Afebrile meningoencephalitis with transient central facial paralysis due to Toscana virus infection, south-eastern France, 2014

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We report a case of meningoencephalitis caused by Toscana virus (TOSV) with central facial paralysis lasting over two days acquired in south-eastern France. The patient was not febrile either before or during the course of the disease. The diagnosis was established by both real-time RT-PCR and virus isolation with complete genome sequencing. This case emphasises the need to consider TOSV in non-febrile neurological syndromes in people living in or having travelled to the Mediterranean area.

In this report, we present a case of Toscana virus (TOSV) meningoencephalitis with a central facial paralysis and without fever, acquired in the close vicinity of Marseille, in southern France. This report should be a reminder for healthcare professionals to consider TOSV diagnosis even in afebrile patients with neurological symptoms.

Case report

On 11 July 2014, a French woman in her forties living in a small city at around 20 km from Marseille had a sudden onset of frontal and temporal lobe throbbing headaches upon awakening, without fever. Symptoms were severe and a few hours later she visited the emergency department of a local hospital with headache, nausea and photophobophobia. On admission, she was still non-febrile and the symptoms were persisting despite oral intake of paracetamol in hospital (1,000 mg). The patient's medical history consisted of asthma during childhood, and no history of recent travel abroad.

Neurological examination revealed (i) a slight stiff neck, (ii) a discrete left central facial paralysis, and (iii) the absence of abnormalities of cranial nerves except discrete left central facial paresis, sensorimotor loss, cerebellar or pyramidal syndromes. She received 20 mg intramuscular nefopam hydrochloride which alleviated the pain.

A lumbar puncture was performed and the analysis showed that the cerebrospinal fluid (CSF) was clear; it contained 475 cells/mm³ (norm: <10 cells/mm³) (90% lymphocytes), and showed hypoglycorrhachia at 2.4 mmol/L (norm: >3 mmol/L) and hyperproteinorachia at 1.78 g/L (norm: 0.4 g/L).

A diagnosis of meningoencephalitis was determined. The patient was treated with acyclovir, ceftriaxone and amoxicillin, and was transferred to the neurology department of the same hospital.

Further laboratory diagnostic and radiological tests To search for the cause of the meningoencephalitis, a series of laboratory tests were performed. Liver function tests and ionogram were normal. Blood levels of glucose, urea nitrogen, albumin, creatinine, lactates, troponin T, C-reactive protein, and procalcitonin were normal. However, creatinine phosphokinase (CPK) level was moderately increased at 368 U/L (norm: <170 U/L). There was a slight increase of fibrinogen rate at 4.76 g/L (norm: 2–4 g/L). Prothrombin time was 92% (norm: 70–100%). Blood cell count was 9,100 leukocytes/μL (norm: 4,000–10,000 leukocytes/μL) (81.5% neutrophils and 13.0% lymphocytes), haemoglobin 13.4 g/dL, and the platelet count 251,000/μL.

Blood cultures collected on day 1 remained sterile. PCR for *Listeria monocytogenes* was negative. CSF Gram staining and culture remained negative; real-time PCR for *Neisseria meningitidis*, *Streptococcus pneumoniae*, herpes simplex virus, varicella-zoster virus, and real-time RT-PCR for West Nile virus and enteroviruses were negative. In contrast, real-time RT-PCR for TOSV was positive (Ct 28) whereas there was no IgG or IgM specific for TOSV in the serum collected at the acute stage. No convalescent serum could be obtained.

As isolation of virus from clinical samples is the gold standard for diagnosis, although seldom performed,

the CSF was inoculated onto Vero cells. Five days later, a clear cytopathic effect was observed and virus isolation was confirmed by the complete genetic characterisation using next-generation sequencing (NGS) based on Ion Torrent technology. The full-length sequence was deposited into the GenBank database. Genetic and phylogenetic analyses using the complete sequence of this strain demonstrate that our patient was infected by a TOSV strain that belongs to the lineage B.

A brain magnetic resonance imaging (MRI) scan indicated a contrast enhancement on brainstem, probably of vascular origin. A second MRI was planned to distinguish between telangiectasia and developmental venous abnormality. Computed tomography (CT) scans and the electroencephalogram (EEG) were normal.

On day 2, headache intensity had reduced and the facial paralysis was no longer present upon clinical examination. Antiviral and antibiotic treatments were stopped when PCR for TOSV proved to be positive. On day 3, the result of the neurological examination was normal; the patient complained of general fatigue and residual headaches reactive to paracetamol; she was discharged from hospital with pain relief medication.

Background

TOSV is an arthropod-borne virus that belongs to the genus *Phlebovirus* within the family *Bunyaviridae*. TOSV is transmitted from phlebotomine sandflies belonging to the subgenus *Larroussius*, such as *Phlebotomus perniciosus* and *Phlebotomus perfiliewi*, although other species might be involved in the circulation and maintenance of TOSV in nature [1]. The geographical area where the presence of TOSV is assessed directly (virus isolation or RT-PCR detection and sequence data) is much larger at present than 10 years ago. Roughly all countries bordering the Mediterranean Sea (southern Europe, northern Africa, and Middle East) are concerned. Since TOSV is an arbovirus (arthropod-borne) human cases of TOSV infection only occur during the period of activity of its sandfly vector, hence April to November, with peaks during the hottest period from July to September. Although TOSV can sometimes be responsible for mild febrile illness, it is commonly causing neurovirulent infections such as meningitis or meningoencephalitis. TOSV is one of the main viral causes of aseptic meningitis during the hot season in south-eastern France when enteroviruses and herpesviruses are most prominent [2,3].

Discussion and conclusion

In addition to the case described here, a bibliographic search in PubMed database from 1971 until now retrieved only two cases of facial paralysis in the context of TOSV infection: (i) a 30-year-old male patient admitted with headache and fever who developed an abrupt right facial paralysis [4], (ii) and a 68-year-old man returning from a 10-day stay in central Italy who developed a left central facial paralysis and a cerebellar syndrome [5]. The clinical manifestations observed

in these two cases were co-incident with fever. The absence of fever from the onset of the disease until the favourable outcome is quite atypical and is noteworthy.

In contrast with the common belief that virus isolation is of poor sensitivity for diagnostic purpose [6], this case is the third successive case of a TOSV neuroinvasive infection for which virus isolation has been successful despite moderate or low virus load in the specimen [5, data not shown]. Accordingly, TOSV isolation should be attempted, whenever possible, as it is the gold standard technique for diagnosis, and it allows further genetic and phylogenetic documentation.

There are three genotypes of TOSV, more or less depending upon the geographical origin: lineage A strains were reported in Italy, France, Tunisia and Turkey; lineage B strains originated from Portugal, Spain, France and Morocco [7]; the lineage C was described recently in Croatia and Greece although the virus has not been isolated so far. In all the countries around the Mediterranean Sea TOSV is endemic and should not be considered anymore as an emerging pathogen but rather as a neglected pathogen. As previously reported, also south-eastern France is endemic for TOSV [8,9]. The average duration of the disease is seven days (3 to 10 days) [2]. Our patient was no exception to this rule. She acquired TOSV infection in July, i.e. during the period when the vector is more active. Encephalitis is frequently encountered in neuroinvasive infections due to TOSV [10]. Of interest is the hypoglycorachia that is unusual with viruses although sometimes reported with TOSV [10].

In conclusion, this case is of interest for the following reasons: (i) it is the first description of a TOSV meningoencephalitis without concomitant febrile syndrome, (ii) it is one of the few cases associated with facial paralysis, (iii) it emphasises the need to consider TOSV as possible cause of typical and especially atypical neurological syndromes in patients living in or returning from TOSV endemic areas, and consider it even in the absence of febrile syndrome.

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Conflict of interest

None declared.

Authors' contributions

Marion Cécile MARLINGE: collected laboratory data and wrote the draft.

Lydie CRESPI: clinical aspects.

Christine ZANDOTTI: laboratory data monitoring.

Géraldine PIORKOWSKI: sequencing and genetic analysis.

Elsa KAPHAN: clinical aspects.

Rémi N. CHARREL: wrote the manuscript.

Laetitia NINOVE: wrote the manuscript and organised the data.

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