Neurology & Neurosurgery

Dawn Collins, John Goodfellow, Dulanka Silva, Ronan Dardis, Sanjoy Nagaraja

Core science, medicine and surgery in one book

Series Editors:
Janine Henderson, David Oliveira, Stephen Parker

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Neurology & Neurosurgery

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Series Editors’ Foreword

Today’s medical students need to know a great deal to be effective as tomorrow’s doctors. This knowledge includes core science and clinical skills, from understanding biochemical pathways to communicating with patients. Modern medical school curricula integrate this teaching, thereby emphasising how learning in one area can support and reinforce another. At the same time students must acquire sound clinical reasoning skills, working with complex information to understand each individual’s unique medical problems.

The Eureka series is designed to cover all aspects of today’s medical curricula and reinforce this integrated approach. Each book can be used from first year through to qualification. Core biomedical principles are introduced but given relevant clinical context: the authors have always asked themselves, ‘why does the aspiring clinician need to know this’?

Each clinical title in the series is grounded in the relevant core science, which is introduced at the start of each book. Each core science title integrates and emphasises clinical relevance throughout. Medical and surgical approaches are included to provide a complete and integrated view of the patient management options available to the clinician. Clinical insights highlight key facts and principles drawn from medical practice. Cases featuring unique graphic narratives are presented with clear explanations that show how experienced clinicians think, enabling students to develop their own clinical reasoning and decision making. Clinical SBAs help with exam revision while starter questions are a unique learning tool designed to stimulate interest in the subject.

Having biomedical principles and clinical applications together in one book will make their connections more explicit and easier to remember. Alongside repeated exposure to patients and practice of clinical and communication skills, we hope Eureka will equip medical students for a lifetime of successful clinical practice.

Janine Henderson, David Oliveira, Stephen Parker
About the Series Editors

Janine Henderson is the Director of Mental Health Education at Hull York Medical School (HYMS). After medical school at the University of Oxford and clinical training in psychiatry, she combined her work as a Consultant Psychiatrist with postgraduate teaching roles, moving to the new Hull York Medical School in 2004 where she was the Programme Director for the MB BS from 2014 to 2017. She has a particular interest in modern educational methods, curriculum design and clinical reasoning.

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Preface

Neurology and neurosurgery inspire a mixture of fear and fascination in most medical students due to the perceived complexity of the nervous system. *Eureka Neurology & Neurosurgery* demystifies the nervous system, and the diagnosis and management of neurological disorders, by integrating the core neuroscience and clinical knowledge in an accessible way.

Chapter 1 covers core neuroscience: the structural framework that underpins clinical practice. Chapter 2 lays out the tools required to apply this knowledge when evaluating and managing neurological patients. Subsequent chapters describe the spectrum of neurological and neurosurgical disorders, from infections to traumatic injury. Clinical cases are brought to life using graphic narratives and neuroradiological imaging, while figures and boxes simplify key concepts and provide clinical correlates. Dedicated chapters cover emergency presentations and the integrated management of patients with chronic neurological conditions. Finally, clinical SBAs provide a useful revision aid.

We hope you enjoy this book and that it provides you with confidence when approaching patients with neurological disorders.

Dawn Collins  
John Goodfellow  
Dulanka Silva  
Ronan Dardis  
Sanjoy Nagaraja  
January 2016
Contents

Series Editors’ Foreword v
About the Series Editors vi
About the Authors vi
Preface vii
Glossary xi
Acknowledgements xii

Chapter 1 First principles
Overview of the nervous system 1
Cells and signalling 12
Development of the nervous system 21
The environment of the brain 26
Cerebrum 41
Thalamus and hypothalamus 52
Brainstem 56
Cerebellum 64
Vertebral column and spinal cord 68
Somatosensory system 77
Somatic motor 84
Reflexes 91
Autonomic nervous system 95
Enteric nervous system 99
Cranial nerves 100
Special senses 107

Chapter 2 Clinical essentials
Introduction 119
Common symptoms and how to take a history 120
Common signs and how to examine a patient 134
Investigations 166
Management options 175

Chapter 3 Increased intracranial pressure and traumatic brain injury
Introduction 187
Case 1 Headache and vomiting 188
Increased intracranial pressure 190
Traumatic brain injury 195
Extradural haematoma 200
Acute subdural haematoma 201
Chronic subdural haematoma 202
Traumatic intraparenchymal haemorrhage 203
Diffuse axonal injury 204
Hydrocephalus 204

Chapter 4 Headache and facial pain syndromes
Introduction 209
Case 2 Headache 210
Case 3 Throbbing headache and reduced vision 212
Migraine 214
Tension-type headache 218
Cluster headache 218
Temporomandibular joint dysfunction 220
Trigeminal neuralgia 220
Giant cell arteritis 221
Headache of increased intracranial pressure 222
Other headache syndromes 223

Chapter 5 Seizures and epilepsy
Introduction 225
Contents

Case 4 Blackout 226
Case 5 Recurrence of seizures 229
Seizures and epilepsy 230

Chapter 6 Neurovascular disease
Introduction 239
Case 6 Blackout 240
Case 7 Sudden onset weakness 243
Ischaemic and haemorrhagic stroke 244
Transient ischaemic attack 254
Cerebral aneurysms 257
Arteriovenous malformations 263
Cerebral venous sinus thrombosis 265
Cavernous sinus syndromes 266

Chapter 7 Neurological tumours
Introduction 269
Case 8 Morning headache 270
Intracranial tumours: general principles 272
Gliomas 278
Glioblastoma multiforme 279
Meningiomas 279
Nerve sheath tumours 280
Pituitary tumours 281
Metastatic tumours 282
Spinal tumours 283

Chapter 8 Neurological infections
Introduction 287
Case 9 Fever and confusion 288
Bacterial meningitis 291
Viral meningitis 295
Encephalitis 296
Brain abscess 298
HIV and associated infections 301
Tuberculosis 303
Spinal infections 305
Herpes zoster and post-herpetic neuralgia 307

Chapter 9 Movement disorders
Introduction 309
Case 10 Tremor 310
Parkinson’s disease 313
Drug-induced parkinsonism 318
Parkinson’s plus syndromes 318
Huntington’s disease 320
Essential tremor 322
Wilson’s disease 323
Restless legs syndrome 324
Tics 325

Chapter 10 Multiple sclerosis and other central nervous system demyelinating diseases
Introduction 327
Case 11 Rapid loss of visual acuity in one eye 328
Multiple sclerosis 330
Other central nervous system demyelinating diseases 338

Chapter 11 Spinal disorders
Introduction 341
Case 12 Arm pain worsened by coughing 342
Spinal syndromes 344
Spondylosis 349
Myelopathy 350
Radiculopathy 352
Lumbar spinal stenosis 354
Cauda equina syndrome 356
Spondylolysis and spondylolisthesis 357
Syringomyelia 358
Spinal cord infarction 359

Chapter 12 Systemic immune disease affecting the nervous system
Introduction 361
Case 13  Generally feeling unwell with weakness 362
Systemic lupus erythematosus 363
Sjögren’s syndrome 366
Vasculitis and polyarteritis nodosa 367
Paraneoplastic syndromes 369
Neurosarcoidosis 371

Chapter 13  Motor neurone and genetic neurodegenerative diseases
Introduction 375
Case 14  Tendency to fall over 376
Motor neurone disease 378
Spinal muscular atrophy 382
Friedreich’s ataxia 384
Spinocerebellar ataxia 386

Chapter 14  Dementia
Introduction 387
Case 15  Change in personality and decline in memory 388
Dementia 390
Alzheimer’s disease 394
Vascular dementia 397
Dementia with Lewy bodies 398
Frontotemporal lobar degeneration 400
Wernicke–Korsakoff syndrome 402
Creutzfeldt–Jakob disease 402

Chapter 15  Congenital and hereditary conditions
Introduction 405
Case 16  Partial seizure 406
Cerebral palsy 407
Myotonic dystrophy 410
Spina bifida 411
Hereditary spastic paraplegia 414
Neurofibromatosis 414
Tuberous sclerosis complex 417
Sturge–Weber syndrome 419

Chapter 16  Peripheral neurological disease
Introduction 421
Case 17  Numbness and tingling in feet 422
Peripheral nerve lesions 423
Muscular disease 433
Neuromuscular junction disease 438

Chapter 17  Emergencies
Introduction 441
Case 18  Acute onset severe headache 442
Case 19  Sudden focal neurological deficit 444
Case 20  Injuries from a road traffic accident 445
Case 21  Status epilepticus 448
Case 22  Acute neuromuscular paralysis 449
Case 23  Unconsciousness and coma 452
Case 24  Fever and confusion 453
Case 25  Increased intracranial pressure 455
Case 26  Cauda equina syndrome 456

Chapter 18  Integrated care
Introduction 459
Case 27  Caring for a stroke patient 459
Stroke 461
Chronic pain 462
Long-term support for chronic neurological conditions 465

Chapter 19  Self-assessment
SBA questions 467
SBA answers 476

Index 483
# Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCDE</td>
<td>Airway, Breathing, Circulation, Disability, Exposure</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADC</td>
<td>apparent diffusion coefficient</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMA</td>
<td>antimitochondrial antibody</td>
</tr>
<tr>
<td>AMPLE</td>
<td>Allergies, Medications, Past medical history, Last meal, Events surrounding injury</td>
</tr>
<tr>
<td>ANA</td>
<td>antinuclear autoantibody</td>
</tr>
<tr>
<td>ANCA</td>
<td>antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>anti-dsDNA</td>
<td>anti-double-stranded DNA autoantibody</td>
</tr>
<tr>
<td>ATLS</td>
<td>Advanced trauma life support</td>
</tr>
<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>AZT</td>
<td>azidothymidine</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood oxygenation level-dependent blood pressure</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CN</td>
<td>cranial nerve</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computerised tomography</td>
</tr>
<tr>
<td>DMPK</td>
<td>dystrophia myotonica protein kinase</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted imaging</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram or encephalography</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>HAART</td>
<td>highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICHD</td>
<td>International Classification of Headache Disorders</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>LMN</td>
<td>lower motor neurone</td>
</tr>
<tr>
<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
</tr>
<tr>
<td>MR</td>
<td>magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OCB</td>
<td>oligoclonal band</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PNS</td>
<td>parasympathetic nervous system</td>
</tr>
<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computerised tomography</td>
</tr>
<tr>
<td>SUDEP</td>
<td>sudden unexpected death in epilepsy</td>
</tr>
<tr>
<td>SUNCT</td>
<td>short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing</td>
</tr>
<tr>
<td>UMN</td>
<td>upper motor neurone</td>
</tr>
<tr>
<td>V</td>
<td>volume</td>
</tr>
<tr>
<td>V&lt;sub&gt;blood&lt;/sub&gt;</td>
<td>volume of blood</td>
</tr>
<tr>
<td>V&lt;sub&gt;brain&lt;/sub&gt;</td>
<td>volume of brain</td>
</tr>
<tr>
<td>V&lt;sub&gt;cerebrospinal fluid&lt;/sub&gt;</td>
<td>volume of cerebrospinal fluid</td>
</tr>
<tr>
<td>V&lt;sub&gt;extra mass&lt;/sub&gt;</td>
<td>volume of extra mass</td>
</tr>
<tr>
<td>V&lt;sub&gt;total&lt;/sub&gt;</td>
<td>total intracranial volume</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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DC, JG, DS, RD, SN

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SN
Chapter 8
Neurological infections

Introduction

The nervous system can be infected by bacteria, viruses, fungi, spirochaetes and prions. Devastating infections such as bacterial meningitis and herpes simplex virus encephalitis are rare. In contrast, nervous system infection due to enteroviruses such as coxsackie viruses is common and less serious.

Opportunistic infections become pathogenic in cases of immunosuppression, for example in people with HIV infection. The causative agents include fungi and latent viruses.

Infection can involve one or more of the following: meninges, in cases of meningitis; brain parenchyma, in encephalitis; spinal cord, in myelitis; nerve roots, in radiculitis; dorsal root ganglia, in ganglionitis; peripheral nerves, in neuritis; arteries, in arteritis; and veins, in phlebitis.

The central nervous system’s immune system is unique because:

- the brain has no lymphatic system
- B cell-mediated defences predominate over T cell-mediated ones
- the blood–brain barrier tightly controls immune cell access

Together, these properties limit oedema and secondary damage during inflammation of the central nervous system in response to infection.

Starter questions

Answers to the following questions are on page 308.

1. How does the immune response in the brain differ from that in the rest of the body?
2. How do immune cells ‘know’ to cross the blood–brain barrier to interact with infectious agents in the brain?
3. Steroids suppress the body’s immune response, so why are they useful for treating infection?
4. Does inflammation damage the brain permanently?
Case 9 Fever and confusion

Presentation
Michael Breckford, a 19-year-old student, is brought into the emergency department confused, drowsy and feverish. He has an abdominal rash comprising small purple macules coalescing into larger patches. The rash does not disappear with pressure.

Initial interpretation
Confusion, drowsiness and fever suggest central nervous system infection, so meningitis, encephalitis and abscesses are possible diagnoses. The non-blanching purpuric rash may indicate systemic meningococcal septicaemia causing impaired coagulation, capillary leakage and haemorrhage. This is an alarming combination of symptoms that warrant urgent assessment with treatment for potential bacterial meningitis.

Even without the rash, a central nervous system infection is likely. Therefore empirical treatment to cover for both viral and bacterial infection would be initiated.

Non-central nervous system infections causing systemic sepsis with metabolic disturbance can produce a similar picture of septic encephalopathy.

History
Michael’s flatmates give a collateral history. He was well until 24 hours ago, when he became increasingly sleepy and missed lectures. At first he had headache, but he became progressively less coherent over the course of the day. An hour ago, they found him feverish and confused so called an ambulance.
Interpretation of history

Patients with central nervous system infection are usually unable to provide a history. In cases of haemodynamic instability caused by sepsis, the priority is treatment of the most serious potential causes, including bacterial meningitis. Every effort should be made to contact the patient’s family, friends and other contacts as early as possible. This is essential to obtain a collateral history regarding the patient’s condition and because the patient’s contacts may also be affected.

Immediate treatment for bacterial meningitis, an acutely life-threatening cause of this presentation, is mandated. Further investigation can continue after initial treatment.

Key differential diagnoses for bacterial meningitis are shown in Table 8.1.

Concomitant treatment with aciclovir is started empirically in cases of suspected central nervous system infection, because herpes simplex virus encephalitis can be missed, potentially leading to severe neurological disability and/or death.

Fever, headache and cognitive changes raise the suspicion of infective meningitis. This presentation triggers immediate assessment, investigation and initiation of empirical antibiotics or antiviral drugs based on local treatment policies.

Further history

Michael has no history of recurrent infections to suggest a primary immunodeficiency. He is not known to be HIV-positive or to have risk factors for HIV.

He has not travelled abroad in years. He has no contact with animals to suggest exposure to an uncommon infectious agent.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Differentiating feature(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis</td>
<td>Acute onset</td>
</tr>
<tr>
<td></td>
<td>Patients often have severe sepsis</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>Usually less severe</td>
</tr>
<tr>
<td></td>
<td>Onset acute (hours to days) or subacute (days)</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>More gradual onset: subacute or chronic (days to weeks)</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve palsies</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>Usually slower onset (subacute or chronic)</td>
</tr>
<tr>
<td></td>
<td>Immunocompromise is a risk factor</td>
</tr>
<tr>
<td>Autoimmune meningitis</td>
<td>Slower onset (subacute or chronic)</td>
</tr>
<tr>
<td></td>
<td>Less severe</td>
</tr>
<tr>
<td>Septic encephalopathy</td>
<td>Cerebrospinal fluid is normal</td>
</tr>
<tr>
<td>Acute subarachnoid haemorrhage</td>
<td>Usually apyrexial</td>
</tr>
<tr>
<td></td>
<td>Sudden onset severe headache (‘worst headache ever’)</td>
</tr>
<tr>
<td>Septic venous sinus thrombosis</td>
<td>Confirmed by neuroimaging</td>
</tr>
<tr>
<td>Carcinomatous or malignant meningitis</td>
<td>History of malignancy</td>
</tr>
<tr>
<td></td>
<td>Usually apyrexial</td>
</tr>
</tbody>
</table>

Table 8.1 Bacterial meningitis and its key differential diagnoses. All present with one or more of the major symptoms of bacterial meningitis (headache, fever, meningeal and altered mental status)

Examination

Michael’s Glasgow coma scale score is E2 (eye opening to pain) V3 (verbal responses: inappropriate words) M5 (movement localised to stimulus) (see page 453). The non-blanching purpuric rash over his abdomen and limbs persists. His neck is stiff to passive movements.
He does not cooperate with neurological examination but can spontaneously move each limb in response to a painful stimulus. His pupils are equal and reactive. He is tachycardic, with a blood pressure of 90/60 mmHg and a temperature of 40.1°C.

**Interpretation of findings**

Michael's tachycardia, low blood pressure and fever indicate systemic sepsis; a large release of inflammatory mediators causes systemic vasodilation, hypotension and tachycardia. Neck stiffness and drowsiness indicate meningeal inflammation and global brain dysfunction. These findings suggest meningococcal septicaemia. Immediate sepsis treatment is required:

- high-flow oxygen
- blood cultures
- broad spectrum antibiotics
- intravenous fluid challenges
- measurement of serum lactate and haemoglobin
- accurate measurement of hourly urine output

Once his condition has stabilised, he needs a lumbar puncture to confirm diagnosis and guide antibiotic therapy. His drowsiness may indicate increased intracranial pressure. Therefore computerised tomography (CT) to exclude a space-occupying lesion must be done before lumbar puncture.

**Investigations**

The CT scan excludes a mass lesion (Table 8.2). Lumbar puncture and the results of cerebrospinal fluid analysis show a high opening pressure (45 cm of H₂O), white cell count >10,000 and low cerebrospinal fluid:serum glucose ratio. Gram stain contains Gram-negative diplococci, which are identified as *Neisseria meningitidis*.

**Contraindications for lumbar puncture**

<table>
<thead>
<tr>
<th>Type</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Glasgow coma scale score reduced or fluctuating (&lt; 13) or decreasing by 2</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs, including pupil abnormalities</td>
</tr>
<tr>
<td></td>
<td>Abnormal posture or posturing</td>
</tr>
<tr>
<td></td>
<td>Papilloedema</td>
</tr>
<tr>
<td></td>
<td>After seizure, before stabilisation</td>
</tr>
<tr>
<td></td>
<td>Abnormal 'doll’s eye' movements</td>
</tr>
<tr>
<td>Systemic</td>
<td>Bradycardia with hypertension</td>
</tr>
<tr>
<td></td>
<td>Immunocompromise</td>
</tr>
<tr>
<td></td>
<td>Systemic shock</td>
</tr>
<tr>
<td></td>
<td>Coagulation abnormalities</td>
</tr>
<tr>
<td></td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Infective</td>
<td>Suspected meningococcal septicaemia</td>
</tr>
<tr>
<td></td>
<td>Local infection at site for lumbar puncture</td>
</tr>
</tbody>
</table>

*Table 8.2* Contraindications for immediate lumbar puncture before neuroimaging. Cerebrospinal fluid analysis is essential for diagnosis and to guide management in central nervous system infection; it is delayed pending neuroimaging only in the conditions listed in this table.

**Diagnosis**

The Gram stain confirms a diagnosis of bacterial meningitis. In many cases, the initial Gram stain can be negative, but a very high white cell count and low cerebrospinal fluid:serum glucose ratio still indicate bacterial meningitis. Culture of cerebrospinal fluid requires a few days to grow and identify an organism.

Michael is given intravenous ceftriaxone based on cerebrospinal fluid culture sensitivities. After 5 weeks on the intensive care unit, he ultimately makes a full recovery.
Bacterial meningitis

Meningitis is inflammation of the meninges, which envelop the brain and spinal cord (see page 27). Bacterial meningitis is the most serious form: untreated, it commonly progresses to overwhelming brain infection, which carries a high mortality.

Patients require early, aggressive resuscitation and treatment. Bacterial meningitis is suspected in any patient presenting with meningism and features of sepsis (a severe bloodstream infection with fever and non-blanching petechial or purpuric rash).

Epidemiology

The annual incidence of bacterial meningitis is 4 per 100,000 in the UK, with peaks in infants and adolescents. Vaccinations against the common causes, *Haemophilus influenzae* type B and *N. meningitidis* type C, have significantly reduced the rate of new cases.

Aetiology

The pathogens responsible for bacterial meningitis vary depending on patient age, immune status and clinical setting (Table 8.3). These associations predict the most effective initial broad spectrum antibiotic therapy if meningitis is suspected.

Pathogenesis

Common bacteria in community-acquired meningitis, i.e. *H. influenzae*, *Streptococcus pneumoniae* and *N. meningitidis*, all normally colonise nasal cavities and skull sinuses.

Invasion of intracranial compartments is more likely in the context of immunodeficiency or a breach in structural defences, for example after trauma or surgery.

Bacterial invasion precipitates an acute inflammatory response with aggregation of polymorphonuclear cells. Spread through the subarachnoid space causes local and systemic complications (Table 8.4).

Clinical features

Meningitis classically presents with fever and meningism (the triad of headache, photophobia and neck stiffness or rigidity). The condition is usually be preceded by a prodrome, such as respiratory tract or ear infection. It is also associated with risk factors depending on the cause, for example traumatic skull fracture with cerebrospinal fluid leak.

The presence of a purpuric non-blanching rash strongly suggests meningococcal septicaemia. The pathogenesis is a systemic inflammatory response with likely disseminated intravascular coagulopathy, causing a combination of severe vasodilation, capillary leakage, haemorrhaging into skin and microvascular thromboses.

Neurological complications include:

- increased intracranial pressure (depressed level of consciousness, headache, nausea and vomiting)
- seizures (in 20%)
- focal neurological deficits (in 10%) and cranial nerve deficits

Aseptic meningitis is diagnosed in cases of increased cerebrospinal fluid white cell count with no organisms identified on Gram stain or standard cultures. Causes include viruses, spirochaetes, parasites, *Brucella* species, *Mycoplasma* species, use of certain drugs (e.g. intravenous immunoglobulin and non-steroidal anti-inflammatory drugs) and meningeal tumour metastases.

Diagnostic approach

The diagnostic approach is identical for any suspected nervous system infection (Table 8.5).

The clinical history, presentation and examination form the initial basis of the diagnostic
### Age-related bacterial causes of meningitis

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Age</th>
<th>Common organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent</td>
<td>&lt; 3 months</td>
<td>Group B Streptococcus, Escherichia coli, Listeria monocytogenes</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>3 months to 18 years</td>
<td>Neisseria meningitidis (meningococcus), Strep. pneumoniae (pneumococcus), Haemophilus influenzae</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>18–50 years</td>
<td>Strep. pneumoniae, N. meningitidis</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>&gt; 50 years</td>
<td>Strep. pneumoniae, L. monocytogenes, Gram-negative bacilli</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Any</td>
<td>L. monocytogenes, Gram-negative bacilli, Strep. pneumoniae, H. influenzae</td>
</tr>
<tr>
<td>Head trauma</td>
<td>Any</td>
<td>Strep. pneumoniae, Staphylococci, Mixed</td>
</tr>
<tr>
<td>After a neurosurgical procedure</td>
<td>Any</td>
<td>Staphylococci, Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Epidemics</td>
<td>Usually 18–50 years</td>
<td>N. meningitidis</td>
</tr>
<tr>
<td>Others</td>
<td>Any</td>
<td>Mycobacterium tuberculosis, Brucella species</td>
</tr>
</tbody>
</table>

**Table 8.3** Prediction of the commonest bacterial causes of meningitis from the clinical setting and patient’s age. Empirical antibiotic therapy is started to cover these organisms, based on local bacterial sensitivities and policies.

### Complications of bacterial meningitis

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Complications</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Arteritis and phlebitis</td>
<td>Blood vessel inflammation</td>
</tr>
<tr>
<td></td>
<td>Ischaemia</td>
<td>Vessel occlusion and thrombosis</td>
</tr>
<tr>
<td></td>
<td>Cranial neuritis</td>
<td>Cranial nerve inflammation</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
<td>Obstruction of cerebrospinal fluid outflow from inflammation</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
<td>Inflammation spreading into focal brain region</td>
</tr>
<tr>
<td></td>
<td>Increased intracranial pressure</td>
<td>Generalised inflammation and oedema</td>
</tr>
<tr>
<td>Systemic</td>
<td>Cardiovascular shock</td>
<td>Hypotension from vasodilation</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>Renal hypoperfusion and nephrotic injury from inflammatory mediators</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation</td>
<td>Platelets and coagulation factors consumed in acute thromboses that cause ischaemia and infarction; state of low platelet and coagulation factor levels then leads to widespread haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Waterhouse-Friderichsen syndrome</td>
<td>Adrenal failure from adrenal gland hypoperfusion and infarction</td>
</tr>
</tbody>
</table>

**Table 8.4** Complications of bacterial meningitis
approach. If there is any suspicion of bacterial meningitis on this initial assessment, broad spectrum antibiotics are commenced immediately prior to investigation, as any delay increases the mortality risk.

Bloods are then obtained for microbiological assessment (cultures) and severity of systemic (e.g. full blood count, renal and liver function) and inflammatory responses (e.g. CRP, white cell count).

Definitive confirmation of intracranial infection is usually made on identification of a microbial organism on cerebrospinal fluid assessment (e.g. bacterial culture, fungal staining and culture, viral polymerase chain reaction). Cerebrospinal fluid is normally obtained following lumbar puncture but this is contraindicated in certain situations (Table 8.2).

In this day and age, rapid access to computed tomography scanning is available as an initial diagnostic tool to exclude a space-occupying lesion and is usually performed prior to lumbar puncture.

Cerebrospinal fluid assessment can be rapidly performed within a short period of time (usually < 1 h) to give an initial idea as to the nature of infection (see Table 8.6) but definitive culture to identify an organism takes at least 48–72 h (if not longer).

Nonetheless, when suspecting intracranial infection, the severity of complications including severe neurological disability and risk of death, means that treatment is commenced as soon as possible before awaiting results of tests.

Bacterial meningitis is confirmed by identification of an organism on cerebrospinal fluid culture. However, empirical antibiotic treatment is started immediately (see page 294).

**Investigations**

Lumbar puncture to obtain cerebrospinal fluid is key to confirming infection, but the procedure is contraindicated in certain

<table>
<thead>
<tr>
<th>Approach to suspected central nervous system infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
</tr>
<tr>
<td>Assess risk factors: HIV, recurrent bacterial infections, head trauma and neurosurgical intervention</td>
</tr>
<tr>
<td>Determine haemodynamic and respiratory status</td>
</tr>
<tr>
<td>Investigations</td>
</tr>
<tr>
<td>Full blood count, urea and electrolytes, liver function tests, coagulation profile, glucose and C-reactive protein</td>
</tr>
<tr>
<td>Blood cultures, throat swabs and serology titres</td>
</tr>
<tr>
<td>CT, CT with contrast and MRI</td>
</tr>
<tr>
<td>Lumbar puncture and cerebrospinal fluid analysis (see Table 8.6)</td>
</tr>
</tbody>
</table>

**Table 8.5** Approach to suspected central nervous system infections (of all causes). If bacterial infection is suspected, aggressive empirical antibiotic therapy is started immediately (see page 294)

<table>
<thead>
<tr>
<th>Cerebrospinal fluid findings in neurological inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of agent</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Bacterial</td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Tuberculous</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
</tbody>
</table>

**Table 8.6** Typical cerebrospinal fluid findings for bacterial, viral, tuberculous and autoimmune causes of neurological inflammation
circumstances (see Table 8.2). Cerebrospinal fluid tests for investigation of neurological infection include the following:

- opening pressure, which indicates intracranial pressure
- white cell count, including the differential test, to help delineate whether the cause is bacterial, viral, fungal or aseptic meningitis
- glucose to distinguish between bacterial, viral and tuberculous causes
- protein to identify hypercellularity and inflammation
- Gram stain to visualise any organisms
- definitive culture for diagnosis and antibiotic sensitivity
- special tests to identify specific pathogens
- oligoclonal bands (OCBs)
  - Paired OCBs (matched immunoglobulin peaks in serum and cerebrospinal fluid) indicate a systemic immune response
  - Unpaired OCBs mean immunoglobulin synthesised in the nervous system
  - Polyclonal OCBs indicate a non-specific immune response in the central nervous system

In Table 8.6, typical cerebrospinal fluid findings in neurological inflammation resulting from bacterial infection are contrasted with findings in other neurological infections. Common organisms visualised by Gram staining of cerebrospinal fluid are:

- Gram-positive cocci (e.g. *Staphylococcus aureus* and *Strep. pneumoniae*)
- Gram-negative cocci (e.g. *N. meningitidis*)
- Gram-negative bacilli (e.g. *Haemophilus influenzae* and *Escherichia coli*)
- Other agents (e.g. *Listeria monocytogenes*)

Management

When there is suspicion of a bacterial cause for meningitis-like clinical features, antibiotics are not delayed until diagnosis. Broad spectrum antibiotics, chosen on the basis of the likely species and local sensitivities, are started immediately. Antibiotic choice is adjusted later, when the species has been identified. The definitive choice is usually a third-generation cephalosporin such as ceftriaxone. An aminoglycoside, for example gentamicin, is usually added for neonates, and ampicillin for neonates and the elderly. The principles of treatment are:

- aggressive early resuscitation with oxygen and intravenous fluid therapy
- intravenous antimicrobial therapy for ≥ 2 weeks

Additional measures are usually required, including one or more of the following:

- Addition of aciclovir if encephalitis is suspected
- Steroids (e.g. dexamethasone 10 mg/6 h), which are usually given for 4 days, to improve morbidity and mortality in the treatment of bacterial meningitis
- Treatment of the precipitating factor (e.g. if meningitis is secondary to cerebrospinal fluid leakage following trauma or iatrogenically following surgery, this must be repaired to prevent future episodes)
- Supportive treatment for shock and increased intracranial pressure (see page 190)
- Management of complications, such as cerebrospinal fluid diversion in hydrocephalus, and abscess evacuation

Prophylaxis

Public health authorities require notification of confirmed cases to enable the tracing of contacts; oral rifampicin prophylaxis is then offered to close contacts.

Prognosis

Mortality of bacterial meningitis varies depending on the pathogen involved and the patient’s age and comorbidities. It is highest in neonates (40–75%) and varies from 7% (in cases caused by *H. influenzae* or *N. meningitidis*) to 20% (in those caused by *Streptococcus* species).
Viral meningitis

Viral meningitis is more common than bacterial meningitis. However, it is usually self-limiting, and patients generally recover without major neurological complications.

Epidemiology
In the UK, 3000 cases of viral meningitis are reported annually. However, the true incidence is thought to be far higher.

Aetiology
Many viral species cause meningitis, the most commonly identified ones being echovirus, coxsackievirus B, HIV and herpes simplex virus type 2. However, in many cases no organism is identifiable by culture or polymerase chain reaction (PCR) detection.

Pathogenesis
A virus can enter the body through a skin lesion or the respiratory, gastrointestinal or urogenital tract, then replicates locally (primary replication). It may then enter the nervous system haematogenously or through a cranial or peripheral nerve, as in cases of poliomyelitis. This often happens after secondary replication at other sites, for example fat and muscle. There is localised cell death and inflammation comprising mononuclear cells, ependymal destruction and meningeal inflammation.

Clinical features
Viral meningitis presents similarly to bacterial meningitis but is usually less severe. Seizures, focal neurological deficits and profound changes in level of consciousness are rare. If such features are present, parenchymal involvement, i.e. encephalitis, is suspected.

Diagnostic approach
Viruses are difficult to culture from cerebrospinal fluid. However, PCR for viral nucleic acids identifies many common viruses, including herpes simplex virus, varicella-zoster virus and enteroviruses. A diagnosis of viral meningitis can be made confidently when the results of cerebrospinal fluid PCR are positive for viral nucleic acids. However, the organism is often not identifiable on PCR, so the diagnosis is based on a typical clinical history of fever, headache and lack of significant neurological deficit, together with cerebrospinal fluid with mildly increased white cell count and other characteristics that differentiate viral from bacterial infection (Table 8.6).

Imaging
Meningeal enhancement is usually visible on contrast-enhanced magnetic resonance imaging (MRI) or CT (Figure 8.1). However, it may also be present in other infective (e.g. bacterial and tuberculous) or non-infective (e.g. autoimmune) causes of meningitis.

Management
Viral meningitis is usually benign and self-limiting. Treatment is symptomatic. Persistence of headache for several weeks or progressive visual impairment may indicate impaired cerebrospinal fluid reabsorption as a result of meningeal inflammation and increased intracranial pressure (see page 190). Cerebrospinal fluid diversionary procedures, such as lumbar punctures or shunting, may be indicated to prevent pressure from causing permanent visual loss.
Encephalitis

Encephalitis is inflammation of the neuronal and glial substance of the brain (parenchyma), and can be caused by any infectious agent or autoimmune process. Herpes simplex virus is the most serious viral cause. Early treatment with the antiviral drug aciclovir reduces mortality from 70% to 20–30%.

Encephalitis can co-occur with inflammation of the:
- meninges (as meningoencephalitis)
- spinal cord (as encephalomyelitis)

Epidemiology

The annual incidence of encephalitis is 1 per 100,000.

Aetiology

The commonest identified viral cause is herpes simplex virus type 1. Others include herpes simplex virus type 2 in neonates, Epstein-Barr virus, varicella-zoster virus and the mumps virus, and in patients with immunodeficiency, cytomegalovirus, HIV and JC viruses. Most epidemics are caused by arboviruses, such those responsible for tick-borne encephalitis and Japanese encephalitis.

Herpes simplex virus enters the body through inhalation. It gains access to the central nervous system through the initial sites of exposure: the olfactory mucosa and cranial nerve (the anterior cranial fossa) and the trigeminal nerve and associated ganglion (the middle cranial fossa). This leads to diffuse inflammation in the basal frontal and medial temporal lobes. Autoimmune causes of encephalitis include:

- sarcoidosis (chronic granulomatous inflammation)
- systemic lupus erythematosus (vasculitis of the meningeal vessels)
- anti–voltage-gated potassium channel complex
- anti-N-methyl-D-aspartate receptor autoantibodies (in anti-NMDA receptor autoantibody-mediated encephalitis)

Figure 8.1 Axial (a) and coronal (b) post-gadolinium contrast-enhanced magnetic resonance imaging scan showing the non-specific features of meningitis. Diffuse leptomeningeal enhancement suggests meningitis, and the dilated ventricles are in keeping with communicating hydrocephalus as its result.
Clinical features

Encephalitis presents with headache, fever, seizures, focal neurological deficits and significant deterioration in mental status. Table 8.7 lists the key differential diagnoses for viral encephalitis.

There may be a prodrome with some causes: parotitis for mumps; rash for measles virus, rubella virus and parvovirus; and myalgias for arboviruses. Herpes simplex virus encephalitis usually has no prodrome; it often presents with seizures and memory and behavioural dysfunction, resulting from temporal lobe inflammation.

In autoimmune encephalitis, there is often a history of other autoimmune conditions. The time course of onset is often days to weeks rather than hours. There is often no fever or laboratory evidence of systemic infection.

Differential diagnosis of viral encephalitis

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Underlying cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space-occupying lesion</td>
<td>Tumour Intracranial abscess</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>Liver failure Kidney failure Drug-induced</td>
</tr>
<tr>
<td>Paraneoplastic encephalitis</td>
<td>Subacute inflammation of brain parenchyma, triggered by a tumour</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Diffuse autoimmune white matter inflammatory process, often with spinal cord involvement</td>
</tr>
</tbody>
</table>

Table 8.7 Differential diagnosis of viral encephalitis. These resemble each other because they present with seizures, focal neurological deficits and deteriorating mental status.

Diagnostic approach

The diagnosis of encephalitis is made when both of the following are found:

- evidence of inflammation from the results of cerebrospinal fluid analysis (e.g. increased white cell count, increased protein concentration and oligoclonal bands)
- clinical (e.g. memory loss) and/or radiological evidence (e.g. high signal changes indicating oedema in the temporal lobes) of focal brain involvement

Cerebrospinal fluid analysis

In viral encephalitis, the cerebrospinal fluid findings are similar to those in viral meningitis (see page 295).

Imaging

Nearly 30% of patients with encephalitis have a normal brain CT. However, 90% have an abnormal brain MRI (Figure 8.2).

Figure 8.2 Coronal T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging scan showing typical features of herpes simplex virus encephalitis. There is increased signal intensity with oedema of the medial temporal lobes (1). In severe cases, focal haemorrhage may be visible in these regions.
In herpes simplex virus encephalitis, electroencephalography (see page 172) shows non-specific features in the frontotemporal regions.

Management
Without treatment, herpes simplex virus encephalitis has high morbidity and mortality. Therefore most clinicians start empirical antiviral treatment in any patient presenting with suggestive features.

Medication
Intravenous aciclovir (10 mg/kg every 8 h) is administered for a minimum of 14 days (21 days in cases of immunodeficiency). The use of corticosteroids to control intracranial pressure and cerebral oedema is controversial. Supportive adjuncts may be needed, for example to control seizures.

Encephalitis with an autoimmune cause often responds to immunosuppression: intravenous steroids followed by intravenous immunoglobulin, plasma exchange and other therapies, if needed.

Brain abscess
An abscess is a localised collection of pus (dead tissue, bacteria and white cells) surrounded by a capsule of fibrotic and granulation tissue; it usually results from bacterial infection. Intracranial abscesses occur at:
- extradural sites (as extradural empyema)
- subdural sites (as subdural empyema)
- intracerebral sites (in brain parenchyma)

Epidemiology
The annual incidence of brain abscess is 2–3 per million. It can occur at any age.

Aetiology
An initial infective process spreads to an intracranial compartment, either haematogenously or locally from adjacent structures. The latter process can be:
- direct (e.g. in a penetrating injury, through direct contact with the dura)
- indirect via contiguous structures (e.g. from a middle ear infection)

The infection provokes an immune response. This causes tissue necrosis and the formation of a collection of pus encased in scar tissue generated by fibroblasts. Identification of the site and source of infection often indicates the likely pathogen (Table 8.8).

Clinical features
The classic triad of features, which occurs in < 50% of cases, comprises:
- fever
- headache
- focal neurological deficits (depending on location)
Table 8.8 Causes of intracerebral abscesses. The site and source of the initial infective process suggests which pathogen is implicated.

<table>
<thead>
<tr>
<th>Mode of spread</th>
<th>Infective sources or underlying pathologies</th>
<th>Likely microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematogenous</td>
<td>Chronic lung infections</td>
<td>Streptococci and Staphylococci</td>
</tr>
<tr>
<td></td>
<td>Infective cardiac endocarditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary arteriovenous malformations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic sepsis</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>Trauma (e.g. penetrating brain injury)</td>
<td>Staphylococci</td>
</tr>
<tr>
<td></td>
<td>Sinus infection</td>
<td>Streptococci</td>
</tr>
<tr>
<td></td>
<td>Facial infections</td>
<td>Streptococci</td>
</tr>
<tr>
<td></td>
<td>Middle ear infections, including mastoiditis</td>
<td>Streptococci, Enterobacteriaceae, Pseudomonas species, Anaerobic bacteria</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (e.g. after neurosurgery)</td>
<td>Staphylococci</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Infection (e.g. HIV)</td>
<td>Any of the above organisms</td>
</tr>
<tr>
<td></td>
<td>Use of certain drugs (e.g. steroids and chemotherapy drugs)</td>
<td>Fungi, Parasites</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>Others (e.g. Listeria and Nocardia species)</td>
</tr>
</tbody>
</table>

Seizures occur in 30% of patients, and features of increased intracranial pressure may also be present. An intracranial abscess is part of the differential diagnosis for any space-occupying lesion visible on imaging. Features of the original infective source, for example sinusitis, pneumonia and endocarditis, may be evident.

Diagnostic approach

The diagnostic approach is as for other infections (see page 293). Urgent imaging with contrast-enhanced CT is indicated (see Figure 17.6a and b), with MRI to clarify the diagnosis (Figure 8.3). The source of the infection is investigated, for example echocardiography is used to assess for endocarditis, and CT sinuses for sinusitis.

Investigations

Contrast-enhanced CT shows a ring-enhancing lesion, comprising of a central area of low density surrounded contrast-enhancing ring of proliferating fibroblasts. There is usually oedema surrounding the contrast-enhancing ring lesion. Causes of a ring-enhancing lesion include:

- abscess
- tumour (primary brain or metastatic)
- cyst (e.g. in toxoplasmosis)
- tuberculosis
- lymphoma
- resolving haematoma
- demyelination plaque (e.g. in multiple sclerosis)
Chapter 8 Neurological infections

Management

The aims of surgery are to obtain microbiological samples for identification of the causative pathogen and its antibiotic sensitivities, and to decompress any mass effect. Empirical antimicrobials are started according to the suspected pathogen, with conversion to targeted therapy once the pathogen is identified through culture and its sensitivities are confirmed.

Surgery

Extradural and subdural empyemas are neurosurgical emergencies. They require urgent surgical evacuation to prevent thrombosis and inflammation of veins and arteries on the surface of the brain. These effects of empyemas can precipitate ischaemic injury and seizures.

Medication

Common regimens include a third-generation cephalosporin, such as ceftriaxone, and metronidazole, to target anaerobic bacteria. In immunosuppressed patients, additional agents may be indicated, for example pyrimethamine, which targets toxoplasmosis; amphotericin B, an antifungal; and ampicillin, which is effective against listeria.

Supportive treatment is also required: anticonvulsants for seizures and eradication of the source to prevent recurrence.

Ideally, tissue and abscess samples are obtained for microbiological diagnosis before antibiotics are started. This may be possible if the patient is clinically well, but antibiotics are not delayed in situations of severe or life-threatening sepsis.

Prognosis

Complications of brain abscess include focal neurologic deficits, seizures, cortical vein thrombosis and hydrocephalus. Subdural empyema has a mortality of between 10−20%, and > 50% of survivors have seizures, hydrocephalus or neurological deficits. The overall mortality of intracerebral abscesses is about 10% with treatment.

Figure 8.3 Differentiation between an abscess and a tumour. (a) Magnetic resonance imaging enhanced by contrast shows a thin-walled ‘ring-enhancing’ lesion. The hypodense centre (1) correlates with the central zone of necrosis and inflammation, whereas the enhancing ring is the capsule of fibroblasts, collagen and vascular proliferation (2). (b) Diffusion-weighted imaging (DWI) (image shown) and associated apparent diffusion coefficient (ADC) maps help differentiate between abscess and tumour. Abscesses have restricted diffusion (3) on DWI: high signal (bright) on DWI and low signal (dark) on ADC. Tumours (not demonstrated here) usually do not: low signal (dark) on DWI and high signal (bright) on ADC.
HIV and associated infections

Human immunodeficiency virus (HIV) is a blood-borne retrovirus that attacks and weakens the immune system, making patients susceptible to a range of opportunistic pathogens that do not usually cause disease. This state is referred to as acquired immunodeficiency syndrome (AIDS).

HIV-associated neurological disease is considered in patients presenting with either viral meningitis, polyneuritis or with one of the less common bacterial, fungal or viral infections. A late complication is progressive multifocal leucoencephalopathy, in which reactivation of a common latent central nervous system virus (specifically the JC virus) causes progressive central nervous system inflammation, focal signs and ultimately death.

Epidemiology

HIV and AIDS are global pandemics. An estimated 40 million people are affected; 30–80% suffer neurological dysfunction.

Aetiology

HIV infection causes profound immunodeficiency by infecting the CD4 subset of T cells (helper cells), which coordinate the entire adaptive immune response. Patients become prone to common and opportunistic infections normally subdued by a healthy immune system. Immune surveillance is also compromised, such that HIV is associated with certain malignancies caused by oncogenic viruses.

Neurological complications are summarised in Table 8.9; they differ depending on the stage of disease.

- **Early stage** (CD4+ > 500/mm): this stage encompasses two phases: acute infection with HIV and the seroconversion phase. Neurological manifestations are due to

<table>
<thead>
<tr>
<th>Stages of HIV infection and neurological complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Early stage</td>
</tr>
<tr>
<td>Acute infection with HIV: usually asymptomatic or with features similar to glandular fever (fever and lymphadenopathy)</td>
</tr>
<tr>
<td>Seroconversion of HIV</td>
</tr>
<tr>
<td>Virus starts to infect cells and replicate over 4–12 weeks; symptomatic or asymptomatic</td>
</tr>
<tr>
<td>Middle stage</td>
</tr>
<tr>
<td>Latent phase: lasts months to years; progressive destruction of CD4 T cells, with weakening of immune system and increase in viral load</td>
</tr>
<tr>
<td>Late stage</td>
</tr>
<tr>
<td>AIDS phase: infection with a variety of opportunistic pathogen precipitates complications</td>
</tr>
</tbody>
</table>

Table 8.9 Stages of HIV infection and neurological complications
complications from HIV infection itself (e.g. HIV meningitis)

- **Middle stage (CD4+ 200–500/mm):** this stage encompasses the latent phase of HIV infection. Neurological manifestations are due to infections and complications from immune-mediated damage (e.g. mononeuritis multiplex)

- **Late stage (CD4+ < 200/mm):** this stage is the development of AIDS with complications from opportunistic pathogens (e.g. cryptococcal meningitis)

**Clinical features**

Primary HIV infection and viraemia can cause a seroconversion illness that is clinically similar to Guillain-Barré syndrome, with fever, lymphadenopathy and neuropathy. Indirect effects arise from opportunistic infection and adverse effects of the highly active antiretroviral therapy (HAART) used to treat HIV. Other peripheral neuropathies in many people with HIV/AIDS are listed in Table 8.10.

**Diagnostic approach**

Demonstration of anti-HIV antibodies confirms diagnosis of HIV. Most HIV-related neurological disorders are usually diagnosed in patients for whom the diagnosis of HIV is already known. Nowadays, it is rare for neurological complications to be the initial presentation of HIV.

**Management**

The aims of management are to:

- treat acute neurological complications (e.g. opportunistic infection and malignancy)
- treat HIV infection with HAART
- assess the efficacy of treatment and monitor for development of drug resistance
- decrease HIV viral load to < 50 copies/mL and increase CD4 T cell count to > 500/mm³

**Medication**

HAART is the standard triple therapy for HIV infection. It consists of two nucleoside reverse transcriptase inhibitors and either a protease Inhibitor or a non-nucleoside reverse transcriptase inhibitor. All these block viral replication enzymes.

Specific opportunistic infections require specific treatments:

- cytomegalovirus infection requires antiviral drugs (e.g. ganciclovir)
- *Toxoplasma* infection requires pyrimethamine
- cryptococcal infection requires antifungal drugs (e.g. amphotericin B)
- primary central nervous system lymphoma requires steroids for oedema, initiation of HAART and chemoradiotherapy

**Surgery**

Neurosurgery may be required if patients develop mass lesions, such as abscess, metastatic deposits and primary central nervous system lymphoma, with associated increase in intracranial pressure, or if there is diagnostic uncertainty requiring tissue sample for analysis.

**Table 8.10 HIV-related peripheral nervous system disorders**

<table>
<thead>
<tr>
<th>Tissue affected</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve roots</td>
<td>Seroconversion illness</td>
</tr>
<tr>
<td></td>
<td>Varicella zoster virus infection</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus infection</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Polyneuropathy similar to Guillain-Barré syndrome</td>
</tr>
<tr>
<td></td>
<td>Antiviral therapy-induced</td>
</tr>
<tr>
<td>Muscle</td>
<td>Myopathy related to zidovudine (azidothymidine, AZT) antiretroviral therapy</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
</tr>
</tbody>
</table>

Specialist imaging can help differentiate lesions in patients with AIDS. For example, thallium single-photon emission computerised tomography distinguishes between a lymphoma and a *Toxoplasma* abscess.
Tuberculosis

Tuberculosis primarily affects the lung but neurological involvement does occur, most commonly in immunosuppressed patients.

The efficacy of antituberculous drug therapy is progressively being limited by increases in multidrug-resistant and extremely drug-resistant strains of Mycobacterium tuberculosis. The reduction in efficacy is caused by resistant strains surviving in immunosuppressed patients treated with standard therapy.

Epidemiology

One third of the world’s population is thought to have been infected by mycobacterium tuberculosis, and new infections are thought to occur in 1% of the population each year. The central nervous system is involved in 10% of patients. In the UK, the annual incidence of tuberculosis is 14 per 100,000; 40% of these cases are in London.

Aetiology

Most tuberculosis infection in humans is caused by M. tuberculosis, a slow-growing aerobic bacillus with a lipid-rich membrane that helps it evade the immune response. It spreads from person to person through inhalation of aerosol droplets.

Pathogenesis

The hallmark of tuberculosis is caseating (cheese-like) granulomatous lesions: tuberculomas. The initial infection is usually pulmonary, but uncontrolled infection can cause bacteremia and haematogenous spread to the central nervous system.

Immune inflammatory responses usually control primary pulmonary infection, instigating a latent phase. Reactivation occurs after immunodeficiency or spontaneously with subsequent bacteremia and haematogenous spread. The nervous system usually becomes affected following reactivation. Three syndromes occur, each with similar incidences:

- Tuberculous meningitis after rupture of foci of tuberculosis from surrounding structures or haematogenous spread
- Tuberculous abscess (tuberculoma) of the parenchyma (cerebral hemisphere, cerebellum or brain stem) or the spinal cord
- Vertebrae osteomyelitis (Pott’s disease) or discitis

Other neurological syndromes include encephalitis, spinal cord myelitis and radiculitis (inflammation of the nerve roots).

Clinical features

Between 90 and 95% of tuberculosis infections are latent, i.e. asymptomatic. Neurological manifestations of tuberculosis depend on the site affected.

- Meninges: an acute fulminant meningitis or chronic, less severe meningitis, with systemic prodromal symptoms and meningism
- Parenchyma: the symptoms typical of any space-occupying lesion and, in 50% of patients with tuberculomas and tuberculous encephalitis, syndrome of inappropriate antidiuretic hormone
- Spine: back pain, fever, malaise and spinal tenderness
- Spinal cord: features of spinal cord and nerve root compression (see pages 344–348)

Complications depend on the site of the pathology, e.g. in meningeal infection the complications that develop in bacterial meningitis (see Table 8.4) also can occur. A parenchymal tuberculoma rarely can rupture into the subarachnoid space to cause meningitis.

Diagnostic approach

Culture of Mycobacterium species from cerebrospinal fluid is diagnostic of neurological infection, but the results are negative in over half of cases. In most cases, diagnosis is made when there is a typical clinical picture, known history of tuberculosis, tuberculosis exposure or tuberculosis risk factors, and suggestive cerebrospinal fluid analysis results (Table 8.6).
Investigations

Neuroimaging and cerebrospinal fluid analysis usually establish diagnosis, but these can be non-specific in central nervous system tuberculosis infection. Up to 30% of patients have normal imaging but the rest have meningeal enhancement, hydrocephalus or the characteristic tuberculoma (Figures 8.4 and 8.5).

In addition to the usual cerebrospinal fluid analyses (Table 8.6), cerebrospinal fluid is sent specifically for staining and culture of *M. tuberculosis*.

Management

Treatment of the underlying tuberculosis infection is prolonged, with a combination of antibiotics used concurrently and chosen according to the strain of tuberculosis and sensitivities. Patients need frequent monitoring for adverse effects and to ensure improvement and that there’s no development of resistance.

Medication

Antitubercular drug treatment is indicated for central nervous system tuberculosis infection. First-line drugs include combination therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Second-line drugs may be required for multidrug-resistant or extremely drug-resistant strains. Steroids decrease morbidity and mortality in central nervous system tuberculosis. Significant adverse effects of tuberculosis therapy include:

- hepatotoxicity from rifampicin
- peripheral neuropathy from isoniazid
- hepatotoxicity from pyrazinamide
- optic neuritis from ethambutol

Surgery

In cases of tuberculosis, surgical treatments are used to:

- aspirate tissue for microbiology analysis

![Figure 8.4](image1.png) Figure 8.4 T1-weighted post-contrast magnetic resonance imaging scans showing tuberculomas (1) in the basal cisterns and left temporal lobe, and meningeal enhancement (2).

![Figure 8.5](image2.png) Figure 8.5 Axial (a) and sagittal (b) post-intravenous contrast magnetic resonance imaging scans showing tuberculous granuloma (1) in L4, with subligamentous spread and vertebral body and disc destruction.
Spinal infections

Infections may involve the vertebral bodies, intervertebral discs or neural elements (spinal cord, nerve roots, etc.). There are three main pathologies:

- **osteomyelitis** (infection or inflammation of bony elements, including marrow)
- **discitis** (infection or inflammation of intervertebral discs and/or disc space)
- **epidural abscess** (pus in the spinal epidural space) or extremely rarely **subdural empyema** (pus in the spinal subdural space)

**Epidemiology**

The annual incidence of vertebral osteomyelitis is 3 per 100,000 in high-income countries.

**Aetiology**

Spinal infections arise from local (direct) or haematogenous spread. Common bacterial pathogens are:

- **Staph. aureus** (especially post-operative or iatrogenic)
- **Pseudomonas aeruginosa**
- **M. tuberculosis** (Pott’s spondylitis)
- **Salmonella** (especially in immunodeficiency and sickle cell anaemia)

Fungal infection is usually caused by:

- **Candida species**
- **Aspergillus species**

Haematogenous spread occurs through the arterial supply or spinal epidural vertebral venous plexus (Batson’s plexus) (see page 72). Possible sources that spread in this way are infective endocarditis, pulmonary infection or generalised septicaemia.

**Clinical features**

Neurological deficits depend on which structure is compressed, and at which level:

- **spinal cord** (myelopathy; see Tables 11.2 and 11.4)
- **nerve roots** (radiculopathy; see Table 11.3 and pages 347 and 345)
- **cauda equina** (cauda equina syndrome; see Table 11.3 and pages 348 and 345)

There is initially severe localised back pain, with paravertebral muscle spasm and focal spinal tenderness on palpation, all resulting from local inflammation. This develops into radicular pain in a belt- or band-like distribution in the dermatome at the level of compression. Next are signs and symptoms of spinal cord dysfunction with weakness and sensory loss, depending on the segmental level affected.

These neurological deficits are summarised in Table 8.11. There may be associated fever and malaise, and increased inflammatory markers. The presentation can be acute (over days to weeks) or chronic (over months).

**Diagnostic approach**

Systemic signs of infection (fever, malaise and increased inflammatory markers) and local signs (back pain, and focal spine tenderness on palpation) suggest spinal infection. Urgent imaging with CT, MRI or both (Figures 8.6 and 8.7) is required. Possible primary sites of sepsis, for example heart murmur in infective endocarditis, must be investigated.

**Prognosis**

The outcome of tuberculosis with neurological complications depends on the patient’s age, the site affected and the severity of presenting neurological deficits. Even with early antitubercular drug treatment and surgical decompression, up to 30% may have persistent neurological deficits.
Management

Principles of treatment include:

- tissue samples for microbiological diagnosis and sensitivities
- empirical then targeted antibiotics to treat infection
- surgical decompression if needed (e.g. abscess evacuation)
- spinal stabilisation, if needed

In the absence of compressive lesions, conservative management is preferred: bed rest and 8 weeks of intravenous antibiotics is followed by 8 weeks of oral antibiotics. Serial MRI is used to evaluate resolution.

### Table 8.11

<table>
<thead>
<tr>
<th>Structure compressed</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Radicular pain in belt- or band-like distribution in dermatome</td>
</tr>
<tr>
<td></td>
<td>Motor deficit: LMN pattern at compression level, and UMN pattern below it</td>
</tr>
<tr>
<td></td>
<td>Sensory deficits below compression level</td>
</tr>
<tr>
<td>Nerve root</td>
<td>Motor deficit: LMN pattern corresponding to muscles supplied by nerve root</td>
</tr>
<tr>
<td></td>
<td>Sensory deficits in dermatome supplied by nerve root</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>Bilateral sciatic pain</td>
</tr>
<tr>
<td></td>
<td>Motor deficit, usually distal leg weakness in LMN pattern</td>
</tr>
<tr>
<td></td>
<td>Deficits in S2–S4 distribution</td>
</tr>
<tr>
<td></td>
<td>Sensory: perianal and saddle anaesthesia</td>
</tr>
<tr>
<td></td>
<td>Motor: loss of anal and bladder sphincter function and tone</td>
</tr>
<tr>
<td></td>
<td>Autonomic: bowel and bladder incontinence or retention</td>
</tr>
</tbody>
</table>

Table 8.11 Summary of neurological features of types of compression caused by spinal infection. LMN pattern of weakness is flaccid weakness, absence of reflexes and reduced tone; UMN pattern of weakness is spastic weakness, hyper-reflexia and increased tone.

**Figure 8.6** Sagittal T2W MRI showing osteomyelitis with discitis and probably vertebral body destruction at C3–C4 level (1).

**Figure 8.7** Axial (a) and sagittal (b) post-contrast magnetic resonance imaging scans of the cervical spine showing a large extradural abscess (1) with associated compression of the spinal cord (2).
Surgery
Indications for surgery include:

- lesion with compression of neural tissue (e.g. epidural abscess)
- failure of medical therapy
- mechanical instability of the spine as a result of bone destruction
- intractable pain
- diagnostic purposes, if other measures have failed

Spinal cord compression secondary to abscesses requires urgent decompression (<24h) to prevent permanent neurological injury, spinal instability and spread to other structures.

Herpes zoster and post-herpetic neuralgia

Primary varicella zoster virus infection causes varicella (chickenpox) or a non-specific flu-like prodrome. During this infection, spread to the nervous system occurs haematogenously or via cranial or peripheral nerves, resulting in long-term latent infection.

Herpes zoster (shingles) arises when the virus is reactivated in the sensory nerve root or dorsal root ganglia, causing a vesicular eruption and pain in the associated dermatome.

Some, but not all people with shingles develop post-herpetic neuralgia. In this condition, fibrosis and myelin loss in the dorsal root ganglia precipitate persistent neuropathic pain.

Varicella zoster encephalitis is a vasculopathy. Small- and medium-sized blood vessels develop inflammation, and the damage precipitates multiple infarcts and cerebral haemorrhages. Multifocal narrowing of blood vessels may be visible on arterial CT or MRI.

Clinical features

In shingles, the severe acute pain and vesicular rash (Figure 8.8) most commonly affect a truncal dermatome, but they can occur in any dermatome and elsewhere (Table 8.12). Patients have usually developed the problem on a background of reduced immunity, for example as a result of recent illness, advanced age, chemotherapy and HIV infection.

Dermatomal pain persisting for >30 days after a shingles attack is pathognomic of post-herpetic neuralgia. Paraesthesias and burning sensations may also be felt in the same dermatomal distribution. Increasing age and more severe pain during the shingles attack make post-herpetic neuralgia more likely to occur.

Figure 8.8 Skin vesicles in a dermatomal distribution in herpes zoster infection.

Varicella zoster virus encephalitis usually occurs only in immunocompromised people and causes multiple focal neurological deficits and cognitive impairment. Diagnosis is confirmed by PCR to identify varicella zoster virus in the cerebrospinal fluid.

Zoster ophthalmicus is involvement of the ophthalmic division of cranial nerve V (the trigeminal nerve). It is an emergency requiring urgent ophthalmological assessment and treatment to prevent permanent visual impairment.

Management

Aciclovir or famciclovir is prescribed to settle the rash of shingles; it reduces the risk of post-herpetic neuralgia. Ophthalmic shingles requires close ophthalmological monitoring to treat any corneal involvement.
Someone who has not had chickenpox can catch it from exposure to live varicella-zoster virus released by the blisters of a person with shingles. However, they cannot catch shingles because it occurs only when latent virus is reactivated.

Varicella zoster virus encephalitis and myelitis are treated with intravenous aciclovir or fomciclovir until cerebrospinal fluid analysis yields negative results with viral PCR. Identification of any immunodeficiency, especially HIV infection, is required.

Antineuropathic medications for post-herpetic neuralgia include amitriptyline, pregabalin, gabapentin and carbamazepine. Transcutaneous electrical nerve stimulation is a non-pharmacological adjunct. Most patients recover within a year, but a small proportion have permanent nerve damage.

### Clinical features of herpes zoster

<table>
<thead>
<tr>
<th>Affected nerve(s)</th>
<th>Clinical feature(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve ganglia and peripheral nerve</td>
<td>Eruption in dermatome supplied by that nerve</td>
</tr>
<tr>
<td>Cranial nerve (CN V (trigeminal nerve))</td>
<td>Involvement of gasserian ganglion (CN V ganglion) and eruption in distribution of the ophthalmic division of the nerve (CN V&lt;sub&gt;1&lt;/sub&gt;) Risk of corneal ulceration</td>
</tr>
<tr>
<td>Cranial nerve VII (facial nerve)</td>
<td>Ramsey Hunt syndrome: vesicles in external auditory meatus associated with ipsilateral facial weakness due to infectious spread through the geniculate (CN VII) ganglion</td>
</tr>
</tbody>
</table>

**Table 8.12 Clinical features of herpes zoster (shingles)**

### Answers to starter questions

1. Inflammation is a major part of most immune responses but is dangerous within the confined space of the skull. Therefore the brain's immune response relies less on T cell-mediated inflammation and more on antibody-mediated defences that attack specific pathogens. Usually (if well regulated) this causes less collateral damage to the brain.

2. Only a small percentage of lymphocytes and other immune cells cross the blood–brain barrier and pass through the central nervous system routinely as part of normal immune surveillance. Special transport systems allow certain cells to cross but impede the passage of others. If cells that have been allowed through the blood–brain barrier then encounter an antigen in the central nervous system, they are programmed to stay within the system, replicate and trigger an immune response.

3. Steroids reduce inflammation and oedema during an immune response, hindering the body’s ability to fight infection but limiting damage caused by the response. This effect is particularly helpful in infections of the brain, because the soft nervous tissue is encased in a rigid skull and therefore susceptible to damage from swelling.

4. Different components of the immune system cause different levels of damage. Antibodies can cause receptor cross linking that blocks them from being activated by their normal stimulating transmitters, which impairs neuronal functioning, activates complement and inhibits neuronal activity but causes minimal or reversible neuronal damage. On the other hand, phagocytic and cytotoxic T cells cause extensive and largely irreversible neuronal loss. Which aspect of the immune system is dominant determines the amount of damage to the brain.