CASE REPORT

A mild phenotype associated with a de novo microdeletion 10q23.1-q23.2: a new patient with a novel feature

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SUMMARY

Chromosome 10q23 contains several genes, including *PTEN* and *BMPRI1A*, the mutations or microdeletion of which are associated with aggressive polyposis and malignancies in children. Deletions in this chromosomal region have also been associated with heart anomalies, developmental delay and macrocephaly. Most of the cases reported involve the *PTEN* and *BMPRI1A* genes, usually associated with complex and severe anomalies. We report a case of a boy with a de novo interstitial microdeletion in 10q23.1-q23.2 spanning 6.7 Mb with boundaries from 82 087 077 to 88 847 906, not including *PTEN* and *BMPRI1A*. Clinical features consisted of mildly dysmorphic facies, frontal telangiectasias, poor scholastic performance and hyperactivity. Furthermore, the boy presented toe anomalies, which appeared to be novel features associated with 10q23 deletion. Further observations of 10q23.1-q23.2 deletions are necessary to confirm the clinical features observed in the proband, and to show that deletion or mutations not involving *PTEN* and *BMPRI1A* may not be associated with severe neurological impairment and malformation anomalies.

BACKGROUND

Array-based comparative genomic hybridisation (CGH) has acquired a role of primary importance in paediatric diagnostic work up. With the use of this relatively modern technology it is possible to not only reach a correct diagnosis, particularly in children with physical and intellectual anomalies, but also to anticipate the clinical course and complications linked to disorders. This is particularly true for several molecular mutations in which clinical signs at a young age may be followed by dangerous clinical evolutions (eg, cancer).

Chromosome 10q23 contains several genes; mutations or microdeletions of *PTEN* and *BMPRI1A* genes are associated with aggressive polyposis and malignancies in children,¹ and also with extraintestinal findings including cardiac anomalies, developmental delays and macrocephaly. We report a case of a boy with a 'de novo' interstitial microdeletion in the chromosomal region 10q23.1-q23.2 that spans 6.7 Mb with boundaries from 82 087 077 to 88 847 906, which does not include *PTEN* and *BMPRI1A*. The clinical examination of the boy was remarkable only for mildly dysmorphic facies, frontal telangiectasias, hyperactivity and toe abnormalities. He also had a history of poor scholastic performance. Toe abnormalities seem to be a novel

feature of this syndrome, although foot abnormalities have previously been reported in 10q23 syndrome. On the basis of the clinical features reported in this patient and those of the few reported patients in the literature, chromosome 10q23 microdeletions that include (or not) *PTEN* and *BMPRI1A* genes are not expectable to be associated with severe neurological involvement and complex malformation anomalies.

CASE PRESENTATION

An 8-year-old boy was first referred to the clinical unit for a diagnostic work up for his poor scholastic performance and restlessness. He was the first-born of healthy non-consanguineous parents. He had a healthy 3-year-old sister. The mother suffered a miscarriage before the birth of the present patient. At the time of delivery, the mother of the boy was 25 years old and the father was 31 years old. The mother denied having had infectious diseases, hypertension, gestosis or consuming drugs or alcohol during the pregnancy. She claimed to have felt normal fetal movements.

The boy was born in the 41st week of gestation from a normal delivery. His weight was 2950 g, length 50 cm and head circumference 35 cm. Apgar scores were 7 and 9 at 1 and 5 min, respectively. He was discharged from the nursery at 3 days of life. Neurodevelopmental milestones were reached normally, but in the first years of life the boy suffered from frequent viral infections.

At the presenting age of 9 years, the boy appeared in good general condition: weight 23 kg (3–10th centile), height 129 cm (25–50th centile) and head circumference 51 cm (75th centile). He showed dolichocephaly (figure 1) and some facial dysmorphic features that were not particularly impressive, such as a high forehead, wide narices, a bulbous tip nose, microretrognathia, protruding ears (figure 2), and teeth with protruding and wide incisors (figure 2). The shoulders were rounded. The hands were short (14 cm) and the second and third toes bilaterally long (5.0 and 4.5 cm, respectively), with a partial syndactyly of the second, third and fourth toes, and clinodactyly of the fifth toe (figure 3). Testicles were normally set. Until now, rectal bleeding had not been reported by the parents, and several haemograms and faecal occult blood tests were negative. No signs of intestinal obstruction were reported. At the neurological examination, the boy showed normal muscular tone and no cranial nerve involvement. Patellar reflexes

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Figure 1 Skull X-ray and sagittal projection of the patient at the age of 9 years. Note the dolichocephaly.

were normal. The boy was particularly restless and hyperactive, however, he socialised well. According to his teachers, his scholastic performance was poor, primarily linked to his severe inattention. A diagnosis of attention deficit hyperactivity disorder (ADHD) combined inattention/hyperactivity was obtained from the Vanderbilt ADHD Teacher Rating Scale and the Vanderbilt ADHD Parent Rating Scale. A Griffin Mental Developmental Assessment showed overall functioning at a 7-year age level (IQ 62, WISC scale). Routine laboratory analyses, including haemogram, hearing tests and EEG (awake and during sleep) were normal. Ophthalmological examinations showed mixed astigmatism and myopia. Chest and heart examination, including thorax X-ray, ECG and echo colour Doppler, were normal, as was abdomen ultrasound. A synopsis of the main clinical signs presented by the patients is reported in [table 1](#).

INVESTIGATIONS

Genetic testing

Chromosomal microarray analysis (180 k chip, Technogenetics, Milan, Italy) was carried out at an average resolution of 100 kb on genomic DNA extracted from peripheral blood cells, using a commercial kit (Mecheray Nagel, Duren, Germany). The patient's DNA was hybridised against reference DNA

Figure 2 The patient at the age of 9 years, showing severe tooth anomalies and protruding ears.

(Promega, Madison, Wisconsin, USA) according to the manufacturer's instructions (Technogenetics, Milan, Italy). A de novo 10q23.1-q23.2 deletion that spanned 6.7 Mb was detected, with boundaries from 82 087 077 to 88 847 906 (hg19 assembly). Such deletion did not encompass the *PTEN* and *BMPR1A* genes and was confirmed by a FISH analysis. The same chromosomal analysis was negative in the parents.

DIFFERENTIAL DIAGNOSIS

A patient, reported by Salvati *et al*² with 10q23 syndrome including *PTEN* and *BMPR1A*, showed mild dysmorphic facies and mild cognitive delay and hamartomatous polyps.

OUTCOME AND FOLLOW-UP

The outcome appears to be relatively good.

DISCUSSION

The microarray analysis, performed on the basis of mildly dysmorphic facies and mild cognitive delay, allowed us to provide a diagnosis of 10q23.1-q23.2 deletion syndrome. Some of the first reports regarding this anomaly occurred between 1985 and 1993, and were described through use of high resolution chromosomal analysis banding.^{3–5} Common features reported in these patients included postnatal onset of short stature, relative hypertelorism and developmental delay. Farrell *et al*⁵ reported some similarities in the facial anomalies of two out of three cases, and these included anteverted nares, long philtrum, wide mouth with downturned corners, ocular anomalies, positional

Figure 3 Toe anomalies of the patient at the age of 9 years. The second and third toes are bilaterally long (5.0 and 4.5 cm, respectively). There is a partial syndactyly of the second, third and fourth toes, and clinodactyly of the fifth toe.

Table 1 Synopsis of the clinical features shown by the proband

Craniofacial dysmorphism	Dolichocephaly High forehead Teleangectasy Wide narices Bulbous nose tip Retrognathia
Ear	Protruding ears
Teeth	Protruding and wide incisors
Extremities	2nd and 3rd toes bilaterally large Syndactyly of 2nd, 3rd, 4th toes Clinodactyly 5th toe

ear anomalies, epicanthic folds, broad forehead and microcephaly.

The reports on this topic increased after the introduction of array CGH examination, which allowed researchers to extend the phenotype of this disorder, with the deletion of some genes thought to be causative of specific features. Menko *et al*⁶ used the single nucleotide polymorphism analysis of DNA on eight patients and reported that the chromosome 10 deletions contained 10 genes including *PTEN*, *BMPR1A*, *MMRN2*, *SNCG*, *C10orf99*, *GLUD1*, *FAM35A*, *MINPP1* and *ATAD1*. Among these genes, *PTEN* is presumed to cause increased risk for developing breast, thyroid, endometrial and some renal cancers.⁷ In addition, the gene has been associated with some severe malformative disorders, such as juvenile polyposis syndrome, Cowden syndrome and Peutz-Jeghers syndrome.⁸ Singh *et al*⁹ suggest that microdeletion in the 10q23 regions may be divided into three subcategories: those characterised by deletion of the *BMPR1A* gene, those with deletions involving the *PTEN* gene and those encompassing a deletion of both genes. It has been hypothesised that deletion of both genes (ie, *BMPR1A* and *PTEN*) may lead to a more severe clinical prognosis and may have an additive effect on the clinical course, including increased predisposition to gastrointestinal (and other organ) malignancies.^{6 8 10}

Most of the 10q23 deletion syndrome cases reported in the literature involve the *PTEN* and *BMPR1A* genes, usually associated with complex and severe anomalies. Salvati *et al*² reported on a young patient with deletion also involving *PTEN* and *BMPR1A* genes who, at the age of 5 years, presented mild rectal bleeding and multiple intestinal polyps with dysplasia. The patient also presented dysmorphic features: sparse hair, epicanthic folds, a hypoplastic nasal bone, protruding lower lip, small ears and a high-arched palate, with normal tooth development and a single café-au-lait spot. Comparing that patient's clinical signs with those of our patient, both presented mild developmental delay and mildly dysmorphic facies, even if with different facial dysmorphic features. Neither displayed any of the clinical signs typical of Cowden syndrome or Bannayan-Riley-Ruvalcaba, which are characterised by severe neurological signs. The clinical phenotype of 10q23 deletion is widely variable; this variability may be linked to the extent of the deletion, to the involvement of additional genes at the same time and to the specific type of genes involved. Yet unknown genetic modifier genes may play a relevant role in the clinical expression of this syndrome.

In the present patient, the clinical features were not impressive, and included mild cognitive and behavioural involvements, and facial dysmorphism. The anomaly of 10q23 syndrome that does not involve the *PTEN* and *BMPR1A* genes has been rarely reported among those patients diagnosed by array CGH

examination. In these cases, until now, no relevant clinical anomalies have been observed; it is even uncertain if some of the severe symptoms may be noticed in the future. The proband showed some of the features reported by other authors, such as dolichocephaly, a broad forehead, bulbous nasal tip and micrognathia. The toe anomalies appear to be novel features that have not yet been reported for this syndrome, although foot abnormalities have been previously reported in 10q23 deletions.

More observations on this topic are necessary to confirm the clinical features seen in the present patient, such as the mild dysmorphic facies and the toe anomalies as features of the condition, and to further confirm that the clinical course of this condition is not severe.

Learning points

- Chromosome 10q23 contains *PTEN* and *BMPR1A*, the mutations of which are responsible for aggressive polyposis and malignancies in childhood, and also for extra-intestinal findings including cardiac anomalies, developmental delays and macrocephaly
- The reported patient presented a 10q23 microdeletion, without *PTEN* and *BMPR1A* involvement. His clinical signs were not impressive, consisting prevalently of mild facial dysmorphic facies, frontal telangiectasias and hyperactivity. He also presented toe anomalies, which were not formerly associated with this 10q23 microdeletion.
- The patient provides confirmation that, when the deletion does not involve the *PTEN* and *BMPR1A* genes, the clinical features may be not severe.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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