

Acute Paralysis and Neuro-inflammation in Jamaican Children during Zika Virus and Dengue Epidemics of 2016

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ABSTRACT

Dengue, Chikungunya virus (CHIKV) and Zika virus (ZIKV) are all transmitted by the Aedes aegypti mosquito and are currently circulating in Jamaica. Jamaica has been experiencing a ZIKV epidemic since February 2016. At the University Hospital of the West Indies (UHWI), Kingston, Jamaica, a cluster of five cases of paralysis attributed to neuro-inflammation was noted amongst adolescents admitted to the institution. Three were diagnosed with acute myelitis and one each with acute disseminated encephalomyelitis (ADEM) and Guillain Barre syndrome (GBS). In these patients, there were common presenting symptoms, characteristic findings of peripheral nerve involvement and a history of contact with persons with symptoms of possible ZIKV in the majority. In only one case was a viral association, Dengue infection, confirmed. This case series suggests a unique clinical pattern of neuro-inflammation in Jamaican adolescents occurring during the ZIKV epidemic and questions the role of the three circulating arboviruses in the pathogenesis.

Keywords: Caribbean, encephalitis, Jamaica, myelitis, paralysis, ZIKV

Parálisis Aguda y Neuro-inflamación en los Niños Jamaicanos Durante las Epidemias de Virus del Zika y el Dengue de 2016

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RESUMEN

Los virus del dengue (DENV), Zika (ZIKV) y Chikungunya (CHIKV) son todos transmitidos por el mosquito Aedes aegypti y están circulando actualmente en Jamaica. Jamaica ha estado experimentando una epidemia de ZIKV desde febrero de 2016. En el Hospital Universitario de West Indies (HUWI), Kingston, Jamaica, se observó un grupo de cinco casos de parálisis atribuida a neuro-inflamación, entre adolescentes ingresados a la institución. Tres fueron diagnosticados con mielitis aguda y uno con encefalomiелitis diseminada aguda (EMAD) y síndrome de Guillain-Barré (SGB). Estos pacientes se caracterizaron por la manifestación de síntomas comunes, hallazgos característicos del compromiso de los nervios periféricos, y una historia de contacto con personas con síntomas de posible ZIKV en su mayoría. Sólo en un caso se confirmó una asociación viral: infección por dengue. Esta serie de casos sugiere un patrón clínico único de neuro-inflamación en los adolescentes jamaicanos durante la epidemia de ZIKV y cuestiona el papel de los tres arbovirus circulantes en la patogénesis.

Palabras claves: Caribe, encefalitis, Jamaica, mielitis, parálisis, ZIKV

INTRODUCTION

Jamaica experienced epidemics of Dengue, Chikungunya virus (CHIKV) and Zika virus (ZIKAV) in 2012, 2014 and 2016, respectively (1, 5). There has only been one case of acute associated paralysis in children at University Hospital of the West Indies during the most recent Dengue and CHIKV epidemics (4, 5). We report five cases of acute weakness associated with neuro-inflammation in fully immunized adolescents admitted to the UHWI during the 2016 ZIKAV epidemic.

CASE REPORTS

Case 1

A 12-year-old female was admitted on June 10, 2016, with a history of severe global headache with phonophobia, unsteady gait and a feeling of “faintness” eight days previously. There was a red, raised, pruritic rash which spread from cephalocaudally, myalgia of the lower limbs and arthralgia of both knees. There was also severe periumbilical abdominal pain, vomiting, decreased urinary frequency and straining to pass stool. There was back pain worsened by neck flexion and low grade fever. There was no recent travel but there were household and school contacts with rash, muscle and headaches.

There was tenderness of both breasts and the mid-thoracic spine, weakness of the left face and of all extremities with generalized hyper-reflexia and flexor plantar responses. There was hyperaesthesia at T10 and impaired vibration at both ankles. The anal wink was absent. Magnetic resonance imaging (MRI) of the brain on day 9 of illness was normal. Magnetic resonance imaging of the spine revealed high T2 signal of the cervical portion of the spinal cord, C2 to C7 which also appeared enlarged (Fig. 1). There was no enhancement with Gadolinium. This was consistent with transverse myelitis.

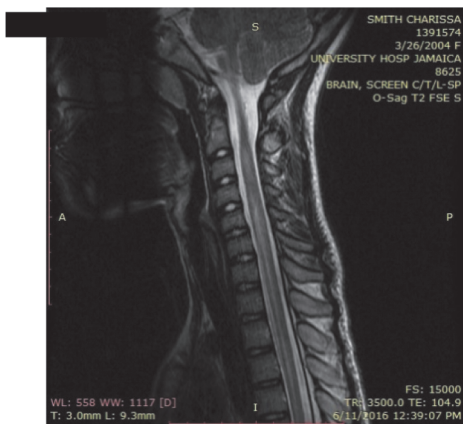


Fig. 1: T2 weighted sagittal magnetic resonance imaging (MRI) of the cervical and thoracic spine showing high signal intensity C2 to T4.

Routine haematology and chemistry were normal. The collagen vascular screen was negative. Cerebrospinal fluid (CSF) protein was 454 mg/L, CSF glucose was normal and negative for oligoclonal bands. Serological tests performed on day 9 of illness for Dengue, CHIKV and ZIKV immunoglobulin M and ZIKV, polymerase chain reaction (PCR) were

negative; CSF ZIKV PCR was also negative. Results of stool viral cultures are pending.

She was treated with intravenous methylprednisolone at 30 mg/kg/d for five days followed by a taper with prednisone. Four weeks later, her symptoms had resolved and her neurological examination was normal.

Case 2

A 15-year-old female was admitted on June 12, 2016 with a history of severe, pounding frontal and right-sided headache occurring six days prior and vomiting with vertigo, low grade fever, diplopia and unsteady gait three days prior. One day prior, she developed malaise, vomiting and a tingling sensation of the left hemibody and right hand. There was no travel history but two household contacts had fever, rash and joint pain. She had experienced severe dengue in April 2016. She was drowsy and there was nystagmus and mild left facial weakness. There was hypotonia and weakness of all limbs with distal hyporeflexia and flexor plantar responses. There was impaired coordination of the lower limbs and left upper limb and the Romberg sign was positive. The gait was wide-based and unsteady. There was hyperaesthesia of the right face. Ophthalmology evaluation was normal.

Magnetic resonance imaging brain on day 7 of illness revealed T2 hyperintense signal within the white matter of the parietal lobes, right crus cerebri, pons, medulla, middle cerebral peduncles and both thalami consistent with ADEM (Fig. 2).

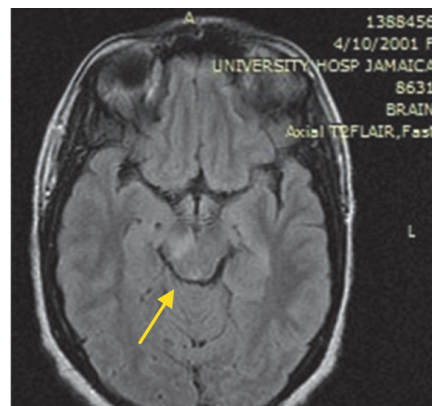


Fig. 2: Axial T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) brain showing high signal intensity of the right crus cerebri (yellow arrow).

Cerebrospinal fluid (CSF) analysis showed 28 WBC/mm³ (98% lymphocytes), normal CSF glucose and protein of 499 mg/L. The collagen vascular screen was negative. Virology tests on day 7 of illness showed CSF and PCR negative for ZIKV and serology negative for ZIKV PCR and CHIKV IgM but positive for Dengue IgM. Stool and nasopharyngeal cultures are pending.

She was treated with high dose methyl prednisolone for five days followed by a taper with prednisone. Eight weeks later, the neurological examination was normal.

Case 3

A 13-year-old male was transferred from another hospital to UHWI on June 13, 2016, with a history of inability to walk for 10 days. This was preceded by fatigue and drowsiness one week before. He was unable to wiggle the toes and experienced paresthesiae in the lower limbs. There was difficulty passing stool, initiating micturition and controlling the urinary stream and one week later he experienced diplopia. There were no other prodromal symptoms but there were numerous contacts with fever, rash and conjunctivitis. Examination revealed ptosis and horizontal nystagmus. There was wasting of both lower limbs with pes cavus deformities, hypotonia and weakness. There was hyper-reflexia at the knees and areflexia at the ankles. The plantar responses were extensor. There was impaired sensation, temperature and vibration, to T10. Ophthalmology evaluation was normal.

Magnetic resonance imaging of the brain and spine on day 10 of illness were normal. The CSF glucose was normal; CSF protein was 502 mg/L. The collagen vascular screen was negative. Serology for Dengue IgM, ZIKV IgM and ZIKV PCR performed on day 10 of illness were negative. Chikungunya virus IgM was equivocal.

A diagnosis of acute myeloneuropathy was made and he was treated with high dose methylprednisolone for five days followed by a prednisone taper. Four weeks later, there was persistent nystagmus, mild lower limb weakness and brisk deep tendon reflexes.

Case 4

A 12-year-old male was admitted on June 26, 2016, with a history of sore throat, fever, drowsiness and lethargy for six days and joint pains and inability to walk for three days. He then developed paresthesiae of the right upper limb and both lower limbs and headache. There was one episode of vomiting five days prior and he developed weakness of the legs and arms and complained of a shock like sensation in the lower limbs three days prior. There was no travel history but there was an ill contact with fever, rash and red eyes two weeks before. The pulse rate was 77 beats per minute (bpm), respiratory rate 16/min and blood pressure 123/97 mmHg. There was tenderness of the abdominal flanks and normal anal tone. He was drowsy with nuchal rigidity, bilateral lower facial weakness and a decreased gag reflex. There was hypotonia and grade 1 power of all limbs with areflexia in the lower limbs. There was impaired sensation to the level of the T10 dermatome. Routine haematology and chemistry were normal. Cerebrospinal fluid analysis showed 25 white blood cells (WBC)/mm³, normal glucose and protein at 837 mg/L.

Serology on day 7 of illness was negative for Dengue IgM; ZIKV IgM was not available. HSV 1 and 2 IgG were positive. He was diagnosed with GBS and treated with intravenous immunoglobulin at 2 g/kg in divided doses over five days. There was intercurrent herpes labialis. There was gradual improvement in muscle strength but hypertension persisted for 21 days. He started ambulating after nine weeks. There

was wasting of all muscle groups and truncal and axial hypotonia. There was weakness of the masticatory muscles, grade 4 power of the small muscles of the hands and lower limbs and hypo-reflexia of the lower limbs.

Case 5

A 12-year-old female adolescent was admitted on September 22, 2016, with a history of numbness of the hands and feet, difficulty walking and pain of the neck and spine for one day. The numbness and tingling began in the fingers of the left hand and progressed proximally then the right upper limb became involved similarly. She also experienced a “shocking” pain to the cervical spine and tingling, numbness and weakness to both lower limbs. There was throbbing, global headache and pain behind the eyes. There was no ill contact or recent travel. One day prior, she experienced pain to the left-side of the thorax and left upper abdomen, swelling and weakness of the left hand and inability to walk. She also had difficulty passing urine and stool.

There was mild left facial weakness and wasting of the left mid-palmar and hypothenar muscles and bilateral pes cavus deformity of the feet, left moreso than the right. There was hypotonia of the left upper and lower limbs, grade 4 power of the left upper and lower limbs and grade 3 power at the left wrist. There was hyper-reflexia at the knees and hypo-reflexia at the left ankle. The left plantar response was extensor. There was impaired sensation of the right hemibody to the level of T4 and hyperaesthesia of the right face. Ophthalmology evaluation was normal.

Magnetic resonance imaging head and spine performed on day 2 of illness showed no intracranial pathology but enhancement of the spinal cord at the level of C2 to C7 consistent with transverse myelitis (Fig. 3).

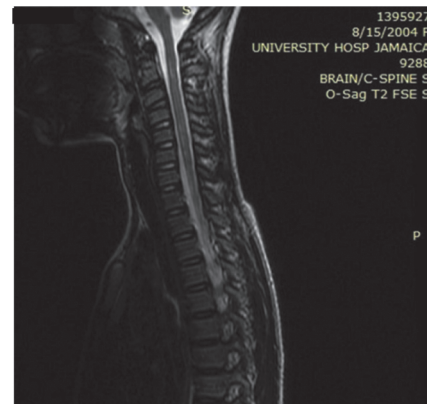


Fig. 3: T2 weighted sagittal magnetic resonance imaging (MRI) of the cervical spine showing high signal intensity C2 to C7.

Cerebrospinal fluid analysis was normal. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were normal and the collagen vascular screen was negative. She was treated with high dose methyl prednisolone for five days followed by a prednisone taper. Virology results are outstanding.

The following tables (Tables 1 and 2) summarize the clinical details of the cases.

Table 1: Demography and symptoms of adolescents admitted to the University Hospital of the West Indies (UHWI) with acute weakness and neuro-inflammation, 2016

Case #	Age (yrs)	Gender	Viral symptoms	Headache	Vomiting	Paresthesiae	Neck/back pain	Bowel/ bladder symptoms
1	12	F	Fever, rash, myalgia, arthralgia	+	–	–	+	+
2	15	F	Fever	+	+	+	–	–
3	13	M	–	–	–	–	+	+
4	12	M	Fever, sore throat, arthralgia	+	+	+	–	+
5	12	F	–	+	–	+	+	+

Key: + Present – Absent

Table 2: Clinical and neuroimaging findings in adolescents admitted to the University Hospital of the West Indies (UHWI) with acute weakness and neuro-inflammation, 2016

Case #	Drowsiness	Facial weakness	Muscle wasting	Muscle weakness	Hyperaesthesiae	Sensory loss	MRI findings	Clinical diagnosis
1	–	+	–	Upper and lower limbs (LL)	–	+(vibration, distal LL)	Transverse myelitis	Transverse myelitis
2	+	+	–	Upper and lower limbs	+	–	ADEM	ADEM
3	–	–	Bilateral pes cavus	Lower limbs	+	+(Sensory level T10)	Normal	Acute myeloneuropathy
4	+	+	–	Upper and lower limbs	+	+(Sensory level T10)	Not done	Guillain Barre Syndrome
5	–	+	Left hand muscles Bilateral pes cavus	Left upper and lower limbs	+	+(right hemibody sensory level T4)	Transverse myelitis	Acute myeloneuropathy

Key: + Present – Absent

DISCUSSION

In this case series of acute neuro-inflammation occurring in adolescents at UHWI, headache, neck/ back pain, paresthesiae and bowel and bladder dysfunction were common symptoms and facial weakness, sensory loss and hyperaesthesiae were common signs. Peripheral nerve involvement was seen in all cases. All three cases with myelitis also had evidence of peripheral nerve involvement with small muscle wasting in two (Cases 3 and 5) and distal sensory loss in Case 1. Case 2 who was diagnosed with ADEM also had findings of peripheral

nerve involvement. Four cases had elevated CSF protein supporting an inflammatory process, however, the virology results were positive in one case only, a 15-year-old with ADEM who had severe dengue two months prior to this presentation.

The occurrence of ADEM and myelitis in Dengue are rare (6–9). Guillain Barre syndrome (GBS) has been more commonly linked to dengue infection in a number of cases series associated with hypokalemic paralysis but also with demyelination (10, 11). The neurologic syndromes associated with Dengue have also been reported in a case series from

Jamaica (12); GBS was diagnosed in 3.7% but there were no cases of acute myelitis. Similarly GBS has been described in CHIKV (13–15) but myelitis and ADEM are less common. ZIKA virus has been linked to congenital microcephaly (16). Severe axonal GBS has also been characterised in ZIKA V but myelitis and ADEM occur less commonly (17, 18). The neurologic complications in children have not been widely reported.

This clustering of cases of acute weakness and neuro-inflammation in adolescents at the UHWI was an unusual occurrence. The pervasive finding of peripheral nerve involvement in all cases – GBS, acute myelitis and ADEM suggests that this may be a unique syndrome. In this series, the cases presented acutely and most experienced rapid recovery suggesting a para – infectious cause. Enterovirus 68 and 71 are associated with epidemics of acute flaccid paralysis (19, 20) but are unlikely in this case series as there was a lack of enteric and respiratory acute prodromal symptoms. West Nile virus, another flavivirus, may also cause acute flaccid paralysis (21). The positive titre for Dengue in Case 2 may have reflected persisting IgM antibodies following severe Dengue two months previously. Dengue IgM has been reported to remain detectable for over three months (22). Polio is unlikely as Jamaica had its last case of poliomyelitis in 1982 (23) and has very high coverage rates (approximately 90%) for polio (24). Jamaica has been participating in the switch from trivalent to bivalent oral polio vaccine (25). Additionally, in this cohort, all children were appropriately immunized for age.

The World Health Organization (WHO) has declared that the cluster of cases of microcephaly and other neurological disorders linked to ZIKA V and reported in Brazil and in French Polynesia constitutes a Public Health Emergency of International Concern requiring a coordinated international response (26). One wonders if the neurological complications herein described, could be related to ZIKA V singly or in combination with the other circulating arboviruses. These complications are best clarified by population-based studies, like those being planned by the Zik Action consortium in Latin America, Europe and the Caribbean (27).

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