A Saudi Patient with an Interstitial Deletion of Short Arm of Chromosome 3 (p13 to p21) and its Association with Joubert’s Syndrome Features

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ABSTRACT
We report a case of 4 weeks old girl with a de novo interstitial deletion of the short arm of chromosome 3 (p13-p21) and clinical findings typical of proximal 3p deletion together with heart defects, choanal atresia, ear anomalies, central nervous system anomalies, renal anomalies and associated Joubert’s syndrome (JS). Family history is unremarkable and parenteral chromosomes were normal. The clinical manifestations of the patient are compared with those of 11 patients previously described with a proximal 3p deletion. The additional JS features associated with this syndrome were described. This is the first case report in English literature describing 3p deletion associated with additional JS features.

Key words: Chromosome 3p, interstitial deletion, Joubert’s syndrome, multiple congenital anomalies

INTRODUCTION
Interstitial deletion of chromosome 3 is rare. To our knowledge, there are only 11 cases of 3p deletion reported in English literature. We report a girl with interstitial deletion of the short arm of chromosome 3 (46, XX, del 3 (p13 p21)) with features of Joubert’s syndrome (JS). JS is a rare brain malformation characterized by the absence or underdevelopment of the cerebellar vermis - an area of the brain that controls balance and coordination.

CASE REPORT
This Saudi female baby born to G4 P3 mother at 38 weeks gestation by emergency caesarian section due to fetal bradycardia. Parents’ were non-consanguineous Saudi couple and the mother is 34-year-old and father 40-year-old. Family history was unremarkable. During antenatal period, there was no history of medication intake or exposure to radiation. Birth weight was 1980 g (10 centile); length: 43 cm (10 centile); head circumference: 31.5 cm (10 centile). After birth, severe respiratory distress was encountered, which required intubation and mechanical ventilation. Bilateral choanal atresia diagnosed and surgical repair of choanal atresia was performed at 1 week. Poor and uncoordinated sucking was noticed, which necessitated tube feeding initially, and later on gastrostomy tube feeding. Echocardiographic revealed patent ductus arteriosus, atrial and ventricular septal defects. Renal ultrasonogram showed hydronephrosis of both kidneys, but voiding cystourethrogram revealed no reflux. The subject had a broad fore head, low frontal hair line, hypertelorism, a short broad based nose with anteverted nares, bilateral microphthalmia, a short philtram, high and vaulted palate, small low set ears with hypoplasia of the upper part of helix. Finger positioning showed camptodactily of the second finger with the third and fourth finger overlapping the index finger. Hands were positioned in an ulnar deviation and transverse crease was found in the palms. She had rocker bottom feet, sandal gaps bilaterally, Figures 1 and 2. The magnetic resonance imaging showed molar tooth sign, absence of vermis with partial agenesis of corpus colossum, Figure 3a and b. Analysis of G-banded chromosomes showed an interstitial deletion of p13 to p21 in the proximal short arm of chromosome 3, Figures 4 and 5. She could not be weaned from oxygen and also had recurrent pneumonia. Patient died at the age of 5 and 1/2 months due to Escherichia coli sepsis. Autopsy was not done due to religious obligations.

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DISCUSSION

To our knowledge, total of 11 cases of the proximal interstitial deletion of the short arm of chromosome 3 have been published, deletion of the short arm of chromosome 3 in association with JS was not reported.

Kumandas et al. reviewed the clinical characteristics of seven cases that fulfill the criteria of JS. JS is an autosomal-recessive disorder, characterized by hypotonia, ataxia, global developmental delay and molar tooth sign on magnetic resonance imaging. A variety of abnormalities described in children with JS, including abnormal breathing,
abnormal eye movements, a characteristic facial appearance, delayed language, hypersensitivity to noise, autism, ocular and oculomotor abnormalities, meningoencephaloceles, microcephaly, low-set ears, polydactyly, retinal dysplasia, kidney abnormalities (renal cysts), soft-tissue tumor of the tongue, liver disease and duodenal atresia. Even within siblings the phenotype may vary, making it difficult to establish clinical diagnostic boundaries of JS.

Dagmar Wieczorek et al. reported a case of interstitial deletion of the short arm of chromosome 3 and charge like phenotype association. Our patient has overlapping chromosomal breaking points and strikingly similar facial appearance; in addition, our patient had bilateral hydrourephrosis, but no coloboma of iris. Neri et al. reported a proximal 3p deletion phenotype including four major manifestations; the first being a characteristic facial phenotype was characterized by a low fore head, epicanticth folds hypertelorism, broad nasal bridge, short stubby nose with anteverted nares, short philtrum, small mouth, micrognathia, low set and dysplastic ears. Thus, in comparison with proximal 3p deletion, our patient has recognizable facial phenotype. In 3 of the 5 reports with the proximal break points in 3p13 no photo of described patient is included in the paper., the patient of Kogame and Kudo and Wyandt et al. illustrated, but show a different facial phenotype. Neri et al. reported 3 major manifestations of the proximal 3p deletion phenotype are limitations of joint movements, deformities, including ulnar deviation of the hands, comptodactyly and calcaneous feet and delayed psychomotor development. Our patient had all these findings.

Other reported anomalies such as heart defects and intestinal malformations including agenesis of gall bladder, posteriorly placed anus and meckel's diverticulum seems to be non-specific. Being also present in other chromosomal rearrangements, they do not defining the proximal interstitial 3p phenotype. In addition to the clinical manifestations mentioned above, which fit into the spectrum of an interstitial deletion of 3p, our patient had bilateral choanal atresia, congenital heart disease (patent ductus arteriosus, atrial and ventricular septal defects). She had also growth retardation, bilateral hydrourephrosis, low set, dysplastic protruding ears, absence of cerebellar vermis and partial agenesis of corpus colossum, which is consistent with JS. None of the reported patients with interstitial deletion 3p had signs of JS. Wieczorek et al. reported its association with charge syndrome. Lin et al. reported a case of direct interstitial duplication of chromosome 4 from 4q28.1 to 4q35 associated with bilateral choanal atresia. The child also had dysmorphic features including a broad nasal bridge, telecanthus, downward slanting palpebral fissures, prominent ears, and mild bilateral clinodactyly of the fifth fingers and bilateral hypoplasia of the second to fifth toenails. There was also a slightly dilated renal collecting system. At the age of 2.5 years, he had moderate global developmental delay, short, wide, tapering fingers and short toes with hypoplastic toenails.

Petek et al. reported a case of a 22-month-old boy with developmental and psychomotor retardation as well as craniofacial dysmorphism, including a cleft lip. Analysis of G-banded chromosomes of the propositus showed a de novo interstitial deletion of the short arm of chromosome 3, del (3) (p13p11).

Hertz reported de novo interstitial deletion of the short arm of chromosome 3 prenatally diagnosed in a male fetus, karyotype 46, XY, del (3) (pter—p14.2:p11—qter). The fetus had craniofacial dysmorphisms, a single transverse palmar crease, ulnar deviation in the wrists, cardiovascular anomalies, a slight ureteric dilatation and a mobile caecum. Short et al. reported deletions of 3p usually involve the terminal portion (3p25). An interstitial deletion of a proximal 3p segment (3p14) was detected at amniocentesis. The clinical and cytogenetic characteristics of this case and of three previously published cases are reviewed. Cardiovascular and gastrointestinal malformations have been reported.

Sichong et al. reported a girl with delayed growth in body height and weight, retarded psychomotor development, facial dysmorphism, high-arched palate, extension defects of elbows, and a probable hearing impairment is presented. A chromosome investigation by both conventional and high-resolution banding techniques revealed an apparently pure interstitial deletion of the proximal segment of the short arm of chromosome 3 (46, XX, del (3) (p11 p14.2) de novo). The paternal karyotype is 47, XY. The clinical features of the patient are compared with those of two previously reported cases in the literature with an interstitial 3p deletion. Wyandt et al. reported an infant with multiple anomalies and developmental delay. During his 1st year he was found to have an interstitial deletion of band p14 from the proximal short arm of chromosome 3. Examination of the father's chromosomes indicates an “inserted Paracentric inversion” in chromosome 3 as the probable origin of the deletion in the child.

**CONCLUSION**

From the above discussion we believe that our patient with the typical phenotype features of 3p (p13-p21) has a unique findings in association the JS, which is characterized by the dysgenesis of the cerebellar vermis with the brain stem malformation comprising the molar tooth sign in magnetic resonance imaging.
REFERENCES

1. Kumandas S, Akcakus M, Coskun A, Gumus H. Joubert syndrome: Review and report of seven new cases. Eur J Neurol 2004;11:505-10.
2. Wieczorek D, Bolt J, Schwechheimer K, Gillessen-Kaesbach G. A patient with interstitial deletion of the short arm of chromosome 3 (pter –>p21.2: p12 –>qter) and a CHARGE-like phenotype. Am J Med Genet 1997;69:413-7.
3. Neri G, Reynolds JF, Westphal J, Hinz J, Daniel A. Interstitial deletion of chromosome 3p: Report of a patient and delineation of a proximal 3p deletion syndrome. Am J Med Genet 1984;19:189-93.
4. Kogame K, Kudo H. Interstitial deletion 3p associated with t (3p–; 18q+) translocation. Jirui Idengaku Zasshi 1979;24:245-52.
5. Wyandt HE, Kasprzak R, Ennis J, Wilson K, Koch V, Schnatterly P, et al. Interstitial 3p deletion in a child due to paternal paracentric inserted inversion. Am J Hum Genet 1980;32:731-5.
6. Lin S, Kirk EP, McKenzie F, Francis C, Shalhoub C, Turner AM. de novo interstitial duplication 4 (q28.1q35) associated with choanal atresia. J Paediatr Child Health 2004;40:401-3.
7. Petek E, Windpassinger C, Simma B, Mueller T, Wagner K, Kroisel PM. Molecular characterisation of a 15 Mb constitutional de novo interstitial deletion of chromosome 3p in a boy with developmental delay and congenital anomalies. J Hum Genet 2003;48:283-7.
8. Hertz JM, Coerdt W, Hahnenmann N, Schwartz M. Interstitial deletion of the short arm of chromosome 3. Fetal pathology and exclusion of the gene for beta-galactosidase-1 (GLB-1) from 3 (p11 – P14.2). Hum Genet 1988;79:389-91.
9. Sichong Z, Bui TH, Castro I, Iselius L, Håkansson S, Lundmark KM. A girl with an interstitial deletion of the short arm of chromosome 3 studied with a high-resolution banding technique. Hum Genet 1981;59:178-81.

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