The Bath Advanced Course 2003: progressive neurological decline

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THE CASE

The story
A young right-handed woman 30 weeks into her third pregnancy presented to the accident and emergency department with a 14-day history of headache; 7 days of progressive left-sided visual blurring, speech difficulties and vomiting; and 2 days of memory impairment, agitation and confusion. The early pregnancy had been uneventful, but at 22 weeks gestation she had been admitted with low back pain and urinary incontinence; MRI of the brain and spine were normal. There was a previous history of asthma, appendicectomy, and a miscarriage 3 years before, with a strong maternal family history of recurrent deep venous thromboses. Her only child had recently contracted chickenpox.

Examination
On initial examination she was poorly co-operative, confused, distressed and agitated. Registration and recall were reduced and she had nominal dysphasia. She was afebrile without meningism. Visual acuity was 6/6 on the right, but reduced to finger counting on the left with an afferent pupillary defect. Ophthalmology assessment showed normal anterior segments but there was a linear patch of ischaemia of the papillo-macular nerve fibre bundle of the left eye. She had a mild right-sided spastic hemiparesis with a right extensor plantar response. Sensory testing demonstrated bilateral inaccuracies in joint position sense, but Romberg’s test was normal.
Investigations

Routine serum biochemistry and haematology were unremarkable apart from mild neutrophilia. Plasma viscosity was normal, antinuclear antibody weakly positive (25 IU/mL; nucleolar pattern) and anti-DNA antibodies negative. Thrombophilia screen including factor V Leiden, lupus anticoagulant, antiphospholipid antibodies, prothrombin 20210 mutations, and paraneoplastic markers were negative, including anti-Hu antibodies. Serum angiotensin-converting enzyme (ACE), immunoglobulins, C3 and C4 complement, copper studies, vitamin B12 and folate were normal, and monospot for EBV was negative. CT brain scan on admission was normal, but MR brain scan with venography the following day suggested left transverse venous sinus occlusion (Fig. 1). Transthoracic echocardiogram was normal. The cerebrospinal fluid (CSF) opening pressure was normal, but there was a lymphocyte pleocytosis of 25/mL with a slightly raised protein of 0.6 g/L (normal 0.15–0.45) and a normal CSF-to-serum glucose ratio. CSF was sent for oligoclonal bands, fungal cultures and herpes simplex polymerase chain reaction (PCR). Serial serum viral studies were negative for hepatitis B and C, cytomegalovirus, mumps, varicella zoster, herpes simplex, EBV and mycoplasma. HIV serology was negative and the CD4 lymphocyte count was normal at 1500 × 10⁹/L. Blood cultures were negative.

Further course and management

Ophthalmology review 1 week after admission identified multifocal nerve fibre layer infarctions. She had become photophobic, dyspraxic and virtually mute, responding mainly ‘yes’ or ‘no’. She repeatedly tried to abscond from the ward. Despite intravenous methylprednisolone (0.5 g daily for 5 days) and 10 days of acyclovir she continued to deteriorate with progressive right hemiparesis, right-sided facial weakness, right homonymous hemianopia and later focal epileptic seizures affecting the right hand that were initially resistant to anti-epileptic drugs. After 11 days she developed an unexplained erythematous blanching rash over her legs, a spiking temperature and splinter haemorrhages, but no meningism. There were no cardiac murmurs and trans-thoracic echocardiogram was again normal. Repeat CSF showed an open-
ing pressure of 18 cm H₂O, 60 white cells/mL (36% polymorphs, 64% lymphocytes), raised protein at 1.16 g/L, with a normal glucose. She was given broad-spectrum antibiotics without improvement. Several electroencephalograms showed only non-specific irregular slow activity. Repeat MR brain scan confirmed left transverse venous sinus occlusion, but also new cortical and subcortical high signal abnormalities in the left occipital, posterior temporal and parietal lobes (Fig. 1).

Owing to her relentless neurological decline, she underwent an emergency Caesarean section on day 21, and delivered a healthy male. Further CSF studies showed an opening pressure of 55 cm H₂O, protein of 0.89 g/L and no white cells.

On day 23 a brain biopsy was undertaken and a diagnosis made.

Her condition deteriorated further and MR brain scans showed progressive and extensive cortical and subcortical hyperintensities, also involving the right posterior hemisphere (Fig. 1). CT head scan on day 40 confirmed significant mass effect, unresponsive to dexamethasone. There were continued focal seizures, decerebrate posturing, and she became vegetative. Bronchopneumonia developed 3 months after her initial admission, and proved terminal.

**CLINICAL DISCUSSION (DR PHIL SMITH)**

This is a tragic case of a young mother delivered of her second child by Caesarean section during her terminal illness. She had succumbed to a rapidly progressive and primarily neurological condition, manifesting as headache, visual disturbance, confusion, drowsiness, dyspraxia, focal seizures and coma, but also with some mild systemic features including intermittent pyrexia, splinter haemorrhages, rash and neutrophilia.

There is a broad differential diagnosis of such a subacute and ultimately fatal encephalopathy.
but several important pointers in this case limit the diagnostic possibilities:

- This was a neurological condition unresponsive to steroids and relentlessly progressing to death.
- The cerebral condition was bilateral and involved both grey and white matter, clinically and radiologically.
- The visual symptoms were significant and probably represented a retinal vascular condition that progressed eventually to both eyes.
- The previous history of back pain and incontinence, sufficiently severe to justify spinal imaging, suggests a possible relapsing condition.
- The condition was complicated by intracranial venous thrombosis.
- The disease was not limited to the CNS given there were splinter haemorrhages, a rash, intermittent pyrexia and neutrophilia.
- The condition was diagnosable by brain biopsy.

The specific diagnostic possibilities fall into three groups: infections, abnormal immunity or neoplasia.

Infections

Infective endocarditis
This should always be considered when fever accompanies multiple organ involvement. Non-infective endocarditis, e.g. Libman-Sacks endocarditis, may also give cerebral involvement with relatively occult cardiac signs. However, in this case there was no cardiac murmur, no response to antibiotics, and blood cultures were negative.

Although a trans-oesophageal echocardiogram was not performed, the standard echocardiogram did not show any vegetations.

Viral encephalitis
This is the most common cause of acute severe encephalopathy in otherwise healthy individuals, causing a rapidly progressive encephalopathy with involvement of both grey and white matter. Herpes simplex encephalitis typically involves the temporal lobes initially, and so here the involvement would be atypical. Furthermore the electroencephalogram did not show periodic complexes and her condition progressed despite acyclovir and steroids. Although this patient was exposed to chickenpox, this would provoke viral encephalitis only in an individual previously unexposed to the virus, and would give a typical rash. Other important causes of encephalitis worldwide, including tick-borne encephalitis, are very unlikely without the relevant travel history.

Progressive multifocal leucoencephalopathy (PML)
PML is caused by a slow papova virus, confusingly called the JC virus, and is almost invariably confined to immunocompromised individuals. Typically there is bilateral multifocal white matter involvement, often starting occipitally and progressing over 3–6 months to death. It is diagnosed on biopsy and is unresponsive to steroids. In this case, however, the only suggestion of immunocompromise was her pregnancy. Her HIV status was negative and her CD4 count was normal. The MRI changes were more asymmetrical than one would normally see in PML and the CSF pleocytosis would also be unusual.

Immune conditions

Multiple sclerosis or acute demyelinating encephalomyelopathy (ADEM)
Many of the features of the case would fit with this illness. The episode of back pain and urinary problems at 22 weeks gestation could have represented a spinal cord inflammatory process suggestive of a recurrent demyelinating condition. There was later extensive high signal on M.R. scanning together with a CSF pleocytosis, which may have been consistent with aggressive demyelination or ADEM. The result of oligoclonal band assessment is unknown, but clearly would have been helpful. However several factors are against ADEM:

- This patient had presented with confusion and had clear involvement of grey as well as white matter.
- The venous sinus thrombosis and retinal involvement would remain unexplained.
- The posterior fossa white matter was spared on imaging.
- The condition was unresponsive to steroids.

Neurosarcoidosis
This is an important differential diagnosis of subacute encephalopathy. The CNS is affected in 5% of cases of systemic sarcoidosis, and involves mainly the cranial nerves, the hypothalamus and the meninges. Investigations may not be particularly helpful in that the serum ACE is raised in only 25%, and CSF pleocytosis and low glucose do not occur consistently.

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Even the MR brain scan does not invariably show abnormalities in the white matter and meninges.

Cerebral lupus
The patient’s antinuclear antibody was only weakly positive at 25 IU/mL, and showed nucleolar pattern more typical of scleroderma than systemic lupus erythematosus. However, given the previous miscarriage history and the family history of deep venous thrombosis, it is important to note that the thrombophilia screen and anti-cardiolipin antibodies were negative. The antidualle-stranded DNA antibody, a specific marker for lupus, was negative, and her condition was not steroid responsive, which would make neuropsychiatric lupus unlikely.

Behçet’s syndrome
This should be suspected whenever encephalopathy and venous sinus thrombosis are associated. However, there was no typical mucocutaneous ulceration or uveitis, and furthermore CNS involvement in this disease often involves the posterior fossa, which was apparently spared in this case.

Paraneoplastic encephalomyelitis
This is a rare, remote manifestation of either small cell lung carcinoma or lymphoma. Typically there is predominantly limbic involvement with severe anorexia, amnesia, anxiety, depression and agitation. The condition is not steroid responsive. Anti-Hu antibody is often present in the serum and CSF, but was negative in this case. Furthermore, cerebral involvement here was much more extensive than would be typical for paraneoplastic encephalomyelitis, and her memory was not selectively involved.

Primary cerebral angiitis (isolated CNS angiitis)
This is a rare condition characterized by widespread involvement of the small arteries and veins (<200 µm diameter), confined to the CNS and leading to multiple small infarcts with associated granulomas, fibrinoid necrosis and infiltration by lymphocytes and mononuclear cells. It affects grey and white matter as well as the meninges. Patients may present with headache and an encephalopathy, with an atypical relapsing-remitting (‘multiple sclerosis type’) course, or with an apparent ‘mass lesion’ with features of raised intracranial pressure, but biopsy of the lesion clearly demonstrating a vasculitic process rather than neoplasm. This condition is often steroid-responsive, but further immunosuppression with agents such as cyclophosphamide, may be required. Most cases are thought to arise spontaneously but some are associated with underlying Varicella zoster infection or lymphoma, and indeed either may have caused the venous sinus occlusion. In this case the onset with headache followed by cortical symptoms, associated with inflammatory CSF and MRI changes could be consistent with isolated CNS angiitis. However, by definition there should be no involvement outside the CNS and so the skin rash, pyrexia and neutrophilia are not consistent with this diagnosis. Furthermore, although retinal vasculitis sometimes occurs, the extensive ocular involvement seen in this case would be unusual.

Neoplastic conditions
Several neoplasms may be considered in the context of this case and local neoplastic invasion may also, in theory, account for the venous sinus thrombosis and retinal involvement.

Gliomas
These normally cause a focal mass, but rarely a more diffuse and aggressive involvement, known as gliomatosis cerebri. The brain is then diffusely swollen, particularly the white matter, with corpus callosum thickening as the glioma crosses the midline.

Carcinomatous encephalitis
Whereas most carcinomas metastasize to the brain as diffuse nodules readily visible on imaging, there may rarely be more diffuse brain involvement (miliary metastases) presenting clinically as cognitive decline, personality change, seizures and meningism. Cerebral imaging may show diffuse involvement or small enhancing nodules, often with an active CSF.

CNS lymphoma
This must be strongly considered as a possible diagnosis. The CNS is involved in 6–8% of systemic non-Hodgkin lymphoma patients, and is closely related to bone marrow infiltration; thus metastatic CNS lymphoma is often diagnosed on bone marrow biopsy. CNS lymphoma involves the leptomeninges and epidural space and sometimes may infiltrate around the spinal roots (neurolymphomatosis). Lymphoma arising de novo within the CNS (primary CNS lymphoma) is almost always a B-cell non-Hodgkin lymphoma. CNS lymphoma typically enhances readily on imaging and is initially highly steroid-responsive, although subsequently relapses. In this case however, there was no mass effect visible on the scan, no enhancement, and no response to steroids.

Lymphomatoid granulomatosis
This is primarily a lung condition, with CNS and skin involvement each in 30% of cases. Patients typically present with fever, malaise, cough and dyspnoea and may show nodular or erythematous skin lesions. Microscopically there is blood vessel infiltration with lymphocytes and plasma cells, and often granuloma formation. The condition is not steroid-responsive and in 10% of cases progresses to frank lymphoma. The clinical progression of the encephalopathy and the MR changes would be similar to those in this case, but the absence of lung involvement would make lymphomatoid granulomatosis an exceptional diagnosis here.

Intravascular (angiocentric) lymphoma (neoplastic angioendotheliomatosis)
This is a distinct possibility. It is a high-grade, large-cell, non-Hodgkin lymphoma with neoplastic mononuclear cells proliferating within the small blood vessels. It particularly involves the CNS and the skin but may also have more widespread systemic features. Characteristically, it causes encephalopathy with rapidly progressive dementia with fever, sometimes Coombs-positive haemolytic anaemia and a rash manifesting as violaceous plaques. Many cases present with lumbosacral cord and root involvement.
before spread to the brain, and it has also been linked to venous sinus thrombosis. Cerebral imaging shows diffuse involvement and the CSF a raised protein but it is often acellular; systemically blood viscosity may be elevated. The condition may respond to steroids early on, but later progresses. Overall the prognosis is poor and most cases are diagnosed at post-mortem.

In conclusion
I feel that there are three main possibilities: lymphomatoid granulomatosis (but only the rare form without pulmonary involvement); isolated angiitis of the CNS (but with underlying lymphoma to explain the venous sinus thrombosis); and intravascular lymphoma, which I feel best explains this patient’s disease.

Dr Phil Smith’s diagnosis:
Intravascular lymphoma.

CNS HISTOPATHOLOGY (DR SAMAR BETMOUNI)
The brain biopsy specimen included cerebral cortex and underlying white matter, and in both there was perivascular lymphocyte cuffing, oedema and reactive astrocytosis. Occasional neuronal nuclei showed viral transformation, some with piecemeal necrosis (Fig. 2). Measles virus antibody was not available at the time of examination, precluding immunohistochemical confirmation of measles virus within the intranuclear inclusions. However, PCR subsequently demonstrated measles virus from the frozen stored biopsy samples of cerebral tissue, and was negative for all other viruses tested. This was therefore a case of subacute sclerosing panencephalitis (SSPE). The histological features typically are variable in their distribution and severity. The regions involved include cerebral cortex, white matter, basal ganglia, thalamus and brain stem. In long-standing cases, the cerebellum and spinal cord may also be involved, the inflammatory response may

Figure 2 Histopathology demonstrating features of subacute sclerosing panencephalitis. (a) Perivascular cuffing by lymphocytes (arrow), (b) reactive astrocytosis visualized using immunohistochemistry with an antibody to glial fibrillary acidic protein (GFAP) (c) hyaline, viral inclusion (arrow).
be less marked, and viral RNA may no longer be detectable. Occasionally neurofibrillary tangles may develop in the hippocampus and neocortex, identical to those seen in Alzheimer’s disease.

**FINAL DIAGNOSIS**
Subacute sclerosing panencephalitis.

**DISCUSSION**
Getting the correct diagnosis in a clinicopathological conference is always a bonus, but how one arrives at a diagnosis is clearly of greater importance from the educational perspective. This is exemplified by Dr Smith’s comprehensive and instructive analysis of this complex and tragic case. However, two important pieces of information had been deliberately kept from Dr Smith, which might otherwise have narrowed his differential diagnosis considerably: a history of a specific childhood infection, and oligoclonal bands in the CSF but not the serum. However, this reflects the ‘real life’ situation to some extent, because the managing physicians were also unaware of these important ‘missing pieces’ during the patient’s early illness.

The patient’s parents reported that she had had measles at the age of 1 year and had never received measles vaccination. Parental concern at the time meant that she had been admitted to hospital overnight for observation, and careful scrutiny of her paediatric records confirmed the typical description of an uncomplicated measles infection.

Serum and CSF viral studies had in fact revealed a striking difference in the titre of measles-specific IgG antibodies between CSF and serum samples. This, coupled with evidence of intrathecal production of antibodies, was strongly suggestive of a diagnosis of SSPE. Furthermore, there were specific defects in the matrix (M) gene of the virus, known to be causally associated with SSPE. The measles genotype identified in our patient was genotype D1. The World Health Organization reference strain of genotype D1 is ‘Bristol.UNK/74’, isolated in Bristol in 1974, and although this is currently inactive, it was one of the wild types of measles virus in the UK during her childhood in Bristol.

We were not able to account entirely for all the clinical features encountered in this case. The effects of normal pregnancy may explain some symptoms such as the low back pain (presumably musculoskeletal) and incontinence, which occurred at the start of her illness. Disinhibition may also have played a part in her sphincter disturbance, but neuropsychiatric phenomena were not prominent at this early stage of her disease. The fever and skin rash which occurred at day 11 of her illness were probably manifestations of a general viraemia. The splinter haemorrhages may simply have been the result of local trauma, particularly as there was no evidence of infective endocarditis, nor of any response to antibiotics. Cerebral venous sinus thrombosis is not a recognized association with SSPE, but in this case there remains a possibility of a link between the two. Although there was a family history of deep venous thrombosis, her thrombophilia screen was negative.

SSPE is caused by a defective measles slow virus infection. The incidence is high in the developing world, but rare in developed countries and has been significantly reduced by effective measles vaccines. Most patients have a history of primary measles infection at an early age (<2 years), and those infected before the age of one carry a 16 times greater risk of SSPE than those infected after 5 years of age (Modlin et al. 1979; Halsey et al. 1980; Aaby et al. 1984). SSPE onset is usually in childhood, at an average age of 6–8 years and with a male to female ratio of 3:1 (Yacub 1996). The clinical features are highly variable. Onset in childhood is usually subtle with behavioural changes and decline in school performance. The second stage after weeks or months includes motor function changes, myoclonic jerks, seizures, cerebellar ataxia and dystonia. 10–50% have ocular and visual manifestations including cortical blindness, chorioretinitis, and optic atrophy. Any visual symptoms usually occur with the neurological manifestations, but sometimes precede them by several years (Green & Wirtschafter 1973). The final stage is marked by stupor, coma, autonomic failure and death, usually 1–3 years after onset.

SSPE beginning in adults is rarer. It presents at a mean age of 25 years (range 20–35 years), often with ocular manifestations as the result of a vasculopathy (Singer et al. 1997). The ocular involvement precedes or accompanies other neurological signs in up to 50% of cases and is attributed to direct viral invasion of the retina (Caruso et al. 2000). The adult-onset form is generally more aggressive than in childhood, and leads rapidly to death.

SSPE during pregnancy is rare, but has been reported up to the age of 27 years (Wirguin et al. 1988). The youngest pregnant case was a 14-year-old presenting in the last trimester with chorioretinitis and progressive dementia (Jayawant et al. 2000). Typical myoclonus may not occur.
in pregnancy-associated SSPE, and the clinical picture more usually resembles eclampsia. The immunosuppressed state of pregnancy probably promotes a more fulminant course (Wirguin et al. 1988), sometimes with the early death of the child in utero, or immediately postpartum.

The diagnosis can reliably be established (as in our patient) if three of the five criteria given in Table 1 are fulfilled (Dyken 1985). MRI is not an essential criterion, and previously has been considered to have only limited role in the early diagnosis of SSPE (Brismar et al. 1996). Despite this, the finding of typical high signal changes, particularly in the posterior cerebral hemispheres, as in this case, is a recognized phenomenon and may suggest the diagnosis. Staging of the degree of white matter changes and atrophy in SSPE on neuroimaging has been proposed as seen in this case (Fig. 1).

There is currently no adequate therapy for SSPE. Thus the recent fall in measles immunization following the controversy over MMR vaccine safety is of particular concern. Uncommonly SSPE can follow primary measles immunization, but in general, large-scale measles vaccination programmes seem to have reduced the risk of SSPE by more than 90% in the developed world (Dyken et al. 1989). The public perception of a benign outcome after measles infection in childhood should be tempered by greater awareness of the real and quantifiable risk of severe long-term measles complications in adulthood.

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**REFERENCES**


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The Bath Advanced Neurology Course 2003: Progressive Neurological Decline in Pregnancy
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