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Differential Contribution of Fraser Syndrome and Anophthalmos: 4 Cases and Review of the Literature

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Abstract

Fraser syndrome is an autosomal recessive genetic malformation. Diagnosis is established by the presence of at least two major and one minor criteria, or one major and four minor criteria. Congenital anophthalmia is the clinical absence of the eye at birth. It results from the absence of development or regression of the primary optic vesicle during embryonic life; it may be isolated or associated with other congenital malformations, and its management requires a multidisciplinary approach.

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It is a rare and extremely serious pathology, due to the degree of impairment of visual function. We decided to use two (2) cases of Fraser syndrome two (2) cases of isolated exophthalmia recorded in our ophthalmology unit to carry out a prospective, cross-sectional observational study to provide a differential approach these two entities and to review the literature through this clinical observation.

Keywords

Fraser syndrome; Anophthalmos: Syndactyly: Cryptophthalmos

Introduction

Fraser syndrome was first described by George R. Fraser in 1962 as an autosomal recessive genetic malformation [1]. Diagnostic criteria are clinical, and include major criteria: cryptophthalmia, syndactyly, genital anomaly. And minor criteria: abnormalities of the ears, nose, larynx and/or palate, skeletal anomalies, umbilical hernias, renal agenesis, and mental retardation in survivors [2]. Congenital anophthalmia is the complete absence of the eye due to defective formation of the optic vesicle during the early stages of gestation [1]. The aim of this paper is to explain the difficulty of managing these pathologies, including the severity of their occurrence, to demonstrate the need for multidisciplinary management and, finally, to review the literature.

Methodology

This was a prospective, cross-sectional observational study covering the period from March 2021 to October 2023, or 33 months of data collected in our ophthalmology unit at the Maradi regional hospital. Our data collection technique was based on consultation of the register of patients followed up and seen in consultation for Fraser syndrome or isolated anophthalmia with no organic cause found.

Case Reports

Clinical observation 1:

A 15-day-old male neonate was referred to the ophthalmology department of the Maradi regional hospital for a poly malformities syndrome with complete bilateral occlusion of the eyelids. The pregnancy was spontaneous and unattended, with no evidence of drug intake or exposure to radiation by the mother during pregnancy.

The pregnancy was carried to term, and the delivery was carried out at home, vaginally, without complication. The newborn was predominantly breast-feeding. The mother was 22 years old and the father 31, all in apparent good health. he was the second of two siblings, the eldest 24 months old, in apparent good health with no malformative anomalies. On admission, the newborn was reactive, with good suction, well coloured, and weighed 3200g, with a head circumference of 34cm and a heel of 50cm.Physical examination to confirm occlusion complete level two eyes (Figure 1). Bidigital palpation

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noted the presence of an eyeball under the skin tissue, an elongated skull with part of the forehead invaded by hair, the root of the nose was depressed, the thoracic limbs showed a shape anomaly, syndactyly of the 3rd and 4th fingers (Figure 2), as did the pelvic limb, syndactyly of the 2nd and 3rd toes (Figure3). Elsewhere, other structures appeared normal.

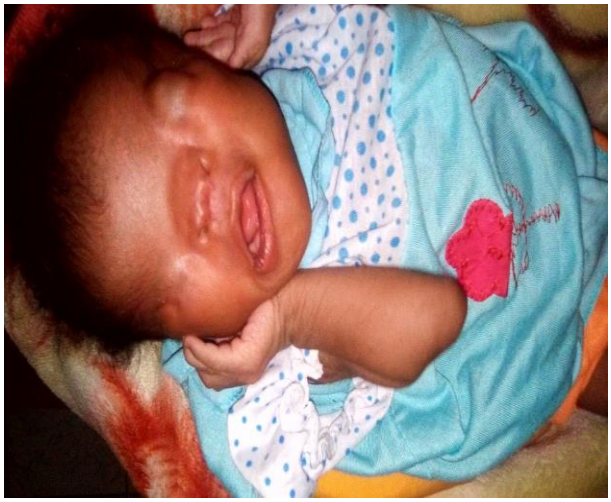

Figure 1: Complete bilateral occlusion of the eyelids (observation 1).

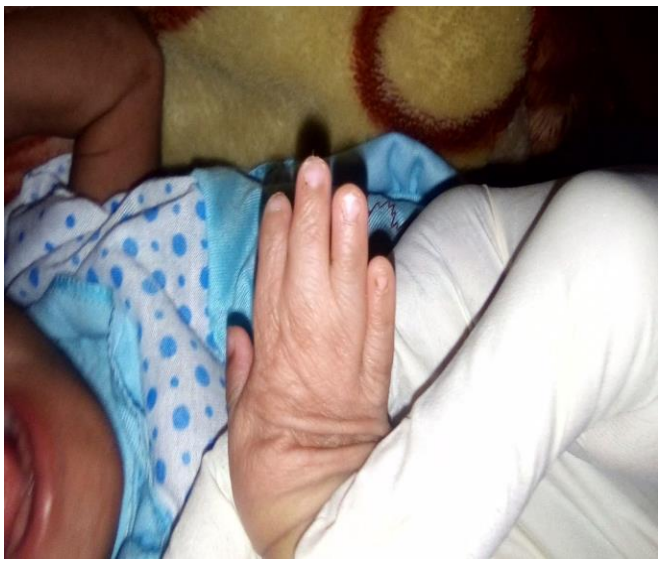

Figure 2 :3rd and 4th finger syndactyly (observation 1)

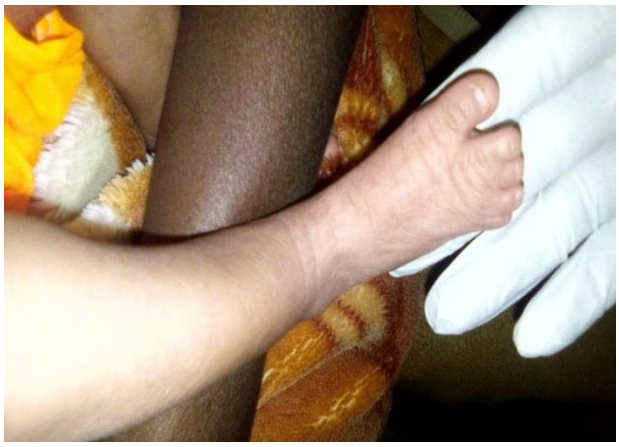

Figure 3: Syndactyly of the 2nd, 3rd and 4th toes (observation 1).

The diagnosis of Fraser syndrome was retained in front of the presence of two major signs and less 3 minor criteria. In particular, cryptophthalmos, syndactyly of the 3rd and 4th fingers, and syndactyly of the 2nd and 3rd toes were considered to be the two major signs, and minor signs such as elongated skull, depressed nasal root, thoracic limbs with anomalous shape, and pelvic limb anomaly.

Observation 2:

This was a female newborn aged 3 days, referred to the ophthalmology department of the Maradi regional hospital for a poly malformative syndrome with an absent eyeball. The pregnancy was spontaneous and unattended, with no evidence of medication, drugs or exposure to radiation in the mother during pregnancy.

The pregnancy was carried to term, and the delivery was carried out at home, vaginally, without complications. The mother, aged 34, and father, aged 40, were all in apparent good health.

She comes from a sibling group of 7 children, of which she is the last, all in apparent good health with no malformative anomalies. It should be noted that there is a notion of first-degree consanguinity between the parents (direct cousins). Note the presence in the history of a similar case in a first-degree cousin with deafness and mental retardation who died at the age of 8.A l'admission, le nouveau-né réactif, avec une bonne sucions, bien colorée, pèse 2980g, un périmètre crânien à 33cm, une talle de 51cm.

Physical examination confirmed a complete bilateral absence of the eyeball in both eyes, by bi-digital palpation and speculum (Figure 4), with pseudo-bald, low-set ears (Figure 5) and depressed nasal root.

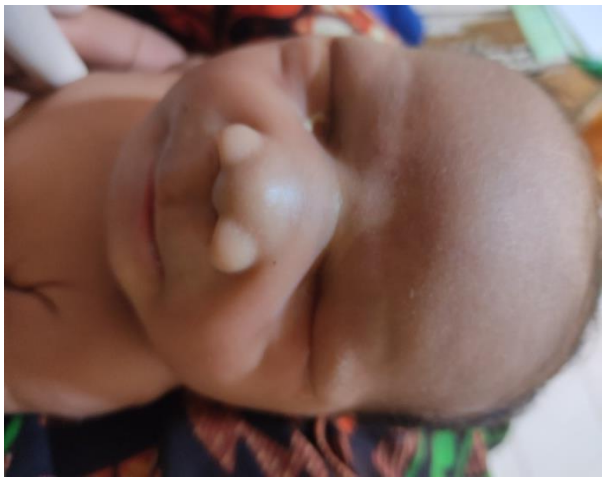

Figure 4: Bilateral anophthalmos (observation 2)

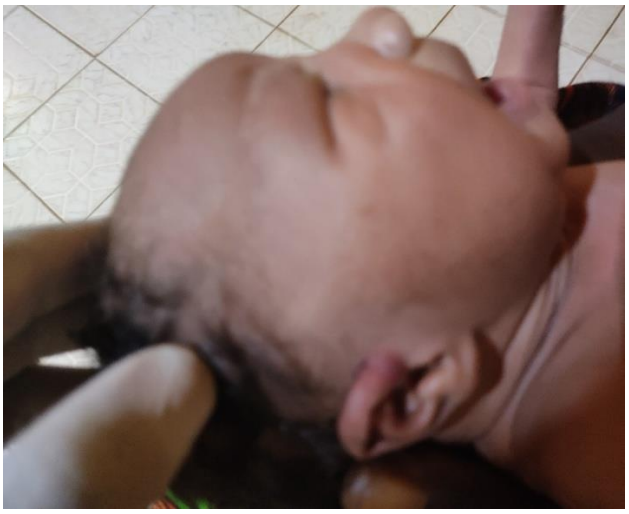

Figure 5: Löw ear implant(observation 2)

The thoracic limbs showed a shape anomaly, stumps following a traditional amputation by ligature of the supernumerary sixth digits (Figure 6 and 7), as well as polydactyly in the pelvic limbs (Figure 8 and 9). Elsewhere, other structures appeared normal.

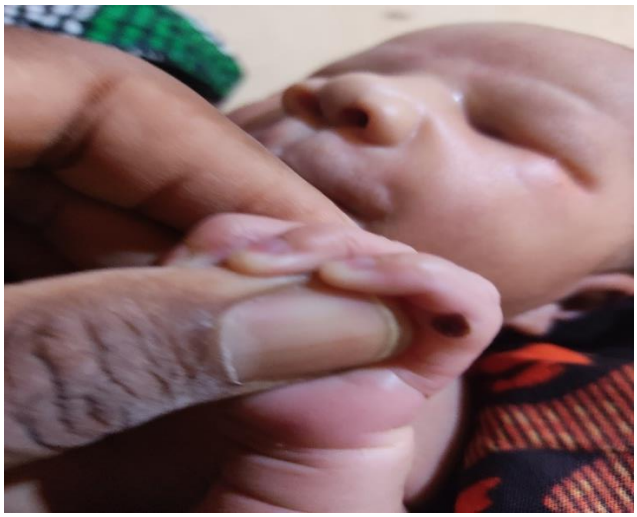

Figure 6: Ligature amputation stump on the left (traditional)

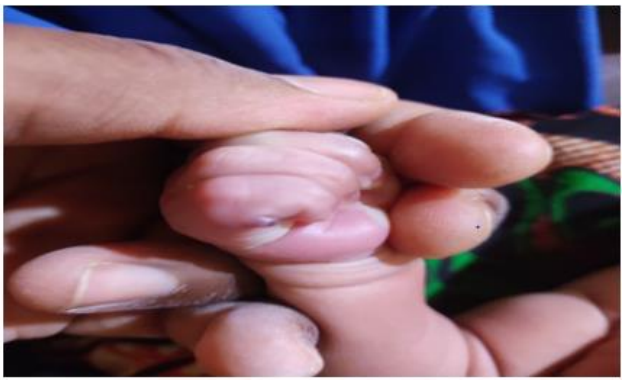

Figure 7: Ligature amputation stump on the right (traditional)

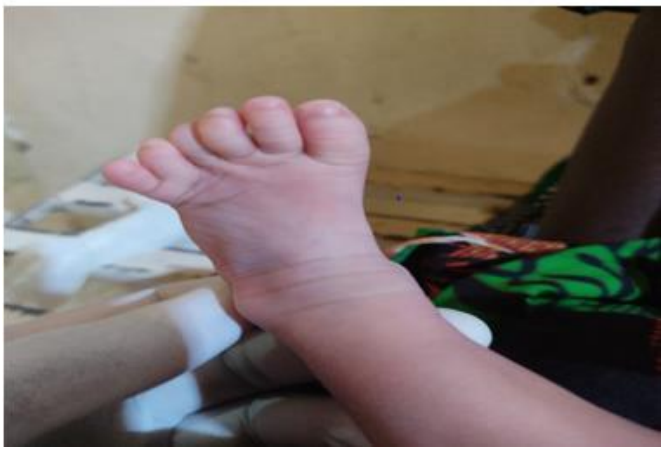

Figure 8: Polydactyly left pelvic limb (observation 2)

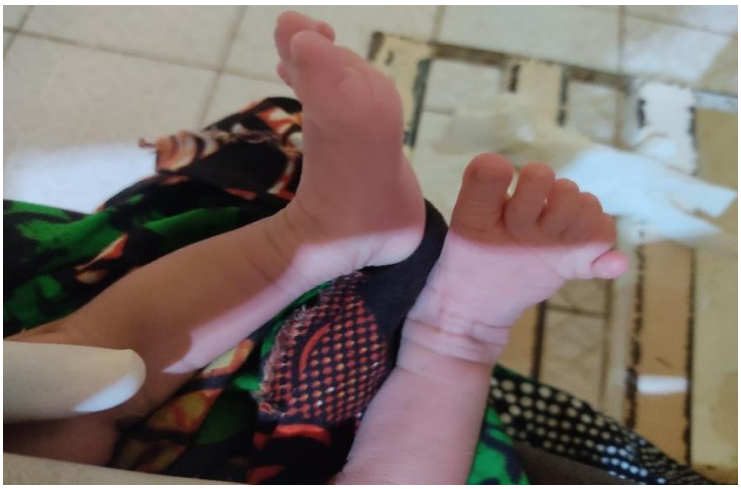

Figure 9: Polydactyly right pelvic limb (observation 2)

The urogenital examination noted an anal imperforation with a genital anomaly involving a lack of differentiation of the labia minora and the clitoris. Due to the parents' disagreement, we were unable to obtain an illustrative image. The newborn was referred to the pediatric surgeon for advice and treatment.

Fraser syndrome was diagnosed on the basis of two major criteria: Genital anomaly and history of a similar case in the family, and minor signs such as anophthalmia, pseudo baldness, low-set ears and depressed nasal root.

Observation 3

This was a 4-day-old male newborn referred to the ophthalmology department of the Maradi regional hospital for an absent eyeball. The pregnancy was spontaneous and unattended, and there was no evidence that the mother had taken any medication, drugs or been exposed to radiation during pregnancy. The pregnancy was carried to term, and the baby was delivered at home, vaginally, without complications. The mother was 37 and the father 48, all in apparent good health. He came from a sibling group of 8 children, of whom he was the youngest, all in apparent good health with no malformative anomalies; there was a notion of first-degree consanguinity between the parents (direct cousins).

On admission, the newborn was responsive, with good suction, well coloured, and weighed 3301g, with a head circumference of 33cm and a heel of 49cm. Physical examination by bi-digital palpation and speculum, completed by ocular ultrasound, confirmed a complete bilateral absence of the eyeball in both eyes. Abdominal and pelvic ultrasound showed no organic anomalies. The diagnosis retained is that anophthalmia isolated no cause was found.A general assessment was carried out, including a cerebro-orbital scan revealing the absence of an ocular bulb in the orbital cavity. (Figure 10 and 11)

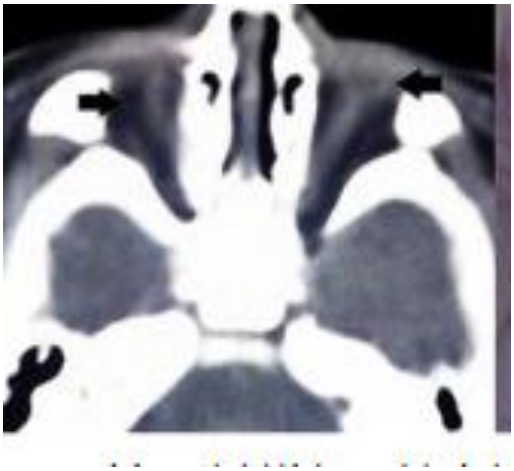

Figure 10: Cerebro-orbital scan revealing the absence of an ocular bulb in the orbital cavity (observation 3)

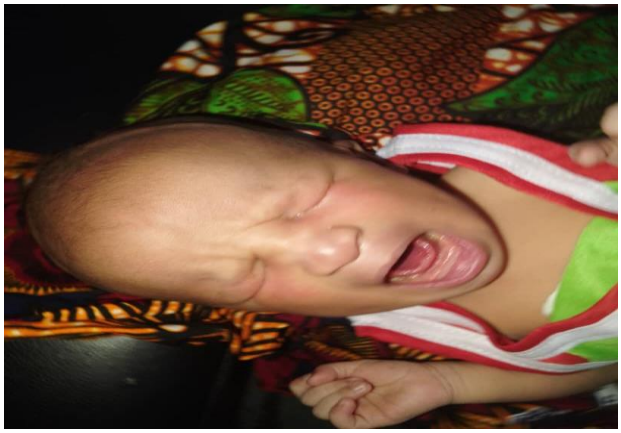

Figure 11 : Bilateral anophthalmes (observation 3)

Observation 4

This 34-month-old male neonate was referred to the ophthalmology department of the Maradi regional hospital because of an absent eyeball. The pregnancy was spontaneous and unattended, with no evidence of medication, drugs or exposure to radiation during pregnancy. The mother is 32 years old and the father is 39 years old, all in apparent good health.

He is the youngest of three siblings, the rest of whom are in good apparent health with no malformative anomalies, although there is some consanguinity between the parents. On admission, he was in general condition, mucous and conjunctival colored, apyretic, with a weight of 14 kg and a height of 86 cm.Physical examination confirmed a complete absence of both eyes (Figure 12), as did speculum examination, with the eyelids difficult to open, the skull elongated and the nasal root depressed.

Elsewhere, the other structures appear normal, and in the absence of organic causes, we have retained the diagnosis of isolated anophthalmos. Our four observations demonstrated the consanguinity of the parents, and we strongly recommended genetic counselling for all our observations.

Our attitude to ophthalmological management consisted of: according to the histopathology of true cryptophthalmia, the cornea is replaced by vascularized fibrous tissue adhering to the skin. Hence our attitude of therapeutic abstention in view of the mediocrity of the results, nevertheless all our four observed patients were referred to the pediatric surgeon in the case of the newborn with anal imperforation and genital anomaly. The geneticist for genetic counselling, and on the ENT side, we referred the newborn to investigate and manage any cases of ear dysplasia, deafness, etc....

Figure 12: Bilateral anophthalmos (observation 4)

Discussion

Fraser syndrome is a rare syndrome first described in 1962 by the British geneticist Fraser [1] cryptophthalmia (xpuKtot;, cache), so named by Zehender and Manz (1872), is not an isolated malformation localized to the ocular region, but part of a generalized malformative syndrome, which constitutes a well-defined clinical entity [1]. Congenital anophthalmia is defined as the complete absence of the eye due to defective formation of the optic vesicle during the early stages of gestation [1]. The etiopathogenesis of Fraser syndrome is debated. It may be due to a primary defect in the formation of the corneal and conjunctival epithelium, or to a failure of programmed cell necrosis, resulting in utero in the opening of temporarily closed areas such as the eyelids, fingers, toes and genitalia [1]. Diagnostic criteria are clinical, and include major criteria: cryptophthalmia, syndactyly, genital anomaly. Minor criteria include abnormalities of the ears, nose, larynx and/or palate, skeletal anomalies, umbilical hernias, renal agenesis, and mental retardation in survivors [2]. Research has identified a gene responsible, called FRAS 1. Approximately 15% of children described in the literature are born to consanguineous couples. Heredity is autosomal recessive [5]. The notion of consanguinity was found in all cases observed; hence our attitude to seek genetic counseling. Diagnosis is established by the presence of at least two major and one minor criteria, or one major and four minor criteria [3].

Cryptophthalmos in the context of fraser syndrome and isolated anophthalmos are serious anomalies that can lead to very severe visual handicaps. They may or may not be hereditary in origin, and may be isolated or associated with other ocular or systemic anomalies. Anophthalmia combined with microphthalmia is

genetically heterogeneous. It can be inherited (recessive or dominant modes), although most non-syndromic cases are sporadic [4]. The main gene responsible is SOX2, followed by OTX2, RAX, FOXE3 and PAX6 [2]. A family history and examination of the parents are essential for etiological diagnosis, genetic study and prevention of recurrence [2]. The management of fraser syndrome and isolated congenital anophthalmia requires a multidisciplinary approach. However, the treatment of cryptophthalmia remains surgical and proves difficult, resulting most of the time in mediocre ocular functional results, hence our therapeutic abstention in the cases observed.

Conclusion

Fraser syndrome and isolated anophthalmos remain a major surgical and aesthetic challenge, particularly in developing countries where the lack of resources and qualified personnel remains a challenge.

The two entities constitute serious conditions when they occur, due to the malformations associated with them, and the severe impairment of the functional prognosis engendered, hence the need for health personnel and the general public to be fully aware of the existence and occurrence of these ocular pathologies.

Conflicts of Interest

The authors declare no conflicts of interest.

Consentement

Written informed consent was obtained from the patients for publication of these case reports and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors' Contributions

All authors have contributed to the realization of the work. They also declare to have read and approved, and to have made amendments to the final version of the manuscript.

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