Adverse Effects of Rabies Pre- and Postexposure Prophylaxis in 290 Health-Care-Workers Exposed to a Rabies Infected Organ Donor or Transplant Recipients

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Abstract

The recent unfortunate rabies transmissions through solid organ transplants of an infected donor in Germany required the initiation of a vaccination program to protect health care workers (HCWs) with close contact to rabies-infected patients. A systematic follow-up of adverse effects was initiated. Rabies postexposure prophylaxis (PEP) was started in 269 HCWs at four German hospitals. Pre-exposure prophylaxis (PreEP) was administered to 74 HCWs caring for an already diagnosed rabies patient. At each vaccination date, HCWs were interviewed for symptoms possibly representing adverse effects. Adverse effects of PEP and PrePEP were compared. Out of 269 HCWs, 216 were included for the investigation of adverse effects. Of these 216 HCWs, 114 (53%) individuals developed at least one systemic adverse effect. Incidences of tiredness (30.6%), malaise (26.4%), headache (26.9%), dizziness (14.8%), and chills (13.0%) declined in the course of PEP ($p < 0.05$), whereas incidences of fever (7.4%), paraesthesias (7.9%), arthralgias (1.9%), myalgias (4.2%), nausea (9.3%), diarrheas (2.8%) and vomiting (1.4%) did not. In 11 (5.1%) HCWs PEP was discontinued mostly due to adverse reactions (four suffered strong headaches, two HCWs meningeal irritations, two chills, one paraesthesia, one malaise, and one a rush). Systemic effects of PEP or PreEP did not differ significantly. Despite relatively high incidences of moderate severe adverse reactions rabies PEP is safe. Strong headache, tiredness, dizziness, and paraesthesias are the most important postvaccinal symptoms. Vaccinees suffering from adverse effects of PEP must be strongly encouraged to complete PEP, as it is to date the only protection against fatal rabies.

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Introduction

Postexposure prophylaxis (PEP) for the prevention of rabies is usually administered only to persons exposed to an animal bite. Recently, a new rabies transmission route occurred by the transplantation of organs from donors with rabies infections not diagnosed in time [1–9]. In such a situation, organ donors and transplant recipients of rabies-infected organs are cared for by health care workers (HCWs) who initially do not suspect rabies and hence are potentially exposed to it. In Germany, in January 2005, six patients received solid organ transplants from one rabies infected donor. Rabies was first suspected and diagnosed 6 weeks after transplantation in one recipient [9]. Consequently PEP was started in a large group of HCWs who were exposed to a recipient or the donor [10]. As many vaccinees complained about a large variety of adverse effects after the first vaccination, we decided to perform a systematic follow-up of all vaccinated HCWs, and to study incidences and dynamics of adverse effects of PEP in a large and homogeneous group of vaccinees during a

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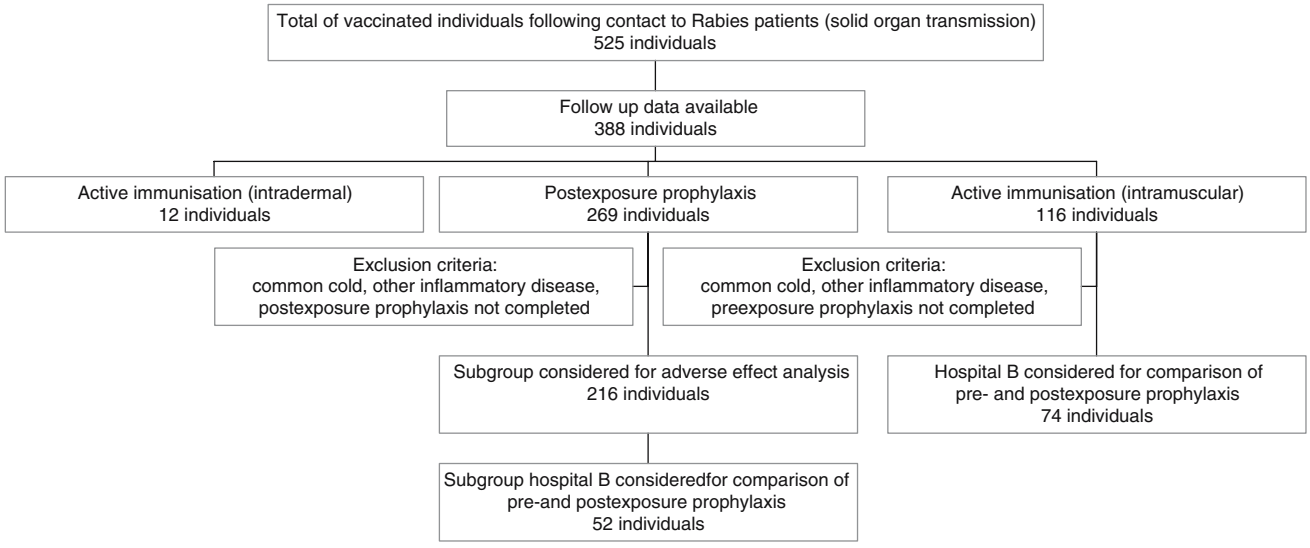

Figure 1. Population of investigated vaccinated health care workers exposed to rabies infected patients.

defined time period. Furthermore, one center cared for a patient for six additional weeks after the diagnosis was made. Consequently, HCWs designated to care for this patient in future received a rapid preexposure prophylaxis (PreEP). We compared adverse effects of the PEP and PreEP groups in order to investigate whether some clinical effects are attributable to the administration of rabies hyperimmunoglobulin.

Methods

An observational study was performed including all HCWs vaccinated against rabies between 15 February 2005 and 25 March 2005 at four German hospitals (university hospitals at Hannover [hospital A], Marburg [hospital B], Mainz [hospital C], and a kidney transplant center at Hannoversch-Münden [hospital D]). In addition, those HCWs in hospital B receiving preexposure prophylaxis (PreEP), because they cared for a recipient with diagnosed rabies surviving for 6 weeks after diagnosis, or analyzed specimens of him, were analyzed separately.

Rabies postexposure prophylaxis (PEP) was performed according to the Essen schedule [11, 12]. HCWs were vaccinated with passive rabies vaccine (hyperimmunoglobulin (Berirab®) 20 IU/kg BW; day 0) and with active rabies vaccine (Purified Chicken Embryo Vaccine [PCEV] [Rabipur®]; days 0, 3, 7, 14, 28). PreEP with active rabies vaccine (PCEV) was performed according to the Essen schedule without passive immunization, in order to develop immunity rapidly.

At each individual vaccination date and 2 weeks after the last injection, any adverse effects which occurred after the previous vaccination were documented using a standardized questionnaire, asking the vaccinees whether they suffered from chills, fever, nausea, vomiting, diarrhea, headache, tiredness, malaise or other side effects. Answers in the latter column were dizziness, paraesthesias, lymphadenopathy, arthalgia and myalgia. For each symptom, the date and hour of the onset were recorded, and only events occurring within 48 h after vaccination were considered. Individuals suffering from acute illness during the initiation of PEP, those who discontinued PEP, and those who had been vaccinated against rabies before, were excluded from further analysis. In addition, HCWs developing symptoms of a common cold during a period of 48 h after vaccination were also excluded from the analysis, in order to reduce any risk of wrongly interpreting symptoms as related to vaccination.

Adverse effects of PEP and PreEP of the HCWs in hospital B were compared in order to investigate whether any clinical effect could be associated to the administration of hyperimmunoglobulin.

Statistical analysis was performed using the ''R'' version 1.9 program for the calculation of 95% confidence intervals, chi-square-tests, Fisher's exact tests, trend tests and relative risks.

Results

As a consequence of rabies transmission by solid organ transplantation in Germany in 2005, a total of 525 rabies vaccinations were started in all involved German hospitals (Figure 1, [13]). Follow-up data were available for 388 vaccinees from four hospitals (hospital A: 128 HCWs, hospital B: 164 HCWs, hospital C: 18 HCWs, and hospital D: 78 HCWs).

After application of exclusion criteria 216 out of 269 HCWs receiving rabies PEP remained for the investigation of adverse effects of PEP. In 11 (5.1%) individuals PEP was discontinued due to adverse effects: six individuals suffered from strong headache, two of them developed meningeal irritation. Two individuals suffered from chills, and one each developed reversible paraesthesias, rush probably due to an allergic reaction, and malaise. We could not find out the reason why five further individuals discontinued PEP after the fourth vaccination even though they reported no adverse effects. Four pregnant women received PEP. None of them developed adverse effects.

At the site of active vaccination (deltoideal) minor local adverse effects were observed (Table 1). No persis-

Table 1
Local adverse effects of the vaccination (216 individuals with completed postexposure prophylaxis).

Symptoms	Deltoideal injection site: 1st vaccination	Deltoideal injection site: 2nd vaccination	Deltoideal injection site: 3rd vaccination	Deltoideal injection site: 4th vaccination	Deltoideal injection site: 5th vaccination	Trend test p-value	Total	%	$CI_{95\%}$	Gluteal injection site: hyper-immunoglobuline	%	$CI_{95\%}$
Tenderness	106	102	82	64	51	< 0.001	405	37.5	34.6–40.7%	46	21.3%	16.0–27.3%
Spontaneous local pain	12	13	12	13	9	0.57	59	5.5	4.2–7.0%	9	4.2%	1.9–7.8%
Erythema	5	3	3	4	3	0.61	18	1.7	1.0–2.6%	4	1.9%	0.5–4.7%
Swelling	4	4	4	4	3	0.74	19	1.8	1.1–2.7%	6	2.8%	1.0–5.9%
Malfunction	7	3	6	4	4	0.46	24	2.2	1.4–3.3%	0	0.0%	0.0–1.7%
Persistent malfunction	0	0	0	0	0		0	0.0	0.0–0.3%	0	0.0%	0.0–1.7%

For each vaccine local effects of each vaccination were counted separately [1,080 intradeltoideal injections of rabies PCEV (Rabipur®) and 216 intragluteal injections of hyper-immunoglobulin (Berirab®)]

Table 2
Systemic adverse effects of postexposure prophylaxis (216 completed postexposure prophylaxes): for each health care worker any particular symptom was recorded only once even if it reappeared after another active vaccination.

Symptoms	Number of symptom positive HCWs	%	$CI_{95\%}$
Tiredness	66	30.6	24.5–37.2%
Malaise	57	26.4	20.6–32.8%
Headache	58	26.9	21.1–33.3%
Dizziness	32	14.8	10.4–20.3%
Fever	16	7.4	4.3–11.8%
Chills	28	13.0	8.8–18.2%
Nausea	20	9.3	5.7–13.9%
Vomiting	3	1.4	0.3–4.0%
Myalgias	9	4.2	1.9–7.8%
Arthralgias	4	1.9	0.5–4.7%
Diarrhea	6	2.8	1.0–5.9%
Paraesthesias	17	7.9	4.7–12.3%
Lymph adenopathy	3	1.4	0.3–4.0%
At least one symptom	114	52.8	45.9–59.6%

tent malfunction occurred. While local pain, erythema, swelling, and temporary malfunction occurred in equal frequencies at all vaccination dates from the first to the last vaccination time point, the frequency of tenderness declined significantly. Also at the site of hyper-immunoglobuline vaccination (gluteal) only mild local adverse effects occurred.

A total of 114 out of 216 HCWs (52.8%) developed at least one systemic adverse effect (Table 2). The 36, 27, 11, 12, six and two vaccinees developed just two, three, four, five, six and seven different systemic symptoms, respectively. During the vaccination period the frequency of postvaccinal tiredness, malaise, headache, dizziness and chills declined significantly (Table 3). Two vaccinees developed headache with reversible meningeal irritations (see above). The only persistent systemic adverse effects developing during the defined observation time were paraesthesia in a finger and arterial fibrillation, occurring in one HCW each. Hospitals A and D recorded significantly more adverse effects than did hospital B ($p < 0.0001$, $p < 0.001$, respectively). No vaccinee developed rabies infection.

In order to investigate whether adverse effects were due to the passive component of the first vaccination rather than to the consecutive active vaccinations, we compared adverse effects of 52 vaccinees of hospital B receiving PEP with those 74 vaccinees of the same hospital who received PreEP. For this analysis we concentrated on data from hospital B because the recording of adverse effects between hospital B and two other hospitals differed significantly and hospital B comprised the

largest subgroup of vaccinees. No significant differences concerning the development of adverse effects between PEP and PreEP were detected (Table 4).

Discussion

The unfortunate incident of rabies transmissions to solid organ recipients by infected donor organs required the initiation of a vaccination program for the protection of exposed health care workers. This situation offered the opportunity to perform a prospective follow-up of adverse effects of PEP in an homogeneous cohort and to determine real incidences of adverse effects: in particular a denominator population was available, which is missing in most published studies as well as in databases recording adverse effects of immunizations (e.g., vaccine adverse event reporting system (VAERS)-data-base from CDC) [14–21] (http://www.vaers.hhs.gov/). Additionally the investigated population consisted of medical personnel which can be expected to be able to describe and document adverse effects in more detail than vaccinees without medical background.

As certain flu-like symptoms are difficult to distinguish from mild vaccination related adverse effects, we applied strict exclusion criteria to avoid overestimation of adverse effect incidences. HCWs in whom we diagnosed unambiguous symptoms of a common cold, other

Table 3
Dynamics of systemic adverse effects during the course of postexposure prophylaxis (216 completed postexposure prophylaxes considered): for each health care worker any symptom was recorded separately after each vaccination.

Symptoms	First vaccination	Second vaccination	Third vaccination	Fourth vaccination	Fifth vaccination	Trend test, p-value
Tiredness	40	30	32	23	22	0.007
Malaise	33	26	23	22	19	0.03
Headache	31	24	21	16	12	< 0.001
Dizziness	21	13	10	9	6	0.001
Fever	10	7	8	6	3	0.06
Chills	14	11	11	8	4	0.01
Nausea	8	8	7	4	3	0.07
Vomiting	0	3	0	0	0	0.2
Myalgias	4	4	4	3	2	0.38
Arthralgias	2	0	2	0	0	0.16
Diarrhea	3	3	1	2	1	0.26
Paraesthesias	7	6	6	5	4	0.34

Table 4
Comparison of systemic adverse effects of postexposure and pre-exposure prophylaxis in hospital B.

Symptoms	Number of symptom positive HCWs receiving postexposure prophylaxis, N = 52	Number of symptom positive HCWs receiving preexposure prophylaxis, N = 74	Relative risk	Chi-square or Fisher's exact test as appropriate p-value
Tiredness	10	16	0.89	0.91
Malaise	9	10	1.28	0.74
Headache	11	11	1.42	0.49
Dizziness	8	6	1.9	0.32
Fever	2	2	1.4	1.0
Chills	2	3	0.95	1.0
Nausea	3	4	1.07	1.0
Vomiting	0	0	n.d.	n.d.
Myalgias	3	2	2.1	0.4
Arthralgias	0	0	n.d.	n.d.
Diarrhea	0	0	n.d.	n.d.
Paraesthesias	4	2	2.0	0.4
At least one symptom	21	26	1.15	0.68

n.d. not defined

inflammatory disorders, or in whom we were not sure to be able to distinguish between symptoms due to vaccination or due to another inflammatory disorder were excluded. So we are confident that this study does not overestimate systemic adverse effects of PEP (active and passive vaccination). However, a slight underestimation due to exclusion of possibly but not definitively vaccination-related symptoms is possible especially in one of the hospitals, as data collection was inhomogeneous between the different hospitals. The lower incidence of detected adverse effects in hospital B might be explained by the fact that this hospital performed the largest vaccination program of all in the same short time period.

The analysis of local adverse effects was not surprising and clearly demonstrates that PCEV – vaccine as well as hyperimmunoglobulin are generally well tolerated at the injection site.

In contrast, we were concerned about the impact of systemic adverse effects following PEP. Compared with published data we observed a higher incidence of strong headache, dizziness and paraesthesias. In two HCWs headache developed to temporary meningeal irritations, and one vaccine walked against a wall as a consequence of dizziness. However, the high incidences of reported side effects reflect also the active surveillance procedure used (questionnaire specifically asking for the reported side effects) and the study population sensitive for adverse effects (medical staff).

Vaccinees should be informed about the high chance of developing those effects. All occupations requiring full consciousness should be undertaken with caution, and stopped immediately if such symptoms develop. Interestingly some symptoms became less frequent over time. One reason could be a bias due to slack documentation of mild symptoms such as tiredness. Another explanation could be that the boosted specific immune response protected against symptoms. On the other hand more serious symptoms such as paraesthesias, headache or dizziness did not decline. These latter effects might be specific to active rabies vaccination. This hypothesis is supported by the finding that systemic adverse effects did not differ between the two vaccinee groups receiving PEP or PreEP, respectively.

The discontinuation of PEP due to adverse effects in eleven (5.1%) vaccinees despite encouragement to complete clearly shows that adverse effects were experienced as agonizing in some individuals. Probably, a preexposure prophylaxis could be borne more easily as only three active vaccinations are required. This should be considered for travelers who are likely to be exposed to rabies and the indication for a preexposure prophylaxis should be made liberally.

Conclusion

Rabies post exposure prophylaxis is safe. Nevertheless, mild systemic adverse effects develop in about 53% of all vaccinees. Strong headache, tiredness, dizziness, and paraesthesias might be the most important symptoms after active immunizations and seem to be specific for the rabies vaccine. Therefore, vaccinees should be informed about the high chance of developing these adverse effects. They should be advised to be careful when driving or working in professions where full consciousness is needed. All frequent symptoms but paraesthesias seem to decline in the course of PEP. Adverse effects might reduce compliance to complete rabies post exposure prophylaxis. Hence, vaccinees must be strongly encouraged to complete PEP, as it is to date the only protection against fatal rabies.

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