Caring for a patient with rabies: implications of the Milwaukee protocol for infection control and public health measures.

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ABSTRACT

We discuss the infection control and public health measures taken whilst managing a case of laboratory confirmed rabies and the challenges faced in implementing these measures. Case management requires intensive multi-disciplinary coordination. The Milwaukee protocol, which to date has 5 reported human rabies survivors associated with its use, has been suggested as a potential management pathway for human rabies. A consensus among hospital and public health clinicians would aid future deployment of this approach in selected cases.

INTRODUCTION

Rabies is a viral illness causing an encephalitis that is almost always fatal. Belonging to the Rhabdoviridae and of the Lyssavirus genus, rabies is a significant cause of mortality in the developing world. Transmission to humans usually occurs via the salivary route as a result of a bite from an infected animal. Dogs account for the majority of cases of animal rabies (54%), although bats are increasingly becoming the source of human rabies in the United States. In the United Kingdom (UK), rabies has been eradicated amongst the terrestrial animal population and therefore recent cases of transmission to humans from terrestrial animals have been associated with exposure whilst abroad. Bats in the UK, however, do carry lyssaviruses thus posing a risk for human rabies acquisition[1]. European bat lyssavirus type 1 (EBVL-1) is the predominant strain circulating amongst bats in Europe[2]. However, within the UK, only cases of EBLV-2 infection have been identified in the bat population[2]. The Daubenton's bat (*Myotis daubentonii*) is the only bat species in the UK in which EBLV-2 has been isolated[2] and in 2002, an unvaccinated bat handler in Scotland who did not receive rabies post-exposure prophylaxis, died from a laboratory-confirmed EBLV-2 infection[3]. Bat bites are typically less conspicuous than those from terrestrial animals and therefore specialist advice should be promptly sought if a bat bite is felt by an individual, regardless of whether a skin break is visible and irrespective of whether the bat species is known[1].

The incubation period following exposure to rabies has been reported to be as long as 19 years although most individuals will become unwell within 90 days of exposure. Initial symptoms are non-specific and include fever, malaise, headache, nausea and vomiting. This prodromal period lasts between 2 and 10 days. Subsequently, infected individuals develop agitation, delirium, hydrophobia and autonomic dysfunction. Ultimately coma and death occur from cerebral oedema or myocarditis.

Early recognition and timely management of exposures protects patients from this fatal viral infection. Where this has failed to prevent disease, caring for patients with suspected and/or confirmed rabies, a Hazard Group 3 (HG3) pathogen, poses a major challenge. Following the survival of a patient[4], the Milwaukee protocol has been suggested as a potential clinical algorithm. However, a co-ordinated approach both between and within relevant organisations is required with early laboratory confirmation in order to avoid exposure of others including health care workers. It is important that preparation and rehearsal of pre-incident planning takes place and that protocols are followed.

We describe the infection control and public health management implications of the Milwaukee protocol in a case of rabies. The patient presented to a District General Hospital and was subsequently managed in partial concordance with the Milwaukee protocol in the Intensive Care Unit (ICU) of a London teaching hospital.

METHODS

Setting

The Queen Elizabeth Hospital located is a District General Hospital in South East London and forms part of the Lewisham and Greenwich NHS trust. A consultant microbiologist is available 24 hours a day for clinical and infection control advice.

The Hospital for Tropical Diseases (HTD) based at University College London Hospitals (UCLH) serves as a tertiary referral centre for infectious diseases. Infection doctors encompassing infectious diseases physicians, virologists and microbiologists provide a 24-hour consultant-led service for clinical advice and referrals. Over 1300 patients are admitted under the care of the infectious diseases team each year. The

hospital is supported by an infection control team (with microbiology and virology support) which provide a 24-hour service. There is also a dedicated occupational health department. For critically ill patients, UCLH hosts a 35 bed Intensive Care Unit (ICU). The unit is staffed by a multi-disciplinary team that cares for approximately 2,500 patients each year.

In the UK, Public Health England provides 24-hour advice regarding management of cases of public health interest.

Summary of the case

The infectious diseases doctor on-call for the HTD received a call from the Emergency department of Queen Elizabeth Hospital, Woolwich referring a 58-year-old patient with suspected rabies[4]. Nine weeks prior to her presentation our patient had sustained a bite by an ownerless puppy to her right forearm whilst in India. She was accepted for transfer to UCLH and admitted directly to the ICU at UCLH the same day. Treatment of the patient was principally guided by the Milwaukee protocol version 3.1 (which is now in its most updated form as version 5.0)[5]. The protocol is based on induced coma and neurotransmitter substrate replenishment, whilst allowing the body's immune system to clear the virus and aims at rebalancing the rabies-induced tetrahyrobiopterin deficiency that leads to dopamine and serotonin deficiency and poor nitric oxidase activity[6]. We were also guided in the infection prevention and control aspects of our case management by the current Department of Health rabies guidance document[7]. Despite the intense multi-disciplinary efforts made, her clinical condition progressively deteriorated. She progressed to profound autonomic disturbance and died 10 days after admission. Pathak et al have published the clinical features, ante- and post-mortem laboratory findings of this case[4].

RESULTS

INFECTION CONTROL MEASURES

Initial Management at the referring hospital

A diagnosis of rabies was suspected by the patient's GP who had a telephone discussion with the emergency medicine consultant at Queen Elizabeth Hospital. The case was subsequently discussed with the microbiology consultant, who alerted Public Health England. Strict infection control precautions were advised and followed. The patient was cared for by a small team of charge nurses and consultants in order minimise exposure. There were no direct exposures to the patient's bodily secretions without personal protective equipment as strict contact precautions were followed from the outset. Post exposure vaccination was offered to 6 members of staff of Queen Elizabeth Hospital, two of whom completed the full 5 doses course. The other 4 staff members opted not to receive the vaccine.

The patient and members of staff at UCLH:

The patient was admitted to a single-bed room with en-suite sanitary facilities, a lobby and negative pressure ventilation on the ICU. Urine and faeces from the patient, although considered non-infectious, were disposed of in an en-suite toilet and any residual matter was put in the clinical waste. Prior to intubation the patient was drooling and producing a significant amount of salivary secretions which were considered infectious. Once intubated, a closed suction catheter system was used for removal of tracheal secretions. Suction containers were disposed of in the clinical waste and subsequently transported away from the clinical area to undergo incineration. Single-use equipment was used as much as possible and discarded in the infectious waste stream. Chlorine dioxide-based disinfectant was used to clean non-disposable equipment. Chlorine-based disinfectants are effective against the rabies virus and thus can be used for chemical disinfection procedures in cases such as ours[7]. Rabies is an enveloped virus with a lipid-containing bilayer thus rendering it susceptible to many commonly used disinfectants including iodine preparations, quaternary ammonium compounds, detergents and other lipid solvents[8].

Visitors and staff entering the room were required to wear personal protective equipment (PPE) consisting of face masks with integral visors for eye protection, gowns and gloves. Standard surgical masks do not provide adequate levels of protection against potential mucocutaneous exposure[7]. The number of people visiting the patient was kept to a minimum. Family members were able to visit with pre-arrangement, wearing PPE as described, one person at a time (with a health care

worker present in the room). Family members were not permitted to be in the room whilst any procedures were being performed on our patient. A single, domestic cleaner, who had been specifically advised on rabies exposure avoidance measures, cleaned the room daily again using disposable equipment where possible and wearing PPE. Table 1 summarises the principal elements of the Milwaukee protocol and the infection control measures taken to minimise risk of transmission.

Following her death, disposable equipment and material (such as window blinds) were placed in the clinical infectious waste stream and removed from our patient's ICU room. The remainder of the patient environment (including the en-suite toilet) underwent a terminal clean with a chlorine-releasing agent using disposable cloths and mops. The body was transferred was transferred to a mortuary with appropriate containment facilities as per the Health Services Advisory Committee guidance[9] for a post-mortem to be conducted. In addition to wearing protective clothing, staff-performing post-mortems on a patient with suspected or confirmed rabies are strongly advised to receive vaccination prior to the procedure[7]. Despite the low risk of rabies transmission, bodies of suspected or confirmed rabies patients should not be embalmed[7].

Table 1. Principal elements of the Milwaukee protocol and the infection control measures taken

Principal elements of the Milwaukee protocol	**Infection control measures taken to minimise transmission risk**
Do not administer rabies vaccine or immunoglobulin to a patient with rabies	Not Applicable
Maintain the patient in isolation Transfer of laboratory-confirmed rabies to a tertiary care facility capable of critical care including intracranial pressure monitoring	Patient admitted to a single-bed room with negative pressure ventilation and en-suite facilities on the Intensive Care Unit and remained in this room throughout her admission Number of staff and visitors kept to a minimum and all required to wear gloves, gowns and face masks with integral visors
Placement of a central venous catheter, urinary catheter & nasogastric tube (nasojejunal tube during the period of ileus encountered)	Procedures performed by experienced senior members of staff wearing gloves, gowns and face masks with integral visors. Urine and faeces disposed of in en-suite toilet
Maintain normovolaemia and serum sodium >145 mEq/L (aiming to control the salt wasting that occurs)	Staff member wearing gloves, gowns and a face mask with an integral visor whilst inserting the oesophageal probe for oesophageal doppler guided sodium and fluid management
Deep venous thromboembolism prophylaxis	Low Molecular Weight Heparin administered by staff member wearing gloves, gowns and a face mask with an integral visor
Aggressive sedation within the first week of hospitalization	Our patient was anaesthetised within the first 48 hours of admission at the point where she became extremely agitated and violent
Ventilate using normal parameters	Secretions and suction containers disposed of in clinical waste. Closed suction catheter system used to remove tracheal secretions
Twice daily venous (for serum electrolytes) and arterial blood sampling	Performed by a member of staff wearing gloves, gowns and a face mask with an integral visor and equipment disposed of in the infectious waste stream. The relevant laboratories informed and samples transferred via a predesignated pathway Further heightened awareness during the latter stages of the patient's illness as increased likelihood of viraemia
Daily electrocardiograms to measure P-R interval and assess for heart block	Performed by a member of staff wearing gloves, gowns and a face mask with an integral visor using a dedicated electrocardiogram machine
Maintain core body temperature of 35-37 degrees Celsius	No extra measures in addition to the infection control precautions already implemented
Administer the antiviral agent Amantadine (has neuroprotective effects)	No extra measures in addition to the infection control precautions already implemented
Salivary sampling every other day for virological monitoring (until 3 consecutive negative results)	Initial salivary samples collected on day 0 & day 1 for diagnostic purposes but then no further samples collected in order to minimise exposure and not felt likely to significantly alter management in our case
Cerebrospinal fluid sampling at baseline and then twice weekly for chemistry and serology	Lumbar puncture not performed to minimise exposure and not felt likely to significantly alter management in our case
Daily transcranial Doppler ultrasound (days 4-8 and 12-15 after hospital admission) to monitor for degree of vasospasm & electroencephalogram monitoring	Performed by staff wearing gloves, gowns and a face mask with an integral visor. Non-disposable equipment cleaned with chlorine dioxide disinfectant after each use
Magnetic Resonance Imaging or Computed Tomography in the second and third week twice weekly until CSF titres stabilize	Patient not transferred out of isolation. Magnetic Resonance Imaging/Computed Tomography not performed to minimise exposure and not felt likely to significantly alter management in our case

The Virology and Occupational Health departments rapidly set up a service for advice regarding post exposure prophylaxis (PEP), vaccine and HRIG administration. Staff (including laboratory staff) and visitors were advised to report all exposures to the ICU and Virology consultants. PEP was considered necessary for all type III exposures[10,11]; (a) mucocutaneous exposure to the patient's infectious secretions and (b) needlestick injuries.

No staff members within the Trust or visitors of the patient were deemed to have had a type III exposure upon assessment of their individual risks. Fifty-nine staff members were identified by the Occupational Health department as being involved in the patient's care and thus potentially having some form of relatively minor exposure in terms of risk of transmission. All staff members and visitors including bank/temporary staff were given both verbal and written information regarding rabies exposure and vaccine administration. As strict infection control precautions including PPE were used by all staff members and visitors, no staff or visitors were considered to have had a 'high-risk' exposure. Nevertheless, all 59 staff members involved were given the opportunity to discuss receiving the rabies vaccine and/or any issues relating to rabies transmission and PEP. Dedicated occupational health, infection control and clinical virology staff were readily available for individual face-to-face discussions between 9am and 5pm, and a consultant clinical virologist was available via telephone for advice out-of-hours. A total of 17 staff at UCLH opted to receive the rabies vaccine; 5 nurses, 8 doctors, 3 other hospital staff and 1 laboratory scientist (table 2). They received a total of 5 doses which were administered on days 0, 3, 7, 14 and 28-30. No staff members or visitors received human rabies immunoglobulin. Routine follow up was not planned after completing the rabies vaccination course but both vaccinated and unvaccinated individuals were given Occupational Health department contact details should any concerns or queries arise at a later stage. There have been no known secondary cases of rabies at over 36 months since our index rabies case.

The Infection Control Team was available throughout to provide further advice where required. Tele-conference meetings involving ICU staff, Virology, Infection Control, Public Health England and the referring hospital took place at least once a day to discuss management of this case including infection control issues.

Table 2. Potentially exposed staff members, rabies vaccination history and rabies vaccine uptake at University College London Hospitals

Staff member type	Number of staff members	Type of exposure	Number previously vaccinated against rabies	Number that received rabies vaccine (number previously vaccinated against rabies)	Number that did not receive rabies vaccine (number previously vaccinated against rabies)
Nurse	33	Had contact with patient but no type III exposures	1	5 (0)	28 (1)
Doctor	20	Had contact with patient but no type III exposures	3	8 (2)	12 (1)
Health Care Assistant	2	Had contact with patient but no type III exposures	0	0	2 (0)
Domestic team member	1	No physical contact with patient and no type III exposure	0	1 (0)	0
Radiographer	1	Had contact with patient but no type III exposure	0	1 (0)	0
Neurophysiologist	1	Had contact with patient but no type III exposure	0	1 (0)	0
Laboratory scientist	1	Handled specimens from patient but no type III exposure	0	1 (0)	0

Type III exposure defined as (a) mucocutaneous exposure to the patient's infectious secretions and (b) needlestick injuries

The UCLH laboratory:

Investigations

The specimens (nuchal skin biopsy, wound biopsy and saliva) obtained on day 1 were initially received in the UCLH Virology laboratory. After giving prior notification, the samples were urgently couriered to the reference laboratory (Veterinary Laboratories Agency) in an appropriately labelled and packed secure metal box following advice for Transportation of Category A Dangerous Goods[12]. Table 3 summarises the precautions taken at UCLH with regards to transporting, processing and the disposal of patient specimens collected.

Table 3. Infection control measures taken for processing of specimens. This information was circulated in the form of a trust rabies case management document to pathology staff critical care staff, infection doctors, infection control doctors and nurses

	Infection control measures taken with our rabies patient's specimens
All specimens	Prior notification of the laboratory and discussion with a senior member of laboratory staff Ward staff to contact courier to transport specimens to laboratory Transported in designated metal high risk containment tin Taken to the relevant laboratory specimen reception "High Risk" sticker placed on all specimens at time of booking onto the UCLH laboratory system Standard precautions followed for sample handling within the laboratory Waste material/specimens retrieved by a designated biomedical scientist, double-bagged and autoclaved prior to disposal
Virology specimens	Prior discussion with virology consultant Couriered directly to the reference laboratory
Microbiology specimens	Prior discussion with microbiology consultant
Haematology specimens	Analysed in a closed system (as normal)
Biochemistry specimens	Centrifugation of samples in the specimen reception area Analysed in a closed system (as normal)

Handling of samples for routine care in Haematology, Biochemistry and Bacteriology was discussed with the laboratories involved. As secretions (saliva, tracheal aspirates, CSF, urine) may contain the virus, such samples were collected only if necessary and with prior arrangement with the laboratories. Processing of routine bloods was carried out on automated platforms (blood is considered non-infectious). Our patient did not require respiratory investigations.

Public Health Management

In accordance with Public Health England's guidance on management of a suspected cases of human rabies, our highly suspected case of rabies required a response level 3, consisting of case management input from multiple organisations[13]. Public Health England was notified on suspicion by the referring hospital and daily teleconferences were held to provide updates and advice on further management of our patient.

DISCUSSION

Management of a patient with rabies poses a major challenge and requires a health care facility that is able to support the augmented care needs of such a patient. Effective communication between healthcare professionals in primary care, secondary care and public health is vital. As described, strict infection control precautions are needed whilst following the Milwaukee protocol and this requires close coordination between several departments and their staff within a hospital.

To date, nosocomial transmission has been limited to solid organ and tissue transplant recipients[14] with no reported acquisition of rabies infection in healthcare workers caring for a patient infected with rabies[15]. There have been 8 documented patient deaths associated with receiving corneal transplants from rabies infected donors[13]. Another patient, however, that promptly received the rabies inactivated vaccine post-operatively on day one, survived after receiving a corneal transplant from a confirmed rabies-infected donor [14,16]. A child that died from canine rabies in the in Democratic of Congo bit two of his relatives whilst unwell[17]. Both relatives received rabies PEP on time and did not develop rabies. In contrast, a patient in China died from laboratory-confirmed rabies after broken skin on his hand (covered by gauze) came into contact with the blood of his relative that he was helping immediately after his relative was bitten by a stray dog[18]. The patient did not seek further medical attention at the time or receive rabies vaccination whereas his relative that suffered the dog bite promptly received the rabies vaccine and survived without complications. The potential consequences of nosocomial rabies transmission are extremely high and its Advisory Committee on Dangerous Pathogens (ACDP) classification as a Hazard Group 3 pathogen means that strict precautions are required.

As typically occurs in the natural history of human rabies, our patient in the early part of her admission was hydrophobic, became extremely agitated and had a violent episode prior to being anaesthetised, intubated and ventilated[4]. Caring for a patient during this stage poses a heightened risk and therefore strict precautions must be

taken with regards to PPE, infection controls and sampling (which should be limited to where necessary).

We were guided by the Milwaukee protocol throughout the care of our patient and closely followed it particularly where we felt it was likely to alter management. We opted not to follow certain parts where we did not think it was likely to have a significant impact on the management of the patient thus minimising potential healthcare worker exposure. The protocol recommends twice day blood tests (particularly for monitoring serum sodium) and arterial blood gases at least twice daily. Although our patient had repeated blood sampling, routine blood tests were limited to only when considered necessary and an internal investigative/sampling protocol was devised for our patient. A decision was made not to obtain serum for blood grouping/typing/cross-matching and O negative blood would have been administered if transfusion was required. Although blood is thought to be non-infectious, there has been suggestions that a viraemia may occur at some stage during infection with rabies[19] and we therefore did not want to put any laboratory staff at unnecessary risk. Collection of salivary specimens every other day (for PCR) and twice weekly CSF (for chemistry, serology and neurotransmitters) as stipulated in the protocol was also not performed. Outside of the direct patient setting, extensive laboratory infection control measures were put into place for collection, transfer and testing of salivary, urine, blood and CSF samples. Several specimens had to be collected frequently throughout this patient's hospital admission. This had significant implications for the haematology, biochemistry, virology and reference laboratories.

Another infection control challenge in managing a patient with rabies is the close central nervous system monitoring required. Although not applicable to our case (as rabies-specific antibodies were not detected) twice weekly MRI or CT imaging following seroconversion in the cerebrospinal fluid is also recommended. This could pose even greater difficulties in management of potential future cases and provisions would need to be made in advance for this when receiving a patient with possible rabies. In our case, we opted not to transfer the patient out of her room to any other parts of the hospital. Imaging was limited to portable methods which could be performed inside the patient's room. Daily transcranial doppler ultrasound monitoring was required in adopting the protocol primarily to monitor for vasospasm and was performed during our patient's admission although equipment and expertise were not requested until day 7 of admission. Portable plain chest radiography was also

performed. Certain minimally invasive procedures were deemed necessary despite the body fluid potential exposure risk. Insertion of a central venous catheter and an oesophageal doppler probe were necessary to monitor and optimise our patient's haemodynamic status. Once our patient progressed to multi-organ failure, venous access was also required for veno-venous haemofiltration. Additionally, as life-threatening arrhythmias are known to occur in patients with rabies, transvenous insertion of cardiac pacing wires was deemed necessary.

De-isolation is considered possible in the most recent version of the Milwaukee protocol, version 5.0[5], once a patient has detectable serum neutralising antibodies (>0.5IU/ml) and salivary RT-PCR is negative on 3 separate occasions. We did not address this aspect of infection control given the patient's demise at day 10.

Despite efforts from the outset to minimise the number of staff exposed to our patient and her specimens, the complexity of managing a case of rabies and following the Milwaukee pathway meant that 59 UCLH staff over the 10-day admission period still had some form of exposure albeit low risk in this case. There remains a potential theoretical risk of transmission to exposed healthcare workers and therefore we did our utmost to ensure timely vaccination of individuals reporting an exposure, who opted to receive the vaccine. The criteria for offering vaccination to healthcare workers was broad with a low threshold for offering the rabies vaccine. The prompt, cautious and highly coordinated approach taken in our case with regards to infection control both in the clinical and laboratory setting meant that there no exposures deemed to be significant/type III exposures on risk assessment. Twenty-nine percent of healthcare workers received the rabies vaccination and in other previous hospitalised rabies cases reported healthcare worker vaccination rates have ranged from 2% to 100%[20]. Comprehensive education and prompt handling of any queries by our infection doctors, infection control and occupational health teams with additional support from Public Health England meant that the majority (71%) of healthcare workers did not receive the rabies vaccine in our case. Establishing a 24-hour vaccine advice and provision service for all potential contacts did however pose a significant challenge. There was a significant time commitment from the staff involved over the patient's 10 day hospital admission and further arrangements had to be made for the healthcare workers being vaccinated to return to the occupational health department on specific days that were in concordance with the recommended

vaccine dose administration schedule. Adopting a reassurance and counselling strategy with the offer of vaccine only for type III exposure may be a consideration in future cases.

Widespread uncertainty remains regarding the clinical, laboratory and public health infection control implications of following the Milwaukee protocol. We look forward to published analysis of outcomes for all cases managed globally with this intervention.
In the future, we hope for evidence to support a consensus for adopting the protocol when caring for certain patients rather than for all human rabies cases. Regardless, care for these patients can put healthcare workers at significant risk and therefore combined multidisciplinary input for safe care is needed. It is therefore vital to seek specialist advice early and liaise with experts daily for diagnosis, management and infection prevention strategies when managing a case of human rabies. In addition to early specialist advice and daily liaison, pre-incident preparation of clinical, laboratory, transport and cleaning protocols and training therein are needed. Additional useful guidance for devising local protocols and managing a rabies case includes the World Health Organisation European Rabies bulletin[21] and the Health Protection Scotland guidance on rabies[22].

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