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CASE REPORT

The clinical approach to a patient with suspected autoimmune encephalitis

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Abstract

We present the case of a 59-year-old woman, admitted to the ICU of our hospital with subacute neurological deterioration and subsequent coma of unknown origin. The diagnostic work-up and treatment of suspected autoimmune encephalitis (AIE) according to national guidelines is discussed. Recent research and clinical guidelines regarding AIE are presented to identify several subtypes of the disease. Due to expert consultation it was possible to treat this patient near her family. Despite adequate treatment, the patient unfortunately did not survive.

Introduction

Acute encephalitis syndromes incorporate a broad spectrum of diseases which involve inflammation of the brain. Acute encephalitis is most commonly caused by infection, primarily viruses. When an infectious cause of neurological symptoms cannot be identified, or the condition of the patient does not improve with empirical treatment, non-infectious causes of encephalitis should be considered. Autoimmune encephalitis (AIE) is a rare but potentially lethal disease, which can be further classified in several autoimmune syndromes. In this case report, we describe a patient with neurological symptoms caused by underlying immune-mediated encephalitis. Furthermore, recent literature regarding a diagnostic approach to autoimmune encephalitis is discussed.

Case

A 59-year-old woman with a history of nicotine abuse, rheumatoid arthritis, depression and hypertension was evaluated at the emergency department for progressive fatigue and a tendency to fall to the left when walking during the last two weeks. She had also complained of blurred vision and dizziness without vertigo. She denied having headaches, fever, nausea, vomiting or tinnitus. Her oral intake had been poor in the last two weeks. Family members noted that she had developed a severe form of agoraphobia in recent months for which she was started on a selective serotonin reuptake inhibitor (paroxetine). Her standard drug therapy consisted of metoprolol, hydrochlorothiazide and ranitidine. She had not used any disease-modifying antirheumatic drugs in the last six years.

On physical examination at the emergency department she was somnolent but not confused or disorientated. Her vital signs and temperature were normal and she did not have any meningeal signs. On neurological examination, she was dysarthric without aphasia. Pupillary reflexes and eye movement tests were normal. Family members had described a possible nystagmus but this was not objectified. There were signs of rigidity of the right arm, but no loss of muscle strength or sensory function of any extremity. Deep tendon reflexes were normal. Standard examination of the chest, abdomen and skin was unremarkable. No external signs of arthritis or lymphadenopathy were found. The laboratory blood tests on admission showed a neutrophilic leucocytosis (leucocytes 19 x 10^9/l; ref. 4-8) with C-reactive protein of 15 mg/l (ref. <5). Liver and kidney laboratory tests

were unremarkable, except for a low sodium concentration (126 mmol/l; ref. 135-145) with a high urine sodium concentration (101 mmol/l). Chest X-ray was normal; CT scan of the brain did not show any abnormalities.

The patient was initially admitted to the internal medicine ward with the presumptive diagnosis of symptomatic hyponatraemia, possibly as a side effect of paroxetine. A few hours after admission she showed signs of altered consciousness and developed total respiratory failure for which she was transferred to the ICU. She was intubated to enable mechanical ventilation. The next day the patient showed clinical improvement and adequate responsiveness. Shortly after successful weaning and extubation, she relapsed into coma with loss of airway reflexes and was re-intubated. Neurological examination did not reveal any new localising abnormalities. The serum sodium concentration normalised after cessation of paroxetine and administration of normal saline solution (0.9%), not exceeding a limit of 8 mmol/l in a 24-hour interval. Cerebrospinal fluid (CSF) analysis showed 43 leukocytes/µl (86% mononuclear) with glucose 6.2 mmol/l (ref. 2.7-4.4) and protein 0.48 g/l (ref. 0.29-0.67). Lumbar CSF opening pressure was not measured. Serum glucose was 9.8 mmol/l. Antimicrobial therapy for a possible central nervous system infection was started with ceftriaxone, amoxicillin, acyclovir and dexamethasone while awaiting the microbiology results. Culture of CSF and viral PCRs were all negative and the patient did not improve clinically. A broad differential diagnostic approach was used to identify the underlying aetiology. The most common structural brain abnormalities were excluded on CT scan. Ischaemic stroke was unlikely considering the subacute onset and progression. Extensive laboratory tests were performed including antibody tests, considering a possible autoimmune encephalitis. Toxicology screening (liquid chromatography–mass spectrometry) was negative. CSF cytological examination showed a non-specific lymphocytosis. Flow cytometric immunophenotyping of CSF showed no clonal abnormalities. The possibility of a paraneoplastic phenomenon was considered, but no signs of malignancy were found on physical examination. CT scans of the chest and abdomen were unremarkable. Ultrasound screening of breast, endometrium and ovaria was negative. Endoscopy of the gastrointestinal tract was also negative.

Non-convulsive status epilepticus was excluded by electroencephalography (EEG) on day 4 of admission. MRI of the brain on day 5 showed diffuse leptomeningeal enhancement infratentorially and supratentorially on T1 imaging with intravenous contrast and increased signal intensity in the sulci, brainstem and mesencephalon on FLAIR *(figure 1, section A)*.

Serum biochemistry tests for ammonia, copper, ceruloplasmin, carbon monoxide, thyroid status and vitamin status provided no

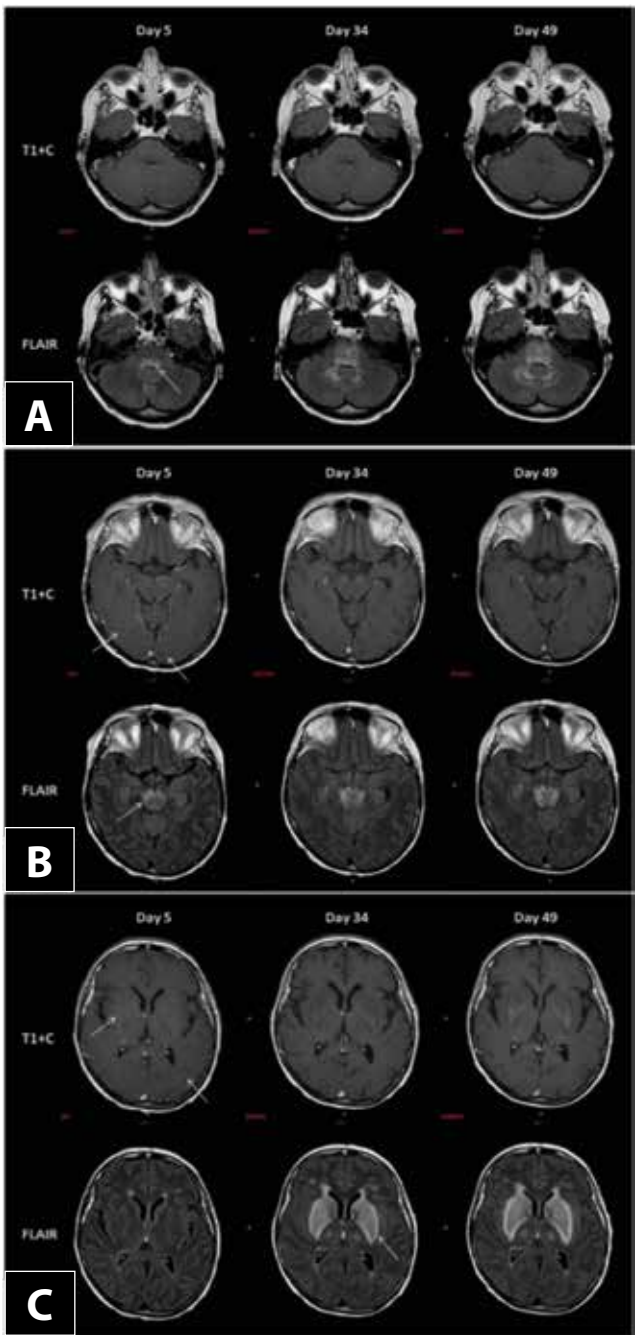

Figure 1. A. Top row: axial T1 with intravenous contrast. Bottom row: axial FLAIR. Arrow bottom row: increased FLAIR signal in brainstem. Progressive FLAIR abnormalities in brainstem and cerebellum on day 34 and day 49

B. Top row: axial T1 with intravenous contrast. Bottom row: axial FLAIR. Arrows top row: Diffuse increased leptomeningeal enhancement supratentorial. Arrow bottom row: Increased FLAIR signal in mesencephalon. Progressive FLAIR abnormalities in mesencephalon on day 34 and day 49

C. Top row: axial T1 with intravenous contrast. Bottom row: axial FLAIR. Arrow top row: diffuse increased leptomeningeal enhancement. Arrow bottom row: symmetrical increased FLAIR signal in basal ganglia and thalami

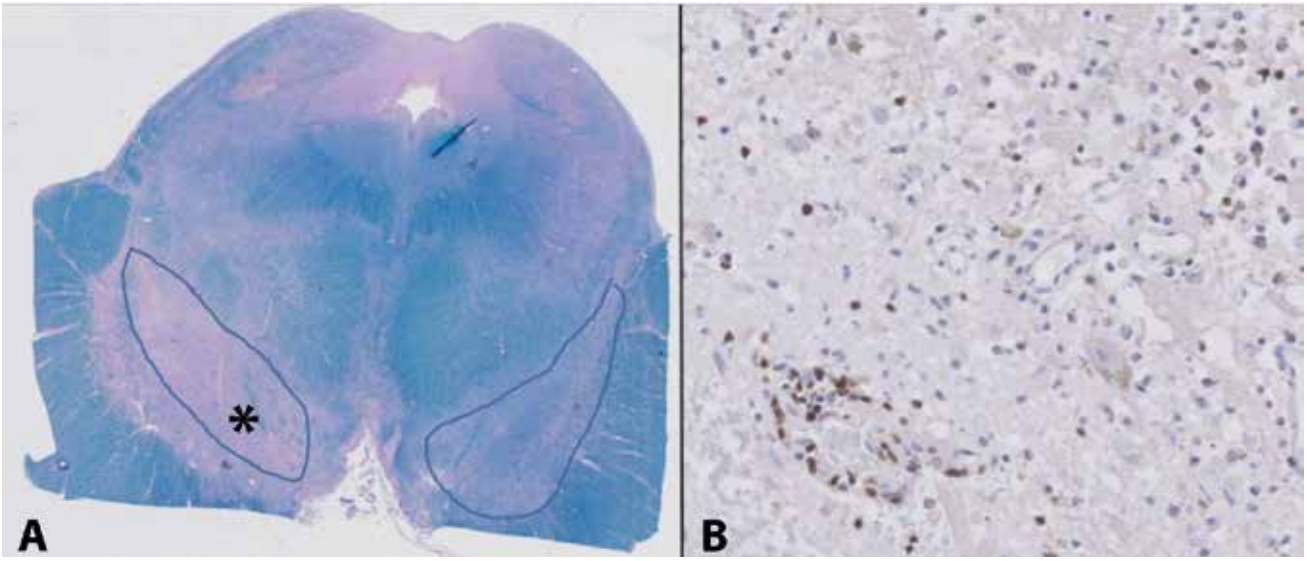

Figure 2. A: Overview of a Luxol Fast Blue (LFB) / H&E stained transverse section through the mesencephalon. The delineated areas represent the substantia nigra. On the left-hand side there is less LFB positivity reflecting loss of myelin, compared with the other side. The asterisk represents the area where Figure B was taken. **B:** High magnification showing CD3-positive T-cells (brown staining) in the substantia nigra. In the left bottom corner CD3-positive cells are seen around a blood vessel. In a lower density these T-cells can also be observed diffusely in the brain parenchyma

directional clues. Systemic antibodies, including ANA, ANCA, anti-ENA, anti-dsDNA and anti-TPO, were negative. Neuronal antibody tests on serum and CSF, including anti-NDMAR, anti-AMPAR, anti-amphiphysin, anti-aquaporin 4, anti-Caspr2, anti-CV2, anti-DPPX, anti-GABA(a/b)R, anti-GAD65, anti-GQ1b, anti-GlyR, anti-Hu, anti-LGI1, anti-MOG, anti-VGKC, were all negative. Immunohistochemistry with serum and CSF on rat brain slices and immunocytochemistry on live rat hippocampal neurons (research laboratory for antibody discovery) was negative.[1] Considering the neurological symptoms progressed rapidly in this patient (<2 weeks) and were preceded by new psychiatric symptoms, in combination with the presence of CSF pleocytosis and MRI abnormalities (although not typical for AIE) and the exclusion of other reasonable causes, a diagnosis of probable autoimmune encephalitis was established in concurrence with local guidelines.[2] After consultation with experts, pulse therapy with high doses of methylprednisolone (1000 mg once daily) and intravenous immunoglobulin (0.4 g/kg/day) was started for five days. Indication for transfer to a specialised centre was discussed but was not deemed necessary at that moment. Unfortunately, the patient showed no response to the treatment. Subsequently, second-line treatment with rituximab (375 mg/m^2 once a week) and high-dose cyclophosphamide (1500 mg (= 867 mg/m^2) once a month) was started on day 24. Follow-up MRI was performed on day 34 of admission and showed symmetrical progressive abnormalities in the mesencephalon, brainstem, basal ganglia and cerebellum *(figure 1, section B)*. A high suspicion of encephalitis persisted. The symmetry of the brain lesions urged us to consider metabolic diseases and other toxic causes. However, additional tests (not shown) were not conclusive for any metabolic disease and toxicological analysis did not detect heavy metal poisoning. A second follow-up MRI of the brain 49 days after admission showed minor progression of the pre-existing lesions *(figure 1, section C)*. A second EEG was performed and showed generalised slowing and background suppression. On neurological reassessments, there had been no ocular, verbal or motor reactivity to stimuli for several weeks. Pupillary, corneal and oculocephalic reflexes were only variably seen, and there were no spontaneous breathing efforts. Therefore, chances of recovery were deemed very low and curative treatment was discontinued, in consultation with the patient's family. She passed away after withdrawal of life-supporting therapy.

On post-mortem examination of the brain, a diffuse chronic encephalitis of the brainstem, cerebellum and cerebrum was found, with secondary neuronal tissue loss. Lymphocytic infiltration was seen diffusely throughout the tissue, but more densely in the substantia nigra and the pons *(figure 2)*. The infiltrate was not atypical (i.e. non-neoplastic) and consisted mostly of CD3-positive T-cells, of which CD4 cells were in favour of CD8 cells. Hardly any CD20-positive B-cells were observed, most likely due to the treatment with rituximab, and only a limited number of plasma cells were present. Furthermore, extensive loss of Purkinje cells was observed. Immunohistochemistry showed no pathological deposition of beta-amyloid, tau or p62, which are linked to neurodegenerative diseases. TDP43 expression, which is linked to neurodegeneration in frontotemporal dementia and amyotrophic lateral sclerosis, was physiological. Diagnostic tests for HSV-1, CMV, EBV, T. Whipplei, JC virus

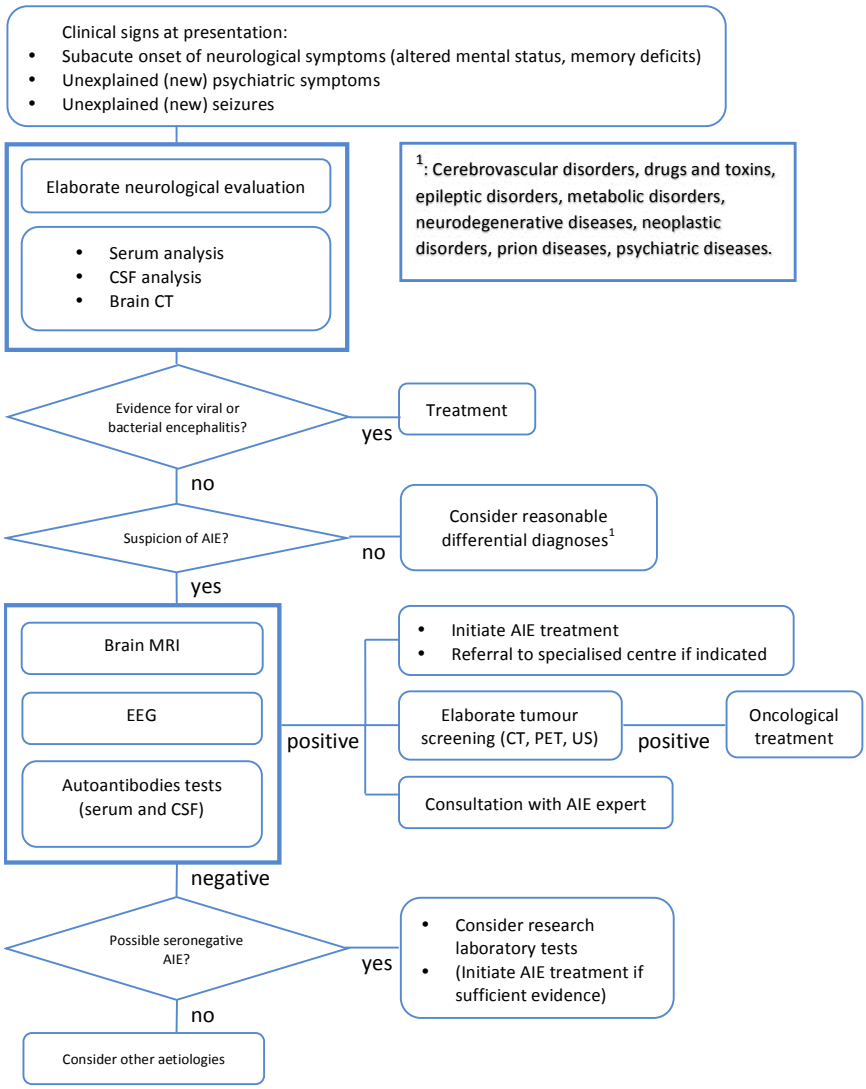

Figure 3. Flowchart of diagnostic approach to suspected autoimmune encephalitis
AIE = autoimmune encephalitis; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; MRI = magnetic resonance imaging; PET = positron emission tomography; US = ultrasound

and Simian virus 40 were negative. IgG4-related disease was considered unlikely because of the relative absence of plasma cells in the specimen.

Discussion

The clinical approach to a patient with encephalitis of unknown origin can be elaborate and requires an organised diagnostic process. Epidemiologically, viral agents are the most common pathogens, especially Herpes Simplex virus.[3] When a viral infection is excluded, AIE (anti-NMDAR encephalitis in particular) should be considered as a differential diagnosis, among other reasonable causes (bacterial, toxic, etc.).[4,5] The terminology can be confusing; the immune-mediated, cancer-related forms of encephalitis are usually referred to as paraneoplastic encephalitis syndromes, while the autoimmune encephalitis syndromes may occur in the presence or absence of cancer. The term autoimmune encephalitis is usually used to indicate diseases with antibodies against neuronal cell surface or synaptic proteins.[6] The current incidence of AIE is not clearly known. Dubey et al. (2018) performed a population-based comparative study between infectious encephalitis and autoimmune encephalitis, which showed a comparable prevalence and incidence, attributable to increased detection.[7] In children, the incidence of anti-NMDA receptor encephalitis, the major cause of AIE, is 0.85 per million children annually.[8] An estimation of the current incidence of AIE in the Netherlands is 90 cases per year, which is approximately 5.3 per million, although incidence figures are increasing (expert opinion, Titulaer).

The clinical approach involves thorough neurological exami-nation and standard diagnostic tests (MRI, CSF analysis and EEG) to guide initial treatment.[2,5,9,10] When the more common causes of encephalitis have been excluded and/or the patient shows no response to empirical therapy, AIE must be considered. Neurological examination is therefore essential and can sometimes provide early clues to a specific subtype of AIE. The flowchart shows the basic steps in the clinical approach to a suspected AIE *(figure 3)*. Additional tests, primarily comprehensive antibody tests which are time consuming, are performed to come to a more conclusive diagnosis and to refine treatment. Graus et al. published a clinical approach algorithm to aid clinicians in the diagnosis of AIE.[5] By using their algorithm, physicians can classify some subtypes of AIE as probable or definite and initiate immunotherapy before the results of autoantibody tests are available. These subtypes include limbic encephalitis, acute disseminated encephalomyelitis, anti-NMDA receptor encephalitis and Bickerstaff's brainstem encephalitis. Another recent study showed that a careful history and examination may provide clinical clues to a specific type of AIE.[10] For example, psychosis and dystonia are associated with anti-NMDA receptor

encephalitis; neuromyotonia, muscle spasms and fasciculations are seen in anti-Caspr2 encephalitis and cranial neuropathies are common with anti-Ma2, anti-Hu, Miller-Fisher and Bickerstaff's encephalitis. While CSF analysis, EEG and MRI are considered to be standard diagnostics, it is also important to understand that the results can be normal in a group of patients with AIE.[9] Additional diagnostic techniques include research evaluation by immunohistochemistry with rat brain slices and immunocytochemistry using rodent live hippocampal neurons, as performed in our case.[1]

The patient we describe was treated according to the guidelines of the Erasmus Medical Centre Rotterdam,[2] of which the diagnostic work-up is based on the algorithm provided by Graus et al. In our case, the patient did not meet the criteria for a specific form of autoimmune encephalitis during life, while many reasonable alternative causes had been excluded. Although appropriate immunosuppressive therapy was started within a week after admission, the patient did not respond to this treatment. Autopsy results supported the diagnosis of seronegative autoimmune encephalitis.

Patients with complex neurological syndromes which require strong immunosuppressive therapy are at risk of severe side effects and/or opportunistic infections. Therefore, they are frequently referred to a specialised centre. In our case, very close and frequent consultation of experts created the possibility to treat the patient in accordance with the latest clinical standards. Whilst also giving her family the possibility to frequently visit and be closely involved in the medical process. Although this case was managed in a primary hospital, we believe that a comprehensive but thorough evaluation of similar complex patients at a specialised centre remains preferential. If no specialised therapy or supplementary tests are indicated, patients can then be transferred back to their local hospital.

Conclusion

This case report describes an approach to a patient with acute encephalitis. Primarily it is a practical example of how comprehensive guidelines for the work-up of the complex diagnosis of autoimmune encephalitis can aid most physicians. Secondly, this case report is an example of how specialised critical care can sometimes be provided in a local hospital in close consultation with experts from academic medical centres. We believe, however, that a comprehensive evaluation for suspected AIE at a specialised centre is the current preference.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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