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Pallister-Killian syndrome

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Study Design A
Data Collection B
Statistical Analysis C
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Manuscript Preparation E
Literature Search F
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ACDEF Aarthi Srinivasan
ABDE Debra Wright

Department of Obstetrics and Gynecology, St. John Hospital and Medical Center, Detroit, MI, U.S.A.

Corresponding Author: Aarthi Srinivasan, e-mail: aarthi.srinivasan@stjohn.org
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Patient: Male, 0
Final Diagnosis: Pallister-Killian syndrome
Symptoms: Decidious tooth • flattened nasal bridge • frontal bossing • grooved palate • low-set ears • mid-facial hypoplasia • nuchal fold thickening • right inquinal testis • shortened upper extremities • undescended left intraabdominal testis • widely spaced nipples
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Congenital defects/diseases

Background: Pallister-Killian syndrome (PKS) is a rare, sporadic, polydysmorphic condition that often has highly distinctive features. The clinical features are highly variable, ranging from mild to severe intellectual disability and birth defects. We here report the first case of PKS diagnosed at our institution in a patient in the second trimester of pregnancy.

Case Report: A pregnant 43-year-old woman presented for genetic counseling secondary to advanced maternal age and an increased risk for Down syndrome. Ultrasound showed increased fetal nuchal fold thickness, short limbs, polyhydramnios, and a small stomach. The ultrasound evaluation was compromised due to the patient's body habitus. The patient subsequently underwent amniocentesis and the karyotype revealed the presence of an isochromosome in the short arm of chromosome 12 consistent with the diagnosis of Pallister-Killian syndrome. Postnatally, the infant showed frontal bossing, a flattened nasal bridge, mid-facial hypoplasia, low-set ears, a right upper deciduous tooth, grooved palate, nuchal fold thickening, widely spaced nipples, left ulnar polydactyly, simian creases, flexion contractures of the right middle finger, shortened upper extremities, undescended left intraabdominal testis, and right inguinal testis.

Conclusions: The occurrence of PKS is sporadic in nature, but prenatal diagnosis is possible.

MeSH Keywords: Mosaicism • Nuchal Translucency Measurement • Polyhydramnios • Tetrasomy

Full-text PDF: http://www.amjcaserep.com/download/index/idArt/890614

Background

Pallister-Killian syndrome (PKS) is a rare genetic syndrome characterized by multiple dysmorphic features and mental retardation. It is caused by supernumerary isochromosome 12p (tetrasomy 12p) [1,2]. PKS was first described in 1977 by Pallister in adults [3], and later in 1981 by Killian and Teschler Nicola in children with mental retardation, severe dysmorphic features, and skin changes [4]. The syndrome is an example of chromosomal mosaicism, as the abnormality is present only in a fraction of cells examined, and the non-mosaic form of tetrasomy 12p is incompatible with intrauterine survival [5,6]. We here report the first case of PKS diagnosed in our institution in a patient in the second trimester of pregnancy. We hope to contribute to the existing genetic literature on this rare disorder through our case report.

Case Report

A 43-year-old Caucasian woman, Gravida 7 Para 3, with a history of 3 previous first trimester voluntary terminations of pregnancies and no significant personal or family history, presented for genetic counseling secondary to advanced maternal age and an increased risk for Down syndrome of 1/30 based on second trimester biochemical screening. Her previous obstetrical history was unremarkable. She has 3 healthy living children. Ultrasound was consistent with 20 weeks' gestation. The fetus was noted to have a nuchal fold measuring 6.6 mm, with head circumference, abdominal circumference, and biparietal diameter all >97th percentile, and femur <3rd percentile. There was no hydrocephalus. The maximum vertical pocket of amniotic fluid measured 85 mm. Fetal evaluation was compromised by maternal body habitus; however, the fetal anatomy appeared normal. The patient was offered an amniocentesis

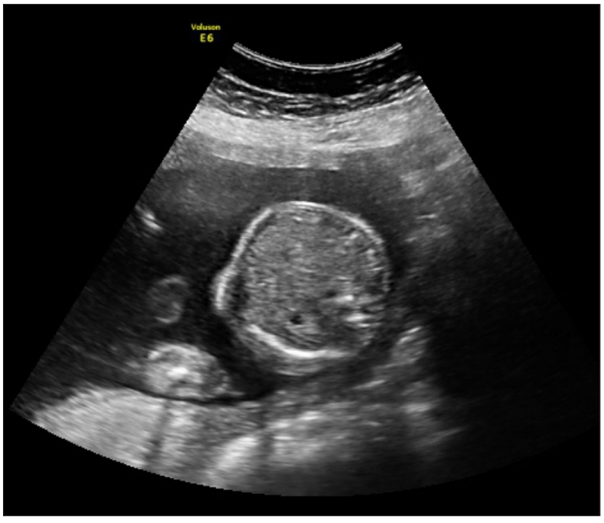

Figure 1. Ultrasound image showing small stomach.

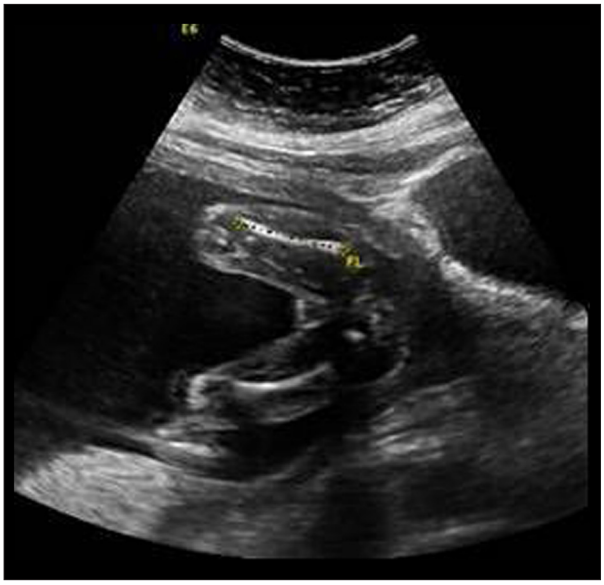

Figure 2. Ultrasound image showing femur length less than the 3rd percentile.

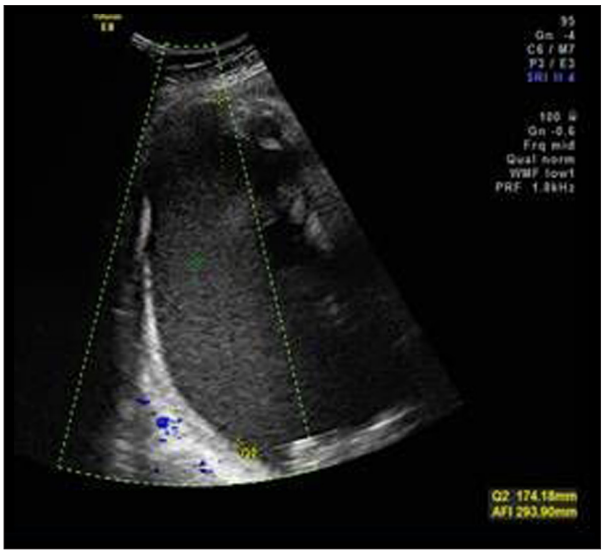

Figure 3. Ultrasound image showing polyhydramnios.

based on the increased risk for Down syndrome and ultrasound findings, but declined.

A follow-up scan at 22 weeks gestation revealed a small stomach (Figure 1) and an amniotic fluid index of 22 mm. The remainder of the anatomical survey appeared normal.

At 29 weeks gestation, biparietal diameter and head circumference measured >97th percentile. The long bones, including the ulna, tibia, and fibula, measured <5th percentile, with the femur <3rd percentile (Figure 2). A small stomach was again noted, as well as polyhydramnios with an amniotic fluid index of 433 mm (Figure 3). The patient agreed to genetic testing.

Table 1. Pallister-Killian syndrome diagnosed prenatally.

Cases	Year	Maternal age	Gestational age	Prenatal findings	Diagnostic test	Karyotype
Gilgenkrantz et al. [7]	1985	36	26	Hydramnios, nuchal edema, short long bones, cardiac defects	Amniocentesis	47,XX,+i(12p)
Shivashankar et al. [8]	1988	32	24	Diminished femoral and humeral lengths, hydramnios and omphalocele	Amniocentesis	47, XY, +i(12p)
Soukups and Neidich et al. [9]	1990	37	20.5	Nuchal edema, short femurs	Amniocentesis	Mosaic 47, XX, +i(12p)
Bresson et al. [10]	1991	28	21	Diaphragmatic hernia, hydramnios	CVS	47,XX,+i(12p)
Sharland et al. [11]	1991	28	21	Hydrops	CVS	Mosaic 47, XX, +i(12p)
Blancato et al. [12]	1992	37	16	Dextrocardia, diaphragmatic hernia	Amniocentesis	Mosaic 47, XY, i(12p)
Priest et al. [13]	1992	32	34	Diaphragmatic hernia, hydramnios	Amniocentesis	47, XX, +i(12)(p10)
Bergoffen et al., Case 3 [14]	1993	36	32	Hydramnios, diaphragmatic hernia, growth restriction	Amniocentesis	47, XX,+i(12p)
Donnenfeld et al., Case 8 [15]	1993	38	22	Diaphragmatic hernia, hydramnios	Amniocentesis	47, XY, +i(12)(p10)
Schubert et al. [16]	1998	44	21	Flat profile, diaphragmatic hernia, enlarged fourth ventricle	Amniocentesis	Mosaic 47, XX, +i(12p)
Chiesa et al. [17]	1998	39	23	Hydramnios, absent stomach, short long bones, esophageal atresia, dilated ventricles	Cordocentesis	47,XX,+i(12p)
Paladini et al. [18]	2000	40	21	Diaphragmatic hernia, rhizomelic shortening, hydramnios, dilated ventricles, flat face, small nose and thin lips	Amniocentesis	Mosaic 47, XY, i(12p)
Langford et al. [19]	2000	30	13	Increased nuchal translucency, hypoplastic left heart, hydrops, diaphragmatic hernia, polydactyly	CVS	Mosaic 47, XY, i(12p)
Antonella et al. [20]	2004	34	14.5	Nuchal edema, diaphragmatic hernia, growth restriction	Amniocentesis	47,XX,+i(12p)
Kim et al. [21]	2008	33	11.5/16	Increased nuchal translucency/ hygroma coli	Amniocentesis	47, XY, +i(12)(p10)

Following consent, amniocentesis was performed, and the amniotic fluid was sent for karyotype and fluorescent *in-situ* hybridization (FISH) for trisomies 13, 18, and 21.

FISH studies were negative and confirmed a male fetus. The full karyotype was reported as 47, XY, i (12) (p10)/46XY; there was an isochromosome of the short arm of chromosome 12 (tetrasomy 12p) in 14/16 colonies, consistent with PKS. The patient presented at 31.5 weeks gestation in preterm labor with bulging membranes. She was admitted, and tocolysis and antenatal corticosteroids for fetal lung maturity were given. The following day the patient underwent an emergency cesarean section for fetal bradycardia. A viable male infant weighing 2.290 kg with Apgar newborn score of 7 and 8 was delivered.

Postnatally, the physical exam revealed classic phenotypic features of Pallister-Killian syndrome. The infant was noted to have frontal bossing, a flattened nasal bridge, mid-facial hypoplasia with low-set ears, a right upper deciduous tooth, and a grooved palate. The head circumference at birth was at the 10^{th} percentile. Ultrasound of the head postnatally revealed enlarged cisterna magna. The nuchal fold was thickened. Nipples were widely spaced. The infant had left ulnar polydactyly, simian creases, flexion contractures of the right middle finger, and shortened upper extremities. Right inguinal testis and a left intraabdominal testis were noted. The infant had hypotonia, bilateral hearing loss, and respiratory distress syndrome due to prematurity. Ultrasound of the abdomen on the first day of life showed a bilateral dilated renal pelvis and nephrocalcinosis. An echocardiogram done the same day revealed small patent foramen ovale, moderate tricuspid insufficiency, and pulmonary hypertension. The patient subsequently underwent Nissen's fundoplication and pyloromyotomy for left congenital diaphragmatic hernia and gastro-esophageal reflux disease. A repeat karyotyping with peripheral blood lymphocytes from the infant demonstrated mosaic 47, XY, +i (12) (p10) [1]/46, XY [29], confirming our prenatal diagnosis.

Discussion

Pallister-Killian syndrome (PKS) is a rare, sporadic, polydysmorphic condition, often with highly distinctive features. It is a tissue-limited mosaicism caused by tetrasomy 12p resulting in craniofacial, cardiovascular, renal, genital, and other systemic malformations [5]. Many affected individuals die in utero or postnatally; a few survive into their early 20 s [5]. This condition can be diagnosed prenatally by chorionic villus sampling, amniocentesis, or cordocentesis. Early prenatal diagnosis helps families to choose between continuation and termination of pregnancy, as it poses significant emotional and financial burden. Families may be better equipped to cope with the pregnancy and the care of the infant after birth when they choose to continue pregnancy. However, the diagnosis in our case was delayed until 29 weeks of gestation because the patient had declined genetic testing initially at the time of the first ultrasound.

The abnormality is commonly detected in skin fibroblasts. The diagnosis of PKS can thus be frequently missed due to the tissue-specific nature of mosaicism, and usually is not detected in rapidly dividing cells such as the peripheral blood cells [6,22]. There are very few reported cases in which the isochromosome was diagnosed in peripheral lymphocytes [23]. The detection rate is 0–2% in lymphocytes, 50–100% in fibroblasts, and 100% in amniocytes and bone marrow cells [24]. The genetic confirmation in our infant was obtained postnatally from culturing peripheral blood cells.

Chiesa et al. in 1988 reported the first case diagnosed prenatally based on fetal blood cells after cordocentesis in the second trimester. FISH was used to identify the interphase or the metaphase cells with the isochromosome [17]. About 60 cases of PKS have been recognized prenatally since. Some of the ultrasound findings noted are hydramnios, short limbs, abnormal hands and feet, diaphragmatic hernia, and an absent or small stomach [25] (Table 1). In 2000, Langford et al. reported the first case of PKS after detecting increased nuchal translucency and hydrops during the initial screen for trisomy 21 at 13 weeks gestation [19]. This patient had an increased nuchal fold thickness, with polyhydramnios and short limbs at 20 weeks gestation. The diagnosis was delayed because the patient declined genetic testing. Congenital diaphragmatic hernia is noted in 40% of affected infants [26–28]. The small stomach noted in this case likely represented a diaphragmatic hernia, although no other chest abnormalities were noted. Advanced maternal age is also a contributing factor for tetrasomy 12p. In 1988, Wenger et al. showed that maternal age was significantly higher in people with PKS than in the general population, similar to that of Down syndrome. Advanced maternal age is a contributing risk factor for aneuploidy from meiotic error, as in the case of tetrasomy 12p [29].

Conclusions

PKS is sporadic in nature, but prenatal diagnosis is possible. The first reported case was diagnosed in 2000 after noting an increased nuchal translucency in the first trimester [11]. In our case the findings of increased nuchal fold thickness, short limbs, polyhydramnios, and a small stomach eventually led to the diagnosis of tetrasomy 12p after amniocentesis.

Statement

The authors have no disclosures or acknowledgements to make.

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