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DECREASING TREND OF ADVERSE EFFECTS OF RABIES VACCINATION

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ABSTRACT

Rabies, since times immemorial, continues to be a cause of serious concern. It is acute progressive encephalitis with a fatal outcome. From being a significant zoonotic disease, this disease assumes the status of a public health hazard with dog being the principal perpetrator. Prophylactic treatments for rabies got initiated in 1885 with thoughtful approach by Louis Pasteur, which later got evolved in order to ensure higher protection and lower incidence of side effects. Today, treatments of pre and post-exposure to the virus are well established, with excellent results of protection for individuals exposed to animals potentially contaminated by the rabies virus. These treatments consist of employing a vaccine solely or in combination with equine immunoglobulin, what contributes, in an important way, to the decrease in the number of cases of rabies.

Key Words: *Immunoglobulin, Prophylaxis, Rabies, Side Effects, Vaccine*

INTRODUCTION

Rabies is acute progressive encephalitis with fatal outcome caused by virus of the family *Rhabdoviridae* and genus *Lyssavirus*, which primarily affects animals with humans being the accidental dead ends (Wiktor *et al.*, 1964). Rabies figures even in Greek mythology, where there are significant reports of this disease along with some of its peculiarities. Initially, there was also a time when rabies was attributed to supernatural phenomena; of spiritual manifestation or to meteorological modifications, thus rabies continued to be an object of fascination, torment as well as of fear (Fishbien and Robinson, 1993). Aristotle, in the 4th century BC, considered rabies as a disease transmissible by bites between animals. Democritus, a Greek philosopher, described it in detail for the first time in 5th century BC. Later, in the first century AD, Celsus again described several aspects of this disease logically emphasized the significance of the rabid animals' saliva in the transmission to man (Steele and Fernades, 1991). Further, Hippocrates referred to rabies encephalitis relating animals and humans. Throughout the human history, rabies has been described as a threat to human being's life. Since historical period, dog has been identified with infecting humans with rabies. Since the Greek's descriptions, however, the symptoms of rabies converted to a synonym of human disease. Yet, it is true even today that occurrence of rabies in domesticated animals eventually makes humans at the high risk of exposure to the virus (Hensley, 1998). Therefore, it can be very well inferred that human rabies eradication depends fundamentally on animal rabies control (Wilde *et al.*, 1991).

In rural as well as urban cycle, dog is the main transmitter; has still not been controlled in several countries. Study of the worldwide distribution of rabies, it is revealed that higher incidence occurs in areas where there is lower control programs efficiency which eventually leads to higher contact between man and animals. At times, even this does not hold true. In case of Brazil, despite the great advances in rabies control, there is still incidence of this disease in the northern, northeastern, central-western, and in some states of the southeastern region, though the southern region is considered a controlled area. Notifications of rabies have been decreasing in Brazil since the 1980's. From 1969 to 1988, in São Paulo, there was a great decrease in the number of cases of human and animal rabies until its total eradication in 1987. According to the National Health Foundation, 26 cases were recorded and confirmed in Brazil in

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2000; from these, four occurred in the central-western region, nine in the north, and 13 in the northeast region.

In countries in Latin America, Asia and Africa, urban rabies is responsible for millions of annual deaths (Baer, 1988). Rabies continues to be an important public health problem in several developing countries in Africa and Asia (Wilde *et al.*, 1987), as well as in South America (Bogel and Motschwiller, 1986, Khwaplod *et al.*, 1996, Quimonez, 1998 and Wilde *et al.*, 1987). Although rabies has a worldwide distribution, Oceania and Antarctica are continents historically free from rabies (Acha and Arambulo, 1985; Nicholson, 1990; Sikes, 1975). Rabies has been eradicated in some areas, such as Japan, England, some Pacific Islands and isolated countries, where the reintroduction of rabid animals is blocked by the quarantine and vigilant entry protocols. Thus, France, Germany, Spain, Canada, and the United States were successful in controlling rabies (Noah *et al.*, 1998).

However, rabies is still a public health problem in almost all the countries of the tropical America, where an average of 300 people die of this disease, and approximately 300 thousand annually receive post-exposure treatment (Acha and Arambulo, 1985). It is major problem in various countries and a constant challenge for those responsible for its control (Baer, 1988). Establishment of new epidemiological concepts of rabies has somewhat strengthened the control measures, especially in endemic urban areas.

Initial Works

Pioneering studies on rabies started in 1880 with Louis Pasteur and his collaborators, who inoculated extracts from brains of rabid animals into the brains of healthy animals, trying to isolate and cultivate the agent responsible for such disease. With these attempts it was fairly concluded that nervous system is the main target for its experimental reproduction (Wiktor *et al.*, 1988). This significant finding laid the foundation of prophylactic approach in 1881 culminating in the institution of specific prophylactic treatments, which are indicated after risk of infection. Soon, in 1885, Pasteur demonstrated that rabies was caused by a virus, and developed a vaccine against it by kind of attenuating the virus by drying the spinal cords of rabid rabbits out in the sun (Hildreth, 1963; Quimonez and Steele, 1998). This initial vaccine showed to be quite efficient though it was not free from adverse reactions such as paralysis of legs. Later, it was determined that this neuro-paralysis developed due to the presence of myelin from the encephalon of the animals used for vaccine preparation (Hay, 1996). However, this vaccine, most significantly, saved the life of the young Joseph Meister, severely wounded by a rabid dog who would otherwise have become a fatal victim if had he not received the vaccine. However, the same vaccine also had its share of failures too when did not offer protection to many other victims.

It is now obvious that though development of rabies vaccine was a great event, yet, the vaccine prepared with attenuated live virus proposed by Pasteur did not demonstrate 100% efficacy. This fact resulted in accusations that the vaccine was not promoting heal, or even it could be transmitting rabies after its administration. It was these adverse reactions caused by this vaccine which motivated the researchers to continue to develop a safer method of protection, which would produce less virulent vaccine in order to avoid risks of accidents. These facts also encouraged the researchers to investigate rabies prophylaxis considering that its virus is pathogenic for all the mammals, in which infection is always fatal.

Inactivation of Rabies Vaccine

One of the significant developments that took place about 30 years after Pasteur's initial works, was development of with anti-rabies vaccines from rabies virus inactivated by phenol. Among the vaccines obtained in this period, the main ones were the Fermi's in 1908 and the Semple's in 1911. However, high incidence of local and systemic reactions and severe neurological complications caused by these vaccines due to the presence of proteins from brain tissue resulted in their lower acceptability (Pilee *et al.*, 1985).

Adverse Effects of Rabies Vaccines

After, it got quite established that myelin was the key factor producing nervous side effects of rabies vaccination; attempts were directed towards finding nervous tissue without the accompanying myelin. In the 1950's, from observations those newborn animals' brains were free of myelin, the Fuenzalida and

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Palácios vaccine that was safer and more potent, was developed in Chile (Afshar, 1979). The anti-rabies vaccine of the Fuenzalida and Palácios type was considered of low risk vis-à-vis neurological complications. As many as 22 severe cases of post-vaccinal accidents were recorded from 1975 to 1979, with 15 (68.2 %) deaths with a proportion of one accident to every 25,763 people that were treated. In fact, the undesirable effects of rabies vaccination continued to haunt by way of mainly local and systemic reaction despite the advances in use of this vaccine.

Managing the Side Effects

The major paradigm shift occurred when substitution of this vaccine with those of virus in cellular culture or in duck embryo was recommended. This shift was necessitated primarily due to the high number of doses used in the immunization scheme with Fuenzalida and Palácios vaccine and also to the frequency of severe neurological complications induced by autoimmune reactions resultant from the myelinated tissue present in the vaccine.

Thereafter, World Health Organization substituted the Fuenzalida and Palácios vaccine with those prepared in cellular tissue culture. Thus, the foundation of second generation of purified, secure and efficient vaccines with low costs was laid. These vaccines were obtained after infecting cultures of primary cells using duck and chicken embryonic eggs. Initially, there were undesirable reactions due to egg protein in the recipients of vaccines made of chicken/duck eggs. Later, this reaction was taken care of by modern purification techniques marking an important stage in the anti-rabies vaccines evolution (Nicholson, 1990).

Though little it may be, yet, there was some reaction due to the injection of a foreign protein of one species into another. Therefore, later, an entirely new concept was ventured into by developing a vaccine from human tissue so that for human prophylaxis the substrate used was from cellular culture of human origin. This way, vaccines in diploid and heteroploid cell culture were originated (Wiktor *et al.*, 1964).

It has been often reported that vaccines prepared in cellular culture induce the production of high levels of neutralizing antibodies against rabies. These vaccines are tolerated; presenting low incidence of neurological reactions and no record of fatal cases have been reported so far.

Meanwhile, development of hyperimmune serum aimed at providing passive immunization against rabies occurred simultaneously with the vaccines (Hildreth, 1963). In 1945, Habel demonstrated, in rabbits immunized with fixed virus, that for obtaining better results in preventive post-exposure anti-rabies treatment, the vaccine must be administered associated with the serum. In 1950, the World Health Organization recommended use of anti-rabies serum due to the high number of studies performed since 1889, when Babes and Lepp demonstrated the virus neutralization in animal serum. Once the high value of hyperimmune serum associated with vaccine was demonstrated this serum was considered a co-adjuvant in rabies prophylaxis, being part of the anti-rabies treatment.

There is a great difficulty related to the serum use due to its high costs and supplying. However, it was also proved that the mortality resultant from severe bites is reduced tenfold if the serum is administered associated with vaccine (Hildreth, 1963). In presence of an imminent risk of rabies infection, thousands of people receive post-exposure treatment (Acha and Arambulo, 1985), considering the high susceptibility to the virus and variability in the disease incubation period.

As a recommendation of the World Health Organization, all people with grade III exposure to animals suspected for rabies must receive anti-rabies prophylactic treatment with serum-vaccination. Thus, while the anti-rabies serum specific immunoglobulin provides a long period of immunization, offering antibodies for immediate protection, the time necessary, from the vaccinal stimulus, for endogenous antibodies production by the organism passes (WHO, 1975). However, utilization of anti-rabies serum of equine origin for prophylaxis in humans was acceptable in the medical practice only three decades ago. Although the use of human anti-rabies immunoglobulin is ideal, with no adverse reactions, its cost is a limiting factor. However, it is evident that only the use of a homologous antibody may prevent the occurrence of severe collateral effects (Cabasso, 1976).

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Anti-rabies serum, used nowadays, consists of a solution of purified immunoglobulins obtained from the serum of hyper-immunized horses. According to Barraviera and Peraçoli, serotherapy must be carefully used since it induces important reactions in the receptor. Although the frequency of accidents caused by the serum is relatively low and generally not severe, it is recommended that the administration of this immunobiological should take place only in hospitals equipped to handle any eventual anaphylactic reactions. The proteins present in equine heterologous serum have immunogenic properties that induce the formation of IgE antibodies in the receptor, and may cause anaphylaxis. Besides, they may also form immunocomplexes with specific IgM antibodies produced during the sensitization process, causing serum sickness (Kaliner and Belev, 1965; King and Tuner, 1993; Nishioka and Silveira, 1992; Tantawichien et al., 1995).

A lot of thought and effort has gone into the serum sickness - a systemic phenomenon of hypersensitivity mediated by immunocomplexes. In 1905, Von Pirquet and Shick described a clinical case with classic symptomatology observed after the application of diphtheric antitoxin. This reaction appears between 5 and 24 days after the use of heterologous serum and is manifested by fever, urticaria, arthralgia, lymphadenopathy, proteinuria, and peripheral neuropathy. It is mediated by IgG and IgM antibodies that bind to equine proteins forming immunocomplexes (Kaliner and Belev, 1965), which are deposited in several tissues causing acute inflammatory process. Nowadays, anaphylactic reaction occurs rarely. The present incidence is limited to 1:40,000 treatments. This reaction, named in the Gell and Coombs classification as type III hypersensitivity (Hay, 1996), activates the complement system and attracts polymorphonuclear cells to the deposition site, causing local tissue damage.

It is recommended a safer production of equine serum or its substitution for homologous serum in order to eliminate the risk of hypersensitivity reactions of the anaphylactic type and mediated by immunocomplexes (Comb and Dwyer, 1963).

The present anti-rabies sera used are purified by enzymatic digestion, precipitated with ammonium sulphate, and the excess of proteins is removed by thermocoagulation. This process provides serum with low concentration of animal protein, making the treatment safe and efficient, and also reducing the incidence of hypersensitivity reactions (Wilde and Chutivongse, 1990; Wilde et al., 1989). The advances obtained throughout the years in rabies vaccination have been exemplary that have contributed to the control and possible eradication of this disease in various regions on the world.

CONCLUSION

There were various adverse effects of inoculating vaccine in its earlier stages of development largely due to presence of nerve tissue in the rabies vaccine. With progressive development of rabies vaccine with continued decrease in the nerve tissue content, the adverse reactions were reduced. In the present times, the adverse reactions associated with rabies vaccine inoculation have been a thing of the past due to zero tolerance to adverse reactions whatsoever. Shifting from nerve tissue to cell culture vaccines has been instrumental in bringing about this change. It is desirable to continue to be sensitive to any adverse reaction that might get associated with rabies vaccination so that side effects of rabies vaccination continue to remain under check.

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