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Causes of delay in offering rabies post-exposure prophylaxis services in Abadeh district of Iran

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ABSTRACT

Objectives: To identify the reasons for delayed reception of post-exposure prophylaxis (PEP).

Methods: In this cross-sectional study, a total of 1 407 individuals with animal bites who were referred to the Abadeh Rabies Treatment Center were investigated using the census method from January 2012 to December 2018. The patients were divided into two groups based on their delay times to referral and receive PEP: timely referral (less than 48 h after the bite) and delayed referral (equal to or longer than 48 h after the bite). Frequency, *Chi*-square, and logistic regression tests were used.

Results: The average delay time was (16.33±11.37) h. Low level of education (*OR*: 3.87; 95% *CI*: 1.19-12.54; *P*=0.02), active economic age (21-35 and 36-50 years-old, *OR*: 12.81; 95% *CI*: 3.16-51.97; *P*<0.001 and *OR*: 3.83, 95% *CI*: 3.83-58.61; *P*<0.001 respectively), occupation (*OR*: 9.16; 95% *CI*: 1.89-44.29; *P*=0.006), long distance from the rabies treatment center (*OR*: 3.41; 95% *CI*: 2.03-5.72; *P*<0.001), bites by household and domestic animals (*OR*: 12.22; 95% *CI*: 2.29-65.18, *P*=0.003), superficial injuries (*OR*: 4.51; 95% *CI*: 1.38-14.73; *P*=0.01), and residence in rural area (*OR*: 12.74; 95% *CI*: 6.58-24.66; *P*<0.001) had significant correlations with delayed referral of victims.

Conclusions: To reduce the delay time, the high-risk groups should be informed about the importance of timely referral *via* educational measures. Furthermore, rabies treatment services should be rendered at the nearest possible center.

KEYWORDS: Rabies; Zoonosis; Post-exposure prophylaxis; Rabies vaccines; Abadeh

1. Introduction

Rabies is a fatal zoonotic disease, which is considered as a public health problem[1-3]. It is transmitted to humans by infected animals' bites such as dogs, cats, foxes, wolves, jackals[4]. After the bite and transmitting of the virus to the victim's body, the virus begins to multiply and enters the central nervous system through the peripheral nerves. Later, it causes inflammation of the brain, followed by clinical signs and death[5,6]. About 60 000 people lose their lives due to rabies annually in the world[7,8].

Rabies has been reported in all parts of the world, but most rabies-induced deaths have been reported in developing countries in Asia and Africa[9,10]. In the past few years, Asian countries of Japan, Singapore, Malaysia, Qatar, Bahrain, and the United Arab Emirates have reported no cases of rabies-induced deaths. However, this disease is not well-controlled in Iran, Turkey, Saudi Arabia, Yemen, and other Middle Eastern countries[11-13].

Iran has been affected by rabies for many years and many people are bitten by aggressive animals annually[14-16]. Due to the endemic nature of rabies among the wild and domestic animals as well as the

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absence of a comprehensive vaccination program for the domestic animals in Iran, it is impossible to control the disease among the animal population. The application of post-exposure prophylaxis (PEP) can activate immunity in the victims before the virus reaches the central nervous system[17,18]. Therefore, every case of the animal bite should be taken seriously and the victims should receive the prevention services as soon as possible. Although anti-rabies vaccines and serum immunoglobulin would impose high costs on governments, PEP services are still effective and can save millions of lives with high cost-effectiveness[19-21]. Today, people have been provided with extensive information about the risks of animal bites and the importance of PEP. As a result, more people refer to rabies centers to receive PEP services. Nearly 20 million people in the world visit the rabies centers to receive the PEP[22] and prophylaxis can reduce the rabies-induced death rate. Considering the 100% mortality rate of this disease, educational programs, and available medical facilities should also be enhanced to control rabies[23].

To the best of our knowledge, there are not sufficient data about epidemiological situation of animal bites and rabies in Abadeh city of Iran. Therefore, this study aimed at identifying the reasons for the delayed reception of PEP in order to reduce the delay time and to provide sufficient facilities.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences and Health Services (code of ethics: IR.SUMS.MED.REC.1397.044).

2.2. Data collection

The information of total animal-bitted cases (1 407 individuals), who referred to the rabies treatment center located in Imam Khomeini Hospital in Abadeh city from January 2012 to December 2018 were studied using the census method. The information was imported into Excel software. Travelers and victims residing in neighboring provinces were excluded. The information was extracted from the Ministry of Health website and was complete, with no missing data (Figure 1).

The city of Abadeh with a population of about 106 000 is located in the north of Fars province in the center of Iran. The residents of this city are mainly farmers and cattle herders. The studied variables in this research included: the victim's demographic information (age, gender, occupation), nationality, educational level, household living condition, and living area (urban or rural), the type of biting animal (dog, cat, and other animals), the domesticated and wild animals, the traceability of the aggressive animals (up to 10 d after the bite), the time of biting (morning, evening, or night), the delay time from the occurrence of biting until referring to the rabies treatment center (the delayed hours), the number of ulcers and the amount of injuries (superficial or deep injuries in the body), and the anatomical location of the wound. In the next step, the patients were divided into two groups based on their delay times: timely referral (less than 48 h after the bite) and delayed referral (equal to or longer than 48 h after the bite). The geographical distance between the locations where biting happened and the rabies treatment center (RTC) was also divided into two groups of less than 30 km and equal to or longer than 30 km. The experts working in the RTC provided the rabies-prevention treatments (injecting the vaccine and anti-rabies serum) according to the wound conditions, the site of the ulcer, the history of receiving the rabies vaccine, the traceability of the attacking animal (up to 10 d after the bite). At the first referral, the expert responsible for the rabies prevention in the center made the decision upon the level of required services and took the necessary measures. Then, the expert provided the victims with the dates of the next visits to receive the rabies vaccine, which could be provided at other health centers and health houses.

The WHO rabies exposure categories are[24]: Category Ⅰ touching or feeding animals, animal licks on intact skin (no exposure); Category Ⅱ nibbling of uncovered skin, minor scratches or abrasions without bleeding (exposure); Category Ⅲ single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure).

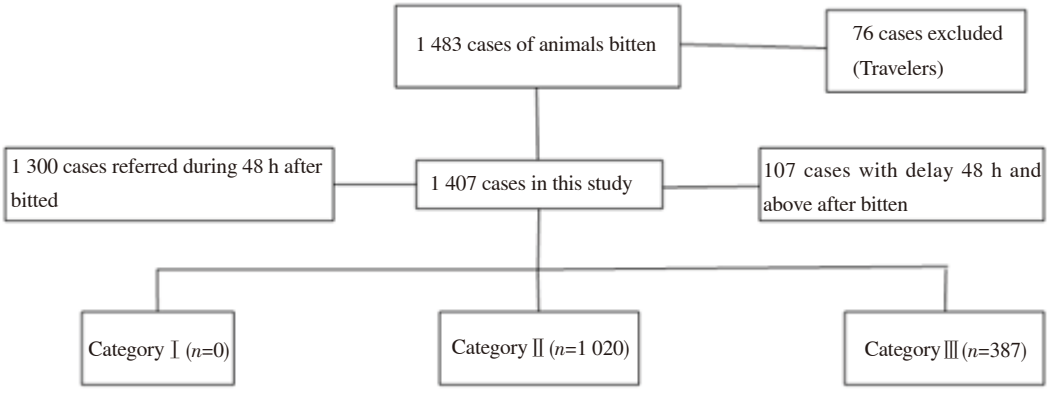

Figure 1. The study flow chart.

2.3. Statistical analysis

The required data were extracted from the archival forms (Iranian Ministry of Health website), entered into Excel 2013 and analyzed by SPSS version 25 (IBM Corp., Armonk, NY, USA). For statistical analysis of frequency, *Chi*-square and logistic regression model were used. For analyzing and determining the relationship between the studied independent variables and the delayed referral, a univariate analysis (*Chi*-square model) was conducted initially. Then the variables with significant results in univariate analysis were further analyzed by the logistic regression model. The significance level of the tests was set at α=0.05.

3. Results

In this study, 1 407 animal-bitten individuals, who referred to the RTC of Abadeh city during 2012 and 2018, were investigated. Most cases occurred in the urban areas, especially among the residents of the suburbs (57.1%). As the findings showed, 1 173 victims (83.4%) were male and 8.6% of them were children with the age of 10-year-old or less. The average age was (33.66±18.97) years and people in the age range of 36-50 years were at higher risks of bites (33.7%). Most victims were engaged in farming and animal husbandry occupations (27.6%). Most bites were done by dogs (77.8%) and the majority of individuals were affected by domestic and household animals (62.1%). Most victims (44.5%) were bitten in the legs (Table 1-3). Results showed that 123 victims (8.7%) did not have good cooperation for receiving the next doses of the anti-rabies vaccine and left their treatment incomplete after the first visit. According to the WHO guidelines, 387 of the animal-bitten people (27.5%) belonged to the third group of anti-rabies treatment; they required an injection of anti-rabies serum and anti-rabies vaccine. The investigations showed that 1 121 animal bite cases (79.7%) referred to the treatment centers during the first 24 h after bites, while 22 victims (1.6%) had a delay of longer than five days. In total, 92.4% of the victims had a delay of less than 48 h. The mean delayed time was (16.33±11.37) h.

The univariate analysis showed significant relationships between the delay in receiving PEP and the distance of the biting location from the RTC location, the place of occurrence (in or out of town) (P=0.03) and the type of residency (P<0.001) (Table 2). The types of biting animals (P<0.001), the bleeding status of the wound, as well as the depth (P<0.001), extent (P=0.009), and the number of injuries (P=0.002) all had significant relationships with the delay (Table 2).

The study also showed the victim's level of education, occupation, and age had significant relationships with delayed referral (P<0.05 (Table 3).

Table 1. Aggressive animals' conditions and injuries' status.

Variables	Delay		Total [*n* (%)]	χ^2	*P*-value
	Under 48 h [*n* (%)]	48 h and above *n* (%)			
Types of animal					
Wild	40 (2.9)	3 (0.2)	43 (3.1)	26.92	<0.001
Stray	477 (33.9)	13 (0.9)	490 (34.8)		
Household and domestic	783 (55.6)	91 (6.5)	874 (62.1)		
Animals					
Dog	1 013 (72.0)	82 (5.8)	1 095 (77.8)	3.18	0.52
Cat	231 (16.4)	20 (1.4)	251 (17.8)		
Wolf/fox	21 (1.5)	0 (0.0)	21 (1.5)		
Sheep/cow/horse	13 (0.9)	2 (0.2)	15 (1.1)		
Others*	22 (1.6)	3 (0.2)	25 (1.8)		
Status of animal					
Under supervision	517 (36.7)	16 (1.2)	533 (37.9)	25.87	<0.001
Unrecoverable	783 (55.6)	91 (6.5)	874 (62.1)		
Bite sites					
Face & hand	26 (1.8)	1 (0.1)	27 (1.9)	0.76	0.85
Trunk	155 (11.0)	12 (0.9)	167 (11.9)		
Leg	576 (40.9)	50 (3.6)	626 (44.5)		
Hand	543 (38.6)	44 (3.1)	587 (41.7)		
Extent of the wound					
Wide	140 (10.0)	3 (0.2)	143 (10.2)	6.87	0.009
Low extent	1 160 (82.4)	104 (7.4)	1 264 (89.8)		
Types of wound					
Deep	229 (16.3)	4 (0.3)	233 (16.6)	13.77	<0.001
Surface	1 071 (76.1)	103 (7.3)	1 174 (83.4)		
Number of wounds					
⩾3	148 (10.5)	2 (0.2)	150 (10.7)	9.39	0.002
<3	1 152 (81.9)	105 (7.5)	1 257 (89.3)		
Bleeding					
Bleeding	304 (21.6)	13 (0.9)	317 (22.5)	7.15	0.007
No bleeding	996 (70.8)	94 (6.7)	1 090 (77.5)		

*Other animals contain rats, squirrel, rabbit and hamster.

Logistic regression analysis indicated that long distance to the RTC site (*OR*: 3.41; 95% *CI*: 2.03-5.72; *P*<0.001), bites by domestic and household animals (OR: 12.22; 95% *CI*: 2.29-65.18, *P*=0.003), superficial injuries (*OR*: 4.51; 95% *CI*: 1.38-14.73; *P*=0.012), low level of education (*OR*: 3.87; 95% *CI*: 1.19-12.54; *P*=0.02), economic-active age groups (21-35 and 36-50 years-old, *OR*:12.81; 95% *CI*, 3.16-51.97; *P*<0.001 and *OR*: 14.99; 95% *CI*: 3.83-58.61; *P*<0.001 respectively), residence in rural area (*OR*: 12.74; 95% *CI*, 6.58-24.66; *P*<0.001), and worker occupation (*OR*: 9.16; 95% *CI*: 1.89-44.29; *P*=0.006) all had significant relationships with delayed referral (Table 4).

4. Discussion

PEP is necessary to prevent the transmission of rabies. However, several factors play important roles in providing full and timely access to PEP services. This study aimed to investigate the

Table 2. Time-location factors.

Variables	Delay		Total [*n* (%)]	χ^2	*P*-value
	Under 48 h [*n* (%)]	48 h and above [*n* (%)]			
Distance					
<30 km	767 (54.5)	32 (2.3)	799 (56.8)	34.11	<0.001
⩾30 km	533 (37.9)	75 (5.3)	608 (43.2)		
Types of residency					
Urban	766 (54.4)	38 (2.7)	804 (57.1)	22.12	<0.001
Rural	534 (38.0)	69 (4.9)	603 (42.9)		
Places of bite					
In town	754 (53.6)	51 (3.6)	805 (57.2)	4.31	0.03
Out of town	546 (38.8)	56 (4.0)	602 (42.8)		
Time of bite					
Morning	405 (28.8)	31 (2.2)	436 (31.0)	1.08	0.58
Afternoon	481 (34.2)	45 (3.2)	526 (37.4)		
Night	414 (29.4)	31 (2.2)	445 (31.6)		
Seasons					
Spring	328 (23.3)	22 (1.6)	350 (24.9)	4.58	0.21
Summer	488 (34.7)	38 (2.7)	526 (37.4)		
Autumn	298 (21.2)	34 (2.4)	332 (23.6)		
Winter	186 (13.2)	13 (0.9)	199 (14.1)		

Table 3. Demographic and social factors.

Variables	Delay (%)		Total [*n* (%)]	χ^2	*P*-value
	Under 48 h [*n* (%)]	48 h and above [*n* (%)]			
Gender					
Male	1 083 (77.0)	90 (6.4)	1 173 (83.4)	0.04	0.83
Female	217 (15.4)	17 (1.2)	234 (16.6)		
Education					
Academic	232 (16.5)	4 (0.3)	236 (16.8)	16.07	<0.001
Diploma and lower	1 003 (71.3)	100 (7.1)	1 103 (78.4)		
Pre-school child	65 (4.6)	3 (0.2)	68 (4.8)		
Job					
Clerk	96 (6.8)	2 (0.2)	98 (7.0)	75.39	<0.001
Worker	153 (10.9)	43 (3.0)	196 (13.9)		
Animal husbandry/farmer	361 (25.6)	28 (2.0)	389 (27.6)		
Student	231 (16.4)	5 (0.4)	236 (16.8)		
Housewife	147 (10.5)	13 (0.9)	160 (11.4)		
Self-employment	247 (17.6)	13 (0.9)	260 (18.5)		
Child (Pre-school)	65 (4.6)	3 (0.5)	68 (4.8)		
Age groups (years)					
⩽10	118 (8.4)	3 (0.2)	121 (8.6)	21.48	0.001
11-20	186 (13.2)	5 (0.4)	191 (13.6)		
21-35	393 (27.9)	39 (2.8)	432 (30.7)		
36-50	423 (30.1)	51 (3.6)	474 (33.7)		
51-65	129 (9.2)	6 (0.4)	135 (9.6)		
⩾66	51 (3.6)	3 (0.2)	54 (3.8)		

Table 4. Results of the logistic regression analysis.

Variables	*OR*	95% *CI*		*P*-value
		Lower	Upper	
Distance				
<30 km	Reference			
⩾30 km	3.415	2.038	5.722	<0.001
Types of residency				
Urban	Reference			
Rural	12.743	6.583	24.664	<0.001
Types of wound				
Deep	Reference			
Surface	4.516	1.384	14.739	0.012
Types of animal				
Wild	Reference			
Stray	0.218	0.041	1.157	0.074
Pet	12.228	2.294	65.183	0.003
Educational level				
Academic	Reference			
Diploma and lower	3.876	1.198	12.546	0.024
Pre-school child	3.465	0.468	25.668	0.224
Age groups (years)				
⩽10	Reference			
11-20	0.613	0.122	3.075	0.552
21-35	12.816	3.160	51.972	<0.001
36-50	14.990	3.834	58.611	<0.001
51-65	3.992	0.776	20.545	0.098
⩾66	3.568	0.500	25.470	0.205
Job				
Clerk	Reference			
Worker	9.162	1.895	44.299	0.006
Animal husbandry/farmer	1.627	0.321	8.248	0.557
Student	0.968	0.156	5.994	0.972
Housewife	2.565	0.468	14.060	0.278
Self-employment	0.770	0.143	4.157	0.761
Child (pre-school)	0.766	0.102	5.736	0.795

reasons for a delay in receiving PEP services in Abadeh city, Iran. Investigated factors included personal, social, economic, time-spatial, aggressive animal conditions and the extent of injuries.

In this study, 1 407 animal-bite cases were studied and the findings showed that 94.2% of the individuals received PEP during the first 48 h after bites. In a study conducted by Khazaei *et al.*[23], 93.4% of the individuals considered the risk of animal bites and the consequences seriously and referred to the rabies treatment center during the first 48 h after the exposure. However, other studies conducted in Iran and other countries of the world reported a lower coverage percentage[8,25].

In this study, the majority of animal bites occurred in males, which is consistent with the results of other studies[4]. In this study, no significant difference was observed between men and women in receiving PEP, which is in contrast with a study conducted by Khazaei *et al.* in Tuyserkan city of Iran, whose result shows more frequent delayed referral in women than men[26].

According to our findings, delayed referrals had a significant relationship with the distance of the rabies treatment center location from the place of bites. In this regard, people living in remote and impassable areas had a long delay. The possible causes can be lack of access to vehicles and health services as well as a lack of knowledge about the serious dangers of animal bites. A study of Joseph *et al.* in India also confirmed our results[8], but a study conducted in Khalil Abad city, northeast of Iran, showed no significant relationship between distance from the rabies treatment center and delayed referral[27].

In our study, victims with deep, multiple, and bleeding lesions referred to the rabies center in a shorter period of time after the bites, which is due to the fact that rabid animals cause more serious damage, patients with injuries of worse conditions are more sensitive to receiving PEP. The behavior of the patients in a similar study was in the same line with the victims of our study[26].

In our research, people were bitten by domestic and household animals, such as dogs, sheep, and cattle referred to the rabies treatment centers with a longer period of a delay than individuals affected by wild and stray animals. It may be attributed that most people do not regard household and domestic animals as sources and vectors of diseases[22]. Some studies conducted in different parts of the world showed that dogs played an important role in the transmission of rabies to humans, and are consistent with the results of the present study[26,28].

In our research, people in the active economic age groups (21-50 year-old) and children(under 10 years-old) had a significant delay in referring to health centers compared to the elderly. In the active economic age group, the reason for the delay was due

to occupational issues such as disagreement of the employer for a leave, lack of alternative work arrangement, the distance of the work location from the rabies treatment center, and lack of awareness about the risk of animal bites. Considering children, superficial injuries and parents' lack of information about the exposure were the main reasons for delayed referrals. The results of the studies in China confirmed the findings of our study[7]. However, no significant difference was observed among different age groups in the study conducted by Samiee *et al.*[29].

In the present study, the average delay time in people with higher academic education level was significantly shorter than those of the victims with lower levels of education, which is due to the awareness of educated people about the dangers of rabies-suspected animals. In a study conducted in India, no significant relationship was observed between the delayed referrals and the victims' level of education[11], but in another study, people with academic education tended to reach the rabies treatment centers in the shortest possible time after bites[30,31].

In the current study, workers referred to the rabies treatment centers with a significantly longer delay than people engaged in other occupations. This may be due to multiple causes such as disagreement of the employer for a leave, working in remote areas low education, and lack of awareness about the animal bite risks. In the study conducted by Esmailzadeh *et al.*, a significant relationship was found between the patients' jobs and delayed referrals[28].

In order to reduce the delay time, training programs on the risks of animal biting should be planned and implemented. Moreover, rabies treatment centers should be established in remote areas and places with a high prevalence of animal bites, so that people affected by animal bites can refer to such centers and receive the required health care in a short time. Some victims of animal bites did not cooperate well and did not refer to the rabies treatment centers to continue their vaccinations at the determined time intervals. In order to reduce the risk of rabies, individuals engaged in agriculture and livestock occupations as well as people who keep guard dogs, domesticated dogs should be vaccinated in cooperation with the veterinary network.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contribution

N.T. developed the theoretical formalism. F.M. and F.S. performed the analytic calculations and performed the numerical simulations. Both A.Karimifard and B.K performed Data Acquisition. Authors A.Kasraei and M.Y. contributed to the final version of the manuscript. A.Karimi supervised the project.

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