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CASE REPORT

Immunoglobulin-responsive chikungunya encephalitis: two case reports

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Abstract Chikungunya virus is an alphavirus transmitted by the mosquito *Aedes*, mainly *Aedes aegypti* and *Aedes albopictus*, that can cause acute illness, mostly self-limited, characterized by fever, maculopapular rash, and disabling polyarthritis/arthralgia, with an incubation period of 1 to 12 days. Chikungunya was largely regarded as a non-fatal and self-limited disease, but recently, serious cases have been reported including some with severe involvement of the nervous system, such as meningoencephalitis, myelitis, polyradiculitis, and polyradiculoneuropathy. In this report, we describe the clinical and laboratory findings of two patients with encephalitis associated with chikungunya in a northeastern city in Brazil, who exhibited a good outcome, with improvement after treatment with i.v. immunoglobulin (IVIg).

Keywords Encephalitis · Chikungunya · Immunoglobulin · Treatment

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Introduction

Chikungunya, in the Makonde language, stands for "that which bends" (Azevedo et al. 2015), an expression that denotes the severity of joint pain in patients affected by the disease. Chikungunya is a virus described primarily in the 1950s in East Africa and is classified as a RNA virus, from the Togaviridae family and alphavirus genus (Azevedo et al. 2015). The vector is the mosquito *Aedes*, mainly *Aedes aegypti* and *Aedes albopictus*.

In 2004, there was a resurgence of the virus in the Indian Ocean Islands with subsequent worldwide spread (Mohan et al. 2010), presenting as a febrile illness associated with debilitating arthritis, skin rash, headache, maculopapular rash, and myalgia. The clinical picture shows an improvement after 10 days, but the joint pain can last from months to years (Gérardin et al. 2015). Chikungunya was largely regarded as a non-fatal and self-limited disease, but recently, serious cases have been reported including some with severe involvement of the nervous system, e.g., meningoencephalitis, myelitis, polyradiculitis, and polyradiculoneuropathy (Donalisio and Freitas 2015; Crosby et al. 2016; Mohan et al. 2010).

Here, we report two patients in Fortaleza, a city in the northeast of Brazil, with chikungunya encephalitis who exhibited an excellent improvement after administration of i.v. immunoglobulin.

Case 1

A 74-year-old man presented with fever, maculopapular rash, and severe arthralgia. After 4 days, he developed confusion and fluctuating level of consciousness and was taken to a local hospital. Upon arrival, the patient was drowsy and disoriented in space and time. After 12 days, he developed paraparesis

Table 1 Results of CSF studies in two patients with chikungunya

	Patient 1	Patient 2
Cell count (cells/mm^3)	90	42
Lymphocytes (%)	91	98
Neutrophils (%)	2	2
Plasma cells (%)	7	0
RBC	1	2
Glucose (mg/dl)	62	59
Protein (mg/dl)	179	100
Cultures	Negative	Negative

with diffuse areflexia. Ancillary tests revealed the following: cerebrospinal fluid (CSF) showing increased cell count with a predominance of lymphocytes and increased protein (Table 1), serology for chikungunya was positive, and electroencephalogram showed disorganized electrical brain activity with the presence of some waves with triphasic morphology. Nerve conduction studies (NCS) and electromyogram (EMG) revealed a sensorimotor axonal neuropathy (Tables 2, 3 and 4). Magnetic resonance imaging (MRI) of the brain showed scattered T2/flair hyperintense foci in the supratentorial white matter in the semioval and subcortical centers, some with high signal intensity on DWI sequence, with no contrast enhancement (Fig. 1). After this initial investigation, treatment with intravenous human immunoglobulin (dose of 400 mg/kg/day for 5 days) was initiated, with significant improvement, after the third day, of his level of consciousness, becoming awake and obeying verbal commands, also becoming oriented in space and time, recognizing family members. On the other hand, paraparesis only improved after 40 days, following plasmapheresis. A follow-up NCS (Tables 5, 6, 7 and 8) showed improvement in conduction velocities over time, and the patient was walking with unilateral assistance after 3 months.

Case 2

An 83-year-old man developed fever with chills, followed after 3 days by important arthralgias. After 6 days, he

Table 2 Case 1: Electrophysiology studies. Motor nerve conduction study

Site	Lat. (ms)	Dur. (ms)	Amp. (mV)	Area (mV ms)	Segment	Distance (mm)	Interval (ms)	NCB (m/s)	CCV	N.D.
Ulnar	Left									
Wrist	2.6	18.0	4.4	31.5	Wrist		2.6			
Below elbow	6.7	16.7	3.8	29.5	Wrist–below elbow	230	4.1	56.1		
Above elbow	9.0	18.0	3.7	30.9	Above elbow–below elbow	105	2.3	45.7		
Underarm	10.7	17.7	3.7	30.7	Above elbow–underarm	85	1.7	50.0		
Ulnar	Right									
Wrist	3.0	16.3	4.6	32.8	Wrist		3.0			
Below elbow	8.2	17.5	4.2	33.3	Wrist–below elbow	240	5.3	45.7		
Above elbow	10.0	16.1	4.1	31.	Below elbow–above elbow	90	1.8	50.0		
Underarm	11.7	16.0	3.7	29.2	Above elbow–underarm	75	1.7	45.5		
Tibial	Left									
Hallucis abductor	3.7	7.2	5.6	14.4	Hallucis abductor		2.3			
Popliteal fossa	14.8	7.7	3.5	14.0	Hallucis abductor-popliteal fossa	400	12.6	31.9		
Tibal	Right									
Hallucis abductor	3.7	7.2	5.6	14.4	Hallucis abductor		3.7			
Popliteal fossa	13.1	8.8	2.3	9.6	Hallucis abductor–popliteal fossa	385	9.4	41.0		
Fibular	Left									
Ext digitorum brevis	3.4	7.1	1.7	5.0	Ext digitorum brevis		3.4			
Fibular head	11.1	13.0	1.0	7.9	Ext digitorum brevis–Fibular Head	300	7.7	39.0		
Popliteal fossa	13.1	12.5	1.1	8.4	Fibular head-popliteal fossa	90	2.0	45.0		
Fibular	Right									
Extens brev dig	3.1	4.5	3.5	1.2	Ext digitorum brevis		3.1			
Fibular head	10.7	9.5	2.4	11.9	Ext digitorum brevis–fibular head	305	7.7	39.9		
Popliteal fossa	12.4	9.3	2.5	12.5	Fibular head–popliteal fossa	75	1.7	45.5		

Table 3 Case 1: Electrophysiology studies. EMG findings summary

Muscle	Side	Ins. act.	Fibs.	Pos. wave	Fasc.	Myo. disch.	Normal MUP	Poly	Low amp.	High amp.	Dur.	Recruit	Int. patt.
Pronator teres	L	Normal	0	0	0	0	0	N	0	0	Long	Reduce	Reduce
1st dorsal inter.	L	Incr.	+2	+2	0	0	0	++	0	0	Long	Reduce	Reduce
Biceps brachii	L	Incr.	+1	+1	0	0	0	++	0	0	Long	Reduce	PI 4
Triceps	L	Normal	0	0	0	0	0	N	0	0	Normal	Full	Full
Vastus lateralis	L	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act
Vastus medialis	R	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act
Gastroc. medial H	L	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act
Gastroc. Medial H	R	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act
Tibialis anterior	L	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act
Tibialis anterior	R	Incr.	+2	+2	0	0	0	–	–	–	–	–	No act

developed lethargy and confusion with disorientation in time and space. Neurological status evolved with worsening level of consciousness, leading to orotracheal intubation (OTI) for airway protection. Head CT scan was performed and did not disclose any abnormalities. CSF studies revealed an increase in the cell count with a predominance of lymphocytes and increased protein (Table 1). At this point, the patient was treated with acyclovir without significant clinical improvement. Three days after admission, laboratory tests showed positive serology for chikungunya, while serology for dengue (IgM and IgG) was negative. Four days after initial neurological symptoms, treatment with i.v. immunoglobulin (IVIg) (at a dose of 400 mg/kg/day for 5 days) was started with significant neurological improvement on the fourth day of infusion, with complete recovery of the encephalitis.

Table 4 Case 1: Electrophysiology studies. Sensory nerve conduction study

Site	Lat. 1 (ms)	Lat. 2 (ms)	Amp. (μV)	Area (μV ms)	Segment	Distance (mm)	Interval (ms)	NCV (m/s)	CCV	N.D.	Temp.
Ulnar	Left										
Wrist–digito V					Wrist–digito V						
					Elbow–digito V						
Ulnar	Right										
Wrist–digito V	2.4	3	5.7	0.2	Wrist–digito V Elbow–digito V	110	2.4	45.5			
Radial	Left										
Wrist–radial	1.5	2.1	8	0.6	Wrist–radial	95	1.5	63.3			
Sural	Left										
Retr exter–lat foot	2.5	3.3	4.6	0.6	Retr exter–lat foot	90	2.5	36			
Sural	Right										
Retr exter–lat foot	2.5	2.9	1.5	0	Retr exter–lat foot	85	2.5	34			
Fibular superf.	Right										
Ankle–dorso foot					Ankle–dorso foot						
Fibular superf.	Left										
Ankle–dorso foot					Ankle–dorso foot						
Median	Left										
Palm	2.2	3	7	0.4	Palm	105	2.2	47.7			

Table 5 Case 1: Electrophysiology studies. Electrophysiology studies after treatment with plasmapheresis. Motor nerve conduction study

	Test	Stimulation point	Lat. (ms)	Ampl. (mV)	Dur. (ms)	Area (mV ms)	Estim. (mA)	Estim. (ms)	Dist. (mm)	Time (ms)	Vel. (m/s)
Right, abductor digiti minimi, ulnar, C8 T1	2	Wrist	3.05	7.17	7.6	22.3	50	0.3	70		
		Elbow	7.15	6.41	7.85	21.8	50	0.3	225	4.1	54.9
		Lower third of the arm	9.21	5.53	8.14	22.5	50	0.3	90	2.06	43.7
		Underarm	10.8	5.28	7.81	22.2	50	0.3	80	1.59	50.4
Left, abductor digiti minimi, ulnar, C8 T1	27	Wrist	2.65	5.56	8.75	22.4	40	0.3	70		
		Elbow	7.05	5.6	8.25	22.7	40	0.3	230	4.4	52.3
		Lower third of the arm	9.45	5.22	8.55	21.9	60	0.3	105	2.4	43.8
		Underarm	11.2	4.92	8.13	19.7	45	0.5	90	1.77	50.4
Right, abductor pollicis brevis, medianus, C8 T1	6	Wrist	4.05	5.38	6.25	19	50	0.3	80		
		Elbow	8.8	5.2	7.1	17.5	30	0.2	245	4.75	51.5
		Lower third of the arm	10.5	5.29	7.05	17.8	30	0.2	90	1.65	56.4
Left, abductor pollicis brevis, medianus, C8 T1	25	Wrist	4.1	6.83	7.05	28.9	55	0.3	80		
		Elbow	8.95	6.43	7.4	26.3	55	0.3	250	4.85	51.5
		Lower third of the arm	10.9	6.46	7.5	27.4	30	0.2	110	1.95	56.4
Right, abductor hallux, tibial, I4 L5 S1	15	Ankle	3.85	7.03	6.4	20.8	100	0.5	70		
		Popliteal fossa	14.7	6.04	7.8	19.5	100	0.5	435	10.8	40.3
Left, abductor hallux, tibial I4 L5 S1	17	Ankle	4.66	5.89	6.67	18.8	100	2	70		
		Popliteal fossa	15.1	3.71	7.25	13.2	100	2	400	10.4	38.3
Right, extensor digitorum brevis, fibular, I4 L5 S1	13	Ankle	4.13	3.35	6.57	11.4	60	0.5	70		
		Fibular head	11.4	2.82	7.5	10.6	60	0.5	275	7.22	38.1
		Popliteal fossa	13.2	2.62	7.5	10.1	60	0.5	80	1.8	44.4
Left, extensor digitorum brevis, fibular, I4 L5 S1	19	Ankle	3.49	2.77	7.76	12	100	1	70		
		Fibular head	11	2.04	8.3	9.6	100	1	288	7.46	38.6
		Popliteal fossa	12.8	1.94	8.39	9.5	100	1	65	1.86	35

Table 6 Case 1: Electrophysiology studies. Electrophysiology studies after treatment with plasmapheresis. Sensory nerve conduction study

	Test	Stimulation point	Lat. (ms)	Ampl. (μV)	Dur. (ms)	Area (nV s)	Estim. (mA)	Estim. (ms)	Dist. (mm)	Time (ms)	Vel. (m/s)
Right, superficial branch of radial nerve, C5 C6	8	1	1.22	24.1	2.73	17.8	20	0.2	78	1.22	64.1
Right, n. medianus	9	Palm	1.85	18.4	1.35	13.6	20	0.2	90	1.85	48.6
Right, n. medianus	11	Wirst	2.54	16.1	3.31	13.9	20	0.2	130	2.54	51.2
Left, medianus	30	Palm	2.2	15.6	1.1	9	20	0.2	95	2.2	43.2
Left, medianus	32	Wirst	3.07	11.6	2.98	11.2	15	0.2	140	3.07	45.6
Right, n. ulnar	12	Wirst	1.96	18	3.14	20.5	12	0.2	120	1.96	61.3
Right, n. ulnaris V dig.	31	Palm	1.59	10	2.46	6.4	15	0.2	95	1.59	59.8
Right, n. peroneus superficialis, L4-S1	24	1		0			25	0.2			
Left, n. peroneus superficialis, L4-S1	22	1		0			25	0.2			
Right, n. suralis, S1–S2	23	1	1.95	7	1.6	6.6	25	0.2	80	1.95	41
Left, n. suralis, S1–S2	21	1	1.75	3.4	1.85	2.8	15	0.2	75	1.75	42.9

Brain MRI performed almost 15 days after hospital admission was normal, when symptoms had resolved almost completely.

Discussion

Chikungunya virus causes acute symptomatic illness. The disease is characterized by fever, rash, and disabling arthralgia, with an incubation period that can range from 1 to 12 days (Ganesan et al. 2008). CNS involvement has been more recently described. However, similar to those of the dengue virus (Nelson et al. 2014), it is uncertain whether the neurological manifestations are due to CNS viral invasion, immune responses, or to both conditions (Das et al. 2010).

There is some experimental evidence of CNS invasion. A study in rats has demonstrated invasion of the choroid plexus and meninges by the virus, however, not of the brain parenchyma (Ziegler et al. 2008). Moreover, in vitro studies have documented virus replication in astrocytes and oligodendrocytes (Das et al. 2015). Additionally, the higher frequency of symptoms related to CNS involvement in the elderly and those with comorbidities, as seen in the present cases, suggests that the virus can manipulate ineffective immune systems to reach the brain and its surrounding structures since immunologic response to antigens in elders weakens and infections tend to be frequent and heavier with increased age (Hjalmarsson et al. 2007; Sansoni et al. 2008).

Another experimental study with monkeys reported a relationship between high levels of cytokines and encephalopathy (Labadie et al. 2010), linking inappropriate immune response

Table 7 Case 1: Electrophysiology studies. Electrophysiology studies after treatment with plasmapheresis. F-wave

	Test	Fmin lat. (ms)	F ampl. (μV)	M lat. (ms)	Fmin-M lat. (ms)	F/M (%)	Max V (m/s)	V (m/s)
Right, abductor digit minimi, ulnar, C8 T1	5	31.3	316	2.75	28.5	2.8		
Left, abductor digit minimi, ulnar, C8 T1	28	32.2	287	2.95	29.3	3		
Right, abductor pollicis brevis, medianus, C8 T1	7	24.2	327	4.3	19.9	3.6		
Left, abductor pollicis brevis, medianus, C8 T1	26	34.5	141	4.25	30.3	1.4		
Right, abductor hallux, tibial, I4 L5 S1	16	57.5	435	4	53.5	3.8		
Left, abductor hallux, tibial I4 L5 S1	18	58.6	377	4.2	54.5	3.9		
Right, extensor digitorum brevis, fibular, I4 L5 S1	14	55.1	173	4.25	50.8	3.9		
Left, extensor digitorum brevis, fibular, I4 L5 S1	20	54.7	102	3.9	50.9	3.1		

Table 8 Case 1: Electrophysiology studies. Electrophysiology studies after treatment with plasmapheresis. EMG findings summary

	Test	Spontaneous activity	Amplitude MUP	Duration MUP	Polyphasia MUP	Pattern
Right, biceps brachii, cutaneous muscle, C5 C6	34		N	N	N	N
Left, biceps brachii, cutaneous muscle, C5 C6	43		N	N	N	N
Right, triceps, radial, C6 C7 C8 T1	35		Increased	Increased	N	Neurogenic
Right, interosseus, ulnar, C8 T1	36		N	N	N	N
Left, interosseus, ulnar, C8 T1	44		N	N	N	N
Right, vastus medialis, femoral, L2–L4a	37		Increased	Increased	N	Neurogenic
Left, vastus medialis, femoral, L2–L4	40		Increased	Increased	Increased	Neurogenic
Right, gastrocnemius, tibial, S1–S2	39		Increased	Increased	Increased	Neurogenic
Left, gastrocnemius, tibial, S1–S2	42		Increased	Increased	N	Neurogenic
Right, tibialis anterior fibular, L4 L5 s1	38		Increased	Increased	Increased	4
Left, tibialis anterior, fibular, L4 L5 s1	41		Increased	Increased	N	Neurogenic

to neurologic manifestations. Taking this into account, a good response to IVIg observed in our two patients suggests that an immune mechanism could be the main cause of the neurological symptoms, since this drug acts by neutralizing the humoral response elicited by the virus.

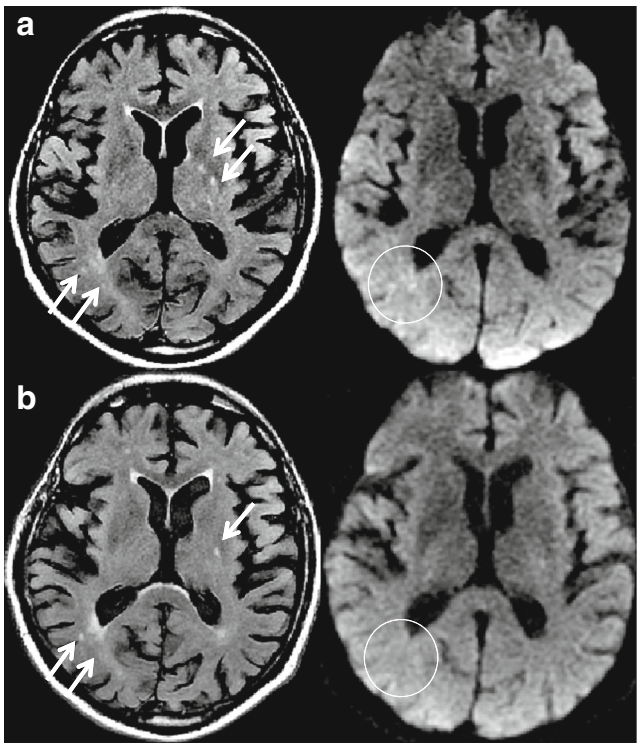

Fig. 1 Case 1: Brain MRI findings. **a** Multiple white matter hyperintensities are shown on FLAIR (*left*, *arrows*) and DWI (*right*, *circle*) predominantly in the periventricular and basal ganglia/capsular regions. **b** MRI of the same patient 4 months later, demonstrating partial regression of the hyperintense foci on FLAIR and disappearance of the alterations on DWI (*circle*). There was no abnormal gadolinium enhancement. Also, note mild diffuse brain atrophy

It is also possible that the involvement of the CNS may occur through viral invasion, associated with an inappropriate immune response (Courderc and Lecuit 2015), justifying higher frequency of these symptoms in the elderly and a good response to immunoglobulin.

Our two patients were infected during a chikungunya outbreak in the city of Fortaleza in 2016, had positive IgM for chikungunya, and tested negative for dengue fever. The CSF changes observed in our patients supported the diagnosis of encephalitis and therefore CNS involvement.

As far as we know, this is the first description of an IVIg-responsive encephalitis due to a chikungunya virus infection. The mechanisms underlying the response to IVIg in our patients are not clear. We can speculate that blockade of a deleterious immune response by IVIg is a possible mechanism. It is more difficult to understand how IVIg could directly affect the viral activity or replication.

However, given the lack of controlled studies about this subject, it is also important to consider that the improvement could be simply explained by natural history of the disease and that improvement after IVIg could be due to chance.

In summary, it is possible that chikungunya encephalitis can benefit from IVIg, at least in certain conditions. However, controlled randomized trials are necessary to better assess this therapeutic possibility.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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