The heart and the brain

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Excluding atrial fibrillation (AF), for which sound guidance exists, managing patients with ischaemic stroke and potential cardioembolic pathologies can be perplexing. Expert enthusiasts cite evidence for the benefits of intervention with warfarin or endovascular device placement. Expert sceptics argue, often citing the same evidence, that associations have been overstated and that superiority of one treatment over another has not been demonstrated. Faced with conflicting advice, what should the utilitarian physician do? In addition to reviewing this important issue, this article will discuss the topical putative link between migraine and patent foramen ovale (PFO) and give a brief résumé of how cardiac testing might help patients with undiagnosed collapses.

Cardioembolism

The list of potential cardioembolic risk factors grows (Table 1), though often with incomplete or conflicting evidence regarding associated stroke risk.[1] Some major cardioembolic risks such as AF are diagnosed without echocardiography. For other risks, criteria are unresolved both for selection of patients for investigation and whether to perform a transthoracic scan, a transoesophageal (TOE) scan or both. This is something of an 'algorithm free zone'. The Royal College of Physicians national clinical guidelines for stroke[2] do not mention echocardiography and there is only a limited recommendation from the Scottish Intercollegiate Guidelines Network to consider this investigation in patients with cardiac disease or unexplained stroke, especially those with multiple events.[3]

The difficulty is that for many of the potential risk factors identified by echocardiography no alternative treatment has yet been demonstrated as clearly superior to 'standard' secondary preven-

Table 1. Pathologies considered as potential cardioembolic stroke risk (lack of evidence does not imply absence of association) (the modalities of echocardiography typically required for diagnosis, transthoracic (TTE) and transoesophageal (TOE), are included).

	Pathologies	Echocardiographic modality
Typically suspected clinically or from ECG	AF	
	Prosthetic heart valve	
	Mitral stenosis	
	Acute MI	
	Infective endocarditis	
Typically diagnosed with echocardiography:		
Reasonable evidence of associated stroke risk	Left ventricular thrombus	TTE
	Dilated cardiomyopathy	TTE
	PFO + atrial septal aneurysm	TOE
	Atrial septal aneurysm; younger patients	TOE
	Left atrial myxoma	
Conflicting or insufficient evidence of associated stroke risk	Left atrial thrombus (without AF)	TOE
	Left ventricular aneurysm	TTE
	Spontaneous echocardiographic contrast	TOE
	Lone PFO in younger patients	TOE
	Atrial septal aneurysm (elderly patients)	TOE
	Aortic arch atheroma	TOE
Unlikely to be associated stroke risk	Lone PFO in elderly patients	TTE
	Mitral valve prolapse	
	Mitral annular calcification	
	Aortic valve sclerosis	
	Valvular strands	

AF = atrial fibrillation; MI = myocardial infarction; PFO = patent foramen ovale.

Key Points

- **There is limited evidence to guide management decisions for patients in sinus rhythm with ischaemic stroke and potential cardioembolic pathology**
- **The identification of the combination of patent foramen ovale (PFO) and atrial septal aneurysm in younger adults with cryptogenic stroke may have important therapeutic implications**
- **The presence of complex aortic arch atheroma is associated with a high risk of future vascular events, but whether this has specific therapeutic implications over and above conventional secondary prevention strategies is as yet unclear**
- **There is increasing evidence for an association between migraine with aura and PFO, and that closure of PFO can influence migraine severity in some individuals**
- **Syncope is frequently misdiagnosed as epilepsy; cardiological investigation may uncover an alternative explanation in a sizeable proportion of individuals with anti-epileptic drug-resistant or atypical seizures**

KEY WORDS: aortic arch atheroma, atrial septal aneurysm, cardioembolism, epilepsy, ischaemic stroke, magnetic resonance imaging, migraine, patent foramen ovale, syncope, transcatheter device closure

tion. It is therefore difficult at present to demonstrate the cost-effectiveness of echocardiography in the management of stroke patients.[1] Until such evidence is available, the criteria for the selection of patients will vary according to an individual clinician's enthusiasm for as yet unproven treatments.

Patent foramen ovale

PFO is found in 22–26% of the general population but in up to 40–45% of patients investigated for stroke. Possible mechanisms for stroke include paradoxical embolism of venous thrombosis (Fig 1) or coexisting disorders such as AF.

Clinical studies

A meta-analysis of case-control studies demonstrated an association between PFO and stroke, particularly for patients under the age of 55 (odds ratio (OR) 3.1).[5] The association was stronger when both PFO and atrial septal aneurysm (ASA) were present. Increased interatrial septum mobility may increase the probability of paradoxical embolism by mechanically directing blood flow from the inferior vena cava through a PFO and into the left atrium.

Conflicting evidence came from a prospective European study in which all patients were treated with aspirin.[6] No difference was found in recurrent stroke rates between patients with or without PFO (4.5% *v* 3.8%) during a mean follow-up of just over three years. For patients with PFO alone the recurrence rate was only 2.8%; estimates of their four-year risk of recurrent stroke were non-significantly lower than for those without PFO (2.3% *v* 4.2%). For patients with both PFO and ASA there was a significantly increased risk of 15.2% at four years (OR 4.17), suggesting this combination rather than PFO *per se* is associated with stroke risk.

The PFO in Cryptogenic Stroke Study (PICSS)[7] found no difference in the two-year risk of recurrent stroke or death in patients with or without PFO (14.3% *v* 12.7%) and no difference in outcomes between those treated with aspirin or warfarin. Contrary to expectations, larger PFOs appeared to be associated with a lower recurrent stroke or death rate than smaller ones (9.5% *v* 18.5%). In this study, the combination of PFO plus ASA was not associated with added risk.

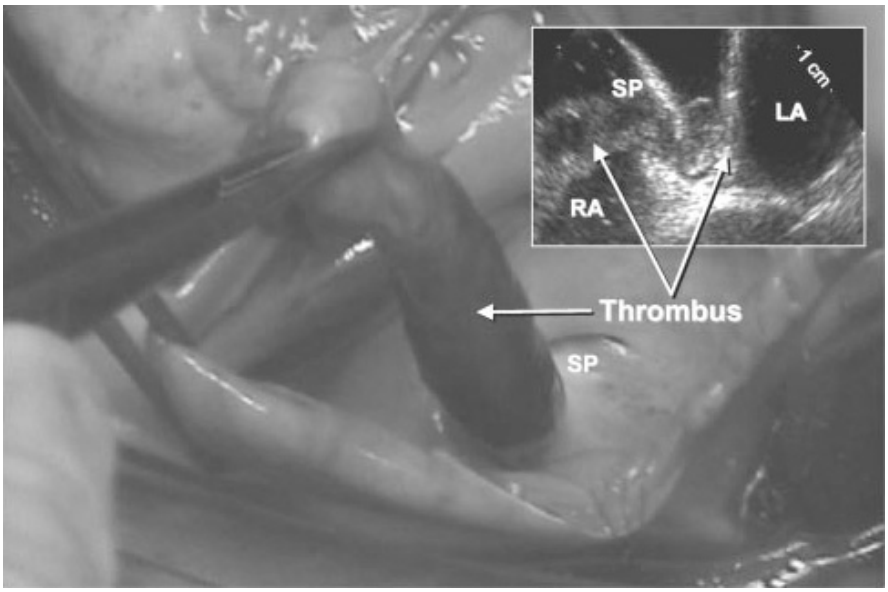

Fig 1. A 30 cm thrombus detected at echocardiography (insert) in a 45-year-old man suffering from pulmonary embolism caused by a fragment breaking off from the tail of the thrombus while lodged at its waist in the foramen (view from the right atrium). LA = left atrium; RA = right atrium; SP = septum primum. Reproduced with permission from Lippincott Williams and Wilkins.[4]

Transcatheter device closure

The procedure of transcatheter device closure of PFO has been adopted with enthusiasm in many centres. It can be undertaken as a day-case under local anaesthetic and could avoid the requirement for protracted and potentially risky medical therapies. Minor (≤8%) and major complications (≤1.5%), including death, cardiac tamponade and massive pulmonary embolism, have been reported. Failure to obtain effective closure ranged from 0–34%.[1] Recurrent stroke has occurred despite adequate closure, suggesting that other undetected pathologies may influence stroke risk in some patients. None the less, when compared with lifelong anticoagulation the risks are likely to be in favour of device closure, but this may not be so when compared with aspirin. Results from randomised controlled trials are clearly needed.

Summary

In summary, there is good evidence in younger patients (<55 years) that PFO in combination with ASA is an independent risk factor for recurrent stroke. Warfarin has not proven beneficial in this setting and, given its risks, should probably be avoided. Pragmatic guidance at present would be aspirin as first-line treatment, with consideration of device closure for individuals experiencing further events. Unfortunately, this recommendation cannot yet be made on the basis of convincing evidence. PFO is unlikely to be of relevance in elderly patients.

Aortic arch atheroma

Stroke has long been recognised as a potential complication of surgical or catheter instrumentation of the aortic arch. Recently there has been interest in the possibility of spontaneous embolisation. Post-mortem and TOE studies have demonstrated an association between unexplained stroke and ulcerated aortic arch plaque, particularly plaque exceeding 4 mm in thickness. Recurrent stroke rates are higher in patients with arch atheroma (3–12% per annum) after

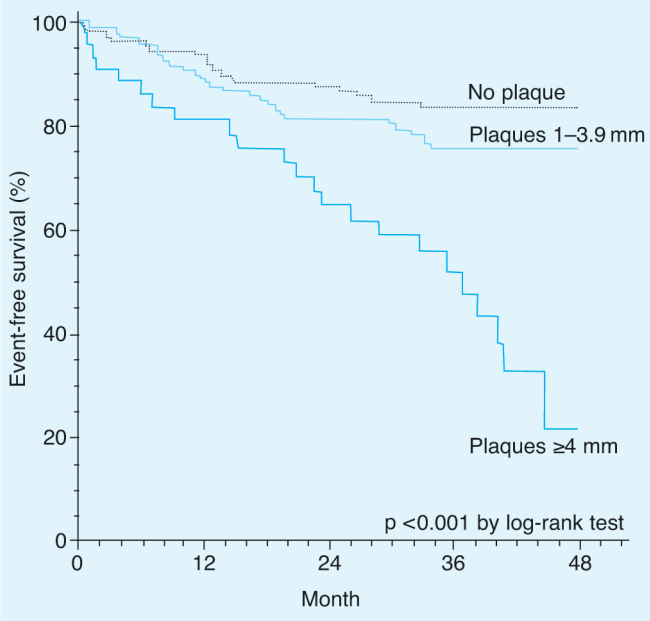

Fig 2. Risk of new vascular events in relation to aortic arch atheroma (combining brain infarcts, myocardial infarctions, peripheral events and vascular deaths). Copyright © 1996 Massachusetts Medical Society. All rights reserved.[8]

adjustment for other risk factors, including carotid stenosis.[8] Aortic arch atheroma also appears to be a marker for a high risk of other vascular events (Fig 2).[8,9] The concept of high-risk 'complex' plaque has been developed, defined as atheroma over 4 mm thick, ulcerated or with mobile elements. This pathology typically occurs in the over-60 age group. An alternative view is that severe aortic arch atheroma is simply a marker for advanced atherosclerotic disease, not an independent risk factor in its own right.[10]

Whether patients with complex plaque in the aorta should be managed any differently (and therefore identified) is unclear. Despite the high risks associated with this condition, and alarming images of mobile thrombus sometimes seen on ultrasound, recommendations to embark on warfarin anticoagulation or surgical endarterectomy are not currently supported by convincing evidence. Until such evidence is available, antiplatelet-based strategies seem most appropriate.

Can patients with embolic sources be identified?

Clinicians face a dilemma for individuals in sinus rhythm of how far to pursue investigation for an occult cardioembolic source. Recent developments in brain imaging may help.

Diffusion-weighted magnetic resonance imaging (DW MRI) is able reliably to detect even very small ischaemic lesions within the first hours after a stroke and can distinguish recent from

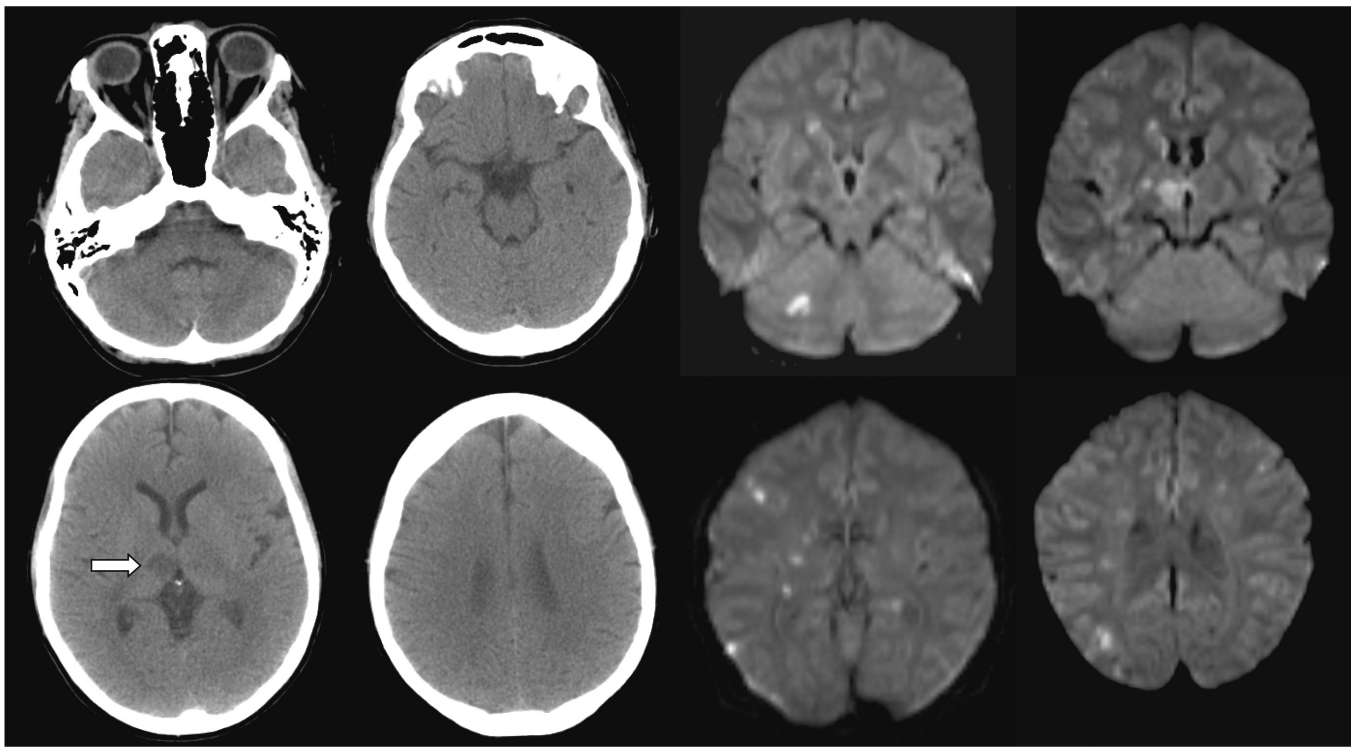

Fig 3. Brain scans from a patient presenting with left-sided weakness and amnesia. Computed tomography (CT) (left) demonstrated a right thalamic infarct (arrow); diffusion-weighted magnetic resonance imaging (DW MRI) (right) showed multiple small acute ischaemic lesions bilaterally in the anterior and posterior circulations. Subsequent echocardiography identified a left atrial myxoma.

Box 1. Preliminary results of the Migraine Intervention with STARFlex Technology (MIST) Trial. ns = non significant; PF = patent foramen ovale; TIA = transient ischaemic attack. Data sourced from Reference 15.

432 patients screened:
age 18–60, >1 year history of migraine with aura, frequent migraine (≥5 days/month), refractory to preventive medication, moderate to large PFO, no history of prior TIA or stroke

163 identified with large PFO, 16 excluded

147 patients randomised: 74 implant; 73 sham procedure

135 patients completed trial

Presented results	**Implant**	**Sham procedure**	
Adverse events	tamponade, pericardial effusion, retroperitoneal bleed, atrial fibrillation, chest pain *frequency not reported*	Incision-site bleed, anaemia, nose bleed, brainstem stroke	
Complete cessation of migraine	n=3	n=3	ns
Reduction in headache by ≥50%	42%	23%	p=0.038
Reduction in headache burden (frequency × duration)	37%	17%	p=0.033

remote infarcts. Different patterns of lesions have been described with DWI in stroke which might suggest different underlying stroke pathologies.

Studies confirm what might intuitively be expected. The presence of multiple lesions in more than one vascular territory of the brain, especially when bilateral, suggests a proximal embolic source and supports investigation for a potential cardioembolic source (Fig 3).[11] Conversely, multiple lesions unilaterally in the carotid circulation tend to be associated with large artery atherosclerosis of the ipsilateral carotid or middle cerebral artery. There is some evidence that paradoxical venous emboli have a tendency to enter the posterior (vertebrobasilar) circulation selectively.[12]

Table 2. Distinguishing between seizures and syncope (features in bold are particularly useful in discriminating).

	Syncope	**Seizures**
Posture	Upright	Any posture
Pallor and sweating	Common	Uncommon
Onset	**Gradual**	**Sudden/aura**
Injury	Rare	Not uncommon
Duration of unconsciousness	Seconds	Minutes
Brief convulsive jerks	Common	Rare
Prolonged convulsive jerks	Rare	Common
Incontinence	Rare	Common
Tongue biting	Rare	Common
Recovery	**Rapid**	**Slow**
Postictal confusion	**Rare**	**Common**
Precipitating factors	**Common**	**Rare**
Response to anti-epileptic drugs	No	Commonly
Ictal EEG	Slow waves/flattening	Focal/generalised spike activity
Single interictal EEG	Epileptiform changes: 0.5% Non-specific abnormalities: ≤25%	Epileptiform changes: 50%

Patent foramen ovale and migraine?

Right-to-left shunting, most often secondary to PFO, has been found in nearly half those with migraine plus aura, which in turn occurs more frequently in populations with a high prevalence of right-to-left shunts.[13] There is a high prevalence of migraine in stroke patients with PFO (27–52%). Plausible explanations for an association include paradoxical micro-embolism triggering migraine attacks and shunting of migraine trigger chemicals from the venous circulation into the brain, bypassing the normal pulmonary 'filter'.

Can a tendency to migraine be affected by closing a patient foramen ovale?

Divers who underwent transcatheter closure of intracardiac right-to-left shunts reported an improvement in migraine attacks following treatment, particularly for migraine with aura.[14] The preliminary results of the Migraine Intervention with STARFlex Technology (MIST) study, the first prospective, randomised, double-blind, placebo-controlled study comparing device closure with a sham procedure, were presented in March 2006.[15] There was no difference in the primary end-point of migraine cessation but headache frequency and 'headache burden' were improved in the group undergoing closure (Box 1). Patients with migraine would be advised to await further studies before exposing themselves to this technique.

Implantable loop recorders

Collapse: the heart, the brain or both?

Implantable loop recorders (ILR) play a vital role in diagnosing infrequent but serious cardiac dysrhythmias. The same technology can be used to identify rare

patients with epilepsy who are prone to serious bradycardia and asystole as ictal phenomena during epileptic seizures (particularly partial seizures originating from the left temporal lobe). Conversely, cardiac dysrhythmia or syncope is frequently identified in patients misdiagnosed with epilepsy who fail to respond to anticonvulsants or who describe atypical 'seizures' (Table 2, Box 2).[16]

Epilepsy diagnosis

In an interesting twist, one group have used ILR recordings to diagnose epilepsy.[17] They described a characteristic appearance to ILR recordings from muscle artefact accompanying tonic-clonic seizures. Recordings demonstrated a tonic phase (sustained, rapid, high frequency myopotentials) changing to a clonic phase (periodic bursts of high-frequency myopotentials) (Fig 4). There are enormous difficulties in obtaining prolonged ambulatory EEG recordings in the community, but this could prove a useful method to identify tonic-clonic seizures in individuals with infrequent attacks.

Box 2. The value of cardiovascular tests to diagnose convulsive syncope in patients with apparent treatment-resistant epilepsy. BP = blood pressure; MI = myocardial infarction. Data sourced from Reference 16.

74 consecutive patients with recurrent seizure-like episodes:

Previously diagnosed epileptic: 41 unresponsive to anticonvulsants, 33 with atypical features (non-convulsive blackouts, pallor, sweating, light-headedness, postural or noxious provocation). Patients with suspected psychogenic non-epileptic attacks excluded.

prior ECG abnormality in 2 (inferior MI and episodic Wenckebach heart block)

alternative diagnosis identified in 31/74 (42%) and 13/36 (36%) taking anticonvulsants

head-up tilt:	**19 (26%)**	*experienced usual symptoms + profound hypotension or bradycardia during testing* *marked abnormal movements in 12/19 (63%): tonic posturing ± multifocal jerking or bilateral synchronous movements*
carotid sinus massage:	**7 (9%)**	*significant ECG pauses*
implantable loop recorder:	**2 (3%)**	*complete heart block* *prolonged sinus pause*
psychogenic:	**3 (4%)**	*panic attack with non-epileptiform shaking and preserved consciousness during tilt-testing* *apparent loss of consciousness with normal heart rate, BP and EEG during tilt-testing* *vasovagal attack during cannulation with typical attack*

After 10 months of follow-up 19/31 (61%) with an alternative diagnosis were symptom-free

11/13 (85%) with an alternative diagnosis and previously taking anticonvulsants successfully discontinued medication

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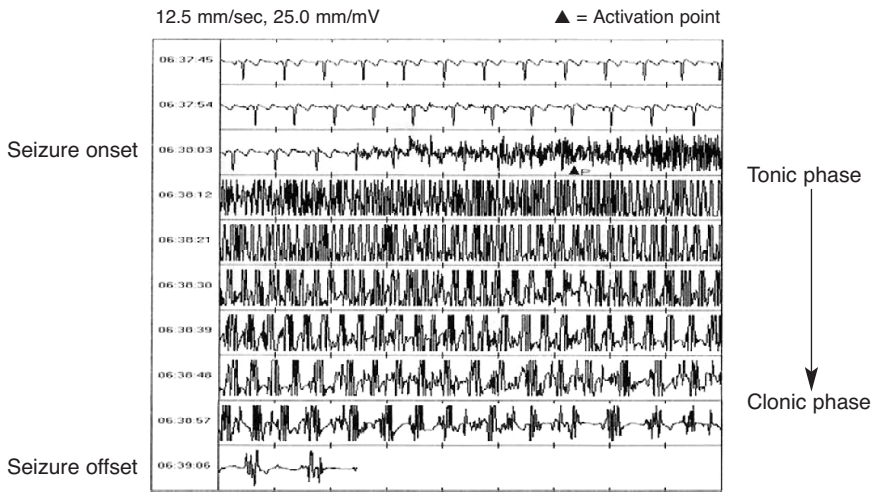

Fig 4. Implantable loop recorder recording of generalised tonic-clonic seizures. Transition to the clonic phase occurs after 22 seconds of tonic activity. The frequency of clonic bursts decelerates gradually from six to one cycle per second over 41 seconds. Reproduced with permission from the Heart Rhythm Society.[17]

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Neurological problems in cancer

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Several neurological problems can arise in cancer (Table 1). This article will focus on the most challenging presentations. Treatment related complications will not be discussed.

Metastasis

Brain metastases

Brain metastases are common (10–30% of cancer patients). The prevalence is rising as survival improves, the population ages and clinically silent lesions are detected with magnetic resonance imaging (MRI). The most common primaries in adults are lung (50%), breast (15–20%) and melanoma (10%). Lung and melanoma tend to produce multiple metastases, limiting treatment options.[1,2]

The distribution of brain metastases occurs in proportion to blood flow (80% cerebral hemispheres, 15% cerebellum, 5% brainstem). Patients present with headaches, seizures and cognitive dysfunction or progressive focal neurological deficits such as hemiparesis, aphasia or visual field defect. Up to a third of metastases escape detection during life.[3] Brain metastases are associated with a poor prognosis. Depending on age, functional status, extent of systemic disease and number of metastases, median survival is 2.3–13.5 months.[4]

Contrast enhanced MRI is the most sensitive test; if a single metastasis is seen on computed tomography (CT), MRI is required to exclude multiple metastases before planning radical treatment. Initial medical management consists of steroids for oedema and anticonvulsants where appropriate. Further treatment may consist of surgical excision or radiosurgery for a solitary metastasis or whole brain radiotherapy.[5,6]

Spinal cord compression

Approximately 5% of cancer patients develop spinal cord compression, in two-thirds of cases in the narrower thoracic canal. Bony spinal metastases arise from any primary malignancy, the most common being prostate, breast and lung.[5] Spinal pain is common; it presents on average 7–15 weeks before neurological signs develop, most commonly as bilateral pyramidal leg weakness. The site of pain or sensory level does not correlate well with the level of cord compression. A high level of suspicion is required and a spine MRI is the investigation of choice. Treatment is with steroids, usually followed by either surgery or radiotherapy.[5]

Neoplastic meningitis

Neoplastic meningitis (NM), resulting from direct invasion of leptomeninges and/or cerebrospinal fluid (CSF) by

Table 1. Neurological problems in cancer.

Metastases	Cerebral Epidural spinal cord compression
Direct tumour infiltration	Cranial nerves Nerve roots Peripheral nerves
Neoplastic meningitis	Cerebral Cranial nerves Spinal cord and roots
Remote effects of cancer	Paraneoplastic disorders Coagulopathy (eg venous sinus thrombosis)
Effects of treatment	Surgery, radiotherapy and chemotherapy