Human Rabies Postexposure Prophylaxis: Experience of a National Pediatric Centre

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Abstract

Introduction: Rabies is a fatal acute infectious disease with a variable incubation period. Portugal is a rabies' free country, certified since 1960, with a recommended vaccination plan after risk contacts. The study aim was to analyse the potential cases of exposure to rabies, in children under 18 years old, evaluate compliance, adverse effects of vaccination and clinical outcomes. **Methods:** A retrospective, descriptive study with the review of clinical records from a Rabies Vaccination Centre, between 2013 and 2016; clinical outcomes were obtained by a telephone survey. The definitions of exposure were based in the World Health Organization (WHO) guidelines. **Results**: ten cases of post-exposure prophylaxis were identified in an age range of 2 to 15 years old, eight within the last two years, and all were imported from endemic countries: Angola, Indonesia, Brazil and China. Nine cases were minor contacts. Transmission occurred through dogs (n = 6), monkeys (n = 3) and bat (n = 1). A five-dose regimen vaccination was proposed in nine and a four-dose in one case; 70% completed the schedule (minimum number of doses = 4). The mean interval between exposure and immunization was 3 days (median = 1). One cutaneous reaction was documented but no serious reactions occurred. **Discussion**: In a period of 42 months, we had an average of 2.9 cases per year of children with potential rabies exposure in endemic countries. Early prophylaxis was administered to this cohort with no significant adverse effects.

Keywords: Child; Post-Exposure Prophylaxis/statistics & numerical data; Rabies/prevention & control; Public Health; Surveys and Questionnaires

Introduction

Human rabies is an infectious viral disease, caused by the rabies virus, of the *layssavirus genus*, Rhabdoviridae family[1], with a 100% lethality rate in the absence of early prophylactic treatment after contracting the virus.[1,2] The WHO estimates that 30,000 to 70,000 people die each year from rabies, mainly due to the inadequate control of rabies in domestic animals. The paediatric population has a higher risk of death from rabies, possibly due to their body size, as there is greater proximity between the inoculation site and the Central Nervous System.[1,3 - 5] More than 95% of deaths occur in Asia and Africa, with a higher incidence and reported deaths in India. In Latin America, there has been a substantial reduction in human rabies cases, following the implementation of rabies vaccination control programmes in dogs[3] and, in Europe, rabies is rare. The lack of valid epidemiological surveillance programmes in countries with a higher number of cases, makes it difficult to assess the evolution of this epizootic.

More than 99% of human rabies cases are attributed to bites from infected dogs. Cats, bats, monkeys, and other wildlife are also potential reservoirs and sources of transmission.[2,3]

Vaccine prophylaxis against human rabies has been available for over 100 years. Nevertheless, most deaths from rabies still occur in countries with inadequate public health resources and limited access to preventive treatment. Simultaneously, there is scarce information on the number of rabies diagnoses and deaths in these countries. About 40% of the bites from animals with confirmed or suspected rabies occur in children under the age of 15.[3] The incubation period is variable, from days to weeks, with a median of three to eight weeks, related to the location and wound characteristics, the distance to the Central Nervous System and the inoculum size.[1, 4-7] The first clinical signs are nonspecific, with fever, anxiety, fatigue, pruritus and hydrophobia. Paraesthesia at the site of the bite is very distinctive. [2-5] The first neurological manifestations appear two to ten days later, ranging from hyperactivity to paralysis. Because of this variability, clinical manifestations are categorised as encephalitic rabies or paralytic rabies. [2-5]

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Acute encephalomyelitis is characterised by dysarthria, dysphagia, sialorrhea, diplopia, vertigo, nystagmus, agitation, visual and auditory hallucinations, maniac state alternated with lethargy, painful contractions of the pharyngeal muscles and polyneuritis.[3,4] Paralytic rabies is characterised by an ascending paralysis and quadriplegia with no hallucinations or painful contractions of the pharyngeal muscles.[3,4] Cardiorespiratory failure occurs rapidly, which is then inevitably the cause of death.[2-5]

Portugal is a country free of animal rabies with no record of autochthonous human cases since 1952, and with a certification of eradication issued in 1960.[1]

With the progression of the epizootic and the increase in the mobility of people worldwide, it is important to maintain effective prophylaxis structures in Portugal. This takes into account the possibility of imported cases from geographical areas where rabies is enzootic and/or epizootic, specifically countries with Portuguese as an official language.[1]

Administration of the rabies vaccine in post-exposure situations is free, and available at the health services listed in the annex of the clinical practice guidelines from Portuguese Directorate-General of Health (DGS): Human Rabies Prophylaxis (*Profilaxia da raiva humana*), no. 003/2013 from 15/03/2013.

For post-exposure prophylaxis, all exposure situations in categories II and III (Tables 1 and 2) should be vaccinated and the vaccine should be administered as early as possible, irrespective of the time after contact, and regardless if the child is assymptomatic.[1,7, 9-11]

The aim of this study is to analyse cases of potential exposure to rabies in children under 18 years, to evaluate the compliance and possible adverse effects of vaccination as well as the clinical course, after the implementation of the Portuguese clinical practice guidelines in 2013.[1]

Methods

In this retrospective descriptive study, we analysed clinical records from children up to 18 years of age, with previous exposure to potentially infected animals or to animals with confirmed rabies, that were followed in the paediatrics outpatient clinic from the Rabies Vaccination Centre in Lisbon (*Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, EPE*), between March 2013 and August 2016. We included all the patients referred to this centre with a history of any rabies contact exposure and an indication to initiate or complete prophylaxis. The presence of clinical or laboratory criteria of human rabies were considered exclusion factors.

We analysed demographic variables, such as age, gender and nationality. Variables regarding cause to prophylaxis were: year and country where exposure took place, type of journey, body location and type of exposure, animal reservoir implicated (species - wild/domestic, rabies status – suspected/unknown/confirmed). The exposure type was classified in categories, according to the WHO criteria (table 1) and the following variables were also studied: time from exposure to post-exposure first dose prophylaxis, previous vaccination status, type of prophylaxis – immunoglobulin and/or vaccination regimens.

Events after vaccination were categorised in: adverse events to the vaccine – local reactions to injection site were considered mild; systemic reactions such as fever, anaphylaxis, Guillain-Barré syndrome among others were classified as severe – and therapeutic failure, if any new symptom suggestive of human rabies occurred. To collect data, we used the patients clinical records. In order to exclude any clinical manifestation and to assess adverse events after vaccination, a brief pre-defined survey was applied to carers. It contained multiple choice and open questions, and it was conducted by telephone in September 2016.

A descriptive analysis of the results was made, and due to the small sample size, quantitative variables are described with median, minimum and maximum, and qualitative variables are presented in absolute (n) and relative frequencies (%).

Results

The identified cases are described in table 3. During the study period, there were ten cases; seven were female

Table 1: Post-exposure prophylaxis according to type of contact and type of exposure.

Category	Type of contact	Type of exposure	Post-exposure prophylaxis recommendations
I	Touching, feeding, licking on intact skin	None	Not indicated
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	*Minor*	Rabies vaccination
III	Transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from licks, exposure to bats	*Major*	RIG + vaccine. Advised to patients with compromised immune system as well. One administration of RIG, preferably with the first dose of vaccine or as soon as possible after vaccination is started. It should not be given seven days after the first vaccine dose.

RIG: rabies immune globulin
Adapted from: Portuguese Directorate-General of Health (DGS): Human Rabies Prophylaxis (Profilaxia da raiva humana), no. 003/2013 from 15/03/2013.[1]

and three were male, with a median age of seven years (minimum age was two years old and maximum age was fifteen years old). There was an average of 2.9 cases per year of children with rabies exposure risk in countries with endemic disease. All cases were imported from endemic countries: five from Angola (four in Luanda, one in Lubango), two from Indonesia (Bali), two from China (Beijing) and one from Brazil (Campinas). Regarding the exposure period, two occurred in 2013, four in 2015 and four in 2016. The involved animals were either stray, wild or without any certifiable vaccination status: dog (n=6), monkey (n=3) and bat (n=1).

Only four out of ten cases occurred when travelling while on holidays. The other cases occurred in the area where the patient lived, since two were from China and four had Portuguese nationality but residency in Angola. In those cases, the vaccine regimen was completed in Portugal, during a vacation period, with the exception of two patients in which the last dosage was already taken in the country of origin. Considering the exposure types, nine were classified as *minor* (scratches, bites to the face, scalp and leg without bleeding) and one as *major* (licking of an open wound on an arm).

The post-exposure prophylaxis (table 2) was performed in the minor exposure cases according to the DGS's recommendations[1]: four doses of the vaccine in two children, and five doses of the vaccine in seven children. In the only major exposure case, the subcutaneous rabies immune globulin (RIG) was administered followed by five doses of the vaccine. The time between the exposure and immunization was three days with a median of one day (minimum: zero days; maximum: 18 days). Seven of the ten cases started the prophylaxis in the country of exposure and the post-exposure prophylaxis was completed (minimum of four doses) by 80%. In the two cases that did not complete the prophylaxis in our centre, it was completed in their country of origin.

It was only possible to establish contact with five of the ten cases by telephone; one mild adverse event was documented during the treatment and there was no serious adverse event.

There were no cases of rabies, but it was not possible to confirm the infectious state of the implicated animals. The maximum follow-up time was three years (between 2013 and 2016).

Discussion

Due to the fact that our country is free of rabies and to the centralisation of the post-exposure prophylaxis in travellers and immigrants from rabies-affected countries or who are continual risk of rabies exposure, there is a lack of knowledge of this disease by most doctors.

This study has inherent limitations due to its retrospective design, the short follow-up, the small number of patients, the difficulty to follow children from other countries and the lack of contacts with local authorities which could report on the infectious state of the implicated animals.

Table 2: Post-exposure vaccination schedule.

Type of previous vaccination	Recommended scheme after exposure
Vaccination status confirmed and completed, either pre or post-exposure	1 dose of IM vaccine
No previous vaccination	5 IM doses: 0, 3, 7, 14 and 28 days 4 IM doses: 0 (2 doses), 7 and 21 days

IM: intramuscular

Adapted from: Portuguese Directorate-General of Health (DGS): Human Rabies Prophylaxis (Profilaxia da raiva humana), no. 003/2013 from 15/03/2013.[1]

Table 3: Descriptive statistics of post-exposure prophylaxis of rabies, between 2013 and 2016, in paediatric consultation of the Rabies Vaccination Centre in Lisbon

Number of cases, n	10
Demographic variables	
Female, n (%)	7 (70%)
Age, median in years [minimum-maximum]	7 [2-15]
Portuguese nationality, n (%)	8 (80%)
Nature of the contact or injury	
Lesion type	
Bite without bleeding wound, n (%)	7 (70%)
Scratch, n (%)	2 (20%)
Licking of a wound, n (%)	1 (10%)
Animal	
Dog, n (%)	6 (60%)
Monkey/chimpanzee, n (%)	3 (30%)
Bat, n (%)	1 (10%)
Exposure type	
Minor, n (%)	9 (90%)
Major, n (%)	1 (10%)
Country of exposure	
Angola, n (%)	5 (50%)
Brazil, n (%)	1 (10%)
Indonesia, n (%)	2 (20%)
China, n (%)	2 (20%)
On holidays, n (%)	4 (40%)
Post-exposure prophylaxis	
Time until prophylaxis, median in days [minimum-maximum]	1 [0-18]
5 doses, n (%)	8 (80%)
RIG, n (%)	1 (10%)
Accomplished prophylaxis, n (%)	8 (80%)*
Adverse events†	
During the treatment, n (%)	1 (20%)‡
After treatment, n (%)	0 (0%)

RIG: rabies immune globulin.

*Two cases that did not complete prophylaxis in our centre and have undertaken to complete it in their country of origin. †Telephonic contact with five of the ten cases.

‡1 case in 5.

Therefore, this study has the purpose of being descriptive and show the reality of a centre which is responsible for the rabies vaccination in Lisbon and Vale do Tejo, Portugal, since the introduction, in 2013, of the 003/2013 of the clinical practice guidelines from DGS.[1] These clinical practice guidelines from DGS are consistent with WHO[3] and Centres for Disease Control and Prevention (CDC)[8] recommendations. Therefore, there are no discrepancies regarding therapy and follow-up of suspected rabies cases.

Our sample comprises children aged between 2 and 15 years old, which is the most frequently exposed age group due to their close relationship with animals.[1,3]

Half of the cases were imported from Africa (Angola) where the disease still exists in domestic dogs, wildlife[5] and where the disease has become enzootic since 2009, due to an outbreak of rabies in animals.[1]

In our sample, four of the ten cases, were signalled by bites from different animals, like monkey and bat. Vaccination is not available for these wild animals, so it is essential to take preventive action, like avoiding direct contact with a potential rabies vector in a rabies-endemic region and stressing the necessity to seek professional assistance immediately after a relevant exposure.

In seven of the ten cases, the first dose of rabies vaccine in exposed children was done in the exposure country and the median time between the contact and the initial prophylaxis was short (only one day). The specific case where the onset of post-exposure prophylaxis was late (18 days) was a Portuguese patient who started the vaccination after arriving in Portugal.

In the only case classified as category III exposure, RIG and the first dose of vaccine were simultaneously administered in our centre, and the entire vaccine regimen was completed, without adverse events.

Regarding adverse events of post-exposure prophylaxis, there were no immediate reactions. However, the assessment of late adverse events, was limited due to the impossibility of contacting all the cases by phone and the absence of clinical observations after the vaccine regimen in five of the ten cases. In the other five cases, one report of a clinical adverse reaction has been documented. It involved a mild skin reaction at the injection site. In the literature, mild adverse events such as erythema and pruritus at the injection site, are described as frequent, but there are no documented serious adverse events.[5,7]

The divulgation of preventive behaviours, major exposure types and the necessity to look for professional assistance immediately after a relevant exposure, must be remembered in the pretravel consultations. The pretravel consultation is a great opportunity to prevent these cases.

All health professionals have the responsibility of referring all humans suspected of being rabid. There are several outpatient clinics with vaccination against rabies in post-exposure situations in Lisbon and Vale do Tejo that are listed in the DGS clinical practice guidelines, Human rabies prophylaxis, n. º 003/2013[1]. The vaccination centre is in Centro Hospitalar Lisboa Norte, and it consists of a medical and nursing evaluation of adults and children. Nowadays, the opportunity to travel around the world is steadily increasing so it is essential to follow this cultural trend, disseminating the importance of going to a pretravel consult before any journey.

WHAT THIS STUDY ADDS

- Although there is no rabies in Portugal, in Lisbon and Vale do Tejo 10 children had to complete or start vaccination against rabies due to exposure in endemic countries.
- The animal bites with indication to prophylaxis against rabies were not exclusively from dogs and included bites from monkeys and bats in our sample.
- Physicians should be alerted to the fact that there is no limit between time exposure and the start of post-exposure prophylaxis, although it must be initiated as soon as possible in a local health service.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Profilaxia Pós-Exposição da Raiva Humana: Experiência de um Centro Nacional Pediátrico

Resumo:

Introdução: A raiva é uma doença infeciosa aguda fatal, com período de incubação variável. Portugal é um país livre de raiva, certificado desde 1960, que cumpre um plano de vacinação recomendado, após contacto de risco. Esta casuística tem como objetivos analisar os casos de potencial exposição a raiva em menores de 18 anos e avaliar o cumprimento da vacinação, efeitos adversos e evolução clínica.

Métodos: Estudo retrospetivo, descritivo, por consulta de processos clínicos de um centro de vacinação contra a raiva, entre 2013-2016; evolução clínica avaliada por contacto via telefone; definições de exposição de acordo com a Organização Mundial da Saúde.

Resultados: Identificaram-se 10 casos de profilaxia pós-exposição, entre 2-15 anos de idade, oito nos últimos dois anos, importados de países endémicos: Angola, Indonésia, Brasil e China. Nove exposições *minor*. A transmissão ocorreu através de cão (n = 6), macaco (n = 3) e morcego (n = 1). Foi proposto esquema de cinco doses de vacina em nove crianças e de quatro doses em um; 70% completaram o esquema vacinal (número mínimo de tomas quatro). O intervalo médio entre exposição e imunização foi de três dias (mediana um dia). Foi documentada uma reação adversa cutânea e não houve reações graves.

Discussão: Num período de 42 meses tivemos uma média de 2,9 casos / ano de crianças com exposição de risco em países com raiva endémica. Nesta coorte verificou-se início precoce da profilaxia com ausência de efeitos adversos significativos da vacinação.

Palavras-Chave: Criança; Inquéritos e Questionários; Profilaxia Pós-Exposição/estatística & dados numéricos; Raiva/prevenção & controlo; Saúde Pública