Review Article

Immune Mediated Male Infertility

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Abstract

This brief review focuses on the interaction between the immune and the reproductive systems. Conditions disrupting the blood testis barrier, laboratory tests for diagnosing antisperm antibodies and the currently available methods of treatment are discussed.

Introduction

Antigens associated with spermatozoa are never exposed to the immune system of the male unless the 'blood testis barrier' is breached. Spermatozoa are antigenically different both from the male who produces them and the female who receives them.

Immune Privilege and the Blood Testis Barrier

During the perinatal period the immune system learns how to recognize the 'self' from the reproductive'non self antigens'. Antigens produced after this period are not recognized as self by the body. At the time of puberty germ cells differentiate to produce mature spermatozoa. This process of Spermatogenesis results in the expression of new sperm antigens. These antigens are not recognized by the body as 'self'. Due to testis being immune privileged, germ cell antigens do not trigger immune response.

The sperm antigens are not exposed to the immune system due to the existence of the blood testis barrier. This barrier is morphologically defined as a series of tight junctions[3] formed by adjacent Sertoli cells. This divides the seminiferous epithelium into a basal compartment where the developing germ cells have free access to the vascular and immune system, and an adluminal compartment just above the barrier which represents the region isolated from the immune system. This adluminal compartment is where spermatogenesis takes place. The Sertoli cells might contribute to maintenance of immune privilege by the production of immunosuppressive proteins into the surrounding environment[4]. Breach in the blood –testis barrier leads to the exposure of spermatozoa antigen(s) to the immune system and production of Antisperm Antibodies (ASAB).

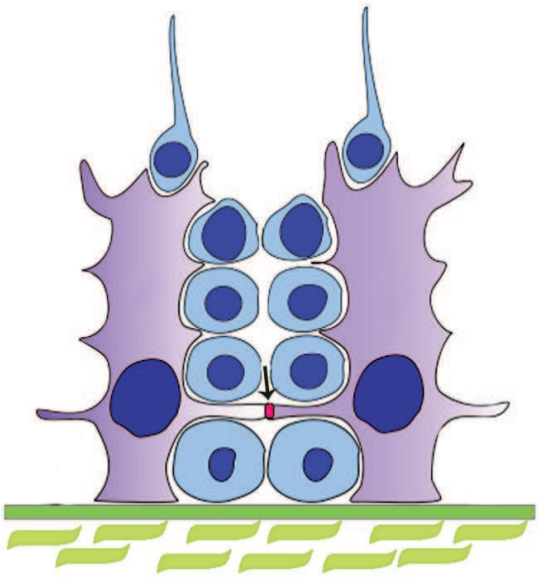

Fig1: Arrow shows the blood testis barrier formed by adjacent Sertoli cells

Pathophysiology of Sperm Antigens: The New Antigens

The acquisition of sperm surface antigens is a complex process. The addition or alteration of sperm surface antigens is thought to occur in the seminiferous tubules and the epididymis[5].Labelling of intact spermatozoa with I125 has revealed 300 different proteins[6]on the sperm surface of the spermatozoa. Although a few antigens like PH-20, Fertilin, CD59, CD52, HE2, HE4, have been identified[7], their exact function and characteristics are not known. In a study done by Claudia et.al.,[8](2001)highly enriched sperm proteins were separated by 2D gel electrophoresis from the seminal plasma of 20 infertile patients who showed ASABs. A total of 18 antigens were identified. Six of the recognized proteins were isolated and identified as Heat shock protein 70, heat shock protein 60, inactive

form of caspase 3, ER60, and 2 subunits of the proteasome. The highest rates of binding of the ASABs was seen with caspase 3 (90%) and ER 60 (95%) in all samples.Further studies are required to characterise and identify sperm membrane antigens responsible for impairing fertilisation.

Conditions that disrupt the blood testis barrier leading to generation of ASABs include testicular trauma[9], varicocele[10], testicular torsion[11], testicular tumour11, vasectomy[12]. Furthermore, Shibahara et al[11](2003) have reported other conditions associated with ASABs, which include spinal cord injury, mumps orchitis, congenital absence of vas and unexplained infertility.

In a study done by Mahdi et. al.,[13] (2011)in 45 infertile women, antisperm antibodies were found in both the cervicovaginal secretions (62.2%) and sera (64.4%) as compared to the control group of 30 fertile women who showed antisperm antibodies value of 3.3% each in the cervicovaginal and sera respectively. The precise mechanism by which antibodies impair sperm egg interaction is unclear. The antibodies may directly bind with the spermatozoa and inhibit motility, or may indirectly cause the release of cytokines from the spermatozoa and impede cell function and also reduce cervical mucus penetration[14]. Some antibodies of the IgA category are known to reduce fertilization rate when bound to the head[11], while IgM antibodies when bound to the head and tail caused the most significant reduction in fertilization rates[11]. This indicates that the ASABs exhibit diversity and heterogeneity.

Laboratory tests for diagnosing antisperm antibodies

Immune infertility in men may present in three ways. 1. It may manifest by the presence of sperm antibodies in the serum, semen or on the surface of sperm. 2. It may manifest by agglutination of spermatozoa in the semen. 3. It may also manifest by a reduction in the ability of the affected sperm to penetrate normal cervical mucus. Fertilization failure in an IVF program and a negative sperm penetration assay may be due to immune infertility. Diagnostic test currently used for evaluating immune infertility are 1. Sperm agglutination test; A. Gel agglutination test; B. Tray agglutination tests; C. Tube slide agglutination test. 2. Indirect immunofloresence. 3. Mixed erythrocyte spermatozoa antiglobulin reaction test. 4. Enzyme linked Immunosorbent assay. 5. Immuno bead test. Currently used tests include the Immuno bead test, Mixed Agglutination Reaction test (MAR).

Mixed Agglutination Reaction test: This test is performed by mixing semen with immunoglobulin G or IgA coated latex beads or red blood cells, and IgG or IgA antiserum on a microscopic slide. If antibodies are present the sperms will form clumps with the coated latex beads, if antibodies are absent the sperms will swim freely. A level of binding greater than 50% is considered significant[15]. This test is useful for detecting direct antibodies in men.

Immunobead test: this test is performed by combining IgG or IgA coated latex beads and washed sperm on the slide. The sperm is washed with media and Bovine serum albumin. Post wash the sperms are placed on slides with IgG or IgA coated latex beads. If antibodies are present the beads will attach directly to the sperm. This test provides more information than the mixed agglutination reaction. The results provide the number of sperms bound by beads and the specific locations were the bead is bound to the sperm. Unlike the MAR test this test can be used to detect ASAB's in the women's serum, follicular fluid, or cervical mucus. A level binding greater than 50% is considered to be of clinical significance[15].

The Immunobead tests, MAR tests and, ELISA have an inherent problem. They do not identify the antibody that is clinically relevant. Only subsets of patients with ASABs have agglutinating and cytotoxic antibodies[16].These tests are unable to determine the number of antibody and antigen molecules involved in binding. These tests only give us ASAB titres; however which of these ASAB's are of clinical significance cannot be determined by these tests[17]. Also these tests do not give information regarding the specific antigens to which antibodies bind and their subsequent impact on spermatozoa function. ASABs have the ability to bind against multiple antigens on the spermatozoa surface[17], which of these antigens are important clinically is still a subject of research. There is a pressing need for developing antigen specific tests which will help us categorize the patients based on sperm functions, and help us in adopting less radical treatment protocols. A series of assays would be more reliable than a single assay[18].

Treatment

Treatment of immune mediated infertility is unsatisfactory. Currently available methods are

1) Barrier contraception – particularly condom, reduces the exposure of female partner to sperm and may reduce ASABs titres. In a case report by Franken[19], a couple with no apparent cause of infertility apart from high ASABs in the women's sera were advised use of condoms for 6 months. The antibody titres were monitored; antibody levels fell after 7 months of therapy. However there was no concomitant increase in the pregnancy rate.

2) Steroid administration[20]-several centres around the world use steroids along with IUI, the most common regimen followed was 20 mg of methyl prednisolone for days 1-10 of the female partner's follicular phase, followed by 5 mg daily for days 11 and 12[20].Continuous treatment with steroids for a period of 6 months may improve pregnancy rate and semen parameters[20]. Steroids reduce the antibody titre by immunosupression. The rationale of steroid therapy is to obtain a proportion of antibody free sperm which would be available for fertilization. However long term use of steroids is associated with the risk of developing diabetes mellitus, hypertension, hypogonadism, steroid psychosis, osteoporosis and harmful changes in the cholesterol levels. Bilateral aseptic necrosis of the femoral head has been reported with intermittent

high dose steroid therapy[21].Due to the doubtful efficacy of steroids along with their long term adverse effects, the use of steroids has come down in favour of ART. However not all patients can afford ART, so steroids may have clinical value and more studies are required on their efficacy and adverse effects

3) In Vitro sperm processing / washing techniques – no invitro sperm processing technique has been able to disrupt the antigen-antibody complexes bound to the sperm surface[22]

4) ART- may help overcome immune mediated infertility. IUI helps to overcome cervical mucus penetration impairment. The pregnancy rate of IUI is variable from 0% to 64%. Nevertheless a good result can be obtained when moderate sperm auto immunisation is present[23]. The effectiveness of IUI is not just the cost factor, but in cases of moderate sperm immunisation the proportion of antibody free sperms in the semen, and its meeting the egg is favoured in a well timed cycle[23]. ICSI is favoured over conventional IVF-ET in case of IUI failure[23]. ICSI has been claimed as the primary treatment choice in immunological mediated infertility, as it overcomes any interference of ASAB with sperm-zona binding, progression of the sperm and ultimately the fertilizing ability[23].

Conclusion

Though there are several tests to detect ASABs, the exact significances of these tests are not known. Besides there is no satisfactory way to treat these couples. There seems to be conflicting evidence with respect to ASABs affecting pregnancy and miscarriage rates. Since there seems to be no satisfactory way to treat these couples in out-patient clinics, ART seems promising. It should be recognised that Immunosuppressive therapy has its own risk in the long term. Intrauterine artificial insemination with husband's spermatozoa has been suggested as an appropriate therapy[23] but the pregnancy rate has been variable. Immune mediated male infertility and ASABs remains a controversial area[24]. Although introduction of assisted reproduction has helped overcome this condition, it has however, raised numerous questions as how to prevent an increase in titres of specific ASABs More work is still needed to understand the cellular interactions between the male gametes and the immune system.

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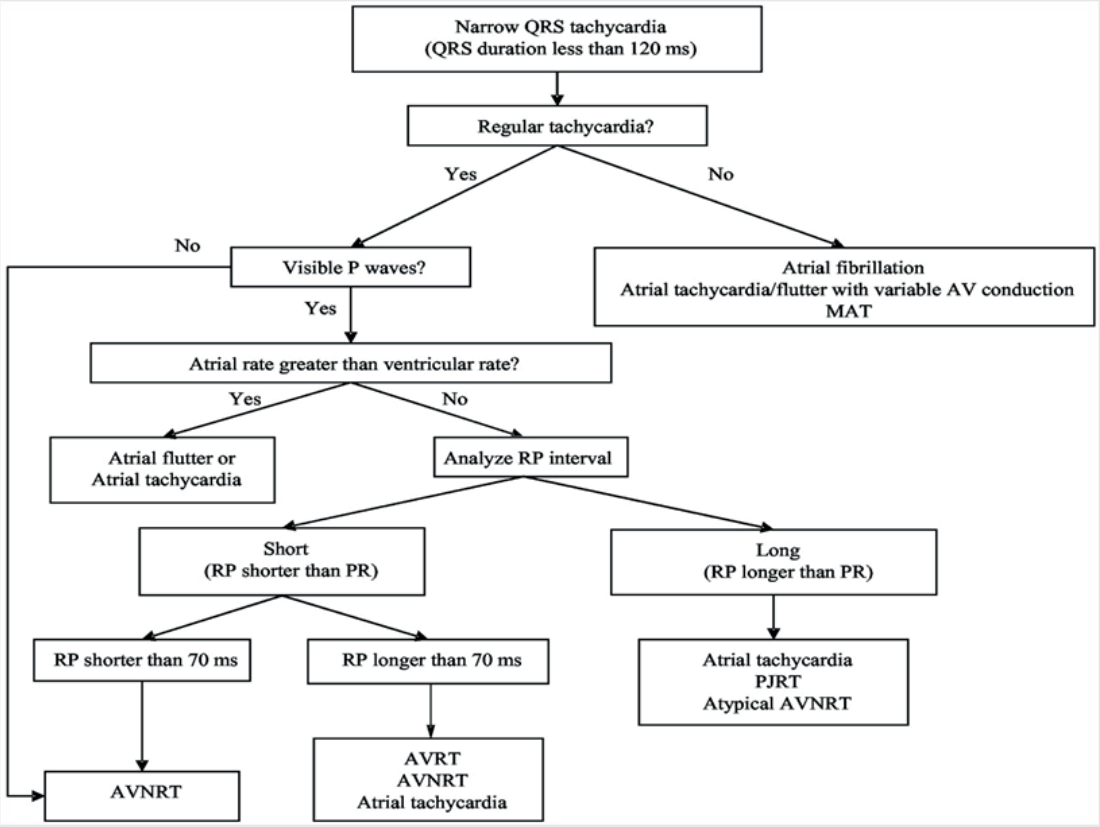
Answer to : **Diagnose the Condition**

ECG shows narrow QRS tachycardia which is regular.RP interval is longer than PR interval. Hence diagnosis could be either 1.Atypical AVNRT 2.Paroxysmal Atrial Tachycardia 3.PJRT. Inview of her previous H/O RHD ,possibility of tachycardia arising from atria is more. SVT got reverted with INJ.Verapamil.



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