International Journal of Veterinary Science and Medicine xxx (xxxx) xxx–xxx

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

International Journal of Veterinary Science and Medicine

journal homepage: www.elsevier.com/locate/ijvsm

Review Article

Advances in rabies prophylaxis and treatment with emphasis on immunoresponse mechanisms

A El-Sayed*

Faculty of Veterinary Medicine, Department of Medicine and Infectious Diseases, Cairo University, Giza, Egypt

ARTICLE INFO

Keywords:
Bat lyssavirus
Biting
Rabies
SAG1
Treatment
Vaccine

ABSTRACT

Rabies is a vaccine-preventable fatal disease in man and most mammals. Although rabies is recorded in 150 territories and is responsible for at least 60,000 human deaths every year worldwide, it is a neglected tropical problem. Most of the rabies free countries are considered to be fragile free as the disease may re-emerge easily through wild mammals. For the performance of effective rabies eradication programs, a complex set of strategies and activities is required. At the time, a joint project of WHO–OIE–FAO which was announced in 2015, plans to control animal–human–ecosystems rabies interface. For effective rabies control, prophylactic policies must be applied. These include various educational outreaches for farmers and people living in endemic areas, enforced legislation for responsible dog ownership, control programs for the free-ranging stray dog and cat populations, field large-scale vaccination campaigns, and the development of new vaccine delivery strategies for both humans and animals. The present work presents the advances in the development of new safe, effective and economic vaccines for domestic dogs, and oral vaccines for the control of the disease in wild animals. It presents also some therapeutic protocols used for the treatment of patients.

1. Introduction

Rabies is a zoonotic viral disease infecting all mammals, resulting in the highest fatality rate among all known infectious diseases. The disease is caused by a negative-stranded RNA "bullet" shaped member of the genus *Lyssavirus,* which is a member of Rhabdoviridae family. Rabies is a vaccine-preventable fatal disease which has almost a case fatality score of 100% in none vaccinated cases [1,2]. The current formal classification of the genus *Lyssavirus* no longer considers genotypes. The genotypes were upgraded to species to be more in agreement with the taxonomical nomenclature used for higher organisms namely, *Rabies lyssavirus*, *Duvenhage lyssavirus, European bat 1 lyssavirus, European bat 2 lyssavirus, Australian bat lyssavirus, Aravan lyssavirus, Khujand lyssavirus, Irkut lyssavirus, Bokeloh bat lyssavirus, Gannoruwa bat lyssavirus, Taiwan bat lyssavirus, Lagos bat lyssavirus, Mokola lyssavirus, Shimoni bat lyssavirus, West Caucasian bat lyssavirus, Ikoma lyssavirus and Lleida bat lyssavirus*. Although, phylogroups are not recognized by ICTV as taxonomical units of classification, rather as an evolutionary and functional sub-classification scheme. Based on such criteria members of the genus are divided into three Phylogroups namely; Phylogroup 1 contains the rabies virus (RABV), Aravan virus (ARAV), Khujand virus (KHUV), European bat lyssavirus type 1 and 2 (EBLV-1, -2), Bokeloh bat lyssavirus (BBLV), Australian bat lyssavirus (ABLV), Irkut virus (IRKV), Duvenhage virus (DUVV) and the two newly recognized Gannoruwa bat lyssavirus (GBLV) and Taiwan bat lyssavirus (TBLV) [3,4]. The phylogroup 1 members seem to have a common ancestor. They are 100% neutralized when rabies-virus-based biologics are used. The second phylogroup contains the African Lyssaviruses. In opposite to the first group, they are not neutralize by rabies virus –based biologics. This group contains the Lagos bat virus (LBV), Shimoni bat virus (SHIBV), and Mokola virus (MOKV). Among phylogroup 2 members, only MOKV was shown to have zoonotic impact. The third phylogroup is represented by the most genetically distant lyssaviruses. It is represented by three members, which have no zoonotic importance, namely, the West Caucasian bat virus (WCBV), Lleida bat virus (LLEBV) and the Ikoma lyssavirus (IKOV) [5,6]. Based on their evolutionary history, members contained within the Rabies lyssavirus species could be divided into two phylogroups bat-related RABVs and dog-related RABVs [7,8].

2. History, distribution and transmission of the disease

The first case of rabies was recorded in 2300 BCE, where Aristotle described the saliva of rabid dog as a venomous. The origin of the word

Peer review under responsibility of Faculty of Veterinary Medicine, Cairo University.
* Address: Faculty of Veterinary Medicine, Giza Square, 11451 Giza, Egypt.
E-mail address: aaelsayed2000@yahoo.de.

https://doi.org/10.1016/j.ijvsm.2018.05.001
Received 21 April 2018; Received in revised form 8 May 2018; Accepted 8 May 2018

rabies comes from the Latin word 'rabere: to be mad' or from the word Rabbahs in old Indian language (Sanskrit) which means (violent) [9–11]. Rabies virus has a wide mammalian reservoir host species from the orders Carnivora and Chiroptera including dog, cat, wild animals as fox, wolves, raccoons, jackal, skunk, coyote, and bats [8]. Infections result mainly from bites of rabied dogs. Rabies virus cannot penetrate intact skin. However, the contact between infected saliva and wounds, mucous membranes or skin abrasions may lead to infections. Aerosol and transplantation transmission were also reported [12–15]. The rabies virus was isolated from the brain and salivary glands of slaughtered dogs to be eaten in South East Asia and some parts of Africa. So that butchers in these countries are at risk [16,17].

Although the humans are considered to be (dead end host), person to person transmission was reported in Ethiopia where the disease was transmitted through direct contact with infected saliva in two patients [5,13]. Additional 15 cases were infected via recipient of transplanted organs or corneas. Transplacental transmission of rabies was also recorded in Turkey. The child was infected inside the uterus before being normally born via the vagina. Vertical transmission is more common in animals than in humans. This may be attributed to the anatomical differences of the placenta between man and animals [18,19].

Rabies occurs in more than 150 countries and territories worldwide (Fig. 1). The disease is a neglected tropical problem because it is distributed mainly in the slums of Africa and Asia. Every year at least 60,000 people die from rabies worldwide. Every 15 min, one person dies and 300 people get in risk mostly children under 15 years. The WHO plans to eliminate human rabies mortalities worldwide by the year 2030. To achieve this goal, a joint project of WHO–OIE–FAO was announced in 2015 to control animal–human–ecosystems rabies interface [5,20–22]. It was previously suggested that different forms of rabies infections exist in nature according to the invading virus [23]. While infection with paralytic rabies virus (PRV) results in dog paralysis within 6 days, the convulsive rabies viruses (CRV) induces convulsions in dogs after a longer incubation period [24]. Rabies caused by some abortive rabies strains – in opposite to encephalic strains- may run unnoticed in man and animals without leaving any health abnormalities. The patients even survive without getting intensive medical care. However, in 60% of the cases, they may suffer later from neurological disorders such as limb paralysis [15,25–27]. It was also noticed, that people bitten by a bat have a better chance to survive than those bitten by a rabied dog [28].

The disease is transmitted mainly through dog bites. Blood and blood products do not play any role in disease transmission as the disease is not accompanied with viremia. In about 54% of the cases the incubation period ranges from 1 to 3 months. In 30% of the cases the incubation period may be less than 30 days, and in 15% may last over 3 months. In the rest cases (1%), the incubation period may extend beyond 1 year. However, in exceptional cases it would extend up to 25 years. The length of the incubation period depends upon many factors including; the species of the biting animal, the severity and site of the bite; the virulence of virus strain and the dose of virus inoculated. In addition to other factors related to the bitten animal including previous vaccination and the general immune status [29–34].

In Europe, rabies was almost eradicated from dogs in the 20 century. However, the virus was kept maintained in wild animals there. The rabies virus became adapted to the red fox (*Vulpes vulpes*) in Russia and east Europe in the 1940 s and spreads west and south words with about 20–60 km per year. Although Europe is almost rabies free continent, new human cases were reported in Europe between 2008 and 2013 The recurrence of rabies in rabies free countries indicates how fragile is the (rabies free Status) as long as the virus is maintained in wild animals [35]. To overcome this problem oral vaccination control programs were applied to eliminate rabies in wild animals. The recent discovery of new rabies virus variants complicates this mission [8,35,36].

3. Advances in rabies prevention and treatment

Prophylactic immunization and treatment of clinical cases are critical components of disease control. However, disease control entails

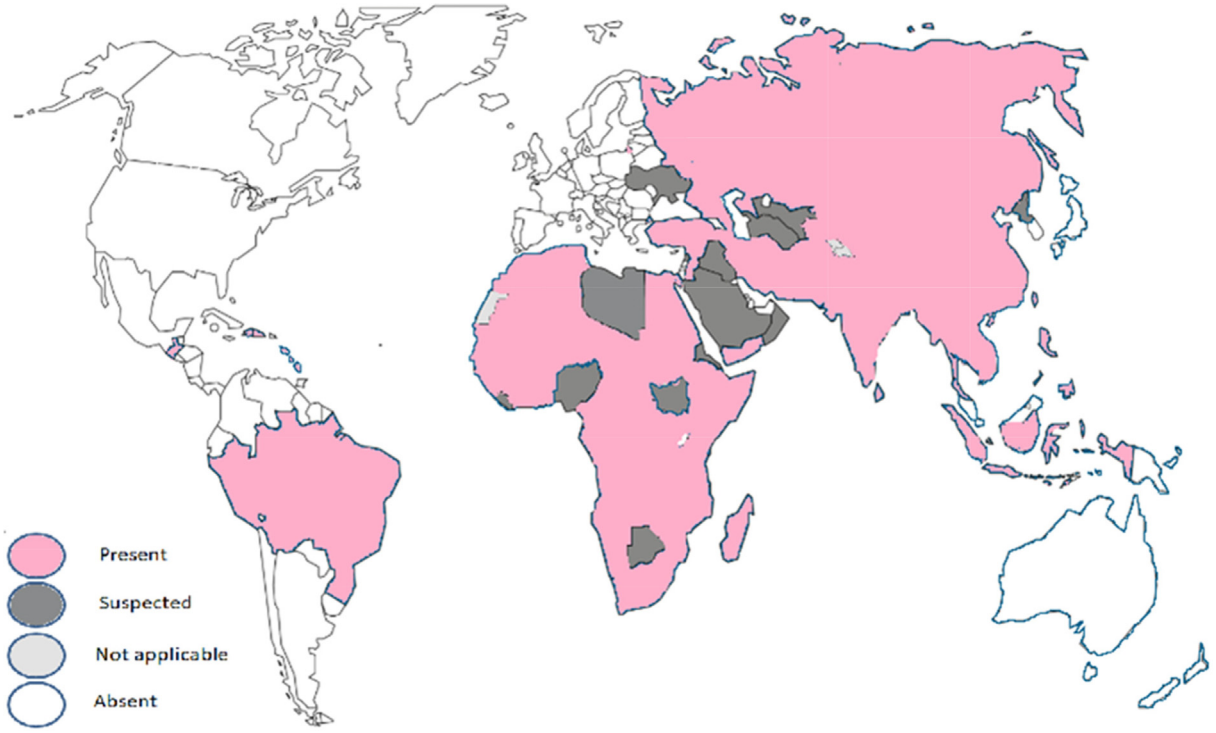

Fig. 1. Global map of dog transmitted rabies to human according to the WHO. The presented data refer to rabies transmission via domestic dogs. Data concerning rabies caused by wild animals are not involved. Wild animals are the major threat for rabies transmission in Europe and North America. Source of the map: WHO map of the year 2015 downloaded from: http://www.who.int/rabies/Presence_dog_transmitted_human_Rabies_2014.png?ua=1.