Partial trisomy 1(q42→qter): a new case with a mild phenotype

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Abstract

We report a female patient with a 46,XX,der(8)t(1;8)(q42.1;p23.3) karyotype who had a mild phenotype characterised by a few subtle dysmorphic features and mild developmental retardation, probably resulting from trisomy 1q42→qter. The deletion on the short arm of the chromosome 8 appeared to be confined to the distal chromosomal segment.

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Keywords: trisomy 1q42→qter; translocation (1;8)(q42.1;p23.3).

Partial trisomy 1q42→qter is a rare chromosomal abnormality often arising from a parental translocation with partial monosomy of one of the other autosomes. For this reason it is not possible to define a distinct phenotype resulting from this chromosomal abnormality, because the coexisting deletion of other chromosomes could be responsible for most of the various clinical signs observed in the phenotype of previous reported patients.¹

We report a new case of a "de novo" trisomy 1q (q42→qter) probably resulting from an unbalanced translocation (1;8)(q42.1;p23.3), who has a mild phenotype. It has been suggested that the clinical phenotype of subjects with a very small terminal deletion of 8p is almost unremarkable from a clinical point of view.^{2,3} Moreover the deletion of chromosome 8 in our patient had the breakpoint at 8p23.3 whereas the other cases of monosomy 8p23 had a more proximal breakpoint on the short arm of chromosome 8 when compared to our patient.⁴ In this report we further delineate the "1q42→qter trisomy syndrome" taking into account the phenotype of our patient and the clinical findings described in other previously reported cases.

Case report

The proband is the first born child of a 23 year old mother and a 27 year old father. The parents were healthy and unrelated. The girl was born at 41 weeks of gestation after an uneventful pregnancy; the birth weight was 3160 g (50th centile), length was 50 cm (50th centile), and head circumference was 38 cm (>95th centile). Clinical evaluation at 3 months of age showed a length of 58.5 cm (25th centile), a weight of 4830 g (25th-50th centile), a head circumference of 41.5 cm (95th centile), wide fontanelles, triangular face, prominent forehead, facial capillary naevi, downward slanting palpebral fissures, long philtrum, and micrognathia (fig 1). Both upper

and lower extremities were normal. Bilateral simian creases were present and the dermal ridges were hypoplastic. The cardiac assessment, including two dimensional echocardiography, was normal. Mild developmental retardation was present at the age of 6 months. Routine analyses were normal. Ultrasound and x ray examinations showed no other congenital malformations. Ophthalmological evaluation was normal.

CYTOGENETIC AND MOLECULAR ANALYSIS

Chromosome analysis was performed on QFQ and GTG banded metaphases from synchronised peripheral lymphocyte cultures. The proband's karyotype showed 46 chromosomes with an additional portion on the short arm of chromosome 8, which probably derived from the terminal part of the long arm of a chromosome 1 (fig 2). The cytogenetic analysis showed that the breakpoint on chromosome 1 is probably located at band q42.1 and on chromosome 8 at band q23.3. The proband's karyotype was interpreted as a "de novo" unbalanced reciprocal translocation and described as follows: 46,XX,der(8)t(1;8)(q42.1;p23.3). The karyotypes of the parents were normal.

Fluorescence in situ hybridisation (FISH) was performed according to the ONCOR

Figure 1 The proband at 3 months of age.

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Figure 2 Three GTG banded metaphases of the two chromosomes 1, of the normal chromosome 8, and of the der(8). Schematic representation of the normal chromosome 8 and der(8).

protocol with minor modifications on metaphases from peripheral blood lymphocyte cultures. DNA biotinylated probes used for FISH analysis were the following: a chromosome 1 specific painting probe (ONCOR); a YAC probe (931-B-2) specific for the D8S201

locus, which maps to 8p23.3⁵; a YAC probe (AFM144xb2), specific for the D8S265 locus, which maps to 8p23.1.⁶

With the chromosome 1 specific painting probe, both the chromosome 1 and the terminal portion of the derivative chromosome 8 were labelled (fig 3A, B). These results confirmed the cytogenetic hypothesis. In order to define with more precision the breakpoint on the short arm of chromosome 8, we used a specific probe for the D8S201 locus which maps to 8p23.3. The hybridisation signal was present on the normal chromosome 8 and absent on the der(8) (fig 3C, D). With the specific probe for the D8S265 locus which maps to 8p23.1, the hybridisation signal was present on both the normal chromosome 8 and the der(8) (fig 3E, F). The breakpoint was located between D8S201 and D8S265. The FISH results confirm the cytogenetic analysis and identify the breakpoint in 8p23.3.

Discussion

After a review of the few previously reported cases of trisomy 1q (q42→qter) it is difficult to define the clinical phenotype of the syndrome.¹ The variability of the clinical presentation in this syndrome has been explained by the presence of the associated chromosomal deficiency of other autosomes.⁷ Macrocephaly with wide fontanelles, craniofacial abnormalities, intrauterine and postnatal growth retardation, developmental delay, and cardiac defects are the clinical findings common to all reported patients.^{1 7-9} However, the clinical signs in our patient are less severe than in the previously published cases. We believe that this could be

Figure 3 (A) FISH with the chromosome 1 specific painting probe. (B) The same metaphase stained with DAPI. The arrows show the chromosomes 1 and the der(8). (C) FISH with the cosmid probe, specific for the D8S7 locus, which maps to 8p23.3. (D) The same metaphase stained with DAPI. (E) FISH with the YAC specific for the D8S265 locus, which maps to 8p23.1. (F) The same metaphase stained with DAPI. The arrows show the normal chromosome 8 and the der(8).

Table 1 Clinical findings in the present case and previously reported cases^{7 8}

Clinical findings	Verschuuren-Bemelmans et al ⁷ Trisomy 1p42→qter, monosomy 15p11→11		Chia et al ⁸ Trisomy 1q42→qter, monosomy 22p12→p11	Present case Trisomy 1q42→qter, monosomy 8p23.3→p23.3
	Case 1	Case 2		
Prenatal growth retardation	+	+	+	-
Macrocephaly	+	+	+	+
Large fontanelles	+	-	+	+
Widely spaced sutures	+	-	-	+
Prominent forehead	+	+	+	+
Facial capillary naevi	-	-	+	+
Downward slanting palpebral fissures	+	+	-	+
Flat nasal bridge	-	-	+	-
Low set ears	-	-	+	-
Micro/retrognathia	+	+	+	+
Cardiac defect	±	-	+	-

*+ present, - absent.

because of the minimal involvement of chromosome 8 in only its distal part, and therefore our case probably represents an example of trisomy 1q syndrome by duplication of the segment 1q42→qter. To our knowledge, only a few cases of probably pure trisomy 1q42→qter have been published.^{1 10-13} These patients present some slight clinical differences, probably because of submicroscopic deficiencies of subterminal telomeric regions of different chromosomes involved in the translocations. We think that the combination of clinical abnormalities, such as macrocephaly, prominent forehead, micrognathia, large fontanelles, flat nasal bridge, low set ears, facial capillary naevi, cardiac defect, and small size for gestational age, could be considered suggestive of trisomy 1q42→qter syndrome. We have compared the clinical findings of our patient with previously reported cases^{7 8} in which the phenotype was determined by the trisomy 1q42→qter without involvement of other telomeric chromosomal segments (table 1). The absence of prenatal growth retardation, cardiac defects, and some dysmorphic signs, such as low set ears and flat nasal bridge, in our patient that are different from the reported patients points to a possible clinical variability in this syndrome. Few cases with deletion of a very short segment of 8p (p23.1→pter) have been reported.^{2 4 14 15} Clinical manifestations in these

patients are variable and some of them showed only mild clinical signs.^{2 3 14} As hypothesised by Wu et al,¹⁵ this clinical variability could be because of different breakpoints within the 8p23.1 region. None of these patients had the breakpoint in 8p23.3 band as our patient did. Congenital heart defects like atrioventricular canal (AVC) seem to be frequent in these distal 8p deletions.⁴ Digilio et al¹⁶ recently identified an "AVC critical region" at band 8p23. However, our case does not have AVC and we think that this contributes to restricting the critical region to 8p23.1-8p23.2.

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