A New Patient with Potocki–Lupski Syndrome: A Literature Review

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Abstract

Speech delay, intellectual disability, and behavioral disturbances are the main clinical manifestations of Potocki–Lupski syndrome. Other features include infantile hypotonia, the absence of major dysmorphism, sleep disorders, and congenital anomalies, particularly of the cardiovascular system. A male patient with Potocki–Lupski syndrome is reported herein. He showed speech and borderline cognitive delay, behavioral troubles with no signs suggestive of autism, in the absence of major dysmorphism. A de novo 17p12-p11.2 duplication spanning 3.6 Mb was detected, with boundaries from 15,284,052 to 18,647,233 (hg19 assembly). At the age of 5 years, the child showed a noticeable improvement of speech skills and a moderate scholastic performance was reached. Upon analysis of the clinical manifestations of the present patient and those reported in existing literature, we found that the syndrome may present in various degrees of clinical expressivity. Affected patients may manifest symptoms ranging from mild behavioral disturbances to severe degrees of autism.

Keywords

- Potocki–Lupski syndrome
- cognitive delay
- autism
- behavioral disturbances

Introduction

The widespread use of array-based comparative genomic hybridization (CGH-array) for genetic diagnosis has allowed us to expand our knowledge regarding several malformative syndromes and disorders.[1,2] Patients with mild dysmorphisms or those presenting unexplained developmental delay can be diagnosed through the use of this technology, yielding remarkable information on the clinical course, complications, and prognostic evolution of several syndromes.

Potocki–Lupski syndrome (PTLS) is caused by a microduplication in chromosome 17p11.2, usually with a length of 3.7 Mb. Its phenotype has been reported as heterogeneous, with a wide range of clinical expressivity and there are no pathognomonic features suggestive of its diagnosis.[3–5]

We report a boy with a diagnosis of PTLS due to de novo 17p12-p11.2 duplication, spanning 3.36 Mb, with boundaries from 15,284,052 to 18,647,233. Hypotonia in his infancy was recorded. The absence of major dysmorphisms, borderline cognitive delay, and behavioral disturbances were the presenting clinical signs. We also summarize the clinical manifestations of cases of PTLS described in existing literature.

Case Report

The proband was first referred to the clinical unit at the age of 2.5 years for a diagnostic workup regarding his psychomotor delay and an episode of simplex febrile seizure. He was the first child born to healthy, unrelated parents. No genetic

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disorders were reported in his family. At the time of delivery, the mother was 25 years old, and the father was 29 years old. During the pregnancy, the mother denied infections and consumption of alcohol or drugs. She claimed to have felt normal fetal movements.

The boy was born at the 37th week of gestation from a difficult delivery due to a short umbilical cord. At birth, his weight was 2,750 g, length 48 cm, and head circumference 34 cm. Apgar scores were 7 and 9, at 1 and 5 minutes, respectively. Suction was poor in the first 24 hours, but soon afterward the baby was breastfeeding, periodically alternating with artificial milk. The parents revealed that the boy showed a motor milestone delay in the first 2 years of life, as he was unable to consistently hold the sitting position at the age of 9 months and started walking with support at the age of 18 months. The language delay was remarkable: lallation started at the age of 20 months, and he pronounced his first single words at the age of 2.5 years. At the age of 18 months, he had presented a single episode of febrile seizures, tonic–clonic, which ceased after 3 minutes without treatment. No further episodes of febrile seizures occurred in the following years.

When first admitted at the age of 2.5 years, the boy showed language delay, aggressiveness, and irascible behavior. His muscle tone was normal, and no feeding difficulties were noticed. His weight was 14 kg, height 90 cm, and head circumference 50 cm (all in the 50th percentile). Laboratory tests were normal, as well as electroencephalogram, electrocardiogram, and abdomen ultrasounds.

At the age of 5 years, the boy presented with normal general conditions; weight was 19 kg, height 113 cm, and head circumference 51 cm (all within the average for his age and sex). His facial dysmorphism was not impressive, although he did display a triangular face and microretrognathia. His ears were bilaterally protruding, with thin helices, deep conchae, and significantly hypoplastic lobules (►**Fig. 1**). Permanent teeth were growing in behind his baby teething in the lower and upper frontal regions. His penis was unusually long (7.5 cm, normal value for age 4.4 cm), but his testicles were normally set. The neurological examination was normal. The boy was particularly irascible, restless, and hyperactive. He showed a good social quotient (Autism Diagnostic Interview-Revised [ADI-R] and Autism Diagnostic Observation Schedule [ADOS]-G scores yielded a result of 45/50), but a severe language impairment, and an overall IQ of 76.

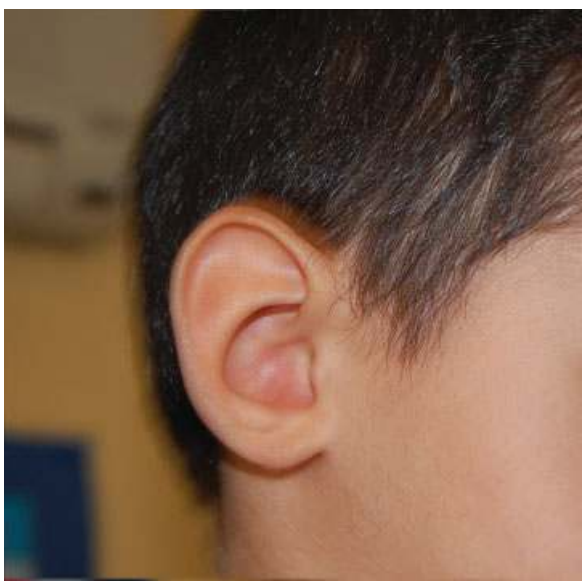

Fig. 1 Patient at the age of 5 years. His ears show thin helices, deep conchae, and hypoplastic lobules.

At the present age of 8 years, he has normal social interaction and plays with his age-mate. He is following a course of speech therapy currently yielding good results. He attends primary school with sufficient performance. No more febrile seizures have been reported so far. He is still particularly hyperactive, irascible, and impulsive.

Genetic Testing

Chromosomal microarray analysis (180K Chip; Technogenetics, Milan, Italy) was performed during his first admission (2.5 years of age) at an average resolution of 100 kb on genomic DNA extracted from peripheral blood cells using a commercial kit (Macherey-Nagel, Duren, Germany). The patient's DNA was hybridized against reference DNA (Promega, Madison, Wisconsin, United States) according to the manufacturer's instructions (Technogenetics). A de novo 17p12-p11.2 duplication spanning 3.6 Mb was detected, with boundaries from 15,284,052 to 18,647,233; hg19 assembly. Copy number variation at microarray analysis was negative for the parents.

Discussion

The patient presented with speech delay, borderline cognitive delay, and behavioral disturbances. Neither sleep problems nor epileptic seizures nor systemic congenital anomalies were reported, and the growth parameter kept within the normal limits. Dysmorphic facial features were not specific but involved the ears and the teeth. There was no progression of the symptoms, and the child had improved noticeably with the speech treatment. The CGH-array revealed a duplication in chromosome 17 (p12-p11.2), extending about 3.36 Mb from 15,284,052 to 18,647,233, and a diagnosis of PTLS was given.

PTLS typically occurs sporadically and arises from de novo microduplications of chromosome 17p11.2, commonly spanning 3.6 Mb. It is also the recombination reciprocal of Smith–Magenis syndrome (SMS),[6,7] a severe dysmorphic syndrome characterized by mild-to-moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems, and is due to a microdeletion within the same region.[6]

The length of the duplication has been reported to be variable in PTLS patients, which could be caused by the presence of a large number of low-copy repeat sequences in this region. Due to this high variability in copy number variation, CGH-array is the most sensitive diagnostic tool while fluorescence in situ hybridization analysis and G-banded chromosome analysis are less effective.[7]

Table 1 Reported patients with Potocki–Lupski syndrome

Authors, year	Patients (*N*)	Age	Birth and neonatal history	Facial dysmorphism	Neurodevelopment	Autism	Failure to thrive	Other features
Potocki et al (2007)[4]	10	2–14 y	SGA 5/10; poor feeding 10/10; hypotonia 10/10	Not strikingly dysmorphic	Developmental delay; cognitive impairment and communication disorders; ADHD	9/10	Short stature 1/10	Cardiovascular anomalies 5/10; kidney anomaly 1/10; scoliosis 3/10
Zhang et al (2010)[3]	5	3–40 y	Poor feeding 3/4; hypotonia 3/5	Not strikingly dysmorphic	Cognitive impairment 5/5; ADHD 4/5; sleep disturbances 4/5	3/5	–	Orthopedic anomalies 2/5; structural kidney anomaly 1/5
Treadwell-Deering et al (2010)[19]	15	7–20 y			Intellectual disability 13/15	10/15		
Yusupov et al (2011)[17]	1 (Mother)			Prominent forehead; frontal bossing; oval face, temporal narrowing short, downslanting palpebral fissures; long and bulbous nasal tip; thin upper lips; long chin	Mild language delay; learning problems			
	1 (First child)		Feeding difficulties; gastrostomy	Prominent occiput; short and downslanting palpebral fissures; deeply set eyes; epicanthal folds; micrognathia; Bulbous tip nose, ears posteriorly rotated, hypoplastic upper helices; preauricular tip	Microcephaly; episodes of status epilepticus; global developmental delay	–	Yes	Mitral and aortic atresia; hypoplastic ascending aorta; large patent arteriosus ductus; swallowing dysfunction; hypothyroidism; strabismus
	1 (Second child)	21 mo	Preterm delivery	Short upslanting palpebral fissures; hypotelorism; bulbous nasal tip; small chin; prominent ears			Yes	
Soler-Alfonso et al (2011)[18]	24 (including 10 patients already reported by Potocki et al [2007])	–	SGA 2/24; hypotonia 21/24; poor feeding 22/24	Micrognathia 14/24; high-arched palate 7/24; submucosal cleft palate 2/24; bifid uvula 2/24	Developmental delay 24/24; microcephaly 2/24	9/24	17/24	Cardiovascular anomalies 10/24; oropharyngeal dysphagia 24/24

(*Continued*)

Table 1 (*Continued*)

Authors, year	Patients (*N*)	Age	Birth and neonatal history	Facial dysmorphism	Neurodevelopment	Autism	Failure to thrive	Other features
Lee et al (2013)[10]	1	3.3 y	AGA; feeding difficulties	Not strikingly dysmorphic; dolichocephaly; mild asymmetric smile	Language delay; mild intellectual disability			
Lee et al (2012)[14]	1	17 y	IUGR, preterm		Language delay; two provoked seizures; mild intellectual disability			
Gulhan Ercan-Sencicek et al (2012)[16]	1		Difficulty nursing		Language delay; intellectual delay			
Popowski et al (2012)[21]	1			Broad nasal bridge, smooth philtrum, mild hypertelorism; asymmetric ears	Nodular cerebellar heterotopia			Left pulmonary isomerism; enlarged abnormally positioned left coronary artery
Magoulas et al (2014)[7]	1 (#1 family [mother])	40	Feeding difficulties; hypotonia; failure to thrive at 3 mo		Intellectual disability; seizures; bipolar disorder; anxiety; ADHD			
	1 (#1 family [first child])	5 y	Hypotonia; feeding difficulties	Not strikingly dysmorphic; triangular face; prominent nasal tip; short filtrum	Global developmental delay; speech delay; tonic–clonic seizures			Hypospadia; joint hypermobility; MRI; syringomyelia C4-T12
	1 (#1 family [second child])			Bulbous nasal tip, short and smooth philtrum; thin upper lip; dental overcrowding				
	1 (#2 family)	24 y		Bulbous nasal tip; mild micrognathia; brachydactyly	Substantial speech delay; learning difficulties		Height $< 3^{rd}$ percentile	Conductive hearing loss; uterine septum
	1 (#2 family)		Difficulties in nursing	Broad nasal bridge; micrognathia				Talipes equinovarus
Sumathipala et al (2015)[20]	1	4 y	Low birth weight (2.885 g)	Subtle facial dysmorphism: triangular face, broad	Severe expressive speech impairment;			Impaired vision

Table 1 (*Continued*)

Authors, year	Patients (*N*)	Age	Birth and neonatal history	Facial dysmorphism	Neurodevelopment	Autism	Failure to thrive	Other features
				forehead, slightly downslanting palpebral fissures, prominent tip of nose, smooth philtrum, and dental malocclusion; clinodactyly of the 5th finger	borderline intellectual disability			
Present patient	1	5 y	Mild hypotonia and poor suction at birth	Triangular face; microretrognathia; ears prominent with deep conchae. Redundant teeth	Language delay; no hypotonia; febrile seizures	No	No	Macrophallus

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AGA, appropriate for gestational age; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; SGA, small for gestational age.

The duplicated region contains *RAI1*, *SMCR5*, *SREBF1*, and *TOM1L2*. Among these, *RAI1* likely plays a critical role in the phenotype: Zhang et al in their study,[3] described three individuals with typical features of PTLS who had a smaller (less than 1 Mb in size) 17p11.2 duplication involving *RAI1* only. This gene encodes a transcriptional regulatory factor that carries out various roles in embryonic and postnatal development and likely in neuronal differentiation.[8–10] A recent case of SMS caused by a frameshift mutation in one copy of *RAI1* suggests it also plays a role in this syndrome.[11] The phenotypic differences may be partially due to haploinsufficiency (SMS) or triplosensitivity (PTLS) of other genes within the common and uncommon intervals. We cannot exclude the possibility that variant alleles on the nonrearranged chromosome may contribute to the heterogeneous clinical presentations of the two syndromes.[12]

As this genomic region is rich in low-copy repeats both larger and smaller recurrent duplications, as well as nonrecurrent duplication events—all containing the dosage-sensitive *RAI1* gene—have been observed in PTLS.

PTLS is an uncommon disorder, with an incidence of approximately 1 in 25,000 live births.[13] Less than 50 individuals with PTLS have been reported.[14,15] The clinical features of the reported patients with PTLS are variable and include minor facial dysmorphisms, intellectual disability, speech delay, and behavioral disturbances (►**Table 1**). The developmental delay ranges from borderline to severe and is the most typical finding in this syndrome, with a prevalence of about 90% (►**Table 2**). Behavioral disturbances range from attention-deficit/hyperactivity disorder and aggressiveness to autistic spectrum disorder, the latter being present in about one patient out of three. Poor feeding and failure to thrive are quite common, present in 55 and 34.5% of patients, respectively. Cardiovascular anomalies (20.7%) and seizures (8.6%) are less frequently reported. Hypotonia may be present as well as a wide range of congenital anomalies, such as microcephaly, ophthalmic, orthopedic, oropharyngeal, and renal anomalies.[16–21]

It is important to underline that, probably because of variant alleles in the nonrearranged chromosome or differences in size of the microduplication,[12] these features may present with a high degree of severity, and the clinical phenotype may vary. For this reason, a clinical diagnosis is

Table 2 Main symptoms presented by patients affected by Potocki–Lupski syndrome

Neurodevelopmental involvement (including learning and language disabilities)	52/58 (89.7%)
Poor feeding in the neonatal period	33/58 (55.2%)
Facial dysmorphism	25/58 (43.1%)
Autism	22/58 (37.9%)
Failure to thrive (or short stature)	20/58 (34.5%)
Cardiovascular involvement	12/58 (20.7%)
Seizures	5/58 (8.6%)

difficult to perform, and the prognosis of affected patients may be difficult to predict.

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