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Anti-Sperm Antibodies: Risk Factors of Positive Serology among Infertile Men Patients in Kisangani-Democratic Republic of Congo

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Abstract

Introduction: Antisperm antibodies (ASA) prevalence is high in Kisangani. ASA are one of the male factors of infertility that can reduce spermatozoa motility and cervical penetration or prevent acrosomal reaction and even alter embryo development. This study aims to determine the risk factors of ASA positivity among infertile men in Kisangani. **Patient and Method:** We conducted a case-control study during a period of 2 years in Kisangani on 111 men who consulted for conception and tested for ASA by ELISA. We did a simple pairing that concerned only the type of infertility. For a better balance between the number of cases and controls per stratum to provide better accuracy in the adjusted OR estimate, we performed a 1:1 match. **Results:** This study showed that businessmen [ORa = 5.0000(1.2452 − 20.0767)] and jobless [ORa = 5.8125(1.1477 − 29.4367)] were at risk of being positive for ASA. Violent blow to testicles [ORa = 6.7391(1.3455 − 33.7545)], cure of hernia [ORa = 4.3478(1.0722 − 17.6299)], Chlamydia infection [ORa = 4.7125(1.3405 − 16.5665)], leucospermia [ORa = 4.1429(1.0406 − 19.7155)] and presence of *Staphylococcus aureus* [ORa = 3.4444(0.6410 − 18.5082)] were associated to positive ASA. **Conclusion:** This study shows that factors that may lead to risky sexual behavior and physical or infectious trauma are important risk factors for ASA positivity. It is therefore necessary to search for them systematically during male infertility in order to guide the search for ASA.

Keywords

Antisperm Antibody, Chlamydia Trachomatis, Men Infertility, Immune

Infertility, Infertility, Democratic Republic of Congo

1. Introduction

Infertility is a disease defined by the lack of clinical conception after 12 months or more of unprotected sexual intercourse, satisfactory in quantity and quality and at appropriate times or after treatment with insemination using donor sperm [1] [2] [3]. Failure to conceive can lead to stress, depression, discrimination, ostracism, economic problems... [4] [5] [6]. For the man, his inability to conceive often means that his virility and sexual power are affected. In African culture it is heavy to carry infertility, especially since the father transmits his name [7] [8]. "Male factor" infertility is seen as an alteration in sperm concentration and/or motility and/or morphology in at least one sample of two sperm analyses, collected 1 and 4 weeks apart [9]. Infertility due to male factor ranges from 20% to 70% and the percentage of infertile men ranged from 2.5% to 12%. Africa and Central/Eastern Europe are the regions having the highest rate of male Infertility [10]. Males with sperm parameters below the WHO normal values are considered to have male factor infertility. The most significant of these are low sperm concentration (oligospermia), poor sperm motility (asthenospermia), and abnormal sperm morphology (teratospermia). As high as 90% of male infertility problems are related to count and there is a positive association between the abnormal semen parameters and sperm count [11] [12] [13]. Among factors that lead to alteration of sperm parameters, there are anti-sperm antibodies (ASA). They induce a decrease in motility of spermatozoa and their cervical penetration by agglutination. They also inhibit the acrosomal reaction by disturbing the membrane permeability of spermatozoa and they can even prevent the development of the embryo resulting in abortions. By attaching themselves to spermatozoa, ASA facilitate their recognition and phagocytosis by macrophages leading to oligospermia [14]-[20]. Globally the prevalence of ASA varies a lot around the world and can reach 64.4% [21] [22] [23] [24] [25]. In man, Maria Khatoon and Col. [23] found 30.3% of seropositivity in infertile men and B.I Adejumo *et al.* [26] found 22.7%. Maindo and Col. in Democratic Republic of Congo found a prevalence of 29.72% [27]. Many factors have been cited as leading to the production of ASA. Among those factors, there is testicular trauma, cryptorchidism, hernia, infections, vasectomy,… [28]-[33].

The aim of this study is to determine risk factors of ASA positivity among infertile men in Kisangani.

2. Patients and Method

During the period of 2 years, from 1 January 2017 to 31 December 2018, we conducted a case-control study on 111 male patients who consulted for conception and in whom the search for circulating ASA in serum was performed. Apart

from that, their medical files should have all data needed for this paper. For ASA search, approximately 5 ml of the venous blood from each of the 111 patients was collected under an aseptic condition. For the separation of serum from whole blood, a centrifugation at 3000 rpm was performed for 5 minutes. Once the serum was obtained, the analysis was performed immediately. If this was not possible, the sample was kept in a sterile tube at a temperature of 2˚C - 8˚C until the time of analysis. The immunoglobulin test was performed by ELISA using the Stat Fax® 4700 device. All the tests were carried out in the Ema Esu laboratory, the only one carrying out this test in the city. Patients with positive ASA serology for Ig A and/or Ig G were considered as cases and those with a negative serology were considered as control. We did a simple pairing that concerned only the type of infertility. For a better balance between the number of cases and controls per stratum to provide better accuracy in the adjusted OR estimate, we performed a 1:1 match. We included in this study infertile men with ASA research result and a medical file having necessary parameters studied in this paper. We excluded those who were in a relationship for less than 12 months and who had a medical file lacking data studied in this paper. Data were collected from medical and laboratory files were encoded using Excel. We used Epi Info® software version 7.2 for data analysis.

We performed a bivariate analysis to measure whether there was a statistically significant difference in the occurrence of an event between cases and controls in relation to a factor; we calculated Pearson's chi-square (p-value). We considered that the difference was significant when p-value was less than 0.05 at the 95% threshold. When the terms of use of Pearson's chi-square were not applicable, we used the Fisher exact test at the 95% threshold with significance when the Fisher exact was less than 0.05.

To measure whether there was an association between the presence of a factor and the occurrence of an event and to evaluate the degree of this association, we performed a multivariate analysis with conditional logistic regression by calculating the adjusted Odd Ratio (ORa), and its 95% confidence interval (CI).

3. Results

Table 1 shows that the majority of patients were had 41 years and over (50.45%), were married (91.89%), were civil servants (53.15%) and had university level (40.54%). In Table 2, according to clinical characteristics, the majority of patients in our study had primary infertility (61.26%) with mean infertility duration of 7.33 ± 5.06 years. In their history, 13.51% had a violent testicle blow, 17.12% had cure of hernia and 4.50% had testicular torsion. There is a history of STIs among 23.42% of them. 5.41% of them have syphilis, 20.72% have chlamydia and 6.31% are positive for HIV. 61.26% of them had a spermogram abnormality. Spermogram abnormalities observed were asthenospermia (44.44%), oligospermia (37.84%), teratospermia (36.04%) and pyospermia (15.32%). Sperm culture revealed the presence of *C. albicans* alone in 6.31% of cases, *C. albicans* associated with *S. aureus* in 9% of cases and *S. aureus* alone in 9% of cases.

Table 1. Socio-demographics characteristics of patients.

Age*		
≤30 years	12	10.81
31 - 40 years	43	38.74
≥41 years	56	50.45
Matrimonial status		
Single	9	9.11
Married	102	91.89
Profession		
Civil servant	59	53.15
Other	13	11.71
Businessmen	18	16.22
Jobless	11	9.91
Motor bike transporter	10	9.01
Niveau d'étude		
Primary	24	21.62
O level	42	37.84
University	45	40.54

*Mean of age = 44.53 ± 9.33 years.

Table 2. Clinical characteristics of patients.

	N	%
Type of infertility*		
Primary	68	61.26
Secondary	43	38.74
Presence of STDs#	26	23.42
Chlamydia test+	23	20.72
Syphilis test+	6	5.41
HIV test+	7	6.31
History of testicle trauma	15	13.51
Cure of hernia	19	17.12
History of testicular Torsion	5	4.50
Anomalies of spermogram	68	61.26
Asthenospermia	49	44.14
Oligospermia	42	37.84
Teratospermia	40	36.04
Leucospermia	17	15.32
Culture of sperm		
C. albicans	7	6.31
C. albicans + *S. aureus*	10	9.00
S. aureus	6	5.41
Sterile	88	79.28

*Mean duration of infertility = 7.33 ± 5.06 years; #STDs (sexually transmitted diseases) studied are *C. trachomatis*, Syphylis and HIV.

As show us results in Table 3, we did not found an association between the level of study and ASA, yet according to profession, we found that being businessman or jobless multiplied respectively by 5 and almost 6 the risk of ASA positivity.

In Table 4, we found that duration of infertility was not associated to ASA positivity. History of testicular trauma was found multiplying by 6 the risk of ASA positivity and among testicular trauma, violent blow to the testicles and cure of hernia multiplied by 6.7 and 4.3 the risk of ASA positivity respectively. Past or current s sexual transmitted diseases multiply by 4.1 the risk of positive ASA. We found that only Chlamydia infection was associated to positive ASA and multiplied by 4.7 the risk of positivity. By analyzing sperm, our study showed that leucospermia multiplied by 4.1 the risk of positive ASA and that the presence of *S. aureus* in sperm culture multiplied by 5.8 the risk of ASA positivity.

4. Discussion

Empirically, we think that the more we are educated the less we adopt these risky behaviors. However, Clark P. and Kohler [34] in Malawi, Glynn *et al.* [35] in Benin, Gregson Zaddell and Chandiwana [36] in Zimbabwe and Hargreaves *et al.* [37] in South Africa found that the level of study high did not negatively influence the number of sexual partners. Also, Clark *et al.* [34] in Malawi and Mmbanga *et al.* [38] in Tanzania also did not find a positive relationship between level of study and condom use. These studies thus show that sexual behavior remains the same regardless of the level of education and therefore all men have the same degree of exposure to risky behavior that can lead to STDs, one of causes of ASA. This can explain why we did not find an association between level of education and ASA.

In our study, we found that businessmen and jobless were at high risk to have a positive ASA. Considering the fact that traders would usually have a short

Table 3. Socio-demographics characteristics and ASA serology.

	ASA+ N (%)	ASA− N (%)	p-value	ORa (CI à95%)
Level of study				
Primary	6 (18.18)	9 (27.27)	0.3782	0.3333(0.1568 − 0.7088)
O level	11 (33.33)	10 (30.30)	0.7915	0.4545(0.2152 − 0.9599)
University	16 (48.48)	14 (42.42)	0.6236	0.8235(0.4059 − 1.6707)
Profession				
Civil servant	5 (15.15)	20 (66.66)	0.0001	0.1161(0.0357 − 0.3779)
Other	1 (3.03)	6 (18.18)	0.0524*	0.1406(0.0423 − 1.6414)
Businessman	11 (33.33)	3 (9.09)	0.0163*	5.0000(1.2452 − 20.0767)
Jobless	9 (27.27)	2 (6.06)	0.0219*	5.8125(1.1477 − 29.4367)
Motor bike transporter	7 (21.21	2 (6.06)	0.0743*	4.1731(0.7969 − 21.8529)

Table 4. Clinical and paraclinical parameters and ASA serology.

	ASA+ n (%)	ASA− n (%)	p-value	ORa (CI à95%)
Duration of infertility				
1 - 2 years	4 (12.12)	7 (21.21)	0.2552	0.5123(0.1345 – 1.9520)
3 - 4 years	11 (33.33)	7 (21.21)	0.2689	1.8571(0.6153 – 5.6056)
≥5 years	18 (54.55)	19 (57.06)	0.8041	0.8842(0.3343 – 2.3388)
Testicular Trauma				
Yes	17 (51.52)	5 (15.15)	0.0017	5.9500(1.8446-19.1929)
No	16 (48.48)	8 (84.85)		
Type of trauma				
Violent testicular blow	10 (30.30)	2 (6.06)	0.0106	6.7391(1.3455 – 33.7545)
Cure of hernia	10 (30.30)	3 (9.09)	0.0302*	4.3478(1.0722 – 17.6299)
Testicular Torsion	2 (6.06)	0 (0.00)	0.4923*	Not difined
STDs	14 (42.42)	5 (15.15)	0.0144	4.1263(1.2735 – 13.3700)
Type of STDs				
Chlamydia	13 (39.39)	4 (12.12)	0.0112	4.7125(1.3405 – 16.5665)
Syphilis	3 (9.09)	2 (6.06)	0.6418	1.5500(0.2417 – 9.9400)
VIH	3 (9.09)	2 (6.06)	0.6418	1.5500(0.2417 – 9.9400)
Leucospermia	12 (36.36)	4 (12.12)	0.0423	4.1429(1.0406 – 19.7155)
Culture of sperm				
C. albicans	6 (18.18)	2 (6.06)	0.1314	3.4444(0.6410 – 18.5082)
S. aureus	9 (27.27)	2 (6.06)	0.0207	5.8125(1.1477 – 29.4367)

*Fisher Exact.

sleep because often busy managing their business and they would often have a high income exposing them to risky sexual behaviors [39], our results may be justified because short sleep and infections are associated with the presence of ACAS [29] [40] [41]. As for the jobless, who have almost nothing to do, they would generally have a long sleep, which is also associated with the presence of ASA [40].

Although the duration of infertility and the type of infertility increase the risk of STDs by increasing risky sexual behavior [42] [43] [44] and STDs are responsible for the production of ASA by antigenic community with the spermatozoa or by destruction of the blood-testicular barrier [45] [46], we found no association between the duration of infertility in men and ACAS positivity. Unlike us, Tennakoon V [47] found the association.

The history of testicular trauma including testicular torsion and cure of hernia were found in our study being high risks for positive ASA. In humans, the conditions destroying the blood-testis barrier are an obvious risk factor for ACAS production, as the immune system comes into direct contact with the antigens

on the surface of the spermatozoon [48] [49] [50]. Štula I *et al* [51] found in their study that ASA increased significantly after hernioraphy. They explained this by 2 mechanisms. The first mechanism is ischemia that occurs during manipulation of the spermatic cord [52] [53]. The second mechanism is rupture of the blood-testis barrier resulting either from the direct lesion of the vas deferens or from its dilation [54] [55]. The occurrence of ASA during violent trauma is explained by ischemia. Indeed, after the violent trauma at the level of the testicles, there is a decrease in the perfusion of the traumatized area with contusion and ischemia. It follows the rupture of the blood-testicular barrier and production of ACAS [51] [56] [57].

In this study, we saw that past or current s sexual transmitted diseases multiply by 4.1 the risk of positive ASA but among STDs studied, only Chlamydia infection exposed at high risk of positive ASA. Microorganisms perform a range of fascinating adjustments to survive in the host. Among the various strategies used by microorganisms to overcome the host's immune response, molecular mimicry allows microorganisms to manipulate host physiology and cellular functions to their advantage by mimicking host proteins and initiating autoimmunity. This phenomenon has been studied globally in the context of autoimmune diseases; however, its implications have also been reported in infertility [57] [58] [59]. Witkin SS as well as Siam EM and Hefzy EM also found a strong correlation between positive ASA serology and that against *C. trachomatis* [60] [61]. Chronic infection of *Chlamydia trachomatis* has been shown to trigger an immune response in the male and female genital tract by antigenic community. Indeed, spermatozoa and chlamydia possess the hyperthermic shock protein Hsp60 which is associated with a humoral immune response. A humoral defense against C. trachomatis can also be directed against spermatozoa with production of ASA [14] [62] [63].

We noted that leucospermia multiplied by 4.1 the risk of positive ASA and that the presence of *S. aureus* in sperm culture multiplied by 5.8 the risk of ASA positivity. In their study, Elizabeth Martinez-Prado *et al.* [64] found that the presence of leukocytes in sperm was significantly correlated with an increase in cytokines IL-6, IL-8 and TNF-a and anti-HSP-60 antibodies. protein present on spermatozoa. It is known [65] [66] that the secretion of cytokines is one of the first signals of innate defense of the host to fight inflammation and infection of the genital tract by causing leukocyte chemotaxis at the site of inflammation and infection. The lymphocytes will thus come into contact with the spermatozoa and trigger the production of ASA [14]. In his study in Nigeria, Ekwere P.D found that in men with ASA, *S. aureus* was the most common germ found in culture [67].

5. Conclusion

This study shows that factors that may lead to risky sexual behavior and physical or infectious trauma are important risk factors for ASA positivity. It is therefore

necessary to search for them systematically during male infertility in order to guide the search for ASA.

Conflicts of Interest

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

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