

A case of human survival of rabies, South Africa

Jacqueline Weyer^{a*}, Veerle Msimang-Dermaux^a, Janusz T Paweska^a, Kevin le Roux^b, Premi Govender^c, Jessica Coertse^d, Wanda Markotter^d, Louis H Nel^d and Lucille H Blumberg^a

^aCentre for Emerging and Zoonotic Diseases and Division for Public Health Surveillance and Outbreak Response, National Institute for Communicable Diseases, National Health Laboratory Service, Sandringham, South Africa

^bAllerton Provincial Veterinary Laboratory, Pietermaritzburg, South Africa

^cProvincial Department of Health KwaZulu Natal, Pietermaritzburg, South Africa

^dDepartment of Microbiology and Plant Pathology, University of Pretoria, Pretoria, South Africa

*Corresponding author, email: jacquelinew@nicd.ac.za

Human survival from rabies is exceptionally rare. We report a case of human survival (with severe neurological sequelae) in a child from South Africa. The patient was exposed to rabid dogs on two separate occasions and subjected to incomplete post-exposure prophylaxis for rabies.

Keywords: human rabies, rabies, rabies survival, South Africa

Rabies, the most deadly infectious disease known to mankind, is caused by rabies or other lyssaviruses. The poor prognosis of rabies is partly explained by minimal host immune response elicited during infection at the wound site and secondly, since the virus is neurotropic, failure to deliver immune effectors effectively to the central nervous system.¹ Before 2004, only five human cases of rabies survival all having received incomplete rabies post-exposure prophylaxis (PEP) were recorded in the literature (Table 1).^{1,2} In 2004, a teenager from the United States developed rabies after a bat exposure. This patient presented the first documented survivor who did not receive any form of immunisation, passive or active, before or after exposure, and was treated using an experimental protocol hinging on induced coma and anti-viral cocktail therapy.³ The mechanism of her survival has invigorated the field of rabies management studies beyond palliative care. Subsequently, several suspected human rabies cases have been treated similarly, of which two attempts had documented survival and another case where possible recovery from rabies using the protocol is argued (see Table 1).⁴⁻⁶ In addition, three cases of survival were recorded in patients that did not receive intensive or experimental treatment.⁶⁻⁸ Here we provide a brief report of the 13th documented case of human survival from rabies in a child from South Africa, who was treated supportively and retained severe neurological sequelae.

On 23 April 2012, a four-year-old boy was attacked by a dog sustaining a category III wound on the left ankle. The child was taken to a local clinic, where his wound was cleaned and a rabies vaccine administered. Despite the child presenting with a category III wound, the child did not receive rabies immunoglobulin, as was indicated. The dog implicated in the exposure died shortly after the incident and was buried at the family homestead without further investigation. The child lived in Mgonyaweni, KwaZulu-Natal, South Africa, which is an area with a high incidence of rabies and dogs at that time. On 16 May 2012, the child was lethargic and experiencing a lack of appetite and confusion; and, was taken to a general practitioner. The child was treated non-specifically including an enema at home without improvement. On 20 May 2012, the child was admitted to a local hospital with fever, headache, confusion, anxiety and

lack of muscle coordination with spasms. At the time of admission, the patient had received three doses of rabies vaccine. A possible diagnosis of rabies was considered due to the history of dog bite and the clinical presentation of the patient, despite the vaccination history. Specimens were submitted for laboratory investigation, including five saliva, two cerebrospinal fluid (CSF) and three nuchal biopsy specimens. These were collected at different time points over a three-week period after the admission. Initially, no serum was tested for rabies antibodies due to the patient's vaccination history. All the specimens repeatedly tested negative by rabies virus real-time PCR.⁹ Extensive investigation to determine other possible causes of viral encephalitis and bacterial meningitis did not provide the diagnosis. It was subsequently revealed that the child was also scratched on the forehead by a neighbour's dog on 29 March 2012, for which the child received no medical attention or PEP. Without improvement of the patient's clinical condition and confirmatory laboratory findings, the dogs implicated in the exposures were exhumed after which decomposed brain material tested positive by rabies RT-PCR.¹⁰ The finding provided circumstantial evidence in support of the clinical diagnosis of rabies. Laboratory investigation on CSF (collected on 28 May 2012 and 16 June 2012) and serum (collected about a month after onset of illness, on 16 June 2012) revealed high levels of virus neutralising antibodies (VNTs) (> 13 975 IU/ml).¹¹ Anti-nucleocapsid antibodies were detected as determined by indirect immunofluorescence assay in the serum with IgG > 1:512 and IgM > 1:512, and in the CSF (both specimens) with IgG > 1:8 192 (IgM repeatedly tested negative in CSF). The patient was discharged from hospital three months after admission with severe neurological damage. On discharge the patient was described as semi-conscious with blank stares and making incoherent sounds. The patient suffered from convulsions and had a poor swallowing reflex only allowing the intake of soft or liquid food. The patient also suffered quadriplegia with foot drop. Two years after the discharge the patient remains bed-ridden without improvement.

The mechanisms of human rabies survival remains to be fully understood. Among the thirteen documented survivors (including

Table 1: Summary of recorded cases of human recovery from rabies virus infection

Case number	Year	Location	Age, Sex	Source of exposure	Rabies prophylaxis, pre or post exposure	Clinical Management	Sequelae	Laboratory findings	Reference
1	1970	United States	6, M	Bat (bitten on thumb)	PEP received: 14 doses of duck embryo vaccine, no immunoglobulin	Supportive	None	Serum VNT* at 1:63 000	[20]
2	1972	Argentina	45, F	Dog (severe bites)	PEP received: delayed, only ten days post exposure, 14 daily doses of suckling mouse brain vaccine with two boosters, no immunoglobulin	Supportive	Mild	Serum and CSF VNT at 1: 640 000 and 1: 160 000	[16]
3	1977	United States	32, M	Laboratory exposure, possible airborne route (vaccine strain)	PEP received: Duck embryo vaccine only, no immunoglobulin	Supportive	Severe	Information not provided	[21]
4	1992	Mexico	9, M	Dog (multiple bites on face)	PEP received: Vero rabies vaccine (four doses) and human diploid cell culture vaccine (one dose), no immunoglobulin. Wound was sutured.	Supportive	Severe	Serum and CSF VNT at peak: 1: 37 800 and 1: 78125	[17]
5	2000	India	6, F	Dog (bites on face and hands)	PEP received: purified chick embryo vaccine, no immunoglobulin before onset	Supportive	Severe	Serum and CSF antibody response measured by mouse neutralization: 1: 265 000 and 1: 124 000 respectively at peak	[18]
6	2004	USA	15, F	Bat	No vaccination or immunoglobulin pre- or post exposure	Treatment with experimental protocol	Mild with recovery	VNT response; No RNA and virus	[3]
7	2007	Equatorial Guinea	5, M	Dog	No vaccination or immunoglobulin pre- or post exposure	Treatment with experimental protocol	Death (Rubin and co-authors argue that death was not related to rabies)	PCR positive on saliva Direct fluorescent antibody test positive on skin; Isolated from skin VNT in serum and CSF	[4]
8	2008	Brazil	15, M	Vampire bat	PEP received: 4 doses of vaccine, no immunoglobulin	Experimental protocol provided, but with vaccination	Mild	PCR positive on skin biopsy	[5]
9	2009	USA (Texas)	17, F	Bats (no specific exposure, but contact reported)	No PEP received. Vaccination and RIG provided as part of management (one month post onset)	Supportive	None	IFA antibodies in serum and CSF; No VNT; No PCR results or virus isolated	[7]
10	2011	USA (California)	8, F	Possibly cats	No PEP received. Vaccination and immunoglobulin provided as part of management	Treatment with experimental protocol	Unclear	IFA antibodies in serum and CSF; No VNT in serum or CSF; No PCR results or virus isolated	[6]
11	2011	India	13, F	Dog (category III dog bite on leg)	No vaccination or immunoglobulin, pre or post exposure	Supportive	None	ELISA antibodies in serum: 1.6 IU/ml	[15]
12	2011	India	17, M	Dog (category III dog bite on leg)	PEP received: delayed, three days after exposure, four doses of vaccine at time of onset, no immunoglobulin post exposure. Immunoglobulin applied after onset of symptoms	Supportive	Severe	VNT antibodies in serum (>1: 16 000) and CSF (>1:8000)	[8]
13	2012	South Africa	4, M	Multiple exposures to dogs One exposure was noted as category III	PEP received: three doses of vaccine after the second exposure, onset of disease before fourth dose was administered, no immunoglobulin	Supportive	Severe	VNT antibodies in serum and CSF (>13 975 IU/ml); IFA antibodies in serum (>1:512) and CSF (>1: 8 192). PCR on saliva, skin and CSF specimen negative.	This report

*VNT: Virus neutralizing antibody titre.

the case described here), four cases were associated with bat exposures. There is increasing evidence indicating distinct clinical and pathological differences between bat-associated and other rabies virus strains. Bat-associated rabies viruses are thought to be less virulent and/or elicit more potent host immune responses than other rabies viruses.^{12–14} This could explain the antibody responses detected in two patients from the United States that were exposed to bats.^{3,7} Of seven reported survivors that had acquired rabies through dog bites (including the case reported here), only two patients did not receive any PEP. The first, a patient from Equatorial Guinea, was treated using a modified Milwaukee protocol and reportedly recovered from rabies, despite subsequently succumbing from complications of prolonged hospitalisation.⁴ The second case was reported in an Indian girl who developed clinical rabies two years after experiencing a category III dog bite, but who recovered without sequelae.¹⁵ For the remaining cases, all but one patient received only partial PEP without immunoglobulin, which is recognised as a common reason for PEP failure with category III exposures.^{16–19} A patient from India received delayed PEP that included immunoglobulin and four doses of vaccine by the time of onset of clinical rabies.⁸

In this report we describe the case of a child exposed to laboratory-confirmed rabid dogs in two individual incidents. Although exposure to rabid animals do not necessarily result in productive infection with rabies virus, it is possible that the patient was infected during both events. The diagnosis of the patient was supported by circumstantial evidence (confirmation of rabies in dogs involved in exposures) and laboratory verification. The pronounced VNT responses measured in a serum sample from the patient were higher than typically reported post-vaccination reports and in line with reports of serological findings for other survivors (see Table 1). The detection of VNTs and IgG in the CSF of the patient supports a rabies diagnosis.

Despite a paradigm shift in perception of human survivorship of rabies, cases of recovery remain rare. The value of treatment for acute rabies cases, the role of strain variations and immunological response intricacies for survival remains to be measured. The poor outcome of the case described here re-emphasises the importance of timely and complete PEP, which remains the only effective intervention for human rabies.

Acknowledgements – Acknowledgement is extended to the medical personnel who provided support and treatment to the patient.

Communications – This report has not been presented formally at meetings.

Declaration of interest – The authors of this manuscript declare no conflict of interest.

Funding statement – None to declare.

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Received: 07-07-2015 Accepted: 03-09-2015