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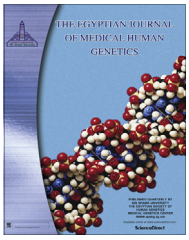

CASE REPORT

Blepharophimosis, ptosis, epicanthus inversus syndrome type 2 with red hair, lymphedema of lower limbs and kidney stones in an Egyptian patient

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KEYWORDS

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Kidney stones

Abstract We report the case of a 2 month old male, 6th in order of birth of 1st cousin consanguineous marriage with the typical features of blepharophimosis, ptosis, epicanthus inversus syndrome (BPES) including bilateral shortening of the horizontal and vertical dimensions of the palpebral fissures, bilateral eye lids drooping, lateral displacement of inner canthi with a small skin-fold obscuring the inner canthus of the eye. Our patient had normal psychomotor development. His father was similarly affected suggesting autosomal dominant inheritance.

The patient had red brown hair, lymphedema of lower limbs and kidney stones which were not reported before with this syndrome. Most probably these additional features are associations with BPES.

1. Introduction

Blepharophimosis, ptosis and epicanthus inversus syndrome (BPES) is an autosomal dominant inherited developmental disorder of the eyelid region and sometimes is associated with reduced fertility in females [1]. Major ophthalmic features present at birth include blepharophimosis, ptosis, epicanthus inversus as well as telecanthus [2].

Here we report an Egyptian patient with BPES, who had the typical features of the syndrome, in addition to red hair, lymphedema of lower limbs and kidney stones after taking the consent of parents.

2. Case report

A 2 month old male, 6th in order of birth of 1st cousin consanguineous Egyptian parents. The patient was delivered at full term by a cesarean section after an uncomplicated pregnancy with no history of drug intake by the mother. His birth weight was 3.100 kg. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of facial dysmorphism noticed at birth. At the age of 1 month, the patient had repeated attacks of vomiting and diarrhea

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associated with repeated hospital admissions. The mother had 4 abortions and 1 neonatal death. His father had the same facial dysmorphism and had corrective eye surgery for ptosis when he was a child. The mother's age was 23 years and the father's age was 29 years at the time of conception. Our patient had normal mental and psychomotor development as he had good head control and adequate intentional smile.

On examination, his weight was 4.100 kg (5th percentile), his length was 51 cm (below 5th percentile), and his skull circumference was 37 cm (5th percentile). The patient had blepharophimosis, ptosis, and epicanthus inversus which were immediately noticed at birth as he had a bilateral shortening of the horizontal and vertical dimensions of the palpebral fissures with bilateral eye lids drooping. At the medial lower lid, a small skin-fold starts and runs upwards and medially, obscuring the inner canthus of the eye (Fig. 1). An increase in the intercanthal distance of both medial canthi was obvious, whereas the interpupillary distance was normal with a slight antimongoloid slant. There is a bilateral convergent squint. He had a flat nasal bridge, high arched palate and small low set ears. He also had sparse red hair (Fig. 2) and a family history of red hair and fair skin color in both the paternal and maternal sides. Both feet showed overriding of the second toe over 3rd toe and dysplastic nails (Fig. 3). He had mild non-pitting edema in the dorsum of both feet and legs to below the knee since birth (Fig. 4). Abdominal examination revealed umbilical hernia. The back, cardiac and neurological examinations were apparently normal. The genitalia were also normal.

Abdomino-pelvic ultrasonography demonstrated bilateral renal stones measuring 4.3 mm in the left kidney and 3.1 mm in the right kidney (Fig. 5). Echocardiography was normal. Urine analysis revealed calcium oxalate crystals. Hemoglobin was 9 mg/dl. Serum calcium, uric acid and albumin were normal. Thyroid function and kidney function tests were normal. Liver function tests were normal. Arterial blood gas and extended metabolic screen tests were also normal. Karyotype as well as visual acuity and fundus examinations were normal.

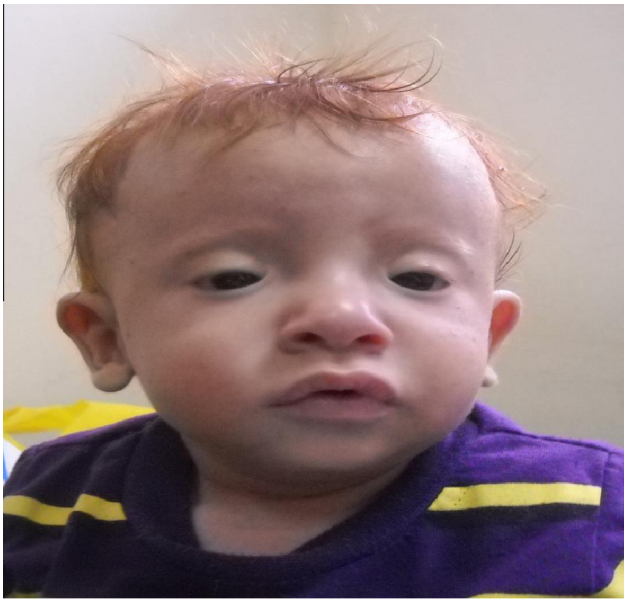

Figure 1 Blepharophimosis, ptosis, and epicanthus inversus.

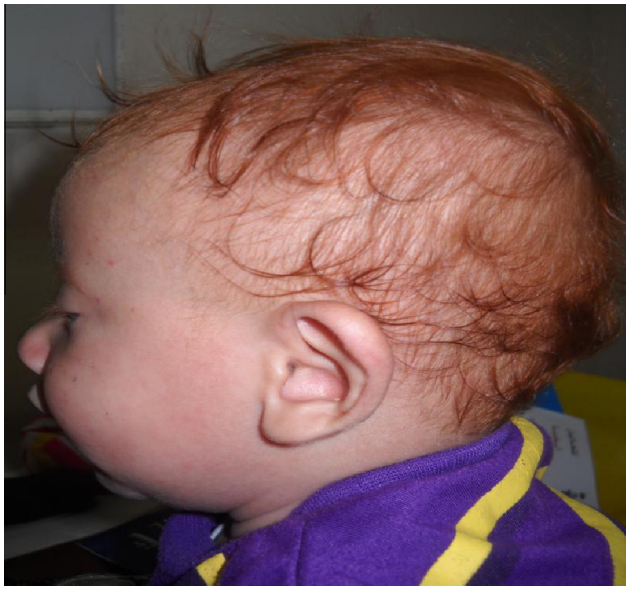

Figure 2 Sparse red hair.

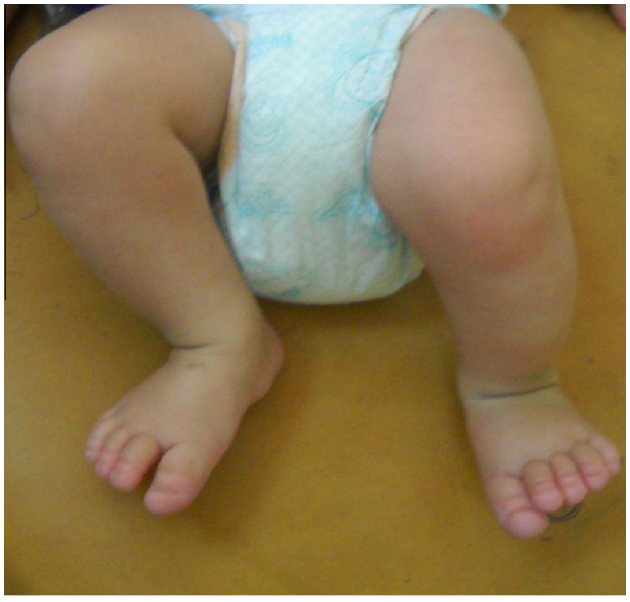

Figure 3 Both feet showed overriding second toes over first and third toes and dysplastic nails.

3. Discussion

Blepharophimosis, ptosis and epicanthus inversus syndrome (BPES) is a developmental disorder for which diagnosis is based on 4 major features: Blepharophimosis (shortened horizontal palpebral fissure) [3]; Ptosis (drooping of eyelids) [4], Epicanthus inversus (vertical fold of skin that stretches from the lower eyelid up toward either side of the nose) and telecanthus (lateral displacement of inner canthi with normal interpupillary distance) [5]. All these features are typically detected in our patient.

There is a high incidence of bilateral strabismus than the general population which can be detected in our patient. There

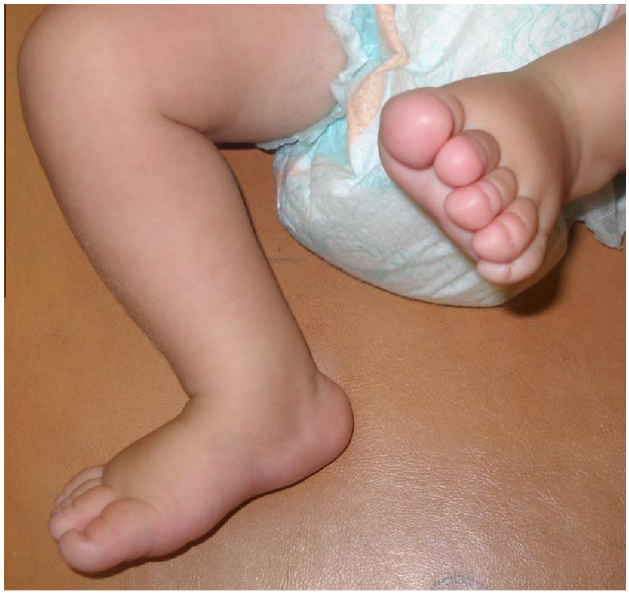

Figure 4 Edema of dorsum of foot.

is also a high incidence of refractive errors in patients with BPES [6], however in our patient visual acuity and fundus picture were normal. Occasional ocular findings reported in some patients include microphthalmos, anophthalmos, microcornea, hypermetropia, and nystagmus [6] which are not detected in our patient.

In addition our patient has some facial features as antimongoloid slant, flat nasal bridge, high arched palate as well as low set ears with less corrugations of ear cartilage. These features were also reported previously in BPES cases [7]. Kokitsu-Nakata and Richieri-Costa [8] reported two patients with BPES, a girl who has in addition a cleft palate and a boy who has in addition a cleft lip. Few patients have a high arched palate as detected in our patient.

Our patient had brown red hair and fair skin which is present in his fathers and mothers families. There were no reports of BPES patients with red hair. The parents of our patient are first cousins, (consanguinity rate is high in Egypt [9]). Red hair is a recessive genetic trait caused by a series of mutations in the melanocortin 1 receptor (MC1R), a gene located on chromosome 16 [10]. Most probably the red hair character in our patient can be explained by consanguinity of parents and autosomal recessive inheritance. There are many kinds of red hair [11], some fairer, or mixed with blond ('strawberry blond'), some darker, like auburn hair, which is brown hair with a reddish tint as in our patient. Skin and hair pigmentation is caused by two different kinds of melanin [11]: eumelanin which is responsible for dark hair and skin and pheomelanin which has a pink to red hue and is present in lips, nipples, and genitals. Red hair has the highest amounts of pheomelanin and usually low levels of eumelanin, and is the rarest natural human hair color [12]. The mutations in the MC1R gene impart the hair and skin with more pheomelanin than eumelanin causing both red hair and freckles [10].

Other anomalies reported in BPES include minor hand and foot anomalies, inguinal hernia and craniosynostosis [13]. Our patient had overriding toes and bilateral non pitting edema of both lower limbs most probably lymphedema.

Costa et al. [14] also reported two boys with BPES. Both of them had a flat philtrum, thin upper lip and a small chin. The first one had in addition inguinal hernia and hypospadias. The second one had abnormal auricles and metatarsus adductus.

Cardiac defects (ventricular septal defect, tetralogy of Fallot and pulmonary stenosis) may also be reported in these patients [7]. Echocardiography detected no cardiac abnormalities in our patient. Abdominal ultrasonography in our patient detected bilateral renal stones and urine analysis revealed calcium oxalate crystals which are not reported previously in BPES. There was no family history of renal stones and no history of intake of diuretics by the mother during pregnancy. Nephrolithiasis, a rare but well-described entity in children, is unknown in newborn infants [15]. About 50% of the pediatric cases of urolithiasis are idiopathic and the rest are due to

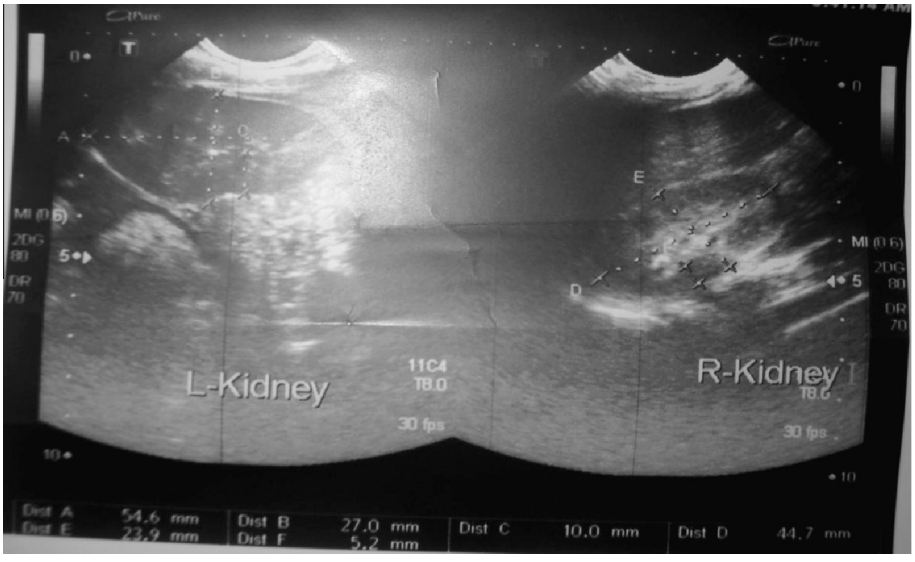

Figure 5 Abdomino-pelvic ultrasonography demonstrated bilateral renal stones.

hypercalciuria (30%) and hyperoxaluria (20%), or rarely due to hyperuricosuria, xanthinuria or hypocitruria [16]. Urine analysis in our patient demonstrated calcium oxalate crystals with no hematuria. Most probably the cause in our patient is hypercalciuria. However the case needs further investigations and follow up.

Our patient has mild non-pitting edema of the dorsum of both feet and legs up to the knees. This is most probably primary lymphedema as it was detected since birth (congenital lymphedema). There are several causes of primary lymphedema including the Turner syndrome, Noonan syndrome, lymphedema–distichiasis syndrome, lymphedema and ptosis syndrome and yellow nail syndrome and hypotrichosis–lymphedema–telangiectasia syndrome [17]; however they are not reported with BPES.

Our patient has most probably congenital primary lymphedema (Milroy's disease) as the characteristic symptoms of the previous syndromes are not detected although our patient has sparse hair as well as dysplastic nails. The lymphatic vessels of the affected edematous areas are thought to be hypoplastic or aplastic and this has to be confirmed by MRI or better by fluorescence microlymphography [18]. This also has to be confirmed by molecular analysis as a c.3109G > C mutation in FLT4/VEGFR3 gene is implicated in Milroy's disease [19].

Most probably the brown red hair, lymphedema of lower limbs and renal stones are in association with BPES in our patient as they are not reported previously with this syndrome.

Two types of BPES are reported [1]. Type 1 which is believed to be more common and includes female infertility as a result of premature ovarian failure in addition to the ophthalmic manifestations. This type is totally penetrant and transmitted by males only, while affected females are infertile. Type 2 is limited to the eye manifestations with fertility in females and males. So this type is transmitted by both affected males and females and its penetrance is 96.5. Our patient has a family history of the affected father with no history of infertility in females. So our patient most probably belongs to type 2.

Mentality as well as developmental milestones are normal in our patient. However mentality as well as developmental delay may be associated in patients with BPES [20].

Pedigree analysis in our patient suggested autosomal dominant inheritance as he has an affected father. The same mode of inheritance was reported in many patients with BPES. However a number of sporadic cases have also been reported [21]. So an informative pedigree is essential for classification. Also genetic counselors must be alert to non penetrance or reduced expression of the gene in some families [22].

It is possible to identify a causative genetic defect in 88% of BPES cases [2]. Among all genetic defects found in BPES, an estimated 75% of cases are due to intragenic FOXL2 mutations [23]; 12% of BPES cases result from deletions involving partial or whole FOXL2 gene deletion [24], and approximately 5% of cases involve regulatory deletions outside the FOXL2 gene [20]. About 2–5% of individuals with BPES have cytogenetic rearrangements, such as interstitial deletions and translocations involving 3q23 [25]. The 3q23 region is considered as the major gene locus for BPES [26]. Zahanova et al. [2] reported a patient with BPES due to a large interstitial deletion, 3q22.3q23, which includes FOXL2 gene who presents with an external genital anomaly, spastic diplegia and speech delay. A second gene locus reported in a large Indian pedigree is located on chromosome 7 p13-p21 [27]. This indicates genetic heterogeneity in BPES. So a high-resolution molecular karyotyping is recommended for patients with BPES. Our patient had a normal conventional karyotype.

The surgical goal in BPES is not only to improve the unusual facial features and the related head posture, but also to improve the peripheral visual field of the patient. The timing for congenital ptosis correction is controversial. Early surgery will prevent amblyopia and late surgery allows for more reliable ptosis measurement which provides a better outcome [21].

To conclude, BPES is a rare disease. Clinical features in BPES cases of Egyptian origin have not been reported. We report a patient with blepharophimosis, ptosis and epicanthus inversus syndrome who has in addition red hair, lymphedema of lower limbs and kidney stones which were not reported before. Being aware of the characteristic clinical features of BPES will aid early genetic diagnosis and inform about possible associated features.

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