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Case Report

Case Report: Spindle Coma in a Girl with Cerebral Rabies Treated with the Milwaukee Rabies Protocol

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ABSTRACT

Rabies has the highest case fatality rate of any human infectious disease. While there has been a recent increase in the incidence of rabies in the United States, detailed reports on cerebral rabies (CR) are rare. Since 2004, initiation of the Milwaukee Rabies Protocol (MRP) has enabled some patients to survive CR. The MRP requires placing the patient in an induced coma, necessitating continuous video electroencephalogram (vEEG) monitoring. To date, serial vEEG findings have not been reported in patients with CR using the MRP. We report the vEEG finding of spindle coma in a girl undergoing the MRP. This may be a unique finding associated with CR and/or MRP intervention. Further studies will be required to determine whether this vEEG finding is characteristic of patients with CR or treated with the MRP.

INTRODUCTION

Rabies is caused by viruses in the *Rhavdoviridae* family and has the highest case fatality rate of any human infectious disease [1]. The virus spreads in a retrograde direction via peripheral nerves to the central nervous system, reaching the brain and preferentially infecting the diencephalon, hippocampus, and brainstem [2]. Manifestation of rabies usually starts with a prodromal phase consisting of non-specific symptoms including low-grade fever, myalgias, fatigue, sore throat, vomiting, and headache [3]. The classic presentation of encephalitic rabies includes fever, hydrophobia, autonomic instability, dysarthria, dysphagia, mental status change, meningitis, and ultimately coma and death [2]. Eighty percent of patients present with the encephalitic rabies, with fewer patients showing paralytic rabies [4]. The rabies virus triggers generalized cerebral vasospasm which is the cause of morbidity and mortality. In the United States (U.S.), there have been only 85 human cases of rabies reported from 1980 through 2015, with an average of two to three reported each year [5]. However, the U.S. reported five cases of rabies in 2021, the highest annual number in a decade [6].

Post-exposure prophylaxis (PEP) for rabies is successful in preventing viral disease progression before the patient shows symptoms [4]. Until 2004, the presentation of cognitive symptoms was associated with 99% fatal outcome [7]. Willoughby et al. [8,9] reported the first unvaccinated survivor of rabies who was treated with the

"Milwaukee Rabies Protocol" (MRP). A natural immune response is thought to be sufficient to clear the virus [10]. Therefore, the rationale underlying the MRP is to protect the brain by reducing inflammation, awaiting the development of antibodies to neutralize the rabies virus. The MRP consists of therapeutic phenobarbital/ketamine coma with continuous vEEG monitoring, antiviral therapy, management of cerebral vasospasm and avoidance of rabies immunization [10]. Since its first use in 2004, the MRP has undergone modifications, the latest (version 6) of the MRP being published in 2018 [11]. Recent review of the MRP, together with the similar Recife Protocol used in Brazil [12], identified a total of 39 reported treated cases with only 11 survivors [11]. Due to inconsistent results, MRP has also received criticism [13]. The MRP still currently remains the last resort treatment used for cerebral rabies (CR) within the US.

Few studies have evaluated the vEEG findings in CR infection including those on the MRP. This is the first case report of a patient with CR treated with the MRP who was monitored with vEEG throughout her hospital stay.

CASE PRESENTATION

Patient Information and Clinical Findings

A previously healthy 10-year-old female presented to a community hospital in October of 2006 with right arm pain, numbness, dysarthria, vomiting, irritability, excessive drooling and dysphagia. She was transferred to a tertiary care hospital for progression of symptoms including altered mental status, dysphagia and breathing difficulty requiring intubation and ventilation. Initial cerebrospinal fluid (CSF) studies showed pleocytosis (26 cells/mm^3) and elevated glucose level of 89 mg/dL. Empiric coverage with vancomycin, cefotaxime, and acyclovir was initiated for presumed encephalitis. Routine (30 minute) EEG, performed on the second day of hospitalization showed frequent spike wave epileptiform discharges from the left and right frontal regions (Figure 1; "F3" and "F4"). She was treated with prophylactic phenytoin.

On the third day of hospitalization, it was discovered that earlier that summer she had received a scratch or bite to her right arm from what she termed a "fluffy bird", later identified as a bat. A serum rabies-virus- specific antibody test was positive; saliva and skin samples reverse transcription-polymerase chain reaction (RT-PCR) were also positive for rabies virus amplicons. Direct fluorescent antibody (DFA) staining of the skin biopsy from the nape of the neck was positive for rabies virus antigens. For further confirmation, the patient's serum, saliva, CSF, and skin biopsy were sent to CDC for rabies virology testing. The patient had not received a rabies vaccine or rabies PEP.

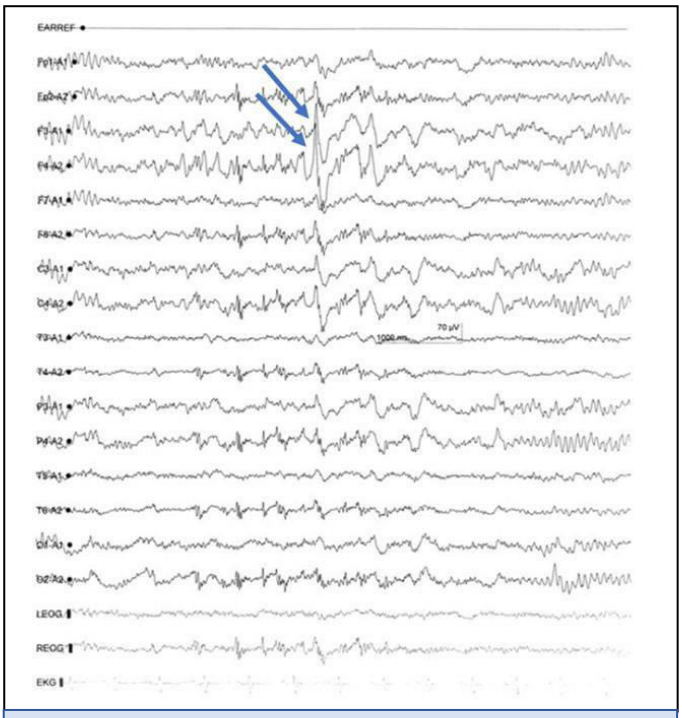

Figure 1: Initial vEEG upon admission showing bifrontal epileptic discharges during sleep (arrows). Stage 2 sleep is characterized by vertex sharp transients and sleep spindles. Sensitivity = 7mV/mm; bipolar montage.

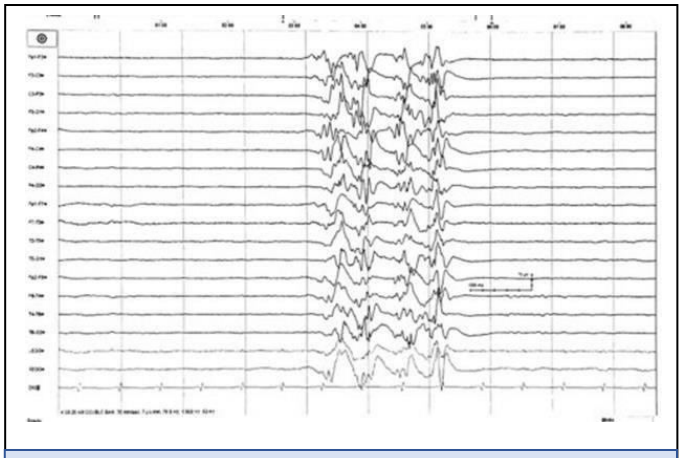

Figure 2: Sample vEEG (days 6-15) showing a burst suppression pattern with bursts ranging from 2.5-10 seconds. Intermixed periods of suppression lasted 10-20 seconds. Sensitivity 7mV/mm; bipolar montage. Phenobarbital levels ranged from 74.1 to 168.7 mcg/ml. This pattern was attributed at least partly to the sedative-hypnotic effect of the medication (phenobarbital) in the Milwaukee Rabies Protocol (MRP).

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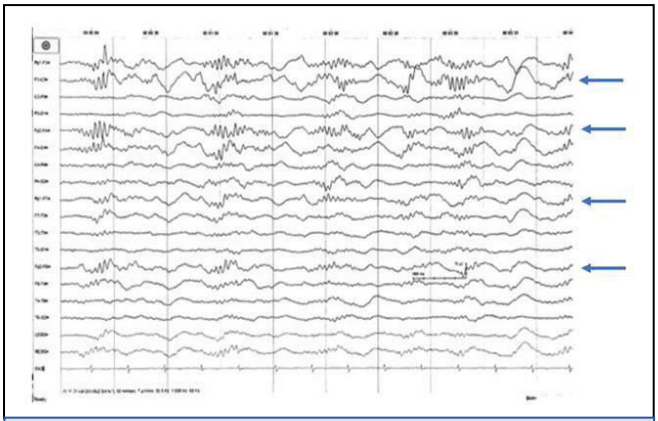

Figure 3: Sample trace from the vEEG (day 16-20) showing spindle coma with an invariant, discontinuous background characterized by periods of diffuse delta activity with superimposed frontal dominant spindle activity occurring every 1-2 seconds alternating with diffuse attenuation of the background (arrows). Phenobarbital levels ranged 22.9 to 58.7 mcg/ml. Sensitivity 7mV/mm: bipolar montage.

THERAPEUTIC INTERVENTION AND OUTCOME

When a diagnosis of rabies was confirmed on day 5, the patient was placed on the MRP with phenobarbital, midazolam, ketamine, amantadine, and intravenous ribavirin and underwent continuous vEEGs. From hospitalization days 6 – 15, vEEG showed burst suppression with phenobarbital levels ranging from 74.1 to 168.7 mCg/ml (Figure 2). The patient was on the MRP for about 10 days, overwhich she showed no improvement and complictions cited below. On hospitalization days 16 - 20, vEEG displayed periods of continuous spindle-like activity characteristic of a spindle coma (Figure 3) with phenobarbital levels ranging from 22.9 to 58.7 mCg/ml. On hospitalizations days 21 – 24, two days before death, the vEEG progressed to low amplitude delta waves, signifying severe encephalopathy.

During this patient's hospitalization, she experienced multiple complications including increased intracranial pressure, cerebral and cerebellar herniation, intracranial venous sinus thrombosis, diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormone, and ribavirin induced pancreatitis. The patient died on hospitalization day 26 (Table 1-Timeline). Postmortem brain tissue biopsy was positive for rabies virus antigen.

Timeline	June	Oct Day1-3	Oct Day5-15.	Oct Day16-20	Nov Day21-26
Event	Bat bite to arm	Altered mental status	MRP	Off MRP	----------Death
EEG		Bifrontal sharps	Burst suppression;	spindle coma	Low amplitude delta

DISCUSSION

In the U.S., CR is a relatively rare infection with an average of two deaths per year since 1980 [14]. This relatively low incidence rate of this infection in the U.S. could be attributed to adequate vaccination of domestic dogs and the availability of the rabies vaccine which prevents 99% of deaths if administered promptly after exposure [14]. However, as mentioned previously, there has been an increase in incidence of rabies cases in recent years in the U.S [6]. The alarming rise in rabies cases emphasizes the relevancy of reporting the unique EEG finding in this case report.

In 1981, Komsuoglu reported periodic discharges in the routine EEGs of patients with CR [15]. Other routine EEG findings in CR have included non-convulsive status epilepticus, focal seizures, and burst suppression induced by midazolam [16], and electrocerebral silence [17]. To date, there are no reports of serial vEEG monitoring specific to patients with CR being treated with the MRP. Although our patient's vEEGs demonstrated burst suppression, similar to previous reported routine studies, her vEEG evolved into spindle-like activity characteristic of a spindle coma picked up on the continuous monitoring. This was seen over five days.

Spindle comas are non-specific and have been reported in association with head trauma, nontraumatic intracranial hemorrhage, cerebrovascular disease, cerebral anoxia, neoplasms, surgery, seizures, and metabolic disturbances [18-20,21]. Drug intoxication has also been reported to be associated with spindle coma, specifically benzodiazepines, barbiturates, and tricyclic antidepressant [18,22]. However, spindle coma has not been reported in patients with CR. It is further uncertain whether the MRP played a role in the appearance of spindle coma. Previous studies suggest that spindles during coma due to various causes are unrelated to prognosis [19] Recent reports, however indicate that they are associated with good prognosis for clinical recovery, since they suggest that bihemispheric' functions are preserved [18,20,21]. Therefore, the role of spindle coma as a prognostic marker

remains controversial since it depends on many factors including age, etiology, depth of coma, duration of the lesion or infection [18]. Our patient expired about one week after she developed spindle coma, posing the question whether spindle coma may be associated with a poor prognosis specifically in patients with CR and/or being treated with the MRP. No previous studies have linked spindle comas with poor prognosis in CR.

The patient's vEEG findings reflected her degree of encephalopathy and progressive neurological decline. The MRP is used to induce vEEG burst suppression, effected by the use of phenobarbital. It is unclear if the emergence of the spindle coma was due to the protocol drugs or intriguingly, due to rabies itself. Thus, future reports describing vEEG results in CR are needed to confirm our findings.

This report is limited in that it is one case, however we feel it worthwhile due to the rarity of CR. The patient was treated with phenobarbital as part of the MRP, and barbiturate intoxication has been associated with spindle coma. However, in this case, the spindle pattern continued when the phenobarbital levels were at non-toxic levels, suggesting that the spindle coma may not have been due to drug toxicity. Further studies in such patients are needed to determine whether spindle coma is either associated with CR or associated MRP treatment.

CONCLUSION

This report documents serial vEEG recordings in a patient with CR treated with the MRP. After cessation of the MRP, a spindle coma pattern emerged. The finding of spindle coma on vEEG has been associated with multiple different etiologies, however, not with a CR infection or the MRP. Although spindle comas have been previously reported to have variable prognosis depending on the etiology, this patient expiring shortly after the appearance of the spindle coma poses a question as to whether it is uniquely associated with a poorer prognosis specifically in patients with CR being treated with the MRP. More reports are needed to determine the validity of this vEEG finding.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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