Neuro-chikungunya: a review

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Abstract

Chikungunya virus is a well-described mosquito-borne alphavirus, responsible for an important human disease. The main symptoms are fever, rash and arthralgia, and when neurological complications occur, they generally appear within 20 days of the onset of CHIKV infection. The aim of this paper is to present a review of the neurological syndromes most commonly found in chikungunya. Articles published in the electronic database MEDLINE/PubMed and Web of Science were used. It is uncertain whether neurological symptoms are due to persistence of the virus or an ineffective immune response. Neurologic syndromes, which include encephalitis, encephalopathy, myelopathy and myeloneuropathy, have been the major cause of death and disability related to CHIKV infection. This paper described all neurologic complications in chikungunya, including the involvement in newborns and the findings in relation to the main diagnostic methods used in neurology, such as MRI, electroencephalography, evaluation of cerebrospinal fluid and electromyography, as well as dealing with these complications. It can be concluded that chikungunya must be on the list of diagnostic possibilities of all patient who develop a neurologic disorder after acute onset of fever and joint pain.

Key Words: Chikungunya, fever, headache, arthralgia.

1. Introduction

Chikungunya fever is caused by an alphavirus belonging to the togaviridae family [1-4]. It is transmitted to humans by the Aedes family of mosquitoes and is thus classified as an arbovirus [5-8]. The first described outbreak of Chikungunya virus (CHIKV) infection occurred in East Africa in 1953 [4]. Since then, many epidemics have been reported in regions of Southeast Asia, sub-Saharan Africa and India; more recently, outbreaks have occurred in several countries in South America [9]. Typical symptoms of CHIKV infection are severe joint pain, high fever, myalgia, vomiting and skin rash [1, 10-16].

Until the 2005-2006 Reunion island outbreak, neurological involvement associated with chikungunya fever was considered rare, with just sporadic case reports [16-20]. However, in the last few years, many authors from different countries have described neurologic alterations in patients [5, 9, 21, 22]. In the majority of cases, patients developed neurological complications within 20 days of the onset of CHIKV infection [9, 23]. It is still uncertain whether neurological symptoms are due to the persistence of the virus or an ineffective immune response [9]. There is no difference in the outcomes between patients treated conservatively and patients treated with steroids [23].

This review summarizes the main articles on neuro-chikungunya published to date. This report only includes studies on patients with neurological involvement and a typical clinical picture of chikungunya infection confirmed by serology.

2. Methods

A literature review, carried out of the PubMed electronic database using the respective specific term, neuro-chikungunya, resulted in 19 articles. Of these 15 articles were included in the study because they reported new or relevant information about the syndrome in question. A few other articles that were not indexed in PubMed were found as references in the indexed publications.

The neurological syndromes most commonly found in chikungunya include encephalitis, myelopathy, myeloneuro-pathy, peripheral neuropathy and optic neuritis. Some information about neuro-chikungunya in newborns was also included in this review.

Encephalitis

All articles published until now show that the most commonly found neurological syndrome in patients with CHIKV is encephalitis [9, 19, 24]. Publications on the most important series are listed in Table 1.

In 1971, Mazaud et al. described one child and three adults with encephalitis associated with CHIKV infection. All patients had excellent recoveries [25].

Rampal et al. evaluated 20 patients with neurological complications due to Chikungunya fever and found altered levels of consciousness early in the course of the disease. The most important signs and symptoms were delirium, disorientation, confusion and drowsiness. Six patients out of 20 developed psychosis. No specific treatment was used as the patients were treated symptomatically. Fourteen of 20 patients gradually improved and six deteriorated due to their neurologic complications and died. Of the six patients who died, one 45-year old presented multiple small hemorrhages with diffuse cerebral edema in a CT scan and the others, who were older, had associated systemic diseases [21]. Note that in this series, mortality was 30%, reflecting the severity of neurological involvement.

In another series, Martins et al. evaluated 22 patients with neuro-chikungunya, ten of whom had altered levels of consciousness. These patients were confused about their temporal and spatial orientation and presented anterograde amnesia. Some of them complained of persecutory delusions and presented suicidal behavior that was controlled with risperidone (2 mg b.i.d.). All patients received supportive care and had satisfactory evolutions within two months of the onset symptoms [9].

Chandak et al. evaluated 49 patients with neurologic symptoms due to chikungunya. Encephalitis was the most common presenting syndrome in 27 (55%) of the patients. Significant neurologic signs included impaired level of consciousness and abnormal behavior. There was no difference in the outcomes between patients treated with steroids and those treated conservatively, however, two patients with encephalitis died. According to the authors, the outcome of the treatment of neurological complications of CHIKV infection is good, with the

mortality in this group being due to the systemic complications [23].

In the biggest series to date, Economopoulou et al. evaluated 147 patients with neurological manifestations associated to CHIKV infection; almost one half (69 cases) presented with encephalitis. In this group, 12 had an underlying neurological condition such as stroke or epilepsy, but most of the encephalitis cases occurred in previously healthy people, which proves that neurological involvement does not depend on the clinical condition of the patient [20].

In another study evaluating 11 female and 12 male patients, Tournebize et al. found 20 (95.2%) suffered from confusional syndrome. The clinical evolution was very good with the symptoms disappearing within a few days after the start of treatment in most patients. Five patients died in this group. Additional tests proved that one of them died from myocardial infarction and the other four died due to comorbidities including alcoholism, vascular dementia and epilepsy [26]. Furthermore, 56.5% of the affected group had a median age higher than 65 years, a condition that is reported to be an independent risk factor in all studies [26, 27].

In the outbreak of northeastern Italy in 2007, only one case was fatal, an 83-year-old male patient with encephalitis. The patient had underlying diseases of hypertension and Parkinson`s disease and presented initially with impaired cognitive ability and an altered level of consciousness. Although this was an isolated case report, it highlights the importance of advanced age and comorbidities in mortality related to CHIKV infection and encephalitis [27].

Regarding the pediatric population, Lewthwaite et al. found seven children with altered mental status among eight who had CHIKV RNA detected in plasma or cerebrospinal fluid (CSF). Even in children, the main neurologic symptom associated with CHIKV infection seems to be encephalitis [28].

In another pediatric series, Robin et al. evaluated 30 patients (23 boys) with a mean age of 5.5 years and neurologic manifestations linked to CHIKV. Twelve (40%) had signs and symptoms of encephalitis such as confusion, somnolence, delirium and obnubilation [29].

All the patients received supportive care but they were not prescribed corticosteroids. Two patients with encephalitis died.

Pellot et al. evaluated nine children with severe forms of CHIKV infection in a pediatric intensive care unit on the French island of Reunion. Four presented neurological symptoms (encephalopathy), one child died and the survivors presented long-term neurologic sequels [30].

Cerebrospinal fluid

In encephalitis, cerebrospinal fluid (CSF) is rather unspecific and may be completely normal or have mild pleocytosis with lymphocytic predominance. There may be a slight increase of protein and glucose levels may be normal or slightly reduced. In the first few days of infection, the presence of CHIKV DNA can be detected using real-time reverse transcription polymerase chain reaction (RT-PCR). After that, the PCR exam becomes negative and immunoglobulin M (IgM) antibodies against CHIKV can be detected by enzyme-linked immunosorbent assay (ELISA) [22, 25-28, 31].

Electroencephalography

Electroencephalography (EEG) is not a very useful examination in patients with encephalitis due to CHIKV infection. Commonly in these cases, a generalized intermittent slow wave dysrhythmia or a normal pattern is observed. Periodic patterns are not identified and only rarely diffuse or focal epileptic elements without abnormal background activity are found. The EEG was normal in six patients that had either focal or generalized seizures during the acute phase of CHIKV infection [17]. Thus, the EEG is a rather non-specific examination for the investigation of neuro-chikungunya [23, 26].

Computed Tomography scan and Brain Magnetic Resonance Imaging

Computed tomography (CT) is generally normal [20, 23] but in severe cases it may show multiple small hemorrhages with diffuse cerebral edema [21]. Chandak et al. performed CT in 20 patients with encephalitis all of whom had normal results [23]. Furthermore, it seems that patients who present mild or moderate forms of neuro-chikungunya have normal magnetic resonance imaging (MRI) [23, 26, 29, 31]. However, patients with a

severe form of the disease may have increased T2 signals in periventricular white matter and in the bilateral centrum semiovale, or even hyperintense nodular lesions in supratentorial regions and cerebellar hemispheres corresponding to areas of hemorrhages found on a brain scan [29].

MRI findings should be interpreted according to the clinical condition of the patient. Chusri et al. found significant changes in the MRI of a 27-year-old patient, who unexpectedly presented altered consciousness on the eighth day after the onset of symptoms of CHIKV infection. MRI showed a hyperintense signal involving both temporal lobes and insular cortices without significant contrast enhancement. The authors discarded the possibility of other infections including the herpes group of viruses [5]. Bilateral frontoparietal white matter lesions with restricted diffusion have been described as an early sign of viral encephalitis [32].

Myelopathy

Chandik et al. found seven patients with myelopathy in 49 individuals diagnosed with neuro-chikungunya. The patients presented paraparesis or quadriparesis and urinary retention. Six of seven patients presented normal spine MRI and CSF parameters were normal or with mild non-specific abnormalities. The normal spine MRI shows that treatment should be guided according to the clinical status of the patient. Five patients improved and two remained stable [23]. Martins *et al*. described a patient who presented transverse myelitis eight days after the onset of fever and arthralgia. The patient presented paraparesis, sphincter dysfunction and changes in sensitivity with remission of the symptoms being achieved with corticosteroids [9].

Myeloneuropathy

There are few descriptions in the literature about this kind of neurologic involvement. Crusri et al. reported a case of a 44-year-old woman, who developed progressive weakness and grade 2/5 areflexia of the proximal muscles of the lower and upper extremities. MRI showed a hyperintense signal of C4-5 spinal cord. Electroneuromyography (EMG) showed no sensorineural action potential and delayed distal motor latencies of the right median and ulnar nerves with little compound muscle action, indicating acute motor and

sensory peripheral neuropathy. CSF was acellular with a slight increase in protein levels. The patient improved with intravenous immunoglobulin (IVIg) [5]. Chandak et al. evaluated seven patients with the main signs and symptoms being motor weakness. CSF showed less than five cells in all and slightly elevated protein levels in five patients. MRI of three patients showed signal changes in the spinal cord suggestive of demyelination and EMG showed acute inflammatory demyelinating polyradioneuropathy in all. Four patients improved, two remained unchanged and one passed away. There were no differences in the outcomes between patients treated with steroids and those treated conservatively [23].

Peripheral Neuropathy

Chandak et al. evaluated seven patients with peripheral neuropathy and seven with myeloneuropathy; demyelination predominated in all. Six improved and one remained unchanged [23]. Wielanek et al. reported on three patients in whom nerve conduction studies after CHIKV infection led to the diagnosis of Guillain-Barré syndrome (GBS). Two patients were treated with IVIg for five days and one received no specific treatment. All recovered partially and could walk with assistance one month later [33]. Tournebize et al. evaluated two patients with GBS with EMG indicating prolonged distal latencies, slow motor conduction velocity and the abolition of potential sensitivities. The patients improved rapidly after receiving IVIg therapy for five days [26].

Optic Neuritis

The largest case series involved 14 patients who developed symptoms compatible with optic neuritis after CHIKV infection. Five of the patients had ocular symptoms during the early phase of systemic symptoms with the pattern of visual involvement being very variable. Twelve patients had papillitis, retrobulbar neuritis or neuroretinitis and two patients had optic tract involvement [22].

The mechanism by which the optic nerve is affected remains unknown. Perhaps there is direct viral involvement in cases of simultaneous onset of systemic and ocular disease and delayed immune response in the cases of delayed optic nerve involvement. The authors concluded that optic neuritis associated with CHIKV

infection is an acute onset inflammatory reaction of the optic nerve [22].

All patients received treatment with 1000 mg/d of intravenous methylprednisolone in divided doses for three days, followed by 1 mg/kg/d of predinosolone for 14 days, with dose weaning over four weeks. In this series, 75% of patients had improved visual function. Some patients that initiated the treatment one month after the onset of visual symptoms had no improvement. It seems that the use of corticosteroids accelerates visual recovery in most patients when treatment is initiated at an early stage of infection [22]. In another series, one patient became completely blind due to retrobulbar neuritis, with temporal pallor of optic disc detected by direct fundoscopy [21].

Neuro-chikungunya in Newborns

Although a considerable number of patients with neuro-chikungunya present good outcomes, the involvement of newborns through vertical transmission calls our attention. The authors of one publication followed up two neonates with vertically transmitted chikungunya fever for three years [34], and found poor neurodevelopment. Both infants were born to mothers who had chikungunya a few days before delivery. Neonates developed encephalopathy within a few days of life. The first neonate presented hypertonia and spastic diplegia in the initial follow-up and at 11 months started with a seizure disorder. His language, conceptual thinking, non-meaningful memory, and non-verbal and numerical reasoning were inadequate. The second neonate had hypotonic cerebral palsy with mental retardation after three years of follow-up [34]. Thus, mother-to-child transmission seems to be associated with very poor neurodevelopmental outcome.

3. Final Considerations

According to the Chusri et al., neurologic complications are the major cause of death and disability in CHIKV infection [5]. Neurologic complications cause prolonged hospitalization and secondary complications such as electrolyte imbalance, bedsores, urinary tract infection, aspiration pneumonia and altered renal parameters [21].

It seems that neuro-chikungunya is the new neurosyphilis of the 21st century. In the early years of the last century,

neurosyphilis caused by *Treponema pallidum* was responsible for several neurological syndromes, and was certainly one of the differential diagnoses of all neurological conditions. Neurologic complications of chikungunya may include encephalitis, optic neuritis, myeloneuropathy, myelopathy, peripheral neuropathy and myopathy [1, 35]. This suggests that chikungunya should definitely be on the list of diagnostic possibilities for all patients who develop neurological disease after acute onset of fever and joint pain.

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Table 1: Encephalitis symptoms according to different authors

Reference	Year	n	Altered level of consciousness n (%)	Abnormal Behavior n (%)
Rampal et al.	2007	20	20 (100)	6 (33)
Tournebize et al.	2008	23	20 (95)	-
Chandak et al.	2009	49	6 (12)	18 (37)
Economopoulou et al.	2009	147	69 (47)	-
Martins et al.	2016	22	10 (45)	6 (18)
		Children		**no data**
Penny Lewthwrite et al.	2003	8	7 (87)	-
Robin et al.	2008	30	12 (40)	-

