Prenatal Diagnosis of *De Novo* Proximal Interstitial 9Q(9Q22.3→31.3) Deletion with a Novel Presentation: Case Report

Yeni Bir Vakada *De Novo* Proksimal İnterstisiyel 9Q(9Q22.3→31.3) Delesyonunun Prenatal Tanısı

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ABSTRACT Currently, there are only few cases reported about prenatal findings of proximal interstitial deletions of 9q and prenatal manifestations of this deletion are still unclear. Amongst small number of reported cases this one is the first report of proximal interstitial *de novo* 9q deletion presenting with low maternal serum plasenta associated plasma protein A (PAPP-A) levels at first trimester screening and ultrasonographic appearance of talipes equinovarus and frontoparietal flattening that may help to elucidate the prenatal presentation patterns of this rare chromosomal anomaly. Here we present a case with *de novo* interstitial deletion of 9q (9q22.3→31.3) prenatally presented by a transient increase in NT thickness, frontoparietal flattening, low PAPP-A levels and talipes equinovarus at first pregnancy of a 28 years old patient to incorporate the current knowledge about prenatal presentation of this rare chromosomal anomaly. This rare genetic anomaly could be detected, at least could be suspected on routine first trimester prenatal screening tests if appropriate findings are observed. Early detection of this anomaly gives an opportunity for early termination for termination demanding families.

Key Words: Nuchal translucency measurement; clubfoot; chromosome deletion

ÖZET Proksimal interstisiyel 9q delesyonlarının prenatal bulguları ile ilgili az sayıda vaka bildirimi bulunmaktadır ve bu delesyonun prenatal manifestasyonları henüz aydınlatılamamıştır. Bildirilen az sayıda vaka arasında bu olgu ilk trimester tarama testinde düşük PAPP-A düzeyleri, talipes equinovarus ve fronto-parietal düzleşme görülen ilk proksimal interstisiyel 9q delesyonudur ve bu nadir kromozomal anomalinin prenatal manifestasyonlarını ayıdınlatma konusunda yardımcı olabilir. Bu nadir kromozomal anomalinin prenatal prezentasyon paternlerine ilişkin mevcut bilgi havuzuna katkıda bulunmak amacıyla burada, 28 yaşında primigravid bir hastada nukal kalınlıkta geçici artış, fronto-parietal düzleşme, düşük PAPP-A düzeyleri ve talipes equinovarus birlikteliği ile prezente olan 9q (9q22.3→31.3) *de novo* interstisiyel delesyonu olgusu sunulmaktadır. Uygun bulguların gözlenmesi halinde ilk trimester tarama testlerinde bu nadir genetik anomalinin saptanması ya da şüphelenilmesi mümkün olabilir. Bu anomalinin erken saptanabilmesi gebelik terminasyonu talebi olacak hastalara daha erken dönemde hem obstetrik hem de emosyonel açılardan daha az travmatik gebelik terminasyonu olanağı sağlayacaktır.

Anahtar Kelimeler: Nukal kalınlık ölçümü; çarpık ayak; kromozom delesyonu

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There are only few cases reported about *de novo* proximal interstitial 9q deletions and its prenatal manifestations. Deletions in the long arm of chromosome 9 might include 9q 22.3 region that was occupied by drosophila patched gene (PTCH). Mutations in this gene is known to be responsible from autosomal dominantly inherited condition, Gorlin-Goltz

syndrome (nevoid basal cell carcinoma syndrome), that presents with multiorgan anomalies predominates in skin, skeletal system, genitourinary system and central nervous system including basal cell carcinomas, odontogenic keratocysts, medulloblastomas, cryptorchidism and ovarian fibromas. Early detection of this anomaly may provide an opportunity for early termination for termination demanding couples so tracing the manifestations of this rare genetic anomaly in routine first trimester screening could have value.

Here we present a case with *de novo* interstitial deletion of 9q (9q22.3→31.3) prenatally presented by a transient increase in nuchal translucency (NT) thickness, fronto-parietal flattening, low PAPP-A levels and talipes equinovarus at first pregnancy of a 28 years old patient.

CASE REPORT

A 28 years old healthy primigravida woman admitted to clinic for routine pregnancy follow-up. Her spouse was 29 years old. Both of the spouses has no family history of Gorlin-Goltz syndrome, any other chromosome disorders or congenital malformations and both of them were free from any other medical co-morbidities such as diabetes, hypertension or smoking. Couple was not consanguineous. The patient has not described any exposure to known or possible teratogens. At 12 weeks gestation first trimester screening test was performed. Maternal serum placenta associated plasma protein (PAPP-A) level was found compatible with 0,60 multiples of the median (MoM) (590 ng/mL) and maternal serum total beta human chorionic gonadotropin (MShCG) level was found compatible with 1.07 MoM (91.6 IU/mL). Ultrasound imaging revealed an increase in NT thickness that was measured compatible with 2.44 MoM (3.6 mm). At this examination, nasal bone was able to be defined and crown-rump-length of the fetus was measured compatible with 12 weeks 1 day gestation (55 mm). The risk of Down syndrome was estimated as 1/104. Estimated risk for trisomy 18 and trisomy 13 was 1/302. Chorionic villous sampling (CVS) was offered to the patient however the couple refused to underwent a CVS owing to the possible risks of the procedure. Ultrasonography examination was repeated at 14 weeks gestation and subcutaneous fluid accumulation was observed to be disappeared. NT was measured to be within normal limits (1.4 mm) according to the gestational age. However this ultrasound examination also revealed talipes equinovarus deformity (Figure 1) at both feet of the fetus in addition to slight flattening at frontoparietal region (Figure 2). Amniocentesis was of-

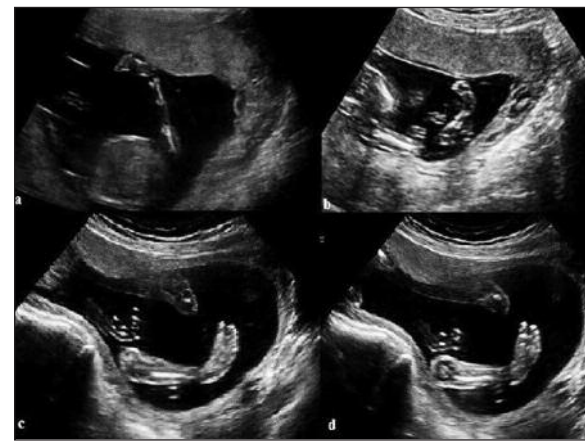

FIGURE 1: Talipes equinovarus deformity detected on ultrasound examination on 14 weeks gestation **(a,b)** and 20 weeks 4 days gestation **(c,d)**.

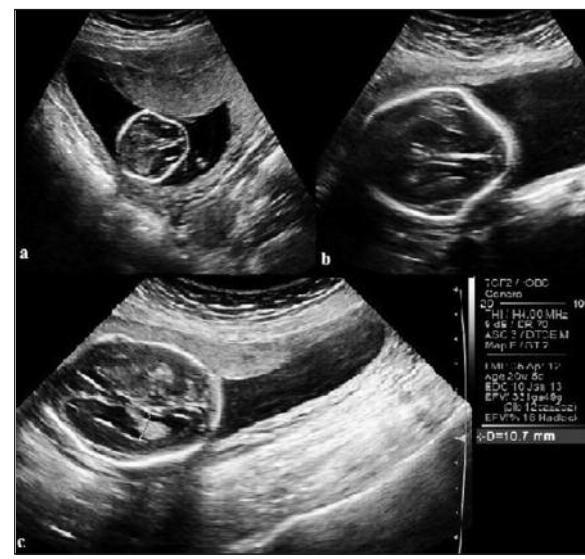

FIGURE 2: Frontoparietal flattening observed by ultrasound examination at 14 weeks gestation **(a)**. At repeat ultrasound examination performed at 20 weeks 4 days gestation frontoparietal flattening could be observed to remain **(b)** besides a slight ventriculomegaly **(c)**.

fered and couple consented the procedure. Amniocentesis was performed at 15 weeks 5 days gestation and a chromosomal structure of 46 XY del (9)(q21::q31→qter) was revealed (Figure 3). To determine the origin of the deletion that has been detected in the long arm of ch9, chromosome analysis was applied to couple and both partners were shown to have normal chromosome structures indicating a *de novo* mutation of 9q(9q22.3→31.3) in fetus. Ultrasound examination was repeated at 20 weeks 4 days gestation. This examination revealed stepping at parietal region, a slight increase in right lateral ventricle diameter (10.7 mm) besides the fronto-parietal flattening and bilateral talipes equinovarus deformity (Figure 1, 2, 4). Owing to anomalies detected on ultrasound examination and the deletion of 9q(9q22.3→31.3), including the region of 9q 22.3 that drosophila patched gene (PTCH) was occupying whom mutation or deletion is responsible for Gorlin-Goltz syndrome, pregnancy termination was offered to couple. Couple decided to terminate the pregnancy at 20 weeks 6 days gestation. A 310 g male fetus was delivered by vaginal route.

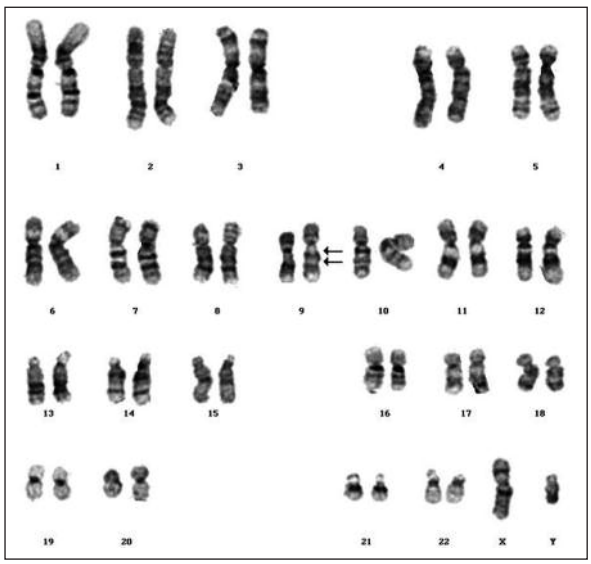

FIGURE 3: Proximal interstitial deletion of 9q (9q22.3→31.3).

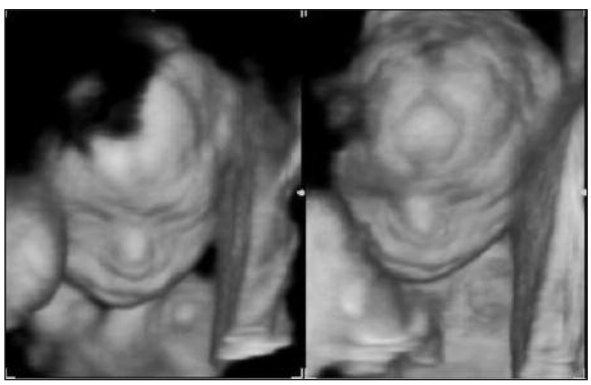

FIGURE 4: 3D ultrasound image of fetal head from anterior aspect.

Ethical issues: A written informed consent was obtained for publication of this case report.

DISCUSSION

There are only few cases reported about *de novo* proximal interstitial 9q deletions and its prenatal manifestations. Increase in NT thickness at first trimester, cystic hygroma, fetal hydrops, low level of maternal serum alpha-fetoprotein and high level of MShCG at second trimester, overgrowth, macrocephaly, chylothorax and intracardiac tumors at third trimester were previously reported in fetuses with proximal interstitial 9q deletions.[1-4] This case demonstrates that chromosome 9q deletions could also be presented by a transient increase in NT thickness and low levels of PAPP-A at first trimester screening besides skeletal deformities like club foot and cranial abnormalities like frontoparietal flattening. These indicate some skeletal and cranial malformations could be seen as early as 14 weeks gestation in cases with proximal interstitial *de novo* deletions of 9q. One of the salient points reported in some of the previous cases of 9q deletions was the normal karyotype result achieved in initial analysis.[1,5] Consecutive analysis were performed with high resolution karyotyping in these previously presented cases thereby features that could raise clinical suspicion about chromosal abnormalities even in the cases with normal initial karyotype analysis could have value. Early detection of these skeletal and cranial malformations as well as the low levels of PAPP-A levels at first trimester besides the transient increase in NT thickness could be valuable to raise suspicion, and for the opportunity of pregnancy termination in case of the detection of a chromosomal anomaly.

Talipes equinovarus (club foot) is a congenital anomaly characterized by invertion and medial rotation of the foot that occurs in 1-3 cases in every 1000 birth.[6] Approximately 1/3 of the cases with talipes equinovarus are isolated cases.[7] However this anomaly could accompany with other malformations involving genitourinary, cardiovascular, musculoskeletal systems and with chromosomal disorders. Relationship between isolated talipes equinovarus and chromosomal aberrations is still uncertain due to small sample sizes and possible biases of the studies.[8,9] Isolated talipes equinovarus has an estimated aneuploidy risk ranging from 1.7% to 3.6% and although karyotyping for isolated cases has been found unreasonable by many authors this issue is still controversial.[8] Complex talipes equinovarus defines the cases with accompanying anomalies. Table 1 summarizes the aneuploidies detected with isolated and complex cases of talipes equinovarus amongst available studies. These studies observed a wide range of structural anomalies accompanying complex talipes equinovarus, including cystic hygroma, ventriculomegaly, omphalocele, neural tube defects, cardiac abnor-

TABLE 1: Summary of chromosomal aberrations accompanying isolated and complex talipes equinovarus.

Author	N of cases (isolated/complex)	N of chromosomal anomaly	Chromosomal anomaly	N of karyotyped cases (t/c)*
Rijhsinghani et al. (1998) [9]	35 (7/28)	5	4 trisomy 18 1 46,XY,-3,+der(3)t(3;6)	(25/22)/35
Carrol et al. (2001)[12]	76 (24/52)	9	6 trisomy 18 1 triploidy 1 45,XO 1 47 XXY†	(56/53)/113
Bakalis et al. (2002)[13]	107 (58/49)	9	7 trisomy 18 1 trisomy 21 1 triploidy	N/A
Mammen et al. (2004)[14]	87 (17/60)	15	8 trisomy 18 3 abnormal ch22 1 trisomy 21 1 triploidy 1 abnormal sex chromosome 1 trisomy 4 and monosomy 18	(51/?)/87
Bar-On et al. (2005)[15]	52 (31/20)	3	1 trisomy 18 1 deletion on long arm of 8q 1 47, XYY	(25/?)/52
Offerdal et al. (2007)[16]	113 (55/58)	15	10 trisomy 18 1 trisomy 13 1 ch 13 del 1 triploidy 69,XXX 1 triploidy 47, XYY† 1 trisomy 21†	(56/53)/113
Canto et al. (2008)[17]	42 (28/14)	3	1 trisomy 18 1 triploidy 1 47, XYY†	(26/14)/42
Lauson et al. (2010)[8]	65 (65/0)	0	-	41/65

*; "t": total number of cases karyotyped, "c": karyotyped cases with complex talipes equinovarus.

†; Anueploidies diagnosed in cases with isolated talipes equinovarus.

malities, polyhydramniosis and renal disorders. In this presented case fronto-parietal flattening, a slight ventriculomegaly and a transient increase of NT thickness were accompanying talipes equinovarus so it could be interpreted within the complex form of anomaly. In existing studies majority of the cases were defined between 16th and 37th gestational weeks however in our case, talipes equinovarus was defined as early as 12 weeks 1 day gestation. There are few cases reported that was detected such early in the course of pregnancy follow-up. This could be due to the early presentation of the anomaly in this rare aneuploidy as well as the technical improvements in ultrasound imaging. Genetic anomalies accompanying with talipes equinovarus seems scattered and a suspicious genetic region that could take part in etiology was unable to be determined currently despite the novel contribution of this case. However predominance of trisomy 18 amongst detected chromosomal aberrations accompanying talipes equinovarus (mostly the complex form) in existing studies could be observed at Table 1.

While some of the cases about 9q deletions exhibit male fetuses with genital anomalies such as ectopic testicles, hypoplastic scrotum and penis, L'Hérmine et al. presented a case with 9q (9q22.2→31.1) deletion and female pseudohermaphroditism.[10] Authors of the publication suggested that sexual development could be related within a region of 9q (9q22.2→31.1). Despite the fact that high frequency of genitourinary anomalies seen in Gorlin-Goltz syndrome supports this hypothesis, in our case with 46XY del 9q(9q22.3→31.3) chromosomal structure, normal male internal and external genitalia were found, suggesting that there might be other genetic regions or factors that may affect sexual development or some probably milder forms of genital malformations might become macroscopically evident in later phases of fetal or extra uterine life. Relatively early termination of pregnancy in our case might hinder the malformation to become evident.[11-17]

An increased NT thickness could accompany with various uncommon aneuploidies. This presented case showed an early resolution of increased NT as in the case with 9q(9q21.1→22.2) deletion reported by Chen et al. and as in the case with trisomy 18 reported by Celentano et al.[2,11]

Whilst supporting the evidence about prenatal presentation of proximal interstitial 9q deletions with a transiently increased NT thickness, this case incorporates the current literature by presenting low PAPP-A levels at first trimester screening and structural deformities detected by ultrasonography such as talipes equinovarus and frontoparietal flattening in prenatal period in a case with proximal interstitial *de novo* 9q(9q22.3→31.3) deletion.

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