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Subacute neurological syndromes

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The enormous importance of the time course of a clinical complaint especially in neurology, emphasised to all of us as medical students, has lost nothing with the passage of (however many) years. If the pace of a neurological symptom is known, the pathological process is staring us in the face. Symptoms of abrupt onset are almost always vascular in origin. Symptoms of subacute onset – progressing over days to weeks – are generally of infective or inflammatory origin.[1] Progression over weeks to months implies tumour, while that over months to years implies a degenerative process. By and large, these rules are ignored at our peril, although of course there are 'catches' for the unwary:

- a previously asymptomatic tumour can cause vascular compromise and present abruptly
- metabolic disorders can present in anything from minutes to years
- infective processes can range from the alarmingly rapid (meningococcus) to the misleadingly slow (Creutzfeldt-Jakob disease (CJD)).

Diffuse or multifocal encephalopathies (Table 1)

In patients presenting with subacute onset diffuse or multifocal encephalopathies (ie typically a mixture of higher function disturbance combined with signs that cannot be localised to a single site), the history usually provides important clues as to likely diagnosis. In others, general findings such as fever point towards an infective cause. Simple blood tests will identify many patients with metabolic causes, though most of them

Table 1. Causes of diffuse or multifocal encephalopathies and focal encephalopathies.

Inflammation	*Multiple sclerosis*** Acute disseminated encephalomyelitis** *Behçet's disease*** *Sarcoid*** Cerebral lupus**
Infection	Viral encephalitis** *Cerebral abscesses** Creutzfeldt-Jakob disease**
Neoplastic	*Cerebral metastases*+ *Primary brain tumours*+
Vascular	*Subdural haematoma*+ *Cerebral venous thrombosis** *Cerebral vasculitis**
Paraneoplastic	Limbic encephalitis**
Structural	Hydrocephalus+
Metabolic and toxic	Alcohol and drugs Hepatic encephalopathy

Italics: those conditions where focal encephalopathy is likely.
Computed tomography brain scan findings: + = highly likely to be abnormal; * = may be normal; ** likely to be normal.

will have altered consciousness without other focal signs. In many such patients admitted on the general medical take the differential diagnosis will remain wide. A computed tomography (CT) brain scan will often then be performed as it is the most widely accessible emergency imaging modality (Table 1). This allows recognition of patients with most primary and secondary tumours, abscesses, subdural haematoma and hydrocephalus.

If the CT brain scan is normal or the abnormalities non-diagnostic, demyelinating pathologies would probably be the most common lesion. A magnetic resonance (MR) brain scan will demonstrate relevant abnormalities in the majority of patients with multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), cerebral lupus, Behçet's disease or cerebral vasculitis. However, it is difficult to distinguish between these entities on radiological grounds and the further diagnosis is usually made with historical or investigative findings.[2] In patients with focal or multifocal cortical deficits, particularly young women on oral contraceptives or postpartum, cerebral venous thrombosis (CVT) should be considered; it is increasingly being diagnosed using MR venography.

Both CT and MR imaging will prove normal in some patients, though the diagnosis may become clear with cerebrospinal fluid (CSF) examination. For viral encephalitis, a high index of suspicion is needed as the fever and other markers for infection may be masked by behavioural changes in the acute phase. CSF examination should help clarify the diagnosis. The CSF may give clues in other situations: for example, low level pleocytosis in MS or ADEM or raised intracranial pressure with CVT.

A small number of patients with an evolving subacute deficit will have normal MR brain imaging and a normal CSF. In these patients there are a few other diagnoses to consider including:

- CJD,[3] where there may be characteristic EEG changes and increasingly recognised (albeit subtle) MRI changes
- Hashimoto's encephalopathy, an inflammatory encephalopathy associated with high antithyroid antibodies
- a paraneoplastic encephalopathy,[4] usually associated with small-cell lung, ovarian or breast cancer
- metabolic disorders such as mitochondrial encephalopathies which usually present more insidiously
- very rarely, non-convulsive status, that is, continuous complex partial seizures or absences, which can be difficult to recognise clinically but is easily clarified with EEG.

For the most part, such patients are likely to be under the care of neurologists by the time the diagnosis is made.

Focal encephalopathy

Many of the conditions that can present with multifocal deficits can also present with focal encephalopathies (Table 1). The investigative approach is as outlined above.

One potential trap is a patient with a seemingly subacute onset hemiparesis that in fact relates to recurrent small strokes from a critically stenosed carotid artery.

Brainstem and cerebellar syndromes

Most causes of focal encephalopathies may affect the brainstem but a few have a predilection to do so.

The brainstem is a common site for demyelination. Listeria monocytogenes meningitis, the fourth most common cause of bacterial meningitis, appears to pick out the brainstem. Wernicke's encephalopathy may develop in thiamine and calorie deficient patients following carbohydrate refeeding. On the ward this may be observed as a progressive deficit.

There may be delayed progression in patients with cerebellar infarcts or haemorrhage following the development of hydrocephalus due to obstruction of the 4th ventricle, thus giving the suggestion of a subacute onset condition. This may necessitate surgical decompression.

Patients with a progressive cerebellar syndrome who have a normal CSF but without MRI abnormalities are likely to have either a paraneoplastic cerebellar degeneration or CJD.

Miller Fisher syndrome, with the combination of external ophthalmoplegia and ataxia, may be mistakenly categorised as a brainstem/cerebellar syndrome. Recognition of this syndrome facilitates prompt treatment (as for Guillain-Barré syndrome) and testing appropriate antibodies (anti-GQ1b).

Spinal cord syndrome

Subacute onset spinal cord syndromes are a medical emergency as the major differential diagnosis lies between a compressive lesion and an intrinsic cord lesion. The spinal cord must be imaged from the clinical level of the uppermost signs to the foramen magnum. Compression may be due to:

- spinal column disease such as herniated discs or spondylitic changes
- malignant compression from bony secondaries

Key Points

Sudden onset neurological syndromes are almost always vascular but there is a wide range of causes of subacute onset neurological syndromes

Most diagnoses will become clear from clinical assessment and, depending on presentation, computed tomography or magnetic resonance imaging of the brain or spine and cerebrospinal fluid examination

When investigations have proved negative, paraneoplastic neurological diseases and Creutzfeldt-Jakob disease should be considered

KEY WORDS: neurological diagnosis, subacute

- epidural abscess, or
- intradural tumours.

If no compression is found, spinal inflammation is the most common aetiology, usually associated with an incomplete spinal cord lesion. As MRI improves, small intrinsic lesions are increasingly visible as are other rarer causes such as spinal arteriovenous malformations.

Meningitic syndrome

It is often not recognised that more insidious meningitis may present with multiple cranial nerve lesions and multiple radiculopathies, sometimes combined with limited 'traditional' signs of meningism (eg stiff neck). MRI with gadolinium may allow visualisation of meningeal disease but CSF examination is crucial. Malignant meningitis, which often takes multiple CSF studies to identify, infections such as tuberculosis or Lyme disease and inflammatory disease such as sarcoidosis, all need to be considered.

Polyradiculopathies, peripheral neuropathies, neuromuscular junction diseases and myopathy

Most of these conditions have been covered in the article by Marguerite Hill on acute and subacute weakness. Rarely, a purely sensory neuropathy can develop, a purely sensory variant of Guillain-Barré syndrome. A slightly more indolent progression may be associated with a paraneoplastic aetiology, particularly associated with anti-Hu antibodies.

Multiple levels

A few patients have a confusing picture suggesting involvement of multiple levels of the nervous system, with a combination of signs of central nervous system and peripheral nerve and muscle involvement. The diagnosis will often be clear because of the context in which this occurs, for example a patient with known malignancy or who is HIV-positive and at risk of multiple pathologies. If there are no systemic clues, the main differential diagnosis lies between inflammatory pathologies such as sarcoidosis or vasculitis, disseminated malignancy and paraneoplastic syndromes.

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