Peters' plus syndrome in an Egyptian patient with some unusual features

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ABSTRACT

We report on a 1 5/12 years old male patient with clinical manifestations of Peters'-Plus syndrome. The patient had Peters' anomaly (central adherent leucoma, bilateral congenital cataract), growth deficiency, disproportionate short stature, mild mental retardation. He had also short hands with nearly complete cutanous syndactly between the third and the forth fingers and broad thumbs, bilateral rocker bottom heals, bilateral partial cutanous syndactly between the 2nd and the 3rd toes with broad big toes and genitourinary malformations with generalized hypotonia.

Some of the features reported in Kabuki make-up syndrome were also present in our patient including mainly hepatomegaly and craniosynostosis.

However in our patient some features were present not reported before in both syndromes including thick tounge, thick everted lower lip, anteverted naris, broad thumb and big toe, kyphoscoliosis in lower back, bilateral rocker bottom heals and splenomegaly.

Key Words:

Peters' anomaly, craniosynostosis, hypospadius.

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INTRODUCTION

Peters' Plus syndrome is an autosomal recessive disorder characterized by anterior eye-chamber abnormalities, disproportionate short stature and developmental delay. Most cases have prenatal growth retardation and postnatally, are disproportionately short. Mental delay was present in 83% of cases. cupid bow shape of the upper lip with a thin vermilion border is a feature; cleft lip, sometimes accompanied by cleft palate, was found in 45% of cases.[1]

After detection of a microdeletion by array-based comparative genomic hybridization, Lesnik Oberstein et al.[2] identified biallelic truncating mutations in the β1,3-galactosyltransferase–like gene (B3GALTL) (13q12.3) in all 20 tested patients, showing that Peters' Plus is a monogenic, primarily single-mutation syndrome. This finding is expected to put Peters' Plus syndrome on the growing list of congenital malformation syndromes caused by glycosylation defects.

B3GALTL is a beta-1,3-glucosyltransferase involved in the synthesis of the unusual O-linked disaccharide glucosyl-beta-1,3-fucose-O- found on the thrombospondin type-1 repeats (TSRs) of many biologically important proteins.

Using an immunopurification-mass spectroscopy method, Hess et al.[3] found that Peters' -plus patients carrying the 660+1G-A mutation in B3GALTL showed only the fucosyl-O- modification in all 4 O-fucosylation sites of the reporter protein properdin. In contrast, properdin from heterozygous relatives and a healthy volunteer showed the glucosyl-beta-1,3-fucose-O- modification. He concluded that Peters' -plus syndrome is a congenital disorder of glycosylation involving defective O-glycosylation of TSRs.

Kabuki make-up syndrome is a mental retardation syndrome with short stature and a characteristic face. The main diagnostic features is the presence of an everted lateral 1/3 of the lower lid and long palpebral fissures. Affected individuals have a broad nasal tip, prominent ear lobes and a cleft or high arched palate. The 5th finger is short and there is persistence of fetal finger pads[4]. Craniosynostosis may be an associated feature as reported by many authors[5,6]. Ewart- Toland et al.[7], also reported a case with sclerosing cholangitis.

CASE REPORT

A 1 5/12 years old male child, forth in order of birth of remote consanguinous parents living in Kafr El-Sheikh, Egypt, with 2.25 kg weight at birth after spontaneous vaginal delivery at term.

The mother presented to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of delayed motor and mental milestones. The patient can sit unsupported and can not say any word, babbling sounds only.

The condition started since birth when the mother noticed that her infant was floppy. Shortly after birth, the patient was admitted to NICU because of high fever, weak suckling and refusal of feeding, with recurrent urinary tract infection. He had a family history of an uncle who died at early infancy with dysmorphic features (not examined) and another family member with epilepsy. The Mother had rheumatic heart disease since childhood (Fig. 1).

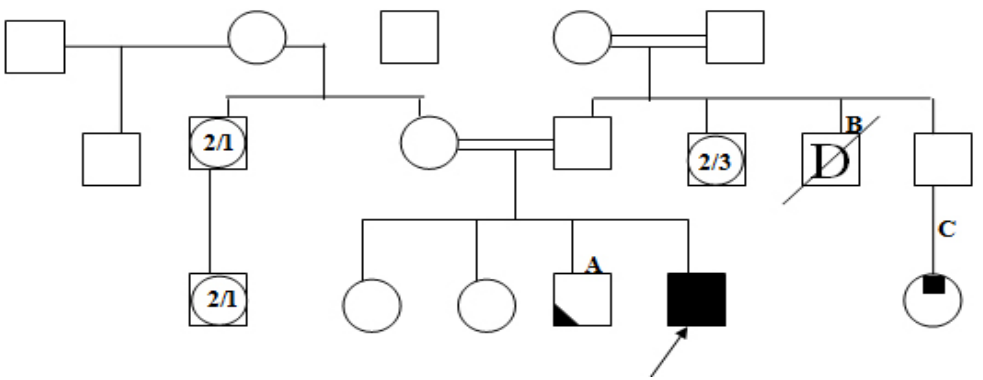

Fig. 1: Pedigree of the patient:
A- Congenital genovarum and defective language development.
B- Dysmorphic features, died at early infancy (not examined).
C- Epilepsy.

The patient had mild mental retardation, weight was 8.5 Kg (< 3rd percentile), length was 73cm (<3rd percentile), span 63 cm, (disproportionate). OFC was 47cm, he had coarse facial features, triangular face, upward slanting palpebral fissures, hypertelorism, low depressed nasal bridge, anteverted nares, broad nasal tip, long philtrum, thin upper lip, thick everted lower lip, full cheeks, retromicrognathia, high arched palate, thick tongue and low set ears (Fig. 2).

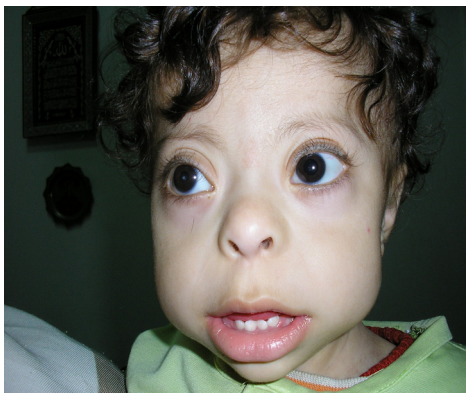

Fig. 2: Photo of the patient demonstrating facial features.

Skull had a thick ridge over the saggital suture giving a scaphocephalic shape to the skull. Skull circumference was 47cm, (50th percentile), with open anterior fontanel measuring 3 x 3.5cm. The patient had proptosis of the eyes with shallow orbits, corneal opacity in the right eye and bilateral cataract.

He had short hands, left nearly complete cutanous syndactly between the third and the forth fingers (Fig. 3), bilateral broad thumbs and simian creases. He also had bilateral rocker bottom heals and bilateral partial cutanous syndactly between the 2nd and the 3rd toes with broad big toes, (Figs. 4and5).

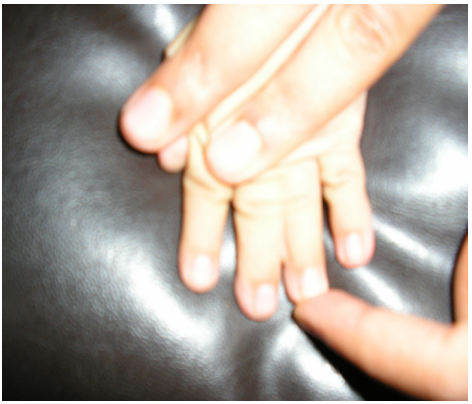

Fig. 3: Hand of patient showing short fingers, coetaneous syndactyly between 2nd and 3rd fingers, broad distal phalanges.

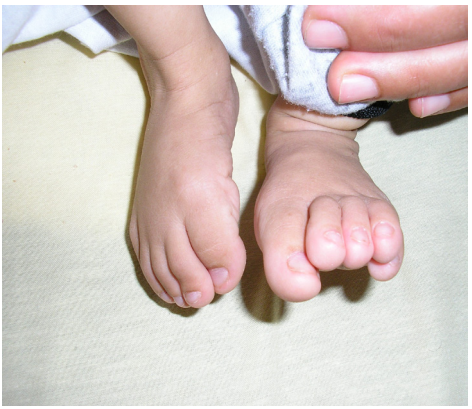

Fig. 4: Foot of the patient showing deviation of big toe laterally and 3rd, 4th and 5th toes medially, broad big toe.

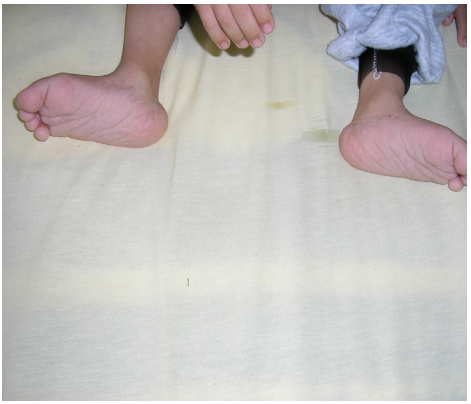

Fig. 5: Foot of the patient showing rocker bottom heel of the patient.

Chest and cardiac examinations showed no abnormality. Abdominal examination revealed generalized abdominal bulge, wide subcostal angle, the umbilicus shifted downwords, hepatosplenomegaly (right lobe of the liver is 5.5 cm below costal margin at the midclavecular line, left lobe was 8 cm at xiphisternum and the spleen was 2cm along its axis).

Genital examination showed bilateral cryptorchidism. The testes were felt at the external ingunal ring. He also had distal penile hypospadius, poorly developed scrotum with light pigmented rugae.

Neurological examination showed generalized hypotonia with hyporeflexia. There was kyphoscoliosis in lower back.

MRI of the brain and echo cardiography were normal. The patient had normal karyotype 46, XY, with normal thyroid function tests, normal liver and kidney function tests. Radiological bone survey was normal apart from hooking of the 1st lumber vertebra. No bony or articular abnormalities could be detected.

Abdominal ultrasound demonstrated bilateral moderate hydronephrosis, hydroureter through the whole visualized course of both ureters, associated with bilateral chronic parenchymatous renal disease of grade II, a picture suggestive of bladder neck obstruction, most probably due to posterior uretheral valve anomaly and mild hepatosplenomegaly.

Opthalmological evaluation showed right central adherent leucoma and bilateral congenital cataract, (Peters' anomaly).

Tables 1 and 2 Compare features of our patient with those of Peters' plus and Kabuki make-up syndromes in literatures.

Table 1: Comparison of features of our patient with those of Peters' plus syndrome in literature[1].

Peters' Plus syndrome: Krause-Kivlin syndrome	**Patient's findings reported in the syndrome**	**Patient's findings not reported in the syndrome**
Mental retardation learning disability in over eighty percent of cases	Mild mentally retarded	
Growth deficiency	Weight (< 3rd percentile)	
Short limbs	Short limbs	
Low birth length	length is 73cm (<3rd percentile), span 67.5cm	
Small head	OFC is 46.5cm, (10th percentile)	
Large head		
Round face		triangular face
Up-slanting	Upword slanting	
Widely spaced eyes	Hypertelorism	
		low depressed nasal bridge
		anteverted naris
		bulbous nose
Long philtrum	Long philtrum	
Thin upper lip with smooth philtrum	Thin upper lip	
Cupid-bow shape of upper lip		
		Thick everted lower lip
		Full cheeks
Small lower jaw	Retromicrognathia	
		High arched palate
		Thick tongue
Small ears Malformed ears Preauricular pits		Low set ears
Prominent forehead Abnormal ossification of the skull	Skull irregular shape with ridges felt, prominent parietal eminences	
Short or broad head		Open anterior fontanel
Central corneal leukoma Anterior eye chamber cleavage disorder Nystagmus Glaucoma Central defect of Descemet's membrane Shallow anterior chamber	Central adherent leucoma	Proptosis of the eyes, shallow orbits

Cataract	bilateral cataract.	
Peters' anomaly	peters anomaly	
Short hands with tapering or webbing of the fingers Cutaneous syndactyly Broad hands Broad feet Short feet Fifth finger clinodactyly	Short hands Partial cutanous syndactly of fingers, toes	Broad thumb, big toe Simian crease
		Bilateral rocker bottom heals
		Hepatosplenomegaly
Genitourinary abnormalities	Bilateral cryptorchidism, distal penile hypospadius, poorly developed scrotum with light pigmented rugae Hydronephrosis, hydroureter, chronic parenchymatous renal disease	
Hypotonia and lax joints	Generalized hypotonia with hyporeflexia	
		Kyphoscoliosis in lower back
Hearing abnormality		
Thin vermilion border		
Broad neck		
Decreased range of elbow motion		
Short lingular frenulum.		
Cardiac defects Atrial septal defects Dilated lateral ventricles		
Cleft lip, Cleft palate		

Table 2: Comparison of features of Kabuki make-up syndrome in literature with our patient features[8].

Kabuki make-up syndrome	Patient's findings reported in the syndrome	Patient's findings not reported in the syndrome
Proportionate short stature		Disproportionate short stature
Dolicocephaly/scaphocephaly/microcephaly Craniosynostosis	Scaphocephaly	Open anterior fontanel
Acquiduct stenosis Lissencephaly/pachygyria/polymicrogyria		
		Triangular face
Large ears Auricular pits/fistulas Prominent ears Simple ear Large ear lobule Underdevelopment of mastoid Abnormal auditory ossicles Cochlear/saccular abnormalities Vestibular apparatus abnormalities		Low set ears
Peters anomaly	Peters anomaly	
Microcornea Proptosis of the eye Microphthalmia Coloboma of iris Coloboma involving optic nerve Coloboma of retina/choroids Nystagnus Strabismus Gase palsy Arched eye brows Long prominent eye lashes Ectropion of the eye lids Wide, long palpebral fissures Epicanthic folds hypertelorism	Proptosis of the eye, shallow orbits Hypertelorism	Bilateral cataract. Upward slanting
Short nasal septum Broad nasal tip Over hanging – depressed nasal tip		Low depressed nasal bridge Anteverted narus, bulbous nose, long philtrum
Small mandible Micrognathia	Retromicrognathia	
Lower lip pits Cleft palate High palate	High arched palate	Thin upper lip, thick everted lower lip, full cheeks
Dental abnormalities Neonatal teeth Oligodontia Abnormally shaped teeth Wide spaced teeth		

Premature development of breast Early puberty in females		
Skeletal abnormalities Absent or hypoplastic clavicles Cone shaped epiphesis/ hypoplastic/ short phalanges, hypoplaslic/ deepset/ small nails		
Eventration of diaphragm, Congenital hernia of diaphragm		
Scoliosis Caudal appendage Sacral dimple/ sinus Hemivertebra Irregular end plates of vertebra spina bifida occulta	Kyphoscoliosis in lower back Hooking of the 1st lumber vertebra	
Postnatal growth retardation		
Mental retardation, Normal intelligence (16%) Developmental delay Convulsions, abnormal EEG	Mild mentally retarded developmental delay	
Dislocation of hip/ patella		
Joint laxity /Hypotonia	Generalised hypotonia	Hyporeflexia
Recurrent infections T cell deficiency Immunoglobulin abnormality	Recurrent UTI	
Cardiovascular anomalies		
Genitourinary anomalies Renal dysplasia Horse shoe kidney Hydronephrosis Double ureter Urinary reflux Dilated ureters Ureteral atresia	Bilateral cryptorchidism Distal penile hypospadius Poorly developed scrotum with light pigmented rugae Hydronephrosis Hydroureter Chronic parenchymatous renal disease	
Biliary atresia/ stenosis Abnormal liver (including function)	Hepatomegaly	
Abnormal dermatoglyphic pattern Brachydactly Clinodactly Skin syndactly of fingers Fetal finger pads	Simian crease Short hands	Partial cutanous syndactly of fingers and toes, broad thumb and big toe Bilateral rocker bottom heals
Anorectal anomaly		
Autism/ autistic behavior		
		Thick tongue
		Splenomegaly

DISCUSSION

Our patient have the main characteristic features of Peters' plus syndrome which are anterior chamber eye anomalies in the form of Peters' anomaly, cataract, central corneal leukoma, mental retardation, growth deficiency, disproportionate short stature, cutenous syndactly, genitor urinary malformations. But the patient did not have hearing defect, cleft lip and or cleft palate, cardiac defect, cupid-bow shape of upper lip, rounded face which are recorded frequently in the syndrome.

Our patient have also some characteristic features of Kabuki make-up syndrome which are mental retardation, simian crease, renal and urinary tract anomalies, hepatomegaly, craniosynostosis and postnatal growth retardation Camera et al.[9]

Triangular face, thick tongue, thick everted lower lip, full cheeks, anteverted naris, broad thumb and big toe, kyphoscoliosis in lower back, bilateral rocker bottom heals and splenomegaly are reported in our patient but not reported in both syndromes.

Analysis of mutations in the β1,3-galactosyltransferase – like gene (B3GALTL) is indicated for genotype phenotype correlation.

Follow up of the patient by kidney function tests, surgery for hydroureter and hydronephrosis will be done. Physiotherapy for the hypotonia and delayed motor milestones and follow up of ophthalmological condition was done.

Camera et al.[9] also reported a patient showed Peters'-Plus syndrome associated with some clinical manifestations of the Kabuki make-up syndrome.

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