De Novo Case of a Partial Trisomy 4p and a Partial Monosomy 8p

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ABSTRACT

The extent of clinical expression in cases of segmental aneuploidy often varies depending on the size of the chromosomal region involved. Here we present clinical and cytogenetic findings in a 5-month old boy with a duplication of a chromosomal segment 4p16.1→4pter and a deletion of a chromosomal segment 8p23.1→8pter. His karyotype was determined by applying classical GTG banding and FISH method (WHCR region, centromere 4, centromere 8, telomere 8p) as 46,XY,der(8)t(4;8)(p16.1;p23.1).ish der(8)t(4;8)(D8S504-,WHCR+,D8Z2+)dn. Parents are not related and have normal karyotypes, indicating de novo origin. We have compared similarity of the clinical features in our proband to other patients carrying only a duplication of the distal part of 4p or a deletion of distal part of 8p or similar combination described in the literature.

Key words: chromosome aberrations, clinical findings, partial trisomy 4p, partial monosomy 8p, phenotypic variability, unbalanced translocation, fluorescence in situ hybridization

Introduction

Extent of clinical expression in segmental aneuploidy often varies with the size of chromosomal region involved. The translocation between short arm of chromosome 4 and short arm of chromosome 8, in either a balanced or an unbalanced form, has been reported several times.¹² Most of unbalanced published cases conferred to derive chromosome 4p implicating on presence of partial trisomy 8p and monosomy 4p, respectively. De novo 4p deletions are reasonably assumed to be single chromosome anomalies. Unbalanced de novo translocations involving the short arms of chromosomes 4 and 8 were detected with an unexpectedly high frequency in Wolf-Hirschhorn syndrome (WHS) patients.³ Patients with der(4) had WHS, whereas subjects with der(8) showed a milder spectrum of dysmorphic features. Zollino et al.⁴ observed that in WHS patients with a de novo unbalanced translocation t(4;8) the breakpoint in 8p recurred always in the same region within olfactory receptor gene cluster. On the contrary, breakpoints in 4p occurred at two different sites; at a distance of approximately 5 and 14Mb from the telomere, thus implying a different extent of the 4p deletion.¹ Phenotype of the unbalanced t(4;8) patients is variable and there is no specific clinical pattern which allows identification of these patients.² The short stature and severe mental retardation of those with the WHS contrasted sharply with the mild to moderate mental retardation, less severe dysmorphic features and physical overgrowth of those with the 4p16.3 duplication.²³

We have compared similarity of the clinical features in our proband to other patients carrying a solely duplication of the distal part of 4p or a deletion of distal part of 8p, and similar combination of unbalanced form, described in the literature.

Case Report

The proband is a 5-month old boy referred for genetic evaluation because of dysmorphic features. He was delivered at term by cesarean section after uneventful pregnancy. At birth, length was 52 cm, weight 3,360 g, and
head circumference 35 cm. There was no family history of malformations or mental retardation. He showed a distinctive facial dysmorphic features: narrow forehead, hirsutism, wide nasal bridge, anteverted nostrils, low set and malformed ears, small mandible and low hairline on the neck. Heart defect was present in the form of atrioventricular septal defect. A bilateral inguinal hernia with undescended right testicle was present. There were unilateral vesicoureteral reflux, grade III and diastasis of the rectus abdominis muscles by 3 cm. Magnetic resonance imaging of the brain showed hypoplasia of the corpus callosum. He had clinodactyly and low inserted third toe. However, there was no growth delay. This study was approved by the Ethics Committee of the University Hospital Centre Osijek and School of Medicine, J. J. Strossmayer University Osijek and the written informed consent was obtained from the parents of the proband.

Cytogenetic and FISH Analysis

Cytogenetic examination of GTG banded metaphases (at resolution of 550 bands) obtained by standard methods, showed an unbalanced proband’s karyotype with extra chromosome material at the short arm of the chromosome 8 (Figure 1) using Olympus BX61 microscope and Cytovision 3.93 software (Applied Imaging, England). FISH (fluorescence in situ hybridization) with specific probes (Vysis/Abbott) for centromere of chromosome 4 (D4Z2), locus specific probe for Wolf-Hirschhorn Syndrome region (WHCR, 4p16.3), centromere 8 (D8Z2) and subtelomere of chromosome 8p (D8S504) on metaphases showed presence of two hybridization signals for probe WHCR (4p16.3) at each of the 4p and one additional signal at the p arm of the derivate chromosome 8 (Figure 2). Subtelomere 8p probe signal is present in only one copy and is missing from the derivative chromosome 8. Subsequent chromosomes analysis of the parents revealed normal karyotypes. The karyotype of proband is then 46,XY,der(8)t(4;8)(p16.1;p23.1).ish der(8)t(4;8)(D8S504-,WHCR+,D8Z2+)dn.

Discussion and Conclusion

We described a proband with dysmorphic features and an unbalanced translocation resulting in both partial trisomy for 4p16.1→pter and partial monosomy for 8p-23.1→pter, respectively. We have compared similarity of the clinical features in our proband to other patients carrying a duplication of the distal part of 4p7,8 and patients carrying a deletion of distal part of 8p9,10–12 as described in the literature (Table 1).

Individuals with deletion of 8p are reported to share a distinctive pattern of clinical features which include low birth weight, congenital heart disease, developmental delay and a characteristic behaviour profile with hyperactivity and impulsiveness. Patients with terminal deletion 8p frequently have heart defects, especially atrioventricular septal defect and this led to the suggestion that this chromosome region may harbour a gene (GATA4, OMIM 600576) important in heart development. Studies with model vertebrate systems have implicated GATA4, transcription factor as a critical regulator of cardiac gene expression and development. It should be noted that not all patients with proven deletion of 8p23.1 have cardiac anomalies. Possible explanations are that the patients without cardiac pathology are not deleted for GATA4 or, compensatory increases in

Fig. 1. Partial karyotypes of the GTG banded chromosomes and ideograms of a proband showing de novo derived chromosome 8.

Fig. 2. Proband FISH analysis (A) using centromere probes 4 and 8 (D8Z2) and locus specific probe LSI WHS-4p16.3 and (B) using centromere probe 8 (D8Z2) and subtelomere probe 8p. D8S504 (Vysis/Abbott).
**TABLE 1**

**LIST OF CLINICAL SYMPTOMS CHARACTERISTIC FOR PARTIAL TRISOMY 4p AND PARTIAL MONOSOMY 8p**

<table>
<thead>
<tr>
<th>Partial trisomy 4p</th>
<th>Partial monosomy 8p</th>
<th>Our case der(8)t(4;8)(p16.1;p23.1)</th>
<th>Case of der(8)t(4;8)(p12;p23)</th>
</tr>
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**Craniofacial anomalies**
- Microcephaly, low hairline, hirsutism, low set and malformed ears, bulbose nose, broad nasal bridge, long eyelashes, synophrys, hypertelorism, micrognathia, pointed chin, short neck
- Microcephaly, craniofacial dysmorphism, high and narrow forehead, small eyes, strabismus, hypertelorism, epicanthal folds, long philtrum, short nose, small jaw, irregularly implanted teeth, micrognathia, thin upper lip, low set and malformed ears, narrow external ear canal, short neck, nystagmus
- Low hairline, hirsutism, narrow forehead, wide nasal bridge, anteverted nostrils, low set and malformed ears, small jaw
- Hirsutism, low hairline, synophrys, high arched eyebrows, short nose with a wide nasal bridge, anteverted nostrils, full cheeks, long philtrum, thin lips, flat palate, widely spaced teeth, low set ears

**Skeletal anomalies**
- Pointed chin, arachnodactyly, clinodactyly, rocker-bottom feet
- Clinodactyly, low inserted thumb, widely spaced nipples, rocker bottom feet, hypoplastic toenails
- Clinodactyly, widely spaced nipples, third toe low inserted
- Small hands with proximal placement of the thumbs, dystrophic nails, fifth finger clinodactyly, widely spaced nipples

**Cardiovascular anomalies**
- Atrial septal defect
- Atrioventricular septal defect, duc tus arteriosus, pulmonary valve stenosis, patent ductus arteriosus, isomerism of the atria, tetralogy of Fallots
- Atrial septal defect
- Mild hypertrophy of the heart

**Urogenital and renal anomalies**
- Shawl scrotum, cryptorchidism
- Hypospadias, undescended testis, cryptorchidism, horseshoe kidneys, bilateral ureteric reflux
- Vesicoureteral reflux grade III right side, bilateral inguinal hernia, diastasis rectus abdominis 3 cm, undescended right testicle (high in scrotum)
- Small clitoris

GATA5 or GATA6 may mitigate the effects of GATA4 deletion, and haploinsufficiency for other cardiac transcription factor genes (e.g. TBX5, NKX2–5) causes congenital heart disease. Alternatively, inherited mutations in other genes or stochastic events may impact on the severity of heart disease in patients haploinsufficient for GATA4. Deletion 8p23.1 should be considered in the differential diagnosis of cases suspected to have velocardiofacial syndrome. Intellectual disability is the most frequently reported developmental outcome. There does seem to be a relation between the size of the deleted region on chromosome 8 and the degree of intellectual disability, with more distal terminal deletions being associated with higher functioning.

On the other hand, more than 75 cases of trisomy 4p have been reported thus far, most of them due to unbalanced translocations. Trisomy 4p has been shown to cause specific phenotype associated with characteristic facial appearance, postnatal growth retardation and severe psychomotor retardation with or without seizures, microcephaly and various major and minor anomalies. The large variability of the phenotype in trisomy 4p syndrome may be explained by the variation in length and the breakpoint location of the duplicated segments on 4p.

To the best of our knowledge, until today there have been only few reports of a combination of duplication 4p16.1→4pter and deletion 8p23.1→8pter syndrome. With exception of microcephaly, synophrys, hypertelorism, retrognathia, pointed chin, short neck and rocker bottom feet, our proband had most of the clinical features associated with dup 4p syndrome. These included low hairline, hirsutism, wide nasal bridge, low set ears, clinodactyly, atrial septal defect and cryptorchidism. The variation in severity of phenotype may be related to such variables as age, sex and different size of chromosome segment involved in dup 4p syndrome, as well as the terminal loss of genetic material of the second chromosome involved in such an unbalanced translocation. The most of the cases of trisomy 4p have been due to unbalanced translocations. In half of the cases, an acrocentric chromosome was involved. The involved breakpoints vary between the cases, with consequently variation in phenotypes.

There are only few published cases with a derivate chromosome 8p and a partial trisomy 4p and monosomy...
REFERENCES

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SAŽETAK

Fenotip pacijenta s djelomičnom aneuploidijom često ima varijabilnu kliničku sliku ovisno o veličini kromosomskog segmenta uključenog u translokaciju. Prikazane su kliničke citogenetičke osobitosti dječaka starog pet mjeseci s duplikacijom dijela kromosoma 4p16.1→pter i s gubitkom dijela kromosoma 8p23.1→pter. Kariotip probanda određen je primjenom klasičnog GTG pruganja kromosoma i korištenjem FISH proba (lokus specifična proba za WHCR regiju, centromera 4, centromera 8, telomera 8p): 46,XY,der(8)t(4;8)(p16.1;p23.1).ish der(8)t(4;8)(D8S504–,WHCR+,D8Z2+)dn. Roditelji nisu u srodstvu i utvrđen im je normalan kariogram. Usporedili smo sličnost kliničkih osobitosti našeg pacijenta s ostalim pacijentima opisanim u literaturi koji imaju samo duplikaciju distalnog dijela 4p ili deleciju distalnog dijela 8p, ili sličnu kombinaciju nebalansiranog kariotipa.