deletion and dystonia and review of the literature

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Abstract

18p deletion syndrome is a rare disorder which is accompanied with mental retardation, facial abnormalities and short stature. Dystonic findings are rarely seen and only 12 cases have been reported in the literature until now. We report here a 26 year old female complaining of spasms on her trunk and limb muscles. Genetic investigation revealed 18p deletion.

INTRODUCTION

18p deletion syndrome (18p-) is a chromosomal disorder due to complete or partial deletion of the short arm of chromosome 18.^{1,2} The main clinical manifestations are mental retardation, short stature and craniofacial dysmorphism, while behavioral abnormalities, autoimmune diseases and dystonia are seen rarely.²

Dystonia is a group of clinically and genetically heterogeneous movement disorders in which there are repetitive, sustained, involuntary contractions; twisting, torsion, spasmodic movements or abnormal postures in muscles of one or more body parts.

At least 15 genes associated with dystonia have been described.³ Of these, DYT7 and DYT15 are in the 18th chromosome.^{4,5} According to our knowledge, there have only been 12 reported cases with 18p deletion syndrome (18p-) and dystonia previously reported in the literature.⁶⁻¹⁴ Various possible explanations have been given for the concurrent presence of this deletion and involvement of DYT7 and DYT15 genes, but no definite conclusion has been made.

We report here a woman of 18p deletion with dystonia, and review the other cases previously reported in the literature. We will try to explain the similar and different features (clinical manifestation, cranial imaging, cytogenetics and response to treatment) of these cases and the reasons for dystonia accompanying 18p-syndrome.

CASE REPORT

A 26-year old right handed female was referred

to our clinic complaining of three months history of involuntary contractions of both of the upper and lower limb muscles and trunk muscles. She reported that initially only the upper extremities were involved with the repetitive, involuntary, intermittent rotating contractions. But these progressed were increased in frequency and intensity, and spread to the lower extremity and trunk. In her developmental history, there was delay in her speech development. Her elementary school result was poor. On presentation; her verbal comprehension was impaired, the vocabulary was limited to a few words, but she was fully independent in self-care.

Physical examination revealed a short stature, round face, low and flat nose, low-set and forward positioned ears, an increased inter-pupillar distance, low posterior hairline, wide and flat neck and tilted forward slouching posture (mild kyphosis) (Figure 1).

On neurological examination, she was alert and orientated. There was bilateral ptosis. Generalized dystonic contractions in the right upper extremity and both lower extremities were observed (Video 1). Cranial area and motor examinations were normal. Deep tendon reflexes were also normal with bilateral flexor plantar responses. Mental examination revealed a timid, childish personality with shallow idea content and borderline mental retardation. No pathology was seen on the cranial MRI and electroencephalography. The patient's dystonia was classified³ as adult-onset, generalized and secondary dystonia. The cytogenetic examination made from peripheral blood with the GTG-banding method revealed a deletion on the



Figure 1: Physical appearance of the patient with monosomy 18p deletion: short stature, low and flat nose, round face, ptosis, wide and low-set ears. (with consent)

short arm of 18th chromosome [46,XX,del(18)(p11.2)] (Figure 2).

There was no response to clonazepam. The patient was then given L-dopa + Carbidopa 375 mg/day for 10 days with no obvious improvement. The patient was then started on tetrabenazine. Within 3 months, the patient’s dystonia improved with only minimal dystonic contractures observed on the right upper extremity (Video 2). The benefit of tetrabenazine continued for 6 months. However, after this period, the symptoms started to progress again and increasing the dose of the drug did not help.

DISCUSSION

18p deletion syndrome (monosomy 18p or 18p-syndrome) was first defined by de Grouchy in 1963¹ and is the partial or complete absence of the short arm (p arm) of the 18th chromosome. 18p deletion syndrome is seen once in every 50 thousand live births.² Its main characteristics are mental retardation, delayed speech development (expressive speech often lags behind other developmental parameters), short stature and facial dysmorphism (ptosis, low and flat nose, low-set and posteriorly rotated ears). Clinical characteristics such as dystonia, behavioral impairments and autoimmune diseases are rare.² Suspicion of a chromosome abnormality usually occurs due to the developmental delays or craniofacial dysmorphism, and the diagnosis is made with cytogenetic examination made from peripheral blood.

Dystonia is a clinically and genetically heterogeneous group of diseases which cause involuntary, repetitive, continuous muscle contractions, twisting and abnormal posture in one or more parts of the body.¹⁵ It is classified according to the etiology, starting age, muscles involved and hereditary characteristics.¹⁵ Thus far at least 15 dystonia genes (DYT 1-15) have been identified.³

Our case is the 13th case with dystonia and 18p-reported in the literature.⁶⁻¹⁴ (Table 1). On review of these cases, a female preponderance (Female/Male: 9/3, the age and sex of one patient is not known,) is observed, and there is no significant difference between the types of dystonia according to the place of involvement (5 generalized, 3 focal

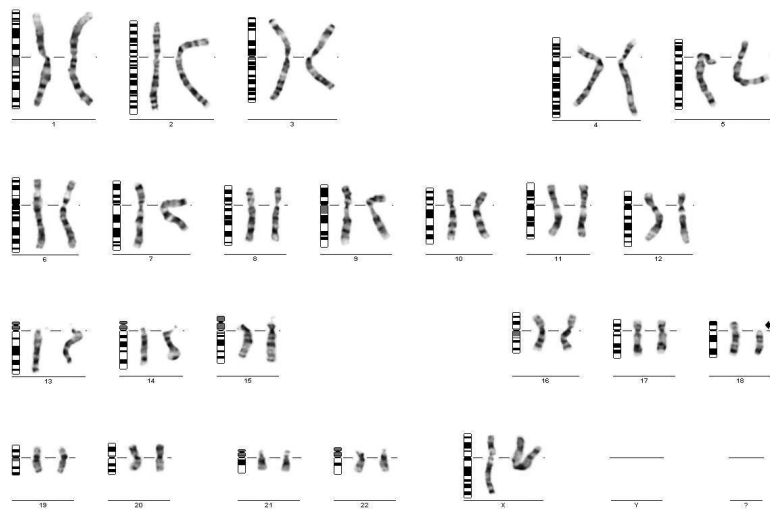


Figure 2: Genetic Analysis of the patient (Deletion on the short arm of the 18th chromosome)

Table 1: Reported cases with 18p deletion syndrome and dystonia: Clinical, laboratory results, therapy and outcome

Publication	Age of onset, sex	Dystonia Type	Other Disease	Clinical Picture	Cranial MRI	Genotype	Therapy
Present Case (2015)	26, F	Generalized	None	Mental retardation, speech lags, facial dysmorphism, short stature	Normal	46,XX,del(18)(p11.2)	No response to Clonazepam and L-dopa. Response for 6 months to Tetrabenazine
Esposito (2013) ⁷	19, F	Generalized	Lupus-like Immunological profile	Mental and motor speech lags, short stature, facial dysmorphism	Normal	18p monosomy 18q trisomy (15 % of cells) 18p11.32p11.21, GNAL gene deletion	No response to Clonazepam, Biperidene and L-dopa. Good and rapid response to Topiramate.
Kowarik (2011) ⁸	28, F Myoclonus-Dystonia	Generalized	Vesicouretral reflux	Mental retardation, speech lags, short stature- facial dysmorphism	Normal	46,XX,18p11.21	No response to Clonazepam, Lorazepam, Biperidene, Thiaprid and L-dopa/Carbidopa
Postma (2009) ⁹	30, F	Generalized	None	Mental retardation, facial dysmorphism, pectus excavatum, clinodactyly on the 5th finger, myoclonic jerk, intentional tremor, balance disorder	Bilateral multifocal increase in white matter signal-mild cortical atrophy	45,XX,-18,-21,+der(18)t(18:21)(p11;q11) 18p11.21	No response to L-dopa. Torticollis is responsive to botulinum toxin injection. Balance disorder is responsive to trihexyphenidyl
Graziadio (2009) ¹⁰	30, F	Focal (eye lid, neck)	Hypothyroidism, Vitiligo	Mental retardation, short stature, facial dysmorphism, corneal opacification, large thorax, cervical kyphosis	Dilated ventricular system, multiple hyperintense foci in centrum semiovale	18:46,XX,del(18)(p11.1)	
Nasir (2006) ¹¹	2, F (mother) 22, M (son)	Segmental (neck, eye lid, right arm, larynx) Focal (chewing and swallowing)	Duodenal atresia, Fallot tetralogy	Mental retardation, speech difficulty Mental, motor and speech lags	?	18 and 14 centromere deletion in each cell, thus a complete deletion of 18p.	Good response to botulinum toxin initially
Awaad (1998) ¹²	15, F	Segmental (right arm, both legs)	Ambiguous genitalia	Mental retardation, aphasia, oromotor apraxia- facial dysmorphism, balance disorder	Bilateral increased multifocal white matter intensity and increased signal in thalamus	46,XY,del(18)(p11.1)	No response to L-dopa/carbidopa. Trihexyphenidyl, baclofen and clonazepam were effective, but sedation from clonazepam could not be tolerated. Intrathecal baclofen and botulinum toxin is effective
Terzon (1998) ¹³	27, M	Generalized		Mental retardation, dysmorphic properties, hypokinesia	?	46,XY,18p-	?
Kakinuma (1994) ¹⁴	?	Focal (both legs)		Bilateral pyramidal tractus symptoms, weakness and concentric visual field defects	?	46, X, dic (Y:18)(p11;p11), inv(9)(p11q13)	?
Klein (1999) ⁶	12, F	Segmental (neck, face, eye lid, oromandibular muscle)		Mental retardation, developmental retardation, dysmorphic features, short stature	Bilateral multiple increased white matter signal fields	45,XX,-18,-21,+der(18q21q)t(18;21)mat.	?
	17, M	Segmental (neck, face, eye lid, oromandibular muscle, arms, trunk)		Mental retardation, speech lags, Dysmorphic features, short stature	Bilateral multiple increased white matter signal fields	18p terminal deletion	?
	15, F	Segmental (back, upper extremities, neck)		Mental retardation, motor and developmental retardation, Dysmorphic features, short stature	Bilateral multiple increased white matter signal fields, anterior part of right thalamus	18p terminal deletion	?

and 5 segmental), and no other accompanying diseases, and, most patients have the frequent 18p- symptoms of mental retardation, speech development defect, craniofacial dysmorphism and short stature, and in those with a cranial MRI result, some have non-specific white matter abnormalities (6 abnormal/3 normal), and on their genotypes 18p11.2 locus is frequently involved. When therapy was initiated, none of these patients responded to L-dopa/carbidopa therapy; benzodiazepines were usually ineffective, and varying degrees of positive results were obtained from tetrabenazine, topiramate, trihexyphenidyl and baclofen.

Why dystonia is rare in 18p- syndrome and why it occurs in some patients is not clear. A gene responsible for late-onset idiopathic focal dystonia (DYT7) was mapped at the 18p11.22 locus in a German family⁵, but the authors could not confirm this in the re-analysis of the original data.¹⁶ A gene responsible for myoclonus-dystonia (DYT15) was mapped at the 18p11.22-31 locus in a Canadian family.⁴ The deletion of the GNAL gene may be the cause of dystonia in patients with 18p-.⁷ The deletion of these genes together or separately may be responsible for this dystonia. Since similar genetic breaking points are present in patients with 18p- without dystonia¹⁷, the width of the deletion cannot totally explain the dystonia. For this reason, an alternative explanation may be decreased penetrance of DYT7 and DYT15 genes. Since dystonia usually starts after the second decade, there is often other associated severe neurological deficits, dystonic symptoms may be missed or overlooked.

We suggest that due to the different phenotypic characteristics of patients and almost normal appearance of some, genetic examination on all individuals with mental retardation and dysmorphic facial features should be performed.⁹ To determine the true frequency of dystonia in 18p- patients, all patients with a diagnosis must be followed-up longitudinally. There should also be more research on different genes that may cause the dystonia in the 18th chromosome.

Video 1. [http://neurology-asia.org/content/20/3/neuroasia-2015-20\(3\)-287-v1.pm4](http://neurology-asia.org/content/20/3/neuroasia-2015-20(3)-287-v1.pm4) Before treatment with tetrabenazine. The patient walks with difficulty because of generalized dystonia.

Video 2. [http://neurology-asia.org/content/20/3/neuroasia-2015-20\(3\)-287-v2.pm4](http://neurology-asia.org/content/20/3/neuroasia-2015-20(3)-287-v2.pm4) After treatment with tetrabenazine. The patient walks and moves in comfort.

DISCLOSURE

Conflict of interest: None

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