

# Seizures and epilepsies secondary to central nervous system Infection

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## INTRODUCTION

Central nervous system infection has long been considered an important cause of seizures and epilepsy, especially in developing countries. One to 5% of epilepsies were presumed to be due to central nervous system infections in countries like the United States, Norway and Israel.<sup>1</sup> In developing countries, this figure is thought to be higher, for example, in India, up to 10% of epilepsy was thought to be due to neurocysticercosis,<sup>2</sup> and in rural Columbia, a prospective study of 643 epilepsy patients showed that up to 14% of the subjects had neurocysticercosis on computerized tomography scan of the brain.<sup>3</sup> A long list of central nervous system infections have been identified either to cause or were associated with seizures (Table 1). This review discusses malaria and Japanese encephalitis, two important causes of seizures in Asia and Oceanian countries where there are recent studies, and Nipah encephalitis which is an emerging disease.

## MALARIA

Malaria affects 5% of the world population at any one time and causes more than 1 million deaths

worldwide annually. Virtually all the death and cerebral malaria is caused by *Plasmodium falciparum*.<sup>4</sup> In adults the incidence of seizure in cerebral malaria varies. In the 1980's 50% of cerebral malaria patients in Thailand and Vietnam was reported to have generalized tonic-clonic seizures.<sup>5</sup> In the 1990's the same countries reported an incidence of 20% or less.<sup>4</sup> In 1989, Kochar *et al* reported a 23% incidence of seizures in Rajasthan, India.<sup>6</sup> The actual reason for the decline is not known, but is believed to be due to the reduction of the use of chloroquin.<sup>4</sup> Most of the seizures in adults were generalized.

In children about 30% of all malarial patients had seizures<sup>7,8</sup> while 60% to 85% of cerebral malarial patients had seizures.<sup>8-11</sup> More than 75% of seizure occurred in uncomplicated malaria and more than 70% of cerebral malarial patients had more than 1 seizure. In endemic and hyperendemic areas in Africa the commonest seizure is partial, which accounts for 52-84% of all seizures; 34% is generalizes and another 14% partial with secondary generalized.<sup>7,9</sup> In Papua New Guinea, on the other hand, generalized seizure accounts for 85% of seizures, and 53% of cerebral malarial patients have status epilepticus.<sup>8</sup>

In an electroencephalographic (EEG) study of

Causes of seizure	Associated with seizures
Bacterial meningitis	Ebstein-Barr virus <sup>28</sup>
Cerebral abscess	Human herpes virus type 6 <sup>29</sup>
Malaria	Congenital varicella zoster virus infection <sup>30</sup>
Encephalitis	Influenza A virus <sup>31</sup>
Japanese encephalitis	Respiratory syncytial virus <sup>32</sup>
Herpes simplex encephalitis	Mycoplasma pneumomoniae <sup>33</sup>
Nipah encephalitis	Coxsackievirus B4 <sup>34</sup>
Relapse Nipah encephalitis	Associate with HIV infection <sup>35</sup>
	Toxoplasmosis
	Cryptococcosis
	Tuberculosis
	Progressive multifocal leucoencephalopathy
	AIDS dementia complex

Table 1: Examples of central nervous system infections associated with seizures

65 children aged 9 months to 11 year old in Kenya<sup>12</sup>, 62% of the subjects had more than 1 seizure, 28% had status epilepticus and 23% had clinically subtle seizure or seizure detected only on EEG. The seizures were clinically classified to be partial motor in 52%, generalized tonic-clonic in 34% and partial with secondary generalized in 14%. The typical EEG findings were characterised by high amplitude diffuse slow waves (>100  $\mu$ V) of 0.5-7 Hz. Very slow waves on admission ( $\delta$  range) are associated with increase mortality (odds ratio of 27), and more than 75% of ictal activities arose from the posterior temporo-parietal regions. Comatose patients often had electrical status.

On long term follow up, 1.7% to 13% developed epilepsy after seizure in cerebral malaria.<sup>9,13</sup> In a case control study of 487 children, cerebral falciparum malaria increased the risk of epilepsy by an odds ratio of 4.4 (95% CI 1.4 - 13.7) whereas malaria complicated by seizure increased the risk of epilepsy by an odds ratio of 6.1 (95% CI 2.0 - 18.3).<sup>14</sup>

### **JAPANESE ENCEPHALITIS**

Japanese encephalitis is numerically the most important viral encephalitis in the world, affecting 50,000 patients with 15,000 death annually. Acute symptomatic seizure is one of the most important presenting features especially in children.<sup>15</sup> Seizures are reported in 7.6% - 85% of patients; up to 20% in adults and 85% in children.<sup>16-19</sup> In a study of 134 children and 10 adults in Ho Chi Minh city<sup>15</sup>, seizure was noted in 41% of patients. When the outcome of the infection was assessed on the Whitley scale, the occurrence of seizure was associated with poorer outcome, and the outcome in patients with multiple seizures was worse than those who had single seizure. Status epilepticus was also associated with increased mortality. In multiple regression analysis, seizure was associated with a poorer outcome with an odds ratio of 6.3 (95% CI 1.52-26). Clinically 31% of the patients who had seizures had generalised tonic-clonic seizure, a third of which had convulsive status epilepticus; 25% had non-convulsive status epilepticus, and 12% partial motor seizures. In the 234 EEG studies done on 55 of these patients, the commonest findings were reactive or unreactive slow waves of low amplitudes with burst suppression. 20% of the patients had seizure recorded, 11% recorded continuous discharges (half of whom had periodic lateralised epileptiform discharges, PLEDs).

Isolated frontal discharges and multiple seizures were recorded in 3.6% of patients each while 1.8% had PLEDs alone. Seizures on EEG were significantly associated with increased mortality (55% versus 9%). On follow up, up to 20% of patients developed epilepsy, though a smaller of 50 children followed up for 45 days did not find any with epilepsy.<sup>20</sup>

### **NIPAH ENCEPHALITIS**

Nipah encephalitis is an emerging infection initially seen among pig farm workers in Malaysia in 1999.<sup>21</sup> Since then it has occurred in recurrent outbreak in Bangladesh.<sup>22</sup> In acute Nipah encephalitis<sup>23,24</sup>, seizures occurred in 23-27% of patients. Seizure was associated with poorer outcome on univariate analysis, though not on multivariate analysis. 30 - 54% of patients suffered from continuous segmental myoclonus, most commonly affecting the diaphragm (32%), arms (14%), legs (10%), neck muscles (9%) and face (1%).<sup>23</sup> Comparatively, seizure occurred in 56% of all relapsed Nipah encephalitis patients reported so far and myoclonus only in 2 patients.<sup>25,26</sup> This is due to the fact that in acute Nipah encephalitis, the pathology was vasculitis and direct neuronal injury caused by the virus<sup>27</sup> while in relapsed Nipah encephalitis, the pathology was that of focal encephalitis.<sup>25</sup> Seizure and myoclonus were not of prognostic significance in both acute and relapsed Nipah encephalitis.<sup>23-25</sup>

### **REMOTE SYMPTOMATIC EPILEPSY**

Overall, 1-5% of incidental epilepsy was thought to be due to central nervous system infections. In a study of 714 patients from Olmsted county, Minnesota<sup>1</sup>, infection increases the risk of epilepsy by 6.9 folds. Overall 4.3% of patients with central nervous system infection suffered from epilepsy. The first attack of epilepsy occurred 2 weeks to 20 years after the initial infection, though the risk was highest in the first 5 years. 71% of the epileptic patients had partial seizures, 26% generalized and 3% unclassified. Risk factors associated with epilepsy were infection occurring at under 5 years of age, encephalitis, seizure during acute infection, and in our observation (Chong HT, Tan CT, unpublished) focal neurological deficits during the acute infection (odds ratio 6, 95% CI 1.22-31.6) and long term disability secondary to the infection (odds ratio 13, 95% CI 2.8 - 69).

## CONCLUSION

Seizure is an important feature of central nervous system infections, especially in children. It often manifests as impaired conscious state. Therefore, EEG is an important investigation in these patients. Seizure is also associated with increased morbidity in malaria and Japanese encephalitis, and with increased mortality in the latter. Central nervous system infection accounts for up to 5% of epilepsy in developed countries, possibly higher in developing countries. Factors associated with increased risk of epilepsy were infection occurring under the age of 5 years, encephalitis, seizure and neurological deficits during the acute infection, and long term disability after the infection.

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