Clinical/Scientific Notes

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ACUTE ZIKA INFECTION WITH CONCURRENT ONSET OF GUILLAIN-BARRÉ SYNDROME

Case report. A 47-year-old Tongan male returning to New Zealand after a 2-week holiday in Tonga presented with 3 days of progressive limb weakness, numbness, unsteady gait, and dyspnea. Two days before departing Tonga (6 days before neurologic symptoms), he developed leg swelling with erythematous and pustular lesions, which were treated with flucloxacillin. He had no medical history, was not taking regular medication, and had a 20 pack-year smoking history.

Examination findings included the following: afebrile, pulse 80 beats/min, blood pressure 150/90 mm Hg, respiration 20 breaths/min, and oxygen saturation 98% (air). Cardiovascular and abdominal examinations were unremarkable. Cranial nerves and eye movements were normal. Limbs were hypotonic with globally reduced power (4/5), areflexia, and absent plantar responses. Temperature and pain sensation were impaired in hands and feet. Proprioception and vibratory sensation were impaired in the feet. Romberg test was positive.

Full blood count, renal function, electrolytes, creatinine kinase, hemoglobin A_{1c}, C-reactive protein, thyroid function, B_{12}, and folate were normal. Liver enzymes were mildly elevated (ALP 122, GGT 251, and ALT 41 IU/L). Antinuclear antibody was 1:160. CSF showed albuminocytologic dissociation: protein 0.69 g/L (reference 0.15–0.45), white blood cells 2/μL, red blood cells 1/μL, and glucose 3.4 mmol/L (serum glucose 6.0). Spine MRI and chest x-ray were unremarkable. Normal cranial MRI excluded concurrent acute disseminated encephalomyelitis. Nerve conduction study on day 2 of admission revealed demyelinating, predominantly motor, polyneuropathy (table).

Serum reverse transcription (RT)-PCR on day 3 after illness onset was negative for chikungunya and dengue RNA and positive for Zika RNA (subsequently negative on day 13). Dengue NS1 antigen (Platelia Dengue NS1; Bio-Rad, Hercules, CA) was negative. Immunoglobulin (Ig)M antibodies (low level) and IgG antibodies (high level) against Zika (EUROIMMUN, Luebeck, Germany) and dengue (PanBio, Brisbane, Australia) were detected on day 3. CSF RT-PCR on day 5 was negative for all 3 viruses.

A diagnosis of Guillain-Barré syndrome (GBS) was made. Worsening respiratory function required ventilation support. Five days of Ig was given (0.4 g/kg/d). Serial quantitative neurologic examination showed a steady decline. He was then given 6 plasma exchanges beginning 5 days after the last dose of Ig, i.e., from day 10 of treatment. Respiratory status improved to not requiring mechanical ventilation by day 21. At day 33, when transferred to rehabilitation, he had persistent limb weakness with best power grade 3/5 and remained bedbound.

Discussion. This case illustrates rapid development of severe acute demyelinating polyneuropathy linked with Zika virus infection. The pustular leg spots were probably infected mosquito bites, although the erythematous skin lesions may have also been related to Zika infection. There are no case reports of Zika-related GBS in New Zealand. There are reports of GBS associated with Zika infection in French Polynesia, South Pacific islands, and South and Central America.[1] It is noteworthy in our case that Zika was detected by PCR in the serum while his clinical status was worsening. RT-PCR for Zika is sensitive and detects viral RNA concentrations as low as 900 copies/mL with high specificity and no cross-reactivity to other flaviviruses including dengue, West Nile, and chikungunya.[2] Although the underlying mechanism remains unclear, GBS has been associated with other flaviviruses (dengue,[3] West Nile virus,[4] etc.). In this case, we demonstrated no evidence of direct CNS infection (negative CSF Zika PCR and normal cranial MRI) but clear evidence of simultaneous systemic Zika infection contemporaneous with the appearance of GBS.

Serologic cross-reactivity between flaviviruses means that currently available IgM antibody assays cannot reliably distinguish between Zika and dengue.[5] The PCR and serology results suggested that the patient had a likely secondary flavivirus infection—a recent Zika virus infection in the context of preexisting anti-dengue antibody.

Unlike recent GBS case reports from 2014 to 2016 with only positive Zika serology (IgM), our case is of particular interest because Zika virus was present in the serum at the same time that GBS was developing. This suggests either direct neural injury by Zika or

Table Nerve conduction study

Type of study	Nerve/site, right	Recording site	Latency, ms	Amplitude, μV	Distance, cm	Velocity, m/s
Sensory	Median/wrist	Digit II	3.91	6.6	13	43.0
Sensory	Ulnar/wrist	Digit V	3.07	5.8	11	49.1
Sensory	Radial/forearm	Thumb	2.19	31.5	11	66.0
Sensory	Sural/calf	Lateral malleolus	3.75	16.3	14	48.9
Motor	Median/wrist	APB	13.54	0.5	7	
Motor	Median/elbow	APB	18.13	0.6	25	54.5
Motor	Ulnar/wrist	ADM	6.88	2.3	6.5	
Motor	Ulnar/below elbow	ADM	11.72	1.1	25	51.6
Motor	Ulnar/above elbow	ADM	13.80	1.7	14	67.2
Motor	Common peroneal/ankle	EDB	12.60	0.9	9	
Motor	Common peroneal/fibula head	EDB	19.58	0.8	34	48.7
Motor	Common peroneal/knee	EDB	21.88	0.8	10	43.6
Motor	Tibial/ankle	AH	9.79	0.8	9	
Motor	Tibial/knee	AH	20.36	0.8	44	41.6
F wave	Median/wrist	APB	No response			
F wave	Ulnar/wrist	ADM	No response			
F wave	Common peroneal/ankle	EDB	No response			
F wave	Tibial/knee	AH	No response			

Abbreviations: ADM = abductor digiti minimi; AH = abductor hallucis; APB = abductor pollicis brevis; EDB = extensor digitorum brevis.

rapid cellular-mediated response to Zika "molecular mimicry" with cross-reactivity against peripheral nerve, rather than an Ig-mediated mechanism, which would usually show a latent period. Flaviviruses are neurotropic, but, neuroinvasion processes are not fully understood. Neuronal virus attachment factors for Zika in the peripheral nervous system may be similar to those for West Nile virus, which are at the sensory nerve endings.[6] After entering the neuron, the virus may then utilize axonal transport to spread in retrograde and anterograde directions.[7] These postulated mechanisms may in part explain rapidity of onset of Zika-associated GBS, but further study is needed because there are no definitive data.

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