CASE REPORT

A Unique Genomic Variant of HDR Syndrome in Newborn

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Background: HDR syndrome (also known as Barakat syndrome) is a rare genetic disorder due to deletions/mutations on specific regions of zinc-finger transcription factor *(GATA3)* gene. **Case Characteristics**: A male preterm infant presented with multiple dysmorphic features characterized by small for gestational age, hypognathia and facial abnormalities. **Observation**: Investigations revealed hypocalcemia and low parathyroid hormone levels and bilateral sensorineural deafness. **Outcome**: Chromosomal microarray analysis revealed a combination of deletion on chromosome 10p (10p15.3p14) with loss of *GATA3* gene and duplication of chromosome 20p (20p13p12.3) as a result of unbalanced 10:20 translocation. **Message**: Detecting this syndrome at neonatal age is very important because it allows early intervention to minimize future clinical problems.

Keywords: *Barakat syndrome, Deafness, Hypoparathyroidism, Renal dysplasia.*

Hypoparathyroidism, deafness, and renal dysplasia syndrome (HDR syndrome also known as Barakat syndrome) is an autosomal dominant disorder with symptoms of hypocalcemia and proteinuria [1]. Phenotypical features are attributed to mutations in the *GATA3* gene on the short arm of chromosome 10, as *GATA3* encodes a transcription factor that is essential for embryonic development of the parathyroid glands, auditory system and kidneys [2]; although, a wide range of phenotypes have been described [3]. We report a unique case of HDR syndrome in a preterm infant with a molecular diagnosis of unbalanced 10;20 translocation involving a combination of loss of function mutation of *GATA3* on chromosome 10p and duplication of chromosome 20p.

CASE REPORT

A male, small for gestational age newborn with birth weight of 1845g was delivered at 35 weeks gestation to a 21-year-old second para mother by Caesarian section secondary to breech presentation and category-2 fetal heart tracing. There was no family history of developmental delay or inherited disorders. Parents were non-consanguineous. Rupture of membranes was noted one hour prior to delivery and meconium stained amniotic fluid was also observed. Infant was delivered by breech extraction and there was a considerable difficulty in delivering the head. He was pale, limp and apneic at birth. He needed chest compressions, endotracheal intubation, and positive pressure ventilation in delivery room. Apgar scores were 1,5 and 8 at 1-, 5- and 10- minutes, respectively.

Physical examination revealed hypotonia and dysmorphic features characterized by wide nasal bridge, down slanting eyes, high arched palate, micrognathia, low set ears, tapered fingers and bilateral overlapping of toes (***Fig.* 1**). He was extubated to continuous positive airway pressure (CPAP). He required CPAP for 10 hours and was treated with ampicillin and gentamicin for 48 hours. His tone improved after 48 hours of life. Full enteral feeds with expressed breast milk were achieved by 4th day of life. A grade 2/6 late-systolic murmur was heard along left sternal

FIG. 1 *(a) Frontal view showing down slanting eyes, broad nasal bridge, prominent forehead; (b) Lateral view showing low set, posteriorly rotated ears with prominent pinna, anteverted nose and micrognathia; (c) Hand showing tapered fingers; and (d) Bilateral feet showing prominent 2nd toe and overlapping of 2nd and 3rd toe with sandal gap.*

border; echocardiogram confirmed small muscular ventricular septal defect.

Initial complete blood count was within normal limits. His metabolic panel was notable for hypocalcemia with serum calcium of 7.2 mg/dL. His discharge calcium level was 8 mg/dL with ionized calcium level of 4.17 mg/dL (Normal 5.1-5.9 mg/dL) and phosphorous level of 9 mg/dL (Normal 4.3-5.4 mg/dL). His parathyroid hormone level at 12 days of life was 13 pg/mL.

The chromosomal microarray analysis revealed a pathogenic deletion from chromosome 10p, including *ZMYND11* gene (OMIM #608668) and *GATA3* gene (OMIM #131320). The analysis also revealed duplication of 20p chromosome. Fluorescent in situ hybridization (FISH) studies using 10p and 20p subtelomeric probes identified that these abnormalities were the result of an unbalanced 10; 20 translocation.

Bilateral sensorineural hearing loss was confirmed with brainstem auditory evoked response testing. Infant was started on low phosphorous formula after consultation with endocrinologist.

DISCUSSION

Many cases of HDR syndrome have been described at different ages and often diagnosed after the onset of symptoms such as hypocalcemia and deafness [4], and associated renal anomalies [5].

Previous studies have shown that mutations or terminal deletions of *GATA3* gene on telomeric portion of 10p chromosome (10p14) are responsible for characteristic phenotype of this syndrome [6]. In addition to features of Barakat syndrome, large deletions on 10p chromosome have also been associated with developmental delay, intellectual disability, autistic behavior, heart defects and immune deficiency [7,8]. The presence and significance of 20p duplication in combination with subtelomeric deletion of chromosome 10p15.3 to p14 have not been reported in literature to the best of our knowledge.

Detailed haplogenetic studies suggested terminal deletion of chromosome 10p15 region involves *ZMYND11* gene and this deletion is associated with characteristic phenotype of high arched palate, webbed toes, intrauterine growth restriction, cognitive deficits, speech disorders, hypotonia and intellectual disability [8,9]. Interestingly, our infant showed normal kidneys with good function. This may be due to low penetrance for renal anomalies as described in some of the previous published studies. It is possible, therefore, that *GATA3* mutations are associated with a relatively varied penetrance and expressivity of the HDR triad features. Clinical features, including hypertelorism, micrognathia and hypotonia have been earlier reported in 20p duplication [10].

The combined information of present and previous published cases suggests that terminal deletion of chromosome 10p14-p15 represent a syndrome with a distinct severe phenotype than previously described.

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