AKADÉMIAI KIADÓ

A fatal rabies case and experiences of a mass post exposure prophylaxis among healthcare workers

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ABSTRACT

We aimed to monitor the adverse effects (AE) and efficacy of post exposure prophylaxis (PEP) in health care workers (HCWs) exposed to a rabies patient. In this study 109 HCWs and eight household contacts were PEP candidates. Contact persons without infection control precautions were in Group I (high risk-82 cases). HCWs indirectly exposed to environmental surfaces were classified in Group II (low risk-35 cases). PEP schedule was rabies vaccine (RBV) + equine rabies immunoglobulin (eRIG) in Group I and only RBV in Group II. Local and systemic AE were observed in all cases. Efficacy of post exposure prophylaxis (PEP) was determined by rabies development in a six month follow-up. 585 doses of RBV have been used in 117 cases and eRIG has been used in 82 cases. 32 Nurses (39%); 22 emergency medicine technicians (26.8%); 12 doctors (14%); six laboratory technicians (0.07%); six radiology technicians (0.07%); four cleaners (0.05%) were in Group I (82 cases), respectively. One doctor, laboratory technician, nurse and radiology technician (0.02%); two emergency medicine technicians (0.04%) and nine cleaners (25.7%) were in Group II (35 cases), respectively. Routes of transmission were blood in five (0.06%); saliva in 14 (17%); sweat in 50 (61%); CSF/serum in five (0.06%); sexual intercourse in one (0.01%); personal equipment in seven (0.09%) in Group I, respectively. Indirect contact was the only route in Group II. The most common local and systemic AE were seen in Group I; pain at injection side (19 cases) and fever (13 cases). Both of them showed statistically significant difference ($P<0.05$). Allergic rash has been seen at only one case. PEP failed in one case where the possible exposure way was sexual intercourse. PEP is the safest way to prevent rabies. Infection control precautions were still not enough applied. eRIGs are also safe and have rare AE.

KEYWORDS

rabies, post exposure prophylaxis, health care worker

INTRODUCTION

Rabies is almost invariably fatal once clinical signs apear as a result of acute progressive encephalitis. Post exposure prophylaxis (PEP) after suspicious contact is life saving. PEP is the combination of wound care (washing and flushing) with administration of rabies vaccine and also if indicated co-administration of rabies immunoglobuline (RIG). Fatal rabies cases occur mainly in those patients who cannot access timely PEP. The indication and procedure for PEP changes with on the type of contact. There are three categories. For category I exposures, no PEP is required; for category II, immediate vaccination is recommended; for category III, immediate vaccination is recommended, and administration of RurinIG, if indicated. The first dose of rabies vaccine should be administered as soon as possible after exposure. RIG administration is recommended after category III exposures of individuals who have not previously been vaccinated against rabies [1]. Theoretically, high-risk exposures to health care workers (HCWs) include impaired skin and/or mucosal contact with

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saliva, tears, respiratory secretions, cerebrospinal fluid, and neural tissue from a patient infected with rabies.Standard infection control precautions would minimize the risk of any such exposure [2–4]. WHO recommends only embryonated egg-based rabies vaccines (CCEEVs) for PEP [5]. Rabies immunoglobuline (RIG) provides passive immunization before the immune system responds. Two types of RIG are widely used: one derives from human blood (hRIG) another from equine blood (eRIG).

In our study we describe a case of rabies infection and the consequently applied infection control precautions in our hospital. A 36-year-old Azerbaijani male patient was admitted to the emergency department (Onsekiz Mart University Medical Faculty Hospital/Turkey) on 14th of August 2018, with complaints of fever and unconsciousness. These complaints continued for three days. The patient's consciousness was clear, his location orientation was exact and his time orientation was weak. He was describing a weakness in his left arm. He had complaints of nausea, vomiting, headache and back pain, hyper salivation. Vital findings were stable, and system examinations were normal except for motor weakness on the left arm. Meningeal irritation findings were negative. Patient was hospitalized with a preliminary diagnosis of encephalitis. Radiological imaging and routine laboratory tests (hemogram, biochemistry of blood and cerebrospinal fluid, urin analysis) have been performed. Cardiopulmonary arrest has been occurred at third day of hospitalization and transferred to intensive care unit. When patient's history was examined again; he was bitten by a dog three months ago in Azerbaijan and PEP was not applied. CSF and saliva PCR tests for rabies have been performed after this information and both of them showed positivity. On the other hand, it was clarified that this patient was admitted to two different hospitals before us on the previous one week. Unfortunately, many of the HCWs who were in contact with this patient, did not take standard infection control precautions. The recommendations of WHO are followed in PEP and it was planned for all HCWs and close contact households. The aim of the study was to evaluate the efficacy and adverse effects of PEP in terms of vaccine and eRIG.

MATERIAL AND METHODS

PEP candidate population was determined 117 in total. Type of contact was determined by interviewing everyone in the study group. These face to face conversations were done by two different teams. If the results of the two interviews were consistent, the category was determined. Study population was divided into two groups. The HCWs who were in direct contact with patient's blood, CSF and body secretions (saliva, sweat etc.) and those living in same house hold were included in first group (Group I). It was defined as those who did not contacted directly with the patient but only with surface of the patient or body secretions might have been spread (Group II). Group I was defined as high-risk and eRIG (Equirab® 1000IU/5mL; eRIG = 40IU/kg) was administered with rabies vaccine (RBV-Verocell; Abhayrab®; 2.5IU/0,5mL) D0, D3, D7, D14, D28. RBV, and eRIG prepared in different syringes and injected IM at opposite body sides. Total eRIG volume per patient was between 10 mL and 18mL. Because of the diffusion problem, eRIG was applied to three different muscle groups in five mL volumes. Group II was defined as low-risk and only vaccination has been done. The vaccination schedule was same as Group I (D0, D3, D7, D14, D 28). All cases in both two groups were questioned for local and general side effects. All study groups were followed up for six months for PEP efficacy. PEP efficacy was determined according to whether rabies clinical symptoms developed or not. Epi Info-CDC and Open Epi programs were used for statistical analysis for determining whether PEP adverse effects between two groups differ or not.

This study has been approved by Onsekiz Mart University Ethics Committee – Turkey (24.07.2019-2019/14).

RESULTS

Total study population was 117 persons. Totally 585 doses of RBV and 82 doses eRIG were used in PEP. General characteristics of two groups have been summarized in Table 1. There were 82 cases (51 male/31 female) in Group I. There were 35 cases (17 male/18 female) in Group II. Average ages of the two groups were similar; 42 in Group I and 38 in Group II. There were 32 nurses; 22 emergency medicine technicians; 12 physicians; six radiology and laboratory technicians and four cleaners in Group I. There were nine

Table 1. General characteristics of two groups

	Group I (N = 82)	Group II (N = 35)
Gender (M/F)	51/31	17/18
Average Age	42	38
Medical Professionals in numbers (%)		
Doctor	12 (14%)	1 (0.02%)
Laboratory	6 (0.07%)	1 (0.02%)
Nurse	32 (39%)	1 (0.02%)
Emergency Medicine Technician	22 (26.8%)	2 (0.04%)
Radiology Technician	6 (0.07%)	1 (0.02%)
Cleaners	4 (0.05%)	9 (25.7%)
Possible Contact Route in numbers (%)		
Blood	5 (0.6%)	–
Saliva	14 (17%)	–
Sweat	50 (61%)	–
CSF/Serum	5 (0.6%)	–
Sexual intercourse	1 (0.1%)	–
Common usage of personal equipment (household)	7 (0.9%)	–
Indirect contact with environmental surfaces	–	35

cleaners; two emergency medicine technicians; one physician, radiology and laboratory technician in Group II. Sweat (50 cases; 61%) was the most often possible route of transmission in Group I. Other routes were; saliva in 14 cases (17%); household in seven cases (0.9%); CSF/serum and blood in five cases (0.6%), respectively. Sexual intercourse has been determined in one case from her declaration. Indirect contact with environmental surfaces was possible suspicious route in all Group II (35 cases).

Two groups were compared in term of PEP side effects (Table 2). In Group I, 21 of 82 patients had local and 14 systemic adverse effects, while the incidence was 42%. In Group II, only nine of 35 patients had local adverse effects but no systemic ones. The incidence of adverse effects was significantly lower in this group (42% vs 25%).

Systemic fever and pain at injection side of eRIG were statistically significant different in Group I ($P < 0.005$). At the other side; tenderness at injection side of vaccination is statistically significant different in Group I ($P < 0.005$).

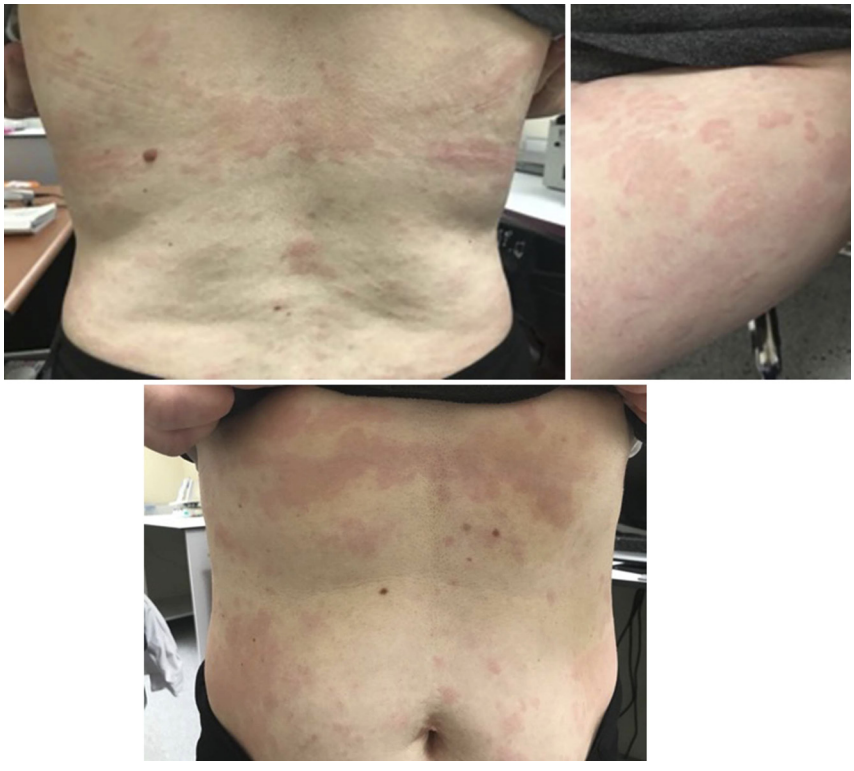
Allergic rash developed in one patient at Group I (Picture). All patients except one case completed the PEP protocol. Only one patient in Group I did not complete vaccination schedule. She was also an Azerbaijani person and had a history of sexual intercourse with the patient who died in rabies infection in our hospital. She died because of a suspicious encephalitis third month after returning to her country.

Table 2. Adverse effects between two groups

Adverse effects	Group I ($N = 82$)	Group II ($N = 35$)	P value
Local			
Tenderness	2	8	0.0009
Pain	19	1	0.006
Systemic			
Fever	13	–	0.009
Allergic rash	1	–	1.000

DISCUSSION

Due to globalization of the world, the term "endemic" causes confusion in terms of terminology. The confirmed human rabies cases in Turkey is one or two annually [6]. But as a matter of fact export cases were not numbered in these kind of statistics. On the other hand; when rabies risk contact reports examined, we see 250,000 cases per year in Turkey [6]. Rabies is a really endemic disease for Turkey with only one case per year? This question confused all health care workers, because animal contact history is essential for physicians for deciding the protocol of PEP. In our study nearly 117 health care workers had to apply PEP (585 doses RBV and 82 doses eRIG), because of the lack of using universal precautions while taking care of a suspicious encephalitis and also lack of animal exposure at the patients' history. This is the first study of mass PEP application to prevent human to human rabies transmission in HCWs



Picture: Allergic rash after eRIG

after Kan VL and colleagues published at 2015 and probably the second in the literature [1].

Vaccination schedule for the PEP in Turkey includes four doses (D0, D3, D7, between D14–28) since 2019. A five-dose scheme was applied (D0, D3, D7, D14, D28), when this study was conducted in 2018 [1].

When the HCWs distribution was examined in the study group, it was seen that the nurses (32%) had most frequently suspicious contact in first group (Table 1). On the other hand, cleaners were in highest number (25.7%) in second group. The ratio of the physicians in Group I is over estimated (14%). According to these results, compliance with infection control measures is quite low in our HCWs.

Sweat was frequently described in group one as possible contact route (50%). It was followed by saliva and blood (Table 1). We believe that sweat contact with impaired skin is not well questioned in these HCWs. It seems plausible that the condition is exaggerated due to the lethal state of the disease. House hold contact considered appropriate to be included in Group I for the same reason, because it did not appear to be a risk that could be taken into consideration. When people were questioned, sexual intercourse details were also obtained. In this case, all of them were included in Group I, because the presence of death risk was not negotiable and interval for PEP was important.

WHO suggests, RIG infiltration into and around the wound: for small wounds, the maximal quantity that is anatomically feasible should be administered. For large and multiple wounds, RIG can be diluted if necessary with physiological buffered saline to ensure the infiltration of all wounds [1]. In our study, since there was no animal contact, the injection site of RIG were determined as the opposite side of the vaccine. Because the volume of eRIG applied was above 5 mL, multiple injection sites were required. WHO does not have a definite recommendation on high volume eRIG injection sites. The lack of interpretation of such practices is also evident in the literature. In this study, we would like to emphasize the difficulty of IM application with volume over 5 mL. Interestingly, when we asked about tenderness at the injection site, it was found to be more frequent in the second group who received only RBV (Table 2). When we asked for the presence of pain at the injection site, it was more common in Group I, who had multiple injections (Table 2).

Risk assessment is essential for deciding PEP. Rabies transmission has not been documented from rabies-infected patients to HCWs or household contacts; although, there is limited surveillance in parts of the world with the greatest number of human rabies cases. In addition, rabies is not transmitted via fomites or environmental surfaces [1]. Due to fear of rabies transmission in HCWs, PEP started without adequate risk analysis. However, since our main objective in this study was not to decide on PEP with risk analysis, we do not believe that the study has methodological shortcomings from this point of view.

Allergic rash after vaccination is frequently described in the literature. There was only one patient in our study (Picture). Since the rash that develops in the patient spontaneously dissolves in five days, it is unlikely to be connected with vaccination and/or eRIG administration.

There are no reports that the Rabies virus transmits with sexual intercourse. Although theoretically the virus can be found in sweat and saliva, despite the affinity to neurons, we think it can be transmitted also by this way. This possibility is further strengthened by the fact that the patient died due to an undiagnosed encephalitis clinic after quitting PEP. But we have still lack of evidence for sufficient support of our claims.

In 35–45% of vaccinated people, minor, transient erythema, pain or swelling occurs at the site of injection. Mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people. Serious adverse events are rare and include Guille-Barre syndrome and allergic reactions [7]. In our study, only the adverse effects outlined in Table 2 were observed. The incidence and diversity of adverse effects observed in this study are less compared with the literature. In terms of side effects, both general and local adverse effects were significantly higher in the first group (Table 2). In our opinion, this is due to multiple eRIG injections. In the second group, only one dose of vaccine injection was made, whereas in the first group a large volume of eRIG (>5 mL) was done and this situation caused adverse effects in Group I frequently (42% vs 25%). To our knowledge, this is the first study comparing this situation in the literature.

eRIG is considerably potent, highly purified and safe, with few adverse events [7]. The results of our study support this situation. It is not appropriate to decide whether the side effects are due to vaccine or eRIG administration, since there isn't any patient group receiving only eRIG.

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