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Duplication of 12p11.23p11.22 Presenting in A Preterm Infant with Anorectal Fistula, Imperforate Anus, Growth Retardation, Bilateral Mild Hydronephrosis and Mild Facial Dysmorphism

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1. Abstract

We are reporting a preterm female infant with duplication of 12p11.23p11.22 presenting with anorectal fistula, imperforate anus, intra-uterine growth retardation, bilateral mild hydronephrosis and mild facial dysmorphism.

2. Case Report

This 630 g, 29 weeks and 5 days' gestation, female infant with history of intrauterine growth retardation was born by an urgent cesarean section with Apgar scores of 4 at 1 and 7 at 5 min.

Mom was 28 years old, gravida 5 para 2113. She has been a smoker for several years. Current pregnancy was complicated by gestational diabetes. Her 1st pregnancy was complicated by gestational diabetes and the infant was born at term with macrosomia. She had another pregnancy with delivery at 32 weeks and 6 days' gestation. That infant had growth retardation and the pregnancy was complicated by gestational diabetes. One other pregnancy was complicated by gestational diabetes and the infant was born macrosomic. She has had one spontaneous miscarriage. The current pregnancy was complicated by severe growth retardation with evidence of reverse end diastolic blood flow on umbilical artery doppler studies. She had BMI of 47 and she has had short interval between pregnancies. She had not gotten a course of betamethasone prior to delivery.

Urgent cesarean section was performed because of non-reassuring fetal heart tracing. The infant was delivered in breech presentation. She had nuchal cord x1. Amniotic fluid was meconium stained. Birth weight was 630 g, length 30.5 cm, head circumference 23 cm. The infant was noted to be in acute respiratory distress soon after birth. She required positive pressure ventilation via face mask in delivery room followed by intubation and was given a dose of surfactant. The infant initially had substernal retractions, tachypnea, and nasal flaring. Clinical picture was consistent with RDS. There was no evidence of significant dysmorphology on admission to the NICU. However, on further assessment during NICU stay she appeared to show dolichocephaly, prominent forehead and metopic ridge, midfacial retrusion, depressed nasal bridge, anteverted nares, and microretrognathia. Echocardiogram showed PFO/ASD. No vertebral anomalies were noted.

The infant was extubated on day 1 to noninvasive ventilation and was weaned to high-flow nasal cannula on day 25 of life. She required caffeine therapy for 5 weeks. She was on oral diuretics for about 3 weeks. The infant was weaned to room air at 12 weeks of life. She was started on feeding protocol on day 1 of life. She received parental nutrition for 16 days followed by feedings of nutramigen and EleCare. The infant required gavage feeding during entire hospital stay. Swallow studies were indicative of significant reflux with nasal penetration. Upper GI series confirmed significant reflux. The infant was on lansoprazole 1 mg/kg twice a day and Sucralfate 20 milligram/kg three times a day. The patient was noted at birth to have extremely preterm genitalia with what appeared to be a patent anus. She passed meconium stools at birth. When she was 9 weeks of age, careful assessment revealed that

the infant had been stooling through a fistulous connection close to imperforate anus. What was previously felt to be an anterior anus was considered a rectoperineal fistula consistent with imperforate anus. The infant had resection of perineal (rectoperineal) fistula with anoplasty, rectum was pulled to surgically created anus. During hospital stay she continued to have significant feeding problems. The stool was positive for lactoferrin. Feedings were switched to Nutramigen at three months of age. pH probe study confirmed significant gastroesophageal reflux. The infant required gastrostomy and fundal plication at three months of age. She had evidence of osteopenia of prematurity manifesting as elevation of alkaline phosphatase. She was on multivitamin with iron and 400 units of vitamin-D per day. She was on zinc sulfate at 1.5 mg/kg per day. Her blood type was O positive, maternal blood type is O positive and Coombs test was negative.

On day 4 of life infant had hypercalcemia with serum calcium of 14.1mg/dl. There was no clinical evidence of fat necrosis of the skin. The infant was given two normal saline IV infusions followed by a dose of Lasix each time. The calcium supplementation was removed from the TPN for a short period. Vitamin D level was 46ng/ml, parathormone was 5 pg/ml, phosphorus level was 2.4mg/dl. 1,25 (OH)2 Vit D was elevated 169 pg/ml (reference range 19.9-79.3). Serum parathormone and vitamin-D levels were reported normal on follow-up. Eye exam prior to discharge was reported normal. Total IgM was within normal range. Urine for CMV was negative. Renal ultrasound showed bilateral mild pelvic caliectasis without overt hydronephrosis. Infant had a spinal ultrasound that was reported normal. Echocardiogram showed normal cardiac anatomy. Skeletal dysplasia panel was reported negative. She passed hearing screen. The newborn state screening report was normal. MRI of the brain was reported normal. Micro array analysis exhibited duplication of 12p11.23p11.22 (which included area of PPF1BP1 gene). Recommendation was made to have a follow-up by primary care provider, pediatric nephrologist, follow up in early intervention program, geneticist, and follow-up by pediatric surgeon. The infant was discharged home on Elecare 24 calorie formula through gastrostomy tube.

3. Discussion

Anorectal malformations have an incidence of 2 to 5 per ten thousand live births. Diagnosis may missed on prenatal studies. In most of the infants, diagnosis is made in the immediate newborn period. The etiology of anorectal malformation appears to be multifactorial. The clinical presentation of anorectal abnormalities is very variable. Significant number of these are low anomalies with a perineal fistula, that can be managed easily. However, high anomalies can be associated with anorectal agenesis with or without fistula or rectal atresia. Almost half of the infants with anorectal anomalies have associated abnormalities [1]. The most common associated abnormality is genitourinary. Associated cardiac abnormality has been reported in one third of the cases, spinal canal defects are seen in about 25%, gastrointestinal abnormalities can be seen in up to 10% of infants. Anorectal malformation with VACTERL anomalies is reported in 4-9% of infants.

Anorectal abnormality can be reported in infants of insulin requiring diabetic mothers and has also been reported in several genetic syndromes like Currarino syndrome, Opitz-BBB syndrrome, Pallister-Killian syndrome, and FG syndrome. [18] reviewed association of diabetes in pregnancy and ano-rectal abnormality. The first study in 2003 found a significantly increased risk with an odds ratio of 2.15. The second study by same author in 2008 reported an odds ratio of 4.32. [19] The infants presenting with rectovesical fistulae should be investigated carefully for spinal anomalies. Detailed physical examination should pay special attention to perineum, location of the defect, anal pit, fistula within vagina or urethra. Presence of a third opening in a female is suggestive of vestibular fistula and two openings are relatively uncommon, presenting with rectovaginal fistula or rectal agenesis without fistula. Plain abdominal radiograph may show gasless terminal rectum or absence of gas around the perineal skin. Invertogram is usually more helpful. Trans-perineal or coccygeal ultrasound done by an expert could be diagnostic. CT scan or an MRI have been used for detailed assessment of structural abnormalities. A male infant with fistula can be repaired soon after birth with posterior sagittal anoplasty. Rectal urinary fistulae require colostomy followed by definitive pull-through procedure at 3-6 months of age. In a female infant with the most common recto-vestibular communication, anorectal repair can be performed. The infants with persistent cloacae may have associated omphalocele and/or spinal defects and a genetic defect. Karyotype and microarray analysis may be needed prior to definitive repair or initial diversion colostomy. The etiology of such malformations remains unclear and is likely multifactorial. Few syndromes with autosomal dominant mode of inheritance such as Townes-Brooks syndrome, Currarino's syndrome, and Pallister-Hall syndrome are associated with anorectal abnormalities.

Pallister-Killian syndrome presents with dysmorphic features and imperforate anus. It is usually due to tetrasomy 12p somatic mosaicism. It is a dysmorphic condition involving several organs. Most fibroblasts have 47 chromosomes with an extra small metacentric chromosome, whereas the karyotype of lymphocytes is normal. The extra metacentric chromosome is an isochromosome for part of the short arm of chromosome 12: i(12) (p10) [2]. This disorder manifests with significant mental delay, skin pigmentation disorder, abnormal facies with prominent forehead, sparse scalp air anteriorly and anteverted nostrils, flat nasal bridge and short neck. Temporal frontal baldness has been reported. described absence of the pericardium and focal aplasia cutis in the axillary area [3]. Associated penial, testicular and ovarian tumors have been reported. Ptosis, nystagmus, wide mouth, long philtrum, and cleft palate have been reported. Other features included single palmar creases, bilateral accessory nipples, small hands and feet with dorsal ede-

ma, and hypoplasia of the labia with a common anal and vaginal opening [4]. Common features included neonatal hypotonia with feeding difficulties, scoliosis, early-onset seizures, hearing impairment, and visual anomalies, such as myopia or strabismus. As babies, frontotemporal hair alopecia was noted that gradually improved with age. Most continued to have areas of alopecia or other hair abnormalities, such as sparse or thick eyebrows. Dysmorphic facial features are variable, and include slanted palpebral fissures, short nose with anteverted nares, long philtrum, tented lip, low-set ears, micrognathia. reported anorectal malformation with polyhydramnios, preaxial polydactyly, and congenital heart disease that was detected prenatally [5]. Fluorescence in-situ hybridization with chromosome 12-specific DNA probes is reliable to detect 12p chromosome. Routine amniocentesis potentially could help in making diagnosis with additional cytogenetic studies. The recommended sample for testing prenatally is amniotic fluid, since cytogenetic diagnosis on chorionic villi can be misleading [6].

Currarino syndrome is an autosomal dominant hereditary condition which is characterized by the triad of sacral abnormalities, anorectal abnormalities most commonly anorectal stenosis and presacral mass consisting of a teratoma, anterior sacral meningocele or both. However only 1 out of 5 cases of Currarino triad has all three abnormalities present. [7, 8] Currarino triad is considered a spectrum disorder with a wide variation in severity. Up to one-third of the patients are asymptomatic and may only be diagnosed during adulthood only on routine radiograph or ultrasound that are performed for different reasons. Currarino triad is most often caused by mutations in the MNX1 gene [9]. Treatment depends on the type and severity of abnormalities present but may involve surgery for anorectal anomalies.

Common presenting features are aplasia or hypoplasia of sacrum, sacrococcygeal teratoma, bifid scrotal, anorectal malformation. Currarino triad is nearly all familial and in 30% sporadic cases are reported. It has also been reported with microdeletions of 7q containing MNX1 gene.

Townes-Brocks syndrome is a genetic condition that affects several parts of the body. It is also called anal-ear-renal-radial malformation syndrome. The most common features of this condition are a imperforate anus, abnormally shaped ears, and hand malformations that most often affect the thumbs. People with this condition often have at least two of these three major features [10].

Other signs and symptoms may include kidney abnormalities, mild to profound hearing loss, eye abnormalities, heart defects, foot abnormalities, and genital malformations. These features vary among affected individuals, even within the same family. Mild intellectual disability or learning problems have been reported in about 10 percent of people with Townes-Brocks syndrome. Mutations in the SALL1 gene cause Townes-Brocks Syndrome [11]. The syndrome presents with neuronal deafness, imperforate anus, hypoplastic thumbs. Thumb malformations may include triphalangeal thumbs, duplication of the thumb or hypoplasia of the thumbs. Renal abnormality may include mild malrotation, ectopic kidneys, horseshoe kidney, renal hypoplasia, polycystic kidneys, and vesicoureteral reflux. Associated cardiac, foot anomalies and genitourinary abnormalities are common. Uncommon associations are iris coloboma, Arnold-Chiari malformation and growth retardation. De novo variants most commonly occur on the paternally derived chromosome 16 [12].

Opitz G/BBB syndrome [13-15] is a genetic condition that causes several abnormalities along the midline of the body. It can be X-linked or autosomal dominant. The common feature is hypertelorism. Affected individuals commonly have defects of the larynx, trachea, or esophagus. The swallowing and breathing problems may lead to recurrent pneumonia or life-threatening respiratory distress. A common defect is laryngeal cleft with major reflex and aspiration pneumonitis. Most males have hypospadias, cryptorchidism, an underdeveloped scrotum, or a bifid scrotum. Mild intellectual disability and developmental delay occur in about 50 percent of people with Opitz G/BBB syndrome. Affected individuals have delayed motor skills, delayed motor milestones, speech impediments, and learning problems. Some have features of autistic spectrum disorders, characterized by impaired communication and social skills. About half of affected individuals also have cleft lip with or without cleft palate. Some have cleft palate without cleft lip. Less common features of Opitz G/BBB syndrome, affecting less than half of people with this disorder, include minor heart defects, imperforate anus, and brain defects such as a hyoplastic or absent corpus callosum. Distinct facial features that may be seen in this disorder include a prominent forehead, widow's peak hairline, flat nasal bridge, thin upper lip, and low-set ears. These features vary among affected individuals, even within the same family.

VACTERL stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. People diagnosed with VACTERL association typically have at least three of these characteristic features. Affected individuals may have additional abnormalities that are not among the characteristic features of VACTERL association. Defects in the bones of the vertebrae are present in two thirds of people with VACTERL association. Sixty to 90 percent of individuals with VACTERL association have narrowing or blockage of the anal atresia. Anal atresia may be accompanied by genitourinary anomalies. cardiac defects occur in 40 to 80 percent of individuals. Cardiac defects can range in severity from a life-threatening problem to a subtle defect that does not cause health problems. Fifty to 80 percent of people with VACTERL association have a tracheo-esophageal fistula. Tracheo-esophageal fistula can cause problems with breathing and feeding early in life. They typically require surgical repair in infancy. Renal anomalies occur in 50 to 80 percent of individuals with VACTERL association. Affected in-

dividuals may be missing one or both kidneys or have abnormally developed or horseshoe kidneys, which can affect renal function. Limb abnormalities are seen in 40 to 50 percent of people with VACTERL association. These abnormalities most commonly include poorly developed or missing thumbs or underdeveloped forearms and hands. VACTERL association occurs in 1 in 10,000 to 40,000 newborns. Most cases of VACTERL association are sporadic. VACTERL association can be familial [16].

FG syndrome is a X linked genetic condition also called Keller syndrome or Opitz-Kaveggia syndrome [20]. This is almost always seen in males with mild to severe intellectual disability, hypotonia, broad thumbs, and wide first toes. There may be partial or complete absence of the corpus callosum. Most affected individuals have imperforate anus. People with FG syndrome also tends to have a distinctive facial appearance including small ears; a prominent forehead; and down-slanting palpebral fissures. Some patients have sensorineural hearing loss and joint laxity that can cause joint contractures. They may have associated heart defects, seizures, cryptorchidism and inguinal hernia. At least two mutations in the MED12 gene, located on X chromosome have been reported.

Effect of smoking and drinking habits during pregnancy have been reviewed. One case control study looked at 216,707 births from the population-based Kanagawa Birth Defects Monitoring Program, to evaluate the effect of maternal smoking and/or drinking during pregnancy on the risk of infants' anal atresia in 1989-1994. The frequency of maternal smoking (including passive smoking) and/or maternal drinking during pregnancy among 84 infants with anal atresia was compared with 174 matched controls. The 84 anal atresia included 49 cases of isolated anal atresia and 35 cases of syndromic anal atresia [17]. Maternal drinking during early pregnancy was associated with an increased risk of isolated anal atresia (OR = 4.8, 95% CI 1.2 to 19.1, $p < 0.05$). A slightly increased trend was also observed in the association of maternal smoking during pregnancy with both. (OR = 1.4, 95% CI 0.5 to 3.6).

Our index patient was born preterm with intrauterine growth retardation. The pregnancy was complicated by gestational diabetes and maternal obesity. Diagnosis was delayed for several weeks; however, the infant was noted to have normal stool pattern. Micro-array analysis exhibited duplication of 12p11.23p11.22. No major cardiac, renal or vertebral abnormalities were noted. Once accurate assessment confirmed that infant had a fistulous connection, a referral was made to a pediatric surgeon and rectoperineal fistula was resected and anoplasty was done. She continued to have significant feeding intolerance. Regular feedings were changed to Nutramigen followed by Elecare. The infant had a Nissen fundoplication and gastrostomy. She will have follow-up by multidisciplinary team of gastroenterologist, pediatric surgeon, high-risk clinic, dietitian, developmental assessment team and the primary care provider.

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