Issues of human rabies immunoglobulin and vaccine: policy versus practice

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ABSTRACT

A retrospective audit was conducted of all issues of rabies vaccine or human rabies immunoglobulin (HRIG) from the Clinical Microbiology Department at University Hospital Aintree for post-exposure prophylaxis. The appropriateness of management was reviewed by a blinded panel, which used guidelines issued by the Health Protection Agency (HPA) as a standard. Thirty-six enquiries, on average 9 days following exposure, led to issues of HRIG, rabies vaccine or both. Dog bites accounted for the majority of incidents. In no cases was the biting animal recorded as having been observed for signs of rabies. Management was judged to have been inappropriate in 9 cases, and documentation was judged to have been unsatisfactory in 13 cases. This study has highlighted several areas of ambiguity in the current guidelines, and a number of deficiencies in the information prompted by the standardized proformas used to deal with post-exposure queries.

Keywords health protection, immunization

Introduction

Rabies is an acute encephalomyelitis caused by rabies virus, which belongs to the Lyssavirus genus and the family Rhabdoviridae. It is transmitted to humans through saliva following the bite of an infected animal and is usually fatal. The number of human cases has been estimated to be between 40 000 and 70 000 per year, with most occurring in developing countries particularly of South and Southeast Asia. All mammals are capable of transmitting rabies virus, although dogs are the major global reservoir. Post-exposure treatment, consisting of wound care, infiltration of the wound with human rabies immunoglobulin (HRIG) and vaccine administration, is highly effective if applied appropriately and early. However, it is expensive, of limited availability and often used inappropriately.

The last human death from indigenous rabies in the United Kingdom was in 1902. However, since 1946, there have been 23 deaths (most recently in 2005) amongst people infected with rabies abroad, none of whom received appropriate post-exposure prophylactic treatment. Bats in the United Kingdom may carry rabies-related viruses, European Bat Lyssaviruses (EBLVs)-1 and -2, which cause a disease clinically indistinguishable from rabies and which caused the death of a bat handler in Scotland following a bite in 2002.

Guidance regarding post-exposure prophylaxis following possible EBLV or rabies virus exposure is available from several sources, including in the United Kingdom the Health Protection Agency (HPA), the Department of Health and the World Health Organization (WHO) (http://www.who.int/en/). The most widely used guidance in the United Kingdom is the ‘Duty Doctor Joint Protocol for Rabies queries’, published by the HPA. An audit of the appropriateness of post-exposure issues by the previous Public Health Laboratory Service (PHLS) in 1990 and 2000 resulted in several key recommendations being made, particularly regarding information-gathering and documentation.

The Department of Clinical Microbiology at University Hospital Aintree (formerly the PHLS Group Laboratory) holds the regional supply of HRIG for the northwest of England and is one of nine such centres in England and Wales. We recently conducted a retrospective audit of all issues of rabies vaccine and HRIG from this centre to assess the appropriateness of management decisions against the Duty Doctor Joint Protocol as a standard.

Methods

Standardized proformas, completed between January 2004 and June 2005 after each telephone enquiry leading to an
issue of rabies vaccine, HRIG or both, were examined. Three different proformas were used during the study period; two of these, including that in current use, had been issued by the HPA, whereas a third was devised locally but followed a format similar to the earlier national proforma. The appropriateness of management decisions was reviewed by a consultant panel, which included a medical microbiologist (R.C.) and a consultant medical virologist from another hospital in the region, both of whom were blinded to the original management decisions. In each case, management was compared with practice guidelines issued by the HPA, and the quality of documentation was graded as satisfactory or unsatisfactory.

Results

A total of 36 telephone enquiries resulted in issues of rabies vaccine, HRIG or both. (In one case, two enquiries on different days were regarding the same patient, and these have been treated as one enquiry for the purposes of this analysis.) Twenty-nine of these enquiries were received in 2004 and seven between January and June 2005. The caller was a hospital consultant, or a consultant at the Liverpool School of Tropical Medicine (LSTM), in 16 cases, a general practitioner in 7 cases, a nurse in 8 cases, a senior house officer in 2 cases and a pharmacist in 2 cases. The identity of the caller was not recorded in one case.

Twenty-eight exposures occurred in countries regarded as being high risk of terrestrial rabies according to HPA criteria (Table 1). Of these, 21 were in countries specifically listed as high risk, and seven occurred in countries which are not listed in the HPA guidelines and which are therefore regarded as high risk by default. The latter included Bangladesh, Cuba, Gambia, Madagascar, Romania and Tunisia.

Three issues of vaccine, HRIG or both, followed exposures occurring in countries listed as ‘no risk’ and described as being free of terrestrial rabies in the HPA guidelines. Two of these were bat bites or scratches occurring in the United Kingdom, whereas the third was a dog bite that occurred in the Dominican Republic. Five calls followed dog or fox bites occurring in Italy, without further information as to the specific region being available in four cases. Italy is listed as ‘no risk’ in the HPA guidelines, except for the northern and eastern borders.

The injuries, whether bites (13 cases), scratches (2 cases) or not stated (21 cases), were caused by a wide range of animals, although dogs accounted for the majority (21 cases, Table 1). The sites of exposure included the arm (4 cases), hand or fingers (9 cases), head (3 cases), buttock (1 case), leg (13 cases) and penis (1 case). The site of exposure was not documented in a further five cases. (Of the three different proformas used to record patient data, only the most recent revision specifically requested information regarding the nature of exposure, e.g. whether a bite or a scratch.) The median age of the victim was 45 years (range 6–70 years; age was recorded in 33 cases). Only three enquiries were concerning victims under the age of 16 years.

Only one patient had been partially immunized against rabies before exposure, having received a single dose of vaccine >3 years previously. Fourteen people had received some post-exposure immunization with HRIG, vaccine or both, before any approach was made to this department. A further 14 patients had received no vaccine or HRIG, and no information about the individual’s vaccination history was recorded in the remaining eight cases.

The issue of vaccine or HRIG occurred a mean of 9 days after exposure (median 6 days, range 1–30 days). HRIG alone was issued in nine cases, all of whom had already received vaccine from the LSTM. Fourteen patients received vaccine only, and 13 were issued with both vaccine and HRIG.

Management was judged to have been appropriate in 27 cases and inappropriate in 9 cases. The reasons for management being judged to be inappropriate included confusion about risk level within Italy (four cases), failure to issue HRIG when this was apparently indicated (four cases) and the issue of HRIG despite an apparently low level of risk (one case). (HRIG was considered to have been inappropriately withheld following a bat bite occurring in India, a dog bite in Pakistan, a fox bite in the Italian Alps and a bite by a lemur which took place in Madagascar. HRIG was considered to have been issued unnecessarily following a bat bite occurring in the United Kingdom, which was judged to have been of low risk according to current HPA guidelines.) In one case (exposure in the Dominican Republic), management was considered to have been appropriate despite conflicting with HPA guidelines, which inaccurately described that country as ‘no risk’. In four cases, HRIG was appropriately withheld on the grounds that a course of vaccination had already commenced >7 days previously, by which time an antibody response is assumed to have occurred.9

Documentation was judged to have been satisfactory in 23 cases and unsatisfactory in 13 cases. Reasons for inadequate documentation included lack of information regarding the nature or timing of exposure, lack of information regarding previous vaccination or post-exposure prophylaxis already received, insufficient information with which to reach an appropriate management decision following a bat bite and the patient’s weight (required to guide HRIG dosage) not having been recorded.

No animals were recorded as having been observed following the bite or scratch, even though one was a zoo animal.
However, this information was not specifically requested on any of the three proformas used during the study period. Furthermore, in most cases, no information was given as to whether the animal was wild or domestic. In one case, however, treatment with HRIG was appropriately withheld on the grounds that the biting animal was a healthy domestic dog.

## Discussion

### Main findings of the study

Possible rabies exposures resulting in calls to this department occurred in a range of countries, with Asian and Eastern European countries accounting for the highest numbers (12 and 7 cases, respectively). The fact that the biting animal was a dog in the majority (58%) of cases and that the predominant sites of exposure were found to be the leg (36%), arm (11%) and hand or finger (25%) accorded with the findings of the only other similar published study from the United Kingdom. The fact that children were relatively underrepresented among this group of patients probably reflects the demography of travellers to rabies-endemic countries. Nine of 36 cases were judged to have been managed inappropriately (including 4 cases in which HRIG was withheld), and in 13 cases, documentation was considered unsatisfactory.

### What is already known on this topic

The onset of rabies may be prevented following exposure by appropriate prophylaxis, which besides wound care may include the administration of rabies vaccine, HRIG or both. The latter is expensive and of limited supply, and several guidelines are in place to ensure its appropriate administration.
An audit of post-exposure prophylaxis in England and Wales in 1990 and 2000 identified several cases of mismanagement and highlighted a number of deficiencies in documentation and information-gathering.1

What this study adds
In assessing the appropriateness of rabies vaccine or HRIG issues, the difficulty most consistently encountered was in estimating the level of risk of the exposure according to HPA guidelines. These guidelines were not found to be sufficiently explicit about how to weigh the risk related to the country of exposure against the type of exposure (including site and whether a scratch or bite). The earlier two of the three proformas used during the study period did not prompt questioning regarding the site and nature of the bite or scratch. In practice, this did not make a significant difference to the management decision when the country was graded ‘high risk’. However, when a country was graded as low risk for terrestrial rabies, the guidance on management was found to be unclear.

Information regarding the prevalence of terrestrial rabies in different countries is available from various sources, which were found in some instances to conflict. For example, the Dominican Republic is specifically listed as ‘no risk’ in the HPA guidelines but as high risk by other sources [e.g. see the Foreign and Commonwealth Office advice at http://www.fco.gov.uk and travel advice available from the National Health Service at http://www.fitfortravel.scot.nhs.uk. Rabies is reported by the regional office of the WHO to be enzootic in the mongoose there, and an annual rabies incidence within the canine population of 5 per 100,000 was reported in 2001 (see Pan American Health Organization website http://www.paho.org/English/HCP/HCV/ZNS/rabia)]. Such discrepancies are confusing and may lead to over- or undertreatment of returning travellers. Confusion about the level of risk in Italy may have contributed to mismanagement in several cases. Italy is described by the HPA guidelines as ‘no risk, except for the northern and eastern borders’, but information about the location within Italy was seldom recorded. In fact, Italy is described by the WHO as ‘rabies-free’, with no indigenous animal or human cases for at least the past 2 years (see http://www.who.int/rabies/rabnet/en and http://www.who-rabies-bulletin.org).

Information about the biting animal, whether wild or domestic, and its availability for observation, was frequently not recorded. Except in one case, where HRIG treatment was withheld, the availability of a domestic or zoo animal for observation did not influence management. A delay in treatment should only be contemplated when the biting animal under observation is an apparently healthy dog or cat from a low-risk area. In other circumstances, delay is unwise, but treatment may be stopped if the animal remains healthy for 15 days.8 Travellers should be educated to take contact details of pet owners after a bite by a domestic animal, and the proformas could be improved by prompting information about the availability of the animal for observation.

A further area of uncertainty relates to possible exposure to EBLV or rabies virus through bat bites or scratches. Because bats are migratory and furthermore may transmit rabies-related viruses where terrestrial rabies is not endemic, possible bat-related exposures need to be assessed by different criteria.4 In such cases, management is guided by an algorithm produced by the Scottish Centre for Infection and Environmental Health and included in the HPA Duty Doctor Joint Protocol.6 In order for this algorithm to be used, information is required regarding not only the nature of exposure and the site of the bite but also the severity of the wound, features of the bat including ideally its species and whether it appears sick or is grounded without apparent injury, availability of the bat for observation, whether the attack was provoked or unprovoked and vaccination status of the person bitten. Most of this information is not prompted by the proformas in national use. Furthermore, even when this information is available, the evaluation of overall risk remains subjective.

Predictably, a low level of pre-exposure immunization was encountered amongst returning travellers in this population, with only one person having been partially immunized several years before exposure. However, this was to be expected because fully immunized travellers would have required post-exposure treatment with vaccine only, and this would have been available from sources other than this department. Nevertheless, this study suggests that at least some travellers to rabies-endemic countries may be unaware of the need for rabies pre-exposure vaccination. (Current guidance is that travellers who will be spending 1 month or longer in rabies-enzootic areas should receive pre-exposure rabies vaccination, unless they are likely to have access to prompt, safe medical care. Those travelling to enzootic areas for <1 month but whose travel activities place them at greater risk or who would have limited access to post-exposure medical care are also advised to receive pre-exposure prophylaxis.)8

As rabies is a catastrophic but preventable illness, unambiguous guidance is required if potential exposure is to be identified and correctly managed. In a large proportion of cases, for instance where the biting animal is a dog and the incident has occurred in a rabies-endemic area, there is little doubt as to the correct post-exposure treatment. However, this study has identified a number of less clear-cut instances
in which unclear guidance and insufficient information may contribute to mismanagement.

**Limitations of the study**

This work was undertaken as an audit of practice in our department, rather than as an epidemiological study. The study population was highly selected in so far as patients fully immunized before exposure, who had received immunoglobulin from other sources or who were unaware of the need to seek medical advice after potential exposure would have been unlikely to have come to our attention. No new epidemiological conclusions can therefore be drawn from this study, and it is not possible to draw conclusions about, for example, how aware unimmunized travellers are of the need for post-exposure prophylaxis. Furthermore, records had only been kept relating to queries that resulted in issues of vaccine or immunoglobulin, rather than those that resulted in no action being taken. The practice of our department has now been changed so that records of all enquiries will be available for the purposes of future audit.

**Summary of recommendations**

(i) Alter proforma to include questions regarding the nature of exposure and the availability of the biting animal for observation and introduce a separate section to cover bat-related exposure.

(ii) Remove ambiguity from HPA Duty Doctor Joint Protocol, particularly with regard to the assessment of risk.

(iii) Ensure that estimates of risk level by country are up to date and accurate.

(iv) Educate travellers not only about pre-exposure rabies immunization but also about recording contact details of pet owners following a bite by an apparently healthy domestic animal.

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**References**