Rare presentation of 6q16.3 microdeletion syndrome with severe upper limb reduction defects and duodenal atresia

Megan L. Donahue & Luis O. Rohena

1Department of Pediatrics, San Antonio Military Medical Center, San Antonio, Texas
2Division of Medical Genetics, Department of Pediatrics, San Antonio Military Medical Center, San Antonio, Texas
3Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, Texas

Correspondence
Megan L. Donahue, Department of Pediatrics, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Ft Sam Houston, San Antonio 78234, TX. Tel: (210) 916-9928; Fax: 210-916-9332; E-mail: megan.l.donahue6.mil@mail.mil

Funding Information
No sources of funding were declared for this study.

Received: 6 August 2016; Revised: 26 January 2017; Accepted: 26 February 2017

Clinical Case Reports 2017; 5(6): 905–914
doi: 10.1002/ccr3.916

Introduction

Deletions of the long arm of chromosome 6 are rare, with a little over 100 patients reported in the literature. Hopkin et al. [1] proposed three different phenotypic groups based on location of the deletion using the 60 reported patients with chromosome 6q deletions at that time. Patients with group A (proximal) deletions 6q11-q16 were found to have higher incidences of hernia, upslanting palpebral fissures, and thin lips. They were less likely to have microcephaly, micrognathia, or heart malformations. Patients with group B (middle) deletions 6q15-q25 were more likely to have intrauterine growth retardation (IUGR), abnormal respiration, hypertelorism, and upper limb defects. Patients with group C (terminal) deletions 6q25-qter were more likely to have retinal abnormalities, cleft palate, and genital hypoplasia. Common among all groups were varying degrees of intellectual disability, developmental delays, hypotonia, ear anomalies, and poor postnatal growth [1]. In patients with middle chromosome 6q deletions, upper limb defects range from minor to severe deformities, with severe deformities being only rarely reported [1–5]. Here, we present an infant with chromosome 6q16.3q22.31 deletion with severe features including bilateral upper limb reduction defects, duodenal atresia, diaphragmatic eventration, mesocardia, and abnormal facies.

Clinical Report

The proband is a male infant born via urgent cesarean section at 32 3 of 7 weeks gestation for decreased biophysical profile and nonreassuring fetal heart tones. He was the product of a third pregnancy of a 32-year-old mother and 33-year-old father. Consanguinity was denied, and the first two pregnancies resulted in healthy daughters.

This pregnancy was complicated by complete placenta previa and prolonged premature preterm rupture of membranes lasting 5 weeks and 1 day. Prenatal ultrasounds beginning at 22 3 of 6 weeks were concerning for duodenal obstruction/duodenal atresia, which was seen on fetal MRI conducted at 28 2 of 7 weeks gestation. Infant was delivered in the breech position and required respiratory support and positive pressure ventilation due...
to weak respiratory effort. Multiple congenital anomalies were noted at initial examination, and genetics consult was completed on the third day of life.

Birth weight was 1150 gm (<5th centile), birth length was 43 cm (50th centile), and birth OFC was 27.5 cm (6th centile). Patient was brachycephalic with very large flat anterior fontanel, splaying of the frontal suture, and flattened occiput. He had a low-lying anterior hairline with hirsute forehead. Palpebral fissures were downslanting. He had no appreciable ocular hypertelorism. Ears were normally positioned but tapered. He had a normal nasal bridge and root with anteverted nares. He had a normal-length philtrum and vermilion border. There was mild micrognathia without cleft palate (Fig. 1). His neck was short. Cardiac examination was without murmurs. Abdomen was soft and nondistended but was being actively decompressed with replogle. Genital examination showed hypoplastic phallus with bilateral cryptorchidism. Buttocks tissue was atrophic. There was no obvious scoliosis or sacral dimple appreciated. Patient was noted to have mild generalized hypotonia.

Bilateral upper extremities were notable for external rotation of the shoulders with fixed flexion deformity and elbow webbing. He had arm reduction bilaterally with mesomelia and single-bone forearms. His right hand had a single digit with intact nail. His left hand showed two syndactyly digits with bifid nail. Lower extremities were grossly normal (Fig. 2).

Imaging of the upper extremities confirmed clinical suspicion of single-bone forearms with bilateral radii and absent ulnae. The right hand was found to have a single metacarpal, a single proximal phalanx, and a bifid distal phalanx. The left hand was found to have a single metacarpal, single proximal phalanx, and two parallel distal phalanges (Fig. 3).

Abdominal plain films showed double-bubble sign concerning for duodenal atresia, which was confirmed on ultrasound day of life 1 (Fig. 4). The patient underwent uncomplicated surgical repair of the atresia on day of life 5. Patient continued to have poor feeding and severe reflux with esophageal and gastric dysmotility. He underwent a fundoplication and percutaneous gastrostomy tube placement at 2 months of age.

Initial head ultrasound on day of life 1 was concerning for bilateral cysts in the caudothalamic grooves consistent with in utero grade 1 interventricular hemorrhages and left greater than right lateral and third ventricle enlargement. MRI of brain conducted at 1.5 months of life showed continued mild dilation of lateral and third ventricles, mild vermian hypoplasia with megacisterna magna and thin, short corpus callosum (Fig. 5). At 18 months of age, he developed focal epilepsy.

Echocardiogram on day of life 3 revealed mesocardia without transposition, trivial mitral and tricuspid regurgitation, and PFO with left-to-right shunt. Spinal ultrasound on day of life 1 showed low position of the conus medullaris at L4 with small lipomas consistent with a tethered cord. In addition to above findings, abdominal ultrasound on day of life 1 also found left renal pelviectasis. Repeat imaging at two months showed no hydronephrosis but bilateral small kidneys both measuring less than 2SD for corrected age.

From birth, patient was noted on serial imaging to have an elevated left hemidiaphragm (Fig. 4). He

![Figure 1](A). Proband at 5 days (A) and 3 months (B). Note tapered ears, downslanting palpebral fissures, anteverted nares, and micrognathia. The latter image demonstrates bifid nail on left hand. Infant had a persistent supplemental oxygen requirement, ultimately requiring tracheostomy.
underwent dynamic studies which demonstrated relative akinesia compared to the right hemidiaphragm consistent with left hemidiaphragm eventration. He underwent plication day of life 27, which required patching at two months of life due to failed plication. Patient continued to have respiratory insufficiency progressing to respiratory failure and required tracheostomy placement at 9 months.

Development of milestones was notably delayed. By 14 months chronological age, patient’s CATCLAMS quotient was only 19% of chronologic age, with most notable delays in adaptive skills, scoring at 1.3 equivalent age months.

Initial concern on genetics evaluation was for Cornelia de Lange syndrome, Fanconi anemia, or segmental aneuploidy. Patient underwent NIPBL, SMC1A, chromosomal breakage and SNP DNA microarray studies. NIPBL and SMC1A testing were both negative. Chromosomal breakage studies were normal but karyotype demonstrated 46, XY,del(6)(q15q21). SNP DNA microarray using Cytoscan HD Affymetrix 2.67 Million SNP + CNV probes further characterized the patient’s deletion as a 17.31 MB interstitial deletion of 6q16.3 with breakpoints of (105,465,388–122,773,040) encompassing numerous genes starting at LIN28B and ending at SERINC1. FISH testing on parents was normal, showing de novo origin of this patient’s deletion.

Figure 2. Limb reduction defects. (A) Left arm and hand at 5 days, note webbing of elbow and syndactyly of the two digits. (B) All extremities at 3 months, note posterior rotation of right arm at shoulder, continued webbing of elbows and forearm, and hand reduction with relatively normal lower extremities. (C) View of right arm and hand from behind, showing posterior rotation and single-digit hand.

Figure 3. Plain films of left and right forearms, demonstrating absent ulnae, single metacarpals, single proximal phalanges, and parallel distal (left) and bifid distal (right) phalanges.

Figure 4. CXR/KUB showing double-bubble sign of duodenal atresia, elevated left hemidiaphragm. Transposed umbilical venous lines secondary to mesocardia.
Figure 5. Brain MRI showing ventriculomegaly and thin corpus callosum.

The content of this manuscript is not considered research at our institution and instead falls into the realm of routine clinical care.

Discussion

We describe a patient with a middle deletion along chromosome 6 found on SNP microarray studies. The predominant features in our patient include severe upper limb reduction defects, duodenal atresia, diaphragm eventration, mesocardia, and brain anomalies.

Many of the findings seen in our patient overlap with Cornelia de Lange Syndrome (CdLS), specifically the upper limb reduction defects, hirsutism, and cryptorchidism, all of which are classic features of CdLS, although he notably did not have other classic features including synophrys and long philtrum. Given that CdLS has specific gene mutations, he underwent sequencing of the NIPBL and SMC1A genes, which account for up to 52% of mutations in patients with CdLS. He also underwent breakage studies to evaluate for Fanconi anemia, which can also present with phocomelia, and SNP DNA microarray to evaluate for segmental aneuploidy. Despite clinical similarities to patients with CdLS, NIPBL and SMC1A testing were negative. Patient was found to have a middle chromosome 6q deletion on both chromosome breakage and SNP DNA microarray studies. Although testing revealed 6q deletion, including both diagnoses in the differential could be important for further patients found to have limb defects and IUGR on prenatal testing.

Our patient demonstrated features found in patients with middle deletions of 6q, although his features were more severe, perhaps due to the size of his deletion. Table 1 compares features of patients with middle deletions of chromosome 6q with those of our patient.

Limb anomalies are well-documented in patients with deletions of 6q between bands 15 and 25. However, many of these defects are minor, including short hands, short and/or tapered fingers, fifth finger clinodactyly, or hypoplastic nails. Reports of patients with major anomalies of the upper extremities have been rarer. Pandya et al. [4] report two patients with significant reductions including radial or ulnar hypoplasia with loss of digits. Duran-Gonzalez et al. [2] and Zherebtsov et al. [5] also report patients with split-hand deformities. Grati et al. [3] report two patients with contraction deformities of the upper limbs, one of which also had camptodactyly and proximal implantation of the thumb. Case 2 reported by Hopkin et al. [1] showed reduction defects most similar to those of our patient with flexion contracture at the elbow, a single arm forearm, and a single-digit hand of the left upper extremity. The length of the deletions of all of these patients, except that of who had a complex deletion/duplication syndrome, is all similar to that of our patient extending 6–7 bands and ranging from 6q15 to 6q23. The greater amount of deleted genetic material in these patients may have contributed to the more severe limb anomalies, although a few other patients with similar deletions have only minor defects. Limb reduction defects are not seen in patients with proximal or distal chromosome 6q deletions.

Although many patients have been reported as having some form of respiratory difficulties, most of these have involved perinatal respiratory insufficiency requiring assistive ventilation. Few have been reported to have severe peripheral anatomic airway disease. Hopkin et al. [1] report a patient with prolonged mechanical ventilation in the setting of laryngomalacia and anomalous subclavian artery suppressing the aorta. Duran-Gonzalez et al. [2] report a patient with pulmonary hypertension and Vlkova et al. [6] report a patient with laryngomalacia and congenital diaphragmatic hernia. To our knowledge, our proband is the first reported patient with congenital diaphragmatic evagination (CDE). Eventrations have been rarely reported in deletion syndromes along other chromosomes, including chromosome 3 [7], in trisomies 13 and 18, and in Fryns syndrome, although diaphragmatic evagination has uncertain genetic etiology. CDE can present in the neonatal period as respiratory distress including tachypnea, accessory muscle use and cyanosis potentially progressive to respiratory failure. If found in other patients with middle chromosome 6q deletions, CDE may represent an important diagnostic consideration in 6q- patients presenting with respiratory distress.

To our knowledge, duodenal atresia has only been reported one other time in a patient with a chromosome 6q deletion. The first case of Pandya et al. [4] described a patient with a deletion 6q16.2q23.1, similar to our patient, who also had duodenal atresia and limb reduction defects, as mentioned above. This patient also
| Case          | Chr. Deletion | Abnormal Head Shape         | Ear Position/shape | Palpebral Fissures | Nose Anomaly | Mouth Anomalies | Retro/ prognathia | Neck        | Major Upper Limb Anomalies | Minor Upper Limb Anomalies |
|--------------|---------------|-----------------------------|--------------------|-------------------|--------------|-----------------|------------------|------------|--------------------------|--------------------------|
| Nakagome     | 6p15q1.1      | Brachycephaly, square face  | Lowset posterior   | Uplanting         | +            | +               | Retro-            |            | Short/stubby limbs       | Tapered fingers          |
| Schwartz     | 6p14q2.2      | Mesomicrophic               | Lowset posterior   | Downslanting      | +            | +               | Pro-             |            | -                        | Tapered fingers with bilateral syndactyly 5th |
| Young        | Pt 2 6q15q2.2 | Dyplastic, prominent       | Downslanting       |                  | +            |                 |                  |            | Long hands/fingers      |                          |
| Nakagome     | 6q15q2.1      | Brachycephaly, square face  | Lowset posterior   | Hypertelorism     | +            |                 |                  |            | Short/5th metacarpals   |                          |
| Park         | 6p2.2 2p2.3.1 | Metopic, left-sided         | Small              | Transverse        |              |                 |                  |            |                          |                          |
| Glover       | 6q15q2.1      | Brachycephaly, square face  | Lowset posterior   | Mongolian         | +            | +               |                  |            | Bilateral triphalangia of thumbs |                          |
| Young        | Pt 2 6q21q2.2 | Dysplastic, prominent       | Downslanting       |                  | +            |                 |                  |            |                          |                          |
| Nakagome     | 6q12.2q1.1    | Brachycephaly, facial      | Lowset posterior   | Hypertelorism     | +            | +               | Retro-            |            | Long hands/fingers      |                          |
| Villa        | Pt 1 6p14q1.6 | Microcephaly               | Uplanting          | +                 | +            |                 |                  |            | Short hands, tapered fingers |                          |
| Villa        | Pt 2 6p14q1.6 | Normocephalic              | Uplanting          | +                 | +            |                 |                  |            | Hypoplasia of ulnar and radial rays, hypoplastic st5 functionless 5th digits, narrow well-formed thumb, index finger nonopposable with boutonniere deformity, absent digits 3 & 4 bilaterally and absent metacarpals 3 & 4 on right | Hypoplastic nalis |
| Pandya       | Pt 1 6p16.2q2.1| Microcephaly, flattened     | Downslanting       | Bilateral         | +            | +               | Retro-            |            | Short hands, tapered fingers |                          |
| Stein        | 6q18.3q2.3    | Wide metopic suture,       | Downslanting       | Hypertelorism     | +            |                 |                  |            |                          |                          |
| Hopkin       | Pt 2 6p16.2q2.3| facial asymmetry,           |                  |                  |              |                 |                  |            | Left hand polydactyly with extra central digit and syndactyly 5th, right hand with central ray defect and absent digits 3 & 4 |                          |
| Case       | Chr. Deletion | Abnormal Head Shape | Ear position/shape | Palpebral Fissures | Nose Anomaly | Mouth Anomalies | Retrognathia | Neck | Major Upper Limb Anomalies | Minor Upper Limb Anomalies |
|------------|---------------|---------------------|-------------------|-------------------|--------------|-----------------|--------------|------|---------------------------|--------------------------|
| Gilhuis    | 6q15q21       | Scaphocephaly, broad forehead | Transverse        | +                 |              |                |              |      |                            |                           |
| Le Caignec | 6q15q21       | Broad, high forehead, coarse faces | Posterior rotate  | Higertelorism     | +            | +               |              |      |                            |                           |
| Groot      | 6q13-22del    | Frontal hypertrichosis | Higertelorism     | +                 | +            | Retro-          | Webbed      |      | Anthrogryus/patient contracts |                           |
|            | +dup (q24.1q25) |                       |                   |                   |              |                 |              |      |                           |                           |
| Pt 3       | 6p14p16       | Narrow bifrontal diameter | Normal set        | +                 | +            | +               | Nuchal edema |      |                           | Left short arm, central ray defects, left 3rd finger, polyphalangy 5 |
| Duran-Gonzalez | 6q15q22.2 | Microcephalic, flat/high forehead | Small Short | Ptosis, microphthalmia | +            | +               |              |      |                           |                           |
| Zherebtsova| 6p16.1q22.32 | Rut occult, heart-shaped face | Low-set, posteriorly rotated, malformed | Higertelorism     | +            | +               | Retro-       |      | Redundant skin, shortwebbed |                           |
| Klein      | 6p16.2q21     | Microcephaly, brachycephaly, bitemporal narrowing | Lowest, protruding, simple helix on right | Higertelorism     | +            | +               |             |      |                           |                           |
| Pt 2       | 6p16.2q21     | Brachycephaly, broad forehead, bitemporal narrowing | Brachycephaly, broad forehead, bitemporal narrowing | Downslanting      | +            | +               | Retro-       |      |                           |                           |
| Pt 3       | 6q15q21       | Microcephaly, low forehead | Lowest            | Higertelorism     | +            | +               | Retro-       |      |                           |                           |
| Pt 2       | 6q14q16       | Macrocephaly, low forehead | Highest           | Dystlastic        | +            | +               | Retro-       |      |                           |                           |
| Rosenfeld  | 1q46.5q5     | Macrocephaly, bitemporal narrowing | Ear pits          | -                 | -            | -               |             |      |                           | Extra creases on fingers  |
| Pt 2q3y    | 6p17q2.31     | Resolved microophyly | Incompletely folded helix on left | -                 | +            | +               | Retro-       |      |                           |                           |
| Pt 3q1y    | Macrocephaly |                       | Upslanting        | -                 | -            | -               |             |      |                           |                           |
| Pt 4q10m   | 6p17q2.21     | Macrocephaly, brachycephaly, small AF, bitemporal narrowing | Small, posteriorly rotated, cupped, unwaved helices | Epicanthic folds, downslanting | Higertelorism | +            | +            | Retro-       |                           |
| Pt 5q10m   | 6p18.3q22.31  | Macrocephaly, brachycephaly | Unwaved helices  | Downslanting      | +            | +               |             |      |                           |                           |
| Pt 6q12y   | 6q17q2.21     | Macrocephaly |                       | Higertelorism     | +            | +               | Retro-       |      |                           |                           |
| Pt 7q5y    | 6q17q2.21     | Macrocephaly |                       | Higertelorism     | +            | +               | Retro-       |      |                           |                           |
| Pt 8q2y    | 6q17q2.21     | Macrocephaly |                       | Higertelorism     | +            | +               | Retro-       |      |                           |                           |

(Continued)
### Table 1. Continued.

| Case | Chr. Deletion | Abnormal Head Shape | Ear position/shape | Palpebral Fissures | Nose Anomaly | Mouth Anomalies | Retro/Prognathia | Neck | Major Upper Limb Anomalies | Minor Upper Limb Anomalies |
|------|--------------|---------------------|-------------------|-------------------|--------------|-----------------|------------------|------|---------------------------|---------------------------|
| Pt 9/12y 6p16.1-q21 | Microcephalic, short forehead, oval face | Prominent forehead | Retracted helix | Hypoplastic anterior helix | Upslanting | - | - | - | Small hands, 5th finger clinodactyly, brachydactyly | |
| Pt 10/9y 6p16.1-q6.3 | Microcephalic | Microcephalic | - | - | - | - | - | - | - | - | |
| Pt 11/11y 6p16.2 | Microcephalic | Small, Cupped, dysplastic | Short, upslanting | - | + | - | - | - | - | - | |
| Izumi (2013) 6p16.1-q21 | Microcephalic, short forehead, oval face | Prominent forehead | Retracted helix | Hypoplastic anterior helix | Upslanting | - | - | - | Small hands, 5th finger clinodactyly, brachydactyly | |
| Vignoli (2013) 6p16.1-q21 | Long face, low anterior hairline | Small, lowset, posterior rotation | Upslanting | + | + | Pro | Short | Short | Short | 5th finger clinodactyly, small middle phalaxies | |
| Donahue (2017) 6p16.3p2.31 | Microcephalic, brachycephaly | Dyplastic | Downslanting | Normal | - | - | - | - | Severe reduction defects as described in text | |

*Lower limb anomalies, scoliosis, hypogenitalia, hypopotonia, respiratory insufficiency, cardiac defects, gastrointestinal defects, brain anomalies, SNHL, poor vision, seizures, other.*

| Case | Lower Limb Anomalies | Scoliosis | Hypogenitalia | Hypopotonia | Respiratory Insufficiency | Cardiac Defects | Gastrointestinal Defects | Brain Anomalies | SNHL | Poor Vision | Seizures | Other |
|------|----------------------|----------|--------------|-------------|-------------------------|----------------|-------------------------|----------------|-------|-----------|---------|------|
| Nakagome (1986) | + | - | + | - | + | + | + | + | + | Developed dystrophy age 11 |
| Schwartz (1984) | - | + | - | + | - | + | + | + | + | Vomiting, irritability, umbilical hernia |
| Young (1985) Park (1988) | + | REF? | - | - | - | - | - | - | - | - | |
| Glover (1988) | + | + | - | - | - | + | + | + | + | Pectus carinatum, umbilical hernia |
| Horigome (1991) | - | + | + | + | + | + | + | + | + | Multip乐视ic kidneys (Potter IIb) |
| Wakahama (1991) | - | + | - | + | + | + | + | + | + | Short stature |
| Vallet (1992) | + | + | - | + | - | + | + | + | + | Ectrodactyly of both feet, obesity, PWS-like |
| Viljoen (1993) | + | + | - | + | + | + | + | + | + | Anteriorly-placed anus, hemi-plastic thoracic |
| Villa (1995) | + | + | + | + | + | + | + | + | + | Anteriorly-placed anus, hemi-plastic thoracic |
| Pandya (1995) | + | + | + | + | + | + | + | + | + | Obesity without food-seeking behavior, |
| Stain (1996) | + | + | + | + | + | + | + | + | + | |

*(Continued)*
| Case          | Lower Limb Anomalies | Scoliosis | Hypogenitalia | Hypotonia | Respiratory Insufficiency | Cardiac Defects | Gastrointestinal | Brain Anomalies | SNHL | Poor Vision | Seizures | Other                      |
|--------------|----------------------|----------|--------------|-----------|--------------------------|----------------|-----------------|----------------|------|-------------|----------|----------------------------|
| Hopkin (1997)| +                    | +        |              |           |                          |                |                 |                |      |             |          | gynecomastia, GH deficiency |
|              |                      |          |              |           | Prolonged mechanical ventilation, anomalous subclavian artery compressing trachea, laryngomalacia | +              | Gastrostomy requirement | +             | +   |             |          |                            |
| Gilhu (2000) | +                    | +        |              |           |                          |                |                 |                |      |             |          | Hypothyroid, GH deficiency |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Le Caignec (2005) | -            | -        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Grati (2007) | +                    | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Duran-Gonzalez (2007) | +          | +        | Pulmonary HTN | +        |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Grati (2007) | +                    | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Klein (2007) | +                    | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Vlckova (2011) | +              | +        | Laryngomalacia, congenital diaphragmatic hernia | +        |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Rosenfeld (2012) | +            | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Izumi (2013) | +                    | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Vignoli (2013) | +               | +        |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
| Donahue (2017) | -                 | -        | Left hemi diaphragmatic herniation | +        |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
|              |                      |          |              |           |                          |                |                 |                |      |             |          |                            |
underwent surgical repair of her atresia, but aside from continued poor growth, no mention was made of her further gastrointestinal course. Our patient, like many others with similar deletions, has had poor feeding and required placement of a gastrostomy tube. While common in duplication syndromes like Down Syndrome, which accounts for 24% of cases in some series [8], duodenal atresias are very rarely seen in other deletion syndromes with isolated cases reported in deletions of chromosomes 2p, 2q, 11q, 9q, and 17q. Duodenal atresias are also seen occasionally in other syndromes including Fanconi Pancytopenia Syndrome, Fetal Hydantoin Syndrome, and Fryns syndrome. Specific genetic etiology is uncertain. Further reports of large segment 6q deletion syndrome patients may uncover more patients with this anomaly and point to an identifiable susceptibility locus.

Similar to many patients identified in our literature review, our patient presented with cerebellar hypoplasia and ventriculomegaly. Of 40 patients reviewed, 21 had reported brain anomalies, four were reported to have normal brain imaging, and no mention was made in 15. Of the 21 with anomalies, seven (33.3%) had corpus callosum abnormalities, of which five (23.8%) were complete or partial agenesis or hypoplasia. Four patients (19%) were noted to have enlargement of ventricles, most commonly lateral and/or third. Also reported were periventricular leukomalacia (7.5%), cerebellar hypoplasia, or atrophy (7.5%) and generalized brain atrophy (7.5%). Additionally, our patient had later development of epilepsy. Stereotypic epilepsy syndromes have previously been described in patients with 6q deletions, especially terminal deletions [9]. Similar structural findings in patients with 6q deletion may help further characterize risks or loci for these epilepsy patients.

Acknowledgments

We thank the family for their participation in this report. We would also like to thank Ms. Grace Balfour and Ms. Kara Carrier, medical photographers, who took the photographs of the patient, and Drs. Christian Carlson and Linda Thomas, pediatric radiologists, who interpreted our patient’s radiographic studies. All authors have no conflict of interests to disclose, and there was no financial support. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, Department of Defense, or the U.S. Government. We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of the data (when applicable), the writing and revision of the document and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approval to use the information and made appropriate acknowledgments in the document; and that each takes public responsibility for it.

Authorship

MLD: involved in study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision. LOR: involved in study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision.

Conflict of Interest

None declared.

References

1. Hopkin, R. J., E. Schorry, M. Bofinger, A. Milatovich, H. J. Stern, C. Jayne, et al. 1997. New insights into the phenotypes of 6q deletions. Am. J. Med. Genet. 70:377–386.
2. Duran-Gonzalez, J., M. Gutierrez-Angulo, D. Garcia-Cruz, L. Ayala Mde, M. Padilla, and I. P. Davalos. 2007. A de novo interstitial 6q deletion in a boy with a split hand malformation. J. Appl. Genet. 48:405–407.
3. Grati, F. R., F. Lalatta, L. Turolla, U. Cavallari, B. Gentilin, F. Rossella, et al. 2005. Three cases with de novo 6q imbalance and variable prenatal phenotype. Am. J. Med. Genet. A 136:254–258.
4. Pandya, A., N. Braverman, R. E. Pyeritz, K. L. Ying, A. D. Kline, and R. E. Falk. 1995. Interstitial deletion of the long arm of chromosome 6 associated with unusual limb anomalies: report of two new patients and review of the literature. Am. J. Med. Genet. 59:38–43.
5. Zherebtsov, M. M., R. T. Klein, H. Aviv, G. A. Toruner, N. N. Hanna, and S. S. Brooks. 2007. Further delineation of interstitial chromosome 6 deletion syndrome and review of the literature. Clin. Dysmorphol. 16:135–140.
6. Vlckova, M., M. Trkova, Z. Zemanova, M. Hancarova, D. Novotna, D. Raskova, et al. 2012. Mechanism and genotype-phenotype correlation of two proximal 6q deletions characterized using mBAND, FISH, array CGH, and DNA sequencing. Cytogenet. Genome. Res. 136:15–20.
7. Sahin, Y., P. O. Kiper, Y. Alanay, T. Liehr, G. E. Utine, and K. Boduroglu. 2014. Partial monosomy 3q26.33–3q27.3 presenting with intellectual disability, facial dysmorphism, and diaphragm eventration: a case report. Clin. Dysmorphol. 23:147–151.
6q- with limb defects and duodenal atresia

M. L. Donahue & L. O. Rohena

8. Dalla Vecchia, L. K., J. L. Grosfeld, K. W. West, F. J. Rescorla, L. R. Scherer, and S. A. Engum. 1998. Intestinal atresia and stenosis - A 25-year experience with 277 cases. Arch. Surg. 133:490–496.
9. Elia, M., P. Striano, M. Fichera, R. Gaggero, L. Castiglia, O. Galesi, et al. 2006. 6q terminal deletion syndrome associated with a distinctive EEG and clinical pattern: a report of five cases. Epilepsia 47:830–838.
10. Nakagome, Y., T. Tanaka, T. Hashimoto, M. Kuyama, and M. Maruyama. 1980. Interstitial deletion 6q in a malformed boy. Ann. Genet. 23:49–51.
11. Schwartz, M. F., S. Kaffe, S. Wallace, and R. J. Desnick. 1984. Interstitial deletion of the long arm of chromosome 6 [del(6) (q16q22)]: case report and review of the literature. Clin. Genet. 26:574–578.
12. Young, R. S., G. S. Fidone, P. A. Reider-Garcia, K. L. Hansen, J. L. McCombs, and C. M. Moore. 1985. Deletions of the long arm of chromosome 6: two new cases and review of the literature. Am. J. Med. Genet. 20:21–29.
13. Park, J. P., J. M. Jr Graham, S. Z. Berg, and D. H. Wurster-Hill. 1988. A de novo interstitial deletion of chromosome 6 (q22.2q23.1). Clin. Genet. 33:65–68.
14. Glover, G., I. Lopez, J. Gabarron, and J. A. Carmona. 1988. Partial monosomy 6q(q15q21) by de novo interstitial deletion. Clin. Genet. 33:308–310.
15. Horigome, H., T. Takano, T. Hirano, T. Kajima, and S. Ohtani. 1991. Interstitial deletion of the long arm of chromosome 6 associated with absent pulmonary valve. Am. J. Med. Genet. 38:608–611.
16. Wakahama, Y., M. Nakayama, and M. Fujimura. 1991. Autopsy findings in interstitial deletion 6q. Pediatr. Pathol. 11:97–103.
17. Valtat, C., D. Galliano, R. Mettay, A. Toutain, and C. Moraine. 1992. Monosomy 6q: report on four new cases. Clin. Genet. 41:159–166.
18. Viljoen, D. L., and R. Smart. 1993. Split-foot anomaly, microphthalmia, cleft-lip and cleft-palate, and mental retardation associated with a chromosome 6;13 translocation. Clin. Dysmorphol. 2:274–277.
19. Villa, A., M. Urioste, J. M. Bofarull, and M. L. Martinez-Frias. 1995. De novo interstitial deletion q16.2q21 on chromosome 6. Am. J. Med. Genet. 55:379–383.
20. Stein, C. K., S. E. Stred, L. L. Thomson, F. C. Smith, and J. J. Hoo. 1996. Interstitial 6q deletion and Prader-Willi-like phenotype. Clin. Genet. 49:306–310.
21. Gilhuis, H. J., C. M. van Ravenswaaij, B. J. Hamel, and F. J. Gabreels. 2000. Interstitial 6q deletion with a Prader-Willi-like phenotype: a new case and review of the literature. Eur. J. Paediatr. Neurol. 4:39–43.
22. Le Caignec, C., A. Swillen, E. Van Asche, J. P. Fryns, and J. R. Vermesch. 2005. Interstitial 6q deletion: clinical and array CGH characterisation of a new patient. Eur. J. Med. Genet. 48:339–345.
23. Klein, O. D., P. D. Cotter, M. W. Moore, A. Zanko, M. Gilats, C. J. Epstein, et al. 2007. Interstitial deletions of chromosome 6q: genotype-phenotype correlation utilizing array CGH. Clin. Genet. 71:260–266.
24. Rosenfeld, J. A., D. Amrom, E. Andermann, F. Andermann, M. Veilleux, C. Curry, et al. 2012. Genotype-phenotype correlation in interstitial 6q deletions: a report of 12 new cases. Neurogenetics 13:31–47.
25. Izumi, K., R. Housam, C. Kapadia, V. A. Stallings, L. Medne, T. H. Shaikh, et al. 2013. Endocrine phenotype of 6q16.1-q21 deletion involving SIM1 and Prader-Willi syndrome-like features. Am. J. Med. Genet. A 161A:3137–3143.
26. Vignoli, A., G. F. Scornavacca, A. Peron, F. La Briola, and M. P. Canevini. 2013. Interstitial 6q microdeletion syndrome and epilepsy: a new patient and review of the literature. Am. J. Med. Genet. A 161A:2009–2015.