Subacute onset encephalopathy: a rare clinical syndrome with many aetiologies

In this issue of the *British Journal of Hospital Medicine* Harrington et al (p. 170) and Willis et al (p. 172) present and discuss two interesting cases. Both cases are characterized by profound subacute onset cognitive dysfunction.

Encephalopathy is frequently seen in acute medicine. Often it is of acute onset where, in the majority of cases, baseline investigations reveal an underlying metabolic, toxic, infectious or structural abnormality. Usually treatment of the underlying abnormality results in rapid improvement in cognition. Subacute (weeks to months) progressive cognitive decline is a less frequently encountered problem. It is an umbrella term, which encompasses all causes of rapidly progressive dementia. What aetiologies can cause this syndrome? To whom does it present? How should it be investigated? From where can expert help be sought?

Causes

The causes of subacute onset encephalopathy are numerous (*Table 1*) but may be loosely categorized into the following non-mutually-exclusive aetio-pathogenetic groupings: neurodegenerative, neuroinfectious, neuroinflammatory and metabolic (Chitravas et al, 2011; Rosenbloom and Atri, 2011). Major mimics of the syndrome include primary psychiatric disorders, particularly schizophrenia and severe depression. Non-convulsive status epilepticus can mimic subacute onset encephalopathy but can also be a consequence of the syndrome's underlying cause.

Willis et al's case illustrates a common finding: often these patients present, or are referred from primary care, to psychiatrists as their initial symptoms may have strong psychological or behavioural features. Frequently it is the onset of seizures that result in a general internal medicine or neurological opinion being sought. Another mimic is seen in patients with a mild, hitherto unrecognized neurodegenerative condition – such as Alzheimer's disease or Lewy body dementia – when an intercurrent infection results in subacute delirium. The underlying chronic degenerative condition is thereby 'unmasked'.

Assessment

Patients with subacute encephalopathy require careful assessment. Special care should be taken to document the family history. Examination should focus on identifying the presence of abnormal neurological signs, e.g. myoclonus, visual field deficits or ataxia. Bedside cognitive examination using standardized protocols, such as the Addenbrooke's Cognitive Examination or Montreal Cognitive Assessment, are very helpful at identifying higher order cognitive dysfunction (see *Resources*). Patients usually require magnetic resonance brain imaging, electroencephalography and CSF examination. Blood tests are helpful to exclude metabolic abnormalities and to seek serological evidence of infection and auto-

Table 1. Causes of subacute encephalopathy in adults

Aetio-pathogenetic group	Example
Neurodegenerative	Sporadic and variant Creutzfeldt–Jakob disease
	Familial prion diseases (e.g. Creutzfeldt–Jakob disease or familial fatal insomnia)
	Unusual presentations of common neurodegenerative conditions, e.g. Alzheimer's disease, frontotemporal dementia, Lewy body dementia
	Huntington's disease
Neuroinfectious	Subacute sclerosing panencephalitis (measles)
	Human immunodeficiency virus dementia (HIV 1 and 2)
	Progressive multifocal leucocencephalopathy (JC virus)
	Progressive rubella panencephalitis
	Sleeping sickness (*Trypanosoma brucei* spp.)
	Syphilis (*Treponema pallidum*)
	Lyme disease (*Borrelia burgdorferi*)
	Whipple's disease (*Tropheryma whipplei*)
Neuroinflammatory	Antibody-associated encephalitis (N-methyl D-aspartate receptor antibody and voltage-gated potassium channel complex antibodies)
	Other paraneoplastic encephalitides (e.g. associated with Hu, CV2 and Ma2 anti-neuronal antibodies)
	Cerebral vasculitis
	Hashimoto's (steroid-responsive) encephalopathy (associated with thyroid microsomal antibodies)
	Neurosarcoidosis
Metabolic	Toxin, e.g. lead poisoning and Marchiafava–Bignami disease
	Wernicke–Korsakoff syndrome
	Rare hereditary metabolic disorders, e.g. Wilson's disease, hereditary diffuse leukoencephalopathy with spheroids, adult polyglucosan body disease, porphyria, mitochondrial encephalopathies

antibodies – often potentially treatable conditions. Structural brain imaging can reveal specific patterns of change associated with specific conditions such as regional brain atrophy in neurodegenerative conditions or signal change in the mesial temporal lobe structures in limbic encephalitis.

In the face of normal structural brain imaging electroencephalography studies can be particularly useful. Electroencephalography is a very sensitive, albeit non-specific, marker of encephalopathy; this can be helpful in distinguishing a primary psychiatric condition from limbic encephalitis. Electroencephalography can identify non-convulsive status epilepticus. And as discussed in the case reports, specific electroencephalography abnormalities can be seen in Creutzfeldt–Jakob disease and subacute sclerosing panencephalitis respectively.

CSF examination was diagnostically helpful in both cases. However, the tests used may not be familiar to all physicians. While core trainees are familiar with requesting 'oligoclonal bands' in patients with suspected multiple sclerosis, in the author's experience they often are not aware of the nature of these bands: they are immunoglobulin G (IgG).

Healthy CSF, being essentially an ultrafiltrate of plasma, contains little IgG; in contrast in plasma it forms a significant proportion of total protein content (≈10%). IgG bands are identified not through separation by molecular size (electrophoresis) but by molecular charge or pH (isoelectric focussing). Synthesis of IgG in the intrathecal space is demonstrated by comparing patterns in time-matched CSF and serum samples. Bands unique to CSF must result from synthesis within CNS or its supporting structures.

The presence of intrathecal IgG synthesis is a very sensitive indicator of intrathecal immune activation. It is rarely found in neurodegenerative diseases but it does not differentiate subacute neuroinflammatory from neuroinfectious conditions. However, if the antigenic specificity of the majority of the oligoclonal IgG bands can be identified as binding to a known pathogen, a specific infectious diagnosis can be made. In Willis et al's case CSF anti-measles IgG was demonstrated, confirming the diagnosis of subacute sclerosing panencephalitis.

In contrast, Harrington et al's case used measurement of two brain-specific CSF proteins. S100b, a calcium-binding protein, is the 'CRP [C-reactive protein] of the brain'; elevated levels are seen in many conditions resulting from either acute or chronic brain injury or inflammation. Raised CSF 14-3-3 protein levels are seen in conditions that cause marked brain or spinal cord neuronal destruction. Elevation of one or both proteins is seen frequently in sporadic Creutzfeldt–Jakob disease but elevated 14-3-3 levels are less common in variant Creutzfeldt–Jakob disease. High S100b and 14-3-3 levels lack specificity to a single condition or pathogenetic mechanism but nevertheless they are useful adjuncts to the diagnostic process (Stoeck et al, 2012).

Conclusions

Diagnosis and management of the patient with subacute onset encephalopathy is cross-disciplinary: neurologists, infectious disease physicians, pathologists and psychiatrists have key roles to play. In the UK, invaluable diagnostic advice for suspected Creutzfeldt–Jakob disease and its mimics can be obtained from the National CJD Research and Surveillance Unit (Edinburgh) and the National Prion Clinic (London). BJHM

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Chitravas N, Jung RS, Kofskey DM et al (2011) Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. *Ann Neurol* **70**: 437–44

Rosenbloom MH, Atri A (2011) The evaluation of rapidly progressive dementia. *Neurologist* **17**: 67–74

Stoeck K, Sanchez-Juan P, Gawinecka J et al (2012) Cerebrospinal fluid biomarker supported diagnosis of Creutzfeldt-Jakob disease and rapid dementias: a longitudinal multicentre study over 10 years. *Brain* **135**: 3051–61

KEY POINTS

- Investigations should seek to exclude reversible causes for subacute onset encephalopathy.
- The national prion services should be involved when Creutzfeldt–Jakob disease is considered possible.
- CSF studies may help to distinguish between infectious and degenerative neurological conditions.

RESOURCES

- Addenbrooke's Cognitive Examination (http://neura.edu.au/sites/neura.edu.au/files/page-downloads/ACE-III%20Administration%20(UK).pdf)
- Addenbrooke's Cognitive Examination Scoring Information (http://neura.edu.au/sites/neura.edu.au/files/page-downloads/ACE-III%20Scoring%20(UK)_0.pdf)
- Montreal Cognitive Assessment (www.mocatest.org/pdf_files/test/MoCA-Test-English_7_1.pdf)
- Montreal Cognitive Assessment Scoring Information (www.mocatest.org/pdf_files/instructions/MoCA-Instructions-English_2010.pdf)
- National CJD Research and Surveillance Unit (www.cjd.ed.ac.uk/index.html)
- National Prion Clinic (www.prion.ucl.ac.uk/clinic-services/)