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Fraser Syndrome: A Case Report

Chaimae Sajoura[1,2,3*], Mohammed Ech-Chebab[1,2,3], Anass Ayyad[1,2,3], Sahar Messaoudi[1,2,3], Rim Amrani[1,2,3]

[1]Department of Neonatology and Intensive Care Unit, Mohammed VI University Hospital, Oujda, Morocco
[2]Faculty of Medicine and Pharmacy of Oujda, University Mohammed First, Oujda, Morocco
[3]Maternal, Child and Mental Health Research Laboratory, Oujda, Morocco
Email: *chaimae.sajoura1998@gmail.com

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Abstract

Fraser syndrome is a rare malformative genetic syndrome whose main manifestations are cryptophthalmia, syndactyly, laryngeal atresia and urogenital malformations. We report the observation of a newborn from a non-consanguineous marriage, admitted to the neonatology and neonatal intensive care unit at Day 1 of life for a poly-malformative syndrome. Clinically, the newborn presented with bilateral anophthalmia, cleft palate, dysmorphic facies with a rounded forehead, hypertelorism, micrognathia, low-set ears and a short neck, syndactility and bilateral cryptorchidism. Trans fontanellar ultrasound revealed tri ventricular hydrocephalus. Cerebral MRI angiography showed malformative tri-ventricular hydrocephalus, hypoplasia of the brainstem and cerebellum, and poly-microgyria. Transthoracic and renal ultrasonography were unremarkable, and the chest X-ray was normal. The authors discuss the malformative clinical and para-clinical aspects of this syndrome, multidisciplinary management and the importance of prenatal diagnosis.

Keywords

Fraser Syndrome, Cryptophthalmia, Newborn, Polymalformative Syndrome

1. Introduction

Fraser syndrome is a rare polymalformative genetic syndrome; first described in 1962 by British geneticist "George Fraser" [1]. Cryptophthalmia is one of the most frequent features of this syndrome (93% of cases). Other anomalies associated with this syndrome are mainly urogenital, laryngeal and cardiac. The etio-pathogenesis of this syndrome is still debated and its management is complex and multidisciplinar.

A population-based epidemiological study of 12,886,464 births using data from the European Network for Congenital Anomalies Surveillance (EUROCAT) of congenital anomalies registries revealed a prevalence of 0.2 per 10,000 births;

and more than 300 cases has been reported so far, the Diagnosis criteria have been defined in 2007.

Cryptophthalmos is the most defining feature, but not an obligatory feature of Fraser syndrome. A wide variability of expression has been observed, making its clinical diagnosis sometimes challenging; in addition, establishing a clear genotype-phenotype correlation has also proved difficult until now.

The objective of this observation is to present a case seen in neonatology and neonatal intensive care unit at the CHU Med VI-Oujda presenting clinical criteria in favour of fraser syndrome, in order to discuss the clinical and paraclinical aspects of this syndrome as well as the importance of multidisciplinary management and especially antenatal diagnosis.

2. Observation

A male newborn from a non-consanguineous marriage was admitted to the neonatology and neonatal intensive care unit at the first day of his age with a poly-malformative syndrome. The mother and father were aged of 34 and 35 years old respectively, and the mother was primiparous with no notable pathological history. The pregnancy was poorly monitored (no morphological ultrasound) and delivered at 42 days' amenorrhea (depending on the date of the last menstrual period and the last ultrasound before delivery), with a cesarean delivery, without suffering or neonatal infection.

The newborn presented with bilateral anophthalmia (**Figure 1**), cleft palate, dysmorphic facies: with domed forehead, hypertelorism, micrognathia, low implanted ears, and short neck, syndactilia (**Figure 2**), as well as bilateral cryptorchidism (**Figure 3**), without anorectal anomalies. Trans fontanellar ultrasound revealed triventricular hydrocephalus. Cerebral MRI angiography showed malformative tri-ventricular hydrocephalus, hypoplasia of the brainstem and cerebellum, and poly-microgyria (**Figure 4**). Transthoracic and renal ultrasound were unremarkable, and the chest X-ray was normal (**Figure 5**).

The newborn was referred to neurosurgery, pediatric surgery and a genetic consultation for specialized care.

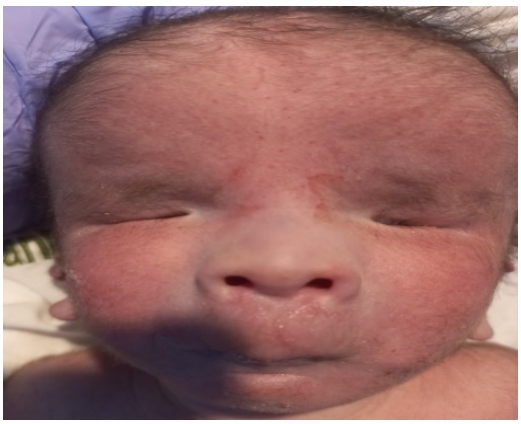

Figure 1. Bilateral anophthalmos.

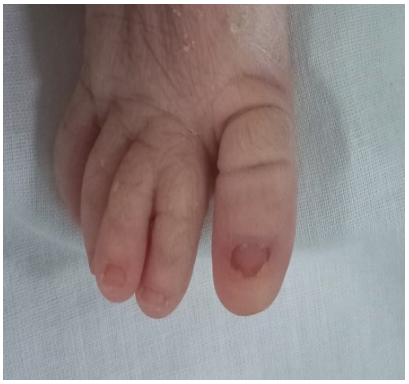

Figure 2. Syndactyly of the toes.

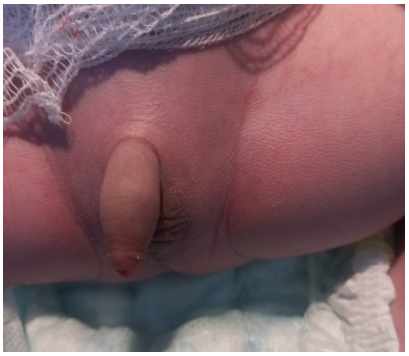

Figure 3. Bilateral cryptorchidism.

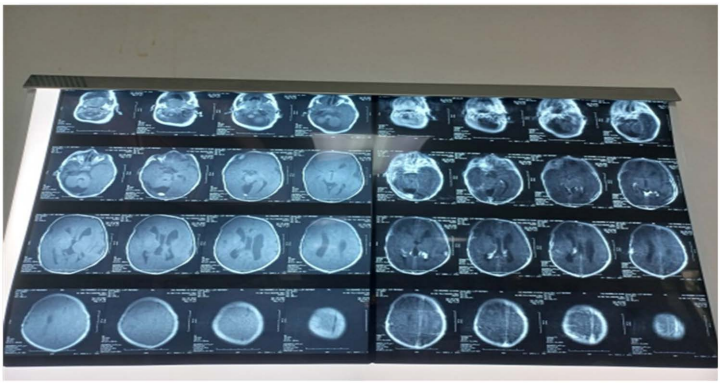

Figure 4. Brain MRI image.

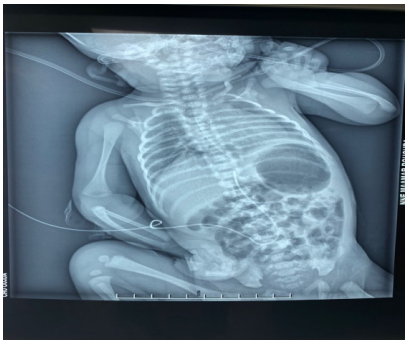

Figure 5. Chest X-ray image.

For the molecular analysis, peripheral blood was collected from the patient and his parents. The karyotype was performed according to standard procedures, and the results are still in progress. Unfortunately, the newborn died at the age of 40 days in the paediatric emergency department, due to complications of severe neonatal respiratory distress + hypovolaemic shock.

3. Discussion

Fraser syndrome is a rare syndrome. Only 3 patient series, totalling 391 cases, have been reported in the literature [2] [3] [4]. The etiopathogenesis is debated and several theories have been put forward: it could be a primary abnormality of eyelid formation with metaplasia of the corneal and conjunctival epithelium [2], a refusal of partially formed eyelids [2] or a failure of programmed cell necrosis which would result in utero in the opening of temporarily closed areas such as the eyelids, fingers, vagina, toes, etc. [3].

Recent work has identified a gene responsible for this syndrome, called FRAS1, and genetic research is underway to identify other genes and their homozygous mutations [5] [6]. Around 15% of children described in the literature are born to consanguineous couples, and the Heredity is autosomal recessive.

This syndrome was first described by George Fraser in 1962 [6]. The diagnostic criteria proposed by Thomas *et al.* [3] are clinical; major criteria include cryptophthalmos, syndactyly, genital anomaly and a history of the same symptoms in family. Minor criteria include abnormalities of the ears, nose, larynx and/or palate, skeletal anomalies, umbilical hernias, renal agenesis, and mental retardation in surviving children. Diagnosis requires at least two major and one minor criteria, or one major and four minor criteria. This patient had three of the major criteria and one of the minor ones.

In general, the malformations associated with this syndrome are multiple and diverse. Cryptophthalmos is the cardinal sign, present in 93% of cases. It is most often bilateral and complete, but its absence does not exclude the diagnosis [7]. Syndactyly is also present in 54% of cases. Other associated ocular malformations include: ankylo-blepharon, lacrimal duct anomalies, microphthalmia and anophthalmia. Numerous other malformations have been described as part of this syndrome: ENT malformations: (ear dysplasia, conductive deafness, bifid nose, broad nasal root, laryngomalacia, laryngeal atresia and choanal atresia), urogenital malformations: (renal agenesis, uni or bilateral kidney hypoplasia, hypospadias, epispadias, testicular ectopy, micropenis, bicornuate uterus and hymenal imperforation), and anal imperforations. More rarely, cerebral and neurological malformations such as microcephaly, myelomeningocele, encephalocele and cardiac anomalies [8] have been reported.

It is important to differentiate between isolated cryptophthalmos and the cryptophthalmos of Fraser syndrome; the latter is characterized by the association of other acrofacial and urogenital malformations [6]. Other facial malformations—in particular fronto-nasal dysplasia (Median cleft facial syndrome)—are also respon-

sible of clinical pictures similar to Fraser syndrome, characterized by acrofacial and urogenital malformations, but also the absence of cryptophthalmos, hypertelorism, epibulbardermoid and transethmoidal and sphenoidal encephalocele [9].

Prenatal diagnosis is crucial for timely diagnosis and therapeutic decisions regarding the course of the pregnancy. It is based on ultrasound examination at the end of the 4th month (18 weeks) of pregnancy [10] [11] [12]. The main signs to look for are: hyper-echogenicity of the lungs in the context of oligo-amnios, non-visualization of the kidneys, microphthalmia and syndactyly. Treatment requires a multidisciplinary approach. Plastic surgery remains the only treatment.

In our case, we proposed an aesthetic surgery consisting of an opening of the two palpebral slits, a plastic surgery of the toes, and a reconstructive surgery of the genital system. Since the Treatment options are limited; genetic counseling therefore plays an important role.

25% of affected children are dead born, and 20% die before the first year of life; mainly due to kidney malformations and/or laryngeal atresia. In the absence of renal agenesis, life expectancy can be considered normal, but survivors suffer of severe mental retardation.

4. Conclusions

Fraser syndrome is a rare malformative syndrome in which cryptophthalmos is the main feature. Renal and laryngeal diseases determine the prognosis. Its management is complex and requires a multidisciplinary team.

Prenatal diagnosis is strongly recommended in consanguineous couples and/or those with similar children/family histories, especially in countries where cousin marriages are very common.

Despite the variability of this syndrome, it remains difficult to fully understand, and genetic research will certainly open up new therapeutic horizons.

Consent

The patient's parents were contacted to explain our goal of sharing their child's case for scientific purposes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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