Unilateral cryptophthalmos with renal agenesis and syndactyly (Fraser Syndrome)
Report of a case with review of the literature

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Abstract Cryptophthalmos is a rare congenital anomaly of eyelids with consequent poor development of the eye which is hidden under the skin. It had been reported in association with other defects, particularly genitourinary malformations and syndactyly. We report a case featuring this anomaly in association with bilateral renal agenesis and syndactyly of hands and feet, with detailed autopsy findings and review of pertinent literature.

Keywords: Cryptophthalmos, renal agenesis, syndactyly, Fraser syndrome, congenital malformation

Cryptophthalmos or ablepharon is a rare congenital malformation characterized by total failure of the development of lid folds, occurring during early fetal development. It results in incorporation of the epithelium that should form the cornea and conjunctiva into the skin which passes without a break from the forehead to the cheek. The poorly formed eye will be present hidden beneath the skin. The condition should be differentiated from other congenital anomalies of the eye and the eyelids such as anophthalmos, microphthalmos, ankyloblepharon, and congenital entropion.

This anomaly can be unilateral or bilateral, complete or incomplete. When it is unilateral, the eyelid can be the site of other malformations such as microblepharon or colobomas. Several reported cases had other associated congenital defects elsewhere in the body including genitourinary malformations, deformities of the nose and ears, and syndactyly of the hands and the feet. The latter feature had been reported frequently to the extent that this association prompted some authors to name this condition as cryptophthalmos-syndactyly syndrome. The association of cryptophthalmos with other congenital anomalies had been called Fraser syndrome by some authors in reference to the work of Fraser who described four cases of cryptophthalmos with multiple congenital malformations in two sibships.

Ballantyne in his book on antenatal pathology gave a good account of the cases which were reported in the last century including the first detailed description of this anomaly by Zeheiner in 1872. Many cases have been reported since with a variety of associated malformations, mostly in the ophthalmological literature. We report a case from Jordan with autopsy findings and review of the literature.

Case report A stillborn female foetus with several congenital malformations was brought to the Department of Pathology of Jordan University Hospital for performance of an autopsy to assess the exact nature of these malformations and to check for the presence of internal anomalies.

The mother was 24 year old G6P3Ab2. She was lactating for 18 months before getting pregnant. During the second and third months of pregnancy, she had vaginal bleeding associated with mild abdominal pain. She was placed on progestogen, and antispasmodic medication. The bleeding stopped, and the pregnancy continued without any further complications. She came to the hospital in labour fully dilated with frank breech presentation. No fetal heart sounds were heard on auscultation or detected by the fetal monitor. A stillbirth female foetus was delivered vaginally.

The father and mother are first cousins. Their three live children are girls, one of whom has

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syndactyly of her hands without any associated other malformations.

**Autopsy findings** The body under examination was that of a female stillbirth which weighed 2865 gms. and measured 44 cms. in length. Examination of the head revealed absence of the left upper and lower eyelids with no palpebral fissure seen. Instead, the skin of the forehead was seen in continuum with that of the left cheek, with no eyebrow or eyelashes noted. The right eyelids were present, but the upper one showed the presence of coloboma (Fig. 1). The right eye was microphthalmic. The nose was malformed with its tip featuring the presence of a prominent notch, giving it a bifid appearance (Figs. 1 and 2). Both ears were low set, and malformed (Fig. 2). Examination of the rest of the body revealed syndactyly of both hands and feet (Figs. 3a, 3b). The external genitalia were unremarkable with no evidence of clitoral hypertrophy noted. No hernias were identified, and no spinal defects were noted.

The skin overlying the left orbit was incised. No lacrimal sac was identified, but a very small rudimentary eye was seen within the orbit surrounded by fatty tissue and few thin bundles of ocular muscles. The optic nerves were seen, but the left was slightly thinner than the right. The optic chiasma and the optic tracts were unremarkable. The brain itself appeared normal grossly. After total removal of the brain from the skull, it was noted the left orbit was smaller than the right orbit, resulting in some degree of asymmetry of the anterior cranial fossa, giving an appearance of cranioscoliosis. The left superior sphenoidal ridge was thinner than the right one, and the inferior sphenoidal wing was poorly developed.

On opening and dissecting the thoracic cavity, it revealed unremarkable lungs, heart, major blood vessels, and thymus. The diaphragm was free of defects. However, the abdominal cavity revealed total absence of both kidneys and ureters. The urinary bladder was hypoplastic. Both ovaries were present, but the uterus was hypoplastic. The vagina was identified, and no fistulas with the rectum or the anal canal were detected. The liver, spleen, stomach, small and large intestine were unremarkable. The adrenals were present, but they

![Fig. 1 - Facial appearance, frontal view. Note absence of left upper and lower eyelids, coloboma of right upper eyelid, low set ears, and bifid nasal tip.](image)

![Fig. 2 - Facial appearance, lateral view. Note left cryptophthalmos, low set left ear, notched nasal tip and receded hair line.](image)
appeared closer to the midline and had rather flattened oval appearance.

**Discussion** Cryptophthalmos is rare. Approximately 80 cases had been recorded in the world medical literature by 1985. Since then, another 9 cases have been reported. The exact pathogenesis is controversial. It could be due to agenesis from primary failure of induction of mesodermal and ectodermal differentiation, or secondary to intrauterine factors such as inflammation resulting in fusion of the eyelids to the globe, or amniotic bands causing pressure on the eyelids and resulting in coloboma formation. Genetic factors appear to play a role in the development of many cases of cryptophthalmos, with several reports describing the occurrence of the anomaly in two or more siblings. Autosomal recessive inheritance noted in 15% of cases especially in families with consanguineous parents. However, familial cases with no consanguinity between the parents had been reported. In the present case, the parents are first cousins. Consanguineous marriages in Jordan are common, and first cousin marriages were encountered in 32.03% of all marriages in one study and in 58.5% of marriage in another study from Northern Jordan. This high frequency of consanguineous marriage could be related to the occurrence of genetic diseases and congenital anomalies in Jordanian children.

Many associated anomalies have been reported in cases of cryptophthalmos. Francois, in his exhaustive study of the subject, reviewed 41 cases reported up to 1969, and added 5 new cases. In an attempt to make some order of the chaotic array of the associated congenital anomalies, he proposed that the anomalies, which he named malformative syndrome with cryptophthalmia, consisted of four components: Cryptophthalmos, dyscephaly, syndactyly, and urogenital malformations.

Cryptophthalmos is usually bilateral, but cases of unilateral involvement had been reported, including the present case. Also, this anomaly can
Fig. 3B - Syndactyly of feet.

be complete or partial with the latter comprising 20% of the reported cases. Attempts of surgical correction of some cases of partial or incomplete cryptophthalmos was not successful generally because the eye globe was poorly developed in these cases.12,13,16,20 Contact lens or prosthetic eye were recommended as the most acceptable methods for cosmetic purposes.20

Craniocerebral anomalies are common in this syndrome, and include deformities of the nose (asymmetry, coloboma of the nares, notching of the tip), deformities of the ears (low set ears, deformed ear pinnae, fusion of the superior edges of the helices to the scalp, stenotic external auditory canal), anomalies of the lip and the palate (cleft lip and cleft palate), meningoencephalocele either frontal23 or basal24 and craniofacial deformities such as asymmetry of head,13 brachycephaly,1 and scaphocephaly.19 In the present case, asymmetry of the skull was evident due to hypoplasia of the left orbit with subsequent shift of the right side of the anterior cranial fossa across the midline and the associated changes in the sphenoidal wings, resulting in cranioscoliosis.

The third component of the syndrome, syndactyly, had been almost a constant feature in most of the reported cases, and this finding prompted some authors to label these cases as the cryptophthalmos - syndactyly syndrome as had been pointed out earlier. However, few cases had been described without associated syndactyly.15,17,18,24 On the other hand, siblings of patients affected by this syndrome were reported to have syndactyly and renal agenesis but without associated cryptophthalmos.25,26 In the present case, one sibling has syndactyly without associated ocular anomalies, but no data are available regarding associated renal anomalies.

Genitourinary malformations reported in association with cryptophthalmos encompass a broad spectrum of conditions including unilateral and bilateral renal agenesis, ambiguous genitalia,1 clitoral hypertrophy,1,17 chordee of the penis,1 agenesis of the urinary bladder,1,11 vaginal atresia,1 hypoplasia of labia majora and minora,1 hypoplasia of scrotum,18 and unilateral poor renal visualization on intravenous pyelogram.7 Some authors emphasized renal agenesis as a key diagnostic feature in the cryptophthalmos syndrome.10,11 In one study, nine cases were reported in four families. All of them died in the perinatal period, and autopsy was performed on six of them revealing renal agenesis, bilateral in three and unilateral in three, thus stressing this feature as one of the diagnostic criteria of this condition particularly in affected cases which are stillborn or died shortly after birth. When the syndrome was found in infants older than 7 days, the clinical manifestations were milder.11

Bilateral renal agenesis was reported in three sibs in one family, with only one of them featuring cryptophthalmos.26 The three sibs were considered as being affected by Fraser syndrome and presenting as bilateral renal agenesis. Renal agenesis in itself is a relatively common congenital malformation with a frequency of 0.12 per 1000 births.26 Several congenital malformations were reported in association with renal agenesis in a study of 155 cases, and include other genitourinary developmental defects, craniofacial anomalies, and ophthalmic defects such as cryptophthalmia, microphthalmia, and cataract.26 But in another study, only one case of microphthalmia was noted in a series of 50 cases of bilateral renal agenesis.27

It is recommended that genetic counseling should be offered to the families of the affected cases, assuming that the mode of inheritance is autosomal recessive, and the risk of another malformed child is 25%. Clinical examination
of the other siblings and performance of renal ultrasonography on them to detect formes frustes cases which can be without the eye defects is recommended."

References