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Case Report

Fraser Syndrome in a Baby Whose Elder Siblings have Hydrocephalus. A New Causal Gene?

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Abstract

Fraser-cryptophthalmos syndrome is a rare, autosomal recessive syndrome characterized by cryptophthalmos (hidden eye), syndactyly, ambiguous genitalia, hypertelorism, a broad depressed nasal bridge, a tongue of hair extending from temple to the brow, umbilical hernia, anal stenosis and diastasis of the symphysis. We report a case of 3-day-old baby whose siblings had hydrocephalus. He was brought to the hospital for deformities. Physical examination revealed absence of eyelids and eyebrow over both eyes. It was completely covered with skin. The nose was broad, flat with a depressed nasal bridge and a groove was present bilaterally on the nares. Ears were low set evoking a Fraser Syndrome. The exact cause of Fraser Syndrome in our patient remains a subject of discussion. Genetical research centre should be built in Madagascar because counseling before any marriage is found to be of paramount important to prevent the multiplication of such malformation.

Keywords: *Anophthalmia; Fraser Syndrome; Hydrocephalus; Madagascar; Genetic Research*

Introduction

Fraser-cryptophthalmos syndrome is a rare, autosomal recessive syndrome characterized by cryptophthalmos (hidden eye), syndactyly, ambiguous genitalia, hypertelorism, a broad depressed nasal bridge, a tongue of hair extending from temple to the brow, umbilical hernia, anal stenosis and diastasis of the symphysis pubis [1,2]. The world incidence of Fraser syndrome would be 0.043 per 10,000 live births. Its prevalence in Europa is estimated, by European Surveillance of Congenital Anomalies, at 0.20 per 100,000 births [3].

Purpose of the Study

The purpose is to report an unusual case of Fraser syndrome in a baby whose elder siblings have hydrocephalus in Madagascar and to compare the history of the patient with the literature.

Observation

A full term 3 day-old delivered vaginally at the hospital vigorous newborn male baby was brought to ophthalmology service of Joseph Ravoahangy Andrianavalona Hospital (HJRA) for multiple congenital deformities. He was the fourth baby of non-consanguineous parents. His mother reportedly accomplished 5 prenatal cares, all serologies TORCH (Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes simplex virus) were negatives but she didn't practice any ultrasonography during the pregnancy. His parents had no remarkable neither

personal nor familial antecedent of malformative disease. She reported to have whitish inodorous leucorrhea during her last pregnancy. She had no past history of X-ray radiation nor self-medication by drug which are incriminated in causing congenital deformity either.

The mother of our patient was addicted to decoction. She neither smokes nor drinks alcohol. Regarding the 3 elder siblings of our patients, the first brother was born premature then he developed a post-natal hydrocephalus. The second sibling was a female who had no health problem. The Third children was a full term male child who developed a postnatal hydrocephalus.

On examination of our patient, the face revealed absence of eyelids and eyebrow over both eyes. It was completely covered with skin. The eyeball was palpable underneath at the left side. The nose was broad, flat with a depressed nasal bridge and a groove was present bilaterally on the nares. Ears were low set (Figure 1). He had no respiratory failure.

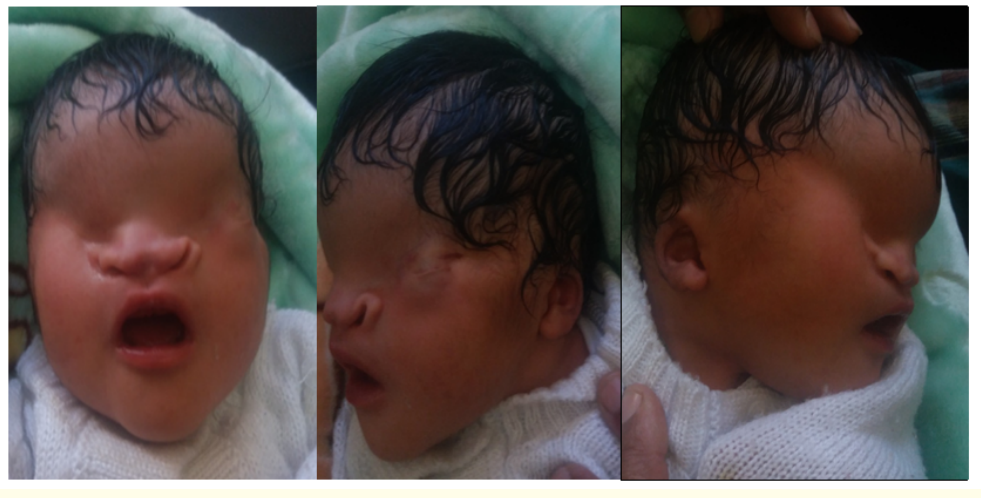

Figure 1: *Facial deformities during Fraser Syndrome.*

The external genitalia were presents. The anal canal was patent. There was partial cutaneous soft tissue syndactyly of fingers (Figure 2) and toes (Figure 3).

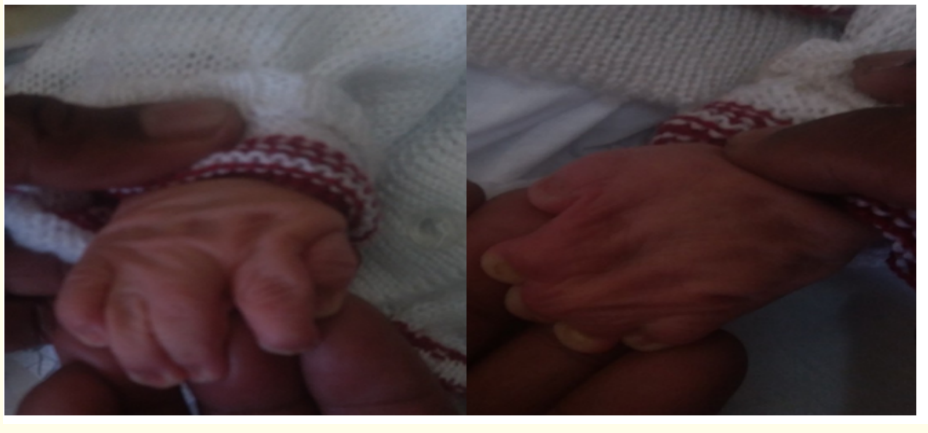

Figure 2: *Syndactyly of fingers of both hands.*

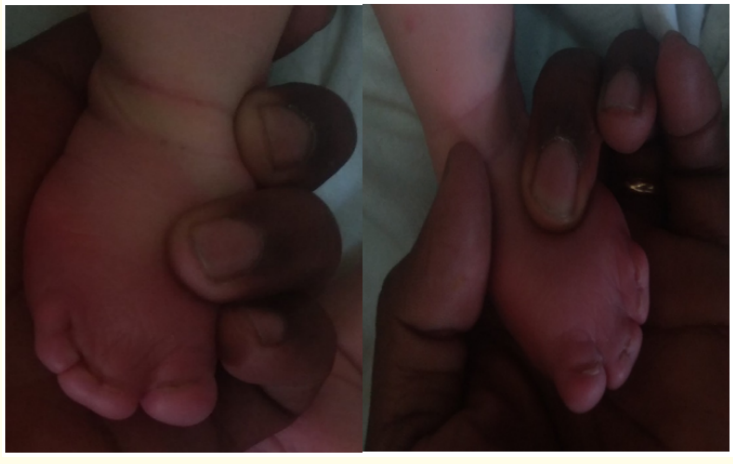

Figure 3: *Syndactyly of toes of both feet.*

We didn't perform any genetical findings, and the parents of the baby disappeared when further findings such as abdominal ultrasonography and CT-scan were prescribed.

We performed an ocular ultrasonography confirming an anophthalmia at the right side and cryptophthalmos at the left sides (Figure 4).

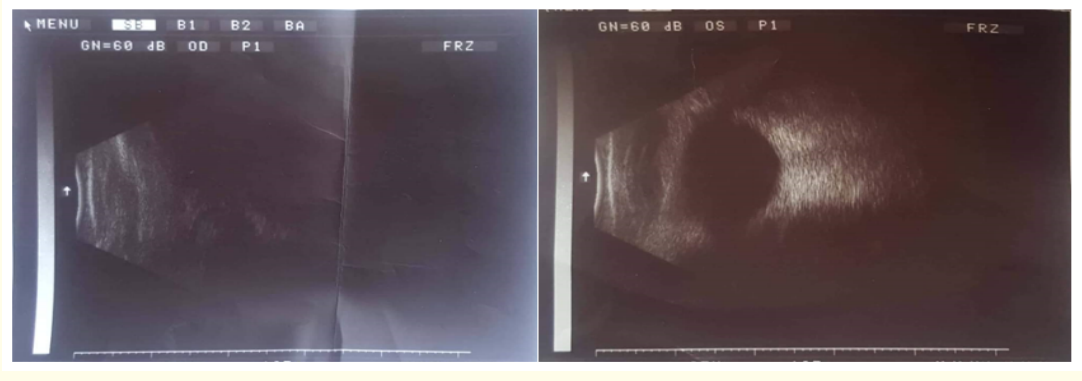

Figure 4: *Ultrasonography showing anophthalmia in right eye and cryptophthalmos in the left side.*

In total, referring to diagnostic criteria of Fraser syndrome, our patient had some major criteria including cutaneous syndactyly, cryptophthalmos and some minor criteria such as ear and nose anomalies. So, the diagnosis of Fraser syndrome was posed.

Discussion

Fraser-cryptophthalmos syndrome is a rare, autosomal recessive syndrome [1].

The most specific for Fraser syndrome (major criteria) included cutaneous syndactyly, cryptophthalmos, ambiguous genitalia, urinary, and respiratory tract anomalies and a positive family history. Less specific congenital anomalies (minor criteria) were ear and nose anomalies, anorectal abnormalities, skull ossification defects, and an umbilical hernia [4].

Pathogenesis of Fraser syndrome is thought to be related to a failure of the programmed cell necrosis or to defects in epidermal adhesion which result in the formation of large blisters during embryonic development [5,6].

Consanguinity is reportedly implicated in the formation of Fraser syndrome. Yan-zaou-tou., *et al.* [7] reported a case of a 6 year-old-child, 3rd child of a sibling of 3 children from consanguineous marriage, presenting unilateral symblepharon, syndactyly of 2nd and 3rd interdigital spaces without any other organic defects in favor of Fraser syndrome. Similarly, in a study conducted by Barisic I., *et al.* based on the data provided by 34 registries from 16 European countries for the 1990–2008 period about Fraser Syndrome in a European Population unveiled that consanguinity was present in 7/26 (27%) families [3]. Moreover, Van Haelst., *et al.* reported a very high consanguinity rate (25/40 families) [4]. In contrast, Farooqui., *et al.* observed a 6 months old male child from Vietnam suffering from a complete bilateral cryptophthalmos. Similarly to our case, there is no history of consanguinity nor familial [8]. Likewise, Sing., *et al.* in India and Naher in Bangladesh reported cases of Fraser syndrome whose family had no history of familial hydrocephalus [9,10].

We found out that none of these aforementioned authors noticed any familial or relatives history of hydrocephalus. Think of this, Barisic., *et al.* exploited data during the 19 years under review of Fraser Syndrome in European countries. They didn't point out any familial background of hydrocephalus of the patients [3]. Hydrocephalus is a disorder of cerebral spinal fluid (CSF) physiology resulting in abnormal expansion of the cerebral ventricles. The known aetiological mechanisms of paediatric hydrocephalus are inflammatory, neoplasm, vascular, congenital aqueduct stenosis, neural tube defects, posterior fossa malformations, developmental cysts. Hydrocephalus has possible genetic origins as well (See table 1) [11]. Nevertheless, in our case, the two elder siblings both have an isolated hydrocephalus. However, these two siblings had no other deformities evoking a Fraser syndrome.

Syndromes	Origin Genes
Hydrocephalus [11]	L1CAM, CCDC88C; MPDZ, AP1S2, POMT1; POMT2; POMGNT1; FUZ, VANGL1/2, CCL2; MTR, MTRR, MTHFR, MTHFD; CC2D2A, TMEM67, MKS1; NF1; Ras-Raf-MEK-ERK, KRAS, BRAF, PTPN11; PTEN; FANCB
Fraser Syndrome [4,12-15]	FRAS1 (607830.0001) FREM2 (608945.0001) GRIP1
Anophthalmia [16]	SOX2 or OTX2

Table 1: *Comparison of possible genetic origins of Fraser Syndrome, hydrocephalus, anophthalmia.*

What is more, most of reported cases of Fraser syndrome had completed the major and minor criteria. In the case of our patient, some of signs were missing such as ambiguous genitalia, hypertelorism, a, a tongue of hair extending from temple to the brow, umbilical hernia, anal stenosis and diastasis of the symphysis pubis.

We summarize in a comparative table below the possible genes causing Fraser Syndrome, hydrocephalus and anophthalmia, we underscore that there was no link in common causal genes of these three diseases. Consequently, they are three different entities.

Apart from possible genetical origin, the mother of our patient was addicted to decoction. Then, Gonzague., *et al.* has already reported a case of newborn from a nonconsanguineous family mother addicted to decoction also who developed congenital bilateral anophthalmia associated with cleft lips and cleft- palate [17].

Through these abovementioned reports, we can affirm that we publish the first case of Fraser syndrome patient whom family has a past history of successive hydrocephalus. This finding hasn't been mentioned yet in the literature.

For none of reported cases of Fraser syndrome patients had any history of hydrocephalus in siblings. That is the reason why we pose these following questions.

Is the causes of Fraser syndrome of our patient are:

- The common known genes of Fraser Syndrome,

- Common genes of hydrocephalus,
- Common genes of anophthalmia,
- New sporadic gene mutations,
- Association of multiple genes,
- Decoction or environment,
- Is there any common gene between Fraser syndrome, hydrocephalus and anophthalmia.

We couldn't answer these questions because we didn't perform any genetic testing nor useful blood test to have a clear- cut-evidence. We need several opinions for experts.

A population accessible genetical research centre should be built in Madagascar. Genetic counseling before any marriage is found to be of paramount importance in our country. All congenital malformation cases in Madagascar should be addressed in order to elaborate more in the investigation and genetical research in order to unveil the real causes of these pathologies. Prenatal ultrasonography should be implemented for each pregnancy in order to detect fetus deformity and to decide the management whether the pregnancy can be continued or therapeutic abortion is proposed.

Conclusion

In conclusion, Fraser syndrome is a rare, autosomal recessive syndrome. The exact cause of this disease in our patient remains a subject of discussion for none of literature reported Fraser Syndrome patient having not only one but 2 siblings who developed postnatal hydrocephalus. An accessible for population genetical research centre should be built in Madagascar. Genetic counseling before any marriage is found to be of paramount important in Madagascar. By knowing the proved cause of congenital deformity, we would be able to put break on the widespread of this pathology.

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