

Research Article

Poor Immune Response to Rabies Post-Exposure Prophylaxis: An Attempt to Understand the Underlying Mechanisms

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Abstract

Background: In a previous study the adequacy of the 4 dose intramuscular regimen for rabies post exposure prophylaxis (rPEP) was investigated and 6, 7% patients were identified as having rabies-specific antibody titers below 0, 5 IU/ml (= poor responders). The aim of the current study was to try to establish the reasons for the poor immune response to rPEP in some subjects.

Methods: Poor responders to rPEP were contacted for a complete medical work-up. In addition, a lymphocyte proliferation assay with rabies antigen was performed to assess the cellular immune response.

Results: Nine rPEP poor responders were included in this study. One patient had a history of malnutrition at the time of rPEP administration. Five subjects had marginally decreased IgG3 levels. The results of the lymphocyte proliferation assay with rabies antigen showed a relatively poor correlation between the humoral and cellular responses. The cytokine profile suggests a globally poorer immunogenic effect of the rPEP in poor responders, more oriented toward a Th2 response with diminished IFN- γ and increased IL-13.

Conclusion: These results did not permit to establish an explanation for the poor humoral response to rPEP in some subjects. Neither immunosuppression, nor the development of an alternative cellular immune response seems to be the reason.

INTRODUCTION

Despite the fact that most countries in the Western Hemisphere have succeeded in eliminating rabies transmitted by terrestrial animals, the disease is still endemic in numerous developing countries [1]. Rabies remains especially widespread in most African and Asian countries and causes an estimated 60,000 rabies deaths worldwide each year.

After potential rabies exposure, a rabies post-exposure prophylaxis (rPEP) is recommended. rPEP comprises an active immunization and administration of rabies immunoglobulins for non-immune patients. One of the most widely used regimens for rPEP has been the Essen regimen, which includes five doses of intramuscular vaccine on days 0, 3, 7, 14 and 28 after exposure. In Switzerland a serological test on day 21 to verify the adequacy of the immune response has always been recommended. A

rabies-specific antibody titer ≥ 0.5 IU/ml measured by the rapid fluorescent focus inhibition test (RFFIT) has been considered as indicative of a protective immune response. Several studies have confirmed the effectiveness of this regimen [2].

In 2010 the Center of Disease Control (CDC) and the World Health Organization (WHO) published new recommendations for rPEP [3,4]. These recommendations were developed to reduce the number of doses for rPEP from 5 to 4. In addition, the CDC stated that post vaccination serological testing on day 21 of the Essen regimen was not necessary as all subjects demonstrate an adequate antibody response [5]. These recommendations were not only influenced by conclusions from research studies, but also by recurrent shortages of rabies vaccine and the fact that many developing countries were encountering difficulties in performing reliable serological testing by RFFIT.

Taking into account these new guidelines, we conducted previously a retrospective investigation about the adequacy of the humoral response in patients who consulted our institution between 2005 and 2011 for an rPEP [6]. This study showed that 6/90 patients (6.7%) had an anti-rabies antibody titer < 0.5 IU/ml after 4 doses. All these patients had an adequate increase of their rabies antibody titer after receiving additional vaccine doses. In an editorial, Henry Wilde suggested that those patients who had not responded adequately to a 4-dose regimen of rPEP probably suffered from a non-recognized immunodeficiency [7].

The objectives of the present study were 1) to investigate whether rPEP poor responders had an immunodeficiency and 2) to investigate if other than humoral mechanisms are stimulated in patients with low antibody response to rabies vaccines. The working hypotheses were that these subjects might have unrecognized immuno suppression or that they develop preferentially a cellular immune response, which is not detected by the usual anti-rabies antibody detection.

METHODS

Enrolment of subjects and blood collection

All patients who had received a rPEP at the University Hospital of Lausanne between 2005 and 2014 and who had an anti-rabies antibody titers ≤ 0.5 IU/ml after 4 doses of vaccine were contacted to be included in the study. These patients are referred below to as poor responders (PR). Although an antibody level of 0.5 IU/ml is usually considered as sufficient for protection, we included patients with 0.5 IU/ml to increase the sample size.

Two comparator groups were made to perform the experimental immunologic tests. The positive control group included 9 patients who had received an rPEP at the University Hospital of Lausanne between 2005 and 2014 and who had anti-rabies antibody titers > 1 IU/ml after 4 doses of vaccine. A negative control group included 9 healthy volunteers who had never received any rabies vaccine.

Evaluation of rPEP poor responders

The PRs were seen for a consultation, which included a complete medical history and a physical examination. The medical history was focused to detect an increased susceptibility to infections. Blood samples were taken to perform the following

investigations: full blood count, measurement of IgA, IgM and IgG levels, as well as the 4 subclasses of IgG, numeration of lymphocyte subpopulations (CD4 cells, CD8 cells, B cells and NK cells), and an HIV test. Evaluation of the humoral response to tetanus, pneumococcal, and hepatitis B vaccinations was also performed. Tetanus antibody levels were measured in patients who had received a dose of tetanus vaccine in the last 10 years. A tetanus antibody level < 0.1 U/ml was considered as abnormal. An assessment of anti-HBs was performed in patients who had been vaccinated within the last 5 years and anti-HBs levels < 10 U/ml were considered as abnormal. Patients who had never received a pneumococcal vaccine in the past were selected to receive one dose of the 23-valent polysaccharide anti-pneumococcal vaccine. Four weeks later the level of antibodies against the serotypes 9N, 11A, 14, 17F, 19F and 23F were assessed. Antibody levels < 0.3 mg/l against more than 4 serotypes were considered abnormal.

Assessment of immune response

Evaluation of humoral response: Rabies antibody titers were determined by the rapid fluorescent focus inhibition test (RFFIT) as previously described [8,9]. These serologies were done by the Swiss Rabies Center, which is accredited as part of the Institute of Virology and Immunology of the University of Bern by the Swiss Accreditation Service (SAS). As an officially approved laboratory of the European pet travel scheme, this laboratory participates each year in the inter-laboratory proficiency testing carried out by the reference laboratory ANSES-Nancy.

Lymphocyte proliferation: Blood samples from all subjects were collected using sodium citrate Vacutainer CPT™ (Becton, Dickinson and Company, Oxford, UK). PBMC were separated by centrifugation, washed and stored in nitrogen until use. Using a methodology similar to ones described in previous studies we cultivated PBMC (250 000 cells per well in triplicates) for 6 days in presence of various doses of rabies vaccine (Flury-LEP strain Purified chick embryo cell rabies vaccine, Rabipur®), a mitogen (phyto hemagglutinin, PHA), or a mixture of recall antigens (tetanus toxoid (TT) Pasteur Merieux; PPD, Tuberculin batch RT50, SSI, Copenhagen, Denmark; and Candida Mannan purified from *Candida albicans*, NIBSC, Hertfordshire, UK, at 10, 5 μ g/ml and 1% final, respectively) or unstimulated (10, 11). After 5 days of culture, supernatants were collected and tritiated thymidine was added (1 μ Ci per well) for 20 hours. Cell DNA from each well was harvested on glass fiber plates and incorporated thymidine was counted (cpm) using a beta counter. Results were expressed as stimulation indices (SI = mean cpm in stimulated wells / mean cpm in unstimulated wells). Preliminary PBMC proliferation experiments performed with PBMC from subjects of the 3 groups (responders, PRs and non-vaccinated) permitted determination that the doses of Rabipur of 25, 2.5 and 0.25 mIU/ml were optimal for the further experiments.

Cytokines: Cytokine response to rabies and to recall antigens were evaluated. IL-10, IL-13, IL-17 and IFN γ were measured in 6-day culture supernatants of the PBMC stimulated with the highest dose of rabies vaccine, the antigen recall mix (memory mix, MM) or unstimulated (NS) using multiplexed particle-based flow cytometric assays Bioplex Cytokine Assay (Bio-Rad Laboratories) and a Luminex 100 analyser, equipped with Bio-Plex manager. Mean fluorescence intensity (MFI) of standards

and samples were analysed in Excel and results expressed as pg/ml.

Statistical analysis

Means were compared by the Mann-Whitney test. Outliers were identified with the Grubbs' test. Linear correlations were tested with the Pearson test.

Ethics statement

The study was conducted according to Good Clinical Practice Guidelines and the declaration of Helsinki. The protocol was approved by the Ethic Committee of the Canton Vaud, Switzerland. All participants gave written informed consent.

RESULTS

Eighteen patients were identified with anti-rabies levels \leq 0.5 IU/ml after 4 doses of rabies vaccine given as post-exposure prophylaxis. Twelve patients could be contacted and 9 subjects accepted to take part in the study. Demographic details of these subjects are summarized in table 1. PR1 to PR7 had received their rPEP months to years before the study was conducted and they had all received additional rabies vaccine doses, which had led to antibody levels $>$ 0.5 UI/ml. PR 8 and PR9 could be included in the study just after day 21 of their vaccination schedule when their anti-rabies antibodies were low. PBMCs could therefore be collected for these subjects before and after receiving additional doses of vaccine.

Medical history and clinical examination

All PRs except subject PR6 had unremarkable medical history and physical examination. Subject PR6 had been hospitalized several times between 2004 and 2008 for malnourishment and

diarrhea. At the time she received her rPEP in 2008, she was undernourished with a BMI of 17 kg/m². Her current clinical examination was normal and her BMI was 18.5 kg/m².

rPEP schedule details of the PRs.

No PR had received rabies pre-exposure prophylaxis (Table 1). All PRs had received human rabies immunoglobulins (HRIG) after exposure. PR3 and PR8 started their rPEP outside Switzerland. All subjects except PR3 received the Essen regimen for their rPEP. PR3 received intradermal vaccination with 2-site injections on days 0 and 3, and 1 intradermal injection on day 7. Strictly speaking this patient had therefore an incomplete post-exposure prophylaxis, as the WHO recommends that intradermal vaccination comprises 2 doses of 0.1 ml on day 0, 3, 7 and 28. PR6 with the medical history of anorexia, had an appropriate rabies antibody titer (2.5 IU/ml) after a 5th vaccine dose. On day 187, her rabies antibody titer had however fallen again to 0.3 IU/ml and she received two additional vaccine doses. On day 353 she had a rabies antibody titer of 5.4 IU/ml.

The patients received either Rabipur® (Novartis Pharma), or Rabies Vaccine Merieux® (Sanofi Pasteur MSD). Lot numbers, potency and number of doses of the Rabipur® vaccines used were as follows: Lot no 397011A, 9.0 IU/dose, 6 doses used; lot no 422011C, 7.0 IU/dose, 1 dose used; lot no 359011C, 7.0 IU/dose, 1 dose used; lot no 378011A, 6.0 IU/dose, 1 dose used; lot no 533011A, 4.1 IU/dose, 1 dose used; lot no 545011C, 7.1 IU/dose, 1 dose used. Lot numbers, potency and number of doses of the Rabies Vaccines Merieux® used were as follows: lot no G1510-4, 4.5 IU/dose, 3 doses used; lot no H1341-4, 5.6 IU/dose, 1 dose used; lot no H1287-4, 8.2 IU/dose, 3 doses used; lot no B0001-9, 6 IU/dose, 3 doses used. The lot numbers were unknown for 9 doses of Rabipur® and for 1 dose of Rabies Vaccine Merieux®.

Table 1: Demographic details and vaccination schedules of the poor responders (PR).

Subject	Sex	Age	Year of vaccination	Vaccination (brand, lot no)*				Days of vaccination	Rabies serology		AB titer at the time of the lymphocyte proliferation assays
				1 st	2 nd	3 rd	4 th		Day [#]	AB titer IU/ml	
PR1	m	62	2007	Rabipur 397011A	Rabipur 397011A	Rabipur 397011A	Rabipur 397011A	D0, D3, D7, D15	22	0.2	1.0
PR2	f	67	2012	Merieux G1510-4	Merieux H1341-4	Merieux H1287-4	Merieux H1267-4	D0, D3, D7, D14	21	0.4	5.2
PR3	m	54	2009	Rabipur*unknown	Rabipur*unknown	Rabipur* unknown	Rabipur* unknown	D0, D0, D3, D3, D7	30	0.5	1.0
PR4	m	27	2009	Rabipur 422011A	Merieux B0001-9	Merieux B0001-9	Merieux B0001-9	D0, D3, D7, D14	23	0.5	0.3
PR5	f	30	2012	Merieux unknown	Merieux G1510-4	Merieux G1510-4	Merieux H1287-4	D0, D3, D7, D129	26	0.3	0.2
PR6	f	30	2007	Rabipur unknown	Rabipur unknown	Rabipur 397011A	Rabipur 397011A	D0, D3, D8, D15	22	0.3	1.6
PR7	f	40	2005	Rabipur 359011C	Rabipur 378011A	Rabipur unknown	Rabipur unknown	D0, D3, D7, D14	21	0.3	8.2
PR8	m	66	2014	Rabipur*unknown	Rabipur 533011A	Merieux K1323-1	Merieux K1323-1	D0, D3, D7, D14	21	0.2	0.2 and 7.0
PR9	m	55	2014	Rabipur 545011C	Rabipur 545011C	Rabipur 545011C	Rabipur 545011C	D0, D3, D8, D15	22	0.2	0.2 and 1.0

*All subjects received the vaccines by the intramuscular route, except PR3 who received intradermal vaccinations; *Vaccine doses received abroad; # count starting on the day of the first dose received.

Laboratory investigations

All subjects had a normal full blood count and a negative HIV test. Results of the PBMC counts were normal in all subjects except PR9 who had mildly decreased CD3, CD8 and NK cells and consequently a higher proportion of monocytes. Five PRs had low IgG3 level between 0.21 and 0.27 g/L for normal values between 0.28 and 1.05 g/L. The evaluation of the humoral responses to other vaccines showed a good response to the tetanus vaccine (antibody titer > 0.1 IU/ml) in all subjects. Two subjects had received hepatitis B vaccination within the last 5 years and anti-HBs levels were > 10 U/ml for both of them. Three subjects agreed to receive a vaccination with a 23-valent polysaccharide pneumococcal vaccine. The results showed that these subjects already had detectable antibody levels to at least 4 of 6 tested serotypes before the vaccination. This element made the evaluation of their response to the pneumococcal vaccination non-interpretable, although we observed a significant increase of their antibody titers after the vaccination.

Assessment of cellular immune response

The capacity of PRs to raise a cellular response in response to recall antigens, a mitogen and to rabies antigens was evaluated by a proliferation assay and compared with the responses obtained in the control groups (Figure 1). Stimulation with the mixture of recall antigens and with a mitogen showed no significant differences between the PRs and the 2 control groups. In response to the rabies antigens, the lymphocyte proliferation was significantly higher in the PRs than in the negative control group ($p = 0.0003$ for the comparison of individual AUC between groups), but lower than in the responders, even if the difference was not significant. Interestingly subject PR6 with a past history of anorexia had a quite poor response in this lymphocyte proliferation assay.

The cytokine profiles after stimulation with antigen recall and rabies were evaluated in cultures of responders and PRs and are shown in figure 2. As observed in the lymphocyte proliferation

assays, cells from responders and PRs produced IL-10, IL-13, IL-17 and IFN- γ in response to recall antigens at similar levels and a similar Th1 (IFN- γ) profile (Figure 2B). In response to rabies antigens, IL-10, IL-13 and IFN- γ were produced in the two groups, but no detectable IL-17. Responders produced higher concentrations of IL-10, IL-13 and IFN- γ than PRs, although the differences were not significant. Moreover, responders showed a Th1 profile and PRs developed a Th2 (IL-13) profile.

The analysis of the correlations between rabies specific humoral and cell (proliferation and cytokine production) responses showed a higher level of correlations in the responders than in PRs (results not shown), perhaps due to the lower level of responses in the latter group. The correlation between the cellular response in the lymphocyte proliferation assay and the anti-rabies antibody levels was weak with a correlation coefficient r of 0.481 (Figure 3).

Results of PR8 and PR9 before and after additional rabies vaccine doses

PR8 and PR9 were included in the study just after day 21 of their vaccination schedule when their anti-rabies antibodies were low (0.2 IU/ml for both subjects). They were evaluated before and after additional vaccine doses. In subject PR8 a 5th vaccine dose induced a rabies antibody level of 0.3 IU/ml. He then received another 2 doses and reached an antibody level of 7.0 IU/ml. PR9 received 2 additional vaccine doses and had thereafter an antibody titer of 1.0 IU/ml. Subject PR8 showed a significant increase of the lymphocyte proliferation after the 7th vaccine dose. The low antibody response of PR9 correlated with a stagnation of the proliferative response and an important increase of IL-13 production.

DISCUSSION

In 2010 the WHO and the CDC recommended for intramuscular rPEP to reduce the number of vaccine doses from five to four [3,4]. A previous study of our group showed however that 6, 7% of potentially rabies exposed subjects did not develop

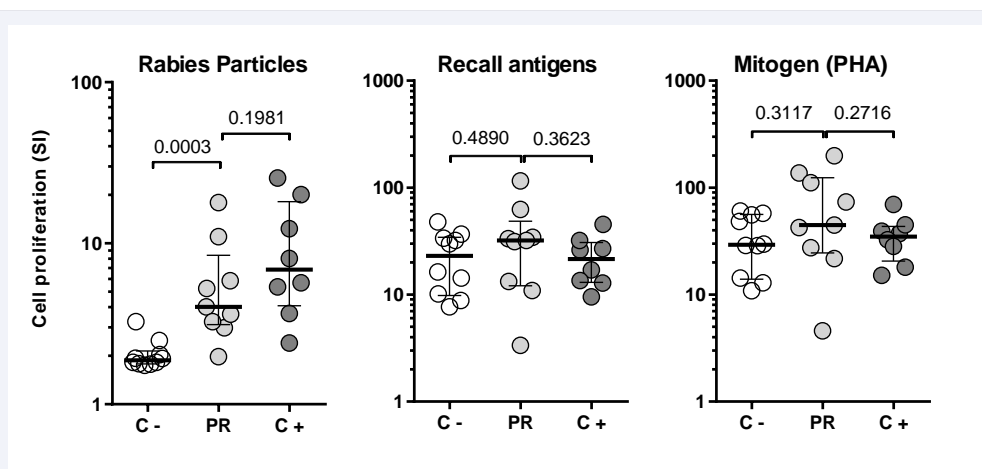


Figure 1 Cell proliferative response in the poor responders. PBMC from subjects of the negative controls (C-, n=10), poor responders (PR, n=9) and positive controls (C+, n=8), were stimulated with rabies antigens, a mixture of recall antigens or a mitogen (PHA). Proliferation was expressed as stimulation indices and presented as area under the curve (AUC) of the dose response to 0.25, 2.5 and 25 mIU/ml rabies vaccine. Individual data are shown with median and quartiles. p values of Mann-Whitney test are indicated.

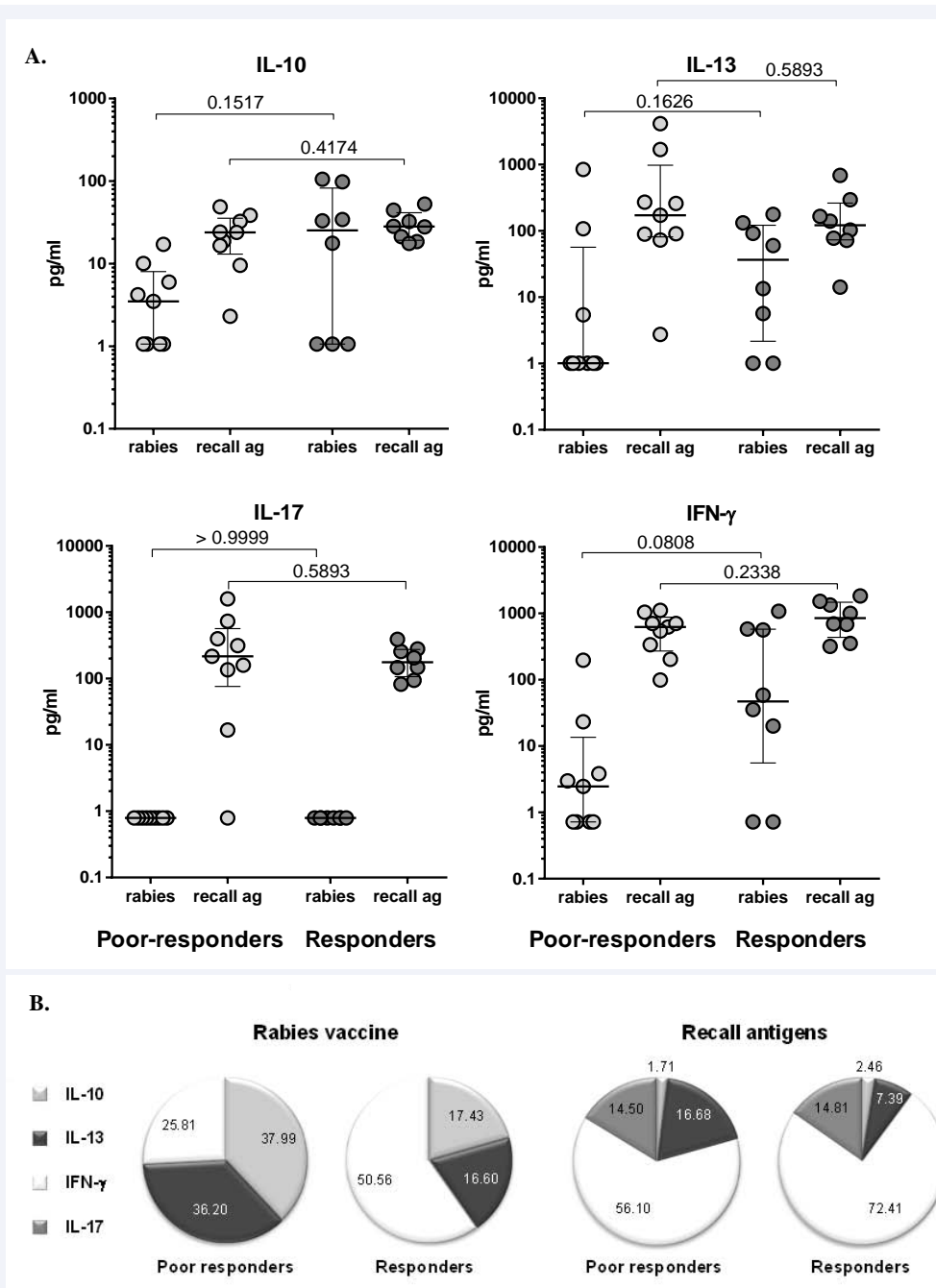


Figure 2 Cytokine profile to rabies and recall antigens in poor responders and responders. PBMC from poor responders (n=9) and responders (n=8) were stimulated with rabies vaccine or recall antigens. Concentrations of cytokines (IL-10, IL-13, IFN-γ and IL-17) measured in culture supernatants are expressed in pg/ml. Individual data are shown with median and quartiles. p values of Mann-Whitney test are indicated.

an appropriate antibody level after 4 doses of rPEP [5].

In the present study we investigated first whether subjects with poor humoral response to an rPEP had any evidence of an immunodeficiency. We evaluated our subjects very thoroughly with an in depth medical history, a clinical examination and the laboratory investigations which are usually recommended for the workup of a suspected immunodeficiency. Our results show that 8/9 of PRs were most probably fully immuno competent at the time they received the rPEP. Only one subject was possibly immuno deficient, because of malnourishment

and chronic diarrhea. Physical examination, immune cell count and assessment of immunoglobulin levels were normal in all subjects, except for the CD8 T-cell count for subject PR9 and mildly decreased IgG3 levels in 5 other subjects. Although these low IgG3 levels are intriguing, these deficiencies can hardly explain the poor immune response to the rPEP. IgG3 deficiency has been mainly associated with recurrent sino pulmonary infections [12]. In our cohort no subject had a medical history of such recurrent infections. To be of clinical significance it is usually considered that the IgG3 level has to be greater than 2

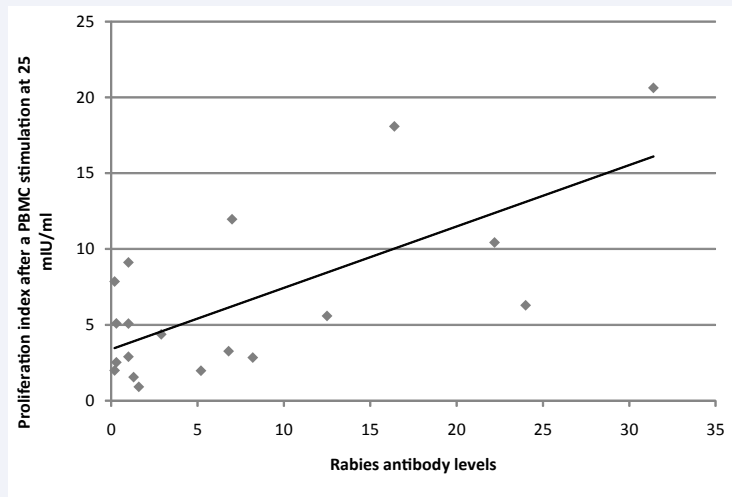


Figure 3 Correlation between rabies antibody levels and PBMC proliferation index. The results show a weak linear correlation ($R = 0.481$ by the Pearson test).

standard deviations below the mean, which was clearly not the case for our patients [13]. In addition, we did not identify in these subjects any abnormal humoral response to other vaccines, such as the tetanus, hepatitis B and pneumococcal vaccines. Finally, lymphocyte proliferation and cytokine production to the recall antigens were at the same levels than responders.

In a second step the cellular immune response to rabies antigen was investigated. It could indeed be postulated that patients with poor humoral response develop possibly a strong cellular immune response, which could be protective. Horowitz et al have shown a strong NK cell response with high IFN- γ production after 3 doses of rabies vaccine [14]. The results of our study show however that PRs had a non-significantly poorer lymphocyte proliferation and IFN- γ production than good responders. The cytokine profile in the supernatant of the PBMC proliferation assays of responders and PRs hint towards a globally poorer immunogenic effect of the rPEP in PRs presenting a profile more oriented toward a Th2-response, with diminished IFN- γ and increased IL-13 production. This is in accordance with a recent study where vaccination induced levels of IFN- γ and IL-4 that correlated significantly with the levels of neutralizing antibodies [15].

The literature lists 0.5 IU/mL as the desirable antibody titer following rPEP, but this antibody level has been picked more or less arbitrarily and is not based on solid scientific data. Some experts would consider that any antibody level after vaccination would be protective, as long as they appear rapidly after exposure. However rare cases of rPEP failures with subsequent deaths have been reported, even in patient receiving correct management as per guidelines [16-19]. The causes of these rPEP failures have always remained unclear. Our data seem to indicate that rabies vaccines are relatively poorly immunogenic in some subjects. Ideally, it would therefore be useful to determine antibody levels by RFFIT on day 21 of the WHO recommended post-exposure prophylaxis to identify patients who do not respond appropriately. It must however be admitted that the RFFIT is not widely available, as it is technically challenging to

perform. The cost of this test of approximately USD 70 can also be a hurdle for its implementation.

It is of concern that some rabies-exposed subjects are potentially not fully protected with the currently WHO-recommended prophylaxis, considering that rabies is invariably a lethal disease. The currently WHO-recommended prophylaxis was published in 2010 and followed a literature review conducted by the Advisory Committee on Immunization Practices (ACIP) of the CDC [5]. The majority of the reviewed studies investigating the immunogenicity of rabies vaccines had been done under strict controlled conditions in young healthy adults. There were actually only 6 studies including a total of 270 patients that had been carried out under real-life conditions and using the Essen regimen. This number of subjects may have been insufficient to identify rPEP failures. As the Swiss rPEP guidelines have always recommended doing a serology on day 21, the Swiss Rabies Center has been able to collect data of rPEP over many years. The Swiss rabies reference laboratory recorded 38 failures with antibody levels < 0.5 U/ml in 257 patients (14.8%) who received an rPEP based on the Essen regimen between 1997 and 2009 (R. Zanoni, personal communication).

Limitations of this study are first of all the relatively small number of subjects included. In addition, blood samples were obtained for 7 subjects only months to years after they had completed the rPEP and more importantly after they had received at least a 5th vaccine dose. Only for PR8 and PR9 could blood samples be obtained before and after the 5th vaccine dose.

In conclusion, our study suggests that rabies vaccines are not very immunogenic in certain subjects for reasons that are difficult to identify. Further work is needed on a larger number of subjects to better understand the protective mechanisms of anti-rabies vaccines.

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