LETTER TO THE EDITOR

To the Editor

Movement Disorders in 18p Deletion Syndrome: A Case Report and Review of Literature

Keywords: 18p deletion syndrome, dystonia, ataxia, vertical supranuclear gaze palsy, myoclonus

The 18p deletion (18p-) syndrome is a common chromosomal anomaly in which all or part of the short arm of chromosome 18 is deleted.[1] It was first reported in 1963 by de Grouchy et al and is clinically characterized by developmental delay, facial dysmorphism, short stature, and mental retardation.[1,2] Movement disorders including dystonia, myoclonus, ataxia, and tics in cases with 18p- syndrome have been reported.[1-10] Vertical supranuclear gaze palsy (VSGP) has not been previously reported. We describe a new 18p- syndrome case presenting with craniofacial and lower extremity dystonia, mild ataxia, and VSGP and review the movement disorders reported in cases of 18p- syndrome.

A 45-year-old woman with a history of cognitive, motor, and speech developmental delay; bilateral hip dysplasia; and no pertinent family history presented with ptosis and progressive deterioration in gait and balance resulting in occasional falls for the past 7 years, and worsening speech for 2 years. On examination, she had short stature, microcephaly, facial grimace (similar to risus sardonicus), facial dysmorphism (including large, low-set and posteriorly rotated ears, hypertelorism, epicanthal folds, low posterior hairline), and ptosis. She had dysarthria and her extraocular movements revealed smooth pursuit with slow saccades horizontally and restricted vertical gaze (more pronounced on upgaze), which responded to oculocephalic maneuver suggestive of VSGP. She had hyperreflexia, craniofacial and lower limb dystonia, and mild appendicular ataxia, but no gait ataxia or parkinsonism. She walked with a dystonic gait. Brain magnetic resonance imaging showed multifocal nonspecific subcortical T2 white matter hyperintensities without any cortical, cerebellar, or brainstem atrophy (Figure 1). Her 24-hour urinary copper was normal. DNA microarray showed a 14,520-kB loss of 18p11.32. She was started on levodopa-carbidopa (100/25 mg) 1 tablet by mouth three times daily. On her follow-up 6 months later, there was moderate improvement in dystonia in her lower extremities and gait.

18p- syndrome has an incidence of about 1:50,000 live births, with more than 150 cases reported to date.[1,2] Females are more commonly affected, with female:male ratio being 3:2.[1] Although most cases (approximately 66%-89%) have de novo deletion of 18p, the remainder result from complex translocation, inversion, or direct transmission.[1,2] Although uncommon, familial transmission have been described, mostly involving the maternal chromosome.[2] Despite approximately 50% of cases having centromeric breakage, 18p- syndrome has a wide clinical heterogeneity with developmental delay, holoprosencephaly, facial dysmorphism, short stature, impaired cognition, and speech and language problems being the major presenting features.[1,2] Cognitive impairment, usually mild to moderate, and behavioural abnormalities such as autism and schizophrenia, is more common in centromeric (18p11.1) deletions.[1,2] The dysmorphism may not be obvious early in life, thereby causing a delay in recognition.[1] Our case was diagnosed at 45 with a de novo deletion involving a 14,520-kB loss of 18p11.32. She had facial dysmorphism, dysarthria, and cognitive impairment.

Twelve of the 67 genes located on 18p appear to be either haploinsufficient (dosage sensitive) or are conditionally haploinsufficient (require an additional genetic or environmental factor along with the hemizygosity) for phenotypic manifestation.[2] One of the dosage-sensitive genes, GNAL (GTP binding protein, alpha subunit), has been linked to adult onset, predominantly craniocervical dystonia (DYT25).[9] Two other dystonia loci, DYT7 and DYT15, are located on 18p, but a recent study doubted the presence of a DYT7 locus.[7,9] One study reported dystonia in only 3% of 58 cases with 18p- syndrome involving GNAL, suggesting a possibility of reduced penetrance.[2,7] Most reported cases of 18p- syndrome are diagnosed early and need to be followed because dystonia may appear later.[2,8] Dystonia may even be missed in the presence of severe neurological and skeletal manifestations.[9] To date, only 14 cases, including ours, of dystonia associated with 18p- syndrome have been described (Table 1). It may manifest as focal,[3] segmental,[5,6,10] multifocal,[7] or generalized,[4,5,8,9] with craniocervical involvement in more than half of them.[5-7,10] The 18p deletion inclusive of GNAL in our patient may have resulted in craniofacial and lower extremity dystonia. Most described cases with dystonia had onset in childhood to adolescence,[5,6,9,10] with one case having onset at age 30.[7] Our case had onset of dystonia at age 38, the oldest reported to date.

The mild appendicular ataxia, hyperreflexia, and VSGP in our case may have resulted from the 18p deletion including AFG3L2

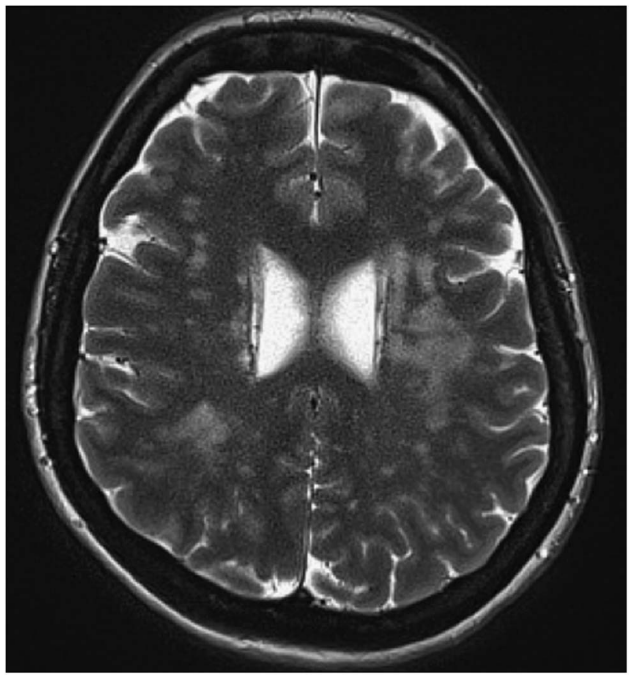

Figure 1: *Magnetic resonance imaging of the brain shows nonspecific white matter hyperintensities on a T2-weighted image.*

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Table 1: Reported cases of movement disorders associated with 18p- syndrome, including our case

				Movement disorders								
Reference	**Number of cases**	**Age of onset of MD (years)**	**Sex**	**Dy**	**Ch**	**Br**	**Mc**	**At**	**Tr**	**Ti**	**Other neurological features**	**Brain MRI**
Kakinuma et al[3]	1	-	-	+	-	-	-	-	-	-	Pyramidal signs and visual field defects	Normal
Tezzon et al[4]	1	26	M	+	-	+	-	-	-	-	-	Normal
Klein et al[5]	3	12	F	+	-	-	-	-	-	-	-	WM hyperintensities on T2-WI
		17	M	+	-	-	-	-	-	-	-	WM hyperintensities on T2-WI
		15	F	+	+	-	-	-	-	-	Pyramidal signs, oromotor apraxia	WM hyperintensities on T2-WI
Nasir et al[10]	2	2	F	+	-	-	-	-	-	+	-	-
		Childhood	M	+	-	-	-	-	-	-	-	-
Wester et al[1]	1	Childhood	F	-	-	-	-	+	-	-	Visual impairment, bilateral ptosis, hypotonia	-
Graziadio et al[6]	1	Late childhood	F	+	-	-	-	-	-	-	-	Dilated ventricles and WM hyperintensities on T2-WI
Postma et al[7]	1	30	F	+	-	-	+	-	+	-	-	WM hyperintensities on T2-WI
Kowarik et al[8]	1	27	F	+	-	-	+	-	-	-	-	Normal
Esposito et al[9]	1	Adolescence	F	+	-	-	+	-	-	-	-	Normal
Hasi-Zogaj et al[2]	3	Childhood	-	+	-	-	-	-	-	-	-	-
		Early childhood	-	+	-	-	-	-	-	-	-	-
		13	-	-	-	-	+	-	-	-	-	-
Our case	1	38	F	+	-	-	-	+	-	-	VSGP	WM hyperintensities on T2-WI

At = ataxia; Br = bradykinesia; Ch = chorea; Dy = dystonia; F = female; M = male; Mc = myoclonus; MD = movement disorders; T2-WI = T2-wighted image; Ti = tics; Tr = tremors; WM = white matter.

(ATPase family gene 3-like 2) gene, which is linked to spinocerebellar ataxia type 28 (SCA 28).[2] SCA 28 is characterized by adult-onset progressive ataxia, ocular abnormalities, and hyperreflexia.[2] To the best of our knowledge, only a single case of 18p- syndrome has been described with a mild gait ataxia,[1] whereas VSGP has never been reported. Our case underlines the importance of eye movement examination in patients with facial dysmorphism. Characteristic facial dysmorphism along with predominant up-gaze restriction in our case distinguished it clinically from Niemann-Pick C, another genetic cause of VSGP with dystonia. Brain magnetic resonance imaging of our case showed multifocal nonspecific subcortical T2 white-matter hyperintensities, which has been reported in 50% of cases with 18p- syndrome.[2]

Myoclonus has been reported in association with dystonia in 18p- syndrome (Table 1).[7-9] One case of 18p- syndrome involving GNAL gene was diagnosed with myoclonic jerks alone at the age of 13.[2] In addition to the epsilon-sarcoglycan mutation on the chromosome 7q21 (DYT11), a locus on chromosome 18p11.22-31 (DYT15) is implicated in myoclonus dystonia.[8] Other movement disorders including chorea,[5] vocal tics,[10] bradykinesia,[4] and tremor[7] have been reported in occasional cases, but always in association with dystonia (Table 1). Various drugs have been used for symptomatic treatment of movement disorders in 18p- syndrome with inconsistent results. Although most cases reported no benefit with levodopa and anticholinergics,[4,8,9] lower extremity dystonia in a patient improved with trihexyphenidyl.[7] No response was seen with biperidin,[8,9] clonazepam,[8,9] lorazepam,[8] or tiapride.[8] One study reported improvement in cervical dystonia in a patient with 18p- syndrome by botulinum toxin injections.[7] The lower extremity dystonia and gait in our case improved with levodopa.

18p- syndrome is a common autosomal deletion syndrome and must be suspected in patients presenting with adult-onset craniofacial dystonia, VSGP, ataxia, and facial dysmorphism. Dystonia is the most common movement disorder reported in 18p- syndrome, and our case is the oldest reported to date, with respect to the age at onset. We report the first case of 18p- syndrome with VSGP, which highlights the significance of eye movement examination in 18p- syndrome. Because the majority of the 18p- syndrome cases are diagnosed early, we suggest a careful observation in the follow-up visits as movement disorders may appear later in life. Symptomatic treatment with levodopa can be helpful for dystonia.

Disclosures

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Statement of authorship

NK undertook conception, design, and writing the first manuscript. PR and MJ undertook review and critique.

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