CASE REPORT

Two Siblings With Complete Globozoospermia

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Abstract

Although globozoospermia (round-headed spermatozoa) is encountered as 0.1% of the infertile population, familial appearance of globozoospermia is extremely limited. In this report, we aimed to describe two male siblings of 26 and 45 years of age with the clinical and pathological details of complete globozoospermia. Both light and electron microscopic examinations were performed for the diagnosis. Of note, the karyotype analyses of the two siblings revealed 46+XY without any microdeletion on chromosome Y. In the available literature, there are only six more reports describing familial globozoospermia. Although association with several aneuplodies has been reported, specific numerical or ultra structural abnormalities in somatic or sex chromosomes have not been clarified. In this sense, the low incidence of the familial globozoospermia may be the primary cause of the failure to demonstrate any specific inheritance in such cases. However, documentation of siblings with globozoospermia may warrant strong and undetected genetic evidence for the pathogenesis of the globozoospermia.

Keywords: male infertility, teratozoospermia, sperm, sterility

Özet

Komplet Globozoospermili İki Kardeş

Her ne kadar komplet globozoospermi tüm infertil popülasyonda %0.1 oranında izlenebilirse de, ailevi globozosperminin görünümü çok daha nadirdir. Bu makalede 26 ve 45 yaşlarındaki erkek kardeşlerin klinik ve patolojik özellikleri tanıtılmaya çalışılmıştır. Komplet glozoospermi tanısı için hem ışık hem de elektron mikroskopisinden yararlanılmıştır. Ayrıca, yapılan karyotip analizinde her iki kardeşin kromozomsal yapısı 46+XY olarak bulunmuştur ve Y kromozomu üzerinde herhangi bir delesyon saptanmamıştır. Mevcut literatür gözden geçirildiğinde sadece altı ailevi globozoospermi rapor edilmiştir. Her ne kadar az sayıda anöploidi vakası belirtilmiş olsa da, somatik veya seks kromozomlarına ait spesifik sayısal veya ultra yapısal anormallik tanımlanamamıştır. Bu anlamda, az sayıda ailevi globozoospermi vakasının mevcudiyeti, bu vakalara has bir kalıtım tipinin gösterilememesi için birincil sebep olabilir. Ancak, globozoospermili kardeşlerin rapor edilmesi, globozoosperminin oluşumunda altta yatması kuvvetle muhtemel bir genetik nedene dikkat çekilebilmesi açısından önemli olabilir.

Anahtar sözcükler: erkek infertilitesi, teratozoospermi, sperm, sterilite

Introduction

Globozoospermia (round-headed spermatozoa) is well-known but a rare abnormality which has been distinguished in two subtypes. Type 1 (true round-head only syndrome) is characterized by a spherical arrangement of the chromatin and a complete lack of the acrosome. The spherically arranged chromatin may be surrounded by varying amounts of cytoplasm (1). Type 2 globozoospermia consists of round-headed sperms that have abnormally spherical chromatin with a formation of the acrosome (2, 3).

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According to the available literature, there is paucity of data for the exact etiology of globozoospermia. Therefore, a wide spectrum of abnormality had been demonstrated in patients with round-headed spermatozoa (4). For example, higher level of sperm aneuploidy (5) and abnormalities in the nucleus, presumably in chromatin packaging (1) have been noted in the available literature. Besides, abnormalities in sperm binding to the egg vestments (6) and the absence of the putative oocyte-activating factor (2) were shown. Due to clinical and ultrastructural findings, it is generally thought to be a sterilizing pathology; but, fertilization and pregnancies can be achieved with intracytoplasmic sperm injection (ICSI). The variety in the success rate of pregnancy and fertilization in ICSI cycles may be associated with the dominant pathology in the individual with globozoospermia.

In this report, we aimed to present two siblings with complete globozoospermia. Although globozoospermia (round-headed spermatozoa) is encountered as 0.1% of the infertile population (7), familial appearance of globozoospermia is extremely limited. The demonstration of siblings with globozoospermia may point towards an undetected inheritance for the transmission.

Case

A 26-year old male patient was admitted to our department with primary infertility of 6 years duration. Medical history, physical and genital examinations of the patient and his female partner revealed nothing significant. Transvaginal ultrasonography and hysterosalpingography of the female patient presented normal genital structures. Based on the criteria for semen analysis of the World Health Organization (Lab manual, 4th edition; 1999), main semen characteristics were as follows; volume=4.2 ml, concentration=120x10^6/ml and total motility=70%. However, the semen morphology revealed a diagnosis of complete globozoospermia (100%, Type 1) which was stained with Diff-Quik as described elsewhere (8). Of interest, after a detailed consultation with the couple, the sibling of the man was noticed to be infertile for the duration of 20 years. The sibling was 45 years old and never had been evaluated for infertility earlier due to socioeconomic factors. The semen characteristics of the sibling were as follows: volume=3.9 ml, concentration= 90x10^6/ml, morphology=complete globozoospermia (100%, Type 1). The medical history of the siblings was not significant. The urological examinations, biochemical and hormonal assays of both brothers were found to be usual. The examination of the round-headed spermatozoa of the first (a) and second (b) sibling under electron microscopy has shown absence of acrosomal structures (Figure 1). A normal peripheral blood leucocytes karyotype (46+XY) was obtained for both brothers. In addition, no microdeletion on chromosome Y was noted. Notably, the siblings have two more brothers and three sisters. Each of them has had one or more children and does not suffer from infertility.

Discussion

Once a couple present with primary infertility, the semen analysis is thought to be the initial examination of the male. Although oligospermia and impaired motility have been associated with lower fecundity rate, the deleterious impact of isolated teratozoospermia is not clear (9). There is paucity of data for the importance of lower morphological scores in the presence of normal total sperm count and motility rate both in normal and assisted cycles. However, well defined morphological abnormalities such as complete globozoospermia and pin-head have been strongly associated with sterility even in assisted reproductive cycles (7, 10). Of interest, the outcome of intra-cytoplasmic sperm injection (ICSI) cycles found to be lower when compared with patients with male factor rather than specific morphological abnormalities (7). Therefore, examination of sperm morphology should not be underestimated in order to define specific sperm abnormalities in male patients with infertility.

The association between male infertility and numerical/ ultrastructural abnormalities in the sex chromosomes has been widely reported. Genetic causes may account for 10-15% of severe male infertility including chromosomal aberrations and single gene mutations (11). However, chromosomal abnormalities of sperm in patients with globozoospermia have not yet been well characterized (12). Although Vicari et al. (13) have suggested a normal level of chromosomal aneuploidies in patients with globozoospermia, Ditzel et al. (12) reported a positive correlation between globozoospermia and higher chromosomal aneuploidies of the chromosomes 13, 16, and 21. Therefore, someone may hypothesize that in patients with globozoospermia, a higher

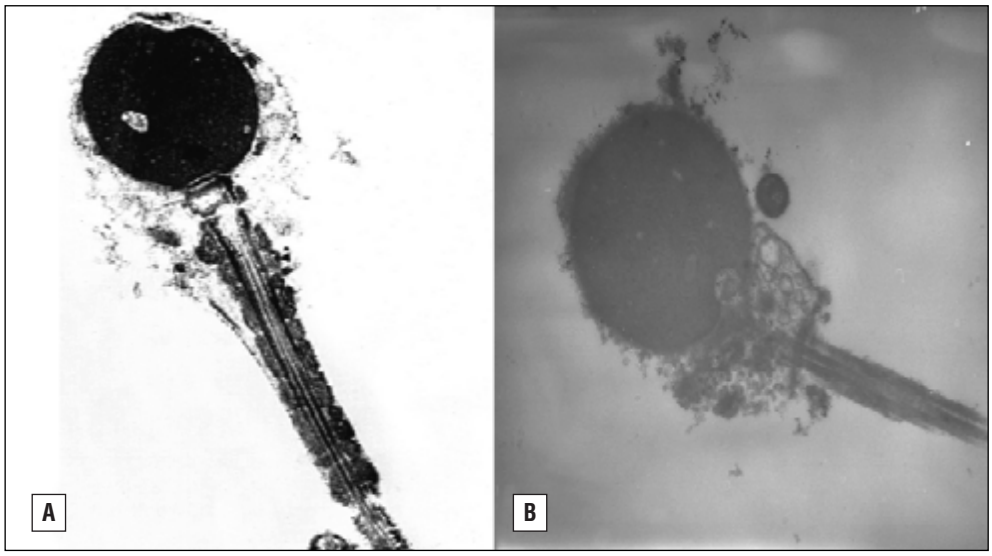

Figure 1. The electron microscopy of round-headed spermatozoa of the first (a) and second (b) sibling, TEM (x600). No acrosomal structures are visualized. Photomicrographs courtesy of Sargon M, MD, Hacettepe University, Department of Anatomy.

Table 1. The available literature for siblings with globozoospermia

Author, year	Siblings	Findings
Kullander and Rausing, 1975[14]	Two siblings	• No disturbance of the endocrine functions. • The blood cells were of 46+XY karyotype. • Investigation of meiosis showed rudimentary second division.
Florke-Gerloff et al., 1984[5]	Two siblings and their father	• The father of the two brothers with exclusively acrosomeless spermatozoa had more than 94% of normally shaped spermatozoa. However, only 10% of these spermatozoa were acrosin positive and only 30% were positive for the outer acrosomal membrane.
Dale et al., 1994[15]	Two siblings	• Normal masculine development and/or a normal aspect of the genitalia. • Sperm fusion capacity could not be triggered by increasing intracellular calcium.
Carrell et al., 1999[1]	Two siblings	• Sibling no. 1 had severely increased aneuploidy of both sex chromosomes (13.5% combined X,Y aneuploidy) and chromosomes 13 and 21 (35.5% and 38.5%, respectively). • The levels of Protamine 1 and 2 were decreased in sibling no. 1.
Carrell et al., 2001[16]	Three siblings	• The sperm aneuploidy rate was significantly increased for chromosome 15 in sibling no. 1, the father of a conceptus with trisomy 15. • Aneuploidy rates were also slightly increased for chromosomes X, Y, and 18 in sibling no. 1.
Kilani et al., 2004[17]	Five siblings	• No noticable differences in sperm morphology or ultrastructure between the samples of brothers with light and electron microscopy. • Normal karyotype.

risk of creating aneuploid embryos after ICSI treatment should be warranted.

A genetic basis for globozoospermia was suspected and is supported by limited number of reports of families with two or more affected siblings (1,5,14-17) (Table 1). Although, some authors suggested that the inheritance of familial globozoospermia may be autosomal recessive (14), autosomal dominant (18), or polygenic (5), the exact mode of inheritance is not clear. By investigating the occurrence of sperm defects in consanguinity, Baccetti et al. reported no additive evidence for an autosomal recessive condition in case of globozoospermia (19). Also, evidence for the participation of Y chromosome microdeletions in globozoospermia could not be established (20). In a recent study (21), a consanguineous family with three affected brothers, in whom the authors identified a homozygous mutation in the spermatogenesis-specific gene SPATA16 has been presented. In our patient, we also failed to present any microdeletion in chromosome Y. The presence of two more brothers without any fertility problems may, though not totally exclude the environmental influences. Also, there had been no one suffering from infertility among the family members of the sibling's parents.

In conclusion, the familial appearance of globozoospermia is extremely rare and the underlying inheritance is not clear. Although several aneuplodies have been reported (Table 1), specific numerical or ultra structural abnormalities in somatic or sex chromosomes have not been clarified. We also failed to show such an aneuploidy or microdeletion. The lower incidence of the familial globozoospermia seems be the main reason in order to demonstrate any specific inheritance in the available studies. However, documentation of the clinical and genetic findings of the siblings with globozoospermia may contribute to describe the pathogenesis of the disorder.

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