CASE REPORT

Meningo-encephalo-myelitis in Children during the Zika Virus Epidemic in Grenada

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ABSTRACT

Zika Virus is neurotropic. We report two children from the Caribbean Island of Grenada, a three-year-old with acute neuro-inflammation who had intractable seizures, meningo-encephalitis, cerebrospinal fluid (CSF) pleocytosis and Zika Immunoglobulin M (IgM) positive acute serology and a four-year-old with acute demyelinating encephalomyelitis manifesting as generalized seizures, optic neuritis, diffuse cerebral dysfunction, encephalopathy, impaired speech and ataxia who also had CSF pleocytosis as well as Zika IgM and Dengue IgM positive acute serologies. Both cases occurred during the 2016 Zika and Dengue fever epidemics in Grenada. Both children recovered completely. The aetiologic role of the Zika and Dengue arboviruses is discussed.

Keywords: Caribbean, children, Dengue, Grenada, Meningo-encephalo-myelitis, Zika

WIMJ Open 2018; 5 (1): 43

BACKGROUND

For decades, arboviruses, in particular Dengue, have been a part of the landscape of Grenada, which is a Southern Caribbean Island with a population of 110 096 and an infant mortality rate of 14.5/1000 live births in 2015 (1, 2). In 2014, Chikungunya emerged with local transmission identified in 45 countries throughout the Americas and Caribbean and 1.7 million suspected cases (3). Chikungunya resulted in 89 childhood hospitalizations in Grenada and 404 reported cases in the under twenty-five-year population. It caused high fever with seizures and arthralgia in the children, but unlike cases in Jamaica did not precipitate encephalitis, or attributable mortality (4).

In 2016, Zika arrived in the Caribbean, including Grenada, where it has been co-circulating with Dengue and the emphasis has been on case surveillance for adult Guillain-Barre syndrome and fetal microcephaly (5, 6).

During the five-year period of 2011—2015, there were only two childhood admissions with the diagnosis of meningitis, or encephalitis, in 2012 and in 2014, respectively. However, during ZIKV's tenure in Grenada, increased cases of encephalitis and/or meningitis were observed in the three to fifteen-year age group, and also a high incidence of Guillain-Barre syndrome in adults. Zika was not initially identified as the aetiology, since Zika testing was not performed in patients presenting earlier and those transferred out were lost to follow-up. We now report herein children hospitalized in Grenada with acute neurological syndromes during 2016.

CASES

During 2016, seven children were admitted to The St George's General Hospital with varied neurologic syndromes. Five were withdrawn from this report; these included a 16 month old with bilateral lower limb weakness with an abnormal broad-based gait, from likely transverse myelitis with incomplete evaluation to confirm acute neuro-inflammation; a six-year-old with headaches followed by generalized seizures for 20−30 minutes with postictal quadriparesis, which resolved within six hours; a 15-year-old with sudden-onset

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 DOI: 10.7727/wimjopen.2017.227

hallucinations and unresponsiveness followed by abnormal gait, disorientation, agitation, muffled speech, who had negative toxicology screen and magnetic resonance imaging (MRI) brain scan, whose symptoms completely resolved after four days; a 15-year-old male with a one week prodrome of left frontal-parietal headaches and fever, who later developed nuchal rigidity, photophobia, generalized tonic clonic seizures, lethargy and right hemipareisis whose radiological imaging confirmed sinusitis and subdural empyema, who was treated successfully with ceftriaxone and vancomycin who was also ZikaV and Dengue IgM seropositive and finally, a suspected case of accidental ingestion of a psychotropic agent. The remaining two neurological cases in children are reported, as follows.

RC, a four-year-old male who had a normal perinatal history and no significant past medical history was hospitalized on August 20, 2016, with a history of sudden onset of headache. He reported this at 5:30 am on the morning of admission, had breakfast and was seated near to his father on the stairs when he slumped, became unresponsive and had a five-minute generalized tonic-clonic seizure. He was rushed to the peripheral hospital where he was noted to be "stretching out", vomited and remained unresponsive. There was no history of ingestion, head injury or fever and no family history of asthma.

On admission, he was sleepy and afebrile with normal vital signs; glucose by finger stick was 86 mg/dL. Pupils were pinpoint and non reactive and his neck was supple. The Glasgow coma scale (GCS) for pediatrics was 10/15. Reflexes was 2^{+}, Babinski positive. Temperature rose to 100.8F and he was cultured and started on IV ampicillin and ceftriaxone to cover for sepsis. Significant investigations revealed white blood cells (WBC) was 17.8 (10^3/uL) with, 81.6% neutrophils (N) and 11.2% lymphocytes monocytes (L) 6.5%, eosinophils 0.2%. Haemoglobin (Hg) 12.0 (g/dL), hematocrit (HCT) 35.0%, mean corpuscular volume (MCV) 76.6 (f/L), platelets (PLT) 342 (10^3/uL). Erythrocyte sedimentation rate (ESR) 58 (mm/hr), magnesium (Mg): 2.7 (mg/dL), calcium (Ca): 10.4 (mg/dL). Sodium (Na): 146 (mmol/L), potassium (K) 4.9 (mmol/L), chloride (CL) 103 (mmol/L), carbon dioxide (CO_2) 15 (mmol/L), blood urea nitrogen (BUN) 10 (mg/dL), creatinine 0.4 (mg/dL). Lactate dehydrogenase (LDH) 673 (U/L). Liver punction test (LFT) results were within normal limits.

Within 12 hours, he was alert and oriented and seemed stable but by twenty-four hours he had visual and auditory hallucinations. He developed dystonic movements, frothed at the mouth then had a generalized tonic-clonic seizure with urinary and fecal incontinence accompanied by bizarre behavior: biting, grabbing, thrashing and unresponsiveness. He was managed with diazepam. He had a second fit within twenty-four hours and was loaded with sodium phenytoin. A computerized tomography (CT) Scan of the head was normal. On day five of admissions, encephalitis was suspected based on continuation of bizarre behaviour, seizures and failure to respond to high dose antibiotics/anticonvulsants. Cerebrospinal fluid (CSF) evaluation revealed 7620 cells/mm^3, glucose 68 mg/dL, protein 505 mg/L. Cerebrospinal fluid culture showed no growth and no differential was done on the CSF cell count. Zika IGM was positive and Dengue IGG/IGM was positive. No arbovirus polymerase chain reaction (PCR) testing was available and no herpes testing was available. He was switched to vancomycin and acyclovir was advised.

The patient had approximately 17 to 20 episodes of seizures daily, all generalized tonic-clonic with duration ranging from 5 to 60 seconds. He also continued with visual and auditory hallucinations with aggressive behaviour and use of obscene language. Valproic Acid was added in an attempt to reduce the superficial seizures. He was transferred to Trinidad. Where he was treated with IV acyclovir and his repeat MRI confirmed changes in the limbic area of the brain. He is back at school and has not reported any new neurological events. He is off medication at this time.

SM is a three-year-old male, with a past history of asthma and a normal perinatal history, he was admitted on October 17, 2016 with a history of sudden hysterical crying followed by a twenty-minute generalized tonic-clonic seizure, without urinary or fecal incontinence. He was taken to the nearest health facility where his temperature was recorded as 38.4 °C. He was unresponsive to painful stimuli. There was no history of fever, head injury, ingestion of poisonous substances or headache. His immunizations were up to date and his milestones were on target. Family history was negative for seizures. He was transferred to the General Hospital. On admission his vital signs were: RR24, P134, T99.4F, Sat 98% on RA. He was lethargic and confused. There was no nuchal rigidity, but he had a bruised lower lip with a hyperaemic right tympanic membrane. All systems were normal. Investigations revealed WBC: 13.9 10^3/uL with 77.8% neutrophils, 14.1% lymphocytes, Hg 12.2 g/dL, HCT 36.6%, red blood cell (RBC) 4.5 10^6/uL, MCV 81.6 fL, PLT 433 10^3/uL. Sodium 140 mmol/L, K 4.1 mmol/L, CL 104 mmol/L, CO_2 12 mmol/L, BUN 12 mg/

dL, Creatinine 0.3 mg/dL, alanine transaminase (ALT) 19 U/L total Bilirubin 0. Mg/dL1. The erythrocyte sedimentation rate (ESR) 13 mm/hr, Ca: 9.6 mg/dL, Mg: 2.1 mg/dL, phosphate (PO4): 4.1 mg/dL. Lactate dehydrogenase: 936 U/L. Non contrast CT of the head was negative. Mid-stream urine and blood cultures revealed no growth. He was commenced on IV ampicillin for his otitis media. On day two of admissions he had his second generalized seizure and these progressed with each hospital day. He was loaded on phenytoin and cefotaxime was added to his antibiotic regime. His seizures continued on maintenance phenytoin and did not respond to the addition of so oral carbamazepine. A CT scan of the head was negative. A lumbar puncture was revealed: cell count was not done, glucose – 59, protein – 357 and culture no growth. Toxicology screen returned negative.

Magnetic resonance imaging showed diffuse high signal in the periphery of the cortical white matter of the parietal, posterior temporal and occipital lobes suspected as mild encephalitis, electroencephalography (EEG) was reported as moderately frequent episodes of duration up to two seconds of bilateral sharp and slow waves without lateralization; compatible with seizure disorder. His seizures continued in spite of phenytoin and carbamazepine so he was weaned off the carbamazepine and switched to valproic acid with some improvement.

A repeat spinal tap revealed cerebrospinal fluid (CSF) 50 cells, glucose – 64, protein – 319. He was started on acyclovir and vancomycin while awaiting transfer to Trinidad for care. Seizures continued. Phenobarbital was added with some success. Zika IGM was positive no Dengue titre was done.

About a month after administration to hospital, he lost vision with a normal fundoscopy. He was transferred to the San Fernando General Hospital to access care of a pediatric neurologist. He was diagnosed with optic neuritis, diffuse cerebral dysfunction, encephalopathy, impaired speech and ataxia. He was treated with high dose IV methylprednisone and immunoglobulin (IVIG). His EEG in Trinidad showed no epileptiform activity but diffuse slowing suggestive of encephalopathy. Visual evoked potentials (VEP) showed bilateral optic nerve dysfunction. He was discharged after 6 weeks, regained his vision and is asymptomatic with normal neurologic examination on last clinic visit in 10 weeks after admission.

DISCUSSION

Zika is a neurotropic virus and its deleterious effects in children have been focussed in newborns affected by mother-to-child transmission with subsequent inflammation of the fetal brain resulting in microcephaly, sensorineural hearing loss and blindness, as well as nervous system involvement in adults who develope Guillain-Barre syndrome (7, 8). However, little attention has been focussed on infections in children with Zika virus infections acquired postnatally and the likely possibility of attributable neurological complications.

Meningo-encephalitis, or encephalitis associated with Zika, including its association with immune activation, has been described in a few adult case reports (9–12), while there are no reports in young children. Acute disseminated (or demyelinating) encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating condition primarily involving the white matter of the brain and spinal cord, usually presenting as an acute-onset encephalopathy associated with polyfocal neurologic deficits and is typically self-limiting. While a few cases of ADEM occurring during the ZIKV epidemic have been reported in adults and in adolescents, reports of young children with postnatal ZIKV infection are notably absent from the literature (13, 14).

On this background, ZIKV's relationship to meningo-encephalitis in paediatric patients in Grenada's Island-population is now being questioned. Herein, we report a three-year-old and a four-year-old, respectively, with supporting clinical, laboratory and radiological evidence for meningo-encephalitis with diagnostic serology for acute Zika and Dengue co-infection as well as ADEM associated with acute Zika infection. Common presentations in both included uncontrollable seizures with altered mental status from encephalopathy and evidence for acute neuro-inflammation with diagnostic cerebrospinal fluid pleocytosis for encephalitis. While the second child also experienced optic neuritis, impaired speech and ataxia. Despite their stormy hospital courses, both children survived and experienced complete recovery.

Neither of these young children reported a viral prodromal phase. Zika is known to be symptomatic in 15–20% of cases, with acute presentations of fever, rash, conjunctival hyperaemia, arthralgia and other symptoms, while 80–85% are asymptomatic, as in our two cases.

Melbourne-Chambers *et al*, as well as Williams and Ali, from Jamaica, another Caribbean Island, reported on several adolescents with acute weakness associated with acute neuro-inflammation, during the 2016 Zika and Dengue fever epidemics there (13–15). The five adolescents with acute neuro-inflammation reported by

Melbourne-Chambers, included three with transverse myelitis, one with Guillain-Barre syndrome and the other with ADEM (13). Soares *et al* reported on ZIKV encephalitis in an adult, like our two patients, whose neurological picture developed rapidly and aggressively; unfortunately their patient suffered fatal brain death shortly after admission (12). Involvement of the optic nerve has been described in infants with intrauterine infection, while optic neuritis, in the setting of encephalopathy with impaired speech and ataxia was identified in one of our patients with positive ZikV IgM titres. However, the contributing role of Dengue should also be questioned, as Fong *et al* reported myelopathy, encephalopathy, delirium and ophthalmoplegia following a three-day history of high-grade fever in an adolescent with Dengue fever (16).

The urban-human cycle of the *Aedes aegypti* mosquito and the possibility of endemicity that exists for Dengue, Zika and Chikungunya viruses co-circulation in Caribbean Island populations raises the question of whether these neurological outcomes are caused by genetic mutations or if prior infection by the other flaviviruses may affect Zika disease outcome. The real question, as suggested by *in vitro* data, is whether Dengue virus infections result in antibody-dependent enhancement of Zika virus infections (17). Therefore, further information about the contribution of these viruses to these neurological and other complications in children could be explored through the ZikAction and ZikAlliance population-based epidemiological cohort studies which were recently funded by the European Commission (18).

ACKNOWLEDGEMENTS

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 734857.

REFERENCES

1. Panagos A, Lacy ER, Gubler DJ, Macpherson CNL. Dengue in Grenada. Rev Panam Salud Publica. 2005; **17:** 225–9.
2. Registry of Grenada – 2015.
3. Centers for Disease Control and Prevention. Where has Chikungunya virus been found? [https://www.cdc.gov/chikungunya/geo/]. Last updated, [22 April, 2016].
4. Christie CDC, Melbourne-Chambers R, Ennevor J, Young-Peart S, Buchanan T, Scott-Brown P et al. Chikungunya in Jamaica–public health effects and clinical features in children. West Indian Med J 2016; **65:** 431–8.
5. Centers for Disease Control and Prevention. Zika Virus in Grenada. [https://wwwnc.cdc.gov/travel/destinations/traveler/grenada]. Last updated, [10 March, 2017].
6. Pan American Health Organization / World Health Organization. Zika - Epidemiological Report Grenada. March 2017. Washington, D.C.: PAHO/WHO; 2017 [http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=35140&Itemid=270]. [16 March, 2017].
7. Rasmussen S, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects – reviewing the evidence for causality. N Engl JMed 2016; **374:** 1981–1987.
8. dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK et al. Zika virus and the guillain–barré syndrome–case series from seven countries. N Engl J Med 2016; **375:** 1598–601, doi: 10.1056/NEJMc1609015.
9. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S et al. Zika virus associated with meningoencephalitis. N Engl J Med 2016; **374:** 1595–6. doi: 10.1056/NEJMc160296.
10. Niemeyer B, Niemeyer R, Borges R, Marchiori E. Acute disseminated encephalomyelitis following zika virus infection Eur Neurol 2017; **77:** 45-6. doi: 10.1159/000453396.
11. Galliez RM, Spitz M, Rafful PP, Cagy M, Escosteguy C, Germano CSB. Zika virus causing encephalomyelitis associated with immuno-activation. Open Forum Infect Dis 2016; 3 doi: https://doi.org/10.1093/0fid/ofw203.
12. Soares CN, Brasil P, Carrera RM, Sequeira P, de Filippis AB, Borges VA et al. Fatal encephalitis associated with Zika virus infection in an adult. J Clin Virol 2016; **83:** 63–5.
13. Melbourne-Chambers R, Christie CDC, Greenaway E, Bullock R. Acute paralysis and neuro-inflammation in Jamaican children during Zika virus and dengue epidemics of 2016 West Indian Med J 2016; **65:** 425–30. doi,10.7727/wimj.2016.526.
14. Williams M, Ali A. Zika Outbreak Associated Neurological Syndromes in Jamaica, West Indian Med J 2016; **65:** 438–41, doi:10.7727/wimj.2016.511.
15. Webster-Kerr KR, Christie CDC, Grant A, Chin D, Burrowes H, Clarke K et al. Emergence of zika virus epidemic and the national response in Jamaica. West Indian Med J 2016; **65:** 243–9.
16. Fong YC, Ko MM, Alan K, Peter B, Lim WK, Rozalli FI et al. Mild encephalitis/encephalopathy with reversible splenial lesion (mers) due to dengue virus. J Clin Neurosci **36:** 73–5.
17. Halstead SB. Biologic evidence required for zika disease enhancement by dengue antibodies. Emerging Infectious Diseases 2017; **23:** doi: http://dx.doi.org/10.3201/eid2304.161879].
18. Christie CDC, Giaquinto C. Unraveling the paediatric and perinatal zika virus epidemic through population-based research. West Indian Med J 2016; **65:** 239–42.

Received October 25, 2017
Accepted December 18, 2017
Published May 02, 2018
Online: www.mona.uwi.edu/wimjopen/article/11537