CASE REPORT

Chikungunya fever presenting with acute optic neuropathy

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SUMMARY

Chikungunya fever is a vector borne virus that typically causes a self-limiting systemic illness with fever, skin rash and joint aches 2 weeks after infection. We present the case of a 69-year-old woman presenting with an acute unilateral optic neuropathy as a delayed complication of Chikungunya virus (CHIKV) infection contracted during a recent trip to the West Indies. She presented to our ophthalmology department with acute painless visual field loss in the right eye and a recent flu-like illness. She was found to have a right relative afferent pupillary defect (RAPD) with unilateral optic disc swelling. Serology confirmed recent CHIKV infection. Treatment with intravenous methylprednisolone was delayed while awaiting MRI scans and serology results. At 5-month follow-up, there was a persistent right RAPD and marked optic atrophy with a corresponding inferior scotoma in the visual field.

BACKGROUND

Chikungunya fever is caused by the Chikungunya virus (CHIKV), which is an insect-borne α virus belonging to the Togaviridae family. It is transmitted to humans by the bite of infected mosquitos,[1] mainly *Aedes aegypti* and *Aedes albopictus*. It was first recognised in 1952 in Tanzania, and has since been responsible for numerous sporadic epidemics in Africa, Southeast Asia and, more recently, in 2007, in India. Since 2003, outbreaks have been reported in the Pacific islands of Madagascar, Comoros, Mayotte, the Seychelles, Mauritius and French Réunion.[2]

After a short latent period (usually up to 8 days), infected patients typically develop an acute fever, diffuse macula-papular skin rash, severe arthralgia and an often long-lasting myalgia.[3] Chikungunya is commonly misdiagnosed as dengue haemorrhagic fever owing to similar symptoms and modes of transmission, notwithstanding its typically self-limiting and indolent course. However, recent outbreaks in India were associated with more severe systemic manifestations and even death.[4] These outbreaks also were reported to have ophthalmic involvement for the first time, including optic neuritis, neuroretinitis and panuveitis.[5–8]

Since December 2013, there has been a CHIKV epidemic in over 30 islands and countries in the Caribbean and Latin Americas, affecting over 776 000 people.[3] Optic neuropathy has previously been reported in a small case series in the Indian subcontinent following CHIKV fever.[6] To the best of our knowledge, this is the first reported case of Chikungunya infection in the UK, presenting as a delayed optic neuropathy.

CASE PRESENTATION

A healthy 69-year-old woman presented with painless right inferior visual field loss for 1 day. She had returned from a holiday in Grenada (West Indies) 3 weeks previously. She did not report of headaches, blurred vision, scalp tenderness or any other symptoms suggestive of giant cell arteritis.

Further questioning revealed an episode of right lower motor neuron facial palsy 5 weeks previously while in Grenada, which had rapidly resolved following treatment with oral prednisolone for 2 weeks by a local physician. The patient also recalled developing a flu-like illness with fever, widespread skin rash and painful wrist joints. On presentation to our team, the fever and rash had resolved, but the joint pain and stiffness had persisted. She admitted to having been bitten by mosquitos while on holiday, and that several close family members had also been affected by a similar illness although they had all fully recovered. The patient suffered from mild asthma and hay fever but otherwise had no significant past medical or ophthalmic history of note.

On examination, unaided visual acuities were 0.02 logMAR ($6/6^{-1}$) in the right eye and 0.12 logMAR ($6/7.5^{-1}$) in the left eye. Anterior segments and intraocular pressures were unremarkable and there was no relative afferent pupil defect (RAPD) at this stage. Direct and consensual pupil reflexes were normal throughout. Visual fields to confrontation showed an inferior altitudinal hemianopia in the right eye, which was confirmed on 120-point Humphrey full field automated perimetry testing (figure 1).

Fundal examination revealed optic disc oedema in the superior half of the right optic nerve head but no hyperaemia or haemorrhages (figure 2). The left optic nerve head was unremarkable, as were the macular and peripheral retinal appearances of each eye. There was no evidence of intermediate or posterior uveitis. Colour vision as tested with Ishihara plates was unremarkable and equal (17/17 test plates) in each eye, and extraocular movements were normal and pain free.

Cranial nerve examination suggested possible involvement of the 5th nerve (numbness of left forehead). The patient also admitted to weakness in her usual voice, suggestive of 9th and 10th cranial nerve involvement. The facial nerve palsy had clinically entirely resolved on presentation to our team. Upper and lower limb neurological examination, including reflexes, was normal.

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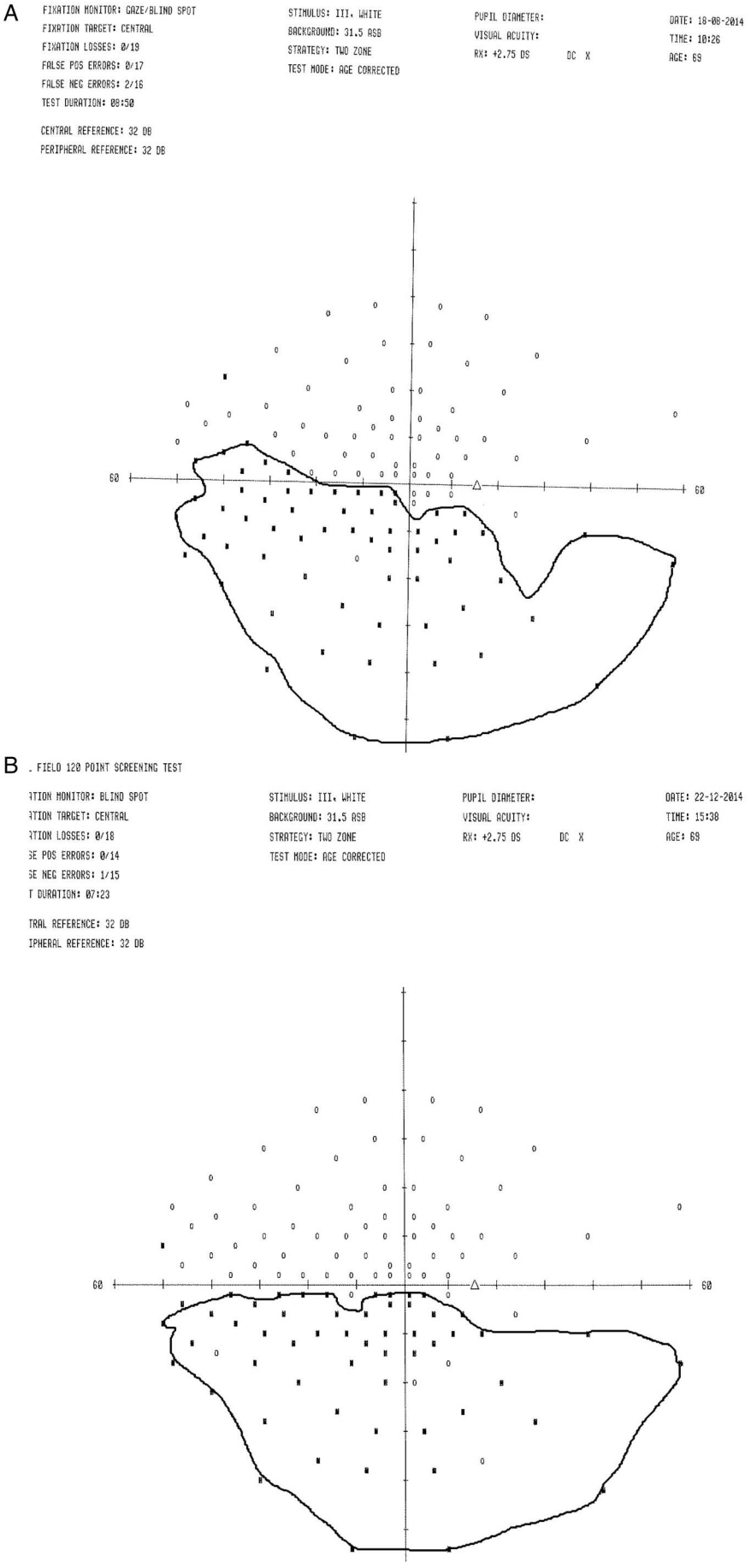
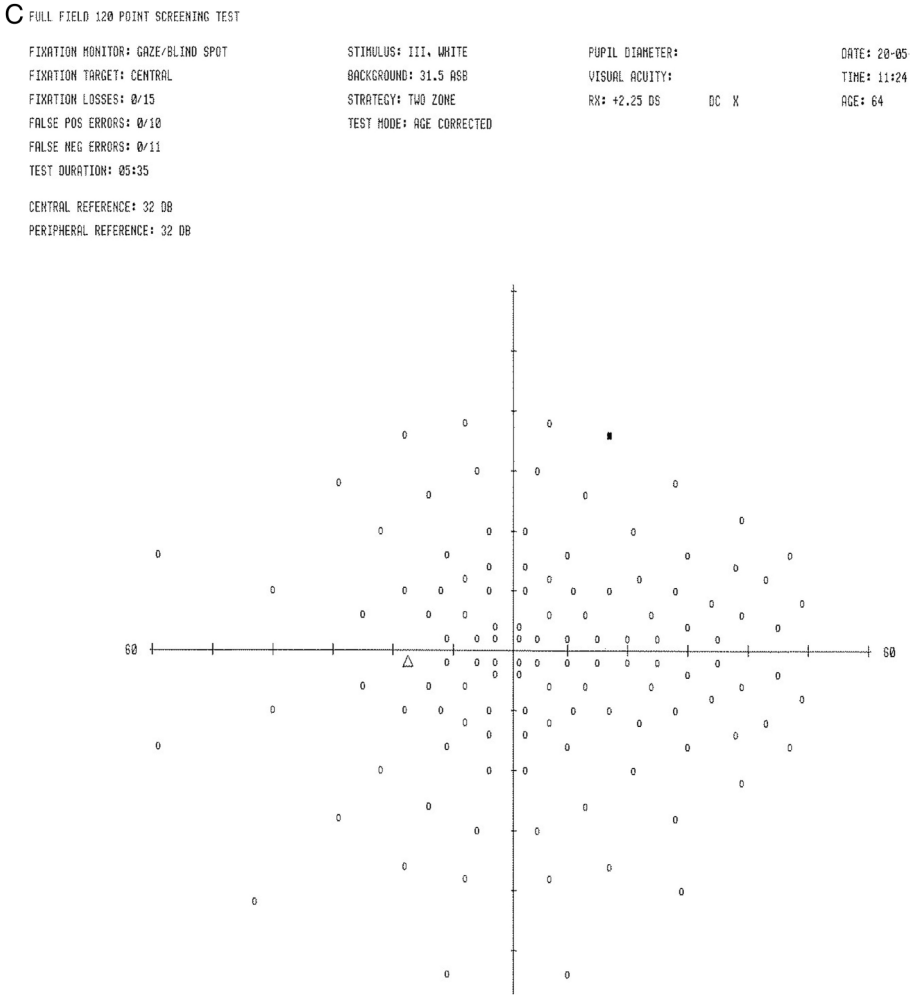


Figure 1 Humphrey Full field 120-point visual fields: (A) Right inferior altitudinal field loss recorded 2 days after presentation; (B) Right visual field 5 months later shows persistent right inferior altitudinal field loss; and (C) Left visual field showed no involvement throughout the 5-month follow-up.

Figure 1 Continued



INVESTIGATIONS

The patient was admitted for urgent investigations under the physician team, to identify any infective cause for the unilateral optic neuropathy. These included serological tests and an outpatient MRI scan. Advice from the neurologists was to withhold intravenous steroids until MRI scan and blood results were available. It was felt that a lumbar puncture was not required as the patient was apyrexial with no symptoms or signs of meningism.

Haematological tests indicated normal neutrophil (4.5×10^9/L) and white cell counts (7.1×10^9/L). The rest of the full blood

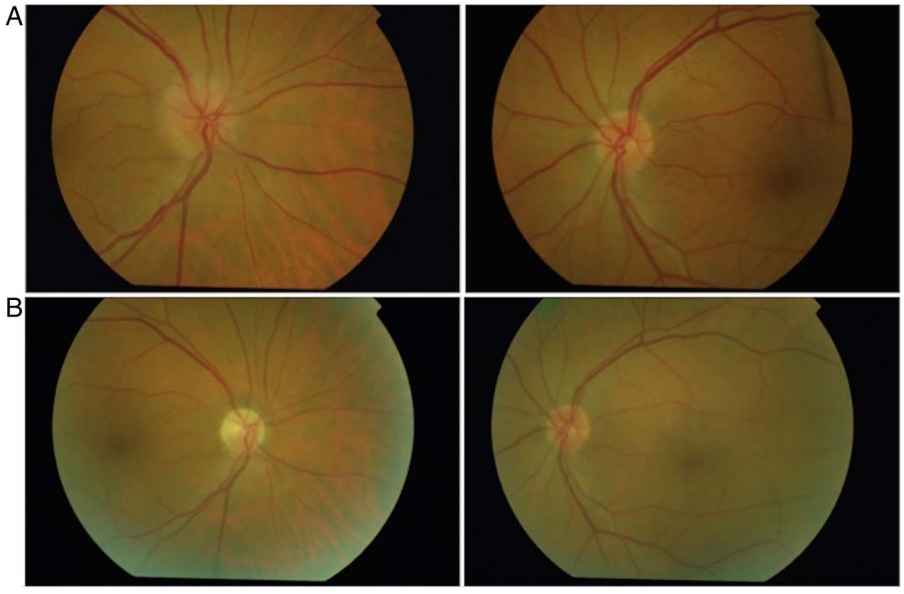


Figure 2 Optic disc photos: (A) Right optic disc oedema at presentation with marked blurring of the superior half. Normal appearance of the left optic disc at presentation with a small cup-to-disc ratio; (B) Marked superior sectoral right optic disc pallor and atrophy at the 5-month follow-up. Small cup-to-disc ratio in the right eye more evident following resolution of oedema. Note normal appearance of left optic disc at 5 months.

count was also within normal parameters (haemoglobin 129 g/L, mean cell volume 80.8 fL), as were the urea and electrolytes. C reactive protein and erythrocyte sedimentation rate were 9 and 49, respectively. Serum electrophoresis was unremarkable, with no paraprotein found. Blood and urine cultures were unremarkable. Chest radiograph showed no abnormality to suggest tuberculosis or sarcoidosis and serum ACE was within normal parameters (38.7 IU/L).

Other tests including HIV, syphilis serology (treponema pallidum haemagglutination assay), antibody antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor (11 KU/L) and Lyme serology were all negative. Immunoglobulin A was mildly elevated (4.05), but IgG and IgM were normal. α-2-Globulin and β-globulin were mildly elevated (11.7 and 13.2, respectively).

CHIKV-specific IgG and IgM antibodies were confirmed using ELISA testing 2 days later, consistent with recent CHIKV infection. Although dengue fever IgM was negative (thereby ruling out active dengue infection), a positive dengue fever IgA suggested previous exposure to dengue viral antigens in keeping with the patient's history of frequent travel to Grenada to visit family.

Gadolinium-enhanced MRI of the brain and optic nerves was performed 4 days after admission, with it being reported as normal by day 6. A few T2 hyperintense signals in bilateral frontoparietal white matter areas were felt to represent non-specific age-related ischaemic changes by the reporting Radiologist. There were no abnormalities to suggest intracranial or orbital space-occupying lesions, and no abnormal contrast enhancement of the optic nerve sheaths to suggest leptomeningeal inflammation.

DIFFERENTIAL DIAGNOSIS

- Non-arteritic anterior ischaemic optic neuropathy (N-AION)
- Arteritic anterior ischaemic optic neuropathy (A-AION), such as giant-cell arteritis
- Typical optic neuritis (ie, demyelination)
- Other inflammatory optic neuropathy—secondary to systemic inflammation or infection
- Guillain-Barré syndrome (GBS) or a variant of it

TREATMENT

Following confirmation of the MRI scan report on day 6, the patient was started on 1 g of intravenous methylprednisolone (IVMP) daily for 3 days, followed by 14 days of oral prednisolone (30 mg daily for 1 week, reducing to 25 mg daily for the second week).

OUTCOME AND FOLLOW-UP

The patient was reviewed regularly on a slit-lamp in the ophthalmology clinic during her admission. Symptomatic extension of the right inferior field loss and progressive right optic disc swelling had occurred by day 2 while awaiting the MRI, and visual acuity had deteriorated to 0.6 logMAR (6/24) by day when colour vision had also reduced to 9/17 Ishihara plates and a right-sided RAPD was elicited.

Initial mild improvement of visual acuity after commencing IVMP was followed by persistent inferior field loss and reduced acuity at the 5-month follow-up (figure 1). The field defect corresponded to a superior sectoral optic disc pallor and persistent right-sided RAPD (figure 2). Direct and consensual pupil reflexes remained unremarkable. Subjectively, the patient continues to experience difficulty with reading and walking down stairs due to the inferior altitudinal field loss in her dominant right eye. There was full recovery of the other cranial nerves involved. A repeat gadolinium-enhanced MRI scan 3-months later confirmed no significant interval change compared to the first MRI scan.

DISCUSSION

Patients with acute onset optic neuropathies should be urgently investigated if they do not meet clinical diagnostic criteria for typical optic neuritis, AION, traumatic optic neuropathy or glaucomatous optic neuropathy. It is highly unlikely that this patient had non-arteritic AION, as the patient had no vascular risk factors, although there were some features of a crowded optic nerve head (the so called 'disc-at-risk') in both eyes. We ruled out giant-cell arteritis based on clinical symptoms, signs and inflammatory markers. Finally, the patient lacked signs of typical optic neuritis, which presents with increased orbital pain on eye movements.

This patient had reportedly developed a right-sided facial nerve palsy prior to returning to the UK. This, together with the possible later involvement of the fifth, ninth and tenth cranial nerves, may suggest multiple cranial nerve involvement due to CHIKV fever. However, this is difficult to prove in our patient. There are a few reports of multiple cranial nerve involvement in the same patient following CHIKV fever, and the virus has been implicated in facial palsy, acute sensorineural hearing loss and external ophthalmoplaegia, before.[1]

Another possibility is that the underlying diagnosis was a mild form of GBS, or a variant such as Miller-Fisher syndrome (MFS), which are immune-mediated peripheral nervous system disorders that may be triggered by viral infections. Our patient had minimal motor weakness and showed none of the classic signs (external ophthalmoplaegia, areflexia or ataxia) of MFS, although facial weakness and oropharyngeal weakness can be the only signs in this condition. During inpatient admission, under close observation, our patient showed no signs of progressive limb or respiratory weakness. It was felt therefore that this may at worst represent a mild form of MFS or GBS-variant and therefore further tests were not clinically indicated. Ancillary tests to support this diagnosis (cerebrospinal fluid analysis, electrodiagnostic nerve conduction tests, antiganglioside antibodies) are not always highly sensitive or specific[9] and, in addition, are time-consuming and expensive, and would not have altered the management in this case. However, they would have been something to consider had the clinical course been different, in order to guide further treatment options. MFS generally follows a benign and self-limiting course without treatment with intravenous immunoglobulin or plasma exchange,[10] and patients with mild GBS who are able to walk unaided can be safely observed until the eighth day to be certain that there is no progression.[10]

The patient's visual loss occurred almost 4 weeks following onset of the typical constitutional symptoms of viral illness. It is therefore difficult to implicate a direct infectious cause as the mechanism of the optic neuropathy. A delayed immune response has previously been suggested as the mechanism, due to either antigen mimicry between CHIKV antigens and normal host tissue proteins or a pathogenic lymphocytic reaction.[11] That said, a previous study on CHIKV related optic neuropathy found that 36% of cases had simultaneous systemic and ophthalmic manifestations.[6] This would conversely suggest a direct viral involvement of the optic nerve. However, the same paper found that 64% of cases had similarly late optic nerve involvement suggestive of a delayed immune response.

The exact mechanisms of neurological involvement are therefore still unclear. Reports of conjunctivitis, anterior uveitis and viral retinitis following CHIKV infection have usually occurred

simultaneously with systemic illness.[5 8 12] This has favoured the argument for a direct ocular involvement of the virus, at least in some cases. Evidence for this has mainly been through the detection of CHIKV antigens in corneal stromal keratocytes and iris stromal fibroblasts in corneal graft patients infected with the virus.[13]

Our patient showed some corticosteroid response when first started on IVMP, favouring an immune-mediated cause rather than a direct infiltrative optic neuropathy. Delaying steroid treatment until day 6 was detrimental because irretrievable optic atrophy had probably already begun as a result of axonal loss.

Our patient may have been at increased risk due to the small optic disc cups present, meaning that any axonal oedema was more likely to cause a mechanical obstruction to axoplasmic flow. This would then have resulted in a compartment syndrome within the optic nerve head, causing ischaemia and eventual retinal ganglion cell death and atrophy.

In hindsight, it is fair to suggest that prompt systemic steroid treatment following confirmation of positive anti-CHIKV serology would have resulted in a more favourable visual outcome. In addition, our case highlights the relatively small time window for effective steroid treatment in Chikungunya-related optic neuropathy, if permanent visual loss is to be avoided.

Learning points

- Any atypical optic neuropathy needs urgent impatient investigation and prompt treatment.
- Chikungunya virus may affect multiple cranial nerves, and a complete neurological examination is therefore paramount in patients presenting with focal neurology and a fever.
- Chikungunya usually follows an indolent course, but optic nerve involvement may cause permanent visual loss if not recognised and treated early.
- Sight-threatening optic neuropathy as a late complication of Chikungunya fever must be suspected in patients returning from endemic areas with vision loss and a history of fever.
- Prompt corticosteroid treatment should take precedence to avoid permanent visual loss, and in this regard all investigations including serology, radiology and neuroimaging must be performed as an emergency to permit systemic steroid administration at the earliest opportunity.

Contributors AA-F saw the patient at presentation and made the initial diagnosis. AAM saw the patient at subsequent follow-ups together with AA-F. AAM obtained consent from the patient and wrote up the case report. AA-F reviewed and amended the case report. Both authors read and approved the final, and revised drafts of the manuscript.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

1 Murthy JMK. Chikungunya virus: the neurology. *Neurol India* 2009;57:113–15.
2 Sudeep AB, Parashar D. Chikungunya: an overview. *J Biosci* 2008;33:443–9.
3 WHO. Chikungunya. Fact Sheet No 327. Updated October 2014. http://www.who.int/mediacentre/factsheets/fs327/en/ (accessed 25 Jan 2015).
4 Bandyopadhyay B, Bandyopadhyay D, Bhattacharya R, *et al*. Death due to Chikungunya. *Trop Doct* 2009;39:187–8.
5 Mahendradas P, Ranganna SK, Shetty R, *et al*. Ocular manifestations associated with Chikungunya. *Ophthalmology* 2008;115:287–91.
6 Mittal A, Mittal S, Bharati MJ, *et al*. Optic neuritis associated with Chikungunya virus infection in South India. *Arch Ophthalmol* 2007;125:1381–6.
7 Chanana B, Azad RV, Nair S. Bilateral macular choroiditis following Chikungunya virus infection. *Eye* 2007;21:1020–1.
8 Lalitha P, Rathinam S, Banushree K, *et al*. Ocular involvement associated with an epidemic outbreak of Chikungunya virus infection. *Am J Ophthalmol* 2007;144:552–6.
9 Green D, Ropper A. Mild Guillain-Barré syndrome. *Arch Neurol* 2001;58:1098–101.
10 Meena A, Khadilkar S, Murthy JMK. Treatment guidelines for Guillain-Barré syndrome. *Ann Indian Acad Neurol* 2011;14(Suppl1):S73-81.
11 Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. *J Ophthalmic Inflamm Infect* 2013;3:35.
12 Parola P, de Lamballerie X, Jourdan J, *et al*. Novel Chikungunya virus variant in travelers returning from Indian Ocean islands. *Emerg Infect Dis* 2006;12:1493–9.
13 Couderc T, Gangneux N, Chrétien F, *et al*. Chikungunya virus infection of corneal grafts. *J Infect Dis* 2012;206:851–9.