BJMG 23 (1), 2020 • 99-102
DOI: 10.2478/bjmg-2020-0014
sciendo

CASE REPORT

PRENATAL DIAGNOSIS OF A *DE NOVO* PARTIAL TRISOMY 6q AND PARTIAL MONOSOMY 18p ASSOCIATED WITH CEPHALOCELE: A CASE REPORT

Karaman A[1,*], Karaman B[2], Çetinkaya A[1,3], Karaman S[4], Demirci O[5]

[*]**Corresponding Author:** Dr. Ali Karaman, Genetics Diagnosis Center, University of Health Sciences, Zeynep Kamil Women and Children Training and Research Hospital, Dr. Burhanettin Üstünel Street, Istanbul, Turkey. Tel.: +90-216-391-0680. Fax: +90-216-391-0690. E-mail: alikaramandr@hotmail.com

ABSTRACT

A 28-year-old woman underwent amniocentesis at 18 weeks' gestation upon detection of increased fetal nuchal fold and parietal cephalocele on the second trimester ultrasound examination. Prenatal microarray showed a *de novo* unbalanced translocation resulting in a gain in 6q and loss in 18p. A female infant was delivered at 38 weeks' gestation. At birth, cephalocele and webbed neck were noted as major dysmorphic features. The case presented here shows how a combination of different genetic studies is used to accurately elucidate a chromosomal anomaly in a prenatal setting.

Keywords: 18p Monosomy; Prenatal diagnosis; 6q Trisomy.

INTRODUCTION

Partial trisomy of distal 6q is a very rare event with only a few cases described in the current literature [1]. It was first reported in 1963 as a distinct phenotype [1]. Common phenotypic features among children with 6q25-q27 partial trisomy include cranial anomalies, facial dysmorphism, anterior webbing of the neck, cardiac anomalies, joint contractures, and profound psychomotor retardation [2,3].

On the other hand, a partial or complete 18p deletion is more common [4]. It was first reported in 1963 characterized as a distinct syndrome presenting with developmental delay, facial dysmorphism, short stature, and mental retardation [1,5]. Movement disorders including dystonia, myoclonus, ataxia, and tic disorder have been reported in individuals with the 18p deletion syndrome [6-8]. Here, we report parietal cephalocele in a fetus with the combined chromosomal anomaly: duplication of 6q25.3-q27 and deletion of 18p11.32-p11.31.

Case Presentation. A healthy 28-year-old woman was referred to the Perinatalogy Department, Zeynep Kamil Women and Children Training and Research Hospital, Istanbul, Turkey, at 13 weeks' gestation for routine fetal ultrasound screening. Fetal ultrasound demonstrated an increased fetal nuchal translucency with a suspected parietal cephalocele, which was confirmed in later ultrasound studies and asymmetric cerebellar peduncles were observed as an additional finding. The baby was delivered by cesarean section at 38 weeks and physical examination confirmed the parietal cephalocele (Figure 1) and facial dysmorphism. This is the third pregnancy of the mother. She has a healthy child and had a pregnancy terminated at 30 weeks' gestation due to Dandy-Walker malformation as well as other congenital anomalies. The non consanguineous couple has no family history of any other congenital malformations.

During her pregnancy, she was referred to the genetics department, and amniocentesis was performed for karyo-typing at 18 weeks' gestation. Chromosome analysis showed an extra substance on 18p. In order to elucidate the origin of the extra genetic material, array comparative genomic hybridization (aCGH) was performed. Briefly, fetal DNA was extracted from the cultured amniotic fluid sample using the Puregene Genomic DNA Purification Kit (Qiagen Inc., Valencia, CA, USA), and studied by whole-genome aCGH using a custom 135K feature platform (de-

[1] Genetics Diagnosis Center, University of Health Sciences, Zeynep Kamil Women and Children Training and Research Hospital, Istanbul, Turkey

[2] Department of Medical Genetics, Istanbul University, Istanbul Faculty of Medicine, Istanbul Turkey

[3] Department of Medical Genetics, Hacetepe University, Faculty of Medicine, Ankara, Turkey

[4] Department of Anesthesia and Reanimation, University of Health Sciences Ümraniye Training and Research Hospital, Istanbul, Turkey

[5] Perinatalogy Unit, University of Health Sciences Zeynep Kamil Women and Children Training and Research Hospital, Istanbul, Turkey

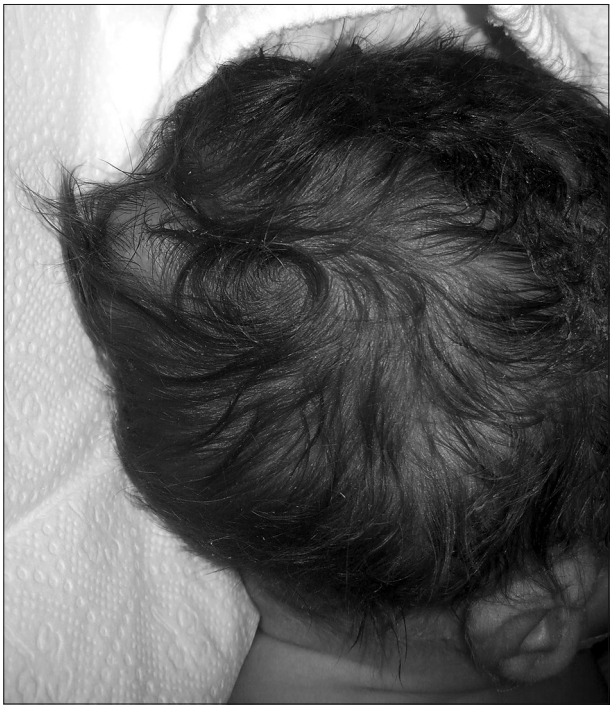

Figure 1. Parietal cephalocele of the affacted individual.

signed by Signature Genetics Laboratories, Spokane, WA, USA; manufactured by Roche NimbleGen, Madison, WI, USA). The aCGH revealed ~12 Mb gain in 6q25.3-q27 region and ~8 Mb loss within 18p11.32-p11.31 [Figure 2(A) and 2(B)]. Fluorescence *in situ* hybridization (FISH) with probes specific to the subtelomeric regions of chromosomes 6q and 18p confirmed the unbalanced translocation (Abbott Molecular, Des Plaines, IL, USA). Assessment of parental chromosomes 6q and 18p by FISH analysis was normal, implying a *de novo* chromosomal abnormality in the fetus. All of studies performed can be summarized as: 46,XX,der(18)t(6;18)(q25.3;p11.31)dn.ishder (18)t(6;18)(qter+,pter-). arr[hg19]6q25.3q27(158,900,454-170,926,593)X3, 18p11.32p11.31(311,463-8,014,484)X1.

DISCUSSION AND CONCLUSION

Unbalanced chromosomal translocations are among the many rearrangements encountered in the prenatal genetic diagnosis. During gametogenesis, human chromosomes occasionally acquire *de novo* structural alterations. Non allelic homologous recombination, non homologous end joining, and replication-based errors are known to underlie *de novo* rearrangements [9]. In addition, catastrophic cellular events designated as chromothripsis and chromoanasynthesis have recently been implicated in complex rearrangements involving one or a few chromosomes [9-13].

The cooccurrence of multiple *de novo* intrachromosomal rearrangements is an uncommon phenomenon that cannot be explained by the aforementioned mechanisms. In 2017, Liu *et al.* [14] analyzed copy number variations (CNVs) in ~60,000 individuals and identified five cases with 5-10 *de novo* CNVs. Interestingly, most of these multiple *de novo* CNVs (mdnCNVs) are large non recurrent duplications, a rare type of human chromosomal rearrangement [13,14]. Liu *et al.* [14] proposed that during oogenesis and early embryogenesis, an "organismal CNV mutator phenotype" could create mdnCNVs.

This mutator phenotype appears to be driven by an unknown factor that is activated in primary oocytes and subsequently lost or silenced in zygotes before the 4- or 8-cell stage. Notably, one of the five cases (mCNV7) carried CNVs only on the paternally derived chromosomes, raising the possibility of etiological heterogeneity among mdn CNVs [14].

Partial chromosomal deletions and duplications, collectively CNVs, are a major contribution to the genome variability among individuals [15-17] and can either be pathogenic or without clinical consequences. A particular class, the microdeletions and microduplications, which alter <5 Mb, have been extensively associated with developmental delay and intellectual disability. There is a

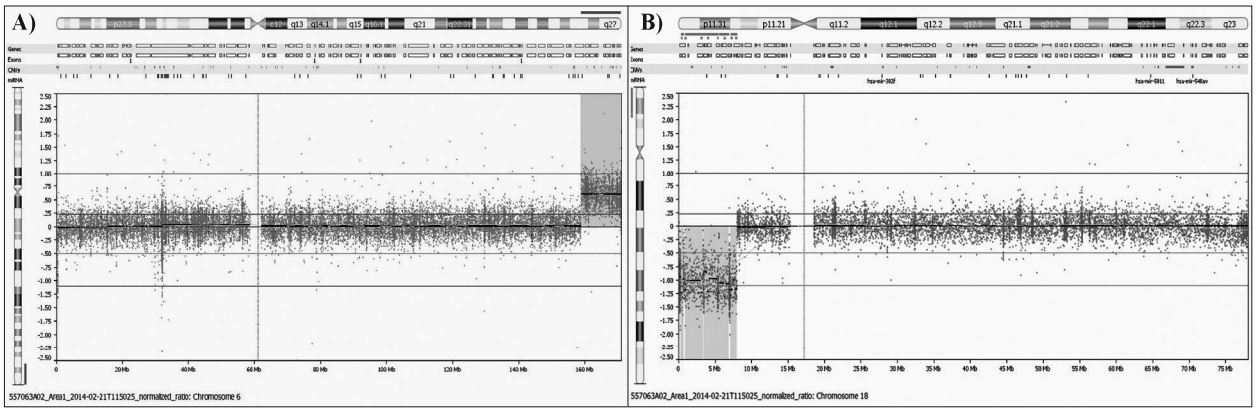

Figure 2. The aCGH showing the loss of 18p11.32-p11.31 (A) and gain of 6q25-27 (B) resulting from the *de novo* unbalanced translocation in the affected individual.

continuous spectrum of phenotypic effects of CNVs, from adaptive traits, to underlying cause of disease, to embryonic lethality [18].

Here, the clinical findings and genetic studies performed to elucidate such a *de novo* structural chromosomal anomaly are discussed. The duplication of distal 6q is a well-recognized postnatal phenotype. Common phenotypic features among children with 6q25-qter partial trisomy include cranial anomalies, facial dysmorphism (slanting palpebral fissures, telecanthus, micrognathia, carp-shaped mouth), anterior webbing of the neck, cardiac anomalies, and joint contractures; and profound psychomotor retardation [1-3]. However, prenatal dysmorphic features of trisomy 6q22.2-q27 was first reported in 1997 in a fetus with absent cerebellar vermis, thick nuchal folds, bilateral hydronephrosis, ascites, bilateral clubfeet, distal arthrogryposis, atrial septal defect, patent ductus arteriosus, and ambiguous genitalia in perinatal ultrasound [19]. All findings with the exception of absent cerebellar vermis were confirmed postnatally. The 6q22-qter duplicated region is substantially larger than the gain on chromosome 6 in the case presented here. The case had increased fetal nuchal fold and asymmetric cerebellar peduncles.

The 18p deletion syndrome has an incidence of about 1:50,000 live births, with more than 150 cases reported to date [20,21]. Although approximately 66.0-89.0% of the cases occur as direct *de novo* deletion of 18p, some are part of a complex translocation or inversion event or even result from unbalanced transmission of a balanced chromosomal event from the parents [20,21]. The uncommon familial transmission mostly involves the maternal chromosome [21]. Deletion breakpoint and clinical phenotypes associated with 18p deletion syndrome is heterogeneous. Associated clinical spectrum mostly involves developmental delay, holoprosencephaly (HPE), facial dysmorphism, short stature, mild to moderate cognitive impairment, speech and language problems, movement disorders including dystonia, myoclonus, ataxia, and tics [20-22]. Our case had facial dysmorphism and parietal cephalocele.

The case presented here does not completely overlap with defined features of either duplication of distal 6q or 18p deletion syndrome, but parietal cephalocele is a midline cranial defect similar to HPE. About 10.0-15.0% of individuals with 18p deletion have HPE [21]. However, deletion of the *TGIF1* gene in 18p11.3 is linked to expression of HPE only in some cases with *TGIF1* deletion suggests that other genetic and environmental factors are involved [23]. It may be possible that in certain conditions, deletion of *TGIF1* gene may also lead to other cranial midline defects, as exemplified by the case presented here. Further investigation is needed to test this possibility.

In prenatal diagnosis, the less expensive conventional karyotyping is the most commonly used test in Turkey. On the other hand, more recently-developed microarray analysis can detect chromosomal imbalances overcoming the limitations of resolution and banding quality that are inherent in conventional karyotype analysis, while not showing how genomic loci are involved [24-26]. Here, the combination of both conventional karyotyping and aCGH suggested an unbalanced translocation and FISH testing confirmed the structural variant, also creating an opportunity for easy screening of the parents for this particular structural variant. Thus, in the age of microarray, we highlight the importance of offering several modalities of genetic tests to patients for delivering a more complete prenatal genetic diagnosis. In conclusion, this study identifies a rare *de novo* 12 Mb terminal gain of 6q in conjunction with 8 Mb deletion of terminal 18p in a fetus and links this structural chromosomal anomaly to parietal cephalocele.

Acknowledgments. We kindly thank the family for their participation in this study.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. De Grouchy J, Lamy M, Theffry S, Arthuis M, Salmon C. Dysmorphic complex with oligophrenia: Deletion of short arms of a chromosome 17-18. Comptes Rendus de l'Académie des Sciences (Paris). 1963; 257(6): 3098-3102.
2. Goh DL, Tan AS, Chen JY, van den Berghe JA. Dysmorphic sibs trisomic for the region 6q22.11?6q23.3. J Med Genet. 2000: 37(11): 889-892.
3. Pivnick EK, Qumsiyeh MB, Tharapel AT, Summitt JB, Wilroy RS. Partial duplication of the long arm of chromosome 6: A clinically recognizable syndrome. J Med Genet. 1990; 27(8): 523-526.
4. Wester U, Bondeson M-L, Edeby C, Anneren G. Clinical and molecular characterization of individuals with 18p deletion: A genotype-phenotype correlation. Am J Med Genet A. 2006; 140A(11): 1164-1171.
5. Hasi-Zogaj M, Sebold C, Heard P, Carter E, Soileau B, Hill A, *et al.* A review of 18p deletions. Am J Med Genet C Semin Med Genet. 2015;169(3): 251-264.
6. Graziadio C, Rosa RFM, Zen PRG, Pinto LL, de C, Barea LM, Paskulin GA. Dystonia, autoimmune disease and cerebral white matter abnormalities in a patient with 18p deletion. Arq Neuropsiquiatr. 2009; 67(3A): 689-691.

7. Postma AG, Verschuuren-Bemelmans CC, Kok K, van Laar T. Characteristics of dystonia in the 18p deletion syndrome, including a new case. Clin Neurol Neurosurg. 2009; 111(10): 880-882.
8. Kowarik MC, Langer S, Keri C, Hemmer B, Oexle K, Winkelmann J. Myoclonus-dystonia in 18p deletion syndrome. Mov Disord. 2011; 26(3): 560-561.
9. Weckselblatt B, Rudd MK. Human structural variation: mechanisms of chromosome rearrangements. Trends Genet. 2015; 31(10): 587-599.
10. Kloosterman WP, Guryev V, van Roosmalen M, Duran KJ, de Bruijn E, Bakker SC, *et al.* Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline. Hum Mol Genet. 2011; 20(10): 1916-1924.
11. Liu P, Erez A, Nagamani SC, Dhar SU, Kołod-ziejska KE, Dharmadhikari AV, *et al.* Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. Cell. 2011; 146(6): 889-903.
12. Kloosterman WP, Tavakoli-Yaraki M, van Roosmalen MJ, van Binsbergen E, Renkens I, Duran K, *et al.* Constitutional chromothripsis rearrangements involve clustered double-stranded DNA breaks and nonhomo-logous repair mechanisms. Cell Rep. 2012; 1(6): 648-655.
13. Collins RL, Brand H, Redin CE, Hanscom C, Antolik C, Stone MR, *et al.* Defining the diverse spectrum of inversions, complex structural variation, and chromothripsis in the morbid human genome. Genome Biol. 2017; 18(1): 1158-1166.
14. Liu P, Yuan B, Carvalho CMB, Wuster A, Walter K, Zhang L, *et al.* An organismal CNV mutator phenotype restricted to early human development. Cell. 2017; 168(5): 830-842.
15. Iafrate AJ, Feuk L, RiveraMN, Listewnik ML, Donahoe PK, Qi Y, *et al.* Detection of large-scale variation in the human genome. Nat Genet. 2004; 36(9): 949-951.
16. Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, *et al.* Large-scale copy number polymorphism in the human genome. Science. 2004; 305(5683): 525-528.
17. Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, *et al.* Global variation in copy number in the human genome. Nature. 2006; 444(7118): 444-454.
18. Hurles ME, Dermitzakis ET, Tyler-Smith C. The functional impact of structural variation in humans. Trends Genet. 2008; 24(5): 238-245.
19. Kulharya AS, Carlin ME, Stettler RW, Huslig M, Kukolich MK, Garcia-Heras J. Prenatal diagnosis of a de novo trisomy 6q22.2-6qter and monosomy 1pter→1p36.3. Case report with a 2-year follow-up and a brief review of other prenatal cases of partial trisomy 6q. Clin Genet. 1997; 51(2): 115-117.
20. Brenk CH, Prott E-C, Trost D, Hoischen A, Walldorf C, Radlwimmer B, *et al.* Towards mapping phenotypical traits in 18p-syndrome by array-based comparative genomic hybridization and fluorescent in situ hybridization. Eur J Hum Genet. 2006;15(1): 35-44.
21. Bangma M, Lunshof S, Opstal DV, Galjaard RJ. Prenatal diagnosis of alobar holoprosencephaly (HPE), cyclopia, proboscis, and isochromosome 18q in the second trimester. Am J Perinatol Rep. 2011;1(2): 73-76.
22. Esposito F, Addor MC, Humm AM, Vingerhoets F, Wider C. GNAL deletion as a probable cause of dystonia in a patient with the 18p-syndrome. Park Relat Disord. 2014; 20(3): 351-352.
23. Recalcati MP, Valtorta E, Romitti L, Giardino D, Manfredini E, Vaccari R, *et al.* Characterisation of complex chromosome 18p rearrangements in two syndromic patients with immunological deficits. Eur J Med Genet. 2010; 53(4): 186-191.
24. Wapner RJ, Martin CL, Levy B, Ballif BC. Eng M, Zachary JM, *et al.* Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012; 367(23): 2175-2184.
25. Hillman SC, McMullan DJ, Hall G, Togneri FS, James N, Maher EJ, *et al.* Use of prenatal chromosomal microarray: prospective cohort study and systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2013; 41(6): 610-620.
26. Yatsenko SA, Davis S, Hendrix NW, Surti U, Emery E, Canavan T, *et al.* Application of chromosomal mi-croarray in the evaluation of abnormal prenatal findings. Clin Genet. 2013; 84(1): 47-54.