CASE REPORT

Severe post-influenza (H1N1) encephalitis involving pulvinar nuclei in an adult patient

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SUMMARY

Neurological complications of H1N1 infections are mostly found in children, but rare cases of acute encephalopathy and post-infectious encephalitis such as acute disseminated encephalomyelitis (ADEM) have been described in adults. We report a case of an adult presenting with a progressive and severe encephalopathy that developed after H1N1 respiratory infection resolution. Cerebrospinal fluid (CSF) analysis was normal, including negative PCR for herpes simplex virus, H1N1, influenza B and JC virus, and absent oligoclonal IgG bands in CSF and serum. Initial CT scan was normal, but later MRI showed posterior multifocal leucoencephalopathy with pulvinar sign. The delayed neurological findings together with the ancillary investigation, namely the MRI pattern with both grey and white matter involvement, raised the possibility of a post-infectious process, rather than an acute encephalitis. Despite aggressive immunotherapy, the patient experienced severe neurological sequelae. Early recognition of ADEM manifestations by those dealing with H1N1 infection is important as early immunotherapy may improve the prognosis.

BACKGROUND

In April 2009, a new strain of human H1N1 influenza A virus was identified in Mexico. The virus quickly spread to other countries, becoming a global pandemic with further waves.¹ Neurological complications from H1N1 infections are mostly found in children with incidence ranging from 1.7% to 15.0%, according to several studies.^{2–7} Common situations include acute reversible encephalopathy and/or seizures, but there are also cases of stroke, Guillain-Barré syndrome, transverse myelitis and post-infectious encephalitis, such as acute disseminated encephalomyelitis (ADEM).^{3–10} Davis and coauthors summarised 32 patients with encephalopathy related to H1N1, mostly under 17 years of age, with a severity ranging from lethargy to coma. The most worrisome complication was acute necrotising encephalitis (ANE) leading to death or severe neurological sequelae such as mental retardation, dementia or extrapyramidal dysfunction.^{11–13} Apart from ADEM, the neuroimaging abnormalities described included non-specific T2 signal abnormalities in the splenium and other areas, focal and generalised cerebral oedema and posterior reversible encephalopathy.³ Furthermore, cerebrospinal fluid (CSF) pleocytosis is rare, viral RNA has not been amplified from CSF and viral antigens have not been detectable in brain tissues, suggesting that CNS complications may be immune-mediated rather than the

result of a direct viral invasion.¹⁴ We report the case of an immunocompetent adult who developed a progressive, severe and irreversible encephalopathy with seizures, involuntary movements and cortical blindness after the resolution of the respiratory infection associated with influenza A H1N1 virus.

CASE PRESENTATION

Our case report begins in February 2013, when an H1N1 infection occurred in our country. A 53-year-old Caucasian woman, living in a rural area of Coimbra district and without a relevant medical or personal history, was transferred to the emergency department of our central hospital, with a 5-day respiratory infection, with rapidly progressive respiratory failure requiring mechanical ventilation. PCR of a nasopharyngeal swab was positive for influenza A H1N1 virus, and cultures of tracheo-bronchial aspirate were positive for multidrug-resistant bacteria (*Acinetobacter baumannii*; *Pseudomonas aeruginosa*). She was admitted to the intensive care unit (ICU) with the diagnosis of H1N1 respiratory infection complicated by pneumonia, and medicated with oseltamivir 150 mg 12/12 h as well as ceftriaxone and azithromycin. She was intermittently sedated with propofol and, although uncooperative, she showed no neurological manifestations. After 2 weeks, the respiratory infection was considered resolved and she was discharged from the ICU to the medicine ward, without invasive ventilation. Over the following days, she began to present focal motor seizures evolving to focal status epilepticus, which was controlled with phenytoin perfusion. The EEG showed diffuse slowing of the background activity, without asymmetries, and brain CT scan and CSF study were both normal. After this, choreoathetosis of the right hemibody emerged and, independently of sporadic seizures, her mental state fluctuated between being awake and answering simple questions, and periods where she was not cooperating and did not make visual or verbal contact.

INVESTIGATIONS

One month after admission, ancillary investigation was repeated: CT scan showed hypodensity, involving bilateral posterior parietal regions; brain MRI confirmed posterior multifocal leucoencephalopathy involving the basal ganglia (figure 1); EEG revealed disorganisation of the background activity with periodic lateralised epileptiform discharges on temporo-occipital regions; the CSF analysis remained normal, while tests for PCR for herpes simplex virus, H1N1, influenza B and JC virus

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Figure 1 Brain MRI showing intra-axial multiple lesions with hyperintense signal on fluid-attenuated inversion recovery/T2, involving both thalamic pulvinar nuclei, frontal and opercular subcortical regions bilaterally, the left temporoparieto-occipital cortex and the right medial temporo-occipital region with discrete overlying parietal involvement. Diffusion-weighted images showing restriction of diffusion of the involved areas.

were negative, and oligoclonal IgG bands were absent in CSF and serum.

TREATMENT

Soon after the first positive CT, treatment with 1 g/day of methylprednisolone for 5 days was performed, without clinical or MRI improvement, and intravenous immunoglobulin (25 g/day) during 5 days was also ineffective. Both strategies were repeated, with no major benefits: epileptic seizure control was achieved, but an irreversible encephalopathic state remained, with delirious speech, visual hallucinations, cortical blindness, bilateral extensor plantar response and involuntary right arm and leg movements.

OUTCOME AND FOLLOW-UP

The patient was permanently institutionalised in a long-term facility and was re-evaluated 2 months after discharge, presenting the same clinical status. A fatal outcome was the result of this disease 2 years after onset.

DISCUSSION

The patient described presented with a severe and rapidly progressive neurological condition characterised by encephalopathy, seizures, involuntary movements and cortical blindness, after the resolution of a life-threatening respiratory influenza A (subtype H1N1) infection, the first respiratory symptoms of which started 3 weeks prior. It is important to state that metabolic disturbances and haemodynamic instability were excluded, antiviral therapy initiated just after the virus identification did not prevent the later neurological deficits and the CSF had normal cell count and biochemistry, and no IgG oligoclonal bands, virus or antibodies were detected even with repeated lumbar punctures.

The delayed profile of clinical findings together with the ancillary investigation, namely the MRI pattern of diffuse multifocal lesions with both grey and white matter involvement, raise

the possibility of a post-infectious immune-mediated process (ADEM), rather than an acute viral encephalitic/meningitic infection. The distinction of these two conditions is important due to their different approaches and prognosis. In ADEM, infectious agents cannot be isolated from neural tissue or CSF, as in the case of our patient, and there is an inflammatory immune-mediated response, with demyelination and grey matter involvement in the MRI. Moreover, while the treatment of the acute encephalitis/meningitis relies on antiviral and antibacterial agents, in ADEM it consists of immunosuppression and immunomodulation with steroids, intravenous immunoglobulin and plasma exchange, since it appears to be a predominantly inflammatory disease.¹⁵ Immunotherapy was ineffective in our patient, with other cases of irreversible encephalitis refractory to treatment already described in children^{10 16} and, more rarely, in adults.^{17 18} Several cases of bilateral thalamic lesions related to H1N1 encephalopathies have been described in the literature.^{12 13 17 19–21} The MRI of our patient showed a bilateral T2 hyperintense pulvinar sign, however, this type of lesion has also been described in other pathologies, mainly post-infectious processes (other than H1N1) and in the variant Creutzfeldt-Jakob disease.²²

Pathophysiology of ADEM related to H1N1 is not well understood, although it has been hypothesised that a prior antigenic stimulus provided by the H1N1 virus can trigger a secondary autoimmune inflammatory response. Accordingly, myelin peptides are similar to several viral sequences and T-cell clones can initiate a cross-reactive antimyelin response.²³ Furthermore, predominance of a T-cell over a B-cell immune response might explain why IgG oligoclonal bands could not be isolated in CSF.²⁴

ADEM is more common in childhood²⁵ and its prognosis may depend on the aetiology: among children with H1N1 infection, the great majority achieved full recovery; on the contrary, for measles-related ADEM, high rates of morbidity and mortality have been described.^{3 26} We reviewed the PubMed indexed

cases of H1N1 encephalopathies in adults (n=8), and all of the three cases identified as ADEM had had a poor outcome;^{18 27 28} in two other cases identified as ANE, a 20-year-old patient had good recovery and a 42-year-old man died without clear information regarding the interval between respiratory and neurological symptoms, making an ADEM diagnosis uncertain.^{10 17} Finally, in the remaining three cases, there was also no clear distinction between acute and post-infectious encephalitis, and two of them had a bad outcome.^{29–31} Thereby, ADEM related to H1N1 is still very rare among adults and can sometimes have a poor outcome, especially in cases of hyperacute forms or ANE.^{17 18 32} The patient described in this report was one of those rare cases with an unfavourable outcome with severe neurological sequelae leading to death in 2 years.

Learning points

- The clinical and imaging features and the severe neurological sequelae at discharge, despite aggressive, prolonged and repeated immunomodulatory therapy, are compatible with the diagnosis of H1N1-related acute disseminated encephalomyelitis (ADEM).
- ADEM is a post-infectious immune-mediated inflammatory process, still rarely described in adults, and, to the best of our knowledge, this is the fourth case of ADEM related to H1N1 that had a poor or fatal prognosis.
- This case occurred in 2013, 4 years after the 2009 global pandemic, and represents a fulminant variant, very uncommon among the reported cases of ADEM in adults.
- Early identification of the neurological manifestations of ADEM by those dealing with H1N1 infection, especially infectologists, internists and intensivists, can be important for an early approach to immunotherapy.

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