Journal of Pediatric Genetics 2 (2013) 141–146
DOI 10.3233/PGE-13058
IOS Press

Case Report

A rare case of de novo mosaicism: Deletion 18p and isochromosome 18q syndrome

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Received 22 May 2013
Revised 3 November 2013
Accepted 15 November 2013

Abstract. Monosomy 18p syndrome is a rare chromosomal disorder with varying phenotypic and clinical manifestations. Dysmorphism, growth delay, delayed speech and mental retardation are a few of the commonest features observed. The cytogenetic findings also vary and may comprise a pure deletion of the entire 18p arm or a deletion of a part of the 18p arm, if involved in a translocation with other chromosomes. Monosomy 18p may either occur by itself or with a structural alteration of the remaining chromosome 18, as a ring or as an isochromosome. The clinical presentation of this syndrome often overlaps with other syndromes. Establishing a cytogenetic diagnosis and understanding the location of the breakpoints is crucial for precise management and follow-up. We present here a rare case with mosaicism for a de novo deletion of 18p with isochromosome 18q in a boy born to a consanguineous Omani couple.

Keywords: de Grouchy syndrome, monosomy 18p syndrome, 18p- syndrome, mosaic 18p-/i(18q) syndrome, trisomy 18q syndrome

1. Introduction

Monosomy 18p syndrome, de Grouchy syndrome is a rare chromosomal disorder occurring in approximately one in 50,000 live births with a female to male ratio of 3:2 [1]. As the clinical features of this syndrome vary from one patient to another, its presentation often overlaps with other genetic conditions. Hence, the diagnosis depends mostly on cytogenetic findings [1,2]. The clinical manifestation varies from mild to moderate mental retardation, short stature, round face with protruding philtrum, palpebral ptosis and large ears with detached pinnae. Speech delay is often observed, and verbal and manual abilities can be highly dissociated. The intelligence quotient (IQ) can vary between 25–75, and around 50 is observed in majority of cases [1,3].

Fifty years since it was first reported by Jean de Grouchy, about 159 cases (including prenatal detection reports) have been recorded worldwide [4]. Deletion 18p is *de novo* in 2/3 of the cases, 1/3 follows transmission with loss of 18p (de novo), parental transmission or malsegregation of a parental translocation or ring 18. Most of the reports are pure deletion 18p, with some partial deletion (18p) as a result of translocation, a few with structural alteration of the other

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18 [i(18q) or r(18)] and few cases present in mosaic form. So far, only a single case report of mosaicism for del(18p)/i(18q) is available in the literature and ours is the second report [5]. Many cases would probably have been misdiagnosed due to non-availability of cytogenetic testing during diagnosis. Hence, cytogenetic testing is critical for proper diagnosis, management and follow-up, as this condition is compatible with life, normal fertility, and can be transmitted to offspring. We present here a *de novo* mosaic 18p-/ i(18q) syndrome, in a boy born to a consanguineous Arabic Omani couple, with a review of the literature.

2. Case report

The proband, an 11-year-old boy, presented to our genetics clinic, with global developmental delay including severe speech and language delay, mild cognitive dysfunction, learning difficulties and dysmorphic features. He was born full term with normal birth weight, following a normal pregnancy of a healthy first-degree consanguineous couple of Arabic Omani descent. His five elder female siblings were all healthy. There was no family history of note.

He had severe speech disorder, characterized by dysarthric features. He conversed with two to three word sentences, had a 20-word vocabulary, but the quality of speech was nasal and unintelligible and could be understood only by his mother. He communicated by producing incoherent sounds and usually pointed to indicate his needs. His hearing was normal and had poor vision despite correction of squint. Fundoscopic examination was normal. His gross motor milestones were mildly delayed. He sat at 7 mo and walked at 13 mo. At present, he walks normally, can run, throw and kick a ball. He can jump, but cannot ride a tricycle. His fine motor skills were also delayed, and he could hold a pen, scribble and could draw a circle but not a triangle. He attends a special needs school and has poor school performance, with difficulty in attention, concentration, comprehension and obeying orders. His IQ test was 59 at 11 yr of age, functioning at a level of mild mental deficiency. He was quiet and shy, but interacts well with his peers. He was toilet trained. He had past history of inguinal hernia repair and recurrent episodes of bronchial asthma.

On examination, height was 126 cm (-3 SD), weight was 26 kg (10 SD) and head circumference 51 cm (50 SD), with relative macrocephaly. He had plagiocephaly and brachycephaly, his neck appeared short, webbed and had low posterior hairline and there was mild facial asymmetry. Ears were large and protruding with prominent ear lobules. Eyebrows were highly arched and were sparse laterally. The nose was long and wide based with bulbous nasal tip, and short columella. The philtrum was short and the mouth was wide with down-turned corners with a prominent lower lip and tented thin upper lip. He had a high arched palate, widely spaced teeth with a single central incisor and anterior overbite (Figs. 1A–1C).

He had alopecia of the temporofrontal region and was noted to have skin and hair pigmentary anomalies typical for mosaicism. His hair had lighter streaks on a darker background. Hypo-pigmented macules were also noted on his forehead, anterior chest wall and on his upper back. Four small café-au-lait spots were noticed on his trunk. Hands had mild cutaneous syndactyly between fourth and fifth fingers bilaterally. He also had thick palmar skin with paucity of creases. He had bilateral cubitus valgus deformity. His gait was ataxic and he was a toe walker. Neurological

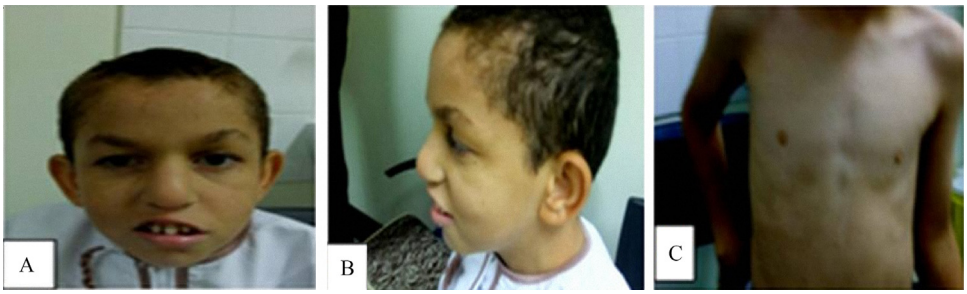

Fig. 1. (A) Hypopigmented macules on the forehead, streaks of lighter hair, long nose with bulbous tip, single central incisor, widely gapped teeth, wide mouth, down turned corners of mouth, prominent ears. (B) Temporal and frontal patches of alopecia, highly arched eyebrow with lateral sparsely. (C) Hypo pigmented patches on anterior chest wall.

examination and magnetic resonance imaging of the brain were normal.

Conventional chromosomal analysis on 30 metaphases from peripheral blood lymphocyte cultures showed two cell lines: mos 46,XY,del(18)(p11)[24]/46,XY,i(18)(q10) [6]. Deletion of the entire short arm of chromosome 18 forming monosomy for 18p and mirror-image of 18q forming i(18)(q) (resulting in trisomy for 18q) was evident from G-banded partial karyotype (Figs. 2A–2B). Fluorescence in-situ hybridization (FISH) on 50 metaphases using whole chromosome paint 18 (WCP18, Cytocell Ltd, Cambridge, U.K) showed del(18p) in 40 metaphases and i(18)(q10) in 10 metaphases (Figs. 3A–3B). The karyotypes of parents were normal. The results were interpreted using International System for Cytogenetic Nomenclature [6].

3. Discussion

Monosomy 18p is a rare genetic disorder where the phenotypic presentation and the cytogenetic pattern varies from one patient to another. It could either be pure deletion of the entire short arm or partial monosomy of 18p, resulting in deletion of part or the entire short arm of 18 [7]. The loss of 18p could be a result of unbalanced whole arm translocation [8]. Our patient had a major clone with deletion of the entire p-arm, thus resulting in monosomy 18p. Studies suggest that the deletion of the entire short arm may manifest clinically with dystonia and a gene for white matter lesions on MRI has been mapped to chromosome 18p [9,10]. Our patient had the whole p-arm deleted in majority of the cells examined, but did not have dystonia or white matter abnormality.

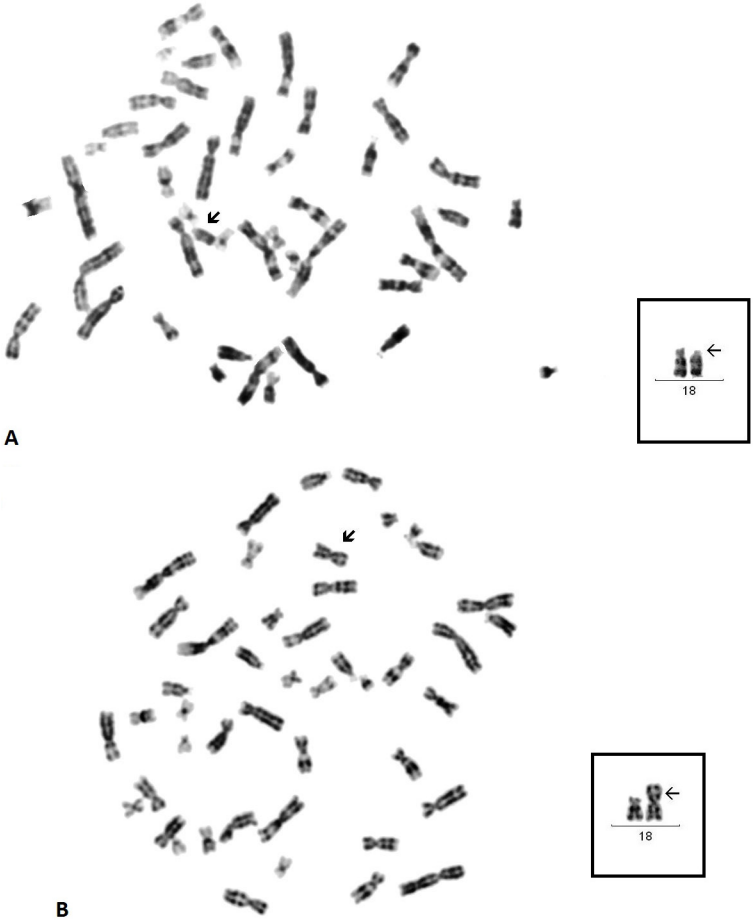

Fig. 2. Metaphase and partial karyotype (arrow) showing. (A) deletion of 18p (B) isochromosome (18q).

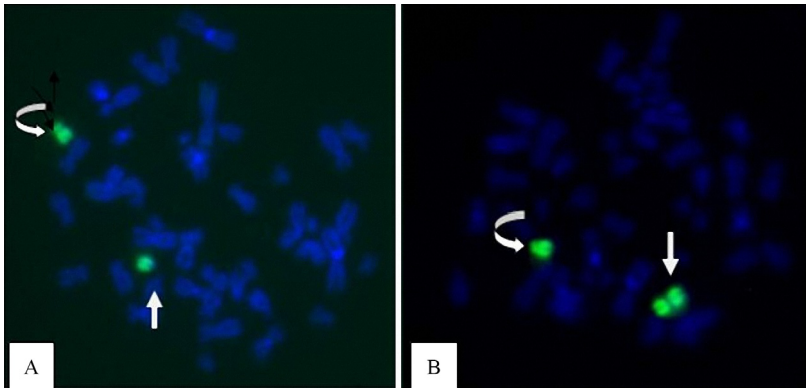

Fig. 3. Metaphase fluorescence in situ hybridization using WCP18 (arrows) showing (A) deletion of 18p (B) isochromosome (18q), (curved arrows) showing normal 18.

Monosomy 18p and i(18q) have been detected on a chorionic villi sample after a sonographic test detected holoproscencephaly and increased nuchal translucencies with facial defects [11]. However, our patient had single large incisor, overbite malocclusion and did not have prenatal ultrasound examination. Patients with this syndrome reported a single maxillary central incisor and a higher caries rate, also, tooth decay with risk of caries [12,13]. Also, there are reports suggesting that growth hormone deficiency occurs with deletions of the distal region of 18p and is involved in the main clinical features of the syndrome and growth hormone deficiency [14]. The growth delay in our patient could be the result of the region of deletion involved. Diaphragmatic hernia has been reported in a 18p- patient earlier. Inguinal hernia of our patient was surgically corrected 2 yr ago [15]. A specific polysaccharide antibody deficiency and immunoglobulin deficiency in a young girl was reported along with 18p- [16]. Two patients with dysmorphic features typical for 18p deletion syndrome showed immunological disorders. Molecular cytogenetic characterization of 18p chromosomal rearrangements using array comparative genomic hybridization and FISH enabled precise identification of cryptic deletion with an inverted duplications [17]. None of these immunological conditions were observed in our patient, except for a history of asthma.

Partial monosomies are generally a result of translocation of chromosome 18 with other chromosomes. A child of consanguineous parents had atypical 18p- syndrome along with partial trisomy 16p, resulting in a chromosomally unbalanced offspring, whose parents carried a familial t(16;18) [18]. White matter abnormalities, mental retardation, facial dysmorphism and an anomalous optic disk with myopia were observed in an 18p- patient who had partial monosomy [19]. Glasses were prescribed to our patient due to poor vision, but optic disk was unaffected. Advanced techniques, for example, array comparative genomic hybridization and FISH, used for mapping phenotypical traits in 18p- syndromes revealed partial monosomy of 18p can be variably sized, as a result of unbalanced translocations, which could thus form a phenotype map for 18p- syndromes [20].

Familial deletion of 18p, where sibs and mother-both had deletion 18p, in which the deletion 18p was vertically transmitted from mother to her offspring, has been reported, indicating that fertility is not affected in patients with 18p deletion [21]. Maternal transmission was reported in another family where the mother had short stature and her two daughters were dysmorphic and mildly mentally retarded [22]. As this child is a de novo patient, the siblings and the parents of our patient showed normal karyotypes. They were healthy with normal clinical features. Recurrence risk for siblings is low in de novo deletions and translocations, but is significant if a parental rearrangement is observed [1].

Isochromosome 18q as a sole anomaly has also been reported in a few patients, who might present with different clinical manifestation as a result of trisomy of 18q. In patients where i(18q) was reported either solely, or along with deletion of 18p, the phenotypic features have had resemblance to those of patients with deletion 18p. Partial 18q trisomy, along with supernumerary 18p isochromosome, has also been reported [23]. In our patient, the i(18q) was observed as a minor clone along with a major clone of 18p-, and thus was present in a mosaic form. Similar

findings from a prenatal finding of i(18q) in a fetus showing holoproscencephaly on ultrasound, from amniocentesis sample at 19 w of gestation, were documented [24]. Prenatal ultrasound examinations and genetic testing are not routinely practiced among the Arab community, due to social/religious reasons. Hence, a prenatal sonographic test was not done for our patient's mother during pregnancy.

There are only two reports of postnatal monosomy 18p syndrome available in the literature, both mosaic forms [5,25]. A patient with del 18p/i(18q), 50% each with a ratio of 1:1, showed phenotypic features of both 18p- and trisomy 18q [6] but in our patient, del(18p) is more frequent than i(18q) and hence probably manifested more clinical features of 18p-. A report of del(18p) and i(18q) in non-mosaic form 46,XX,i(18)(q10),del(18)(p11) was reported in a baby born to a non-consanguineous couple in contrast to the consanguinity observed among parents of our patient [26]. Whether consanguinity has any influence in the segregation of chromosome abnormality or not is debatable. The clinical features present in the previous mosaic patient (felled back sternum, contraction of external auditory meatus, femur luxatus congenitus) were absent in our patient [5]. A patient with mosaic ring chromosome 18 [45,XX,-18/46,XX,r(18)/46,XX,dicr(18)] with features similar to 18q- syndrome was documented [27]. Similarly, patients with ring chromosome 18, usually sharing clinical features of 18q- syndrome and less frequently to 18p- patients, have been reported [28].

The clinical and molecular characterization of patients with 18p deletion have shown that those who have had a deletion in the centromeric region at 18p11.1 had mental retardation, and those who had deletion at a more distal breakpoint (distal 18p11.21), had normal / marginal mental development [3]. Attribution of clinical features to different parts of the short arm of chromosome 18 may eventually help to identify genes responsible for specific symptoms in those syndromes [18]. The deletion in our patient was at p11.1, close to the centromeric/ proximal region. The IQ of our patient was 59, and he showed mild mental retardation, whereas the IQ generally varies between 25-75, and around 50 is observed in majority of the reported cases. Other factors that influence variability may include age, incomplete penetration of the trait, undetected mosaicism and the uncovering of recessive trait by the deletion [20].

In conclusion, cytogenetic testing is critical for understanding the karyotype and to confirm the diagnosis. Testing can determine if pure monosomy 18p (partial or entire) is present, and if so, identify the location of breakpoints, both in deletions as well as structural alterations, like isochromosomes or rings, and then phenotypic features can be correlated and evaluated accordingly. Accurate phenotypic prediction in patients with monosomy 18p is necessary for precise genetic counseling. Many cases that could be missed in diagnosis, can be helped with precise cytogenetic diagnosis, which is critical for proper management and follow up, as this condition is compatible with long life and fertility.

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