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1 **Immune Response to Rabies Post-Exposure Prophylaxis in patients with non-HIV**
2 **secondary immunodeficiencies**

3

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1 **Immune Response to Rabies Post-Exposure Prophylaxis in patients with non-HIV**
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4 **Highlights Section**

5 Rabies vaccine response may be altered in immunocompromised individuals.

6 We studied the immunogenicity of rabies post-exposure prophylaxis (PEP) in individuals with
7 non-HIV secondary immunodeficiencies.

8 An inadequate response was documented in 6/28 non-HIV immunocompromised patients
9 using ELISA.

10 This altered response was not explained either by the characteristics of patients or by the PEP
11 regimen they received.

12 These findings support the WHO recommendation to assess post-PEP response in these
13 patients to detect non-responders.

14

15

16 **1. Introduction**

17 The number of immunocompromised adults is significant in most countries, and is likely to
18 increase in the coming years due to the expanding indications for immunosuppressive
19 therapies along with development of new drugs, as well as the increase of life expectancy [1].

20 Immunocompromised patients are more able to travel abroad due to improvement in medical
21 management and quality of life and consequently, they are more likely to be exposed to
22 tropical diseases including rabies. Currently, immunocompromised travelers represent up to
23 1%-2% of travelers seen in US travel clinics [2]. Immunocompromised travelers need specific
24 pre- and post-travel management. Notably, immunosuppression can constitute a

25 contraindication to live vaccines and can also results in low immunogenicity and effectiveness
26 of inactivated vaccines [3].

27

28 Rabies is a zoonosis transmitted to humans by direct contact with saliva of an infected animal
29 through bites, scratches or contamination of broken skin or mucosa [4]. Rabies is responsible
30 for a viral acute encephalitis most invariably fatal after the onset of neurological symptoms,
31 causing around 60,000 human deaths every year, mainly in Asia and Africa [5]. Animal-
32 associated injuries are not rare in travelers [6] and, in rabies enzootic countries, should lead to
33 a prompt post-exposure prophylaxis (PEP). PEP consists of the administration of a series of
34 rabies vaccines and the administration of rabies immunoglobulins (RIG) inside and around the
35 wound in case of severe exposures [4]. Rabies is fully preventable by adequate PEP in
36 immunocompetent individuals. However, in immunocompromised patients, PEP might be less
37 immunogenic [7], with a potential risk of encephalitis and death.

38

39 Several studies evaluated the immunogenicity of PEP in HIV-positive patients. Recently,
40 Sirikwin *et al* reported the efficacy of rabies vaccination in 27 HIV-positive patients including
41 individuals with CD4+ T cell counts below 200 cells per microliter [8]. According to the
42 SAGE Working Group on Rabies vaccines, people living with HIV would most likely
43 respond to PEP as well as persons not living with HIV, as long as their infection is controlled
44 [9]. However, in non-HIV immunocompromised patients, the net state of immunosuppression
45 is difficult to determine and there is currently no biomarker that can routinely predict the
46 efficacy of post-PEP immune response [3]. The high variability of immunosuppressive
47 conditions and the limited number of data call for targeted studies. We aimed to conduct a
48 retrospective study to determine the immune response to PEP in non-HIV
49 immunocompromised individuals to identify factors associated with inadequate response.

50

51 **2. Patients and methods**

52 2.1. Patients

53 This retrospective study was conducted in patients with non-HIV secondary
54 immunodeficiencies, attending care at the Antirabies Clinics of Paris and Nantes, France from
55 2013 to 2018. Patients were included in the study if: (1) they had acquired
56 immunodeficiencies at the time of the PEP, including hematopoietic malignancies, treatment
57 with radiation or with immunosuppressive drugs; (2) they were older than 18 years; (3) they
58 had received a full course of PEP after a rabies exposure; and (4) they had been tested for
59 post-PPE antibody titers. HIV-positive patients and patients with primary immune
60 deficiencies were excluded from this study. This study is compliant with European General
61 Data Protection Regulation (GDPR) and French Data Protection Act n°78-17 (CNIL MR004).
62 All subjects were informed about this study.

63 Data were extracted by reviewing both electronic medical records and paper charts. Extracted
64 data included patient demographics, medical conditions and immunosuppressive drugs,
65 characteristic of the rabies exposure, PEP regimen and post-PEP rabies antibodies titer.

66

67 2.2. Determination of antibody titer

68 Post-PEP measurement of rabies antibodies was carried out on an out-patient basis in
69 different medical laboratories using the PLATELIA™RABIES II ELISA method, an enzyme-
70 linked immunosorbent assay (ELISA) based on the detection and titration of the anti-
71 glycoprotein antibodies [10]. According to World Health Organization (WHO), an adequate
72 rabies antibody titer was defined as ≥ 0.5 IU/ml [4]. The maximum rabies antibody level
73 measured by ELISA was 4 Equivalent (E)U/mL, and levels higher than this were reported as
74 >4 EU/mL.

75

76 2.3. Statistical analysis

77 Data were expressed as proportions (%) for categorical variables, and median for quantitative
78 variables. Categorical data were tested for statistical significance with Fisher's exact test.
79 Quantitative variables were compared using Mann-Whitney test for non-normal distributions.
80 P-values < 0.05 were considered significant.

81

82 3. Results

83 During the study period, 28 immunocompromised individuals were included (17 women and
84 11 men), while during the same period 5379 patients sought medical care at the two clinics.
85 The characteristics of the patients are shown in Table 1. The median age of the patients was
86 47.5 years ranging from 25 to 85 years. All patients had secondary immunodeficiencies
87 induced by drugs taken for inflammatory bowel diseases (n=9), inflammatory rheumatic
88 diseases (n=6), solid organ transplantations (n=3) and other chronic diseases (psoriasis,
89 multiple sclerosis, chronic myeloid leukemia, uveitis, relapsing polychondritis, Behçet's
90 disease and nephrotic syndrome). Most frequently prescribed drugs were methotrexate, tumor
91 necrosis factor (TNF) inhibitors, azathioprine and mycophenolic acid. Rabies exposure
92 occurred in a rabies enzootic country for 16 patients including 7 patients exposed in Asia and 6
93 in Africa. Exposure was mostly mediated by a dog (n=21), but 4 patients were bitten by a
94 non-human-primate, 2 by a cat and 1 was exposed to a bat. Eighteen individuals had a
95 category III exposure (transdermal bites or scratches, contamination of mucosa or broken skin
96 with saliva, direct exposure to bats) and 10 had a category II exposures (nibbling of
97 uncovered skin, minor scratches without bleeding). None of the patients had pre-exposure
98 prophylaxis before traveling. PEP was initiated 2 days in median after exposure [min 0; max
99 20]. All individuals received a 4 or 5-dose intramuscular PEP regimen (12 and 16 patients,

100 respectively) and 3 patients began the PEP during their travel abroad. Fourteen individuals
101 received Human RIG including 7 individuals out of 18 with category III exposure.
102 In the study population, blood samples were collected for rabies antibody titration 38 days in
103 median after the initiation of PEP [min 20; max 78]. Six individuals exhibited an inadequate
104 immune response after PEP, defined as a post-vaccination rabies antibody titer below 0.5
105 EU/ml (Table 1). Among these patients, 4 were men, the median age was 50.5 years, ranging
106 from 33 to 85 years. Two patients were receiving methotrexate respectively for ankylosis
107 spondylitis and severe psoriasis, one was receiving mycophenolate mofetil and corticosteroids
108 for a nephrotic syndrome, one patient had azathioprine for an inflammatory bowel disease,
109 one was treated with fingolimod for multiple sclerosis and the last one had corticosteroids (10
110 mg per day) for uveitis. Four of these patients had received a 5-dose intramuscular PEP
111 regimen, two a 4-dose regimen and 3 of them had been administrated RIG. After serological
112 findings, five individuals received an additional dose of vaccine and exhibited a satisfactory
113 rabies antibody titer on further serological test. The last patient declined an additional dose
114 but was still alive at follow-up in 2019, 5 years after exposure. The results of the univariate
115 analysis (Table 2) are inconclusive regarding the effect of the immunosuppressive conditions,
116 immunosuppressive drugs, age and delay between the initiation of PEP and serological testing
117 on the antibody response response to PEP.

118

119 4. Discussion

120 Many circumstances induce immunosuppression, however the American Advisory Committee
121 on Immunization Practices (ACIP) consider that conditions that might alter vaccine response
122 are primary immunodeficiencies and secondary immunodeficiencies such as HIV/AIDS,
123 disseminated malignant neoplasm, chronic renal disease, asplenia and immunosuppressive or
124 radiation therapy [3]. Limited data are available on rabies vaccine response in patients with

125 non-HIV immunodeficiencies. Some studies reported post-PEP immune response in patients
126 with heterogeneous conditions such as solid organ transplantation [11,12], malnutrition [13],
127 end-stage renal failure [14], diabetes or pregnancy [15]. Our study reports the largest
128 experience of post-PEP response assessment in non-HIV immunocompromised patients.
129 Every patient received a WHO-recommended vaccine regimen but only 7 of the 18 patients
130 with category III exposures had RIG administration. This small proportion could not entirely
131 be explained by the initiation of PEP abroad (3 patients) and may reflect the insufficient
132 knowledge of WHO recommendations among French health care workers [16]. An inadequate
133 immune response after PEP has been documented in 6 non-HIV immunocompromised
134 patients out of 28 attending 2 French Antirabies Clinics. The analysis did not reveal any
135 significant difference among the variables tested between individuals with adequate and
136 inadequate responses to PEP. In particular, we did not evidence any impact of the regimen of
137 PEP or the administration of RIG on the response to rabies vaccine in our study population.

138 The main limitations of the current study are its small sample size and the heterogeneity of
139 patients' characteristics, of PEP regimens and delay between PEP and rabies antibody
140 titration. These limitations are explained by the retrospective study design of this research and
141 the limited number of immunocompromised patients seeking medical care for PEP. Another
142 significant limitation is the use of ELISA to determine the post-PEP rabies antibodies titer
143 whereas WHO recommends the use of seroneutralization techniques such as the rapid
144 fluorescent focus inhibition test (RFFIT). RFFIT is performed only in reference laboratories
145 for Rabies and is not used for routine purpose, whereas ELISA is the routine method used to
146 assess immune response after PEP and PrEP in many countries, as this method is convenient
147 and available in most medical analysis laboratories. Several studies have demonstrated that
148 serology results using ELISA are comparable to RFFIT method and ELISA is considered to
149 be a reliable alternative when RFFIT is not available [10,17,18]. We thus considered that the

150 use of ELISA was representative of real life clinical practice and a suitable alternative to
151 seroneutralization techniques in our setting.

152 An inadequate immune response after PEP had been documented in around 20% of our study
153 population of non-HIV immunocompromised patients. However the antibody titration may
154 not reflect the actual level of protection of patients as humoral response represents only one
155 aspect of the immune response to rabies virus. Rabies specific cell-mediated immune
156 response is not yet clearly understood but may play a non-negligible role in the protection of
157 patient [12]. Furthermore, ELISA may under evaluate rabies antibody titrations close to 0.5
158 UI/ml and may result in more immune responses considered as inadequate [18]. We therefore
159 believe that the proportion of patients with inadequate immune response observed in this
160 study may be overestimated. However, due to the almost invariably fatal outcome of rabies
161 after the onset of symptoms an additional booster dose of vaccine seems a justified caution in
162 patients with titers below 0.5 UE/ml using ELISA.

163

164 Our study is inconclusive regarding the effect of the immunosuppressive conditions,
165 immunosuppressive drugs or age on the response to PEP. However, all the 6 patients treated
166 by TNF inhibitors exhibited a good response as well as the 2 patients treated by dasatinib for
167 chronic myeloid leukemia and the 3 solid organ transplant recipients. Immunosenescence is
168 known to be responsible for poor response to vaccination. Mills *et al* demonstrated that
169 seroconversion rate after rabies pre-exposure prophylaxis in Australian travelers was
170 significantly lower with increasing age [19]. Our study population may be too small to
171 evidence an effect of age on the immunogenicity of rabies PEP, or this impact could be
172 abrogated by the effects of immunosuppressive drugs on immune response.

173

174 Finally, no benefit of a 5-dose regimen compared to a 4-dose regimen was demonstrated on
175 seroconversion rate in our study. In the second WHO Expert Consultation on Rabies
176 published in 2013 [20], the experts recommended to deliver RIG and a complete series of 5
177 intramuscular doses of rabies vaccine as PEP in immunocompromised individuals with
178 category II ou III exposures. These guidelines have slightly changed since 2018, as the new
179 WHO report recommends the use of the best PEP options available (the most immunogenic
180 regimen, high-quality vaccines and RIG) in immunocompromised patients [4]. Our finding
181 strengthens the current WHO experts' recommendations and support the possible use of a 4-
182 dose regimen in immunocompromised patients (Zagreb regimen or modified Essen regimen).
183 We believe that the systematic determination of post-PEP response 2 to 4 weeks after
184 vaccination in non-HIV immunocompromised individuals, as recommended by WHO when
185 it's feasible, is relevant as around 20% of our study population presented a response
186 considered as inadequate. This assessment allowed clinicians to administrate an additional
187 dose of vaccine in 5 of the 6 non-responders who subsequently obtained an adequate immune
188 response.

189

190 In conclusion, an inadequate immune response after PEP had been documented in around
191 20% of our study population of non-HIV immunocompromised patients using ELISA.
192 Inadequate response was unpredictable and not explained either by the characteristics of
193 patients or by the PEP regimen they received. These findings support the WHO
194 recommendation to use the best PEP options available in immunocompromised patients
195 including intramuscular 4-dose regimens and to assess post-PEP response to detect non-
196 responders, who might require an additional dose. Further studies, involving a larger number
197 of patients and using seroneutralisation tests, are needed to identify factors associated with
198 inadequate response to rabies PEP in non-HIV immunocompromised patients.

200 **Conflict of interest and author declaration**

201 The authors have no known conflict of interest associated with this publication. Contribution
202 and authorship: PeP, PhP, HB and PC designed the study. PeP conducted the data analysis
203 and prepared the manuscript. All authors contributed to the final report for submission. We
204 confirm that the manuscript has been read and approved by all named authors and that they
205 are no other persons who satisfied the criteria for authorship. We further confirm that the
206 order of authors listed in the manuscript has been approved by all of us. Funding for the
207 study: No funding was received to conduct the study. Clinical trial registration: This study has
208 not been registered in a clinical trial registry. This study is a non-interventional study
209 performed on pseudonymized medical data collected during standard clinical care. According
210 to the EU regulation and French law registration was not required.

211

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217

218

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281

Table 1. Characteristics of non-HIV immunocompromised patients (n=28).

Gender/ age	Exposure (animal, category, country)	Underlying disease	Drugs	PEP	Rabies antibody titer (EU/ml)
F/25	Dog, III, France	IBD	Azathioprine	4 doses	1.7
M/33	Dog, III, France	IBD	Azathioprine	4 doses	< 0.5
M/43	Dog, III, France	IBD	Infliximab	4 doses	1.3
M/26	Dog, III, China	IBD	Azathioprine, Infliximab	4 doses	1.3
F/25	NHP, II, Vietnam	IBD	Adalimumab	5 doses + RIG	3.6
F/34	Dog, II, Romania	IBD	Azathioprine, Mesalazine	5 doses + RIG	1.4
F/56	Dog, II, France	IBD	Azathioprine	4 doses	> 4
M/29	Dog, III, Thailand	IBD	Azathioprine	5 doses + RIG	2
F/61	Dog, II, Cambodia	IBD	Azathioprine	5 doses + RIG	> 4
F/54	Dog, III, Morocco	IRD	Hydroxychloroquine, Corticosteroid	4 doses	> 4
F/35	Dog, III, France	IRD	Methotrexate	4 doses	0.6
M/85	Dog, III, France	IRD	Methotrexate	5 doses	< 0.5*
M/56	Dog, III, France	IRD	Methotrexate, Abatacept	5 doses + RIG	> 4
F/53	NHP, II, Peru	IRD	Methotrexate, Adalimumab	4 doses	3.6
F/59	NHP, II, Indonesia	IRD	Methotrexate	5 doses + RIG	> 4
M/59	Dog, III, France	IRD	Etanercept, Leflunomide, Corticosteroid	4 doses	1.26
M/69	Dog, III, Thailand	SOT	MMF, Everolimus	5 doses	0.8
F/50	Dog, II, Madagascar	SOT	MMF, Ciclosporine, Corticosteroid	5 doses	0.5
M/49	Dog, III, France	SOT	Tacrolimus + Mycophenolate sodium	4 doses + RIG	3
F/38	Dog, III, France	CML	Dasatinib	5 doses + RIG	2.4
F/45	Dog, III, Morocco	CML	Dasatinib	4 doses	2.1
M/67	Dog, III, Armenia	Psoriasis	Methotrexate	4 doses + RIG	< 0.5*
F/25	Cat, II, Morocco	Psoriasis	Methotrexate	5 doses + RIG	> 4
F/46	Bat, III, France	Multiple Sclerosis	Natalizumab	5 doses + RIG	1.6
F/40	Dog, II, Cuba	Multiple Sclerosis	Sphingosine	5 doses + RIG	< 0.5*
F/51	NHP, III, Senegal	Nephrotic Syndrome	MMF + Corticosteroid	5 doses + RIG	< 0.5*
M/50	Dog, III, Vietnam	Uveitis	Corticosteroid	5 doses	< 0.5*
M/39	Cat, II, Algeria	Behçet Disease	Adalimumab + Corticosteroid	5 doses + RIG	2.7

PEP: post-exposure prophylaxis; F: female; M: male; IBD: inflammatory bowel disease; IRD: inflammatory rheumatic disease; SOT: solid organ transplant; CML: chronic myeloid leukemia; MMF: mycophenolate mofetil; RIG: rabies immunoglobulins; *: individuals with adequate response after an additional dose of rabies vaccine.

Table 2. Characteristics of non-HIV immunocompromised patients in function of their immune response to rabies post-exposure prophylaxis (n=28).

	Inadequate response (< 0.5 EU/mL) n=6	Adequate response (≥ 0.5 EU/mL) n=22	p (Fisher's exact test or Mann Whitney test)
Male	4	7	0.17
Median age (min; max)	50.5 (33;85)	45.5 (25; 69)	0.31
Methotrexate	2	4	0.58
Antimetabolite	2	9	1
TNF inhibitors	0	6	0.29
4-dose PEP regimen	2	10	0.61
RIG	3	11	1
Median time lapse between end of PEP and serology (min; max)	12.5 (7;50)	10.5 (0;37)	0.95