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Case Report

A Rare Case of Genito-Patellar Syndrome (GPS) From Khartoum-Sudan

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Genito-patellar syndrome (GPS) is a newly described condition that comprises absent patellae, genital and renal malformations, joint dislocation, flattened nasal bridge, short stature and mental retardation. Agenesis of corpus callosum is one of the recognized features. More recently, cardiac anomalies and ectodermal dysplasia have been suggested as additional features. Severe symptomatic osteoporosis, endocrine abnormalities including primary hypothyroidism and delayed puberty, sensori-neural hearing loss and cleft palate are additional features. Prenatal diagnosis is possible. We report here this rare syndrome in a seven days old male baby delivered after a term pregnancy but without regular antenatal care.

Keywords: Absent patellae, genital and renal malformation, joint contracture, Sudan.

INTRODUCTION

Genito-patellar syndrome (GPS) is a newly described condition that comprises absent patellae, genital and renal malformations, joint dislocation and mental retardation (Valérie Cormier-Daire, 2000; Reardon, 2002). Agenesis of corpus callosum is one of the recognized features of the syndrome (Abdul-Rahma, 2006). In normal individuals, the patellae begin ossifying between ages 1.5 - 4 years in females and ages 2.5 - 6 years in males (Campeau and Brendan, 1993). Twelve patients with ages from 15 days to 12 years and two affected fetuses have been reported (Penttinen et al., 2009). Prenatal diagnosis is possible for families in which the disease-causing mutation has been identified. Most of patients with genitopatellar syndrome die in the first year of life and rarely survive to the second decade (Valérie Cormier-Daire, 2000). Cormier et al suggested mosaic trisomy 8 syndrome, facio-genito-popliteal syndrome, nail-patella syndrome, the rapadilino syndrome and Coffin-Siris syndrome as differential diagnoses (Valérie Cormier-Daire, 2000).

The term genitopatellar syndrome was coined by Valérie Cormier-Daire and the condition is now known as genitopatellar Syndrome (GPS).

More recently, cardiac anomalies and ectodermal dysplasia have been suggested as additional features of this syndrome (Abdul-Rahma, 2006; Lifchez et al., 2003).

Congenital heart disease may include atrial and ventricular septal defects, patent ductus arteriosus and dilated aortic arch (Armstrong and Clarke, 2002). Two additional patients were reported with genitopatellar syndrome that expanded the spectrum of anomalies to include radio-ulnar synostosis (Abdul-Rahma, 2006).

Genitopatellar syndrome (GPS) and Say-Barber-

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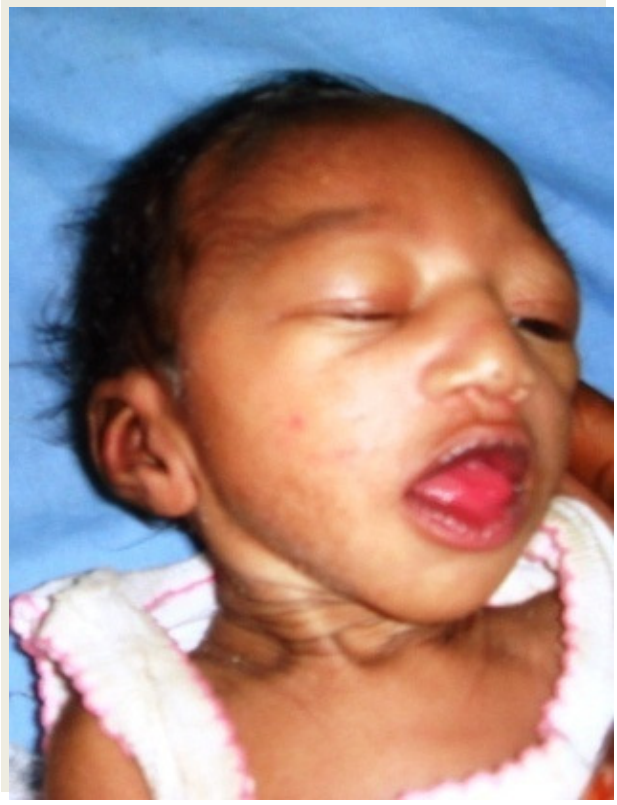

Figure 1. The facial dysmorphic features.

Biesecker-Young-Simpson syndrome (SBBYSS) are KAT6B gene related disorders.

Management include educational intervention and speech therapy beginning in infancy. We report here this rare case in a seven days old male baby delivered after a term pregnancy but without regular antenatal care.

CASE REPORT

A seven days old male baby from a consanguineous parents presented with limbs deformities. He was an outcome of term pregnancy without regular antenatal care. The mother noticed that her abdomen was small in size compared to gestational age. No fever or skin rash during pregnancy that ended by vaginal delivery at home. Soon after birth the mother noticed the deformities of both lower limbs in form of abnormal flexion of the hips and knees and abnormal shape of the feet. The mother noticed that his urine output was of small amount. The mother started breast feeding. He was not vaccinated. He had two elder brothers of 6 and 3 years, alive and well but had a brother who died at the age of 3 days with the same skeletal deformities and dysmorphic features. The family was rearing cats in the home.

On examination the baby was conscious and active. There was multiple dysmorphic features (Figure 1). Vital signs were normal. The weight was 2 kg (<3rd centile), length: 50 cm (at 50th centile) and head circumference: 30 cm (< 3rd centile) with craniocynostosis. Coarse triangular face, broad nose with high nasal bridge and micrognathia. The cranial nerves were intact. Neck was normal. Cardiovascular, chest and abdominal examination was normal. Penile size was of 1.5 cm on stretch with underdeveloped scrota and undescended right testes. Upper and lower limbs revealed hypertonia and hypereflexia. Planter reflexes were equivocal. Primitive reflexes were present and normal. The right hip was flexed at ~ 60º, left hip flexed at ~110º. The right and left knees were flexed at ~ 90º. There was an skin dimple over patellar regions with bilateral talipes equinovarus. The back was normal. (Figure 2 and 3)

Blood count and peripheral blood picture were normal. Urine analysis was normal. TORCH screening was negative. X ray of the knees showed total absence i e agenesis of the Patella where bone calcification could not be identified. (Figure 4, 5 and 6). These findings were cosidered as manifestations of genito-patellar syndrome. Abdominal ultrasound revealed a normal liver and spleen with small sized kidneys. MRI brain and echocardiography were planned but not done as the baby died soon later. Blood urea, creatinine and electrolytes were normal.

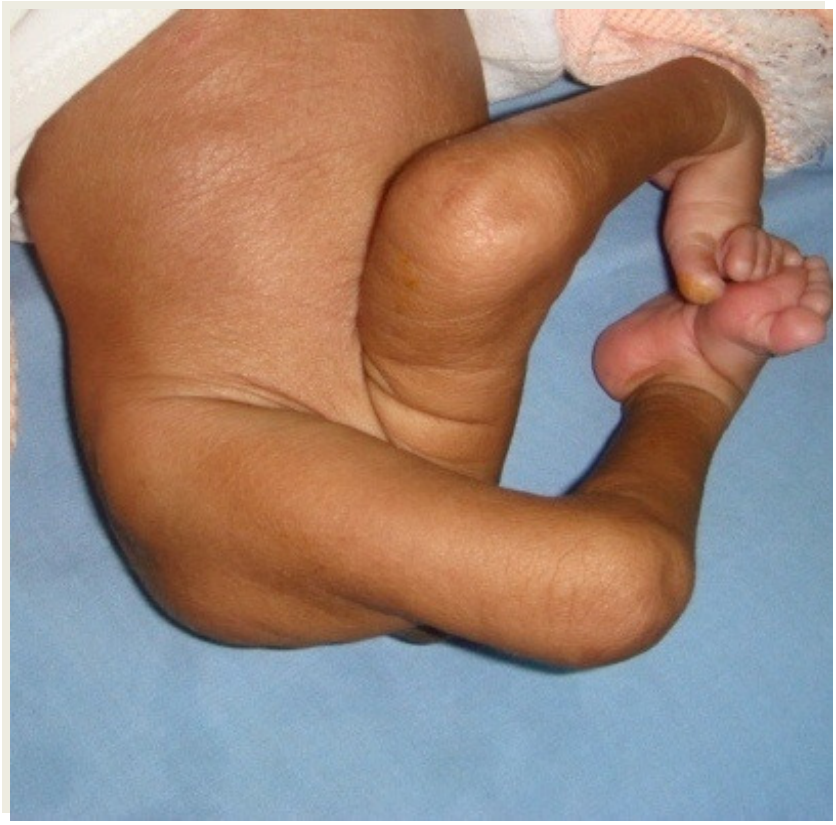

Figure 2. Flexion deformities of both lower limbs including hips, knees and feet.

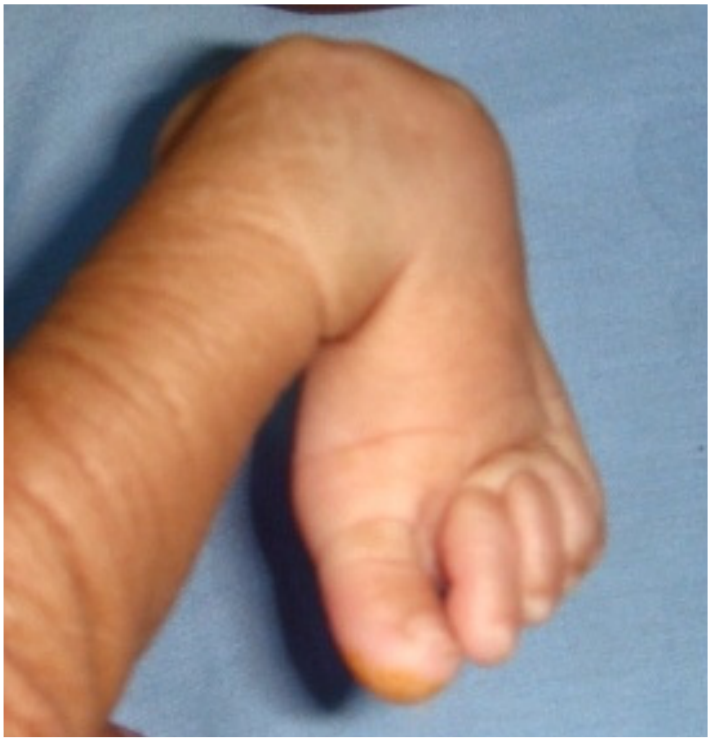

Figure 3. Clubbed left foot.

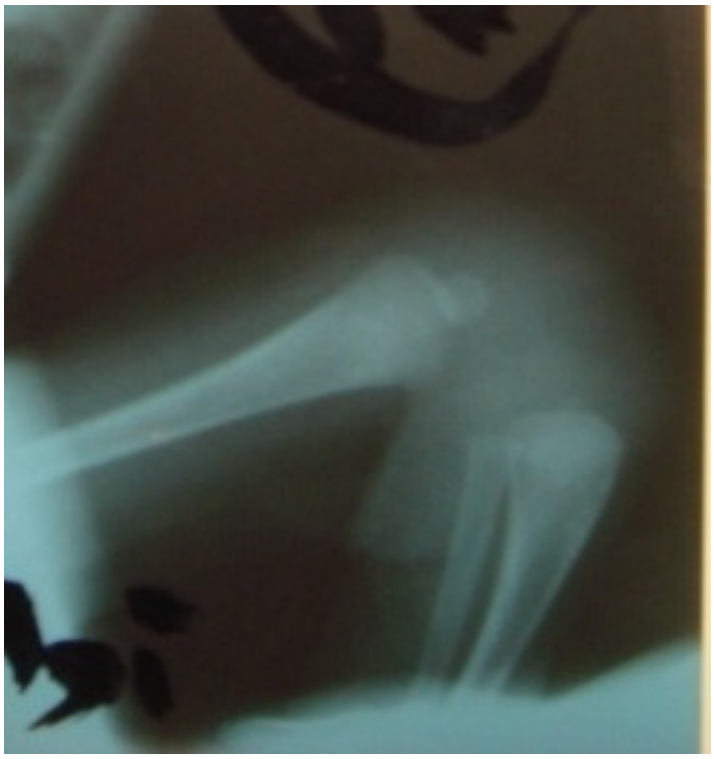

Figure 4. X-ray of the left knee.

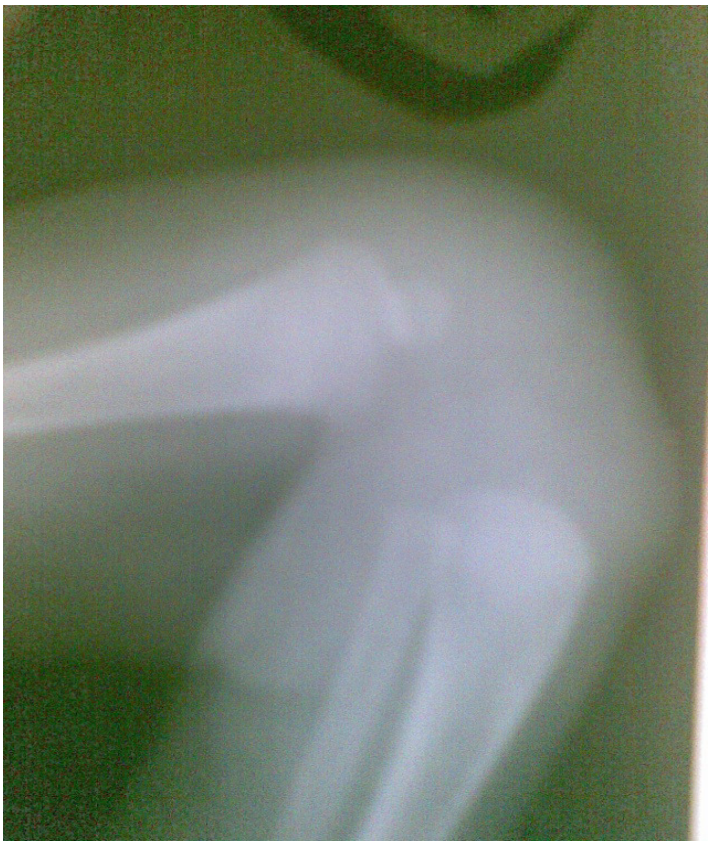

Figure 5. X-ray of the right knee.

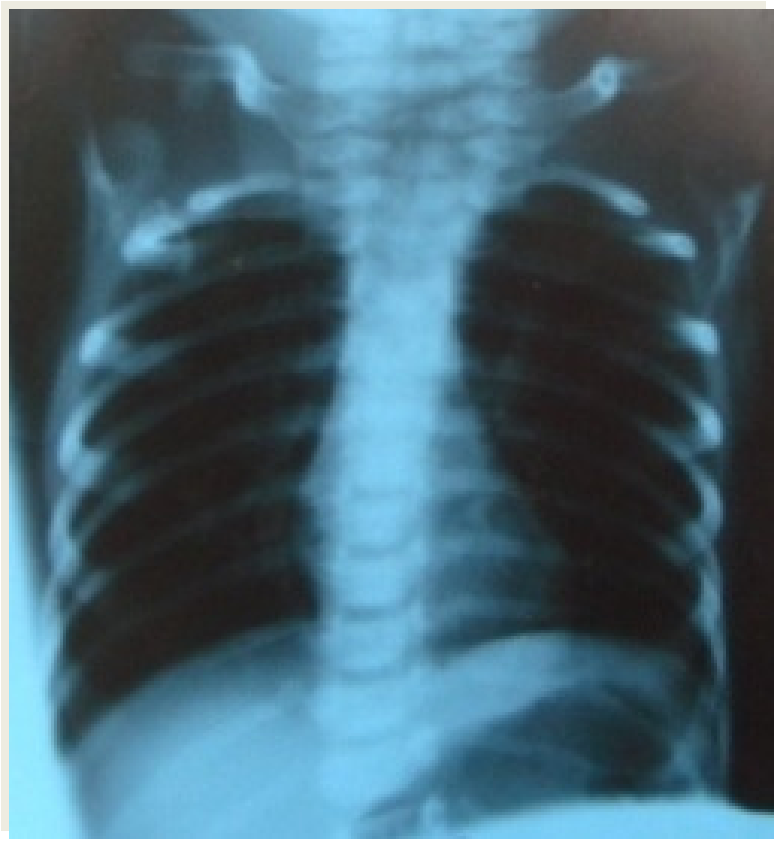

Figure 6. X-ray of the Chest.

DISCUSSION

Worldwide, there are 12 reported cases of genitopatellar syndrome. Their ages ranged from 15 days to 17 years (Penttinen et al., 2009). The syndrome shows male predominance as ten of reported cases were boys (83.33%) and two were girls (16.66%). This could be ascribed to the easier recognition of genital anomalies in males (Valérie Cormier-Daire, 2000). Our reported case is seven days old being the youngest living reported case and a male which is consistent with male predominance of the syndrome. He was an outcome of consanguineous parents unlike most of the reported cases. The ocurrence of agenesis of the corpus callosum and multiple renal cysts led us to consider Meckel-Gruber, Zellweger, Fryns, Aicardi syndrome and glutaric aciduria type 2 syndromes as a differential diagnoses (Armstrong and Clarke, 2002). To diagnose KAT6B mutations (GPS and SBBYSS) we need two major features or one major and two minor features (Penttinen et al., 2009). Our patient had dysmorphic features in form of coarse triangular face, broad nose with high nasal bridge, micrognathia and five major features namely: Genital anomalies (undescended right testes and scrotal hypoplasia), microcephaly, flexion deformities (at the hip, knees and club feet), renal anomalies (renal dysgenesis) and absent patellae. This is in favour of diagnosis of genitopatellar syndrome (GPS) and makes our case the 13th reported case worldwide.

Most of the reported cases had renal anomalies namely hydronephrosis and/or multicystic kidney as a major feature. In our case the ultrasound revealed small sized kidneys and the possibility of dysgenesis of the kidneys couldn't be ruled out. Five or more reported cases had respiratory difficulties and/or lung disease that could be attributed to the renal anomalies reported which is not in our case as there was no respiratory difficulty or laryngomalacia inspite of the presence of renal anomaly.

In 1988 Goldblatt et al first reported a 4-year-old boy with hypoplastic patellae, mental retardation, scrotal hypoplasia, skeletal deformities, renal anomalies, flattened nasal bridge and short stature. Later, in 2000, Cormier-Daire et al reported seven patients belonging to five unrelated families, of three French and two Portuguese, with genital anomalies as scrotal hypoplasia and cryptorchidism in the boys and clitoral hypertrophy in the girls, facial dysmorphism, renal anomalies, absent patella, and severe mental retardation in the two survivors.

L Armstrong and J T R Clarke reported a 3 month old baby boy with features consistent with GPS and had bilateral cervical ribs and pale optic nerves (Armstrong and Clarke, 2002). It could be the 1st reported case with

Table 1. Features of our patient compared to those of previously reported patients

The Dysmorphic and other features	Our case	Armstrong et al	Goldblatt *et al*	Cormier-Daire *et al*						
				1	2	3	4	5	6	7
Microcephaly	+	+	+	+	+	+	+	+	+	+
Agenesis of corpus callosum	_	+		+	+	–	+	?	–	+
Hypotonia	Hypertonia	Central		+	+	+		+	+	
Other features										
Coarse face	+	+	+	+	+	+	+	+	+	+
Broad/large nose	+	+	+	+	+	+	+	+	+	+
Micrognathia	+	+	+	–	+	–	+	+	–	+
Lung, respiratory difficulties	_	+		+	+	–	+	+	–	+
Flexion deformity										
*** Hips**	+	+		+	+	+	+	+	+	+
*** Knees**	+	+	+	+	+	+	+	+	+	+
*** Club feet**	+	+		+	+	+	+	+	+	+
Skeletal survey										
!Brachydactyly	-	–			+	+			+	
!Hip dislocation	-	–	+	+	+	+			+	
!Pelvic hypoplasia	-	–		+	+	+			+	
Renal anomalies	dysplastic	UHC MC	Ectopic, dysplastic	HN	HN MC	HN	UHN MC	HN	UHN	HN MC
Genital anomalies										
Clitoral hypertrophy				+						
Scrotal hypoplasia	+	+	+		+	+	+	+	+	+
Cryptorchidism	+	+	+		+	+	+	+	+	+
Patellae	csa	csa, ns, d	r, d	a	csa	a	csa	csa	a	csa

UHN: uretrohydronephrosis. MC: multicystic. HN: hydronephrosis. csa: clinically suspected to be absent. a: absent. ns: normal size. r: rudimentary. d: dislocated.

such anomalies as all reported cases including ours had no cervical ribs or pale optic nerves. They also reported central Hypotonia and peripheral Hypertonia in their case (Armstrong and Clarke, 2002), and Cormier-Daire et al reported hypotonia in most of their cases (Valérie Cormier-Daire, 2000). In our case there was hypertonia and hyperreflexia in all limbs.

Penttinen et al had reported a 17-year-old female with a phenotype consistent with GPS, and being the oldest reported patient, she is the first one showing severe symptomatic osteoporosis and endocrine abnormalities including primary hypothyroidism and delayed puberty. They suggested that these novel findings are also manifestations of GPS (Penttinen et al., 2009). Corinna et al reported a female with sensori-neural hearing loss, cleft palate and hypothyroidism in addition to the known anomalies (Bergmann et al., 2011).

There were some rare features reported like cardiac anomalies, endocrinal, ectodermal dysplasia and other features like the case reported by L Armstrong and J T R Clarke with soft redundant skin suggested tissue laxity which is not present in all other reported cases including our case and in the case reported by Goldblatt et al with short stature. It was the only case reported with short stature as all the reported cases including ours had normal length. Corinna Bergmann reported a case of GPS with cleft palate and senso-neural deafness which was the only reported case with such features (Bergmann et al., 2011). (Table 1)

KAT6B-related disorders are inherited in an autosomal dominant manner. The mutations are actually in the same exon, although in a different region, and the disease has different symptoms. They have both recently been shown to be caused by distinct mutations in the histone acetyltransferase KAT6B (Bergmann et al., 2011; Campeau et al., 2012; Simpson and Deshpande, 2012). All variants are de novo dominant mutations that lead to protein truncation. Mutations leading to GPS occur in the proximal portion of the last exon and lead to the expression of a protein without a C-terminal domain. Mutations leading to SBBYSS occur either throughout the gene or more distally in the last exon. Features present only in GPS are contractures, anomalies of the spine, ribs and pelvis, renal cysts, hydronephrosis and agenesis of the corpus callosum. Features present only in SBBYSS include long thumbs, long great toes and lacrimal duct abnormalities. Several features occur in both such as intellectual disability, congenital heart defects and genital

and patellar anomalies (Campeau et al., 2012; Simpson and Deshpande, 2012).

Individuals with two major features or one major feature and two minor features are likely to have a KAT6B mutation (Campeau and Brendan, 1993). The major features include: genital anomalies (Females: clitoromegaly and/ or hypoplasia of the labia minora or majora. Males: cryptorchidism and scrotal hypoplasia), patellar hypoplasia/agenesis, flexion contractures at the hips and knees including club feet, agenesis of the corpus callosum with microcephaly, hydronephrosis and/or multiple renal cysts. The minor features include: congenital heart defect, dental anomalies (delayed eruption of teeth), hearing loss, thyroid anomalies, anal anomalies (anal atresia or stenosis, rectal duplication and an anteriorly positioned anus), Hypotonia and global developmental delay/intellectual disability (Campeau and Brendan, 1993).

Management include educational intervention and speech therapy beginning in infancy. Orthopedic intervention is needed for contractures and club foot . Physical therapy to help increase joint mobility. Routine management of cryptorchidism, congenital heart defects, dental anomalies, hearing loss, thyroid anomalies and ophthalmologic findings is also needed (Campeau and Brendan, 1993).

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