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Review article

Dengue-associated hypokalemic paralysis: Causal or incidental?

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ABSTRACT

Dengue-associated hypokalemic paralysis is considered an important but under-emphasized neuromuscular complication of dengue virus infection. Review of the published literature reveals that 35 instances of hypokalemic paralysis associated with dengue have been recorded from the Indian subcontinent and all but two, were males. The median age of presentation is 29 years and moderate to severe grade pure motor quadriparesis is precipitated during the phase of defervescence of moderate to high-grade fever. Recovery starts within 12 h of potassium supplementation and is usually complete in a couple of days. Redistribution or increased loss of potassium from the body is speculated as the pathophysiological mechanism involved in the causation of hypokalemia. It is not possible to derive the exact etiopathological correlation from the published literature either due to a lack of comprehensive reporting or inadequate work-up of the patients. Curious is the fact that only 35 patients had manifest-paralysis when more than two-thirds affected with the dengue virus exhibit hypokalemia; whether this indicates a genetically mediated channel disorder or an incidental association remains to be seen.

Contents

1. Introduction

Dengue is one of the most rapidly growing mosquito-borne viral infections across the world with more than 40% of the world population, 2.5 billion people, at risk. More than 100 countries in the world are endemic of dengue virus infection with the American, South-east Asian and the Western Pacific regions being the most affected ones [1]. The Asia-Pacific region alone is the home to approximately 75% of the population at risk amongst whom India falls into the category of highly endemic countries. The epidemiology of dengue has evolved over the past five decades in India where the regional restriction to Southern and North-western states is no more valid and has given way to a pan-India distribution [2]. Against the apparent burden of

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dengue pegged at approximately 34% of the global total, the unapparent burden of dengue may well be three times of this number which either goes undiagnosed or unreported [2,3].

2. Dengue virology

Dengue is the second most common cause of mosquito-borne viral infection and is caused by four antigenically distinct serotypes of dengue virus (DENV) viz. DEN1 to DEN4. DENV is a single stranded RNA virus, genus *Flavivirus*, with seven non-structural and three structural genes coding the various protein structures of the virus. *Aedes aegypti* and *Aedes albopictus* are the two main vectors responsible for the transmission of DENV.

3. Classification of neurological complications of dengue

Dengue shock syndrome is the most important and the best recognized complication of DENV infection besides hepatic and cardiac impairment. Acknowledging the now well characterized neurotropic nature of DENV, the World Health Organization has incorporated the neurological manifestations of dengue into its latest guidelines [1,4]. The neurological complications of dengue can be classified into cerebral manifestations, neuromuscular or immune-mediated complications, and neuro-ophthalmological complications. Encephalopathy, encephalitis and stroke (ischemic, hemorrhagic) are the most common cerebral manifestations, which is the largest category of neurological complications by DENV. Neuromuscular or immune-mediated is the next category of complications, predominantly comprising of Guillain–Barre syndrome, myositis, hypokalemic paralysis, acute disseminated encephalomyelitis, acute transverse myelitis and plexopathy. Maculopathy and retinal vascular involvement are the commonest neuro-ophthalmological manifestations associated with DENV infection [5,6].

Dengue-associated hypokalemic paralysis (D-HypoKP) is an emerging neuromuscular complication of DENV infection. It is an underemphasized entity that deserves special mention because of its rapidly evolving course, benign nature, exquisite responsiveness to minimal potassium supplementation and confusion with entities causing rapidly progressive quadriparesis. Since data on D-HypoKP is heterogeneous and available only in the form of case reports, we planned a critical appraisal of the published literature to crystallize this aspect to the best possible extent. A *PubMed* and *Google* based search was performed to look for published articles related to D-HypoKP using the terms “dengue and hypokalemia”, “dengue and hypokalemic paralysis”, “dengue and paralysis”, “dengue and metabolic complications” and “dengue and neurological complications”. The retrieved articles were then manually sorted on the basis of publications “citing/reporting temporal association of hypokalemia with motor paralysis of any grade”. At least 14 reports, including the first description of hypokalemic paralysis in a patient with dengue by Gupta and co-workers in 2009, have been published in the past 4 years; the documented 35 instances of D-HypoKP were, hereby, utilized to construct the review and develop the applicable generalizations [7–19] (Table 1). Care was taken to ensure that the known causes of secondary hypokalemic paralysis (Table 2) had been ruled-out in cases included in the review.

4. Case illustrations

4.1. Case-1

A 32-year-old man was referred for intravenous immunoglobulin administration (suspecting Guillain–Barre syndrome) to our department, a tertiary care neurology facility, with weakness of all 4 limbs and 3 days of high-grade fever. The weakness started on the 3rd day of fever and progressed over 8–10 h whereby he became bed-bound. Family history or use of any medication was not present. Examination was suggestive of hyporeflexic quadriplegia with neck flexor weakness. Left ankle reflex was normally elicitable. There was no suggestion of sensory or cranial nerve dysfunction, respiratory muscle involvement or impaired sphincter control. Laboratory evaluation was suggestive of low potassium (1.8 mEq/L), normal blood-gas parameters, low transtubular potassium gradient (2.3), slightly elevated creatine kinase (138 IU/L) and normal thyroid function tests; Non-structural (NS1) antigen was positive. The platelet count was 1,20,000/mm^3. Recovery started within an hour of initiating fruit juice and was complete over the next 10–12 h with further potassium supplementation.

4.2. Case-2

A 22-year-old man presented with a history of acute onset rapidly progressive quadriparesis culminating into a bed bound state over a period of 18–24 h. He had a history of moderate to high-grade fever 2 days prior to the onset of weakness. There was no history of sensory abnormalities, bladder/bowel involvement, rash, myalgia, arthralgia, headache or retro-orbital pain. During examination, his vital signs were stable and the higher mental functions, along with the cranial nerves, were intact. Motor examination revealed hypotonia in all 4 limbs with grade 2/5 power according to the medical research council (MRC) grading and hypoactive deep tendon reflexes. Serum potassium was low (2.49 mEq/L), blood-gas parameters were within normal limits, transtubular potassium gradient was 2.14, and creatine kinase was high (2646 IU/L); thyroid function tests were normal. The patient was detected positive for NS1 antigen. Abnormalities in the blood count were in the form of thrombocytopenia (96,000/mm^3) and leucopenia (2720/mm^3). With potassium supplementation, patient started recovering in 4 h and attained premorbid status over the next 48 h.

4.3. Case-3

A 26-year-old man presented with acute onset rapidly progressive quadriparesis preceded by 2 days of high-grade fever. The weakness was first noticed upon waking up in the morning and developed over 12–18 h to a bed bound state. There was no history of sensory abnormalities, bladder/bowel involvement, rash, myalgia, arthralgia, headache or retro-orbital pain. During examination, his vital signs were stable and the higher mental functions, along with the cranial nerves, were intact. Motor examination revealed hypotonia in all 4 limbs with grade 1/5 power according to the MRC grading and hypoactive deep tendon reflexes. Serum potassium was low (2.2 mEq/L), blood-gas parameters were within normal limits, transtubular potassium gradient was 2.18, and creatine kinase was high (542 IU/L); thyroid function tests were normal. The patient was detected positive for NS1 antigen. The only abnormality in the blood count was thrombocytopenia (78,000/mm^3). With potassium supplementation, patient started recovering in 3 h and attained premorbid status over the next 36 h.

Our unpublished observations from electrophysiological studies reveal low compound muscle action potentials (CMAPs) coupled with robust sensory nerve action potentials (SNAPs) in patients with D-HypoKP during the period of maximum disability. At no juncture CMAPs became un-recordable and, the CMAP and SNAP amplitudes normalized in 72 h with recovery of the patients. Electromyography did not reveal any abnormal insertional or spontaneous activity. Motor unit potential (MUP) dropout was observed along with low amplitude polyphasic potentials with early and complete recruitment, suggestive of a myopathic pattern. The “potassium exercise test” and the “prolonged exercise test” done at 3 weeks post-discharge, to ascertain whether the episode of hypokalemia was actually the first episode of a familial variety or not, was found to be within normal limits in the patients [20–22].