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SHORT REPORT
Four cases of acute flaccid paralysis associated with chikungunya virus infection

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SUMMARY

The recent epidemic of chikungunya fever (2005–2006) in India has affected millions of people. The Andaman and Nicobar Islands, an archipelago situated in the Bay of Bengal 1200 km from peninsular India, also witnessed an outbreak of chikungunya fever starting in July 2006 which affected thousands of people. Chikungunya fever classically manifests as high fever, myalgia, arthralgia and arthritis and in a certain percentage of cases with maculopapular rashes. However, deviation from the classical clinical features of chikungunya fever was reported in the earlier and recent epidemics. During the recent epidemic in the Andaman and Nicobar Islands we came across ten cases of flaccid limb weakness following symptoms and signs suggestive of chikungunya fever. In four subjects we confirmed the diagnosis of chikungunya virus infection by serological method (IgM ELISA method). This is the case report of those four subjects.

Chikungunya fever is a viral disease caused by chikungunya virus (CHIKV) which is a member of the genus *Alphavirus* in the family Togaviridae. The disease was first discovered by Marion Robinson and W. H. R. Lumsden in 1955 following an outbreak on the Makonde plateau along the border between Tanzania and Mozambique in 1952. The name derives from a Kimakonde root verb, *kungunyala*, meaning 'to dry up or become contorted', specifically modified in early times to describe the bent posture of patients guarding painful joints.

CHIKV infection typically causes a self-limiting but debilitating illness characterized by high fever, headache, and body ache with arthralgia. The arthralgia is polyarticular involving the large and small joints of limbs and is often associated with objective signs of arthritis. In 30–40% of patients a maculopapular rash on the trunk and extensor surface of the extremities is seen [1]. The fever subsides after 1–10 days but the joint pain may continue in some patients for a few months, or even years. There is no specific treatment and the symptoms resolve over time. CNS involvement, consisting of menigismus, nuchal rigidity, opthalmoplegia, slurred speech, and limb weakness, has been described rarely, and persistence convulsions associated with neurological sequelae have been reported in infants [2–4]. Acute polyneuropathy and paralysis occurred in a laboratory-confirmed case [4, 5]. During the recent epidemic in the Indian Ocean islands, 12 cases of meningoencephalitis were confirmed as being caused by CHIKV infection [6].

In India there was an outbreak of chikungunya fever during 1963–1964 in Calcutta and in 1965 in Chennai. The last epidemic reported from India was

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in 1973 in Barsi in the state of Maharastra. After a lull of more than three decades the virus again struck India. The present outbreak was first reported from the southern Indian state of Andhra Pradesh in November–December 2005. An estimated 1·38 million people across southern and central India developed symptomatic disease during 2005 and 2006 [7]. The Andaman and Nicobar Islands situated in the Bay of Bengal, 1200 km from peninsular India also witnessed an outbreak of chikungunya fever beginning in July 2006 [8]. Estimations from hospital-based surveillance statistics indicated that more than 50 000 subjects suffered from symptoms suggestive of chikungunya fever between July 2006 and December 2006 in Port Blair, the capital of the Andaman and Nicobar Islands, where more than 100 000 people live.

In August and September 2006 we had ten cases of acute flaccid limb weakness following symptoms and signs suggestive of chikungunya fever. In four subjects we could establish the diagnosis of chikungunya fever by serological method. The details of the cases are described below.

Case 1

A 28-year-old male patient, not a known diabetic or hypertensive, was admitted on 30 August 2006 with complaints of acute-onset rapidly progressive weakness of both lower and upper limbs of 1 day's duration. The patient had fever, generalized body ache and pain involving the large and small joints of the upper and lower limbs for the past 3 weeks. The joints involved were shoulder, elbow, wrist, knee, ankle, and the metacarpophalangeal and interphalangeal joints of the fingers and toes. The fever subsided after 3 days but arthralgia and myalgia continued although the severity was reduced. One day prior to admission he developed weakness of both lower limbs, which progressed rapidly and involved the upper limbs within 24 h. There was no history of diplopia, dysphagia, dyspnoea, and bladder or bowel involvement. There was no history of sensory symptoms.

Examination revealed a pulse rate of 80/minute, blood pressure of 170/70 mmHg, and a respiratory rate of 20/minute. There were no rashes or evidence of arthritis. CNS examination showed that his higher mental function and cranial nerves were normal. There was hypotonia of all the four limbs. Power was grade II for both upper limbs and grade I for both lower limbs. Distal muscles were weaker than proximal muscles. His sensory system was normal. All deep tendon reflexes were absent and plantar was mute.

Investigations: haemoglobin, 13 g%, total count, 9200; neutrophil, 70%; lymphocyte, 25%; eosinophil, 5%; erythrocyte sedimentation rate (ESR), 45 mm/h; random blood sugar, 135 mg%; blood urea, 19 mg/dl; serum creatinine, 0·8 mg/dl; serum sodium, 137 mmol/l; serum potassium, 3·6 mmol/l. ECG was normal, anti-CHIKV immunoglobulin M (IgM) (CHIKV IgM) antibodies were positive, and dengue IgM antibodies (all four dengue serotypes) were negative.

The patient was treated with an injection of 1 g methylprednisolone in one pint of normal saline over 4 h for 3 days. He started improving after the first dose and regained normal power after 3 days. He was discharged on 4 September 2006.

Case 2

A 55-year-old male patient, not a known diabetic or hypertensive, was admitted on 2 September 2006 with complaints of weakness of both upper and lower limbs with an inability to walk for 1 day. He also had breathing difficulty with an increased rate of respiration. The patient had fever, generalized body ache and pain in multiple joints a week ago, that lasted for 3 days. There was no history suggestive of sensory system involvement. There was no history of diplopia, dysphagia, and bladder or bowel involvement.

On examination the patient was conscious, febrile, with a pulse rate of 100/minute, blood pressure of 110/70 mmHg and a respiratory rate of 34/minute. There was hypotonia of all four limbs. The power in upper limbs was grade II and in the lower limbs grade I. All the deep tendon reflexes were absent and plantar was flexor. There was no cranial nerve involvement and sensory system examination was normal. The patient was treated with an injection of 1 g methylprednisolone in one pint of normal saline over 4 h for 5 days plus other supportive measures. However, the condition of the patient deteriorated in hospital and he developed respiratory muscle paralysis. He needed ventilatory support for a week. He also had acute renal failure and was treated with peritoneal dialysis. An insulin injection was given to control his blood sugar. At the end of 4 weeks his general condition improved and he was discharged.

Later in January 2007 when he was reviewed, he was able to walk with support. The power in his limbs

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was grade IV and his blood sugar and renal functions were normal.

Investigations: haemoglobin, 9 g%, total count, 7200; neutrophil, 65%; lymphocyte, 28%; eosinophil, 7%; ESR, 40 mm/h; random blood sugar, 408 mg%; blood urea 26 mg/dl; serum creatinine, 0·9 mg/dl; serum sodium, 141 mmol/l; serum potassium, 3·9 mmol/l. ECG was normal, anti-CHIKV IgM antibodies were positive, and dengue IgM antibodies (all four dengue serotypes) were negative.

Case 3

A 65-year-old male patient, a known diabetic for the past 12 years, on oral anti-diabetic and insulin with diabetic retinopathy and nephropathy was admitted on 4 September 2006 with complaints of weakness in both lower limbs of 3 days' duration and both upper limbs of 2 days' duration. The patient had fever and generalized body ache lasting for 1 day, 15 days ago. There was no history of any sensory symptoms, or bowel or bladder involvement. On examination he was afebrile, with a pulse rate of 112/minute, blood pressure of 160/90 mmHg, and a respiratory rate of 20/minute. CNS examination showed that his higher mental function and cranial nerves were normal. Motor system examination showed that he had grade II–III power in both lower limbs and grade III–IV power in both upper limbs. There was generalized hypotonia. Deep tendon reflexes were absent and plantar was flexor. His sensory system examinations showed that there was impairment of touch and pain sensation in the dorsum of right foot and hyperaesthesia in the lateral aspect of left foot. Other systems were normal.

Investigations: haemoglobin, 10 g%, total count, 6000; neutrophil, 62%; lymphocyte, 34%; eosinophil, 4%; random blood sugar, 456 mg%; blood sugar (fasting), 371 mg%; blood sugar post-prandial, 440 mg%; blood urea, 90 mg/dl; serum creatinine, 2·6 mg/dl; serum sodium, 144 mmol/l; serum potassium, 4·9 mmol/l; serum bilirubin, 0·5 mg/dl; serum glutamic oxaloacetic transaminase (SGOT), 25 U/l; serum glutamic pyruvic transaminase (SGPT), 38 U/l; serum alkaline phosphatase, 182 U/l; platelet count, 150 000/mm^3; urine albumin, ++. ECG was normal, anti-CHIKV IgM antibodies were positive, and dengue IgM antibodies (all four dengue serotypes) were negative.

The patient was treated with an injection of 1 g methylprednisolone in one pint of normal saline over 4 h for 3 days. An injection of insulin infusion was given to control his blood sugar. He started improving after the first dose of methylprednisolone and recovered completely after 3 days.

Case 4

A 38-year-old male patient was admitted on 9 September 2006 with complaints of fever, myalgia and arthralgia involving the large and small joints of the upper and lower limbs of 4 days' duration and insidious onset, rapidly progressive ascending weakness of all four limbs of 2 days' duration. The patient had received treatment elsewhere and his fever, myalgia and arthralgia had subsided after 2 days. There was no history of dyspnoea, dysphagia, sensory symptoms or bladder and bowel involvement.

On examination his higher mental functions and cranial nerves were normal. Motor system examination showed that tone was decreased in all four limbs; muscle power was grade II–III in both lower limbs and grade III–IV in upper limbs. Distal weakness was more than proximal and neck flexors were weak. All deep tendon reflexes were absent and plantar was flexor. Sensory system examination was normal.

Investigations: haemoglobin, 12 g%, total count, 7200; neutrophil, 59%; lymphocyte, 38%; eosinophil, 8%; random blood sugar, 325 mg%; blood sugar (fasting), 402 mg%; blood sugar post-prandial, 463 mg%; blood urea, 52 mg/dl; serum creatinine, 1·2 mg/dl; serum sodium, 136 mmol/l; serum potassium, 4·5 mmol/l. ECG was normal, anti-CHIKV IgM antibodies were positive, and dengue IgM antibodies (all four dengue serotypes) were negative.

He was treated with an injection of 1 g methylprednisolone in one pint of normal saline over 4 h for 3 days, an injection of huminsuline (regular) and analgesics. The patient started improving after the second dose of methylprednisolone and was discharged after 1 week once his blood sugar was under control.

Acute demyelination of peripheral nerves can occur following many bacterial and viral infections. The pathological basis of this is an immune dysregulation mediated by autoreactive T-cells and humoral antibodies against peripheral nerve antigens. A preceding infection triggers an autoimmune response through molecular mimicry in which the host generates an immune response against an infectious organism that shares epitopes with the hosts' peripheral nerves [9].

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Flaccid limb weakness following CHIKV infection was reported from India in the 1964 epidemic. There have been reports of neurological diseases including 12 cases of meningoencephalitis and encephalopathy in the recent epidemic in the Indian Ocean islands [3, 10]. The clinical spectrum of chikungunya fever observed during the recent epidemic acquires special significance because previous outbreaks in India (1963 and 1973) were caused by the Asian genotypes, but the 2005 epidemic in the Indian Ocean islands and the 2006 epidemic in India have been attributed to the East African genotype [11].

In our series of four case reports all had progressive weakness of all four limbs which was ascending and symmetrical. All had areflexia and the disease course was <4 weeks. In all four subjects the aetiology of CHIKV infection was established by the IgM ELISA method. However, there are some noteworthy points in all these four subjects:

- very rapid progression of neurological deficit;
- non-involvement of cranial nerves;
- dramatic response to injection of methylprednisolone.

The pathological basis of peripheral nerve damage following CHIKV infection is not established. The dramatic response to injection of methylprednisolone raises a doubt that the immune response in these four cases could be mediated by T-cells and inflammatory cytokines.

In conclusion, in this case-series of four subjects who developed acute flaccid limb weakness following symptoms and signs suggestive of chikungunya fever the aetiology of CHIKV infection was established. We encountered similar cases (six more) when the chikungunya fever epidemic was ongoing in the Island. Hence it shows that CHIKV infection can cause acute flaccid paralysis. Understanding the pathological basis of acute flaccid paralysis following CHIKV infection is one of the questions for further research.

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DECLARATION OF INTEREST

None.

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