A case of human survival of rabies, South Africa

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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).2–4 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.5 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 was repeatedly tested negative by rabies virus real-time PCR.6–9 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.

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 15 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. 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 quadriaparesis with foot drop. Two years after the discharge the patient remains bedridden 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

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

*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.5,7 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.7 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 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.

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References

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