Subacute sclerosing panencephalitis in pregnancy

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We present a case of subacute sclerosing panencephalitis that developed in a previously healthy 29-year-old pregnant woman who had returned from a trip to rural India shortly before the onset of symptoms. She was admitted to hospital at 27 weeks' gestation with a history of cognitive decline and difficulty completing simple tasks. She had no clinical signs of infection. The working diagnosis was autoimmune encephalitis, although extensive investigations did not lead to a final classifying diagnosis. The patient became comatose and developed hypertension, and an emergency caesarean section was done at 31 weeks to deliver the child, who seemed healthy. The patient died about 6 weeks after the onset of symptoms. The patient was found to have had subacute sclerosing panencephalitis at autopsy. In this Grand Round, we review the clinical features and treatment of subacute sclerosing panencephalitis, and the epidemiological and public health aspects of the case.

Introduction

Subacute sclerosing panencephalitis is the most devastating consequence of an often remote measles infection. Subacute sclerosing panencephalitis occurs almost exclusively in children and usually years after the primary measles infection. The long latency of its development, its aspecific presentation, and the fact that laboratory and imaging findings can be deceptively normal all make for a difficult diagnosis, and the disease is often misdiagnosed or diagnosed late, only after a long list of differential diagnoses has been excluded. Once diagnosed, subacute sclerosing panencephalitis is not easily treated, but progresses relentlessly until death. While subacute sclerosing panencephalitis cannot be cured, it can be prevented through measles vaccination, and it has become a very rare disease, most likely through the worldwide use of effective vaccines. Here, we report the case of an adult patient who was admitted to our hospital with a rapidly progressive encephalopathy and behavioural changes.

Case presentation

The patient was born at a military hospital in rural southern India in 1985 and migrated to Canada in 2009. Her past medical history was unremarkable, and she received routine childhood vaccinations, including measles vaccination at age 1 year. As an adult she had mild environmental asthma and suffered miscarriages at 18 gestational weeks in 2012 and at 12 gestational weeks in 2013. Her prenatal serology was typical: positive measles IgG (30·5 IU/mL); positive rubella IgG (87·2 IU/mL); positive varicella IgG; negative hepatitis B surface antigen; negative syphilis antibody screen; cervical swabs negative for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, bacterial vaginosis, and trichomonas; and negative HIV serology.

She became pregnant for the third time and at 21 weeks' gestation she and her husband travelled to the state of Tamil Nadu in India, where they stayed in a small village and visited the port city of Tuticorin. During her stay she was exposed to chickens and wild pigeons on her parents' property and had several mosquito bites. She drank only bottled water and avoided raw fruits and vegetables as much as possible. She did not take malaria prophylaxis. Her 4 week stay was noteworthy only for a mild upper respiratory illness with coryza, cough, rhinorrhoea, and malaise for several days, which had resolved by the time she returned to Canada.

7 days after her return to Canada she developed mild confusion and intermittently unbalanced gait. Over the next few days she developed difficulty with common tasks such as starting and driving her car. 5 days after the onset of her initial symptoms, she developed bizarre behaviour, disorientation, disturbed sleep, and incomprehensible speech. Her husband brought her to the hospital for further evaluation, where she was seen 7 days after symptom onset.

In the emergency room, she was found to be afebrile and haemodynamically stable with no abnormalities on routine blood tests, including a normal complete blood count and differential. The neurology service was consulted. In the neurological exam, the patient was unable to recall and name routine objects and had difficulty following commands. The motor exam showed normal strength with mildly increased tone, which was more noticeable in the right compared with the left extremities, and brisk deep tendon reflexes throughout. In the cerebellar exam, the patient had difficulties with rapid alternating movements in both arms and a wide-based gait with a tendency to veer to the left. The rest of the neurological and physical examination was normal, which included ultrasound and biophysical profile assessment of her pregnancy. She was admitted to the neurology service for further investigation.

Results from an extensive diagnostic investigation during her hospital stay showed few abnormalities. Cerebrospinal fluid was tested on three occasions and showed no abnormalities in cell counts, protein content, and glucose content (table 1). The cerebrospinal fluid was negative for oligoclonal bands. Several infectious and autoimmune causes were investigated in cerebrospinal fluid and found to be negative: viral

nucleic acid testing; herpes simplex virus 1 and 2; varicella zoster virus; enterovirus; parvovirus; fungal culture; *Crypotoccus neoformans* antigen testing; Gram stain; acid fast bacilli staining; bacterial and mycobacterial culture; antibodies against N-methyl D-aspartate receptor (NMDA) NR1 subunit, leucine-rich, glioma inactivated-1 receptor, contactin-associated protein-like 2 autoantigen, aquaporin-4, and the gangliosides GM1, GM2, GM3, GD1a, GD1b, GQ1b, and GT1b. Blood and urine cultures were negative for bacterial, viral, or fungal pathogens. In view of her travel history, malaria thick and thin smears were done and were negative. Serological analyses involved tests for Eastern equine encephalitis virus (negative), Powassan virus (titre 1/20), chikungunya virus (IgM negative), Jamestown Canyon virus (IgM negative), snowshoe hare virus (IgM negative), dengue virus (IgM negative and IgG positive suggestive of remote infection), Japanese encephalitis virus (titre 1/80), *Mycoplasm pneumoniae* (IgM negative), rubella virus (IgM negative and IgG positive, 5·6 IU/mL), West Nile virus (IgM negative and IgG positive with high avidity suggestive of remote infection), brucella (negative), *Leptospira* species (negative), and *Orientia tsutsugamushi* (negative). Nucleic acid testing for enterovirus, parechovirus, and West Nile virus viraemia was negative. Nucleic acid testing of the bronchial alveolar lavage specimens was negative for influenza A and B RNA, respiratory syncytial virus RNA, parainfluenza virus RNA, human metapneumovirus RNA, enterovirus RNA, rhinovirus RNA, human coronavirus (229E, NL63, OC42, HKU1) DNA, and adenovirus DNA. Legionella antigen testing on urine was negative. PCR for rabies in a saliva sample was negative.

MRI of the brain showed no abnormalities in the first weeks after symptom onset (figure 1), and results from electroencephalogram (EEG) registrations showed no epileptiform changes.

The patient was treated empirically for viral encephalitis and bacterial meningitis until the appropriate test and cultures were reported negative. A working diagnosis of autoimmune encephalitis was then made and she was treated with high dose intravenous methylprednisolone. 3 days after admission to hospital, she became somnolent and developed bilateral upgoing plantar reflex responses. The patient became hypoxic shortly afterwards because of an aspiration pneumonia; she was intubated and admitted to the intensive care unit, and given broad spectrum antibiotics for possible infectious causes. She became comatose despite treatment with intravenous immunoglobulins, plasmapheresis, rituximab, and antiseizure medications. At 31 weeks gestation, she developed hypertension and pre-eclampsia was suspected. Because of this complication, the child was delivered by emergency caesarean section. She was delivered of a healthy boy, and the hypertension resolved soon afterwards. She then developed acute tubular necrosis, which was confirmed with a renal biopsy, and was started on haemodialysis. She remained comatose and repeat cranial MRI showed diffuse hyperintensity in the brainstem and cerebral cortex, brain oedema, and brain herniation (figure 1). She died soon afterwards, 6 weeks after symptom onset.

	Day of stay in hospital		
	1	10	27
Glucose (2·2–3·9 mmol/L)*	3·2	4·5	4·0
Protein (0·15–0·45 g/L)	0·26	0·22	0·23
Total IgG (0·000–0·058 g/L)	Not tested	0·118	Not tested
Red blood cells ($0·0–5·0 \times 10^6$ cells per L)	0·6	36·1	2·8
White blood cells ($0·0–5·0 \times 10^6$ cells per L)	0·0	3·3	2·2
Xanthochromia	Negative	Negative	Negative

Cerebrospinal fluid measurements on day 1, 10, and 27 of stay in hospital (normal range).*Blood glucose (2·5–11·0 mmol/L) day 1 of hospital stay 5·0, on day 10 of hospital stay 6·2, and on day 27 of hospital stay 7·5.

Table 1: **Cerebrospinal fluid analyses**

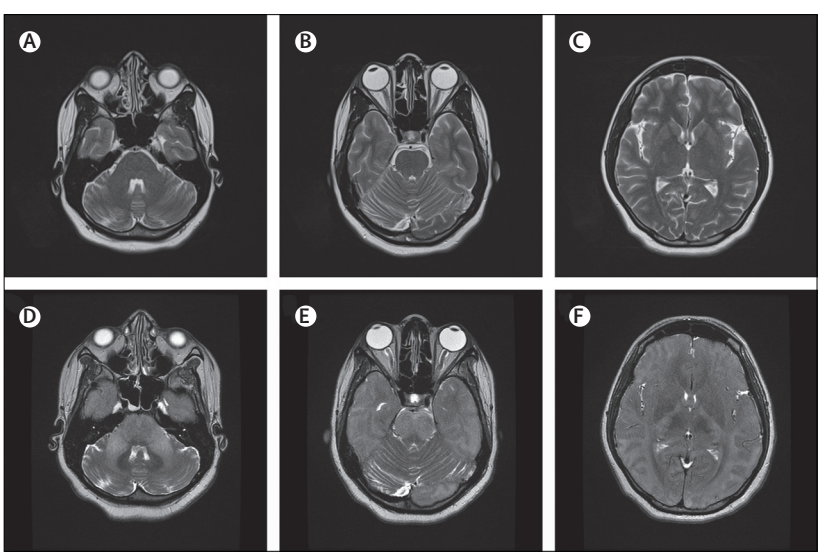

Figure 1: **T2 weighted MRI scans from the time of admission and shortly before death**
Normal findings early in the course of the disease at time of admission (A–C). Brain oedema and diffuse hyperintensity in the cerebral cortex, particularly in the occipital lobe, and throughout the brainstem shortly before death (D–F).

Findings at autopsy

Gross examination of the brain showed generalised oedema and central herniation with associated temporo-occipital acute cerebral infarction. Diffuse encephalitis with associated astrocytic gliosis and neuropil loss was present in multiple areas of the cortex and thalamus. The brain had numerous eosinophilic viral inclusions, which were both nuclear and cytoplasmic. Transmission electron microscopy images