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Virology Question and Answer Scheme (VIROQAS)

Severe encephalitis in a previously healthy teenager: Who is the real culprit?

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1. Case report

A 14-year-old French boy was admitted to a primary care hospital with headache, vomiting, dysarthria and acute confusion. He had a feverish peak the day before and 2 weeks prior to his presentation, he complained of headache, earache, rhinorrhea and a transient diarrhea. The medical history was not remarkable and he did not recently travel outside France. He was apyrexial on admission and the physical examination revealed no significant findings. The basic blood chemistry and blood count were normal, and the screening of toxics was negative. The C reactive protein and serum procalcitonin were 10 mg/L and 0.10 ng/mL respectively. CSF analysis showed 49 WBC/mm^3 with lymphocyte predominance (90%), protein 1.16 g/L, glucose 5.2 mmol/L and lactate 2.2 mmol/L; and CT scan of the brain was normal. Infectious meningoencephalitis was suspected, and the patient treated with intravenous ceftriaxone and acyclovir. Twenty-four hours later, his condition worsened increasingly. He became unconscious and agitated. He presented continuous involuntary movements without seizures, abnormal eye movements and intense hypertonia and hyperreflexia of all four limbs. The patient was therefore admitted to the ICU. He had a temperature of 40.3 °C (104.5 °F), heart rate of 145 beats per minute, blood pressure of 151/75 mmHg, respiratory rate of 36 per minute and oxygen saturation of 97% on 21% FiO_2. Initial laboratory tests on admission to ICU (see Table 1) found a mild lymphopenia (with a CD4/CD8 ratio at 1:2) and a significant elevation of creatine phosphokinase. A new CT scan and a magnetic resonance imaging were normal. Electroencephalography showed diffuse slowing. Microbiological investigations were also initiated. Blood and CSF bacterial culture remained negative, and *Mycoplasma pneumoniae* serology was negative. Many virological tests were performed in the blood and the CSF as shown in Table 2. A significant level of anti-VCA IgM antibody and a very low level of anti-HSV IgM antibody were observed in serum. An equivocal reaction

Table 1
Results of initial laboratory tests on admission to ICU.

Laboratory test	Value	Reference value
Blood		
WBC (n/mm^3)	7780	4500–14500
Hemoglobin (g/dL)	11.5	11.5–16
Platelets (n/mm^3)	219	150–400
Neutrophils (n/mm^3)	5500	1500–8000
Monocytes (n/mm^3)	800	200–800
Lymphocytes (n/mm^3)	1400	1500–7000
Glucose (mmol/L)	5.95	3.34–5.56
Blood urea nitrogen (mmol/L)	8.63	1.66–6.64
Creatinine (μmol/L)	115	5–97
Na^+ (mmol/L)	142	132–145
K^+ (mmol/L)	3.4	3.1–5.1
Cl^- (mmol/L)	102	95–110
ALT (U/L)	52	15–40
AST (U/L)	40	10–40
LDH (U/L)	311	120–300
CPK (U/L)	2389	20–260
CRP (mg/L)	28	<6
Procalcitonin (ng/mL)	0.6	< 2
Cerebrospinal fluid		
WBC (n/mm^3)	13	–
Protein (g/L)	0.83	0.10–0.60
Glucose (mmol/L)	3.2	2.8–4.2
Cl^- (mmol/L)	133	118–130
Lactate (mmol/L)	2.02	1.00–1.65

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Table 2
Results of initial virological investigations.

Virological test	Result	Assay (manufacturer)
Blood		
IgG anti-measles	Positive	ELISA (Euroimmun AG)
IgM anti-measles	Negative	
IgG anti-mumps	Negative	ELISA (Euroimmun AG)
IgM anti-mumps	Negative	
IgG anti-HSV	Negative	ELISA anti-HSV1/2 (Euroimmun)
IgM anti-HSV	Positive (low signal)	
IgG anti-VCA (EBV)	Negative	CLIA LIAISON (Diasorin)
IgM anti-VCA (EBV)	Positive	
IgG anti-EBNA (EBV)	Negative	
IgG anti-CMV	Positive	CLIA LIAISON (Diasorin)
IgM anti-CMV	Equivocal	
Heterophile antibody test	Positive	Agglutination (Servitex MNI)
Serum interferon alpha	Negative	Bioassay (in-house test)
HIV-1/2 serology	Negative	Architect HIV Ag/Ab (Abbott)
EBV DNA	Weak signal	Real time QPCR (Argene)
CMV DNA	Negative	Real time QPCR (Argene)
HSV DNA	Negative	Real time QPCR (Argene)
HHV6 DNA	Negative	Real time QPCR (Argene)
Cerebrospinal fluid		
IgG anti-measles	Negative	ELISA (Euroimmun AG)
IgM anti-measles	Negative	
IgG anti-mumps	Negative	ELISA (Euroimmun AG)
IgM anti-mumps	Negative	
HSV DNA	Negative	Real time QPCR (Argene)
VZV DNA	Negative	Real time QPCR (Argene)
EBV DNA	Negative	Real time QPCR (Argene)
CMV DNA	Negative	Real time QPCR (Argene)
Enterovirus RNA	Negative	Real time QPCR (Argene)
HHV6 DNA	Negative	Real time QPCR (Argene)
Adenovirus DNA	Negative	Real time QPCR (Argene)

was also found for anti-CMV IgM. The heterophile antibody test was positive and interferon alpha was undetectable in serum. A low signal was observed for EBV DNA in the blood (below the quantification threshold). All the assays performed in the CSF were negative.

Question 1: Do you consider this to be a viral disease based on these results?

Question 2: Do you think other viruses need to be investigated?

Question 3: What's your final diagnosis in light of additional results provided?

See evidence-based opinion overleaf.