CASE REPORT

Rabies encephalitis in a child: a failure of rabies post exposure prophylaxis?

Faten Tinsa,[1] Aida Borgi,[2] Imen Jahouat,[1] Khadija Boussetta[1]

[1]Department of Pediatrics B, Children's Hospital Bechir Hamza of Tunis, Tunis, Tunisia
[2]Pediatric Intensive Care Unit, Children's Hospital Bechir Hamza, Tunis, Tunisia

Correspondence to
Dr Aida Borgi,
aidabdoc@yahoo.fr

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SUMMARY

Rabies remains a serious public health problem in many developing countries. The diagnosis is easy when a non-immunised patient presents with hydrophobia and hypersalivation after a bite by a known rabid animal but more difficult when a patient presents atypical symptoms after having received rabies postexposure prophylaxis. Rabies postexposure prophylaxis failure is rare. We report a case of a 6-year-old boy who presented febrile seizure with agitation and cerebellar signs, without hydrophobia or hypersalivation, 17 days after a dog bite. Despite four doses of rabies vaccine and immunoglobulin, he died. Diagnostic confirmation of rabies encephalitis was made in post mortem on brain biopsies by fluorescent antibody technique.

BACKGROUND

Rabies is fatal encephalitis of viral origin in humans and some other mammals. It is estimated that up to 40–60 000 cases of human rabies occur annually, and dog bite is the cause of over 98%.[1] It is still a major health problem in the developing world and has medical and economic implications: nearly 4 million people receive post exposure prophylaxis (PEP) annually.

In Tunisia, rabies PEP (RPEP; vaccine+immunoglobulin) is free of charge and is included in the national rabies control programme. There are specialised centres in many regions of our country for RPEP.

One or two cases of fatal human rabies have been recognised per year in Tunisia; in these cases, the victims generally did not consult after a dog bite and did not receive prophylaxis.

True prophylaxis failures are rare and the most cases of RPEP management failure are due to errors of management. We report a case of a 6-year-old child who presented with rabies encephalitis and died despite RPEP.

CASE PRESENTATION

A 6-year-old boy was transferred from a regional hospital to our department for febrile seizure. He was healthy and had no immunosuppressive disease or treatment. He was bitten by a stray dog 17 days previously on the forehead. RPEP was started on the same day he was bitten. He received a maximum dose of equine rabies immunoglobulin (ERIG) 40UI/kg (Pasteur) into the wound and the rest intramuscularly into the deltoid region on day 0 after wound cleaning and four doses of rabies vaccine (purified chicken embryo rabies vaccine PCEC, Rabipur, Novartis vaccines) intramuscularly into the deltoid region on days: 0, 3, 7 and 14 following WHO guidelines (ESSEN regimen+ERIG). The vaccine and ERIG were not out of date and were correctly kept at 4–8°C before using. ERIG and vaccine were administrated in different arms. Wound suture was performed on day 0 after ERIG administration. The boy had presented 3 days before admission to our department with vomiting and fever, but without hydrophobia or hypersalivation. On admission, he was febrile at 39°C. He had conjunctivitis. There was a bite mark sutured on the front of his forehead near the left eyebrow, which measured 3 cm×4 cm. On neurological examination, the child had strabismus and was agitated. He had cerebellar ataxia and his reflexes were brisk in the lower limbs. There were no signs of respiratory or cardiac failure.

INVESTIGATIONS

Laboratory investigations revealed neutrophilic leucocytosis, normal C reactive protein, blood glucose, electrolytes, liver and renal function tests. Brain imaging was requested but could not be performed.

DIFFERENTIAL DIAGNOSIS

Herpes encephalitis was discussed because of it frequency and severity and acute disseminated encephalomyelitis (ADEM) was a close possibility because the illness developed within 2 weeks of starting antirabies immunisation.

TREATMENT

The patient received acyclovir, despite the suspicion of rabies encephalitis.

OUTCOME AND FOLLOW-UP

The patient developed seizure and cardiac arrest, and died on the same day. On autopsy, biopsies of cerebral cortex, cerebellum, hippocampus and medulla were positive for rabies antigen on fluorescent antibody technique.

Rabies vaccine was given to the family and all the healthcare workers with possible percutaneous or mucous exposure to the patient's saliva before confirmation of the diagnosis. The stray dog died few days before the child's admission and was positive for rabies antigen on fluorescent antibody technique on brain biopsies.

DISCUSSION

The clinical course of human rabies is classically divided into four stages: incubation period, prodrome, acute neurological phase and coma. The

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incubation period usually lasts between 20 and 90 days, but intervals as short as 4 days or as long as 19 years have been reported. It is understood that shorter incubation times often correlate with severe bite exposures to the head and neck. In our patient, the first symptoms were present at day 14 post exposure and this short incubation may be explained by the severe bite in the face, which is a richly innerved area. This short incubation, despite RPEP, made the diagnosis of rabies difficult, and therefore the other possibilities of viral encephalitis or acute disseminated encephalomyelitis were discussed. The patient received acyclovir to cover herpes virus and an MRI of the brain and cervical spine was indicated but the patient died rapidly.

The prodromal symptoms of rabies are typically 'non-specific' and frequently not recognised by practising clinicians. The majority of rabies cases are of the classic encephalitic or 'furious' form, while a progressive paralytic illness has also been described. Reports suggest that in classic rabies, hydrophobia is the most characteristic and widely known feature, occurring in up to 80% of cases. In a study by Chhabra *et al*,[2] only 5% of patients with rabies did not have hydrophobia.

Aerophobia is described as a prominent symptom and can be elicited by the 'fan test'. Agitation alternating with calm is another prominent feature of 'furious' type cases as well. Local sensory symptoms such as paraesthesias or itching occur in as many as 30% of 'furious' as well as paralytic patients. Patients with 'furious' type disease die earlier on average (5 days) than those with the paralytic form (13 days). The diverse clinical features of each rabies case may relate to different viral tropisms, routes of neural spread, different sites of neural involvement and variable immune responses.[3 4]

In our case, the child presented with fever, vomiting, seizure, agitation and ataxia. Hypersalivation and hydrophobia, the predominant features of a 'furious' form, were not present. These features made the diagnosis of rabies encephalitis difficult, especially in this child, who had received four doses of rabies vaccine and ERIG, and ADEM was a close possibility because the illness developed within 2 weeks of starting antirabies immunisation. MRI imaging is not specific for rabies encephalitis and showed bilaterally symmetrical hyperintensities in T2 and fluid-attenuated inversion recovery images involving the dorsal brain stem, thalamus and basal ganglia, as well as the central grey matter of the spinal cord.[5] Conventional reverse transcriptase-PCR and Real-time PCR (TaqMan) have been described for the detection of rabies virus RNA from cerebrospinal fluid and are useful for the diagnosis of rabies encephalitis especially if the bite wound is not reported.[6] However, these tools of diagnosis are not employed in our country and the diagnosis confirmation is usually made in post mortem by fluorescent antibody technique.

Given the uniformly fatal outcome of clinical rabies, prevention is essential. RPEP usually prevents the development of rabies if given correctly and early on the day of the bite. However, in some cases, failure to RPEP occurs and only pre-exposure immunisation followed by post exposure boosting has provided complete protection against disease. If pre-exposure immunisation has been administered, subsequent exposure to rabies does not require ERIG, however, it does require a short two dose booster vaccine course on days 0 and 3; no deaths have been reported in cases where pre-exposure and post-exposure vaccines were given. Ideally, everyone living in dog rabies enzootic areas should have pre-exposure immunisation, but this is limited by the high cost of vaccine in developing countries and it is reserved for veterinarians in our country. Actually, the vaccine cost can be reduced by using low dose intradermal regimens.

Practically, RPEP begins with immediate and thorough washing of all bite wounds and scratches with soap and water to reduce the viral load at the site of inoculation. Then, RPEP involves the administration of ERIG at the site of inoculation and a vaccination schedule that must be strictly followed. Some cases of failure associated with immunoglobulin administration distant from the wound emphasise why rabies immunoglobulin should be thoroughly infiltrated into the wound and the area surrounding it.

Wilde[7] reported seven cases of RPEP management failure due to errors of management. The most common causes for failure of RPEP were: (1) rabies immunoglobulin was not used at all or injected only intramuscularly and not into the wounds; (2) not all wounds were injected with immunoglobulin; (3) A 6-day delay in the prophylaxis; and (4) wounds were sutured before immunoglobulin injection.

True prophylaxis failures are rare. Wilde presented a series of seven cases, of what appeared to be true PEP failures. These cases represent a very small number, compared to the millions of PEPs that are administered worldwide every year. All the apparently true failures reported involved wounds in highly innervated regions of the body such as hands and face. Indeed,[7] Hemachudha *et al*[8] and Shantavasinkul *et al*[9] reported a prophylaxis failure in three patients.

In our case, RPEP was started following WHO guidelines: on day 0, the patient received the first dose of rabies vaccine intramuscularly, into the deltoid region and ERIG (40 U/kg) around and into the bite wound, and the rest of the immunoglobulin intramuscularly on days 3, 7, 14 and 28.[1] The child appeared to have received timely and appropriate PEP, yet he died of rabies; the wound in the face, a zone richly innerved, may explain the failure of the prophylaxis. However, it is impossible to completely exclude errors in management and a small transdermal puncture wound may have been missed and not irrigated, disinfected and injected with immunoglobulin. The bite wound was sutured early on the same day, which can also explain the failure of RPEP. This action could have enhanced spread of the virus and rapid viral entry into the peripheral nerves, where viruses are in an immunoprotected environment.

Learning points

- Post exposure prophylaxis PEP is not always effective.
- Treatment failure is not uncommon, and is mostly due to: inappropriate wound cleansing; improper technique of vaccine and equine rabies immunoglobulin (ERIG); no ERIG being given; delayed treatment; and low potency of vaccine or ERIG.
- Pre-exposure rabies vaccine with booster doses after rabies exposure is effective.
- Physicians must be aware of the clinical characteristics of rabies and know how to prescribe vaccines and ERIG appropriately.
- Rabies encephalitis is a fatal disease and animal rabies control and surveillance are mandatory, especially in endemic area.

Competing interests None.

Patient consent Obtained.

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