

Research on the rabies and rabies vaccines

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Abstract. Rabies is a highly lethal disease with a long history that most of the patients were infected by dog bites. Therefore, the scientific popularization and research of rabies are particularly important. This article mainly analyzes rabies from three aspects: the rabies virus, the rabies vaccines and treatment methods. Firstly, the infection mode and characteristics of the rabies virus and some clinical features after human infection with the rabies virus were analyzed, so as to facilitate people's understanding of the infection route and reduce the infection rate. The introduction of clinical features also made it easier for doctors or relatives of patients to determine whether patients were infected with rabies. Enable patients to get effective treatment quickly. The rabies vaccine is the main measure to prevent rabies. This part lists the history of human rabies vaccines and introduces some successful human rabies vaccines. Finally, the current treatment status of rabies is introduced, the methods that may play an important role in the treatment of rabies in the future are proposed, and the possibility of rabies being cured is confirmed. However, due to the complex mechanism of rabies itself, it is still necessary to continue to study rabies in order to completely defeat this disease.

Keywords: rabies, virus, vaccine, treatment, clinical feature.

1. Introduction

Rabies—a disease that has existed for over 4000 years on earth [1]. It is caused by an unusual virus called rabies virus [2]. The virus has a specific intrusion system. Most viruses mainly invade the immune system, but their main target is the nerves. When a human being is transmitted by the bite of a rabid animal, the rabid animal introduces infected saliva into the wound, where the virus can multiply locally in muscle or skin. Because of their low presence levels, it is difficult for the immune system to detect and clear them. Finally, it disables the brain from functioning normally, which is the reason that it is hard to cure. Up to now, people haven't found a reliable therapeutic method to cure a patient who was already showing symptoms of rabies. When a human who was infected with rabies shows symptoms of rabies, it means that the human will lose his life. Due to the rapid progression of rabies, its main target is the brain, so doctors have no time to save people's lives and the nerves are unrecoverable. It caused that rabies has a staggering 99% fatality rate. Therefore, after possible infection with rabies virus, rabies vaccine is the only means to prevent rabies. Rabies can be cause by a lot of animals' bite, which carries the rabies virus, such as, dogs, cats, bats and so on. Although there are many animals whose bite can infect and cause this disease, at present, most people lose their life by infecting with the rabies virus by biting by a rabid dog. In order to reduce number of people who died of rabies and exhance the knowledge

that people know about the rabies, it is necessary to research the mechanism of rabies and search how to prevent and cure rabies. In this paper, the pathogenic mechanism, clinical features and rabies vaccine of rabies virus will be introduced. At the same time, it will also answer the questions in the article.

2. Rabies

2.1. *Rabies virus*

Rabies virus is an enveloped RNA virus, and it is the prototype of the genus *Lyssavirus* in the family *Rhabdoviridae* [3]. Besides, there are many different strains because of different genotypes. The genotypes responsible for causing human rabies are types 1 and 3–7 [4]. First of all, it can invade human cells, which are the skin cells or the muscle cells, and replicate in human cells by using the nutrients in cells to produce a large number of viruses. Then the new rabies virus can repeat the process to infect the other cells. Until there are enough virus that can lead to the human develop a disease, and research indicate that the virus will attack the nerves which in the brain [5].

After the rabies virus penetrates the axon of a neuron, the microbe sheds its membrane and releases its proteins and RNA, which travel to the cell body. The viral RNA generates messenger RNAs (transcription), which in turn use the cell's machinery to produce the virus's five proteins, they are nuclear protein(N), phosphoprotein(P), matrix protein(M), glycoprotein(G) and RNA-dependent RNA polymerase(L) [2]. The viral RNA then makes copies of itself, which, along with the proteins, assemble into new microbes that emerge from nerve dendrites to attack the next nerve cell [5].

Rabies virus prefer to infect the brain. After the virus inside the cortex, it spreads rapidly in order to attack the different area in the brain. Especially, the brain stem and spinal cord are both the first sites for viral infection [6]. And the cerebellum, which coordinates body movements, the hippocampus, which is involved in short-term memory, and the limbic system, which regulates emotions, are the areas that the rabies virus is most likely to attack [5].

2.2. *Clinical features*

There are two different kind of clinical features for rabies: furious rabies and paralytic rabies. About two-thirds of patients will have symptoms of mania, and the rest of the symptoms will be paralysis. Research shows that the clinical stages of rabies are: incubation, prodrome, acute neurological signs, coma, and death [7].

The incubation period can take weeks or even years, but it typically lasts one to two months on average. It is the time which provide time for the virus to replicate. By the time a patient develops symptoms such as fever, flu-like symptoms, and gastrointestinal disorders, the virus has spread widely throughout the central nervous system, which also means that the patient has entered the prodrome. In this case, pain or paresthesia at the site of the bite is well known as a diagnostically useful prodromal symptom occurring in one-third to two-thirds of cases [8]. The cause of this phenomenon is dysfunction of the dorsal root ganglion caused by immune attack. In the next phase, patients may have the following symptoms: fluctuating consciousness, hydrophobia or aerophobia inspiratory spasms, signs of autonomic dysfunction, until they coma and death [7].

2.3. *Cured case*

The first patient to be cured was an American student who contracted the rabies virus from a bat in 2004. But there were many doubtful points in this case; for example, no virus strain could be isolated from the case, so the virulence of the virus could not be verified [9].

3. Rabies vaccine

According to Figure 1, the timeline shows the history of the human rabies vaccine; in the following, we will introduce some of the human rabies vaccines.

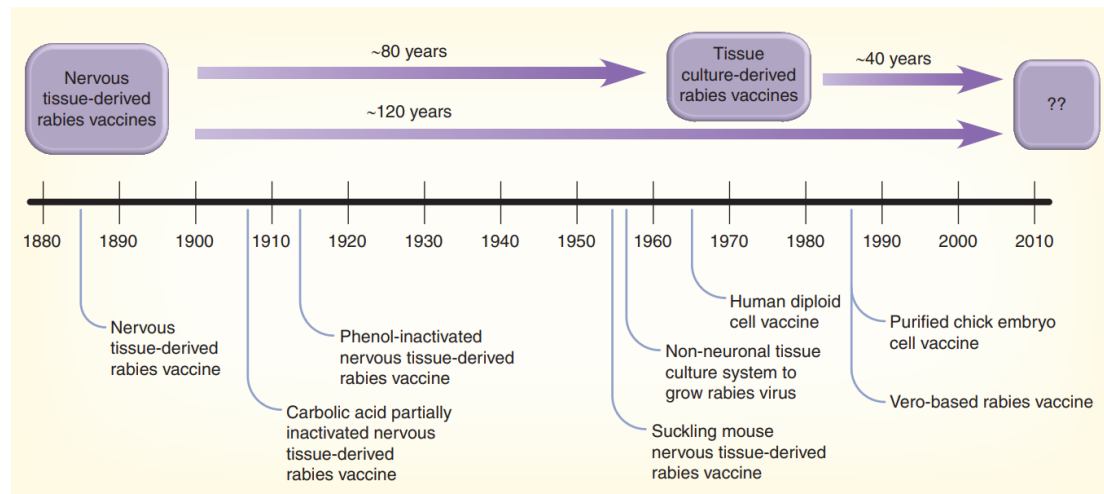


Figure 1. Timeline of human rabies virus vaccine development [10].

3.1. The first rabies vaccine

The first rabies vaccine for human in the world is made by a French Microbiologist who called Louis Pasteur in 1882. The vaccine successfully saved the life of a boy who was bitten by a rabid dog. In fact, this rabies vaccine is the spinal cord of rabbits infected with the rabies virus, which has been dried for 14 days and emulsified. Because of their poor knowledge at the time, people just knew that the vaccine could save patients who were bitten by rabies dogs, but they didn't know the mechanism behind it. Pasteur's vaccine is a mixture of inactivated and live viruses, which means that at the end of the treatment period, the patient was essentially being inoculated with the virulent rabies virus. Therefore, there were some people died after being injected with Pasteur's vaccine. It can be seen that although this vaccine can save some people's lives, its safety is poor [11].

3.2. The development of vaccine

In order to enhance the safety of rabies vaccine. Two scientists, Fermi and Semple, find that it was viable to kill the live virus by adding phenol. Unfortunately, phenol can distort the protein structure and the antigenicity of rabies virus, so that the ability of vaccine to prevent rabies has been greatly reduced [12].

There are many vaccines like this, such as the neural tissue vaccine (NTV), which can cause encephalitis after injection due to myelin allergy in vaccine preparation, and the crude vaccine and avian embryo vaccine, which have poor prevention effects and serious adverse reactions. The primary hamster kidney cell vaccine was invented. It is the first human rabies vaccine that uses cell culture technology, but its influence and application are also limited [13]. The first human diploid cell (HDC) strain, WI-38, was established in 1961. Through unremitting research on this, HDC vaccine(HDCV) was been invented. Rabies HDCV is recommended as a golden reference vaccine by the World Health Organization due to its safety. This vaccine also has the disadvantage that it is expensive and not everyone can afford it [11]. No matter what the type of rabies vaccines are, Virus-neutralizing IgG (but not IgM) antibodies (VNAs) against RV glycoprotein (G) are considered protective [10].

3.3. Alternative development of rabies vaccines

Despite the undoubted success of the current commercial rabies vaccine, there have been several attempts to develop alternative vaccines, all of which have taken advantage of the genetic manipulation revolution [14]. The key target of antibodies is the viral glycoprotein. The glycoprotein is the only exposed protein on the virion surface, and many antigenic sites have been identified on this protein that bind to neutral monoclonal antibodies [15].

Now, this alternative to rabies vaccine has demonstrated its excellent anti-infection ability by rapidly inducing high titers of RABV neutralizing antibodies in many animal models. But up to now, the rabies vaccine are still the main means to prevent rabies.

4. Discussion

There is no effective treatment for rabies. After treatment, very few patients survive. Many antiviral drugs have been used to treat human rabies. Antiviral drugs combined with a therapeutic coma should help clear the virus and allow the patient to recover. But none of the treatment regimens consistently succeeded in eliminating the rabies virus from the human body, only slowing the course of the disease in patients [4].

One of the problems with treating the disease is that the virus cannot be treated once it reaches the central nervous system, as neither existing vaccines nor IGRs can penetrate the blood-brain barrier (BBB). An ongoing mouse study includes increasing blood-brain barrier permeability to overcome this difficulty [16]. However, despite the increased survival of the mice, the study raised some safety concerns about compromising the integrity of the blood-brain barrier. The central nervous system [17]. Bispecific antibodies (BeAb) are also a promising option for the treatment of rabies. These antibodies come from the latest advances in cancer immunotherapy [18].

5. Conclusion

In general, rabies is a very serious threat to human life. Therefore, it is very important for people to deal with dog bites. Rabies vaccine should be injected as soon as possible after exposure to prevent illness and death. Although the rabies vaccine can protect against rabies, most of them need to be injected multiple times. Once forgotten, it may lead to inability to resist rabies. It still leads to illness and death. Therefore, it is particularly important to increase people's awareness of rabies and rabies vaccines. It is very important to research the therapy for rabies. And there are still many people dying from rabies all over the world. If rabies can be cured, many lives will be saved. Regarding the treatment of the disease, bispecific antibodies are a hope because of its potential to act against the virus after crossing the blood-brain barrier [19]. Although the article introduces some of the pathogenesis of rabies, some human rabies vaccines and possible future treatments. However, due to the complexity of rabies itself, some mechanisms have still not been studied. Therefore, the research and treatment of rabies, and even the development of rabies vaccines are facing many challenges.

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