Initial Seronegative West Nile Virus Encephalitis in an Immunocompromised Child

ABSTRACT:

We present a case of initial seronegative West Nile virus (WNV) encephalitis in an immunocompromised child due to B-cell Acute Lymphoblastic Leukaemia. Although diagnostic guidelines for WNV infection exist, we highlight that these may not be met in immunocompromised patients who may have a delayed immune response.

INTRODUCTION:

There have been frequent European outbreaks of West Nile virus (WNV) over the last decade with 2018 seeing a ten-fold increase in cases in Hungary and an eightfold increase across Europe, predominantly in Italy, Greece and Romania1. WNV, however, is not endemic in the United Kingdom. Although diagnostic guidelines for WNV infection exist2 3, we highlight that these may not be met in immunocompromised patients who may have a delayed immune response.

CASE REPORT:

A 7 year old girl with a history of B-cell Acute Lymphoblastic Leukaemia (ALL) on maintenance treatment (UKALL 2011 Regimen A), presented to her local District General Hospital (in a town in a suburb of London) with a history of two days of fever and headache. Her symptoms started a day before returning from a three week holiday in Hungary in August 2018. Her only reported outdoor activity was swimming in a local lake. There was no history of animal contact or insect bites. She had completed the third cycle of maintenance treatment, consisting of intrathecal methotrexate six weeks prior to the admission, intravenous (IV) vincristine and dexamethasone one month previously and was on daily 6-mercaptopurine. No blood products were given in the preceding month.

On presentation she was empirically treated for potential neutropenic sepsis with piperacillin/tazobactam and gentamicin while blood results were awaited. Her initial laboratory findings showed white cell count 4.8x109/L (normal range 6-13x109/L), neutrophils 4.4x109/L (normal: 2.0-8.0x109/L), lymphocytes 0.2x109/L (normal: 1.0-5.0x109/L), blood film demonstrated leucopenia but no blasts, C-reactive protein 3.9mg/L (normal: 0-5mg/L) with normal renal function, liver function and coagulation profile. Four days into her admission she developed focal seizures with eye deviation and dystonic posturing associated with autonomic dysfunction. These did not abate with IV lorazepam and IV phenytoin. She became encephalopathic and her seizures becoming generalised tonic clonic in nature. She was intubated and transferred to the tertiary hospital paediatric intensive care unit. Midazolam infusion was started for seizure control. Her antibiotic treatment was changed to meropenem and clarithromycin (to cover mycoplasma and other atypical organisms causing encephalitis), while anti-fungal cover with amphotericin B and antiviral treatment with aciclovir was added.

Contrast enhanced MRI head showed bilateral asymmetric non-enhancing thalamic punctate and speckled lesions of the left basal ganglia and midbrain. There was swelling and oedema of the right cerebellum. An EEG showed slow waveform in keeping with encephalopathy. NMDA receptor antibodies were negative. Cerebrospinal fluid (CSF) analysis performed after transfer to tertiary centre showed WCC 13 cells/μL (normal: <5 cells/uL), RBC<3 cells/μL (normal: <5 cells/uL) with normal protein (0.35g/L; normal: 0.15-0.45g/L) and glucose 3.5mmol/L.

Extensive microbiology investigations were performed for bacterial, viral and fungal pathogens including negative bacterial blood, urine and CSF cultures, negative 16s, mycobacterial, herpes simplex virus (HSV), varicella zoster virus (VZV), enterovirus, parechovirus, mumps PCR in CSF, negative blood PCR for Epstein-Barr virus, cytomegalovirus, adenovirus, HSV, VZV, human herpes viruses 6 and 7, negative respiratory viral panel PCR, negative cryptococcal antigen in CSF, HIV antigen/antibody negative, negative blood galactomannan and Beta D glucan and negative blood serology (IgM and IgG) for mycoplasma, tick borne encephalitis, rickettsia, leptospirosis, toxoplasma and sandfly fevers. On day 4 of symptoms, the patient’s serum pan-flavivirus PCR was negative, WNV IgM was 15.5 (cut off 15) and WNV IgG was negative 0.297 (cut off on 1.1). The IgM results were felt to be likely due to cross-reaction and not indicative of WNV infection. CSF results from day 7 from symptom onset were also negative for pan-flavivirus PCR. Repeat serum serology 8 days from symptom onset showed that WNV IgM was slightly lower at 14.5 (negative), and IgG 0.319 (negative). A repeat CSF sample sent 30 days from symptom onset demonstrated an elevated protein level but normal other parameters (WCC<3 cells/μL (normal: <5 cells/uL), RBC<3 cells/μL (normal: <5 cells/uL), protein 1.19g/L (normal: 0.15-0.45g/L) and glucose 3.1mmol/L). The CSF was not tested for pan-flavivirus PCR. However, serum on day 32 from symptom onset showed significant increases in both IgM and IgG; WNV IgM 443 and WNV IgG 4.855 confirming a diagnosis of West Nile virus encephalitis. The WNV testing (both PCR and serology) was performed at the national reference laboratory (Public Health England).

During the period of diagnostic uncertainty, the patient was treated empirically for presumed post-infectious autoimmune encephalitis with a three day course of IV immunoglobulin and a three day course of IV methylprednisolone. Unfortunately, despite intensive neurorehabitilation she developed asymmetric 4 limb dystonic cerebral palsy (Gross Motor Function Classification System Level 5). She passed away 21 months later due to ALL relapse.

DISCUSSION:

WNV is a single stranded RNA virus which is part of the *Flaviviridae* family and is transmitted from birds via the *Culex* mosquito vector4, although transmission can also rarely occur through blood products and organ transplantation5.

The incubation period for WNV is between 3-14 days5. Most patients (around 80%) are asymptomatic with WNV infection but if symptoms develop, these are usually non-specific such as fever, myalgia, nausea, vomiting, diarrhoea and maculopapular rash5 6. Progression of WNV infection into neuroinvasive disease (meningitis, encephalitis, acute flaccid myelitis) occurs in around one in 150 cases4. Management is supportive although case reports and series of treatments such as interferon alfa and IVIG have been described in the literature6.

The diagnosis of WNV relies on showing an antibody response (WNV IgM and IgG) in serum or CSF or determining the presence of WNV in blood or CSF (usually by detection of viral nucleic acid using PCR) or histologically in tissue2 3.

Although PCR is most sensitive in detecting WNV in CSF and serum, low level of viraemia at the time of clinical presentation may mean that WNV is undetectable.2 Serum WNV RNA levels become undetectable after a median of 6.1 days (day 15 in 95%) after the mosquito bite7 which may explain the negative PCR results in our patient. She also only had a relatively mildly raised CSF white cell count (WCC) despite severe clinical disease. One study8 reported up to 5% of patients with WNV meningitis / encephalitis had normal CSF WCC and that the CSF WCC was only a modest predictor of disease outcome. In addition, as she was very leucopenic at the time the CSF was undertaken, she may not have been able to mount a normal WCC reaction in the CSF.

If WNV IgM and IgG is positive, confirmation is required with a plaque reduction neutralizing test as there is cross-reactivity with other flaviviruses (e.g. St Louis Encephalitis virus, dengue, yellow fever)2. Data from unscreened blood donors suggest the median time from WNV RNA detection to IgM becoming positive is 3.9 days (10 days in 95% of cases), and IgG 7.7 days (16 days in 95%)7. However, seroconversion may be delayed or absent in immunocompromised patients2 due to decreased humoral response secondary to immunosuppression9,10 which we believe occurred in our case.

Cases of seronegative WNV encephalitis in immunocompromised adult patients are limited but have been summarised recently11. Only two paediatric cases of seronegative WNV encephalitis have been described in the literature. In one case WNV was transmitted through stem cell transplantation in a eight year old9 and in the other WNV was acquired while on immunosuppression post renal transplant in a 14 year old10. However, it is unclear if the seronegative results described in these cases were due to testing been performed too early in the disease course before the IgM seroconversion was detectable.

We describe a case of a child on treatment for ALL, with initial seronegative WNV encephalitis and seroconversion only confirmed six weeks after symptom onset. We hope this case highlights that immunocompromised children may not show the typical immune response to infection including for WNV and repeat serological testing should be done when there is diagnostic uncertainty especially if there is exposure history and clinical symptoms.

REFERENCES:

1 European Centre for Disease Prevention and Control. Surveillance Report West Nile virus Infection Annual Epidemiology report for 2018. 2019. Available from URL: <https://www.ecdc.europa.eu/sites/default/files/documents/west-nile-fever-annual-epidemiological-report-2018.pdf> [Accessed 16/4/20]

2 Centers for Disease Control and Prevention. Division of Vector-Borne Disease. West Nile Virus in the United States: Guidelines for Surveillance, Prevention, and Control. 2013. Available from URL: https://www.cdc.gov/westnile/resources/pdfs/wnvGuidelines.pdf [Accessed 29/6/2019]

3 Commissioning Implementing Decisions (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitons. Official Journal of European Union. 2018. Available from URL: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0945> [Accessed 16/8/20].

4 Bai F, Ashley Thomspon E, Vig PJS, Arturo Leis A. Current Understanding of West Nile Virus Clinical Manifestations, Immune Responses, Neuroinvasion, and Immuneotherapeutic Implications. Pathogens. 2019:8,193. Available from doi:10.3390/pathogens8040193

5 Anesei JA, Silveira FP. Arenavirus and West Nile Virus in solid organ transplant recipients: Guidelines from American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplantation. 2019;33:e13576. Available from doi:10.1111/ctr.13576

6 Herring R, Desai N, Pames M, Jarjour I. Pediatric West Nile Virus-Associated Neuroinvasive Disease: A Review of the Literature. Pediatric Neurology. 2019;92:16-25. Available from doi:10.1016/j.pediatrneurol.2018.07.019

7 Busch MP, Kleinman SH, Tobler LH, Kamel HT, Norris PJ, Walsh I, Matud JL, Prince HE, Lanciotti RS, Wright DJ, Linnen JM, Caglioti S. Virus and Antibody Dynamics in Acute West Nile Virus Infection. JID. 2008;198. Available from doi:10.1086/591467

8 Tyler KL, Pape J, Goody RJ, Corkill M, Kleinschmidt-DeMasters BK. CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. Neurology. 2006;66:361-365. Available from: doi:10.1212/01.wnl.0000195890.70898.1f

9 Kitagawa MG, Ettinger N, Erklauer J, Change E, Herce H, King K, Naik S. Transmission of West Nile Virus Through a Hematopoietic Stem Cell Transplant. Journal of Pediatric Infectious Diseases Society. 2018;7(2):e52-54. Available from doi:10.1093/jpids/pix100

10 Wilson MR, Zimmermann LL, Crawford ED, Sample HA, Soni PR, Baker AN, Khan LM, DeRisi JL. Acute West Nile Virus Meningoencephalitis Diagnosed Via Metagenomic Deep Sequencing of Cerebrospinal Fluid in a Renal Transplant Patient. American Journal of Transplantation. 2017;17:803-808. Available from doi:10.1111/ajt.14058

11 Goates C, Tsuha S, Working S, Carey J, Spivak ES. Seronegative West Nile Virus Infection in a Patient Treated with Rituximab for Rheumatoid Arthritis. The American Journal of Medicine. 2017;130(6):e257-e258. Available from doi:10.1016/j.amjmed.2017.01.014