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REVIEW ARTICLE

Antisperm antibodies and fertility association☆

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Antisperm antibodies; Autoimmunity; Spermatozoa; Immune infertility; Gamete interaction; Reproduction

Abstract
Objective: To evaluate the relation between antisperm antibodies (ASA) and human fertility by reviewing the scientific literature of the last 45 years.
Methods: We carried out a review of scientific literature about antisperm antibodies and infertility published in Spanish or English in databases as Pubmed, Medline, Scielo, some books and another gray literature include information related to this review and that is published in the last 45 years.
Summary of evidence: Infertile couples suffers infertility by immunological mechanisms mainly by the presence of antisperm antibodies ASA in blood, semen or cervicovaginal secretions; the formation of ASA in men and women may be associated with disturbance in immunomodulatory mechanisms that result in functional impairment of sperm and thus its inability to fertilize the oocyte.
Conclusion: Immunological infertility caused by ASA is the result of interference of these antibodies in various stages of fertilization process, inhibiting the ability of interaction between sperm and oocyte.

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Anticuerpos antiespermatozoides y su asociación con la fertilidad

Resumen
Objetivo: Evaluar la importancia de los anticuerpos antiespermatozoides (AAE) y su relación con la fertilidad humana mediante una revisión de la literatura científica de los últimos 45 años. Métodos: Se realizó una revisión de la literatura científica basada en investigaciones realizadas sobre anticuerpos antiespermatozoides e infertilidad publicada en español e inglés en bases de datos del área de la salud, Pubmed, Medline, Scielo, libros y otra literatura grís que incluya información afín a la revisión y que se encuentre publicada en los últimos 45 años. Resumen de evidencia: Parejas infértiles padecen de infertilidad causada por mecanismos inmunológicos, principalmente por la presencia de AAE en sangre, semen o inclusive en secreciones cervicovaginales; la formación de AAE en hombres y mujeres puede estar asociada a trastornos en mecanismos inmunomoduladores, que traen como consecuencia la alteración funcional del espermatozoide y por ende su incapacidad para fecundar al ovocito. Conclusión: La infertilidad inmunológica causada por AAE es el resultado de la interferencia de estos anticuerpos en las diferentes etapas de la fecundación, inhibiendo la capacidad de interacción entre el espermatozoide y el ovocito. © 2012 AEU. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

According with World Health Organization (WHO) infertility is defined as the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. The high and growing prevalence and incidence rates of infertility have become world health problem that lead to organic and psychosocial impairment in couple and finally rebound in personal quality of life. In 2009, infertility world prevalence was between 50 and 80 million cases, although these figures vary between different regions. In Latin America prevalence of infertility was 12.8% of couples in 2010; in Colombia, between 16% and 20% of couples in reproductive age suffered infertility in 2010.

Several risk factors are involved in pathogenesis of infertility; some of them are alterations in spermatogenesis due to testicular cancer, aplasia of the germinal cells, varicocele, defect in the transport of the sperms, or environmental factors as well as congenital anomalies, infectious diseases, bilateral tubal occlusion, pregnancy-related infections, alterations in conventional and functional parameters of semen and the presence of antisperm antibodies (ASA), however, of all cases between 10% and 25% are idiopathic in which it is not possible elucidate etiology of infertility.

ASA have been considered as infertility cause in around 10–30% of infertile couples, in whom ASA have been found in semen, plasma, anti sperm, follicular liquid, as well as cervicovaginal secretions. High levels of ASA are present in patients with clinical history of testicular torsion, testicular carcinoma, epididymitis orchitis, bilateral orchitis with extensive destruction of seminiferous tubules, seminal infections, varicocele and inflammation induced by genital infection and vasectomy. Besides, between 40% and 70% of vasectomized men develop detectable ASA.

In both men and women, ASA production are directed against spermatic surface antigens, interfering with sperm motility and transport through the female reproductive tract and inhibiting capacitation and acrosome reaction. The other hand, ASA have an indirect mechanism of action to mediate the release of cytokines which affect to spermatic function and impair sperm-cervical mucus interaction, induce sperm cytotoxicity, increase sperm phagocytosis, or inhibit embryo development and implantation. As result, natural pregnancies rates decrease. However, some authors have reported that ASA could not cause infertility, even when in 60% of healthy men ASA have been found in serum, and between 15% and 30% of them ASA are linked to sperm. Moreover, ASA have been found in cervical mucus in 2% of women.

Immune infertility

Immune infertility is one of the major causes of infertility in humans triggered by activation of immune system, which entails production of specific antibodies against sperm. In infertile couples with unknown cause of infertility, presence of ASA in women is suspected when they show abnormal postcoital test that could be indicative of immune infertility. In men, presence of ASA is suspected when sperm agglutination is detected in seminal analysis. However, sperm agglutination may be due to factors unrelated to ASA, even more, presence of antibodies is not always associated to sperm agglutination.

Immune infertility in man

Testes are specialized compartments in which spermatogenesis is developed. Hemato-testicular barrier, with tubular and vascular sections, is located in each testis. Tubular section comprises basal lamina of seminiferous tubules, germ cells and Sertoli cells. Germ cells are surrounded by cytoplasmic extensions of Sertoli cells, which are
responsible for orchestrating and regulating spermatogenesis. Cytoplasmic membranes of Sertoli cell are hermetically sealed, isolating spermatogenesis of immune system. Due to its phagocytic capacity, Sertoli cells are also involved in phagocytic removal of sperm, cytoplasmic debris and residual body of spermatides (immune response stimulators). Sertoli cells display testicular antigens to immune system inducing local tolerance, probably, by activation of suppressor cells. Intercellular junctions of Sertoli cells arise in puberty, when mitosis of Sertoli cells is stopped and spermatogenesis begins. The haploid cells originated by meiosis might be recognized by immune system being necessary to isolate them. Germinal cells and sperm have specific membrane antigens. These antigens are expressed during meiosis and remain during spermatogenesis. Additional membrane antigens appear in sperm after spermatogenesis phase during sperm maturation and transit through the epididymis. Due to the presence of peritubular immunoregulatory system and the isolating developed by hemato-testicular barrier, generally sperm does not trigger an immune response.

Capillary endothelial cells form vascular compartment. Those cells have low permeability and hamper the passage of cells (lymphocytes) and proteins of high molecular weight (immunoglobulins and proteins of the complement system), developing a role of barrier function in hampering the passage of immune components into tubular section. Sperm surface antigens are recognized as foreign after process of self-tolerance during perinatal stage; in this moment sperm antigens are syntetyzed. However, amount of antigens may traverse rete testis and induce immunological tolerance. Thus, local immune-regulation is developed in testes. Both, local immune-regulation and hemato-testicular barrier inhibit the production and function of ASA.

Additionally, immunoregulatory control is developed by paracrine function of the hemato-testicular barrier. This control stimulates the release of specific immunoprotective substances from Sertoli and Leydig cells, which inhibit lymphocyte blastogenesis and mediate cell lysis. These immuno suppressive substances have an important protective function against immune response against sperm. Between them are found: anti-inflammatory cytokines (interleukin [IL]-1, IL-10, IL-13, IL-14), transforming growth factor β (which inhibit pro-inflammatory activity and active some cytokines like T cells growth factor [TCGF]), activin, 2-macroglobulin and β-melanocyte stimulating hormone.

Lymphatic system of the testes crosses the interstitial spaces between the seminiferous tubules. Macrophages are placed around tubules and express abundant HLA-D molecules on their surface, which play an important role in antigen presentation and in immune response. However, hematotesticular barrier slows the passage of blood components through it, as it is put into evidence by the low levels of immunoglobulin, macrophages and leucocytes inside seminiferous tubules. Development and function of antibodies, besides immunomodulatory elements, may play as trigger agent of inflammatory response and causes male infertility.

Immune regulation can play an important role in immunological suppression in testis, because some components of seminal plasma act suppressing macrophages and neutrophils’ capacity to recognize and phagocytize antigens; they inhibit antigen recognition and elimination by suppression of NK cells and cytotoxic T cells as well as complement system activity, in special C1 and C3 fractions, lowering lytic activity of antibodies; and likewise components of seminal plasma can modify antigens composition preventing antigen–lymphocyte interaction. Moreover, prostaglandin H2 synthase, placed in rete testis and epididymis, interferes prostaglandin synthesis. The role played by prostaglandins is to promote the chemotactic response of suppressor T lymphocytes in the subepithelial tissue of epididymis and vas deferens, and acting in defense against sperm antigens stimulation of immune system. Some seminal plasma components, including glycoproteins and poliamines, suppress proliferation of lymphocyte as well as immune mechanisms, which might react against sperm. T helper lymphocytes, placed in the subepithelial tissue of epididymis and vas deferens, reduce antigen recognition by lymphocytes B, to decrease the humoral response.

Immune infertility in woman

In woman, although the mucosa is more heavily exposed, unlike man, female reproductive tract have not immunological barrier. Moreover, sperm, which are recognized as strangers by the immune system, do not trigger humoral immune response. Sexually active women are exposed to million sperms in each intercourse, and fertilization would be compromised if they were immunized against sperm. The effects of immunization against sperm include: sperm agglutination, reduced motility of the sperm, embryo implantation failure or increased phagocytosis of sperm. Cervical mucus is an element of immune system with capacity to respond to infectious agents, strange antigens and, occasionally, sperm antigens. Subepithelial plasma cells of Fallopian tubes, uterus and vagina plasma cells have the capacity to produce immunoglobulin class A. These antibodies are present in cervical mucus and can affect to sperm preventing them from entering into the uterus, Fallopian Tubes and, finally, spermatozoa–oocyte interaction.

After semen is deposited in vagina, sperm-binding effect is developed by ASA, and sperm become less permeable to cervical mucus. However, non-agglutinated sperm pass through Fallopian tubes to peritoneal cavity and can induce macrophage phagocytosis. These macrophages go to peripheral lymphoid organs, where macrophages containing phagocytized sperm (maintaining antigenic properties) activate T cells and B-lymphocytes. Leukocytes in seminal plasma comprise neutrophil chemotactic factors. After intercourse and ejaculation, those factors attract a large number of neutrophils. Immobile sperm is phagocytized and removed from insemination place by neutrophils. Once initiated the immune response, posterior intercourses act as re-stimulation. Hence, when a woman is exposed to sperm antigens, her antibodies titles are not enough to cause infertility, but these women are susceptible to this condition when over-stimulation
of the immune system occurs. This cause may be correlated with a defect in the presence or response of immunosuppressive factors. Women with high titers of antibodies antisperm show significant inhibition of in vitro fertilization.

For all these reasons, it may be deduced that ASA production in men and women can be associated to: a disturbance of normal immunoregulatory mechanisms, accidental rape, physical trauma, chemical trauma or iatrogenic infection in the hemotesticular barrier or to an obstruction in the male reproductive ducts. As a result, sperm are recognized as antigens and humoral immune response is triggered by B-lymphocytes that release ASA. Cellular response is achieved by T-lymphocytes’ activation, the release of cytokines and complement system activation. ASA production is the result of autoimmune response in men and of alloimmune response in women, and it is associated with idiopathic infertility in human beings.

ASA are detected in 1.4% of fertile women due to the presence of immunosuppressive factors in vaginal fluid, meanwhile in infertile women the rate is 2%. In contrast, ASA incidence in fertile men and women is lower than 2% in serum, sperm and cervical mucus, and in infertile ones the range is from 5% to 25%.

### Antisperm antibodies: action mechanism

The function of immune system is to identify antigens, including sperm antigens, and to react by several mechanisms, including the production of antibodies. Antibodies are the antigen receptors and effectors molecules involved in the humoral immunity. Their interaction with antigens leads to activation and response of B-Lymphocytes. Antibodies are produced by B-Lymphocytes and are expressed in 2 ways: (a) binding to lymphocyte membrane, like antigens receptors setting of cellular response; or (b) once secreted, antibodies bind to antigen triggering the activity of innate immune system (antibody mediated neutralization, complement immune system activation, opsonization of antigens that promote phagocytosis) which lead to activation of antibody-dependent-cell-mediated-cytotoxicity.

In humans, there are 3 immunoglobulin (Ig) classes of antibodies antisperm: Ig G, Ig A and, in lower levels due to its large size, Ig M. In both men and women, their production is due to auto-antigenic and iso-antigenic properties of spermatozoa. The amount and class ASA bind to spermatozoa are important because each ASA shows different ability to impair the sperm binding to the egg zona pellucida. Antibodies, independently to their class, may bind to different parts of sperm and each antibody has regional specificity or, on the opposite, it can bind to all spermatozoa surface. Antibodies binding to spermatozoa surface are associated to sperm agglutination and immobilization. Several sperm agglutination patterns have been identified in serum of patients incubated with their own sperm: head to head, tail to tail, head to tail and by the end of the tails. This patterns proved the existence of different sperm auto-antigens. ASA bind to antigens of acrosome, postacrosomal and equatorial region, middle-piece and tail. ASA against sperm head may interfere with the acrosome reaction or to occlude sperm membrane receptor binding to egg zona pellucida. These ASA interfere with fertilization. However, the union by the end of tail may be responsible of sperm motility decrease, causing a deleterious effect in sperm displacement. ASA activity is amplified in presence of complement, causing sperm immobilization and disruption of sperm membrane integrity.

### Pathophysiology of antisperm antibodies

Seminal plasma IgG is involved in cytotoxicity phenomena and trigger phagocytosis mediated by macrophages and the complement. Thus, sperm is inactivated. Although the hypothesis is that the antibodies contact sperm through a prostate transudate, low levels of antibodies have been detected in rete testis fluid and in epididymal fluid in rabbits. On the other hand, antibodies are released from uterus transudates, endometrium and follicular fluid. Nearly 1% of the serum IgG is present in male reproductive tract secretions. Levels are increased in serum of infertile men and in cervical mucus of their couples. These facts suggest that these antibodies are produced by exposure to membrane antigens after spermatocapitation.

ASA type IgA has been detected in seminal plasma of infertile men. IgA bind only to sperm head, impairing their fertilizing capacity. The presence of polymeric IgA in cervix, Fallopian tube and subepithelial tissue of endocervix has been confirmed by immunohistochemical studies. These female reproductive structures are the source of secretory IgA and IgG in women. Secretory IgA is produced by cervical mucous membrane and does not proceed from blood circulation.

ASA type IgM usually is not detected in human seminal plasma. IgM have been detected in vaginal washings of patients with vaginitis, and can reduce fertilization rates to 44%. IgM are macroglobulins that are capable to bind to antigens with multiple epitopes and to bind complement triggering cellular lysis. Moreover, these immunoglobulins have strong agglutination ability and reduce sperm motility. In the same way, the union IgA-sperm in cervical mucus reduces the progressive displacement of the sperm. IgM bind to sperm head and tail, reducing drastically the sperm fertilization.

At first stages of immune respond against sperm antigens IgM are produced, and then their levels decrease progressively. In the following stage, B-lymphocytes replace IgM for other isotypes of Ig (IgG, IgA). IgG antibodies levels raise and remain constant in serum for a long time. IgA levels are higher in infertile couples than in fertile couples.

Once produced, ASA can be found in blood plasma whether there has been sperm antigens extravasation toward the peripheral circulation resulting a systemic immunization; in seminal plasma, the immunization takes place when a local antibodies production takes place or antibodies arrive from serum or cervicovaginal secretions. In autoimmune male and female, sperm antigens may be extravasated to peripheral circulation.
of their fertile couple, from seminal plasma and cervical mucus. 37

As consequence to low number of patients with ASA, there are no significant statistics regarding predominant antibody isotype and its location on sperm. However, studies have reported that sperm mobility are interfered when at least 50% of motile sperm are covered by type IgA antibodies, and these can directly lower the rate of fertilization. 25,28 Antigenic epitopes, placed in low-density zones of sperm membrane, show more affinity to local IgA than to IgG, in infertile men and in their couples. Moreover, IgG have low levels of reactivity against sperm antigens. Probably, infertile men have antigenic predisposition before sperm capacitation as consequence to a sperm inherent aberration or to a premature capacitation. These reasons suggest that spermatozoa in infertile men have a premature loss of acrosome and then, immune system should be exposed to new antigens. Non-capacitated sperm stimulate a strong response of ASA in serum and seminal plasma of infertile couples. The immune response is stronger with capacitation probably by the appearance of new antigens. 37 Furthermore, activated lymphocytes and macrophages are present in semen of infertile men. 32 Sperm viability, motility and the capacity to penetrate eggs are impaired by the products of those cells. 31,32 All these reasons proved that cellular immunity could develop a significant role in male infertility. 31,32

In women, IgG are the main serum antibodies whilst IgA are the predominant in genital secretion. After intercourse, sperm antigens can contact with subepithelial B-lymphocytes through micro-injuries in genital epithelium. As result lymphocytes are triggered and produce IgA into female genital tract. 8 Oral and rectal administration of semen triggers the production of antibodies in serum of homosexual men and in genital secretions in rodents. 8

Regarding complement, it removes strange materials and improves the destruction and cleaning of sperm alloantigens and autoantigens. 33 Complement cascade has been reported in cervical mucus and follicular fluid (in Fallopian tubes and uterus). 21 The activation of complement system in female genital tract causes immune alterations of sperm. 29 Complement substances are produced by endometrial cells and are modulated by gonadal hormones and cytokines. Both, cervical epithelium and uterine secretions provide complement substances to cervical mucus, necessary for cytolytic reaction. 22 C3 and C4 components of complement are present in infertile men, but in fertile ones these components may not be found. C5b are deposited in follicular fluid. This component may impair calcium homeostasis affecting to: sperm motility, acrosome reaction and, in last instance, egg fertilization. 23 Other components of complement cascade have not been measured and are not present in seminal plasma during lysis mediated by antibodies. Even if complement inhibitors were present in genital secretions, they could suppress their activity. 20 MCP (membrane cofactor protein, CD46), decay accelerating factor ([DAF], CD55) and P18 (CD59) are proteins that inhibit complement activation. They are located in acrosome and protect sperm against complement attack in the male reproductive tract. 25,39

Analyses in serum of infertile males and females have been performed in different studies in order to determine the presence of ASA and their relationship with reproduction. In them levels of antibodies with capacity to react with at least one sperm antigen have been isolated. 8,20,21,28,40 The presence of ASA in fertile men and women might reflect a normal physiological phenomenon. 8,21,37,40 For detection of ASA in serum and in genital secretions the following procedures have been used: agglutination methods, sperm immobilization test, immunoblotting, immunonephelometric binding test (IBT) and indirect immunofluorescence assay (IFA).

Antigens

The sperm presents antigens on the periphery as well as embedded in the membrane; the distribution is as follows: the acrosome on the head, and the tail in the seminal fluid. Some of these antigens can be found in other body cells and others are specific to the spermatozoid. 9 Several sperm-specific antigens have already been identified, 18,20,21,38 and others are being investigated with specific monoclonal antibodies. 25 The membrane antigens can be isolated, in a limited way, in other tissues such as the placenta, ovaries, brain and neoplastic tissues. 20,21,41 The antigens of the major histocompatibility complex with capacity to stimulate immune response in sexually active women are not expressed in the sperm. 20

Sperm present antigens that appear in different stages of development. These antigens, present from the beginning of sperm, stick after ejaculation and are involved in the process of maturation and fertilization; they also act as protectors against the immune system of the female reproductive tract. 9 Sperm capacitation is an important process for fertilization; the acrosome antigens detachment, the organization of surface antigens and the activation of sperm motility occur during that process. These changes resulting from capacitation can activate the antibody response. 37 Sperm from infertile individuals contain normal antigens as well as special antigens which react with autoimmune serum; this shows the inability to demonstrate significant differences in serum reactions of fertile and infertile men with normal sperm antigens. 41

Sperm membrane is composed of a set of proteins, oligosaccharides, and lipids which are involved in various mechanisms previous to fertilization including recognition of the oocyte by sperm, and they can also stimulate the production of ASA. 40 Some of these antigens are: acrosin, 12,18 a 15-kDa glycopeptide that reacts with immobilizing antibodies, a 14-kDa polypeptide which appears in individuals classified as idiopathic infertile, 21 nuclear auto-antigenic sperm protein (NASP) (histone-binding) that affect fertilization rate, 12 H-Y antigens, hyaluronidase, protamines, DNA polymerase, 17 fertilization specific antigen (FA-I Y), 17,24,28,41 and the dodecamer peptide sequence (YLPVGGLRRIGG designated as YLP12) involved in the union of sperm and oocyte, 12,18,41 heat shock proteins (HSP70, HSP90) that are present on the surface of the sperm 31 and phenotypes of human leukocyte antigens A28 and Bw22 (genetic influence on the immune response). 8
Detection of antisperm antibodies

ASA can be detected either directly on the sperm membrane or indirectly in serum, cervical mucus, follicular fluid or seminal plasma.\(^\text{42}\) Direct ASA test is performed by two ways: the mixed antiglobulin reaction test \((\text{MAR}-\text{test})\) and direct immunobead test \((\text{D-IBT})\).\(^\text{15,42,43}\) The latest WHO guide now recommends both.\(^\text{44,45}\) Briefly, sperm sample is mixed with an antiglobulins or immunobeads suspension; the mixture is incubated and, next, sperm interaction with reactive particles \((\text{antiglobulins or immunobeads})\) is tested. In indirect test, sperm are pre-incubated with the liquid in which ASA are being tested.

Sperm immobilization test is other way to determine the presence of ASA in a fluid. This test detects indirectly in a fluid the sperm-immobilizing antibodies. Presence of complement system is necessary to take place the immobilization reaction \(\text{(reviewed in Shibahara H et al.)}\).\(^\text{46}\)

Treatment of antisperm antibodies

ASA test is recommended in those cases in which no disorder is found in woman and furthermore significant changes in spermiogram are not noted. It is necessary to take into account that in certain cases, ASA are not the only causal factor of infertility.\(^\text{5}\) Once ASA are identified as the cause of infertility, several therapeutic protocols are employed to act against this reaction.\(^\text{46}\) Among treatments targeted to prevent ASA effects are: the use of condom, immunosuppressive therapy with corticosteroids, gamete intrafallopian transfer, sperm washing combined with intrauterine insemination and intrauterine artificial insemination.\(^\text{8,17}\)

The use of condom as treatment reduces contact between woman and sperm after intercourse, reducing system activation in woman. However, the cessation after long-term therapeutic use of condom in patients diagnosed of immune infertility, does not assure an improvement of the fertilization rates.\(^\text{8,13,30}\) On the other side, immunosuppressive therapy with corticosteroids has been employed in couples with ASA, reducing ASA levels and increasing the chance of pregnancy.\(^\text{5,23,46}\) However, this therapy has not effect on patients in whom ASA are binding to spermatozoa\(^\text{4}\); furthermore, this treatment has long-term side effects like the following: aseptic necrosis of the hip, exacerbation of duodenal ulcers and cardiovascular effects.\(^\text{8}\) Sperm washing is other method to remove ASA from the sperm surface, but is inefficient because ASA exhibit high affinity for sperm antigens,\(^\text{8,32}\) and it may cause irreversible loss of sperm motility. Although sperm washing reduces the union between sperm and ASA, it does not improve pregnancy rates.\(^\text{8}\) Gamete intrafallopian transfer \((\text{GIFT})\) and intrauterine artificial insemination \((\text{IUI})\) are methods to treat patients with infertility associated with ASA.\(^\text{46}\) However, \textit{in vitro} fertilization rates are low if more than 80% of the overall sperm surface is bound to IgA and IgG.\(^\text{8}\) IUI has been employed in women with ASA in cervical mucus \(15\%\) of these patients achieve a pregnancy after several cycles of treatment.\(^\text{8,46}\) GIFT\(^\text{34}\) has been used for couples in which man has more than 70% of ASA type IgG and IgA are bound to sperm surface, but \textit{in vitro} fertilization is possible if antibodies are placed in sperm tail and not possible if they are placed in the sperm head.\(^\text{8}\)

Conclusion

In conclusion, fertility is affected negatively by the presence of ASA in men and women. Immunological infertility caused by ASA is the result of interference of these antibodies in various stages of fertilization process. ASA are produced as consequence sperm exposure to immune system due to disturbances in immunoregulatory mechanisms of testes. This cause of infertility must be assessed in order to know the mechanism of action of antibodies and to identify the way in which affect to fertility, and thus to establish accurate treatment for each couple, because ASA are not always the cause of reproductive problem.

Conflict of interest

The authors declare that they have no conflict of interest.

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