SHORT REPORT

West Nile virus meningoencephalitis complicated by motor aphasia in Hodgkin's lymphoma

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A 4 year old boy with Hodgkin's lymphoma was admitted to the paediatric ward with meningoencephalitis dominated by generalised seizures and motor aphasia. Serum IgM specific antibodies to West Nile virus were positive. In view of ongoing neurological deterioration and immunocompromised state he was treated with oral ribavirin for 14 days. A gradual improvement was noted within two weeks of therapy initiation, and with intensive supportive care he recovered completely after four months.

West Nile virus (WNV) is a member of the family Flaviviridae, which also includes the St Louis encephalitis, the Japanese encephalitis, and the hepatitis C viruses. The natural reservoir of the virus is wild birds and it is transmitted by mosquitoes to humans, horses, and other domestic animals, which are incidental hosts.[1] Until recently West Nile fever (WNF) was considered a benign illness with most human infections being asymptomatic. When clinically apparent, WNF is usually mild in children and young adults, but tends to be more severe in the elderly.[1] The most frequent manifestations of WNV infection are fever, headache, myalgia, diffuse lymphadenopathy, and non-pruritic maculopapular rash which occurs in about 50% of patients.[2] Neurological manifestations are uncommon and range from mild aseptic meningitis to severe encephalitis (which is extremely rare in children).[1 2]

In Israel WNV is endemic. Several outbreaks of WNF have occurred in the past,[3–5] the last one being in 1981.[5] An outbreak of WNF took place in Israel between August and October 2000. The vectors of WNV were mosquitoes of the Culex species; the reservoir was wild birds (pigeons, storks, and crows).[6] A total of 417 people were serologically confirmed to have the disease, of whom 24 were children. Thirty three people died; all were over 50 years of age.[7] We describe a 4 year old immunocompromised boy who was admitted during this outbreak with severe WNV meningoencephalitis complicated by prolonged motor aphasia. This rare clinical course, its implications in immune deficient children, and treatment strategies are discussed.

CASE REPORT

A 4 year old boy was diagnosed in May 2000 with stage 1 Hodgkin's lymphoma. Chemotherapy was started using the ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) protocol. In September 2000, during his third session of chemotherapy, he was admitted to the paediatric ward for an acute febrile illness of two days duration. On admission physical examination revealed an alert and cooperative boy. His temperature was 38.7°C, blood pressure 94/64 mm Hg, and pulse rate 110/min. There was no evidence of meningeal irritation and the rest of the physical examination was unremarkable. White blood cell (WBC) count was 8120/mm^3, with absolute neutrophil count (ANC) 5930 cells/mm^3, haemoglobin 108 g/l, and platelet count 326 000/mm^3. Blood chemistry and chest *x* ray examination were normal. Blood and urine cultures were obtained, and therapy with pipercillin/tazobactam 240 mg/kg/day and gentamicin 5 mg/kg/day initiated.

Three days later his neurological status deteriorated. He became lethargic, disoriented, and experienced repeated episodes of generalised seizures. Physical examination revealed neck rigidity and positive Brudzinski sign. His haemodynamic state was stable and no rash was noticed. WBC count decreased to 3150/mm^3 with ANC 1610 cells/mm^3. Sodium was 138 mmol/l and potassium 4.5 mmol/l; glucose, calcium, and general chemistry were normal, C reactive protein (CRP) was 5.6 mg/dl. A lumbar puncture was performed; cerebrospinal fluid (CSF) white cell count was 180/mm^3 with 60% polymorphonuclear cells and 40% lymphocytes, protein was 109 mg/dl, and glucose 55 mg/dl (85 mg/dl in serum). No malignant cells were found and the CSF bacterial culture was sterile. Polymerase chain reaction (PCR) for herpes simplex DNA was also negative. Serologies for mycoplasma, Epstein–Barr virus (EBV), and cytomegalovirus were negative. An electroencephalogram revealed generalised slow waves in the delta range compatible with severe encephalitis. A brain computed tomography scan was normal. With the presumptive diagnosis of meningitis, antimicrobial treatment was changed to intravenous ceftriaxone 100 mg/kg/day, intravenous vancomycin 40 mg/kg/day, and intravenous aciclovir 30 mg/kg/day until microbiology and PCR virology results became available. The WBC and ANC continued to decline in parallel to neurological deterioration, reaching their nadir on the sixth hospital day (WBC 1070/mm^3 and ANC 310/mm^3).

Despite aggressive treatment with mannitol and anticonvulsive medications, the neurological abnormalities progressed. He developed motor aphasia, became completely bedridden, and required nasogastric feeding. His Glasgow coma scale was 7 of 15, yet there was no need to ventilate him and he remained haemodynamically stable. At this stage the results of serum IgM specific antibodies to WNV, obtained on the fourth day after admission, were reported to be positive. On the eighth day after admission, ribavirin 200 mg four times daily had been given via nasogastric tube for 14 days. Repeated blood counts showed no evidence of haemolysis as a complication of the ribavirin treatment; there was a gradual increase in both WBC count and ANC, reaching normal values on the 12th day after admission.

Slow improvement in neurological state was noted at the beginning of the third week. With the help of intensive auxiliary and supportive care (physical and occupational therapy)

Abbreviations: ANC, absolute neutrophil count; CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; PCR, polymerase chain reaction; WBC, white blood cell; WNF, West Nile fever; WNV, West Nile virus

his neurological deficits gradually disappeared, and he was discharged 28 days after admission. The motor aphasia was the last to resolve, lasting more than three months. At follow up, eight months after discharge, he had achieved complete neurological recovery and had completed the course of chemotherapy.

DISCUSSION

In the past decade, several epidemics of WNF have occurred throughout the world, including the Czech Republic,[8] Romania,[9] Russia,[10] and the United States.[11–13] The 1999 outbreak in New York was the first reported WNF outbreak in the Western hemisphere.[11] These reports changed the general conception of WNF being a mild febrile illness with limited CNS involvement and very low mortality rate. In the Romanian, Russian, and New Yorks epidemics a high percentage of CNS involvement was reported, as well as high mortality rates (4.3%, 4.0 %, and 11.5%, respectively[7–12]).

The Israeli 2000 outbreak was characterised by a country-wide spread, high percentage of neurological involvement (73% of hospitalised patients), especially in the elderly, and a high case fatality rate.[7] Even in these epidemics, however, severe neurological morbidity did not occur in children.

Of the 24 children diagnosed with WNF during the 2000 outbreak in Israel, all but one had mild disease. Most had aseptic meningitis. Our patient had the most severe course in the infected paediatric population, probably a result of his immunocompromised state.

The most common CNS manifestations of WNV are aseptic meningitis, encephalitis, myelitis, radiculopathy (a Guillain-Barré like syndrome), and peripheral neuropathy.[7–10 12 13] To our knowledge, motor aphasia as a complication of WNV encephalitis has not been reported. It seems that the severe manifestation in our patient occurred in part because of his immunodeficiency.

The complete recovery of our patient took place in conjunction with the increase in WBC and ANC (host immunity), both to the normal range, and initiation of ribavirin treatment. Ribavirin is a synthetic guanosine analogue that inhibits replication of DNA and RNA viruses.[14] Ribavirin and interferon alfa 2b are very active against hepatitis C virus, which belongs to the Flaviviridae family, to which WNV also belongs.[14 15] A recent in vitro study showed the inhibitory effect of ribavirin on WNV replication and on its cytopathic effect in neural cells.[16] This suggests that ribavirin could be effective in patients with WNV infection.

A multicentre clinical trial of ribavirin in WNF patients was initiated in the Israeli 2000 outbreak (unpublished data). Although our patient was not included in this trial (inclusion criteria >17 years), we decided to treat him with this agent in view of his progressing neurological deterioration and failure of the previous therapy. We assume that the combination of recovered host immunity and antiviral medication resulted in his gradual later improvement.

In summary, immunodeficiency places children at increased risk for severe WNV neurological disease. Early diagnosis and restoration of host immunity are crucial. Ribavirin, an experimental treatment for this infection, should be considered if spontaneous improvement does not occur.

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