ORIGINAL ARTICLES

Euroroundup

RABIES IN EUROPE IN 2005

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Rabies is still present in Europe in 2005. Its incidence in humans remains limited (fewer than 5 human cases per year) through the application of strict prophylactic measures (anti-rabies treatment) and by means of veterinary rabies control measures in the domesticated and wild animal populations. The main indigenous animal reservoirs are: the dog in eastern European countries and on the borders with the Middle East; the fox in central and eastern Europe; the racoon dog in northeastern Europe; and the insectivorous bat throughout the entire territory. Finally, each year, cases of animals with rabies imported from enzootic areas are reported, showing the permeability of borders and traveller's lack of consideration of the rabies risk. These importations constantly threaten the rabies-free status of terrestrial animals in western European countries and complicate the therapeutic decisions taken by physicians in the absence of information regarding the biting animal.

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Rabies is still present in Europe

Rabies is a lethal form of encephalitis [1]. It is induced by neurotropic viruses of the *Lyssavirus* genus. Rabies prevention methods are known since Louis Pasteur and described in specialised reports from the World Health Organization (WHO) [2]. However, the estimated rabies morbidity in humans remains high worldwide: approximately 40 000 to 50 000 deaths per year. Finally, about 10 million anti-rabies treatments are still distributed annually. From a virologic point of view, 7 lyssavirus genotypes have been identified based on the comparison of their gene sequences.

Rabies is still present in Europe. Its incidence is low (fewer than 5 human cases per year) and stable. Three lyssavirus genotypes are endemic: genotype 1 or rabies virus (RABV), which infects terrestrial animals, and genotypes 5 and 6 or European bat lyssavirus type 1 (EBLV-1) and type 2 (EBLV-2) [3-4]. In addition, imported cases with viruses of other genotypes can appear in Europe. Europe has quality anti-rabies vaccines and immunoglobulins. This article describes the epidemiologic status of animal and human rabies in Europe.

Animal rabies

Introduction

Rabies is a zoonosis with a complex epidemiology. Its description requires a clear definition of the terms used. The term 'reservoir' is used to define a susceptible animal species, which by itself sustains the infection or the epidemiologic cycle in a given geographic area. The term 'vector' is used to define any susceptible animal species, reservoir or not, which can constitute an effective transmitter of the infection to another animal species or humans. Symptoms of rabies in infected animals correspond to those associated with encephalitis. Thus, they are not characteristic and the diagnosis of certainty is based exclusively on laboratory tests [2,5,6].

In Europe, several epidemiologic cycles of rabies coexist. These epidemiologic cycles are characterised by an animal species reservoir of a lyssavirus variant that is specifically adapted to it. However, these variants maintain the ability to infect other mammals. These mammals then become either an epidemiologic 'cul-de-sac' (e.g., humans) or a non-reservoir vector species, or secondary species in the epidemiologic cycle responsible for a limited chain of transmission (e.g., bovines infected by fox rabies).

During the last century, important modifications of the epidemiologic cycles of rabies in Europe were observed, and the establishment of new epidemiologic and biologic investigations revealed evidence of new epidemiologic cycles.

The remainder of this article will review the different epidemiologic cycles presenting a risk in Europe: rabies in domesticated carnivores, or canine rabies; rabies in the fox, or vulpine rabies; and rabies in bats (chiroptera).

Canine rabies

Affected species

The dog constitutes the only reservoir and the main vector. However, numerous other species of domesticated mammal (cows, sheep, goats, pigs, cats and ferrets) can be infected and thus constitute efficient vectors between dogs and humans on one hand and other domesticated or wild animals on the other.

Although there have been exceptional cases, such as infection in the laboratory or contamination in captivity through infected wild animals, rodents and lagomorphs (rabbits, hares and pikas) do not constitute infection relays.

History

The canine rabies which once affected all of Europe progressively disappeared in the majority of countries in central and western Europe during the first half of the twentieth century. This disappearance was probably linked more to the enforced circulation restriction of animals than to a policy of animal vaccination. Nevertheless, epidemiologic and genetic analysis of the isolates show that canine rabies remains in certain European countries, as well as on the borders of Europe. To the east of Europe, the canine type isolates are still responsible for enzootic rabies areas, for example in Turkey and the rest of the Middle East. In addition, isolates whose genetic characteristics make them part of the canine-type virus were identified sporadically in the 1990s in the former Yugoslavia and Hungary [3]. The epidemiologic and virologic data available for the more northern countries (Ukraine,

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Belarus and Russia) do not allow the exclusion or confirmation of a residual presence of canine-type isolates in these regions. To the south of Europe, canine rabies is endemic in all the North African countries of the Maghreb. All these viruses belong to lyssavirus genotype 1 and to the phylogenetic line common to the viruses circulating in Europe, the Middle East and North Africa [7].

Current situation

Today, canine rabies has disappeared from the countries of the European Union. The main risk, therefore, resides in the translocation of uncontrolled animals originating from neighbouring countries to the east and south of Europe. The risk can also originate from more distant areas of enzootic rabies by way of illegal importations from, for example, Asia, or sub-Saharan Africa. Many recent examples show that travellers are not aware of the sanitary risks they take and impose on their environment by travelling with their non-vaccinated dogs to an endemic region or by adopting animals from an endemic area to take back home with them at the end of their holiday.

Rabies in wild terrestrial animals

Affected species

The main epidemiologic cycle of rabies in wild animals in Europe is maintained by the red fox (*Vulpes vulpes*). Another epidemiologic cycle, maintained by the racoon dog (*Nyctereutes procyonides*) originally native to Asia, seems to be developing in the Baltic countries and in Poland [3].

The non-reservoir infection vectors are the same animal species as those described in the case of canine rabies.

History

The spontaneous mutation capability of the rabies virus allows it to generate mutants during its multiplication; some of these can randomly show a selective advantage for animal species other than the original reservoir species.

A mutant of the rabies virus once adapted to the dog seems to have changed vector in the 1930s to 1940s at the Russian-Polish border. A new virus adapted to the red fox appeared. The area of epizootic rabies then expanded rapidly in all directions, with an average progression of 20 km to 60 km per year, expanding into several countries in eastern, central and western Europe. The maximum north-south extension in western Europe was reached in the late 1970s, extending from the Netherlands to Italy. The maximum extension to the west was reached in 1989, covering a large portion of the northeastern quarter of France. Today this extension has been arrested and the front of enzootic vulpine rabies has been pushed back to central Europe thanks to the oral vaccination of foxes [8].

The initial efforts to distribute anti-rabies vaccine baits started in Switzerland in 1978. This strategy of oral vaccination of foxes then began in Germany in 1983, followed by Italy in 1984 and then by Belgium, France and Luxembourg in 1986. Despite these measures, the highest number of registered cases in wild animals in Europe was reached in 1989. In the same year, the European Commission subsidised the campaigns at 50%, on condition that the vaccination plans included coordination across borders. Thus, the Czech Republic in 1989, Hungary and the Slovak Republic in 1992, Poland in 1993, Slovenia in 1995, and then many other countries, began to undertake oral vaccination campaigns of larger or smaller scale.

The current situation

Numerous European countries are today free of rabies in terrestrial animals: Ireland, the United Kingdom, Sweden, Norway, Finland, Denmark, the Netherlands, Luxembourg, Belgium, France, Switzerland, the Czech Republic, Italy, Spain and Portugal.

Chiroptera rabies

Bat rabies has long been recognized in Europe. The first isolates were obtained in 1954. Beginning in 1985, important campaigns to capture and test bats were undertaken in Denmark and the Netherlands and revealed the importance of enzootic rabies areas. Since the end of these exploratory campaigns, approximately 50 cases per year have been diagnosed in numerous European countries. Another article in this issue discusses this topic specifically [9]. The number of human cases is limited (four human cases since 1977).

Human Rabies

Introduction

Rabies is a disease with known methods of prevention [2]. It results exclusively from animal contamination by bite wound, scratch wound, or licking of mucous membranes. The several cases per year in Europe result from inadequate or absent care of infected patients. The most frequent causes are the absence of administration of post-exposure treatment (PET) [10], the absence of administration of anti-rabies immunoglobulins and delayed care after contamination. There is no direct interhuman contamination. However, some cases of rabies transmission through organ transplant have been described worldwide, with three cases recently reported in Germany [11].

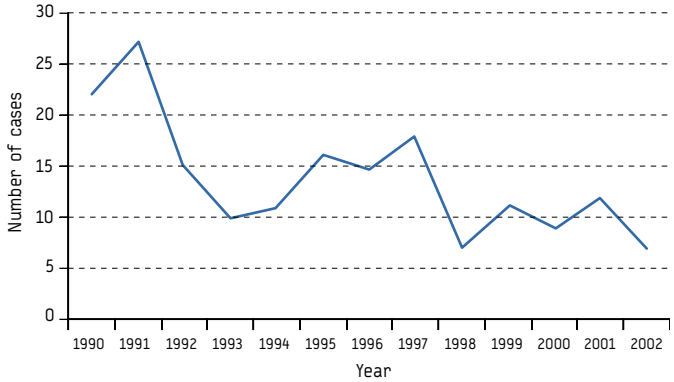
Human rabies cases in Europe arise in two epidemiologically distinct situations: indigenous cases from contact with an infected animals in a known enzootic areas, or imported cases resulting from a visit to an endemic region, usually in Africa and Asia. These two situations will be addressed separately.

Indigenous human rabies

The number of human cases of indigenous origin recorded in Europe diminished in parallel with the retreat of the vulpine rabies 'front' [Figure 1]. From 2000 to 2004, 45 cases of indigenous human rabies were reported, all in countries where the vulpine enzootic rabies continues (see below), in central and eastern Europe [Table 1], [Figure 2]. No cases were identified during this period in the regions where only canine rabies is present (Turkey for example). This difference is probably not related to a higher pathogenicity of the vulpine virus compared with the canine virus in humans but rather to a failure to implement human rabies prophylaxis procedures. As an illustration of this, the number of human cases that occurred in western European countries affected by vulpine rabies is low . In France for example, more than 49 000 cases of animal rabies have been recorded and no indigenous human case has ever been reported. However, a significant number of anti-rabies treatments (3000 to 10 000 per year) were administered in France when vulpine rabies was enzootic.

Figure 1

Total number of human rabies cases notified in Europe, 1990-2002



Source: [12]

TABLE 1

European autochtonous human cases

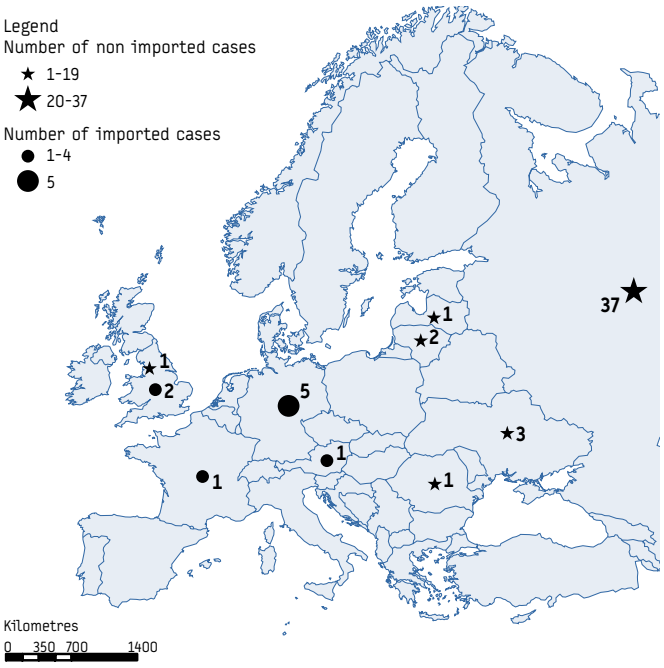
Country	2000	2001	2002	2003	2004	Total
Latvia				1		1
Lithuania	1				1	2
Romania	1					1
Russia	7	10	5	3	12	37
Ukraine			1	2		3
UK			1*			1
Total	**9**	**10**	**7**	**6**	**13**	**45**

* EBLV-2 rabies encephalitis in a bat handler, Scotland, UK

Sources: [13-17]

FIGURE 2

Cumulative numbers of human rabies cases in Europe by country, January 2000 to June 2005



The five human cases reported in Germany were two imported cases and three cases in recipients of organ donation from an imported case. The autochtonous case in the UK was infected with EBLV-2 in 2002

Sources: [11, 13-17]

With the exception of the patient from the United Kingdom in 2002, all of these cases were attributed to infections with genotype 1 lyssavirus (classic canine rabies).

Infectious contact with a wild or a domesticated carnivore was reported for any of these human cases excepted the case from the United Kingdom in 2002 and Lithuanian case in 2004.

The origin of the infection of the Lithuanian case diagnosed in 2004 could not be determined; it concerned a 5 year old boy living in a rural region where cases of vulpine rabies are regularly recorded [18]. The patient from Scotland in the United Kingdom diagnosed in 2002 died of an encephalitis due to EBLV-2 virus for which bats are the reservoirs (see specific article in this issue) [19]. This patient, a professional bat handler, endured several dozens of bites during the course of each capture season. He had not been vaccinated prophylactically against rabies and he did not wear gloves while handling bats. The last known bite before appearance of symptoms had been inflicted by a Daubenton's bat (*Myotis daubentonii*) approximately 2 months before the onset of rabies symptoms [20]. The patient had not received PET after any of his bites. This was the fourth case of rabies due to EBLV described worldwide and the second attributable to EBLV-2. The first case concerned a Finnish bat handler who captured and handled bats in Switzerland and Finland, and who died of rabies in 1985 [21-22]. A case of human rabies caused by EBLV-1 was described in the former Soviet Union in 1985 in an 11 year old child, [23]. An earlier case had been suspected in 1977 in the Soviet Union in a 15 year old child, but could not be confirmed due to the lack of characterisation of the viral strain [21]. The recent case in Scotland has resulted in vaccination recommendations for bat handlers in most western European countries [24-25].

Human rabies by importation

The imported cases of human rabies, although rare, reflect travellers' lack of awareness of the rabies risk [26]. From 2000 to July 2005, 6 imported cases have been reported in Europe [TABLE 2], [FIGURE 2]. Among them, 3 cases of infection occurred on the African continent (Morocco, Niger, Gabon), 2 infections occurred on the Indian subcontinent and one infection occurred in Asia (Philippines). In the case imported from Gabon to France in 2003, the patient had not been bitten or scratched and the contamination was attributed to licking of the mucous membranes while playing with an asymptomatic dog in an urban area [27]. Imported human rabies cases can escape diagnosis in the absence of reported exposure to the virus (unconscious patient) or notification by the patient (nonaggressive excreting animal, contact with a species not known by the patient as a rabies vector, ignorance of the situation in the country visited). Human rabies can also present in a nonspecific form. Recently, this weak clinical specificity and the absence of a witness account of exposure to rabies led to the acceptance of a young German woman as an organ donor [28]. The organs of this patient, who had originally been admitted to the psychiatric ward of a hospital, were transplanted to six recipients (two corneal transplants, one liver transplant, one pancreas transplant and two kidney transplant recipients). The recipients of the two kidneys and the

TABLE 2

Human rabies cases in Europe, 1 January 2000-1 July 2005

Year / Country	2000	2001	2002	2003	2004	2005
Germany					1 (India)	1§ (India) + 3 (grafts)
Austria					1 (Morocco)	
France				1 (Gabon)*		
UK		2 (Philippines, Nigeria)				

* No bite or scratch reported

§ Case giving rise to a case following graft

Sources: [11, 13-17]

pancreas developed rabies encephalitis in the 3 weeks following the transplant. The two recipients of the corneas underwent an excision of the grafts and received PET. The recipient of the liver had been vaccinated prophylactically several years before and he received PET. This unusual but dramatic event underlines the necessity to consider rabies when evaluating encephalitis of unknown cause, particularly in a patient who has travelled abroad. A meticulous examination of medical records before removal of organs for donation should also be recommended for patients presenting with nonspecific neurological signs of undetermined origin [29]. This review of the record has to take into consideration the available epidemiologic elements to identify exposure to exotic infectious agents or agents not elicited at the time of the diagnosis.

Conclusion

Rabies remains present in Europe. The decline of vulpine and canine rabies highlights the emerging risks related to the increase in travel to regions where rabies is enzootic and the increase in contacts between humans and bats. These risks should not overshadow the importance of vulpine rabies, which is still responsible for the majority of European cases and still far from elimination.

Many patients ignore the indigenous or imported rabies risk and the existence of pre-symptomatic excretion in carnivores with rabies. Finally, countries recently declared free of rabies are vulnerable to the threat of the illegal importation of infected animals. This risk is increased by the freedom to travel within the European Union, and it is therefore mandatory for these countries to educate their populations regarding anti-rabies measures so that they can react rapidly to an importation incident. In view of the complexity of rabies epidemiology in Europe, it is important to keep health professionals, particularly physicians and veterinarians, regularly informed and updated in order to maintain vigilance. Recommendations to improve control measurements of animal rabies in Europe and in the rest of the world like preventing human transmission or infection were recently published in the WHO Expert Consultation on Rabies [2].

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