A Case of Concurrent 3p26.3-p35.3 Deletion and 9q34.2-q34.3 Duplication in Monozygotic Twin Males

Maini T[1], Lebel RR[1], Black J[1], Cherrick I[2], Brescia N[3], O'Malley J[2]

1. Section of Medical Genetics, SUNY Upstate Medical University Norton College of Medicine, Syracuse, NY, USA; 2. Department of Pediatrics, SUNY Upstate Medical University, Syracuse, NY; 3. Department of Pediatric Neurology, SUNY Upstate Medical University, Syracuse, NY

Abstract

Monochorionic diamniotic male twins were vaginally delivered at 33 weeks, to a 32-year-old G3P2 mother. The union between the parents was non-consanguineous. Intrauterine growth restriction of twin B was noted. There was need of ventilatory support for both twins and both were found to be small for gestational age.

Both twins presented with micrognathia, hypotonia, low birth weight, bilateral ptosis, and gastric anomalies. Twin A was noted to have an atrial septal defect and a left SVC to the coronary sinus, left sided hydronephrosis and an undescended left testis. He failed his newborn hearing test in both ears. Twin B was noted to have an undescended right testis and left sided hydronephrosis. Additionally, he failed his newborn hearing screen in the right ear. Twin A was found to have seizures soon after birth and Twin B developed them later in his life. For both boys, microarray revealed a 10,138 kbp deletion of 3p26.3-p25.3 and a 4,031 kbp duplication of 9q34.2-q34.3. Follow-up karyotype for both displayed46,XY,der(3;9)(p25.3;q34.2). The 3p anomaly overlaps with that of 3p deletion syndrome, with features including low birth weight, microcephaly, ptosis, micrognathia, hypertelorism, hypotonia, psychomotor and growth delay, hearing deficits and intellectual disability. Congenital heart disease, gastric and renal abnormalities are also commonly seen. The 9q34 duplication is a much rarer genetic abnormality and is associated with developmental and speech delay, poor feeding, and musculoskeletal abnormalities. Both twins remained in the NICU for an extended period after birth. Six days after discharge from the NICU, twin A was readmitted to the pediatric ICU due to concerns of seizures. Twin B was transferred to the PICU from the NICU. Recurrent admissions followed for Twin B, due to apneic episodes and feeding difficulties. He was found to have advanced pulmonary dysfunction and expired at 9 months of age; his autopsy showed pulmonary interstitial fibrosis, a dilated pulmonary artery, and right ventricular hypertrophy and dilation. Examination of the brain demonstrated acute on chronic diffuse hypoxic and ischemic damage and a mal-rotated right hippocampus lacking a dentate gyrus. Twin A had a similar but less fulminant course notable for apneic episodes, failure to thrive and seizures. He was transferred to comfort care and he expired at 14 months of age. No autopsy was performed. While 3p distal deletion syndrome is well established in the literature, 9q duplications are seldom reported. The combination of both a 3p deletion and a 9q duplication has not been reported to date, and its occurrence in monozygotic twins is extraordinary and warrants further study.

Methods

SNP microarray was performed using the Affymetrix Cytoscan HD platform including more than 2.6 million copy number markers with a median spacing of 880bp. Total genomic DNA was extracted from lymphocytes, amplified by PCR, and hybridized to the Cytoscan HD genechip. Data were analyzed using the Affymetrix Chromosome Analysis Suite (ChaS) version 4.2.1 and interpreted based on the NCBI genome build hg19 (Genome Reference Consortium Human Build 37 [GRCh37]). Pathogenic findings were verified by an orthogonal method, fluorescent *in situ* hybridization (FISH), using probes targeted to the locus of interest (Empire Genomics, Buffalo, NY).

Discussion

- As there is no report of both the two copy number variants discussed here, we were limited to compare the patients to the few reported instances of one or the other (3p deletion or 9q duplication). We located one published case of 9q33.3-q34.1 duplication, and one in the Decipher database of 9q34.3 duplication.
- Our patients shared failure to thrive and developmental delay/disability with the two cases, hypotonia, hearing deficit; but ours displayed a more severely adverse phenotype.
- Similarly, we found one published case of a large 3p deletion, and one other in Decipher. Again, growth and psychomotor delays were in common with our patients, but overall a milder phenotype than what we observed. Facial dysmorphism was also a common finding.
- Persons with one or the other variant had substantially better developmental and survival phenotype than did either of the twins with both variants. This is not a surprising observation, but leads us to consider their reporting to be warranted. The extraordinary fact that they were monozygotic twins further emphasizes the learning opportunity they offer.
- It should be noted that decision making in the care of our twin patients was a multidisciplinary effort and included pediatric genetics, pediatric palliative care, general pediatrics and pediatric neurology among other services in the care team

Conclusions

Combination of a large 3p deletion and 9q duplication found simultaneously in the same two patients is reported here for what appears to be the first time. The severity of the phenotype is manifested as seen in the attached table. Maternal karyotype was normal (46,XX), but we have not been able to document paternal karyotype. Thus, origin of the apparent unbalanced translocation may be paternal balanced translocation, *de novo*, or cryptic gonadal mosaicism.

Table 1

Features	Fu 3p26.3-p25.3 Deletion[1]	Gawlik-Kuklinska 9q33.3-q34.1 Duplication[2]	Decipher1 3p26.3-p25.3 Deletion[3]	Decipher2 9q34.3 Duplication [4]	Twin A	Twin B
Duplication/ Deletion size	10.095 Mbp	7.26 Mbp	9.52 Mbp	600.56 Kbp	10, 138 Kbp deletion in 3p26.3-p25.3 4031 Kbp duplication in 9q34.2-q34.3	10, 138 Kbp deletion in 3p26.3-p25.3 4031 Kbp duplication in 9q34.2-q34.3
Birth Weight	3.05 Kg	3.3 Kg	N/A	N/A	2.08 Kg	1.9 Kg
Head Circumference	N/A	34 cm	N/A	N/A	30.7 cm	30.4 cm
Birth Length	N/A	58 cm	N/A	N/A	44.5 cm	43 cm
Hypotonia	+	+ (postnatally)	N/A	+	+	+
Hearing Deficit	-	-	N/A	+	+	+
Intellectual Disability	+	+	+	+	N/A	N/A
Failure to Thrive	+	+ (postnatally)	N/A	+	+	+
Age last seen surviving	1 years	16 years	N/A	N/A	14 months	9 months
Dysmorphic Features	bilateral ptosis, high palate, micrognathia	Retrognathia, mild hypotelorism, horizonal palpebral fissures, arachnodactyly with camptodactyly, scoliosis, genu valgum, pes planus, enlargement of tongue base and tonsils, hypertrophy of soft palate and uvula	Short stature, tooth malposition, microcephaly, polydactyly	Single palmar crease, sandal gap, preauricular pit	Micrognathia, bilateral ptosis, left sided hydronephrosis, undescended left testis, Microcephaly,	Down-slanting palpebral fissures, micrognathia, bilateral ptosis, Undescended right testis and left sided hydronephrosis, cleft palate
Other organ Malformation	Hyperhidrosis, GERD	Obesity, secondary amenorrhea, Obstructive sleep apnea	AV canal defect, VSD, feeding difficulty febrile seizure	N/A	Failure to thrive, seizures, apneic episodes, Atrial Septal defect, GERD, left SVC to the coronary sinus	Apnea, seizures, GERD, Failure to thrive, seizures

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