

Deletion of 3p26.3 And Duplication of 17p13.3 In A Male Infant with Esophageal Atresia, Tracheoesophageal Fistula, Intrauterine Growth Retardation, Cryptorchidism, Hypospadias and Sacral Abnormality

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1. Abstract

Deletion of distal portion of short of chromosome 3 and duplication of short-arm of chromosome 17 are rare genetic disorders. There are no case supports in literature where a deletion of chromosome 3p or duplication of chromosome 17p has been reported with esophageal atresia/ tracheo esophageal fistula. Our index patient had no family history of any genetic abnormalities. We are reporting an infant with esophageal atresia, tracheoesophageal fistula, intrauterine growth retardation, cryptorchidism, hypospadias and sacral abnormality with deletion of 3p26.3 and duplication of 17p13.3. The clinical presentation is generally associated low birth weight, growth retardation, mental retardation, facial dysmorphism. Duplication of 17 P 13.3 has been reported to be associated with facial dysmorphism, corpus callosum hypoplasia, cerebellar hypoplasia and moderate mental retardation. Deletion of chromosome 3 could be familial or de novo.

2. Case Report

2055 g, 38 weeks and 2 days' gestation, small for gestational age, male infant born by cesarean section with Apgar's of 2 at 1 minute and 6 at 5 minutes. Mom is 29 years old, gravida 1 para 0. She did not have a history of smoking, drug abuse or alcohol intake. Pregnancy was complicated by worsening preeclampsia and HELLP syndrome. She was given a course of betamethasone to improve

fetal lung maturity and she was on IV magnesium sulfate. She was on labetalol and nifedipine prior to delivery. Prenatal labs were unremarkable. Prenatal studies were consistent with intrauterine growth retardation, polyhydramnios and 2 vessels umbilical cord. The infant required positive-pressure ventilation/CPAP in the delivery room. One hour following admission to the newborn nursery, the infant became pale and apneic with oxygen desaturation to 52%. The infant was transferred to neonatal intensive care unit. Upon transfer, he developed increased work of breathing and sub-sternal retractions, he was placed on bubble CPAP 6 cm. His head circumference was 32.4 cm. Length was 47 cm.

Physical examination was remarkable for mild respiratory distress, grade 1 hypospadias, a sacral dimple, and 2 vessels umbilical cord. His muscle tone and activity were appropriate. The orogastric tube could not be advanced to the stomach. X-ray revealed esophageal atresia with air in the proximal pouch and stomach (Figure 1). Prior to surgery, the infant had rigid bronchoscopy that confirmed esophageal atresia with distal tracheoesophageal fistula arising from the posterior membranous portion of the trachea about 1cm above the carina with a large and well-developed upper pouch. There was a mild degree of tracheomalacia. There was no evidence of an upper pouch fistula on bronchoscopy or at the time of the surgical repair. Muscle sparing right posterolateral thoracotomy was done for repair of esophageal atresia and closure of trachea-esoph-

ageal fistula. The distal esophageal segment was trimmed, and continuity of esophagus was re-established, a JP drain was placed. He was on respiratory support for 48 hours after surgery. A contrast study was done postoperatively to establish esophageal continuity and to confirm that there was no mediastinal leak. The study was reported normal. The infant was started on Nutramigen feedings and feedings were progressively advanced. He required parenteral nutrition for 2 weeks. By day 14 of life, the infant was on full feedings tolerating Nutramigen/ breast milk. The infant was discharged home on day 25 of life. The discharge weight was 2380. Total IgM was in normal range, urine for CMV was negative. MRI of the head was reported normal. He had normal neurological examination. Ultrasound of the spinal canal revealed mildly low position of the conus medullaris ending at distal L3 level with fatty infiltration and borderline thickened filum terminale. There was fusion of lower sacral elements. Postoperatively, infant was fed Nutramigen feedings and he was on lansoprazole 1 milligram/kg per dose q 12 hours. Renal sonogram showed mild grade 1 hydronephrosis bilaterally. Testes were not visualized on the sonogram, however, during surgery they were found high in the inguinal canals. The echocardiogram showed patent ductus arteriosus, patent foramen ovale/atrial septal defect, mild tricuspid regurgitation, biventricular hypertrophy with normal aortic arch. No other vertebral anomalies were noted. Micro array analysis showed 1.2 Mb deletion of 3p26.3 and 124 kb duplication of 17p13.3. Parents were instructed to have their genetic studies.



Figure1: Orogastric tube in the proximal esophageal pouch

3. Discussion

We are reporting a male infant who presented with esophageal atresia (EA), distal tracheoesophageal fistula (TEF) and associated abnormalities with partial deletion of short arm of chromosome 3 and partial duplication of short arm of chromosome 17. Tracheoesophageal fistula is a relatively life-threatening condition where an abnormal communication exists between the esophagus and trachea [1]. Polyhydramnios is a common association [2]. Majority of infants with EA/TEF do not have a genetic abnormality. An isolated TEF is supposedly a multifactorial in origin. EA/TEF can be associated with trisomy 13, 18 or 21. It has been reported

with VACTERL syndrome. EA/TEF has been reported with genetic syndrome such as CHARGE syndrome, Feingold syndrome, anophthalmia-esophageal-genital syndrome, Pallister-Hall syndrome, Fanconi anemia, and chromosome 22q deletion syndrome. Infants with EA/TEF are unable to swallow their saliva and generally present with excessive drooling along the corner of the mouth. They can have mild to severe respiratory distress. In most of the infants, the diagnosis is made early when a feeding tube cannot be advanced into stomach. The affected infants are at great risk of aspiration pneumonitis. Most infants have episodes of coughing, gagging or choking. They can also experience repeated episodes of desaturation and duskiness. Some may have significant stridor related to tracheomalacia. Tracheomalacia may contribute to severe respiratory distress and a need for respiratory support.

Almost half of the infants with an EA/TEF have associated birth defects. Cardiac abnormalities can include ventricular septal defects, atrial septal defects, right-sided aortic arch or tetralogy of Fallot [3]. Gastrointestinal problems are duodenal stenosis, bowel atresia, imperforate anus, Meckel's diverticulum or ano rectal abnormalities. The VACTERL association is an entity with vertebral, anorectal, cardiac, trachea-esophageal, renal and limb defects [4]. 87% of infant with tracheoesophageal fistula/ileal atresia have esophageal atresia with distal trach esophageal fistula [1]. Only 8% of patients have isolated esophageal atresia without any fistulous communication with trachea [1].

Skeletal anomalies have been reported that includes hemivertebrae, radius bone abnormality, amelia, phocomelia, polydactyly, syndactyly, lower limb defects, and scoliosis/kyphosis. Overall incidence of EA/TEF is 1 in 2000-4000 live births. The diagnosis may be suspected prenatally by a small or absent stomach bubble on antenatal ultrasound scan at around 18 weeks' gestation. The likelihood of an atresia is increased by the presence of polyhydramnios. Polyhydramnios alone is a poor indicator of EA because polyhydramnios has numerous etiologies. The newborn infant of a mother with polyhydramnios should always have a nasogastric tube passed soon after delivery to exclude esophageal atresia. Typically, in esophageal atresia the catheter will not pass beyond 9–10 cm from the lip. A chest X- ray may reveal additional anomalies such as a double bubble appearance of duodenal atresia, vertebral or rib abnormalities. The diagnosis of isolated esophageal atresia without a fistula should be suspected when the initial X-ray shows gasless abdomen. A preoperative rigid or flexible bronchoscopy should exclude associated fistula. The incidence of significant gastroesophageal reflux and the subsequent need for a fundal plication procedure is much higher following anastomosis. Anastomotic leaks occur in 15–20% [5]. Minor leaks can be detected with contrast study usually performed on day five to seven postoperatively. Majority of the minor leaks will seal spontaneously but there is an increased incidence of subsequent stricture formation. Anasto-

motric strictures develop in 30–40%. The incidence of recurrent tracheo-esophageal fistula is reported between 5–14% [6]. Some degree of esophageal dysmotility is likely to be present. This may lead to swallowing difficulties. Gastroesophageal reflux disease can cause recurrent chest infections, emesis, and heartburn related to esophagitis. There is a risk for Barrett's esophagus and respiratory complications such as asthma.

The terminal deletion of short arm of chromosome 3 was studied in a family. Amongst the four generations of this family, most were carriers of deletion of chromosome 3p. One male infant in the family had microcephaly, corpus callosum dysgenesis, and minor dysmorphism. One other family member had autism, speech delay and learning disabilities [7]. In another report, terminal deletion of distal portion of short arm of chromosome 3 was associated with growth retardation, developmental delay, mental retardation, dysmorphism, microcephaly and ptosis. Involvement of CHL1 gene has been associated with significant mental retardation [8]. Lype and associates investigated a large five generation family where seven individuals had micro deletion of 3p. The involved individuals also had 4p16.1 duplication. The range of features were severe neurological outcome, Wolf Hirschorn syndrome and dysmorphism [9]. Petriczko and associates reported familial monosomy of 3p 26.3 and trisomy of 4q32.2 that presented with progressive ataxia, intellectual disability and dysmorphism. Father of the patient had balanced reciprocal translocation of chromosome 3p and 4q [10].

A duplication of chromosome 17p 13.3 has been reported to show intellectual impairment, autism and brain MRI abnormalities. Chromosome 17p13.3 is a gene rich region and its deletion can be associated with Miller-Dieker syndrome. Curry and associates have reported 34 patients with duplication of 17 p 13.3. There was wide variability of phenotypes and cognitive development. Involvement of YWHAE and LIS1 gene was associated with facial dysmorphism, abnormality of the corpus callosum, cerebellar vermis and associated autistic spectrum disorders [11]. One male infant has been reported to show polymicrogyria with de novo duplication of chromosome region 17p13.3 p 13.2. [12]. Psychomotor developmental delay, hand eye incoordination, speech delay, hypotonia, dysmorphism and narrow corpus callosum has been reported in an infant with duplication of 7p13.3 [13]. 17p13.3 duplication involving BHLHA9 and YWHAE genes is associated with autism, facial dysmorphism, behavioral problems and mental retardation [14]. In 1 study where 7678 patients were referred with unexplained learning difficulties and/or autism, with or without other congenital abnormalities. Eight had microdeletions and five had micro duplications in 17p13.3. [15].

There are no case supports in literature where a deletion of chromosome 3p or duplication of chromosome 17p has been reported with esophageal atresia/ trach esophageal fistula. Our index patient

had no family history of any genetic abnormalities. He had ASD and PDA, mild hydronephrosis, bilateral undescended testes, and grade 1 hypospadias. His neurological exam was unremarkable, and MRI of the head was reported normal. This infant will have multidisciplinary follow-up in early intervention program, high-risk Newborn Clinic, follow up by nephrologist, urologist, and cardiologist. He will have a careful assessment of his neurological status. Infant will need a follow up neuroimaging of sacral spine. Parents have been instructed to get a follow up by the geneticist.

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