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Epidemiology of human rabies in Turkey: 1992-2007

Aim: Rabies continues to be a public health problem in Turkey; however, the number of reported cases has decreased in recent years and 1-2 cases of human rabies are reported annually to the Ministry of Health (MoH). Epidemiological and demographic features, clinical findings, and prophylaxis of human rabies reported to the MoH between 1992 and 2007 were evaluated.

Materials and Methods: Rabies has been reported in Turkey since 1930. Data on human rabies have been available from the MoH since 1992. In this study, data on human rabies were analyzed retrospectively. The provinces, rabies risk exposure date, age, gender, type of animal, and prophylaxis program of the patients were recorded. Diagnoses of the cases were made based on clinical or laboratory findings.

Results: Thirty-nine human rabies cases (31 male, 8 female) were reported to the MoH between 1992 and 2007. Diagnosis of 17 rabies cases was confirmed by pathological findings or detection of the viral genome by PCR. The remaining 22 cases were confirmed according to epidemiological data and clinical findings. Mean age of the patients was 28.6 ± 19.3 years (range: 5-69 years). The 3 provinces that most frequently reported human rabies were İstanbul (11 cases), Şanlıurfa (5 cases), and İzmir (4 cases). Among the 39 cases, 29 were attributable to dog bites, 3 were related to wild animal exposure, and in 2 cases there was a history of contact with foxes. Twenty-two of the 39 patients did not receive post-exposure prophylaxis. In the remaining 17 patients the first dose of vaccine was administered 15 days after exposure to 5 patients, 12 patients were vaccinated on the day of rabies risk exposure, but 7 of these 12 patients did not receive any rabies immunoglobulin. In 5 patients the immunoglobulin was administered 3 days after exposure. Vaccination and immunoglobulin administration were performed at the appropriate time in 2 patients.

Conclusions: According to these results, dogs were most responsible for the development of rabies. Among the 39 patients, 37 either did not receive post-exposure prophylaxis or were inappropriately administered vaccine and immunoglobulin. Human rabies developed in 2 patients despite the fact that vaccination and immunoglobulin administration were performed at the appropriate time and dosage.

Key words: Rabies, Turkey, prophylaxis

Türkiye’de İnsan Kuduzu Olgularının Epidemiyolojisi: 1992-2007

Amaç: Kuduz yılda bir-iki vaka ile de olsa ülkemizde halen sorun olmaya devam eden bir halk sağlığı problemidir. Bu yazıda 1992-2007 yılları arasında kuduz tanısı ile Sağlık Bakanlığına bildirilen olguların epidemiyolojik ve demografik özellikleri, klinik özellikleri ile uygulanan profilaksi şemalarının incelenmesi amaçlandı.

Yöntem ve Gereç: Kuduz Türkiye’de 1930 tarihinden itibaren bildirim zorunlu bir hastalıktır. Kuduz olgularının detaylı bilgileri 1992 yılından itibaren Sağlık Bakanlığı kayıtlarında mevcut olup; bu veriler retrospektif olarak analiz edildi. Olguyu bildiren il, kuduz riskli temas tarihi, olguların yaşı, cinsiyeti, kuduz riskli temasa neden olan hayvan ve temas sonrası profilaksi durumları kaydedildi. Kuduz olgularına tanısı laboratuvar incelemeleri ile ya da klinik olarak konulmuştu.

Bulgular: 1992-2007 yılları arasında Sağlık Bakanlığı’na 39 kuduz olgusu (31 erkek, 8 kadın) bildirildiği saptandı. Otuz dokuz olgudan 17’sinin tanısının laboratuvar olarak doğrulandığı, kalan 22 vakaya epidemiyolojik öykü ve klinik bulgulara göre tanı konduğu belirlendi. Olguların yaş ortalamaları $28,6 \pm 19,3$ (min. 5, max. 69) idi. Kuduz riskli temasın gerçekleştiği il olarak İstanbul ilk

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sırada gelirken (11 olgu) bunu sırası ile Şanlıurfa (5 olgu) ve İzmir'in (4 olgu) izlediği saptandı. Kuduz riskli temasa en sık yol açan hayvanın köpek olduğu (29 olgu), ikinci ve üçüncü sırada vahşi hayvan (3 olgu) ve tilkinin (2 olgu) yer aldığı belirlendi. Kuduz tanısı konan 39 olgudan 22'sinin temas sonrası profilaksi almadığı belirlendi. Kalan 17 olgudan 5'ine ilk doz aşının 15 gün veya daha geç yapıldığı, zamanında aşı programına başlanan 12 olgunun 7'sinde anti-serum uygulanmadığı saptandı. Anti-serum uygulaması yapılan 5 olgunun ikisinde anti-serum ve aşı uygulamasının zamanında başlandığı saptandı.

Sonuç: Ülkemizde görülen kuduz olgularında kuduz riskli temasa en sık yol açan hayvanın köpek olduğu belirlendi. Kuduz gelişen 39 olgunun 37'sinde profilaksi programının geç veya eksik uygulandığı iki olguda ise zamanında ve uygun dozda profilaksi yapılmasına rağmen kuduz geliştiği belirlendi.

Anahtar sözcükler: Kuduz, Türkiye, profilaksi

Introduction

Rabies is a lethal form of encephalitis caused by the rabies virus (1). Approximately 55,000 people die annually due to rabies, according to World Health Organization (WHO) data (2). Most rabies cases were reported from Asian and African countries, and 30%-50% of them were in patients under the age of 15 years (2). The incidence of rabies is very low in Europe and the virus exists in wildlife. The main epidemiologic cycle is primarily maintained by the red fox (3). It is reported that canine rabies does not exist in western European countries; however, the risk is present in southern and western Europe because of uncontrolled animals (3).

The incidence of human rabies is very low throughout the world. On the other hand, it is still reported in Turkey due to the lack of control of stray animals (4-6). In the present study, epidemiological features, transmission route, prophylaxis schedule, and clinical findings of rabies cases were evaluated, based on Ministry of Health (MoH) data from 1992 to 2007.

Patients and methods

In Turkey notification of rabies and risky contact is performed according to the legal regulations set forth by the Rabies Control and Protection Directive and the Communicable Diseases Notification System Directive (7-9). Cases of probable human rabies are reported within 24 h to the MoH. Details, such as patient history, complaints, clinical findings, and prophylaxis, are sent to the MoH via fax or regular post by the Provincial Health Directorate.

In the present study, case reports that were sent to the MoH from the Provincial Health Directorate were evaluated retrospectively. Patient demographic features, province of residence, animal contact, time of rabies risky contact, wound location, presence of a prophylaxis schedule and its appropriateness, clinical findings, and duration between exposure and complaints were recorded. The cases were evaluated in 2 groups: probable cases and confirmed cases.

The confirmation criteria used for diagnosis of the rabies cases are described below (10):

- Detection of rabies virus antigens with direct fluorescent antibody (DFA) in post-mortem samples (especially brain tissue);
- Identification of rabies virus antigens with DFA from a corneal smear or nerve tissue samples taken from hair follicles in the neck;
- Isolation of rabies virus from brain tissue, saliva, or cerebrospinal fluid (CSF) samples (animal inoculation or tissue cultures);
- Detection of neutralizing antibodies in $\geq 1/5$ titers in serum or CSF with the rapid fluorescent focus inhibition test (RFFIT) in unvaccinated individuals;
- Detection of rabies virus genomic sequences with polymerase chain reaction (PCR) in post-mortem or ante-mortem samples (brain tissue, skin, cornea, or saliva).

Case classification:

Probable case: A case compatible with the clinical description and with a medical history of rabies risky contact;

Confirmed case: A probable case laboratory-confirmed by one of the laboratory results.

Rabies risky contact

All domestic and wild animal bites pose a risk for rabies. Other exposures accepted as posing a risk for rabies are open wounds, incision or mucous membrane contact with potentially infectious material, such as saliva or neural tissues, and lacerations (7).

Appropriateness of prophylaxis

The Rabies Protection and Control Directive and WHO's Updated Rabies Prophylaxis Guide were used for evaluation of the appropriateness of prophylaxis (7,11).

Results

There were 39 cases of rabies reported to the MoH between 1992 and 2007. Diagnosis was confirmed in 17 (43.6%) cases. In the remaining 22 cases, diagnosis was performed according to epidemiological history and clinical findings (Table 1). Of the 39 cases, 31 (79.5%) were in males and 8 (20.5%) were in females. Mean age of the patients was 28.6 ± 19.3 years (range: 5-69 years).

Table 1. Distribution of suspected and confirmed human rabies cases, according to year.

Year	Confirmed cases	Probable cases	Total
1992	2	3	5
1993	4	0	4
1994	0	1	1
1995	1	0	1
1996	1	0	1
1997	0	5	5
1998	1	2	3
1999	3	4	7
2000	0	3	3
2001	1	2	3
2002	0	1	1
2003	0	1	1
2004	2	0	2
2006	1	0	1
2007	1	0	1
Total	17	22	39

İstanbul was the province with the most rabies cases (n = 11), followed by Şanlıurfa (n = 5) and İzmir (n = 4) (Table 2). The most frequent risky animal contact was with dogs (29), followed by wild animals (3) and foxes (2) (Table 3). When the patients were evaluated regarding post-exposure prophylaxis, 22 were unvaccinated and 17 were vaccinated. Among the vaccinated patients, 5 were vaccinated 15 days after exposure and 12 were vaccinated on the exposure day. Of the 12 patients vaccinated on the exposure day, 7 were not administered rabies immunoglobulin. Of the 5 patients that were administered rabies immunoglobulin, 2 were given rabies immunoglobulin on the exposure day. In 2 of the remaining 3 patients, rabies immunoglobulin was administered on the first and ninth day after the exposure. In 1 case, a suture was performed before rabies immunoglobulin and vaccine administration. Rabies developed in 2 cases despite the fact that prophylaxis was performed at the appropriate time and with the proper dose (Table 4).

The time between rabies risky contact and symptom onset was between 14 days and 1 year for confirmed cases, versus between 15 days and 3 years for probable cases. In confirmed cases the duration between symptom onset and death was 1-13 days, versus 1-5 days for probable cases.

Diagnosis of rabies was confirmed pathologically in 16 cases. In 1 case the PCR test was positive. The site of exposure was the head and the upper extremities in 28 (71.8%) cases (Table 5). Symptoms and clinical findings were compatible with the paralytic form of rabies in 6 cases and the other 33 cases involved the encephalitic form (Table 5).

Discussion

Rabies occurs in all countries, except Antarctica and some island countries. It is one of the most frequent causes of viral mortality in developing countries (12). Unfortunately, Turkey is the only European country in which street rabies-related human cases occur because of stray animals. When the annual distribution of probable and confirmed cases was evaluated in this study, 1 or 2 cases were observed annually during the last 5 years (Table 1). Annually, more than 10 million people, mostly in Asia, receive

Table 2. Distribution of human rabies cases, according to province.

Province	Confirmed cases (n = 17)	Probable cases (n = 22)
İstanbul	5	6
Adana	1	1
İzmir	4	0
Manisa	2	1
Gaziantep	0	2
Zonguldak	1	0
Kocaeli	1	0
Şanlıurfa	0	5
Adıyaman	2	0
Siirt	0	3
Kilis	0	1
Şırnak	0	1
Bursa	0	1
Bingöl	0	1
Ağrı	1	0

Table 3. Distribution of human rabies, according to exposure time and animal contact.

Exposure time/ Animal contact	Confirmed cases (n = 17)	Probable cases (n = 22)
Exposure time		
January	2	3
February	1	1
March	2	2
April	1	1
May	0	1
June	-	-
July	2	2
August	3	1
September	3	4
October	1	2
November	0	1
December	0	2
Unknown	2	2
Animal contact		
Dog	12	17
Wild animal	0	3
Fox	1	1
Donkey	1	0
Unknown	3	1

Table 4. Distribution of human rabies cases, according to type of prophylaxis.

Vaccination	Confirmed cases	Probable cases
Unvaccinated	10	12
Vaccinated		
4-dose HDCV*	1	6
3-dose HDCV*	2	0
2-dose HDCV*	1	0
1-dose HDCV*	2	2
15-dose nerve tissue vaccine	0	1
4-dose nerve tissue vaccine	1	0
Unknown	0	1
Rabies immunoglobulin administration	3	3
Appropriateness of rabies immunoglobulin administration	1	1
Appropriateness of post-exposure prophylaxis	1	1
Duration between rabies risky contact and vaccination (day)	0.** – 60	0**.-19

*Human diploid cell vaccine

**Rabies risky contact day

Table 5. Exposure site, symptoms, and clinical findings of the human rabies cases.

Exposure site/Symptoms and clinical findings	Confirmed cases	Probable cases
Exposure site		
Head	5	8
Upper extremity	8	7
Lower extremity	0	2
Unknown	3	3
Undetected	1	0
Symptoms and clinical findings		
Hydrophobia, aerophobia	8	11
Agitation, confusion	5	9
Extremity pain, paresthesia, extremity weakness, paralysis	3	3

post-exposure vaccination against the disease, according to the WHO (2). Nerve tissue vaccines, which cause neurological side effects, are still used in some countries. In Turkey, use of nerve tissue vaccine has decreased since 1986 and only cell culture vaccine has been used since 1996. Cell culture vaccine is supplied by the MoH and all post-exposure prophylaxis is free of charge. According to the present study's results, nerve tissue vaccine was used in only 2 patients; all other patients were vaccinated with human diploid cell vaccine. We think that the decrease in the number of cases was associated with the use of human diploid cell vaccine and horse-originated rabies immunoglobulin distributed by the MoH.

Eleven cases were reported from İstanbul, 5 from Şanlıurfa, and 4 from İzmir. This could be related to İstanbul's uncontrolled stray animals and large population. An evaluation of the epidemiological distribution shows that Southeast Anatolia and East Anatolia were the areas in second place for frequency of cases.

Worldwide, dogs account for 54% of animal rabies, terrestrial wildlife accounts for 42%, and bats account for 4% (12). The epidemiology of human rabies reflects the epidemiology of animal rabies (13). In developing areas where canine rabies remains common, most human cases result from dog bites (12). In a study by Si et al. in which rabies epidemiology was investigated it was reported that 87.5% of 244 human rabies cases were caused by dog bites and 3.7% by cat bites between 1999 and 2007 (14). In a study performed between 1980 and 1996 in

the USA Noah et al. reported that among 32 cases, 17 (53%) were associated with rabies virus variants found in insectivorous bats, 12 (38%) with variants found in domestic dogs outside the United States, 2 (6%) with variants found in indigenous domestic dogs, and 1 (3%) with a variant found in indigenous skunks (15). Because all dogs are vaccinated and controlled, most human cases develop after exposure to wild animals in developed countries (3).

Rabies is preventable with appropriate wound care and post-exposure prophylaxis. Rabies prevalence of the animal, type of animal, and type of exposure (with provocation or not) are important factors in deciding if post-exposure prophylaxis is needed. In Turkey exposure to all stray animals has to be thought of as rabies risky exposure.

Of the 39 cases in the present study that were reported to the MoH as confirmed or probable cases, in 22 (56%) post-exposure prophylaxis could not be given because the patients did not present to a healthcare center for prophylaxis. In all, 17 patients presented for post-exposure prophylaxis, but 5 of them were late. The other problem that must be stressed is the low immunoglobulin administration rate. There are also some problems regarding timely immunoglobulin administration and appropriate techniques in clinical practice. Education programs for the general public and healthcare personnel must be ongoing.

Previous recommendations have called for half of the dose to be injected around the wound and the remainder to be injected intramuscularly in the gluteal region (12). Recently, the WHO and CDC

recommended that all of the rabies immunoglobulin should be injected into and around the wound (11,16,17). Failure to inject rabies immunoglobulin or surgical closure of the wound prior to immunoglobulin injection has been associated with the development of rabies, despite other appropriate post-exposure prophylaxes (12,18). In the present study the development of rabies in 2 cases despite prophylaxis might have been due to improper administration site of rabies immunoglobulin; however, we were unable to obtain the details concerning immunoglobulin injection in and around the wounds.

There is no established specific treatment for rabies once symptoms have begun (12). Thus post-exposure prophylaxis is crucial. Variables affecting the development of rabies include viral inoculums, number of bites, and bite localization. The incubation period for rabies varies from a few days to over 19 years (12). In the present study the incubation period was between 14 days and 3 years. Initial symptoms resemble those of other systemic viral infections, including fever, headache, malaise, and disorders of the upper respiratory and gastrointestinal tracts (12,20). Initial neurological symptoms may include subtle changes in personality and cognition, and paresthesia or pain near the exposure site. Rabies is

rarely considered early in the differential diagnosis (12). The prodrome is reported to occur between 4 and 10 days (20,21).

Human rabies infections are divided into 2 forms: encephalitic and paralytic. The encephalitic form presents with hydrophobia, delirium, and agitation. About a fifth of patients present with the paralytic form and have little clinical evidence of cerebral involvement until late in the course of the disease (12). In the present study 6 cases were clinically compatible with the paralytic form. Clinical findings indicated the encephalitic form of rabies in the remaining 33 cases.

Death usually occurs 18 days after the onset of symptoms (20). In the present study death occurred 1-13 days after the onset of symptoms. The short duration between symptom onset and death might have been related to delayed presentation for post-exposure prophylaxis.

In conclusion, the most important problem in Turkey is the low rate of presentation for post-exposure prophylaxis. To solve this problem, education programs for the general public about the prophylaxis of rabies must be ongoing.

References

1. Warrel MJ, Warrel DJ. Rabies and other lyssavirus diseases. *The Lancet* 2004; 363: 959-69.
2. World Health Organization. Rabies, key facts. Available from: <http://www.who.int/mediacentre/factsheets/fs099/en/> Accessed date: 13.10.2008.
3. Bourhy H, Dacheux L, Strady C, Mailles A. Rabies in Europe in 2005. *Eurosurveillance* 2005; 10: 213-16.
4. Göktaş P, Özyürek S, Karagül M, Sarı A. Kliniğimizde İzlenen Yedi İnsan Kuduzu Olgusu *Klinik Derg* 1995; 8: 120-1.
5. Sengoz G, Kart Yasar K, Karabela SN, Yildirim F, Vardarman FT, Nazlıcan O. Evaluation of cases admitted to a center in İstanbul, Turkey in 2003 for rabies vaccination and three rabies cases followed up in last 15 years. *Jpn J Infect Dis* 2006; 59: 254-7.
6. Büke M, Karakartal G, Günhan C, Serter D, Yüce K, Otkun M. Ege bölgesinde 49 olguyla kuduzun epidemiyolojik özelliklerinin değerlendirilmesi. *İnfeksiyon Dergisi* 1987; 1: 69.
7. Sağlık Bakanlığı Temel Sağlık Hizmetleri Genel Müdürlüğü, Kuduz Korunma ve Kontrol Yönergesi. 09.05.2001, B100TSH011002/7755.
8. Sağlık Bakanlığı Temel Sağlık Hizmetleri Genel Müdürlüğü, Bulaşıcı Hastalıkların Bildirimi Sistemi Yönergesi. 24.02.2004, B100TSH0110001/1534.
9. Umumi Hıfzıssıhha Kanunu. Kanun no: 1593. 6.5.1930 tarih 1489 sayılı resmi gazete.
10. Bulaşıcı Hastalıkların Standart Tanı Rehberi, Sağlık Bakanlığı, Temel Sağlık Hizmetleri Genel Müdürlüğü (Bulaşıcı Hastalıkların Bildirimi Sistemi Yönergesi: 24.02.2004, B100TSH0110001/1534 eki) 2005, Ankara.
11. Current WHO guide for rabies pre-and post-exposure prophylaxis in humans. Available from: <http://www.who.int/mediacentre/factsheets/fs099/en/>. Accessed date: 13.10.2008
12. Bleck TP, Rupprecht CE. Rhabdoviruses. In: Mandell GL, Bennett JE, Dolin R, editors. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Churchill Livingstone; 2005. p.2047-56.

13. World Health Organization. World Survey of Rabies No. 35 for the year 1999. Geneva: World Health Organization, 2002. Available at <http://www.who.int/emc-documents/rabies/whocdscsreph200210.html#english%20contents>.
14. Si H, Guo ZM, Hao YT, Liu YG, Zhang DM, Rao SQ et al. Rabies trend in China (1990-2007) and postexposure prophylaxis in the Guandong province. *BMC Infectious Diseases* 2008; 8:113. doi:10.1186/1471-2334/8/113.
15. Noah DL, Drenzek CL, Smith JS, Krebs JW, Orciari L, Shaddock J et al. Epidemiology of human rabies in the United States, 1980 to 1996 *Ann Intern Med* 1998; 11: 922-30.
16. Centers for Disease Control and Prevention. Human rabies prevention—United States, 1999: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Morb Mortal Wkly Rep.* 1999; 44(RR-1): 1-40. Available at <http://www.cdc.gov/ncidod/dvrd/rabies/professional/publications/ACIP/ACIP99.pdf>.
17. World Health Organization. WHO recommendations on rabies post-exposure treatment and the correct technique of intradermal immunization against rabies. Geneva, World Health Organization; 1997. Available at <http://www.who.int/emc-documents/rabies/whoemczoo966c.htm>.
18. Wilde H, Sirikawin S, Sabcharoen A, Kingnate D, Tantawichien T, Harischandra PA et al. Failure of postexposure treatment of rabies in children. *Clin Infect Dis* 1996; 22: 228-32.
19. Whitley RJ, Middlebrooks M. Rabies. In: Scheld WM, Whitley RJ, Durack DT, editors. *Infections of the Central Nervous System*. 1st ed. New York: Raven Press; 1991. p. 127-144.
20. Fishbein DB, Bernard KW. Rabies virus. In: Mandell GM, Bennett JE, Dolin R, editors. *Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone; 1995. p. 1527-43.
21. Hemachuda T, Phanthumchinda K, Phanuphak P, Manatsathit S. Myoedema as a clinical sign in paralytic rabies. *Lancet* 1987; 1: 1210.