

CASE REPORT

Globozoospermia

Sandhya Krishnan

ABSTRACT

Globozoospermia is a severe form of terato-zoospermia characterized by round-headed acrosome-less spermatozoa. The main problem is low fertilization rate due to lack of acrosome. We report successful pregnancy outcome of intracytoplasmic sperm injection (ICSI) treatment in a case of globozoospermia.

Keywords: Globozoospermia, Male infertility, Round-headed sperm cells.

How to cite this article: Krishnan S. Globozoospermia. *Int J Infertil Fetal Med* 2014;5(1):27-29.

Source of support: Nil

Conflict of interest: None

Date of Received: 09-02-14

Date of Acceptance: 18-03-14

Date of Publication: April 2014

INTRODUCTION

A 25-year-old female presented to our clinic with primary infertility of 6 years duration. She had regular menstrual cycles (3/30 days) and mild dysmenorrhea. Husband was 43 years old, chronic smoker (40 cigarettes per day), occasional alcoholic, known diabetic since 5 years, hypercholesterolemia since 5 years on atorvastatin. He had undergone bilateral varicocelectomy 4 years back for grade-2 varicocele. His semen analysis report was volume-2 ml, 86 million count, 40% total motility and 4% sperms with normal morphology (krugers criteria), 90% with amorphous heads. Scrotal Doppler suggested bilateral mild epididymitis with inflamed cords and grade 1 varicocele and right epididymal cyst. Couple had taken three cycles of ovulation induction and intrauterine insemination but failed to conceive.

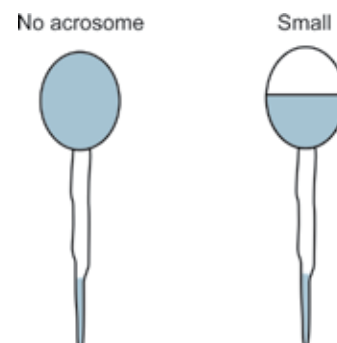
Couple was planned for antagonist protocol and intracytoplasmic sperm injection (ICSI) in view of abnormal sperm morphology at our center.

Stimulation was started on day 2 of cycle with injection recombinant follicle stimulating hormone 200 IU (recagon organon, oss, the Netherlands) subcutaneously for 10 days and injection ganirelix 0.25 mg subcutaneously (inj. organon, organon, oss, the Netherlands), from 6th day of

stimulation for 5 days (Flexible antagonist protocol). On 10th day of stimulation, she had four follicles of 18 mm size, seven follicles of 16 to 17 mm, and eight follicles of 14 to 15 mm size. Peak estrogen level was 2897 picogram per ml. Injection human chorionic gonadotropin (hCG) (urinary), 5000 international unit intramuscularly (ovutrig hp, VHB Life Sciences, Mumbai, India) was administered and oocyte retrieval was done 35 hours later on 12th day. A total of 18 oocytes retrieved. Semen sample on the day was analyzed under inverted microscope revealed 100% globozoospermia. Semen preparation was done by density gradient method using sil-select plus-(silane coated colloidal silica EBSS/HEPES; Fertipro, Belgium). A total of 10 mature oocytes were inseminated by ICSI procedure. Six fertilized and five cleaved. Fertilization rate was 60% and cleavage rate was 83%. Three top-quality embryo were transferred on day 3 after oocyte retrieval and three top quality were frozen. Luteal support was given with vaginal progesterone. Serum beta hCG done 14 days after embryo transfer was 239 international units per liter. Ultrasound done after 3 weeks of embryo transfer confirmed triplet intrauterine pregnancy. Fetal reduction was done at 10 weeks using 4 ml 1:1 KCL solution injected intracardiac into the most approachable fetus and observed until complete cessation of fetal heart. Fetal heart rate of the other two babies were normal at the end of the procedure. Pregnancy continued as twins.

DISCUSSION

Globozoospermia is an uncommon sperm disorder (incidence <0.1%) associated with infertility which until the advent of ICSI in 1992 was considered intractable. The first live birth from globozoospermia was reported in 1995 (Trokoudes et al 1995). Subsequent studies have suggested that despite successful fertilization, such sperms are unable to perform oocyte activation after ICSI.¹



Consultant

Department of Reproductive Medicine, Bangalore Assisted Conception Centre, Bengaluru, Karnataka, India

Corresponding Author: Sandhya Krishnan, Consultant, Department of Reproductive Medicine, Bangalore Assisted Conception Centre, Bengaluru, Karnataka, India, e-mail: sandhyasatheesh@gmail.com

Two types of globozoospermia have been reported.² Type 1 is characterized by complete lack of acrosome and acrosomal enzymes. These spermatozoa are unable to penetrate zona pellucida causing primary infertility. Type 2 have some acrosomal covering with a conical nucleus which may be surrounded by large droplets of cytoplasm material indicating secondary degenerative changes. Infertility in this type is caused by subsequent poor motility.

Total globozoospermia is diagnosed by the presence of 100% round-headed spermatozoa lacking an acrosome. It is still unclear whether patients whose ejaculate contains both normal and globozoospermic cells (partial globozoospermia) suffer from a variation of the same syndrome. Apart from the fact that affected males suffer from reduced fertility or even infertility, no other physical characteristics can be associated with the syndrome.⁵ ICSI is a treatment option for these patients, although low fertilization rates after ICSI show a reduced ability to activate the oocyte.⁵

In globozoospermic sperm, the use of acrosome markers has demonstrated an absent or severely malformed acrosome. Chromatin compaction appears to be disturbed but is not consistently over- or undercondensed. In some cases, an increased number of cells with DNA fragmentation have been observed.³

The pathogenesis of globozoospermia most probably originates in spermiogenesis, more specifically in acrosome formation and sperm head elongation. Together with the occurrence of affected siblings, these findings indicate a genetic origin, which makes globozoospermia a good candidate for genetic analysis. More research is needed to elucidate the pathogenesis of globozoospermia to further understand globozoospermia as well as abnormalities in spermiogenesis and spermatogenesis in general.³

The first to mention 'Rundkopfspermatozoen' (round-headed spermatozoa in German) after light microscopic analysis was Meyhöfer (1965). In 1971, Schirren et al described the fine structure of these round-headed sperm cells as determined by electron microscopy and discovered that their round shape was caused by a round nucleus lacking an acrosome. Wolff et al first suggested the term 'globozoospermia'.³

The most striking features of the unique ultrastructure were complete lack of both an acrosome and a postacrosomal sheath. Thin chromatin threads radiated toward the highly modified nuclear envelope. Some cells showed a partial or total absence of a nuclear envelope. Abnormally arranged mitochondria and tubular derangement in the axoneme were common findings such spermatozoa are incapable of fertilization.⁴ Biochemically, these sperms are characterized by absence or reduced activity of acrosin (acrosomal protease) or calicin (cytoskeleton protein). The globe head is associated with rounded or abnormal-shaped nuclei with

large vacuolar regions. The chromatin is often spherically arranged, surrounded by large amounts of cytoplasm. The middle piece and tail exhibit structural abnormalities and abnormal mitochondria.¹

This form of infertility is of genetic origin and is generally transmitted as autosomal recessive traits.⁷ Acrosome agenesis or globozoospermia results from perturbed expression of nuclear proteins or from an altered Golgi-nuclear recognition during spermiogenesis. Failed fertilization after ICSI of acrosomeless sperm is consistent with an inability of sperm to activate oocytes. Acephalic spermatozoa result from a head-neck defect due to a failure of migration of the tail anlagen and related centriole to the caudal pole of spermatids. An abnormal sperm centrosome function may explain the defective embryo cleavage after ICSI with sperm carrying a fragile head-neck junction. Primary cilia dyskinesia (PCD) and dysplasia of the fibrous sheath (DFS) are isolate defects associated with absent or greatly reduced sperm motility due to an abnormal ciliary structure and function PCD or to a DFS. Numerous defective genes are potentially involved in human isolated teratozoospermia, but such defects have not been defined at the molecular level in most cases. ICSI is the only available method for obtaining live births with sperm carrying these defects, but the outcome is poor and the genetic risk for the subsequent generation can not be determined.⁵

Pathogenesis

In globozoospermia, one or more of the sperm-remodeling mechanisms in spermiogenesis appear to be impaired four possible mechanisms have been postulated to explain the absence of the acrosome.

First—the acrosome may develop separately from the nucleus to be lost in the sertoli cell.

Second—the acrosomal vesicles do not fuse and even detach from the nuclear membrane.

Third—the acrosomal granules may be formed but degenerate subsequently. A malfunctioning golgi apparatus was, therefore, postulated as a possible cause of this malformation of the acrosome.

Fourth—the caudal manchette may be absent or malfunctioning.

Functional Aspects

Acrosomal Markers

Acrosin and the outer acrosomal membrane were absent in mature globozoospermic spermatozoa. Studies have shown eight times decreased amount of proacrosin in globozoospermia.

Phospholipase A2, which is believed to play a role in the acrosome reaction by hydrolysing fatty acids, which

are linked to membrane phospholipids overlying the acrosome. Its activity in globozoospermic cells was significantly lower. The adhesion and penetration failure observed in globozoospermia might be caused by membrane defects vesicle-associated membrane protein or synaptobrevin was only found in rudiment form on globozoospermic cells when used as an acrosome marker, again pointing at a defect acrosome formation.

Fertilization Capacity

Literature indicates that no spontaneous fertilization occurs in case of total globozoospermia. Several authors tested the fertilization capacity of human round-headed spermatozoa in animal models. These spermatozoa were capable of penetrating the cervical mucus (Jeyendran et al 1985)¹² but did not succeed in fertilizing (zona-free) hamster oocytes, unlike spermatozoa of fertile men. On performing ICSI in the presence of the calcium ionophore A 23187 appeared to be able to overcome the failure in oocyte activation.⁶ Once the zona pellucida and the oolemma are bypassed, round-headed spermatozoa can fertilize the oocyte, leading to embryo development and pregnancy.¹⁰

Viability

No decreased percentage of viable sperm cells were encountered (Jeyendran et al 1985 and Check et al 1993).¹³

Molecular Aspects

Chromatin condensation is disturbed in globozoospermia, with a high heterogeneity in the degree of maturity both Baccetti et al (1996)¹⁴ and Vicari et al (2002)¹⁵ found an increased percentage of DNA fragmentation in globozoospermic sperm cells compared with fertile controls (10 vs 0.1% and 37 vs 22.5%, respectively).

Cytogenetics of Sperm Cells

Whether morphological sperm deformities are linked to sperm cell chromosomal abnormalities has been investigated extensively but is still controversial Machev et al⁹ have reviewed these papers, who concluded that increased aneuploidy rates occurred mostly in the acrocentric (13, 14, 15, 21, 22) and sex chromosomes and that these findings do not differ from other types of infertility a genetic basis for globozoospermia was suspected and is supported by several case reports of families with two or more affected siblings. As for the pregnancy outcome, Nagy et al⁶ reported that although the fertilization rate was decreased in cases in which morphologically abnormal spermatozoa were used, no increase in the number of spontaneous abortions or congenital defects occurred. The patients with globozoospermia had no increased aneuploidy has been recently reported in

a study by Perrin et al.¹¹ In conclusion, genetic research on globozoospermia is still in its initial stages but will undoubtedly prove to be invaluable in elucidating the processes of spermiogenesis and spermatogenesis in general and of the etiology of globozoospermia in particular. Mode of inheritance of this condition has not yet been established.⁸

REFERENCES

1. Stone S, Ó Mahony F, Khalaf Y, Taylor A, Braude P. A normal live birth after intracytoplasmic sperm injection for globozoospermia without assisted oocyte activation: case report. *Hum Reprod* 2000 Jan;15(1):139-141.
2. Singh G. Ultrastructural features of round-headed human spermatozoa. *Int J Fertil* 1992 (Mar-Apr);37(2):99-102.
3. Dam AH, Feenstra I, Westphal JR, Ramos L, van Golde RJ, Kremer JA. Globozoospermia revisited. *Hum Reprod Update* 2007 Jan-Feb;13(1):63-75.
4. Pedersen H, Rebbe H. Fine structure of round-headed human spermatozoa. *J Reprod Fertil* 1974 Mar;37(1):51-54.
5. Francavilla S, Cordeschi G, Pelliccione F, Bocchio M, Francavilla F. Isolated teratozoospermia: a cause of male sterility in the era of ICSI? *Front Biosci* 2007 Jan 1;12:69-88.
6. Nagy ZP, Verheyen G, Tournaye H, Van Steirteghem AC. Special applications of intracytoplasmic sperm injection: the influence of sperm count, motility, morphology, source and sperm antibody on the outcome of ICSI. *Hum Reprod* 1998 Apr;13(Suppl 1):143-154.
7. Dirican EK, Isik A, Viedan K, Sozen E, Suludere Z. Clinical pregnancies and live births achieved by intracytoplasmic injection of round headed acrosomeless spermatozoa with and without oocyte activation in familial globozoospermia: case report. *Asian J Androl* 2008 Mar;10(2):332-336.
8. Dam AH, Ramos L, Dijkman HB, Woestenenk R, Robben H, van den Hoven L, Kremer JA. Morphology of partial globozoospermia. *J Androl* 2011 Mar-Apr;32(2):199-206.
9. Machev N, Gosset P, Warter S, Treger M, Schillinger M, Viville S. Fluorescence in situ hybridization sperm analysis of six translocation carriers provides evidence of an interchromosomal effect. *Fertil Steril* 2005 Aug;84(2):365-373.
10. Kilani ZM, Shaban MA, Ghunaim SD, Keilani SS, Dakkak AI. Triplet pregnancy and delivery after intracytoplasmic injection of round-headed spermatozoa. *Hum Reprod* 1998 Aug;13(8):2177-2179.
11. Perrin A, Louanjli N, Ziane Y, Louanjli T, Le Roy C, Gueganic N, Amice V, De Braekeleer, Morel F. Study of aneuploidy and DNA fragmentation in gametes of patients with severe teratozoospermia. *Reprod Bio Med Online* 2011 Feb;22(2):148-154.
12. Jeyendran RS, Van der Ven HH, Perez-Pelaez M, Crabo BG and Zaneveld LJ. Development of an assay to assess the functional integrity of the human sperm membrane and its relationship to other semen characteristics. *J Reprod Fertil* 1984;70:219-228.
13. Check JH, Kozak J, Katsoff D. Hypoosmotic swelling: evaluation of sperm tails using strict criteria in cases of globozoospermia. *Arch Androl* 1993;30:125-128.
14. Baccetti B, Collodel G, Piomboni P. Apoptosis in human ejaculated sperm cells (notulae seminologicae 9). *J Submicrosc Cytol Pathol* 1996;28:587-596.
15. Vicari E, Perdichizzi A, De Palma A, Burrello N, D'Agata R, Calogero AE. Globozoospermia is associated with chromatin structure abnormalities: case report. *Hum Reprod* 2002;17:2128-2133.