Disorders Mainly Affecting White Matter

7

Contents

7.1 Introduction – Focus on White Matter Involvement

Many brain diseases are accompanied by white mater (WM) hyperintensity on T2-weighted (including FLAIR) magnetic resonance imaging (MRI) and by low attenuation on computed tomography (CT) scans. In some diseases, hyperintense lesions in the WM may accompany certain primary neurodegenerative (mostly grey matter) disorders, such as multisystem atrophy (MSA) or adult polyglucosan body disease (APBD). A special category is constituted by vascular disease, in which both grey matter and WM are affected (see chapter 6).

The current chapter focuses on disorders primarily affecting WM, encompassing classic WM diseases like inherited leukodystrophies, but also others with a predominant WM involvement, like some infections, inflammatory demyelinating diseases, and, finally, toxic and traumatic leukoencephalopathies. Obviously, the grey matter can be involved as well in some prototypical WM diseases (e.g. multiple sclerosis [MS]). Extensive grey matter involvement in MS accounts, in part, for the pattern of cognitive impairment.

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7.2 Infections

7.2.1 Introduction

Numerous infections affect the central nervous system (CNS) leading to meningitis, encephalitis, cerebritis or brain abscess. In most cases, the relationship with systemic infections is obvious, and secondary cerebral involvement manifests without cognitive decline as the lead symptom. This chapter restricts itself to those viral, bacterial and spirochetal infections that may first present with cognitive impairment or dementia and have no associated brain swelling. Those infections that do have associated brain swelling (e.g. Herpes simplex encephalitis and progressive multifocal leukoencephalopathy [PML]) will be discussed in Chap. 8. The findings in syphilis overlap with certain types of vasculitis due to involvement of the vascular wall.

7.2.2 Viral Infections Leading to Dementia

There are several viral infections that can lead to dementia. Some cases of acute viral encephalitis present with cognitive decline, but patients with chronic viral encephalitis more typically have cognitive impairment or dementia as the presenting symptom. Apart from herpes simplex encephalitis, most acute encephalitides are very uncommon (e.g. varicella zoster virus, human herpes virus, Japanese encephalitis and tick-borne encephalitis) and are beyond the scope of this book. The current section on viral encephalitis with dementia therefore concentrates on chronic viral encephalitides leading to dementia, that is HIV-1 encephalitis (HIVE) and subacute sclerosing panencephalitis (SSPE).

7.2.2.1 HIV Encephalitis

Synonyms
Human immunodeficiency virus (HIV) encephalitis (HIVE), HIV encephalopathy, AIDS dementia complex.

Aetiology and Histopathology

The human immunodeficiency virus (HIV-1) is a lentivirus that was discovered in 1983, shortly after the first reports of acquired immune deficiency syndrome (AIDS). When CD4 counts fall below 400/mm^3, CNS infection occurs, leading to HIV-1 encephalitis (HIVE); at autopsy, more than 80% of patients have CNS abnormalities. The resultant dementia syndrome, called HIV encephalopathy or AIDS dementia complex, occurs in 25% of patients with AIDS. In certain cases, dementia is the first presentation of AIDS, and serves as an indicator disease for the diagnosis of AIDS. With the advent of highly active antiretroviral therapy (HAART), opportunistic infections have become less common, survival extended, but there is some evidence that HIVE might have become relatively more common. More recently, HIV-associated neurocognitive dysfunction (HAND) syndrome has been recognised in patients with HIV treated during long periods of time with anti-retroviral therapy – so far, neither the pathophysiological mechanism is known, nor there is an established imaging correlate.

Macroscopically, HIVE brains show cerebral atrophy, white matter pallor and, occasionally, calcifications of the subcortical nuclei. Microscopically, pathognomonic multinucleated giant cells (MGC) are found, resulting from the fusion of infiltrating macrophages. In addition, there are abundant macrophages, as well as microglial nodules. These abnormalities are first found in the deep grey matter structures and surrounding white matter. In later stages, there is spreading to the cortex. Typically, inflammatory cells are absent in this immunodeficient disorder. Viral proteins can be indirectly detected by using immunocytochemistry or an enzyme-linked immunosorbent assay (ELISA), whereas viral nucleic acid can be detected using PCR or in situ hybridisation, even in patients with dementia without MGCs. How established HIVE leads to dementia is unclear, since neuronal damage is not always extensive. Speculation exists about excitotoxicity of viral products, or neuroglial infection. Only in a percentage of patients with HIVE feature accompanying damage to CNS tissue, including myelin pallor. This constellation is sometimes referred to as HIV encephalopathy, a term originally used to describe the neuropsychological findings of AIDS dementia.

Clinical and Laboratory Findings

The essential features of ADC are insidious progressively disabling cognitive impairment accompanied by motor dysfunction, speech problems and behavioural change. Cognitive impairment is characterised by mental slowness, memory disturbances and poor concentration. Focal cortical symptoms have also been described as the sole presenting feature (apraxia, aphasia and agnosia). Motor symptoms include a loss of fine motor control leading to clumsiness, poor balance and tremor. Behavioural changes include apathy, lethargy and diminished emotional responses and spontaneity.

Neuroimaging Strategy and Findings

HIVE is best demonstrated on heavily T2-weighted or FLAIR images (Fig. 7.1) The findings include a mild to moderate increase in signal intensity throughout the periventricular white matter, with no typical predilection – the subcortical U-fibres are characteristically spared. Diffuse cerebral atrophy is evident in advanced stages. In some cases, the white matter abnormalities are not diffuse, but rather focal, and may be indistinguishable from other related pathology, including CMV, lymphoma and PML. Administration of contrast material is essential in patients with AIDS and a differential diagnosis of HIVE. Whereas most opportunistic infections will show enhancement (either in brain parenchyma, the ependyma or meninges), this is typically absent in HIVE. The absence of enhancement in HIVE does of course not rule out PML, but the place and type of lesions usually readily distinguishes the two. PML lesions usually extend into the subcortical U-fibres (and even cortex), with markedly increased signal intensity and some swelling, whereas HIVE results in a more subtle abnormality with less involvement of the U-fibres and cortex, and no swelling. Following therapy, an immune-reconstitution inflammatory syndrome (IRIS) may occur with enlargement of lesions and contrast enhancement. On precontrast T1-weighted images, the signal intensity in HIVE lesions is normal, which helps to differentiate HIVE from PML, in which markedly reduced signal intensity is found. Similarly, the magnetisation transfer ratio is much lower in PML than in HIVE lesions. MR spectroscopy is more sensitive than MR imaging in the detection of HIV infection of the brain, showing increased choline and myo-inositol in the early (asymptomatic) stages. Lowering of *N*-acetylaspartate (NAA) occurs in cases of HIV encephalopathy, and becomes more obvious in the case of dementia. There are no indications for single photon emission computed tomography (SPECT) or positron emission tomography (PET).

7.2.2.2 Subacute Sclerosing Panencephalitis

Synonyms
Subacute sclerosing panencephalitis (SSPE), inclusion body encephalitis

History, Aetiology and Histopathology

Whereas measles infection can cause an acute meningoencephalitis, in rare cases – for example in the immunocompromised host – a subacute encephalitis follows. More relevant in the context of dementia is an entity called subacute sclerosing panencephalitis (SSPE), which develops 6–8 years after an asymptomatic phase of acute measles infection that occurred during early childhood. Dawson first described the disorder in 1934 under the name ‘inclusion body encephalitis’, whereas the name SSPE was coined by van Bogaert. This disorder has become extremely rare in the Western world following effective vaccination programmes, but it is still relatively common in Eastern Europe and Asia (esp. India). SSPE is probably determined by a slow infection caused by the hypermutated measles virus with defective M-protein.

Histopathological changes involve the cerebral cortex and white matter, as well as the brainstem, with sparing of the cerebellum. Nerve cell destruction, neuronophagia and perivenous cuffing are found. In the white matter, myelin and axons degenerate, and fibrous gliosis occurs; characteristic eosinophilic inclusions are found in the cytoplasm and nuclei of neurons and glial cells.

Clinical and Laboratory Findings

The onset of SSPE typically occurs in childhood or adolescence; however, cases have been reported with a

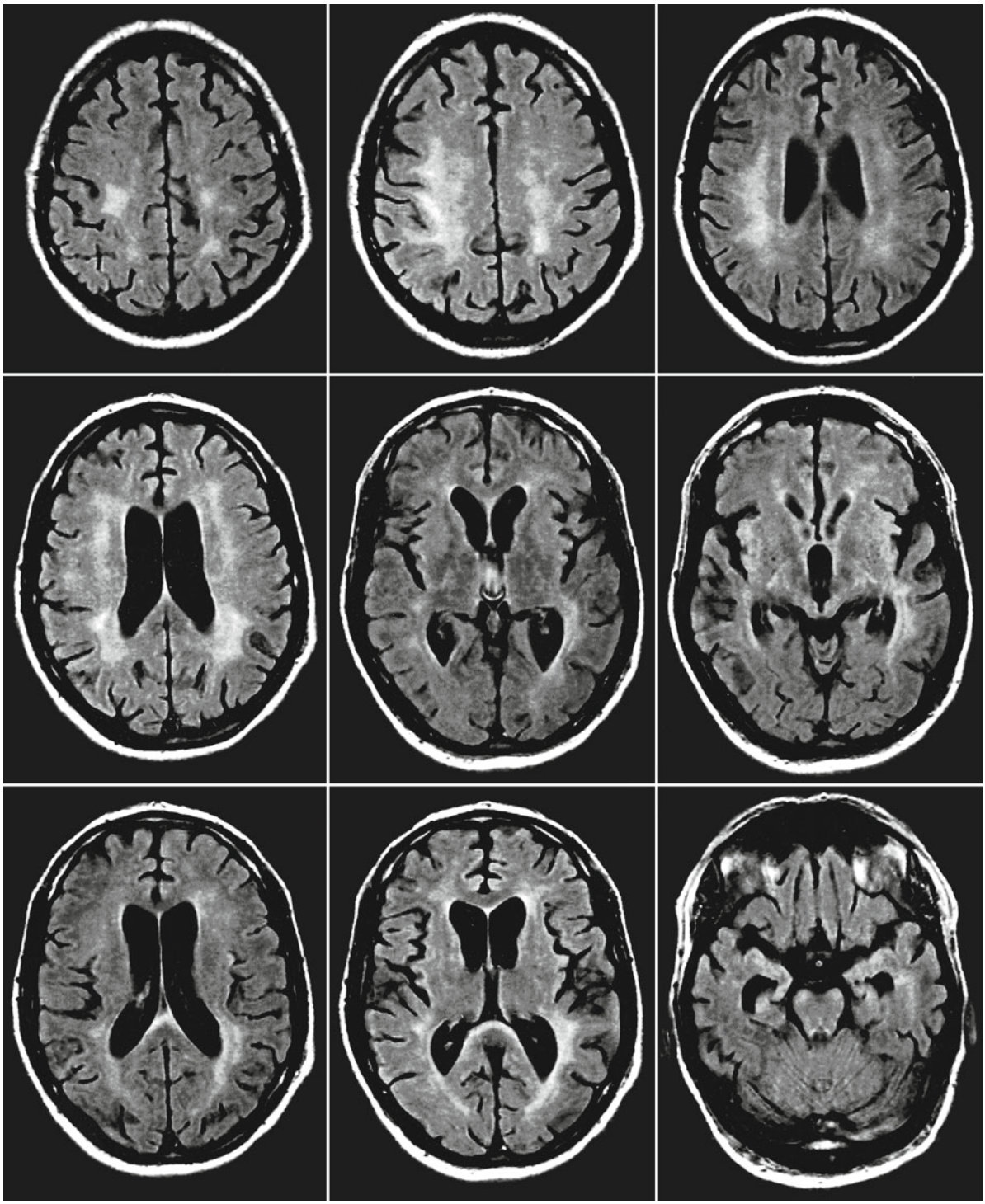

Fig. 7.1 HIV Encephalitis (HIVE). This 43-year-old man presented with subcortical dementia, gait disorders and incontinence. Axial FLAIR images showed ill-defined areas of increased signal intensity throughout the white matter (no enhancement was seen after gadolinium injection). Note also the prominent atrophy, especially in the temporal regions. The subtle and widespread involvement suggested HIV-encephalitis, and subsequent testing revealed HIV antibodies, leading to the diagnosis of AIDS

later onset between 20 and 35 years. SSPE typically has an insidious onset, with subtle slow cognitive decline and behavioural change. A typical feature is the occurrence of rhythmic attacks of myoclonus, seizures and ataxia, finally leading to complete neurological deterioration, with rigidity, unresponsiveness and autonomic dysfunction. Characteristic periodic slow-wave complexes with high voltage are observed on EEG, that can even occur in the asymptomatic stage (Rademecker complex). Ocular and visual manifestations are reported in 10–50% of patients, which include cortical blindness, chorioretinitis and optic atrophy – visual manifestations are relatively more common in adult-onset disease. Death occurs after several months to years, but in a small number of cases (5%) remission occurs. The diagnosis is based on the typical EEG, strongly increased CSF IgG (with normal protein), and strongly raised measles antibody titres (higher in CSF than blood). If recognised early, treatment with interferon and antiviral medication may be beneficial, but inevitably the disease is fatal.

Neuroimaging Strategy and Findings

In the early stages, MRI displays non-specific periventricular white matter lesions, or may even be normal. After several months, lesion sites observed on MRI include the parietal/ occipital grey matter, the adjacent white matter and sometimes the basal ganglia. With time these lesions may become less conspicuous, and lead to marked atrophy (Fig. 7.2). In the later stages, migratory lesions are found in the striatum, with hyperintensity on T2-weighted images starting in the putamen, followed by the caudate, but with initial sparing of the globus pallidus and thalamus. These can be

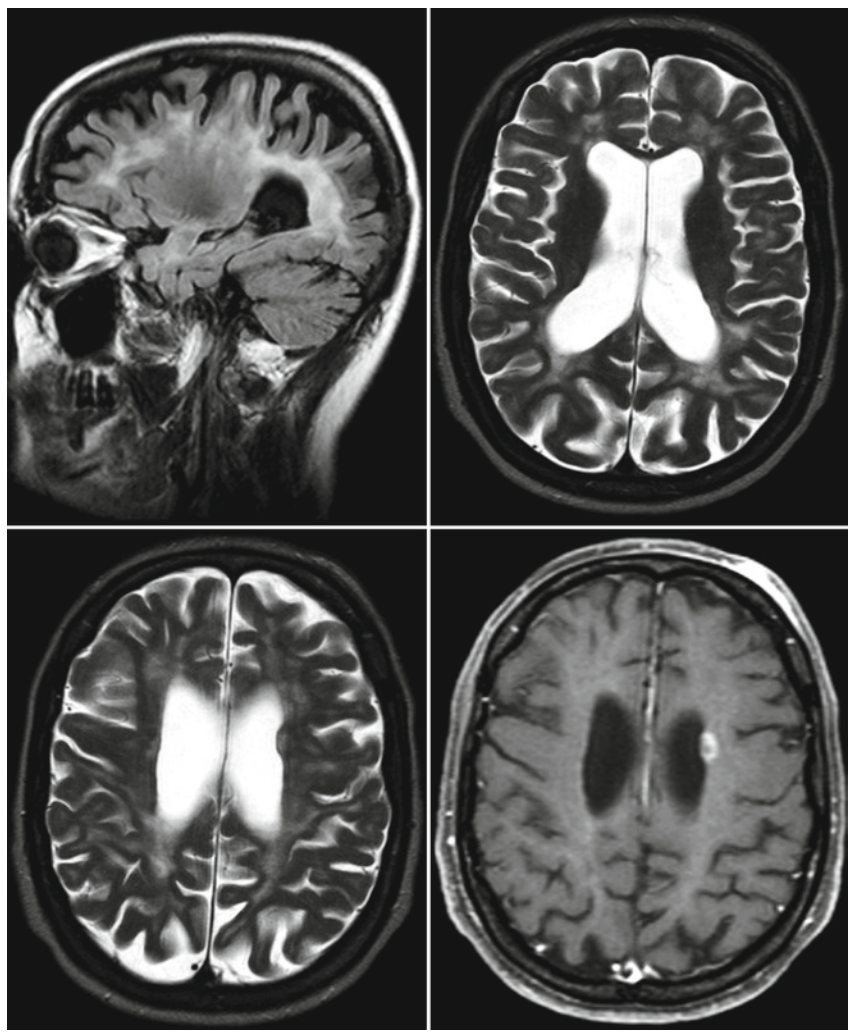

Fig. 7.2 Subacute sclerosing panencephalitis (SSPE). This 35-year-old lawyer presented memory and concentration problems for several months before developing a subacute deterioration with reduced consciousness and epilepsy. MRI revealed white matter abnormalities on FLAIR (*upper left panel*) and T2, partly diffuse, but also partly focal, with one lesion enhancing after gadolinium (*lower right panel*). Note the marked ventricular dilatation secondary to white matter loss

followed by lesions in the substantia nigra and dentate nucleus, clinically evidenced by the occurrence of parkinsonian features.

7.2.3 Bacterial Infections: Whipple's Disease

Aetiology and Histopathology

The disease that carries his name was first described by George Hoyt Whipple in 1907, and it took until about the end of the XXth century before the gram-positive actinobacteria *Tropheryma whipplei* (*T. whipplei*) was finally cultured. Primary Whipple's disease of the brain is extremely rare, but cerebral involvement may also secondarily occur in the course of a systemic infection.

Clinical Presentation and Treatment

Although the primary manifestations are gastrointestinal (e.g. malabsorption), a variety of neurological features occurs in about one third of patients with systemic disease: cognitive changes and altered consciousness, ophthalmoplegia, ataxia, and myoclonus. Preceding systemic manifestations include weight loss, fever, abdominal pain, joint pain and lymphadenopathy. In cerebral Whipple's disease, the most common manifestations are hemiparesis, cognitive dysfunction, seizures and abnormal eye movements. Investigations include duodenal biopsy looking for PAS positive inclusions. The diagnosis of cerebral Whipple's disease is suggested by PCR for *T. whipplei* in CSF. Treatment requires a combination of antibiotics for years, and may be difficult in patients with neurological involvement.

Neuroimaging Strategy and Findings

MRI may provide a diagnostic clue in patients with primary cerebral infection by showing multifocal lesions with enhancing nodules, but may be normal, especially in secondary cerebral involvement. MRI abnormalities more frequently occur than CT abnormalities, but are still only found in 50% of cases. Lesions show T2 hyperintensity, usually no mass effect, and are located in the medial part of the temporal lobes, the hypothalamic region, or in the pons. Lesions sometimes enhance with gadolinium (Fig. 7.3). Moderate to severe atrophy is a frequent finding. In some cases, multiple mass lesions are found. Spectroscopic and PET/SPECT findings are largely unknown.

7.2.4 Spirochetal Infections and Dementia

7.2.4.1 Neuroborreliosis

Synonyms
Cerebral Lyme Disease, Neuroborreliosis

Aetiology and Histopathology

The name is derived from the city of Lyme in Connecticut, where this infection was first recognised in 1975. It is caused by *Borrelia burgdorfferi*, a spirochetal bacteria living in infected ticks in woods. Through the bloodstream, spirochetes may reach the CNS and infect astrocytes, and induce cytokine release with neurotoxic effects. Alternative pathophysiological mechanisms postulated are an immune response or vasculitis induced by the infection.

Clinical Presentation, Diagnosis and Treatment

The annular erythematous skin reaction that follows the bite of an infected tick (erythema migrans) occurs in 80% of cases, but may be overlooked. In the subacute and chronic phase, neurological symptoms occur in approximately 5% of patients, and include meningitis, radiculoneuritis and even encephalitis. In the late persistent phase, chronic encephalomyelitis occurs in rare cases, which may induce cognitive impairment, weakness in the legs, awkward gait, facial palsy, bladder problems, vertigo and back pain. A variety of psychiatric symptoms can also occur. Diagnosis can be confirmed by serological testing (ELISA followed by Western blot) and treatment with antibiotics like doxycycline.

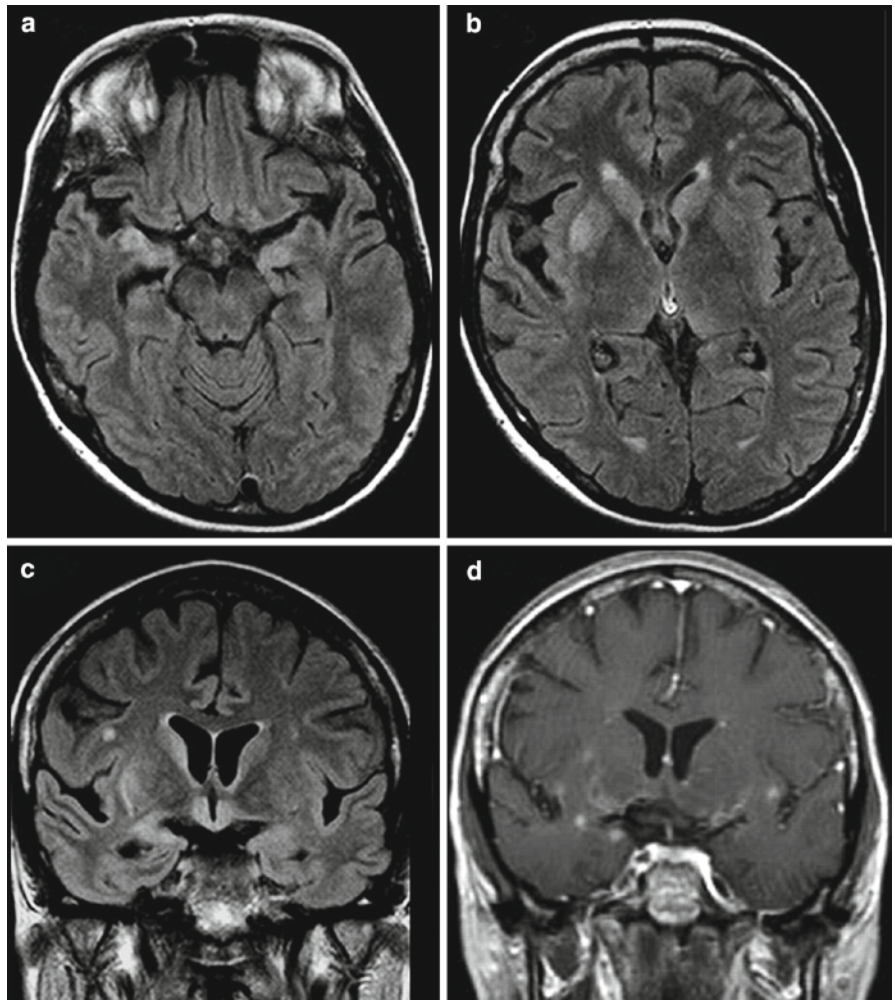

Fig. 7.3 MRI findings in active cerebral Whipple disease. (**a**, **b**) Axial FLAIR and (**c**) coronal FLAIR images reveal atrophy of the right mesial temporal lobe with persisting signal abnormality suggesting gliosis. Oedema is present in the left mesial temporal lobe, caudate heads and right putamen. (**d**) Coronal contrast enhanced T1-weighted image shows patchy nodular enhancement involving the mesial temporal lobes, insular cortex and lenticulostriate vessels. (Reprinted with permission from Panegyres PK, *Pract Neurol* 2008;8:311–317)

Neuroimaging Strategy and Findings

Many subjects will have normal structural imaging findings. In those with abnormal imaging, enhancement of leptomeninges and (cranial) nerves may be seen with gadolinium. In the chronic phase, non-specific scattered white matter lesions can be found, indistinguishable from age-related white matter lesions, but sometimes also mimicking inflammatory disorders like MS. Rarely, isolated or multiple mass lesions are found, sometimes with enhancement. SPECT and PET may reveal patchy hypoperfusion, especially in the white matter and subcortical grey matter.

7.2.4.2 Neurosyphilis

Synonyms
Neurosyphilis, generalised paresis of the insane, dementia paralytica *dementia paralytica.*

Aetiology and Histopathology

Infection with *Treponema pallidum* may cause neurosyphilis many (6–50) years after primary infection. The incidence of syphilis is rising in Eastern Europe and co-infection with HIV may interfere with treatment. Like neuroborreliosis, the first stage of

neurosyphilis is meningitis, with or without cranial nerve palsy, which can be followed after many years by meningovascular and late vascular stages.

Histopathologically, meningovascular syphilis features endarteritis with perivascular inflammation. The resulting inflammation and fibrosis may induce aneurysmal dilation and luminal narrowing, leading to cerebrovascular thrombosis, ischaemia and infarction. Leptomeningeal granulomas, called gummas, are well-circumscribed masses of granulation tissue (avascular), caused by a cell-mediated immune response to *T. pallidum*. They are often located in the dura, secondarily involving the underlying cortex.

Clinical Presentation, Diagnosis and Treatment

About 50% of cases with neurosyphilis present with psychiatric disturbances including psychosis, cognitive decline and dementia. The remainder present with stroke, probably secondary to vasculitis, cranial nerve palsy, epilepsy (due to focal irritation by gumma) and spinal cord syndromes (including tabes dorsalis). The full-blown picture of neurosyphilis (also referred to as 'general paresis of the insane') includes dysarthria, myoclonus, hyperreflexia and Argyll-Robertson pupil. The diagnosis can be difficult, especially when VDRL serology is negative. Treatment is with antibiotics (e.g. penicillin G), which may be less effective in patients with HIV.

Neuroimaging Strategy and Findings

CT and MR may show cerebral infarction (territorial or lacunar). Arteritis can be revealed by means of catheter angiography (DSA) or MRA (Fig. 7.4). MRI may show non-specific white matter lesions that sometimes involve the basal ganglia and the medial temporal lobe. Gadolinium injection may reveal granulomatous meningitis (thickened, enhancing meninges), sometimes with accompanying hydrocephalus. Gummas are enhancing focal masses in the dura that are predominantly hyperintense on T2-weighted images, but may also present foci of low signal intensity. Generalised atrophy may develop, and the medial temporal lobe may be atrophied, especially in patients with general paresis. In cases with normal MRI, SPECT may reveal hypoperfusion.

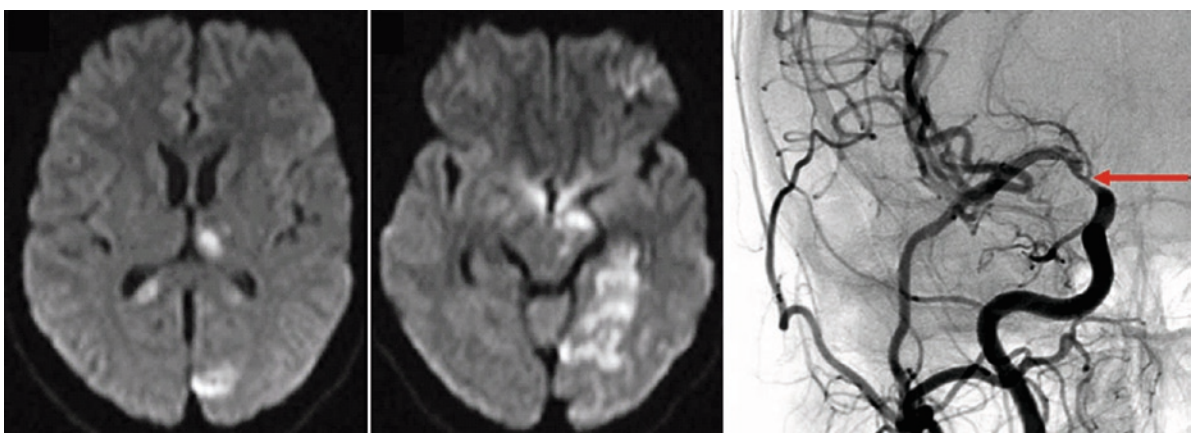

Fig. 7.4 Imaging findings in neurovascular syphilis. This 29-year-old woman was found in a confused state. She was noted to be both alert and cooperative, but disorientated in time and place. There was significant memory impairment involving episodic and prospective memory, and both immediate and delayed recall of visual and spatial information. Reading, writing and naming were normal. Retrograde memory was intact. DWI (*left*) demonstrated multiple areas of ischaemia, including in the left hippocampal region and the left thalamus. Catheter angiography (*right*) revealed stenosis of the distal supra-clinoid right internal carotid artery (*red arrow*). CSF analysis revealed signs of meningitis and positive VDRL assay (1:80), which was confirmed by blood serology that also revealed HIV-1 infection. The patient was treated for large-vessel CNS vasculitis secondary to meningovascular neurosyphilis with intravenous penicillin G for 14 days alongside initiation of highly active anti-retroviral therapy (HAART). After 3 months, the patient was orientated in person, place and time. Immediate recall had normalised but profound difficulties with delayed recall remained. (Reprinted with kind permission from Killian O'Rourke, *J Neurol* 2010;257:669–671)

7.3 Inflammatory Disorders

7.3.1 Introduction

This section deals with inflammatory disorders that affect the CNS and cause cognitive impairment or dementia. The prototypical primary inflammatory CNS disorder is multiple sclerosis and its monophasic variant, ADEM (Sect. 7.3.2). Secondary CNS involvement occurs in a variety of systemic inflammatory disorders. In most cases of secondary CNS involvement, cognitive decline is very uncommon, for example in Behcet's disease; these will not be considered in any detail. In others, CNS involvement occurs more frequently, and can even be the presenting symptom, such as in neurosarcoidosis (Sect. 7.3.3). In terms of pathogenesis and symptomatology, overlap exists with vasculitis (see Sect. 6.5.2).

7.3.2 Multiple Sclerosis and ADEM

Synonyms
Multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM)

Introduction and History

Already at the time of its first description by Charcot in 1868, it was recognised that MS is not simply a white matter disease, but also affects grey matter. Whereas traditionally regarded as a neurological disorder impacting mainly spinal cord function, the cognitive dysfunction associated with MS and ADEM is belatedly receiving more attention. Cognitive dysfunction is an important cause of disability in these demyelinating disorders with profound consequences for patients and their families. MRI studies have revealed the extent of cortical lesions and grey matter atrophy, in agreement with histopathological studies. Although the cognitive deficits in MS and ADEM arise from both white and grey mater destruction, this chapter will concentrate on the grey matter and neurodegenerative aspects of these disorders.

Aetiology, Histopathology and Genetics

The cause of MS being unknown, one can only speculate about the aetiology of (cortical) MS lesions. Like their white matter counterparts, cortical lesions are defined by focal demyelination although this can only be detected with immunohistochemical stains. There is relatively little inflammation in the cortical MS lesions; damage to neurons, reduction of synapses and dendritic pathology, however, may explain the cortical thinning observed in later phases of the disease. Of special interest are the type III cortical lesions with a subpial configuration, which can be quite extensive in progressive cases, occupying most of the neocortex. They have fuelled speculations that subpial lesions are due to some diffusible factor arising from the meninges or CSF – perhaps antibody and B-cell mediated – a hypothesis so far unconfirmed. Several susceptibility genes for MS have been identified, mostly in the HLA region, but none are specifically related to grey matter involvement or cognition. APOE4 may be a risk factor for more rapid progression in MS and there have been reports that a polymorphism of the APOE regulatory region is associated with cognitive impairment in patients with MS.

Cortical involvement can be limited in early cases – perhaps with a preponderance of cingulated/frontotemporal involvement. In progressive phases, cortical involvement can be quite extensive, and even outweigh white matter damage (Fig. 7.5). Of special interest is the involvement of deep grey matter structures including the hippocampus in MS. Imaging and immunohistochemical studies both reveal frequent and extensive involvement of the hippocampus in MS (Fig. 7.6), associated with memory impairment. Involvement of the thalamus has been related to fatigue. The thalamus is also frequently involved in ADEM, a disease which otherwise has a higher propensity for (cortical) grey matter involvement than MS.

Clinical Presentation, Epidemiology and Treatment

MS often presents with focal neurological deficits caused by lesions in an eloquent long tract, like optic neuritis or a spinal cord syndrome. At the time of presentation, most patients have clinically silent dissemination in space on their MRI scan (Table 7.1), illustrating that clinically silent lesions are common, including the juxtacortical

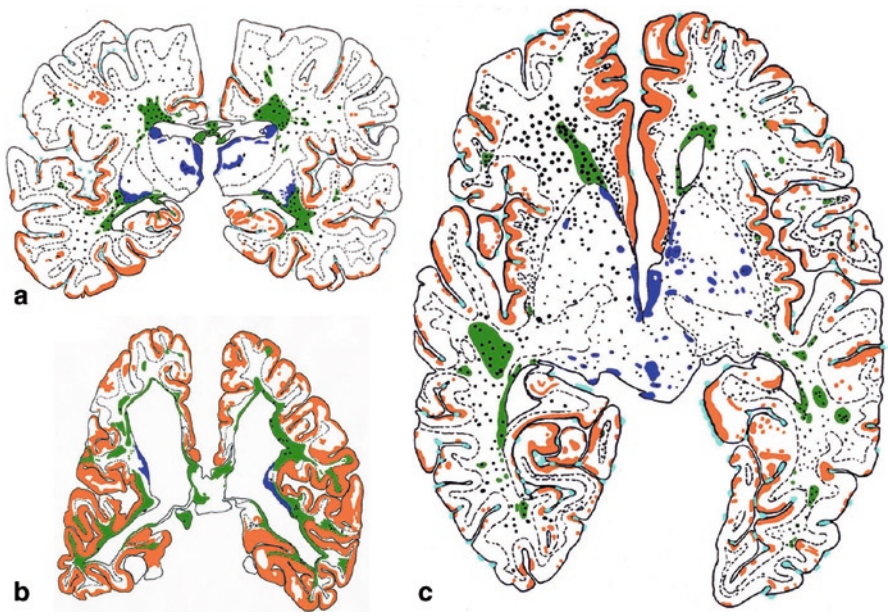

Fig. 7.5 Camera Lucida drawings showing distribution of MS lesions at post-mortem. Focal WM plaques are depicted in *green*, cortical lesions in *orange* and deep GM lesions in *blue*; *black dots* represent perivascular inflammatory infiltrates. (**a**) Secondary progressive MS; male patient, aged 43 years, 16 years of disease duration; moderately affected brain with focal periventricular WM lesions and cortical lesions mainly affecting the cingulated cortex, the insular cortex and the basal temporal cortex. (**b**) Secondary progressive MS, female, aged 46 years, 16 years disease duration; extremely severely affected brain with massive atrophy, extensive cortical demyelination and widespread periventricular demyelination in the white matter. (**c**) Primary progressive MS; aged 55 years, 5 years disease duration; relatively few and small focal white matter lesions, but extensive cortical demyelination, mainly in the cingulated cortex, the insular cortex and the basal temporal cortex. In addition, there is massive diffuse inflammation in the normal-appearing white matter. (Reprinted with kind permission by Kutzelnigg and Lassmann from Handbook of Neurology 2008)

Fig. 7.6 Hippocampal demyelination (Kindly provided by Jeroen Geurts). Myelin staining shows normal myelin density in the hippocampus in a control subject (*top panel*). Note varying degrees of demyelination (outlined in *red*) in the hippocampi of three different MS patients (*bottom panel*), showing almost complete demyelination of the hippocampus and surrounding tissue in one of the cases

Table 7.1 MRI criteria for MS

- Clinical presentation suggestive of MS
  - Other diagnoses ruled out by appropriate tests
    - Consider MRI 'red flags' (Charil, *Lancet Neurol* 2006)
- Dissemination in space (DIS)
  - Clinically: poly-symptomatic onset
  - MRI: 3 or more modified Barkhof criteria
    - ≥1 juxtacortical lesion
    - ≥1 gadolinium enhancement (or ≥9 T2 lesions)
    - ≥1 infratentorial lesion
    - ≥3 periventricular lesions
  - If CSF abnormal: 2 brain lesions sufficient
- Dissemination in time (DIT)
  - New clinical symptoms
  - Repeat MRI: Gad-enhancement or new T2 lesions

Source: (*Ann Neurol* 2005;58(6):840–846)

lesions typical of MS. True cortical syndromes like aphasia, however, are extremely uncommon in MS. There is an increased frequency of epilepsy in MS, attributable to cases with relative high numbers of (juxta) cortical lesions. In established cases of MS, neuropsychological testing reveals cognitive impairment in up to 40% of cases: typically, the deficits are subcortical with declines in attention, concentration, memory and executive function, and worsen with disease progression.

Occasionally, cognitive deficits (or frank dementia) may be the presenting feature of MS and the diagnosis is often only considered after MRI (Fig. 7.7). CSF oligoclonal bands provide supportive evidence. Disease-modifying therapy for MS is clearly reducing relapses and development of (white matter) lesions on MRI, and is likely to reduce progression of cognitive deficits; some studies suggest some symptomatic benefit with cholinesterase inhibitors, but good evidence from large controlled trials is lacking.

Whereas MS, by definition, is disseminated in time, ADEM usually is a monophasic acute demyelinating disorder with a spatial dissemination pattern quite similar to MS. The clinical presentation of ADEM is more often encephalopathic than MS, including drowsiness, disorientation and epilepsy, reflecting its greater propensity for grey matter involvement. Relapsing forms of ADEM can occur, often triggered by the same type of initiating event (e.g. infections or vaccination).

Neuroimaging Strategy and Findings

MRI is the imaging modality of choice (Table 7.2). In addition to the standard protocol with T2 and T1-weighted images (with gadolinium), additional sequences like FLAIR and double-inversion recovery (DIR) are useful. Compared to FLAIR, DIR employs a second inversion pulse, thereby not only nulling CSF signal as in FLAIR, but also white matter signal.

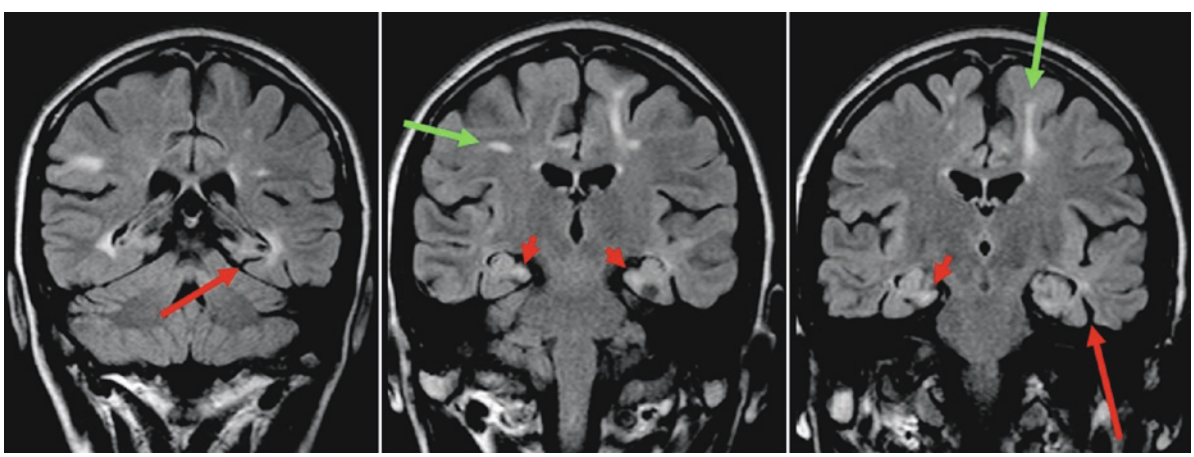

Fig. 7.7 Cognitive presentation in MS. This 25-year-old female patient with MS presented with sudden and rapid onset of memory and concentration deficits, leading to social and psychological invalidity within 3 years. Coronal FLAIR images show multiple typical MS lesions with an ovoid shape in the deep and periventricular white matter (*green arrows*). Intriguing is the extensive amount of cortical involvement in the hippocampus (*short red arrows*) which has led to hippocampal atrophy, as evidenced by widening of the collateral sulcus (*long red arrows*)

Table 7.2 Neuroimaging protocol and findings

MRI Sequences
- 3D sagittal FLAIR isotropic
- 2D transverse proton-density/T2-weighted
- 2D transverse post-gadolinium T1-weighted
- Optional: double inversion recovery (DIR)
  - MRS, DWI not useful, except for pseudotumoural MS

Brain MRI findings in MS
- White matter lesions
  - Periventricular and juxtacortical
  - Ovoid shape due to perivenular origin
  - Temporal lobe typically affected as well
  - Infratentorial lesions: brainstem, cerebellum, spinal cord
  - Gadolinium-enhancement and T1-black holes
    'Open-ring sign' in pseudotumoural MS
  - Corpus callosum involvement and 'Dawson fingers'
- Focal cortical lesions
  - Cortical lesions enhance less frequently than WM lesions
  - Truly intracortical lesions are best seen using DIR
  - Juxtacortical lesions (U-fibres) more easily detected using FLAIR
  - Hippocampal lesions best seen on coronal images
- Cortical atrophy
  - Cortical thinning best seen using advanced post-processing
  - Focal cortical atrophy related to (juxta)cortical lesions

Brain MRI findings in ADEM
- Larger, more oedematous lesions
- Variable pattern of enhancement (all lesions, some, or none), mostly depending on the stage of the lesions
- More frequent grey matter involvement
  - Including thalamus and basal ganglia
- Frequent infratentorial lesions
- No new lesions at follow-up

Differential diagnosis of MS and main differentiating imaging findings	
• ADEM	Larger and more fuzzy lesions Marked thalamic involvement
• Leukodystrophies	Symmetric white matter involvement • More extensive cortical lesions in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
• Vascular disease	Lacunes, infarcts, microbleeds
• Infections	Asymmetrical/discontinuous lesions in PML

The resulting images (Fig. 7.8) are grey matter only images and display lesions with even brighter signal.

Advanced MRI techniques are being used in a research setting, but have little diagnostic value. For example, abnormal MTR or FA have been reported in the cortex of patients with MS, and reduced NAA and increased MI/Cr ratios in deep grey matter structures like the thalamus and hippocampus. High field imaging may offer better visualisation of cortical involvement (Fig. 7.9) in the future. Cortical thickness reduction can be better detected using advanced image processing techniques (Fig. 7.10).

There is no established role for nuclear imaging in individual patients, although reduced metabolism on FDG-PET is found on a group-level, whereas increased PK11195 binding (a glial marker) has been reported in grey matter.

7.3.3 Neurosarcoidosis

Synonyms
Neurosarcoid; CNS sarcoid; Cerebral Besnier–Boeck–Schaumann disease

Aetiology and Histopathology

Sarcoidosis is a granulomatous inflammation of unknown aetiology that may involve all organs, including the CNS. The histopathological hallmarks include epithelioid granulomas without staining for infectious agents and usually without caseation. These granulomas often incorporate multinucleated giant cells and lymphocytes and are found in the leptomeninges, for example around the cranial nerves and pituitary stalk. Secondary demyelination may occur especially around Virchow–Robin spaces.

Clinical and Laboratory Findings

Whereas sarcoidosis is a relatively common disorder, only ~5% of the cases have clinical CNS involvement, giving an estimated prevalence of ~1:100,000 for neurosarcoidosis. Subclinical involvement probably occurs in 15–20% of cases. The most common manifestation is cranial nerve palsy, followed by headache, epilepsy, pituitary insufficiency and myelitis. In a small number of cases, cognitive impairment is observed. Incidentally, psychosis and dementia have been reported as the presenting feature. A definitive

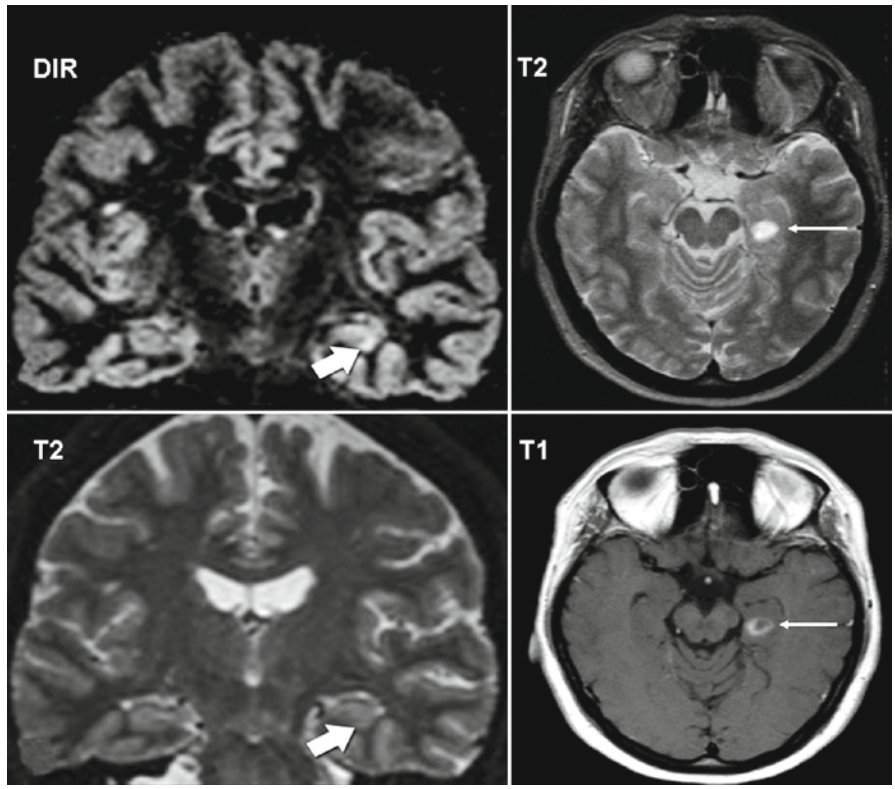

Fig. 7.8 Hippocampal involvement on MRI (Kindly provided by Jeroen Geurts). Coronal DIR image (*upper left*) shows lesion with high signal intensity in the left hippocampus of patient with MS (*short arrow*) that is hard to see on conventional T2-weighted image below. On the right side, transverse T2 and gadolinium-enhanced T1-weighted images show an active lesion in the left hippocampus (*long arrows*) in another patient

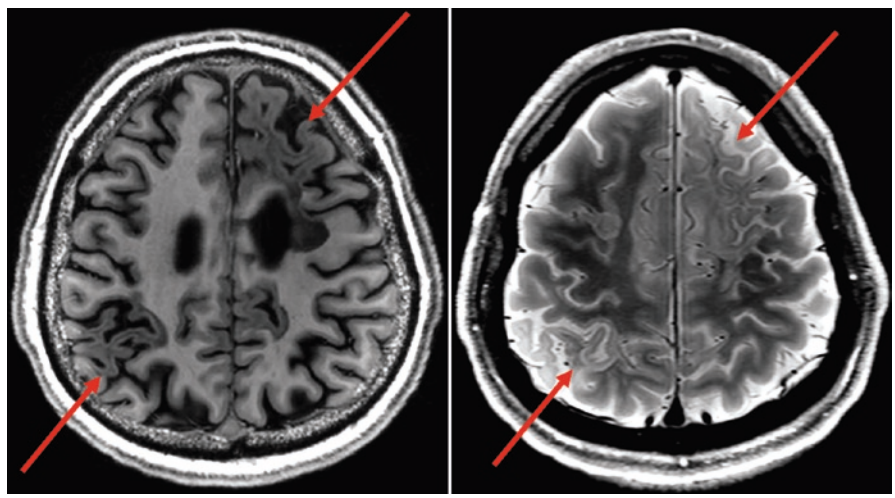

Fig. 7.9 Cortical involvement in MS at 7T (kindly provided by Wolter de Graaf). Note extensive involvement of the juxtacortical white matter on heavily T1-weighted (*left*) and T2-weighted (*right*) MR images with extension into the cortex and accompanying atrophy (*arrows*). (Massimiliano Calabrese, *Neurology* 2010;74:321–328)

diagnosis requires histopathological confirmation. The diagnostic process should confirm CNS involvement and then provide supportive evidence for the underlying disease; in the absence of a positive tissue biopsy, the most useful diagnostic tests are gadolinium-enhanced MRI of the brain and CSF analysis, although both are non-specific. The Kveim test is no longer used because of the risk of transmitting infection. High resolution CT of the chest can be virtually diagnostic in the correct context. Gallium scanning may show patchy uptake in the mediastinum and parotids.

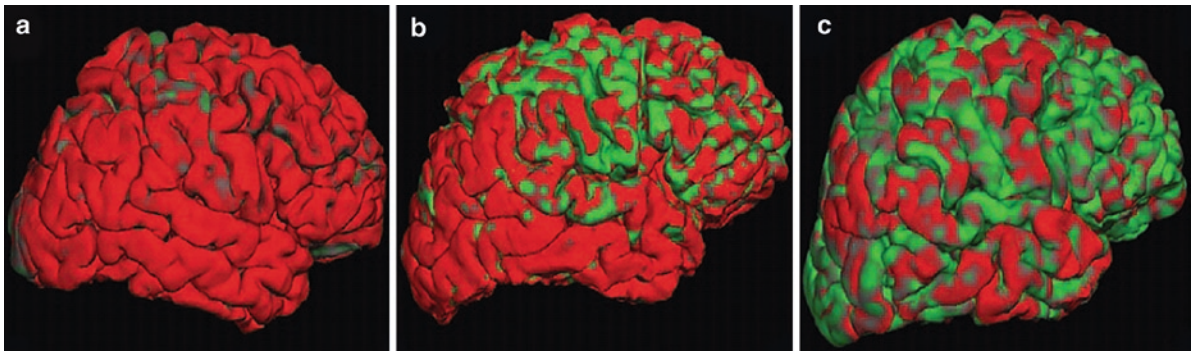

Fig. 7.10 Cortical thickness (CTh) maps in MS. Lateral views of a 3D representation of the brain with CTh maps overlaid in a *red/green* colour scale on the typical (mean) case for each group: (**a**) a healthy 35-year-old man without neurologic problems, mean CTh 2.53 mm; (**b**) a 36-year-old cognitively normal man with 5 years of disease duration of relapsing remitting MS (RRMS), mean CTh 2.32 mm; (**c**) a 34-year-old man also with 5 years of disease duration of RRMS but with cognitive impairment, mean CTh mm 2.05. Cortical thinning below 2.0 mm is displayed in *green*. Normal cortical areas thicker than 2.0 mm are displayed in *red.* (Reprinted with permission from *Neurology* 2010;74;321–328)

Neuroimaging Strategy and Findings

MRI is the imaging method of choice and administration of contrast mandatory to show the typical leptomeningeal enhancement that may extend into the Virchow–Robin spaces or along the cranial nerves (Fig. 7.11). The differential diagnosis includes primary CNS angiitis, lymphoma, tuberculosis and histiocytosis. In cases with extensive granulomatous inflammation, CSF flow may be obstructed leading to hydrocephalus. Non-specific periventricular hyperintense lesions can be seen on T2-weighted images that may strongly resemble multiple sclerosis. Dural lesions may mimic meningioma.

7.3.4 Coeliac Disease

Synonyms
C(o)eliac sprue, non-tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance

Aetiology and Histopathology

Coeliac disease is a multiorgan systemic disease that most commonly affects the gut but also affects other organs, especially the skin. It probably is an autoimmune disease caused by gluten. Up to 10% of patients with coeliac disease and gastrointestinal symptoms have otherwise unexplained neurological symptoms, most often ataxia and peripheral neuropathy. In a small number of subjects with coeliac disease, cognitive decline and even dementia occur, sometimes associated with increased celiac disease activity. The cause of CNS involvement in coeliac disease remains elusive – theories include immune cross-reactivity with CNS antigens and metabolic impairment due to malabsorption.

Clinical and Laboratory Findings

Cognitive dysfunction may feature memory impairment, acalculia, confusion and personality change. In some cases, cognitive decline may be rapid, and lead to suspicion of Creutzfeld–Jacob disease. The diagnosis of celiac disease is based on small bowel biopsy, detection of antigliadin and anti-endomysial antibodies, tissue transglutaminase immunoglobulin A positivity and response to gluten-free diet. Diminution of CNS symptoms by such a diet suggests causality, but does not provide definitive evidence.

Neuroimaging Strategy and Findings

MRI may show generalised cerebral atrophy and hyperintense lesions on T2-weighted and FLAIR images. The latter may include confluent periventricular changes

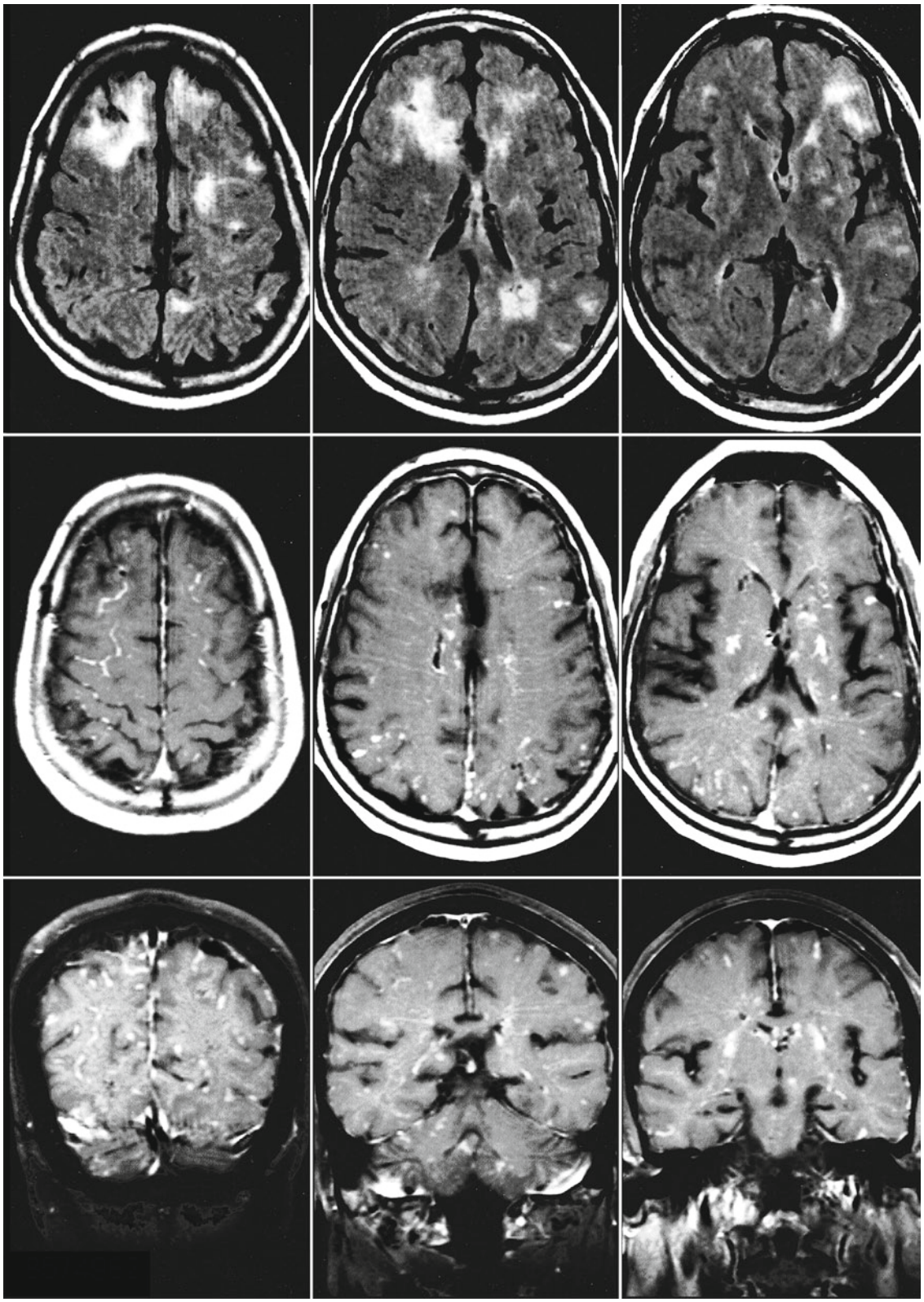

Fig. 7.11 Neurosarcoidosis. A 35-year-old man with auditory problems and neurosarcoidosis developed cognitive disturbances, characterised by a frontal syndrome. The FLAIR images show multifocal white matter lesions, in the periventricular and subcortical regions. The middle row (transverse T1) and bottom row (coronal T1 with fat suppression) show extensive enhancement of the leptomeninges and Virchow–Robin spaces

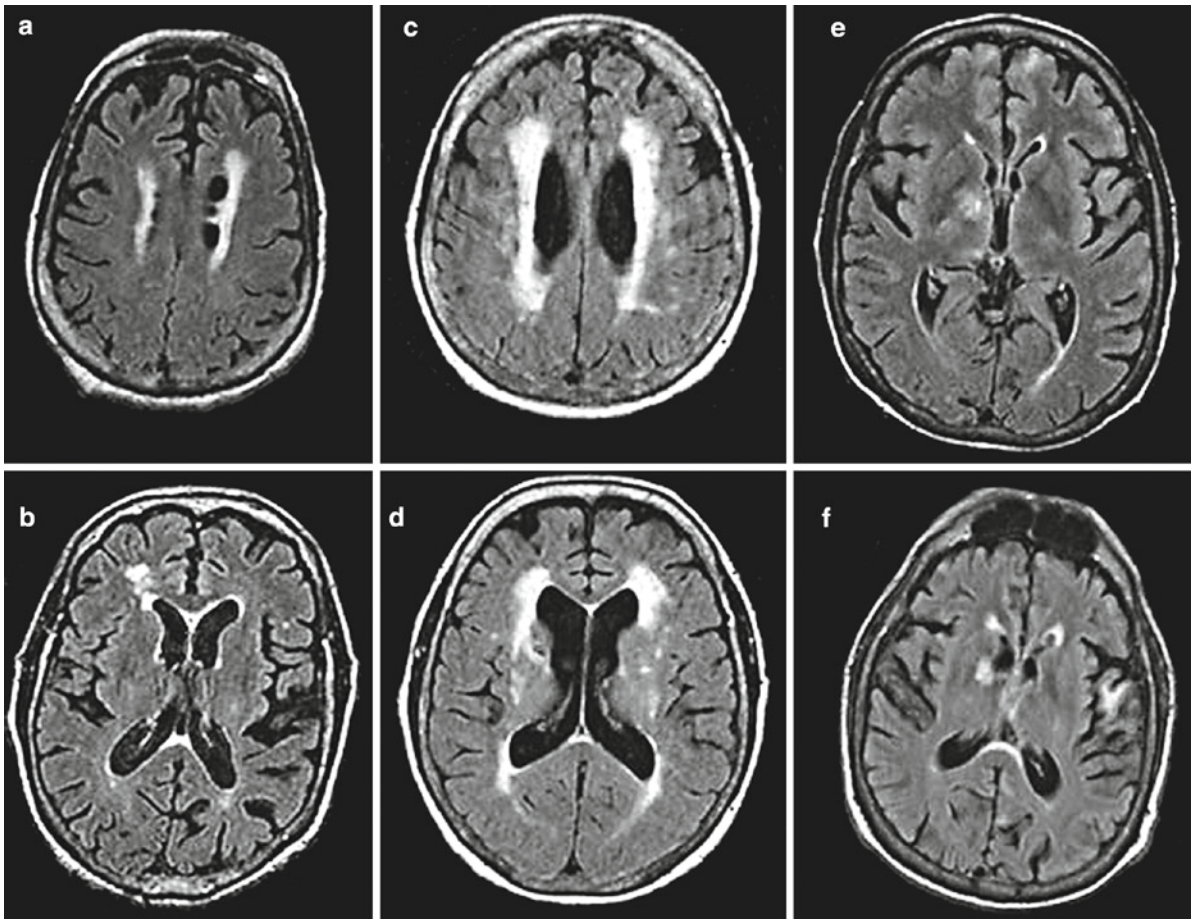

Fig. 7.12 MRI findings in celiac disease with cognitive impairment. FLAIR abnormalities vary between patients, and include confluent areas of periventricular hyperintensities (**a**), scattered hyperintense foci involving the subcortical and deep white matter (**b**), or a combination of both (**c**, **d**). The interval change over a period of four months in one patient reveals increased signal intensity in the right thalamic lesion and the appearance of a new subcortical lesion in the left temporal lobe (**e**, **f**) (Reprinted with permission from Keith Josephs, *Arch Neurol* 2006;63: 1440–1446)

(Fig. 7.12a), patchy cortical and subcortical areas of hyperintensity (Fig. 7.12b), or both (Fig. 7.12c and d).

7.4 Inborn Errors of Metabolism

7.4.1 Introduction

A large number of inborn errors of metabolism produce white matter demyelination, referred to collectively as leukodystrophies. Many individual disorders are extremely rare; however, as a group, the leukodystrophies are not uncommon. Most of the leukodystrophies present early in life and many are fatal in childhood. Although dementia may be a later feature of some of these aggressive early-onset diseases, these are beyond the scope of this book. By contrast, a number of leukodystrophies present later in life and do have cognitive decline as a characteristic feature – in this chapter, we will consider some of the more common ones that do so. In addition to the known disorders discussed, there are still a number of unclassified leukodystrophies (e.g. orthochromatic leukodystrophies) that escape current classification systems.

The cardinal imaging feature of the leukodystrophies is involvement of the white matter, with hyperintensity on T2-weighted and FLAIR images. Involvement usually occurs in a strictly symmetric fashion (except for some mitochondrial disorders). The corticospinal tracts and cerebellum are frequently involved structures. In most diseases, there is little in the way of enhancement (except in adrenomyeloneuropathy), which differentiates them from inflammatory disorders like MS and vasculitis. Important diagnostic clues can be obtained from the family history, and from additional involvement of the peripheral nervous system, the eyes, adrenal glands, tendons or other organs. Extensive laboratory and genetic testing is very important in the diagnostic work-up.

7.4.2 Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Synonyms
Fragile-X premutation carrier syndrome

Aetiology and Genetics

Fragile X syndrome is caused by a full-blown trinucleotide repeat mutation, (large >200 CGC expansion) in a gene called FMR1 (fragile X mental retardation gene 1) on the X-chromosome, leading to defective/absent protein production. It is the major genetic cause of mental retardation and autism. Patients with FXTAS have smaller, so-called 'premutation', expansions (50–200 CGC repeats) in the FMR1 gene leading to *excess production* of the FMR1 protein with a later and more subtle onset of symptoms: progressive cerebellar and cognitive dysfunction.

Clinical Presentation and Work-Up

FXTAS usually develops between the ages of 50–80, mostly in men. Symptoms include intention tremor, ataxia, neuropathy, mood instability, irritability, changes in personality in association with memory loss and intellectual decline. The diagnosis (Table 7.3) is based on three factors:

1. Positive carrier testing for the FMR1 premutation
2. Typical findings on neurological examination
3. MRI suggestive of FXTAS

Individuals with FXTAS are often misdiagnosed with other conditions including Parkinson's disease or MSA or considered to have an idiopathic cause of cerebellar degeneration or peripheral neuropathy.

Neuroimaging Findings

MRI can play a crucial role in the diagnosis of FXTAS, by showing characteristic symmetric lesions hyperintense on T2-weighted images in the cerebellar hemispheres close to the dentate nucleus and both middle cerebellar peduncles (MCP sign, Fig. 7.13). In addition, WM lesions can be seen in the cerebral hemispheres hemispheres. Generalised atrophy is an associated feature, and cerebellar atrophy additionally supports the diagnosis (Table 7.3).

The differential diagnosis of the MCP sign includes paraneoplastic syndromes, multiple sclerosis, and post-radiation therapy, MSA, dentatorubral-pallidoluysian atrophy (DRPLA) and Wilson's disease.

Table 7.3 Diagnostic criteria for FXTAS

Definite FXTAS	Probable FXTAS	Possible FXTAS
Intention tremor *or* gait ataxia *and* MCP sign on MRI *or* intranuclear inclusions on post-mortem	Intention tremor *and* gait ataxia *or* MCP sign on MRI *and* a minor clinical feature: parkinsonism, executive function deficits, moderate short-term memory deficiency	Intention tremor *or* gait ataxia *and* WM lesions on MRI in the cerebrum *or* moderate generalised brain atrophy

The differential diagnosis of the MCP sign includes paraneoplastic syndromes, multiple sclerosis (MS), and post-radiation therapy, MSA, DRPLA and Wilson's disease

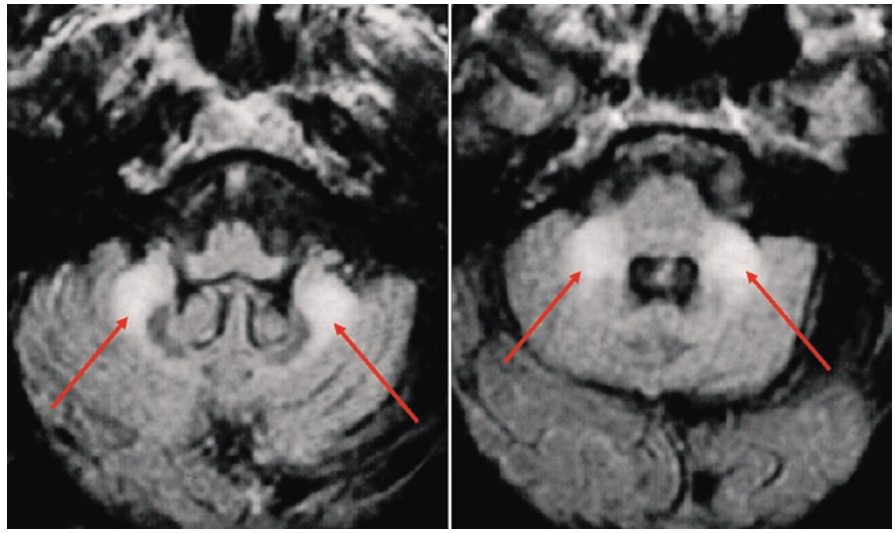

Fig. 7.13 The 'MCP sign' in FXTAS. This 61-year-old man with fragile X premutation showed hyperintense signal (*red arrows*) in the middle cerebellar peduncles (MCP) and adjacent inferior cerebellar white matter on FLAIR images. (Reprinted with permission from Brunberg – *AJNR* 2002;23:1757–1766)

7.4.3 Mitochondrial Dementia

Synonyms
Mitochondrial disorders; respiratory chain disease, mitochondrial myopathy (and numerous specific syndromes – see below)

Aetiology and Genetics

Mitochondrial disorders are caused by acquired or inherited mutations in one of the genes encoding the respiratory chain proteins within mitochondria. These can either be mutations in mitochondrial DNA (with a strictly maternal inheritance), as in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) and Kearns–Sayre syndrome (KSS), or a chromosomal mutation, as found in Leigh syndrome.

Clinical Presentation and Work-Up

Mitochondrial disorders are typically multi-system in nature: depending on the gene and protein involved, many organs of the body can be affected, but the brain is particularly vulnerable due to its high energy demand. Systemic involvement (e.g. myopathy, cardiac or gastrointestinal symptoms or haematologic disorders) may precede CNS manifestations. The same mutation may cause a different type of organ involvement in different individuals. Cerebral involvement can present with psychiatric symptoms (altered consciousness, personality change, psychosis) or cognitive decline (verbal, executive, visuo-spatial). A feature of some mitochondrial disorders with cognitive involvement may be an episodic encephalopathy. Brain MRI and MR spectroscopy are important diagnostic pointers as well as tests of serum and CSF pyruvate and lactate. Diagnostic confirmation may be provided by histopathological examination of affected tissue (e.g. muscle biopsy) and/or genetic testing for (mitochondrial) mutations.

Neuroimaging Findings

Plain CT scans of the brain may show calcification; whereas MRI shows hyperintense lesions on T2-weighted and FLAIR images, often involving the deep grey matter or the cortex. Structures frequently involved are the lentiform nucleus, periaqueductal grey matter and dentate nucleus (e.g. in Leigh syndrome). In MELAS, multifocal cortical lesions can be found (Figs. 7.14 and 7.15). In the acute phase, lesions may have associated swelling and show restricted diffusion on DWI. In the chronic phase, tissue loss ensues. Despite its lower energy demand, white matter is also frequently involved and sometimes even in isolation (e.g. diffuse U-fibre involvement in KSS). In mitochondrial neurogastrointestinal encephalopathy (MNGIE) a diffuse symmetrical

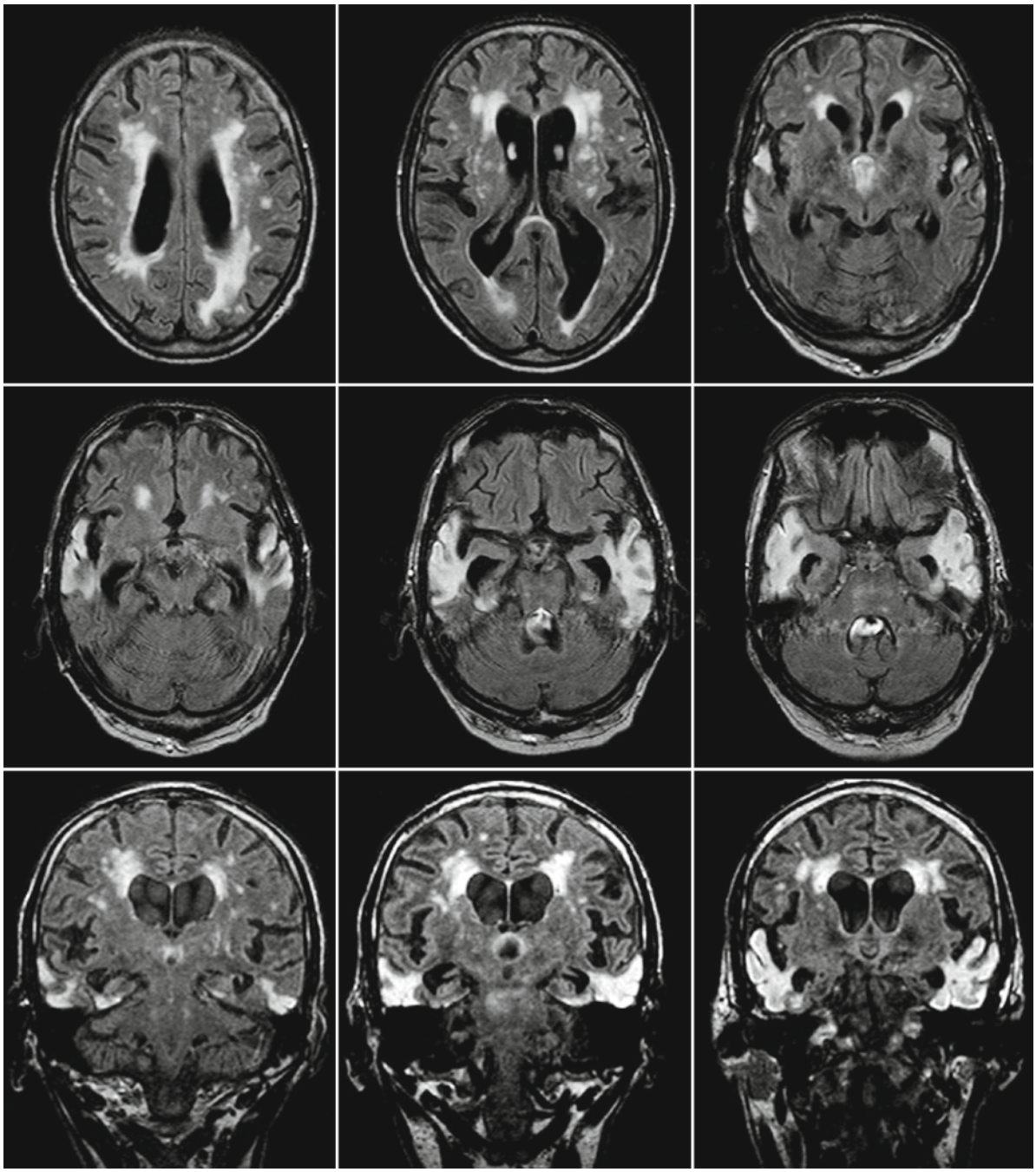

Fig. 7.14 Adult-onset mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). A previously healthy 60-year-old man presented with cognitive impairment. MRI showed scattered white mater lesions, but also extensive bilateral temporal lesions involving both white and grey mater, consistent with non-territorial ischaemia. Laboratory work-up revealed MELAS. (Case kindly provided by Debbie Duyndam)

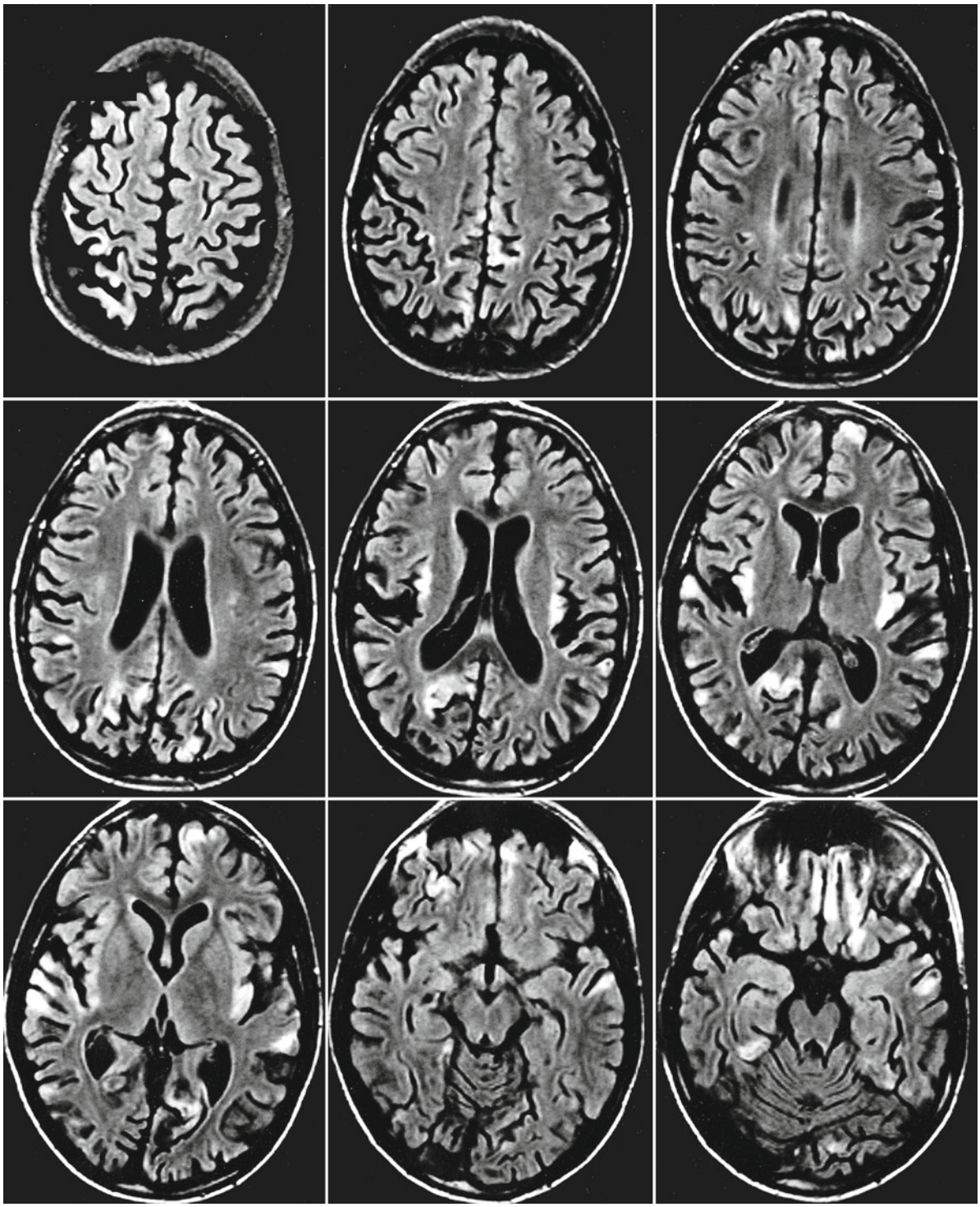

Fig. 7.15 Cognitive impairment in a child with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). Axial FLAIR images from a 9-year-old boy with MELAS who developed cognitive impairment and then progressive dementia. Note multiple hyperintense lesions in the cortex with a random distribution, some with associated atrophy, and others (apparently more acute) with associated swelling

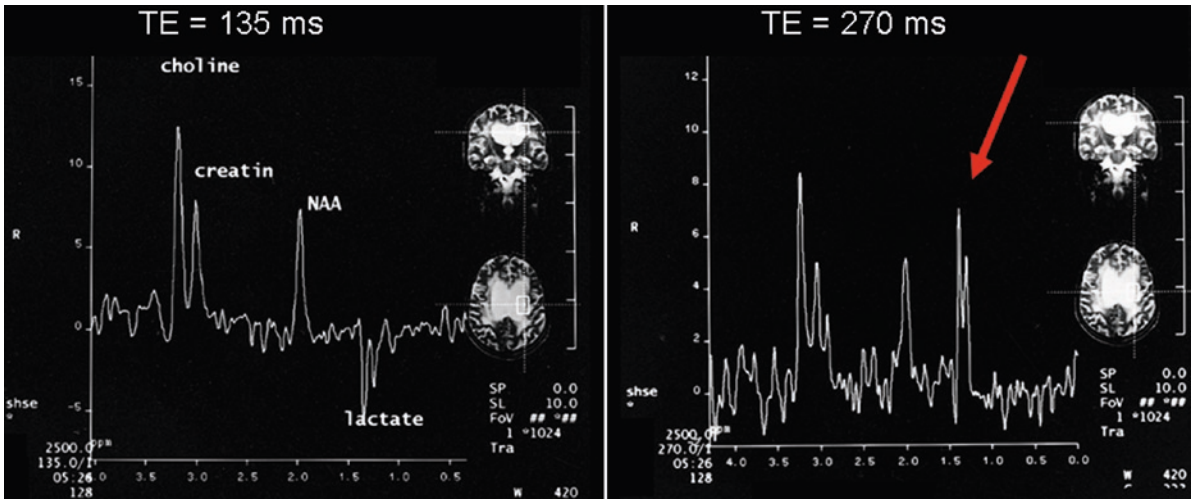

Fig. 7.16 Lactate on MR spectroscopy. Single-voxel spectroscopy revealing a lactate doublet resonating at 1.35 ppm. Note that at TE = 135 ms the phase is negative, but positive at TE = 270 ms due to J-coupling

leukoencephalopathy sparing the corpus callosum is seen. MR spectroscopy can be very useful by demonstrating lactate (a doublet resonating at 1.35 ppm) – see Fig. 7.16.

Differential diagnosis includes hypoxic insult, moyamoya disease, vasculitis, ADEM, vascular dementia (including CADASIL) and prion disease. In addition to examining the pattern of lesions, MR angiography and gadolinium-enhancement can be useful in the work-up. Lactate found by spectroscopy occurs in all ischaemic disorders, but when found throughout the brain and beyond periods of clinical deterioration should raise suspicion of a mitochondrial disorder.

7.4.4 Diffuse Neurofibrillary Tangles with Calcification (DNTC)

Synonym
Kosaka–Shibayama disease

Introduction

Kosaka proposed the term 'DNTC' for a rare form of presenile dementia in 1994 when he added two cases to the first one described in 1973. Since then, 30 more cases have been reported. Most patients are Japanese; only one Caucasian has been described.

As the name suggests, DNTC is characterised by its imaging and histopathological features: imaging shows cerebral calcification and frontotemporal atrophy, whereas autopsy findings reveal neurofibrillary tangles and neuropil threads with an absence of amyloid plaques. In the early stages of the disease, cognition may be preserved. The disorder may be underrecognised due to similarities with Fahr's syndrome.

Clinical Presentation

Women are four times more commonly affected than men. The youngest patient reported was 48-years-old, but most patients present with symptoms in their sixth decade of life. Generally, the first symptoms are amnestic problems with early dysexecutive and frontal behavioural changes. Hallucinations, delusions and depression may accompany the neurological deterioration and parkinsonism is present in about half of the patients reported. A variant of the disorder with agnosia and apraxia as well as biparietal atrophy on MRI mimicking Alzheimer's disease has been reported. The duration of illness ranges from 3 to 24 years.

Differential Diagnosis

Fahr's syndrome (synonyms Chavany–Brunhes syndrome and Fritsche's syndrome) is a hereditary disorder characterised by movement disorders (such as rigidity, hypokinesia, tremor, choreoathetosis and ataxia), behavioural and mood disturbance, and dementia. In contrast to DNTC, the latter is never the presenting symptom. Imaging in both disorders shows a characteristic pattern of calcification in the basal ganglia and the cerebellum. A similar pattern of calcification, without asymmetric frontotemporal atrophy, can be seen in hyperparathyroidism with abnormal serum calcium and phosphorus, pseudoparathyroidism, mitochondrial encephalopathy, and lead poisoning. The cognitive and behavioural features may mimic FTLD or AD. However, imaging features of calcification combined with atrophy of the superior temporal gyrus and hippocampus point towards a diagnosis of DNTC.

Neuroimaging Findings

Essential imaging features are calcification in the cerebellum, basal ganglia and sometimes periventricular white matter, best seen on CT or with susceptibility-weighted MRI. Asymmetric atrophy of the temporal and frontal lobes is present with involvement of the superior temporal gyrus, parahippocampal gyrus and hippocampus. Several authors have added the finding of focal lesions hyperintense on T2-weighted MRI in the centrum semi-ovale, temporal and frontal lobes, probably associated with arteriosclerotic changes in arteries (please note that none of these patients suffers from hypertension). SPECT and PET imaging may show decreased blood flow or hypometabolism in the temporal and frontal lobes. Notably, with FDOPA-PET, no abnormalities in the basal ganglia have been discovered (Fig. 7.17).

7.4.5 Cerebrotendinous Xanthomatosis (CTX)

Synonyms
Cerebrotendinous xanthomatosis (CTX), van Bogaert–Scherer–Epstein syndrome

Aetiology, Genetics and Histopathology

CTX is a rare metabolic disorder (MIM #213700) with an autosomal recessive mode of inheritance first described by van Bogaert in 1937. In patients with CTX, bile acid synthesis is impaired due to a defect in the activity of the hepatic mitochondrial enzyme sterol 27-hydroxylase of the cytochrome P450 family. Excessive cholestanol accumulates in many tissues (tendons, brain and lung). An indirect effect is a low level of HDL that may lead to the accumulation of tissue sterols in atheromas and xanthomas by reduction of reverse sterol transport. The gene CYP27A1 has been mapped to chromosome 2q: the gene has been cloned, its structure determined and a number of different mutations reported.

Neurological dysfunction results from the deposition of cholesterol and cholestanol in the nervous system and the replacement of cholesterol by cholestanol in myelin layers, affecting the stability of the myelin sheath. Macroscopic findings include generalised brain atrophy with multiple yellowish deposits in the choroid plexus and white matter. Microscopically, extensive demyelination and gliosis is observed in the cerebellar white matter and the pyramidal tracts with multiple dispersed lipid crystal clefts. In addition, there is accumulation of foamy cells and homogeneous myelin-like material, especially around the vessels. Since accumulation of cholesterol and cholestanol may be neurotoxic, there is axonal damage and loss as well.

Clinical Presentation and Treatment

Most patients are of borderline or low intelligence and their school performance can be poor. The more specific clinical manifestations usually appear in late childhood or early adolescence, or even later. Early manifestations of the disease include cataracts, diarrhoea and (Achilles) tendon xanthomas. During the second and third decades, neurological problems gradually become manifest with signs of cerebellar ataxia, spastic paraparesis and tetraparesis, signs of dysfunction of the posterior columns and of a peripheral neuropathy. About 40% of patients develop epilepsy. In the third decade, a decline in intellectual functions usually occurs, but there is a wide range in the rate of cognitive decline. Changes in personality and

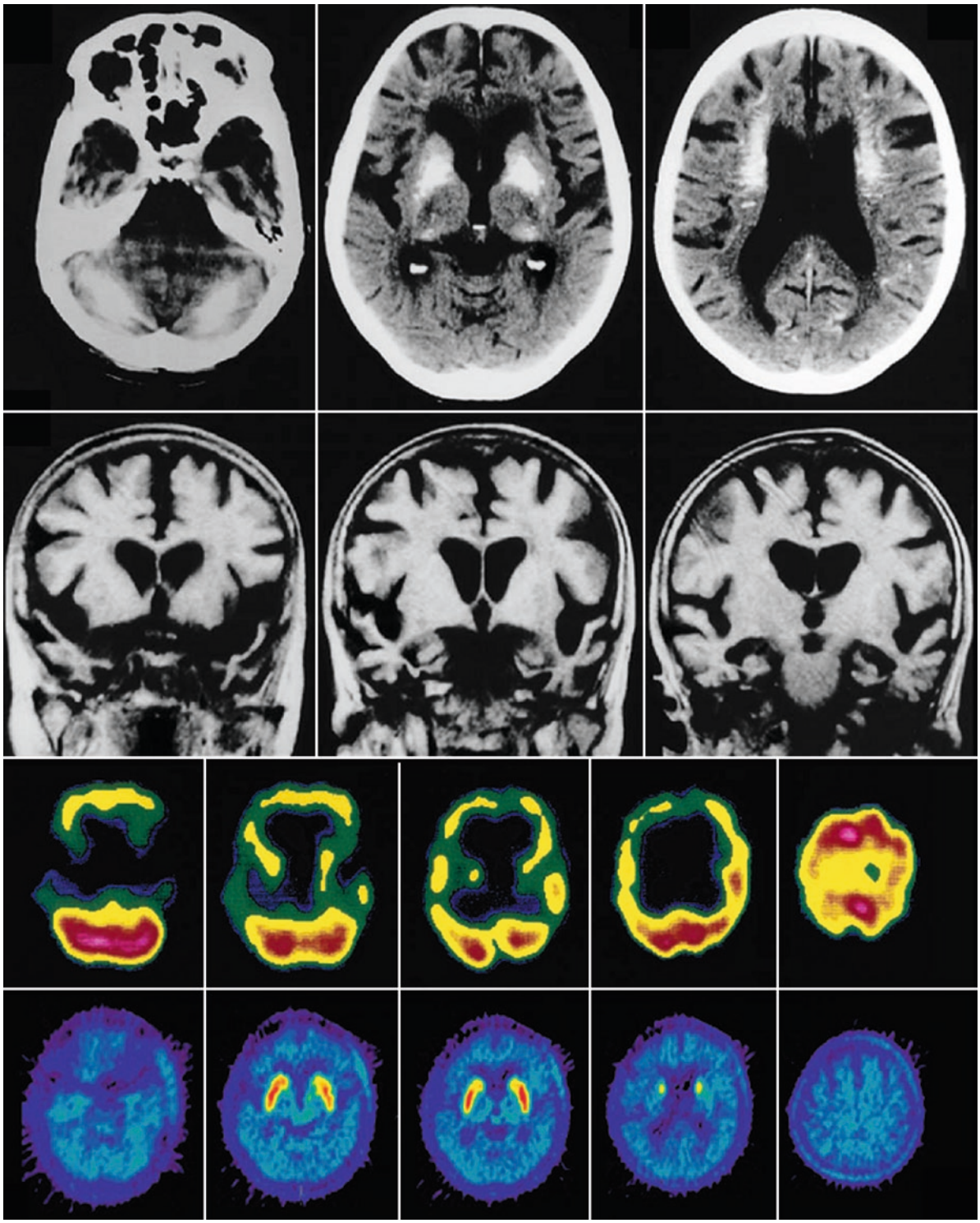

Fig. 7.17 Neuroimaging in diffuse neurofibrillary tangles with calcification (DNTC). This 76-year-old woman presented with altered behaviour, memory impairment, and the MMSE score was 17/30. Cranial computed tomography (CT) (*top row*) shows symmetrical calcification of the cerebellum, basal ganglia, pulvinar, and of the deep and periventricular white matter. Coronal T1-weighted MRI (*second row*) shows symmetrical atrophy of the temporal and frontal lobes. Atrophy is particularly distinct at the temporal tip, although the entire temporal lobe is involved. SPECT (*third row*) shows a marked reduction in blood flow mostly in the temporal lobes. Blood flow and metabolism in the basal ganglia, parietal and occipital lobes, and cerebellum were normal. A PET scan (*bottom row*) using [18F]6-fluoro-L-DOPA shows normal uptake in the basal ganglia. (Reprinted with permission from *J Neurol Sci* 2003;209:105–109)

psychiatric symptoms may be present. Many other signs and symptoms may also be present, including optic atrophy, muscle wasting, parkinsonism, impaired lung function, osteoporosis and endocrine dysfunction. There are no obligatory signs (tendon xanthomas can be absent) and there is a marked variety in nature and degree of progression, even within one family. The diagnosis, therefore, can easily be missed, perhaps particularly when cognitive decline is the presenting symptom. Biochemical diagnosis is made by determining the excessive urinary excretion of bile alcohols and the serum cholestanol levels. The diagnosis can be confirmed by demonstrating lack of sterol 27-hydroxylase activity in fibroblasts. CTX is a treatable disorder. Treatment with chenodeoxycholic acid interrupts the vicious circle of defective endogenous bile acid synthesis leading to absence of negative feedback, and increased cholesterol. The progression of CNS damage can be halted or delayed, with a reversal of cognitive symptoms and improved motor function.

Neuroimaging Strategy and Findings

Structural imaging using CT or MRI may reveal cerebral and cerebellar atrophy. Parenchymal abnormalities are best appreciated on MRI, and include ill-defined hyperintense lesions in the periventricular region on T2-weighted images, combined, in some patients, with focal lesions in the deep white matter. In some patients, there are prominent perivascular spaces. More characteristic lesions are found in the basal ganglia and posterior fossa (Fig. 7.18). Hyperintense lesions are found in the medial part of the globus pallidus in the majority of patients, and involvement of the corticospinal tracts is frequently observed. The most characteristic and frequent finding, however, is cerebellar involvement, starting with lesions in the dentate nucleus, extending towards the corpus medullare. Such lesions show high signal intensity on T2-weighted images and are isointense or, when extensive, hypointense on T1-weighted images. In patients with long-standing disease, areas of decreased signal intensity can be seen on T2-weighted images in the dentate nucleus (hyperdense on CT) (Fig. 7.18). Additional lesions can be found in the inferior olive and the descending tracts in the spinal cord. Technetium-99m brain SPECT may reveal severe cerebellar hypoperfusion.

7.4.6 Adult Polyglucosan Body Disease (APBD)

Contribution by Bert-Jan Kerklaan

Synonyms
Glycogen storage disease type IV, glycogenosis type IV, glycogen branching enzyme type IV deficiency, amylopectinosis, Andersen's disease.

Introduction

Adult polyglucosan body disease (APBD) is a rare metabolic disorder characterised by accumulation of carbohydrate inclusion bodies in the brain and other organs, such as, muscles and nerves. So far, at least 50 cases have been described. The first patient reported in 1971 was a 59-year-old man with dementia, walking difficulties, urinary incontinence and deficits of the peripheral and central nervous system. Since then, progress has been made in unravelling the biochemical and genetic background of this disorder and exploring of the clinical spectrum. Certain imaging features are highly specific; however, APBD appears to be underdiagnosed.

Clinic Features, Diagnosis and Therapy

The clinical picture is characterised by progressive gait difficulties with spasticity and peripheral sensory loss, urinary incontinence and progressive cognitive deficits. Symptoms most commonly appear in the fifth and sixth decades of life. Patients complain of gait and voiding problems, but mild cognitive deficits arefrequently already present and the majority develop dementia during follow-up. The speed of cognitive deterioration is highly variable and survival ranges from 2 to 25 years. The pattern of cognitive dysfunction is also variable, ranging from memory problems, executive dysfunction to a more pure frontal dementia.

As the disorder is defined by the finding of polyglucosan bodies, the clinical spectrum has broadened over recent years. Extrapyramidal and autonomic symptoms, epilepsy, cardiomyopathy and muscle spasms have been reported to accompany the typical clinical profile of APBD, possibly as part of a concomitant disorder. A myopathy or demyelinating neuropathy

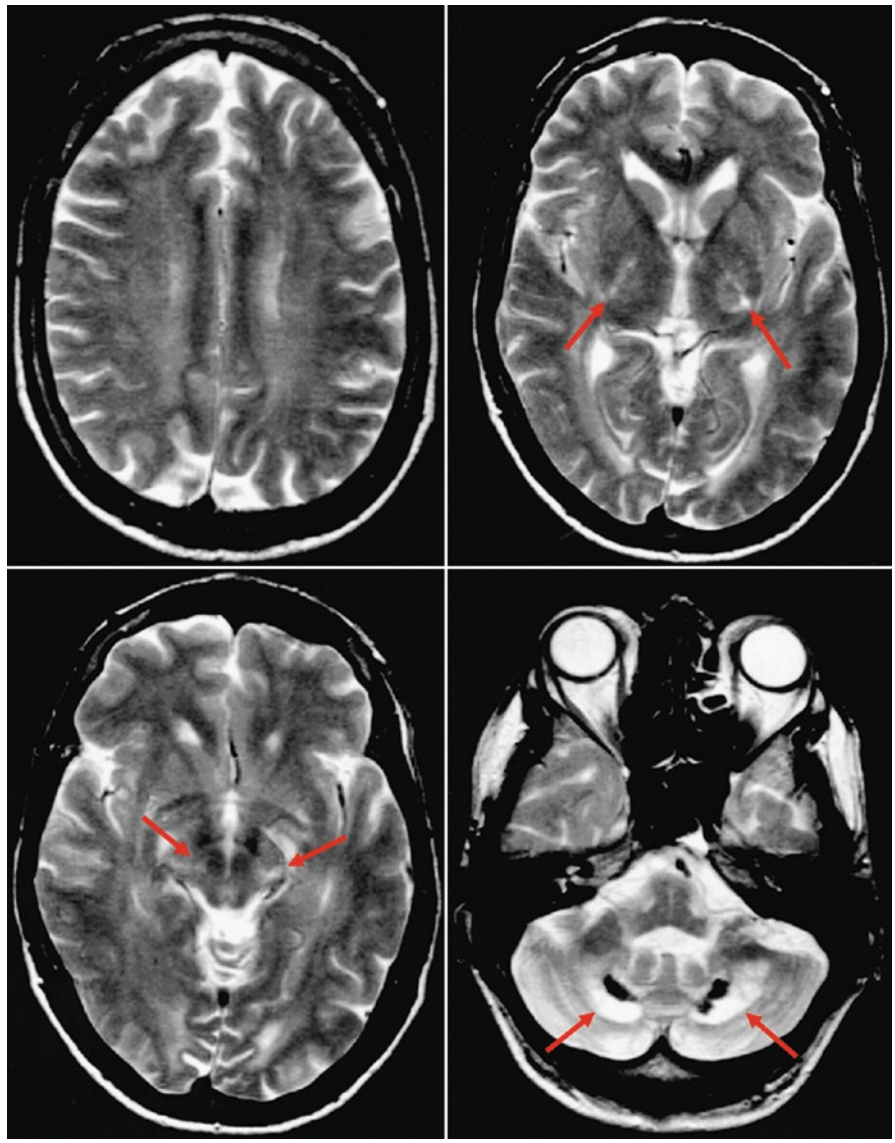

Fig. 7.18 A 51-year-old man with CTX. Transverse T2-weighted images show normal ventricles, a normal cortical pattern, and symmetrical hyperintensity of the supratentorial white matter, most markedly in the optic radiations, posterior limb of the internal capsules, and the corticospinal tracts in the mesencephalon (*arrows*). In the posterior fossa, high signal intensity is seen in the corpus medullare of the cerebellum (*arrows*), in which sharply demarcated and irregular hypointense structures are embedded. These dark areas represent cholestanol deposits and haemosiderin in the dentate nucleus

may also occur without involvement of the central nervous system.

The diagnosis of APBD is confirmed by demonstrating glycogen branching enzyme deficiency in skin fibroblasts, nerve or muscle. When a deficiency is demonstrated, genetic testing should follow, although a known mutation may not be found. A typical clinical profile with a normal enzyme level is an indication for biopsy of the sural nerve or axillary sweat glands, looking for a certain amount and specific distribution of polyglucosan bodies. Therapy is symptomatic.

Differential Diagnosis

The differential diagnosis of the combination of cognitive deficits, gait difficulties with spasticity, incontinence and polyneuropathy in adults is broad and encompasses hereditary disorders including CADASIL and the leukodystrophies, metabolic disorders such as B12 deficiency, toxic encephalopathy (e.g. secondary to chemotherapy or organophosphate), infectious disorders such as syphilis, neuroborreliosis and HTLV-1, paraneoplastic conditions and inflammatory disorders

such as neuro-Behçet, SLE and neurosarcoidosis. CADASIL, leukodystrophies, vitamin B12 deficiency, SLE and neurosarcoidosis generally have a distinctive pattern of white and grey matter involvement on MRI.

Pathophysiology

APBD is clinically differentiated from the ordinary glycogen storage disorder (GSD) type IV by the age of onset and the organs involved. GSD type IV is a rare autosomal recessive disorder typically affecting the heart and liver of young children with a very poor prognosis. The disorders have in common the accumulation of polyglucosan bodies – inclusion bodies composed of glucose polymers – in affected organs. Polyglucosan bodies have been associated with numerous CNS disorders with different distributions and morphologies. Polyglucosan bodies in APBD are located in neuronal processes throughout the brain and spinal cord and in axons of motor and sensory nerves, but can be found in other organs as well.

APBD is most common in Ashkenazi Jews, with a limited number of mutations in the glycogen branching enzyme gene on chromosome 3 described. Different mutations in the same gene have been detected in non-Jewish people with clinical and pathological APBD. Patients heterozygous for the mutation have only a partial biochemical effect, suggesting an autosomal recessive mode of transmission.

Neuroimaging Findings

MRI demonstrates non-enhancing lesions hyperintense on T2-weighted images progressing towards confluent and symmetric involvement of the periventricular WM, including the internal and external capsules, but with initial sparing of the corpus callosum and subcortical U-fibres. Involvement of the white matter may spread into the region around the fourth ventricle and the temporal poles (see Fig. 7.19). Typically, hyperintensity on T2-weighted images is found in the cervicomedullary region extending to the medulla and pons, with relative sparing of the centre of the pons except for the long tracts. These changes are accompanied by cerebral and spinal atrophy. MRS of the brain shows increased levels of lactate with decreased levels of NAA, in accord with tissue damage involving both axons and myelin.

7.4.7 Neuroaxonal Leukodystrophy (NAL)

Synonyms
Neuroaxonal leukodystrophy with spheroids; Leukoencephalopathy with neuroaxonal spheroids; hereditary diffuse leukoencephalopathy with spheroids (HDLS)

History and Histopathology

Hereditary diffuse leukoencephalopathy with spheroids is an autosomal dominantly inherited progressive condition, first described by Axelsson in 1984. Additional cases have included individuals without a family history (probably *de novo* mutations). The disease is characterised by a loss of myelin and axons, with lipid laden macrophages and gliosis. The central hallmark of neuroaxonal leukodystrophy (NAL) is axonal spheroids – these eosinophilic axonal swellings are observed in the grey matter in a number of conditions including degenerative and metabolic diseases, intoxication, trauma, tumours and neuroaxonal dystrophies, including adult neuroaxonal dystrophies, neurodegeneration with brain iron accumulation (NBIA) and Nasu–Hakola disease (PLOSL). When axonal spheroids are confined to the white matter, the most important disorder to consider in adults is NAL.

Clinical Presentation, Epidemiology and Treatment

There is a large variation in symptomatology and presentation: subtle changes in personality, disorganisation and forgetfulness as well as progression to severe impairment in multiple domains of cognition, with basic neurological functions becoming impaired only late in the course of the disease. The clinical features are caused by early destruction in the deep white matter of the prefrontal cortex, followed by the white matter deep to the association areas of the parietal and temporal lobes and by secondary degeneration in the

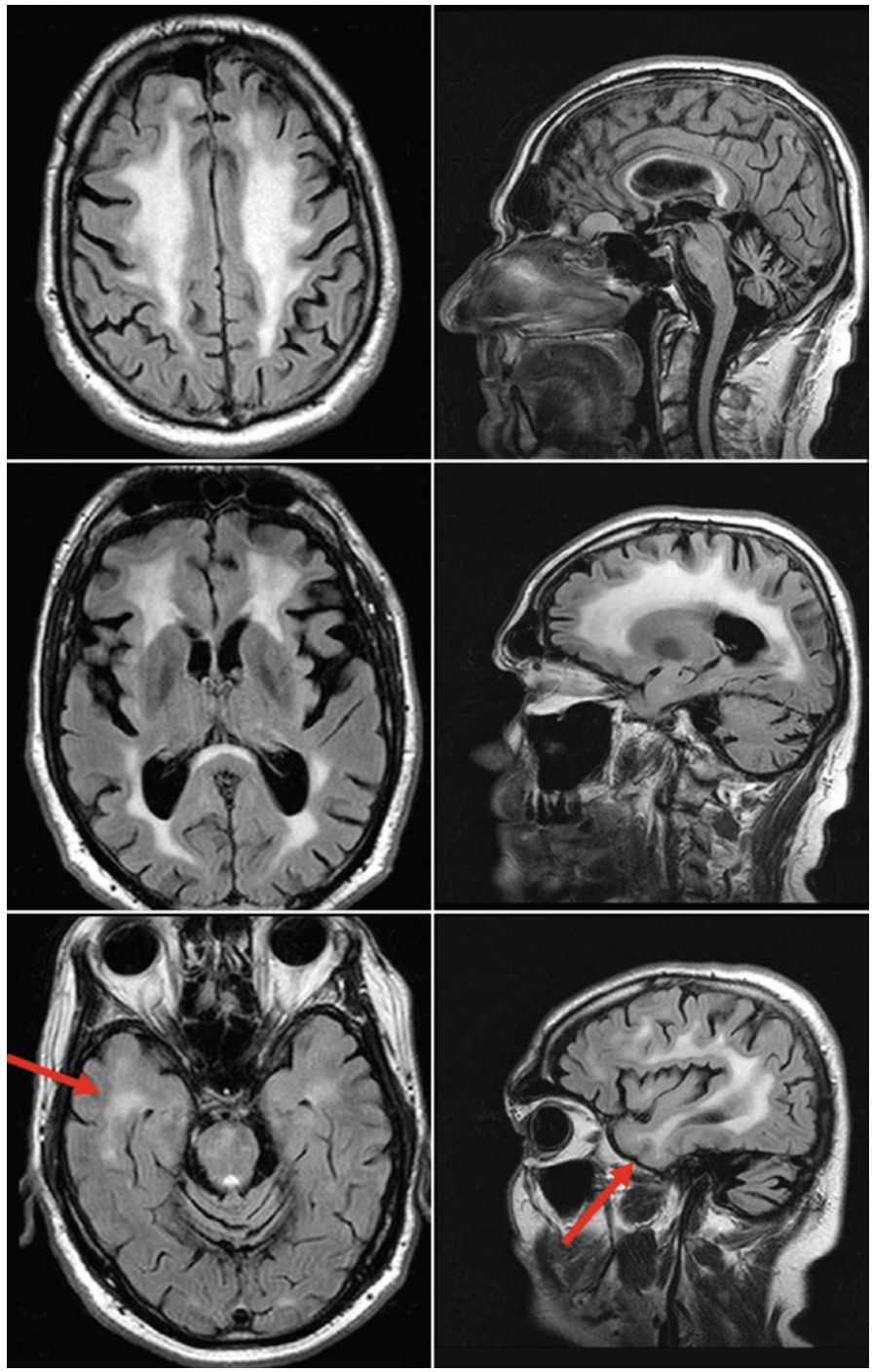

Fig. 7.19 This 59-year-old man was referred with cognitive decline of unknown origin. MRI revealed a diffuse leukoencephalopathy. Contrary to ischaemic white matter disease, the temporal lobes were affected as well (*red arrows*), narrowing the differential diagnosis to CADASIL, multiple sclerosis (MS), myotonic dystrophy and APBD. Subsequent laboratory testing confirmed the diagnosis of APBD

Box 7.1 Neuroimaging findings in NAL and differential diagnosis

MRI (and to a lesser extent CT) demonstrates selective white matter involvement and atrophy of the frontal lobe consisting of:

- Selective frontal subcortical atrophy
  - Ventricular enlargement, especially of the frontal horns
  - Corpus callosum atrophy, especially of the genu
- Bilateral, symmetrical, usually confluent (but may be patchy) signal abnormalities in the white matter of the frontal lobes
  - T2 hyperintense and T1 hypointense on MRI, hypodense on CT
  - Involving the periventricular and subcortical white matter
  - Sparing the U-fibres
- Additional involvement of the parietal white matter later in disease
- Signal abnormalities may extend downwards through the posterior limb of the internal capsule into the brain stem and pyramidal tracts
- Lack of contrast enhancement

Differential diagnosis and main differentiating imaging finding

• FTLD	More cortical atrophy • Less white matter signal change
• Other leukodystrophies	Additional white matter findings • Posterior fossa lesions in ALD • Enhancement in Alexander • Liquefaction in VWM
• Post-traumatic gliosis	Cortical gliosis, focal atrophy, MBs
• Vascular disease	Temporal lobe involvement in CADASIL
• Infections	Asymmetrical/discontinuous lesions in PML
• Inflammation	Discontinuous focal lesions in ADEM/MS

thalamus. Individuals may be thought to have MS or FTD or another leukodystrophy (see Box 7.1). Exact prevalence is unknown. There seems to be overrepresentation of women. Diagnosis can be confirmed only by biopsy or at autopsy – no genetic or laboratory marker is known. Survival after diagnosis ranges between 2 and 20 years in published cases. Treatment is symptomatic.

Neuroimaging Strategy and Findings

Brain MRI is the imaging modality of choice; there is no established role for nuclear imaging or advanced MR techniques. The main findings are summarised in Box 7.1, along with clues for the differential diagnosis of NAL. A typical example of NAL is presented in Fig. 7.20.

7.4.8 Late-Onset Metachromatic Leukodystrophy

Synonyms
Metachromatic leukodystrophy (MLD); leukodystrophy with arylsulphatase deficiency.

Aetiology, Genetics and Histopathology

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease characterised by demyelinating white matter damage and an accumulation of sulphatides in brain and other tissues. Incidence is approximately 1/40,000. The majority of MLD cases are caused by deficient activity of arylsulphatase A (ASA) encoded on chromosome 22. Rarely, MLD is due to saposin-B deficiency – a sphingolipid activator. Metachromatic material (cerebroside sulphate) accumulates in brain oligodendrocytes and microglia, peripheral nerve Schwann cells and kidneys. Due to an unknown mechanism, accumulation of lysosomal sulphatide leads to demyelination starting in the periventricular white matter without accompanying inflammation.

Clinical Presentation and Therapy

The three clinical forms – late-infantile, juvenile and adult – are due to different levels of residual enzyme activity. The adult form may present as late as 60 years of age. Adult onset MLD usually first presents

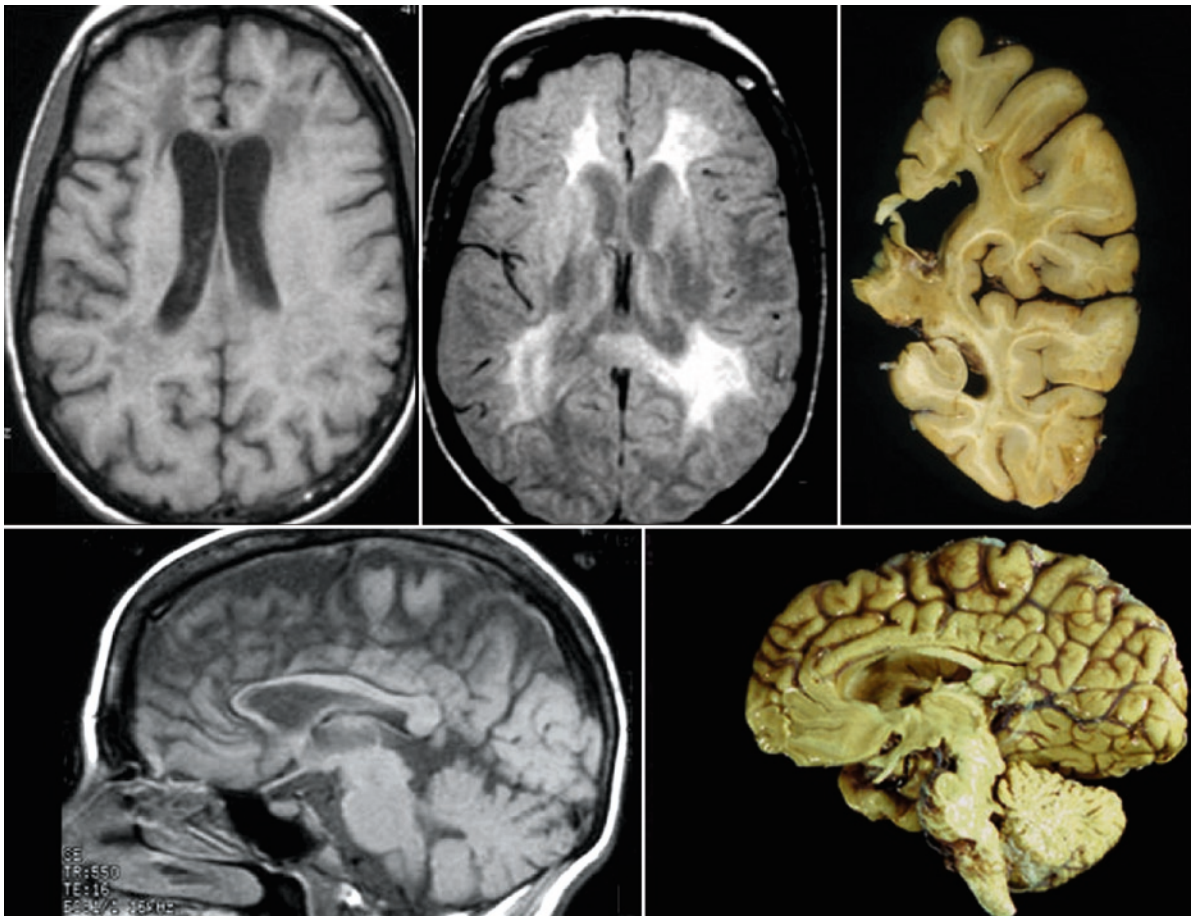

Fig. 7.20 MRI and post-mortem findings in NAL. This 40-year-old woman had a 3-year history of cognitive and behavioural decline followed by more rapid clinical deterioration which included cortical blindness. MRI demonstrates abnormal signal in the white matter underlying the prefrontal cortex and mildly enlarged lateral ventricles, as well as atrophy of the anterior part of the corpus callosum. She died at the age of 45 years and autopsy confirmed leukodystrophy with neuroaxonal spheroids. Note extensive thinning and brown discolouration of the corpus callosum and enlarged lateral ventricle on the mid-sagittal section. Coronal section of the parietal lobe (in a different patient) demonstrates grey discolouration of the white matter with U-fibre preservation. The parietal lobe is more severely affected than the temporal lobe white matter. (Modified with permission from *Brain Pathol* 2009;19:39–47)

with psychiatric symptoms and cognitive decline. The phenotype may resemble schizophrenia or a frontal dementia. Progressive paresis of arms and legs develops subsequently, followed by cerebellar ataxia and extrapyramidal symptoms. The diagnosis is based on measurement of arylsulphatase-A in blood or urine. Therapeutic options include bone marrow transplantation, stem cell therapy and enzyme replacement.

Neuroimaging Strategy

The earliest imaging feature (which may be present in asymptomatic subjects) is the development of initially faint sheet-like changes in periventricular white matter with relative sparing of U-fibres (Fig. 7.21). These are best seen on T2-weighted MRI. There may be a frontal predominance – frontal and parietal/occipital regions are most affected in mild disease. The corpus callosum is involved relatively early but not to the same extent as in ALD or globoid cell leukodystrophy (GLD). As the disease becomes more severe, radial stripes appear peripherally. This tigroid pattern reflects zones of spared myelin in a perivascular distribution within affected white matter. Involvement of the cerebellar white matter and brainstem and basal ganglia may all occur but are usually late findings. After injection of contrast there is no enhancement. Central atrophy develops in later stages. Proton MR

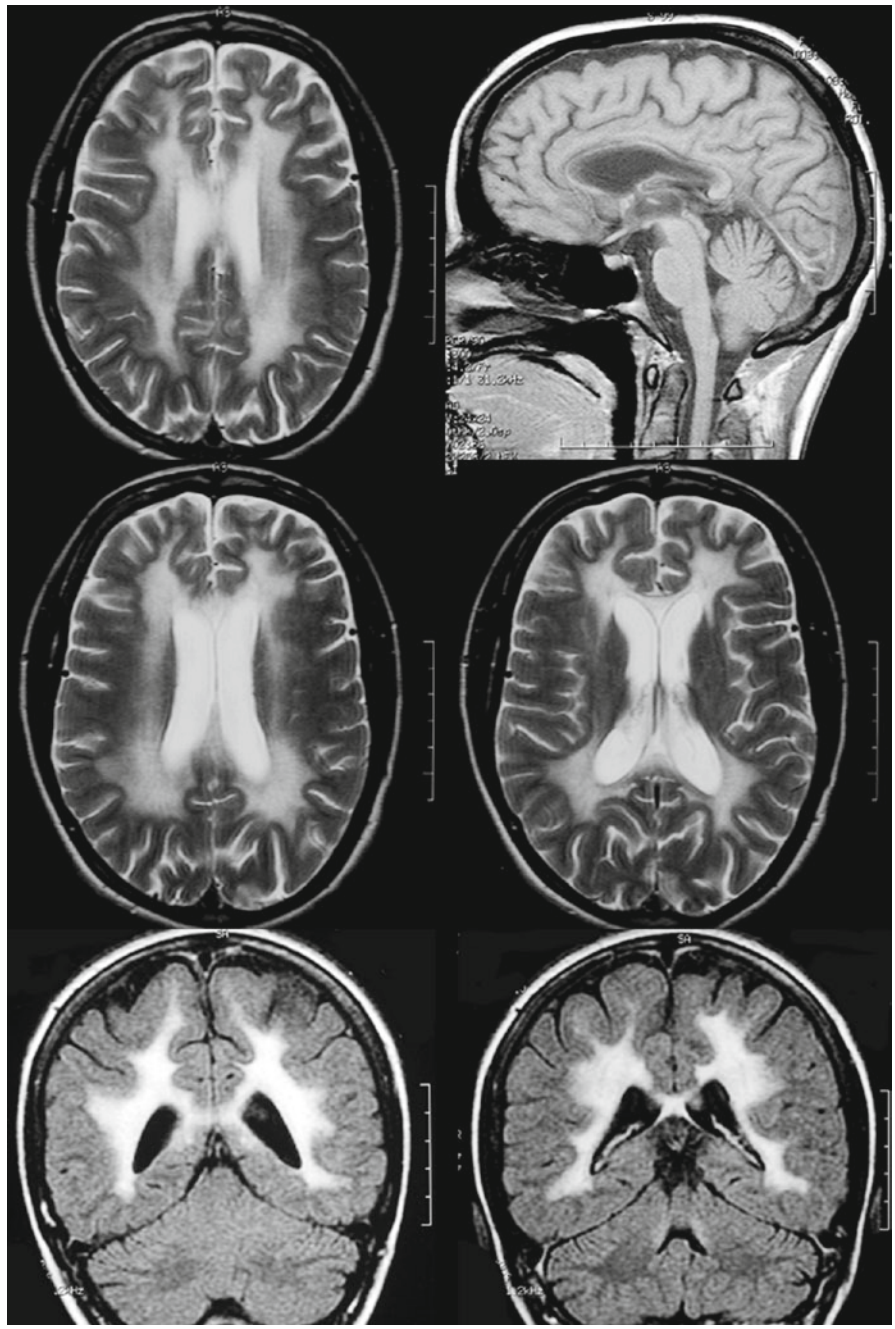

Fig. 7.21 MRI findings in Metachromatic leukodystrophy (MLD). This 30-year-old women presented with memory complaints. Changes in character had been noted by family members and she was thought to be depressed. MRI shows confluent periventricular high signal with severe corpus callosum atrophy. Subsequent laboratory testing revealed abnormally low arylsulphatase-A in leukocytes and the diagnosis of MLD was made. (Case kindly provided by Henry C. Weinstein)

spectroscopy shows a decrease in NAA and high choline, reflecting axonal damage and myelin breakdown – increased myo-inositol probably reflects gliosis. PET or SPECT may reveal thalamic and frontal hypometabolism.

7.4.9 Adrenomyeloneuropathy (AMN)

Synonyms
Adrenomyeloneuropathy (AMN), myeloneuropathy variant of ALD; adult-onset adrenoleukodystrophy

Aetiology, Genetics and Histopathology

AMN is the adult-onset form of X-ALD, and has a similar X-linked recessive inheritance. X-ALD and AMN share an impaired capacity to degrade very-long-chain fatty acids (VLCFA), caused by a defect in peroxisomal oxidation. The disease is caused by mutations in the ABCD1 gene that causes a loss of function of a peroxisomal membrane protein whose role is thought to be related to transport of VLCFAs. Other (unknown) genetic or environmental factors (e.g. head injury) may perhaps contribute to explain how individuals in the same family may have different phenotypes. Histopathologically, axonal degeneration with demyelination is found in descending spinal cord tracts. In the cerebral form, demyelination occurs in the cerebellar and cerebral white matter (especially in the splenium of the corpus callosum and the posterior limb of the internal capsule); the active edges of demyelination feature inflammation.

Clinical Presentation and Laboratory Findings

AMN usually presents in the third or fourth decade of life, but occasionally as late as at the age of 60 years. In the typical spinal form, affected males show a slowly progressive paraparesis, urinary incontinence of the urgency type, cerebellar ataxia and signs of a peripheral neuropathy (sensory and autonomic). About half of the patients show signs of cerebral involvement with slowly progressive mild cognitive dysfunction. Visual memory is usually the most affected. Emotional disturbances and depression may occur. AMN should be considered in the differential diagnosis of young-onset dementia, certainly when presenting with spastic paraparesis and urinary incontinence in men.

AMN should also be considered in women, since 10–15% of women heterozygous for X-ALD develop AMN of variable severity around the age of 40 years. Brain MRI may be normal or show involvement of the pyramidal tracts, corpus callosum, and the periventricular white matter with a posterior predilection. In contrast to men, VLCFA may yield false-negative results in heterozygous women and DNA analysis is the recommended test in women.

About two thirds of patients with AMN have overt or biochemical signs of adrenocortical insufficiency, which may precede or follow neurological dysfunction. The disease is slowly progressive over decades, and no effective therapy exists.

Neuroimaging Strategy and Findings

About 50% of symptomatic patients with AMN have abnormal brain MRI scans at presentation, and the extent of cerebral involvement is much more variable than in X-ALD. Presenting findings include signal changes in the posterior limb of the internal capsule and splenium of the corpus callosum (Fig. 7.22). Subsequently, abnormalities become visible in the cerebral peduncles and cerebellar white matter. After contrast injection, enhancement is seen in the most recently affected regions. MR of the spinal cord shows atrophy. MR spectroscopy in cases of cerebral involvement may show decreased NAA and increased choline, reflecting axonal damage/loss and demyelination, respectively.

7.4.10 Vanishing White Matter Disease (VWM)

Synonyms
Childhood ataxia with central nervous system hypomyelination (CACH), Cree leukoencephalopathy, vanishing white matter (VWM), leukodystrophy with ovarian failure, ovarioleukodystrophy

Clinical Presentation and Aetiology

The name ‘vanishing white matter disease’ (VWM, OMIM #306896) was coined by van der Knaap in 1997. Previously, this disease has also been described as ‘childhood ataxia with central hypomyelination’ (CACH). It is caused by mutations in any of the five genes encoding subunits of the eukaryote translation initiation factor EIF2B, located on chromosome 3q. Whereas initially thought to be a homogenous disease affecting young children, VWM has a wide phenotypic variation and may present at all ages. In adult-onset cases, the initial presentation may include seizures, psychiatric symptoms, motor deterioration or dementia. The characteristic clinical features of VWM in children – episodes of rapid and major neurological deterioration provoked by fever or minor head trauma – may be absent in adult-onset cases.

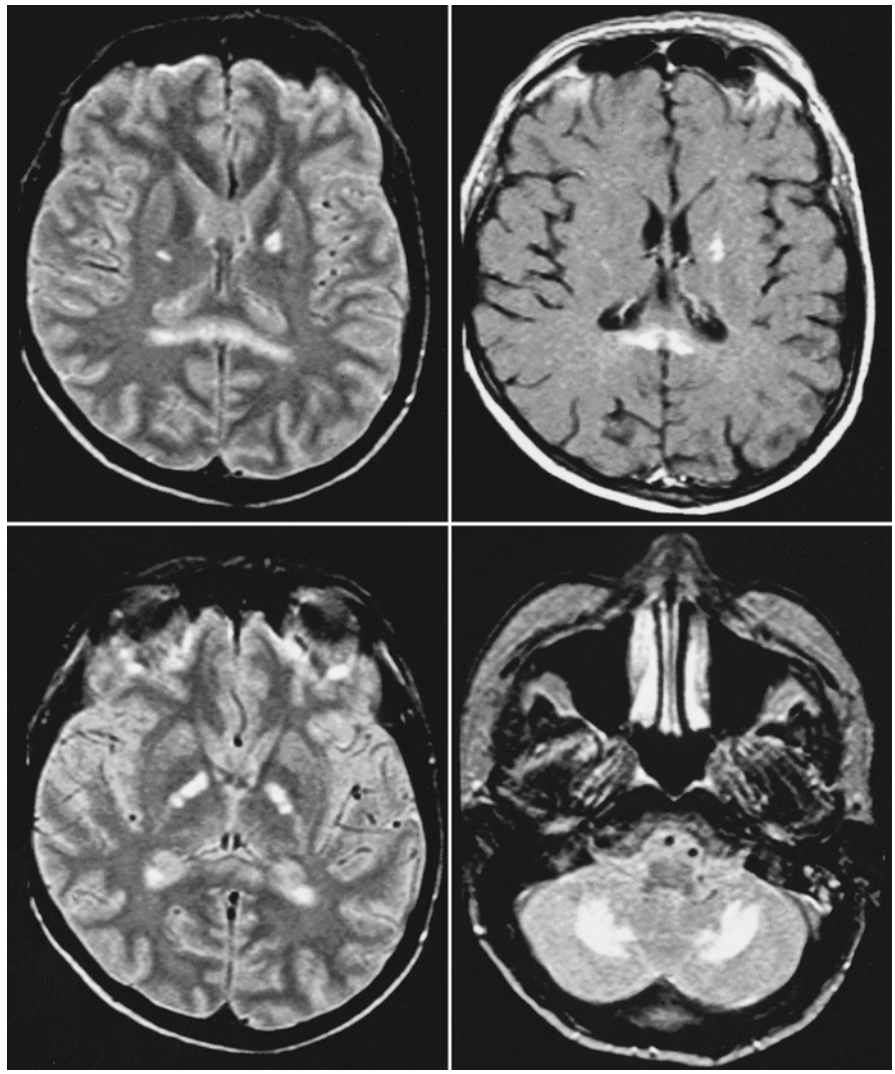

Fig. 7.22 MRI findings in AMN with cerebral involvement. This 58-year-old man was wheelchair-bound at the time of the MR examination and had lost most of his cognitive abilities. Proton-density-weighted MRI shows involvement of the splenium of the corpus callosum, the internal capsule and cerebellar white matter. Note enhancement of the most rostral active zones with gadolinium (*upper right*)

Histopathology

The hallmark pathology of VWM is rarefaction of the deep and periventricular white matter in the frontal and parietal lobes, with relative sparing of the temporal lobes, the corpus callosum, the visual pathways, the anterior commissure and internal capsule. Microscopically, the affected white matter shows myelin pallor, thin myelin sheaths, vacuolation, myelin loss, cystic changes and, rarely, active demyelination. Axonal loss is complete in areas with cavitation, and may be spared in other regions. The radiating stripes as seen on MRI appear to correlate with preserved blood vessels accompanied by reactive astrocytes.

Neuroimaging Findings

MRI of the brain can be diagnostic in full-blown cases of VWM, showing diffuse and homogeneous white matter hyperintensity on T2-weighted images, with remarkably low central signal intensity on T1-weighted images, proton-density and FLAIR images, reflecting severe tissue rarefaction not seen in any other leukodystrophies (Fig. 7.23). In early cases, diagnosis may be more difficult, certainly when tissue rarefaction is not yet apparent. Proton MRS shows a spectrum similar to that of CSF with some lactate and glucose and no or minor ‘normal’ resonances, but may be unremarkable in earlier stages.

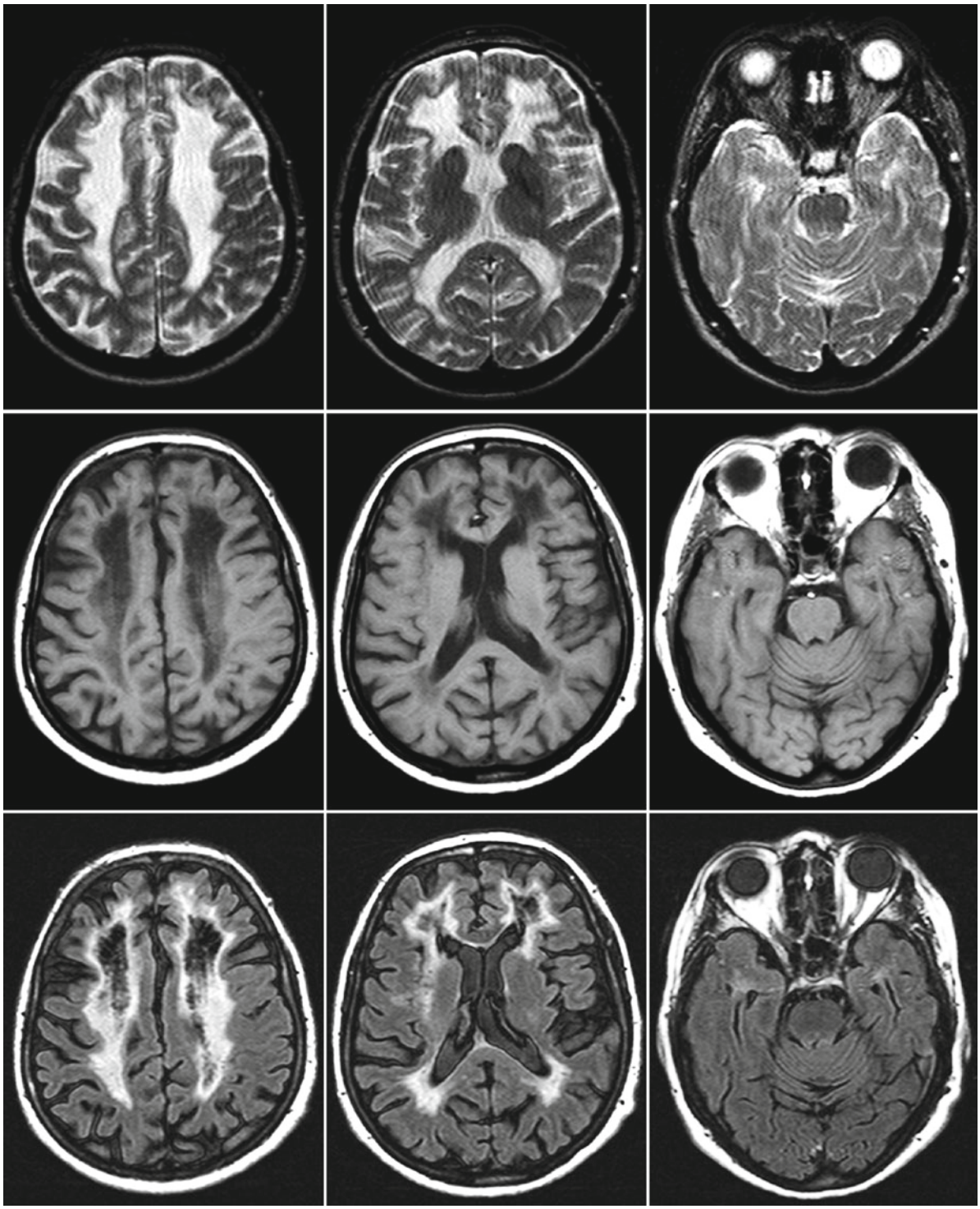

Fig. 7.23 MRI findings in adult-onset VWM. This 55-year-old woman had difficulties at work in the preceding months. The family noted a progressive neglect in personal hygiene, reduced variety in cooking, memory deficits and repetitive speech. MRI revealed a diffuse leukoencephalopathy on T2-weighted images (*upper row*) with characteristic low signal intensity on T1-weighted and FLAIR images (*middle* and *lower rows*) with a central "dot-and-stripe" pattern of preserved tissue. (Based on a case reported by Gascon-Bayarri in *JNNP* 2009, with special thanks to Marjo van der Knaap)

7.4.11 Globoid Cell Leukodystrophy (Krabbe's Disease)

Synonyms
Globoid Leukodystrophy (GLD); adult-onset GLD; Krabbe's disease

Aetiology, Genetics and Histopathology

GLD is a rare autosomal recessive lysosomal storage disorder caused by mutations in the galactocerebrosidase (GALC) gene – over 70 different pathogenic mutations are already known. Deficiency of GALC leads to accumulation of galactosylceramide within multinucleated macrophages of the white matter, forming characteristic 'globoid' cells. A metabolite of galactosylceramide accumulates which is toxic to oligodendroglia and results in damage (demyelination) of the peripheral and central nervous systems. The disease may be subdivided into three types based on age of onset: the most common is the infantile form (with a severe/rapidly progressive phenotype); a rare juvenile form (between 2 and 10 years) and an even rarer adult form, with onset after 10 years, also exist.

Clinical Presentation

Adult forms of GLD have a milder but variable phenotype and a slower rate of progression. Symptoms and signs include spasticity, dementia, ataxia, peripheral neuropathy, and loss of vision. Occasionally, individuals may present with spastic paraparesis and only mild cognitive problems. Nerve conduction can be normal or only mildly affected. Age of onset and survival widely vary even within families. Diagnosis is confirmed by markedly reduced GALC activity in leucocytes. Stem cell treatment appears promising in infantile GLD.

Neuroimaging Findings

MRI shows periventricular white matter abnormalities with relative sparing of the arcuate fibres. The posterior limb of the internal capsule and the corticospinal tracts in the brainstem are involved in most cases. A number of case reports suggest that the earliest and occasionally only site of involvement is the corticospinal tracts (Fig. 7.24). White matter hyperintensities on FLAIR and T2-weighted imaging are common in the more posterior brain regions, with frequent involvement of the splenium of the corpus callosum – a pattern similar to adrenoleukodystrophy (ALD). Atrophy is more conspicuous than in MLD. There is no enhancement after contrast injection. MR spectroscopy shows a decrease in *N*-acetylaspartate and sometimes (not always) high choline.

7.5 Toxic Leukoencephalopathy and Dementia

Mike P. Wattjes

7.5.1 Introduction and Classification

This chapter deals with acquired cognitive decline due to toxic encephalopathy secondary to a selected number of causes. In general, toxic encephalopathy associated with cognitive impairment can be caused by:

- Exogenous/endogenous deprivation of metabolic factors
  - e.g. abnormal intake/uptake/metabolism of vitamins
- Exogenous toxic substances due to substance abuse or inadvertent exposure
  - e.g. drugs, organic solvents
- Endogenous accumulation of toxic substances due to abnormal metabolism
  - e.g. inherited leukodystrophies Sect. 7.4)
- Secondary changes due to vascular pathology or hypoxia

Certain disease entities are based on a combination and/or overlap of the above categories (e.g. dialysis dementia). Toxic encephalopathies are quite heterogeneous in terms of the underlying epidemiology and pathophysiology. However, they all share a specific histopathological feature: demyelination. This can occur in a direct toxic way or be secondary to vascular

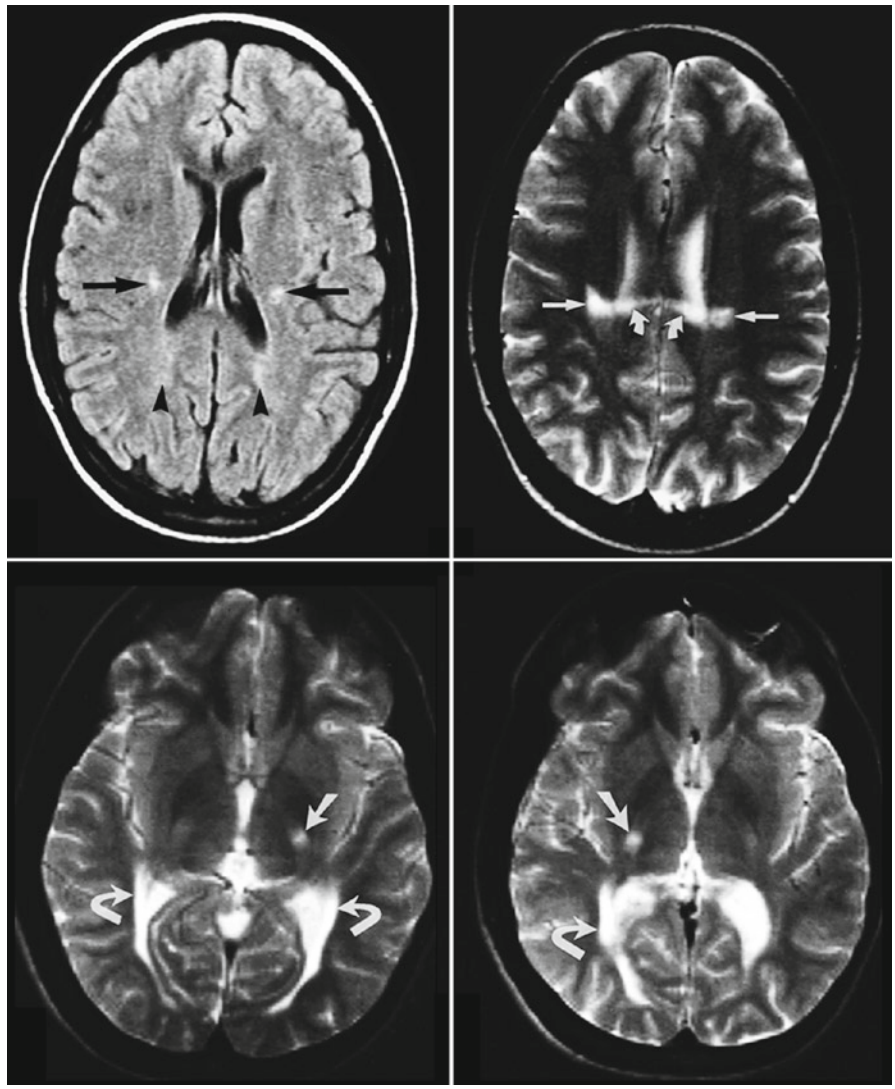

Fig. 7.24 MRI findings in GLD. *Upper row* shows images of an 18-year-old patient. Axial FLAIR image on the left shows symmetrically increased signal intensity within the pyramidal tracts (*straight arrows*) and parieto-occipital white matter (*arrowheads*) extending into the corpus callosum (curved arrows on T2-weighted image on the right). The lower row is from his18-year-old monozygotic twin brother presenting with behaviour changes and cognitive decline. Note T2-hyperintensity in the left and right pyramidal tracts (*straight arrows*), and bilateral increased signal intensity in the optic radiation (*curved arrows*). (Courtesy of D.J. Loes, M.D.)

damage and hypoxia. Demyelination can occur diffusely in certain metabolic disorders and toxic diseases, but may also more selectively affect targets such as the midbrain, like in Wernicke's encephalopathy (WE). The histopathological hallmark of demyelination cross-links to other forms of toxic encephalopathy associated with cognitive decline, such as iatrogenic (treatment associated) pathology, like in post-radiation and chemotherapy-related encephalopathies (see Sect. 7.6).

A full description of all toxic encephalopathies is beyond the scope of this book. The current chapter focuses on a certain selection of disorders, which are relatively prevalent or present with typical imaging vignettes. In fact, many other toxic agents such as heavy metals (lead, mercury, tin, arsenic, manganese), drugs (e.g. opiates, cocaine) as well as metabolic factors including hormones (e.g. testosterone, oestrogens, thyroid hormone), and vitamins (vitamin D deficiency) can also lead to toxic encephalopathy. Some of them are discussed in other chapters and others are not associated with discernible neuroimaging findings. Therefore, they are rather diagnosed on clinical and laboratory findings. However, many need to be considered in the differential diagnosis of the diseases discussed in the following chapters.

7.5.2 Vitamin B Deficiencies

7.5.2.1 Vitamin B1 Deficiency

Synonyms
Wernicke's encephalopathy (WE), Korsakoff's syndrome, thiamine deficiency, beriberi

History

WE was first described by Carl Wernicke in 1881 as acute superior haemorrhagic polioencephalitis in two patients with alcohol abuse and in another one with persistent vomiting due to pyloric stenosis after the ingestion of sulphuric acid. The association of WE with malnutrition and thiamine deficiency as an underlying causative factor has been discovered by Campbell and Russell in 1941.

Epidemiology, Aetiology, Clinical Presentation and Treatment

The prevalence of WE in autopsy studies (0.8–2.8%) is substantially higher than clinically reported (0.04–0.13%) and occurs especially in patients with alcohol abuse. WE is associated with many clinical conditions impairing the absorption of thiamine:

- Chronic alcohol abuse
- Malnutrition/unbalanced nutrition
- Chronic gastro-intestinal diseases, recurrent and prolonged vomiting and diarrhoea
- Thyrotoxicosis, magnesium depletion
- Genetic factors
- Haemodialysis, chemotherapy
- Chronic infectious disease (HIV/AIDS), malignancies

Although WE is associated with alcohol misuse, alcohol in itself does not directly cause thiamine deficiency. However, chronic alcohol misuse is associated with unbalanced nutrition and alcohol raises the demand for thiamine. WE is more common in men than in women (male-to-female ratio 1.7:1). A mortality rate of 17% has been reported.

The clinical manifestations of thiamine deficiency in the nervous system can be subdivided into severe short-term deficiency with CNS symptoms (encephalopathy) and mild- to long-term deficiency leading to damage of the peripheral nerves. The early clinical signs of WE are non-specific (headache, fatigue, irritability) which makes an early diagnosis of WE rather difficult. The classical clinical presentation is characterised by oculomotor symptoms, altered consciousness and ataxia. However, this classical triad initially described by Wernicke is only present in 16–38% of the patients.

Recently introduced diagnostic criteria require two of the following criteria for WE:

- Dietary deficiency
- Oculomotor abnormalities
- Cerebellar dysfunction
- Altered mental status/mild memory impairment

Mental status changes occur in the vast majority of WE patients ranging from confusion, apathy, concentration deficits to hallucinations, coma and death. Some patients develop Korsakoff's syndrome, which is characterised by a disproportionate decline of working memory, whereas other cognitive domains are relatively spared. Such patients show severe anterograde amnesia with disorientation in time. Occasionally, emotional changes (euphoria, blandness etc.) may occur.

WE and Korsakoff's syndrome should be treated with a minimum of 500 mg of thiamine hydrochloride intravenously, three times daily, for 2–3 days. In the case of an effective response, treatment should be continued with 250 mg of thiamine daily (intravenously or intramuscularly) for 3–5 days. Dosages of thiamine between 100 and 250 mg are not sufficient to adequately restore the vitamin status.

Aetiology and Histopathology

Thiamine is absorbed in the duodenum and transported through the blood-brain barrier by active and passive mechanisms. In neurons and glia, thiamine is converted to thiamine pyrophosphate, which is involved in several biochemical pathways including the intermediate carbohydrate metabolism (ATP production), lipid metabolism (myelin sheaths, cell membranes) and synthesis of amino acids and neurotransmitters. In addition, thiamine is involved in synaptic transmission (acetylcholinergic, serotonergic).

Due to the normal storage capacity of thiamine in the body, thiamine deficiency leads to neuropathological changes only after 2–3 weeks. After that period, the function of certain thiamine pyrophosphate-dependent enzyme pathways (tricarboxylic acid cycle, pentose-

phosphate pathway) starts to decline. This leads to an impaired use of glucose and to a deficient cellular energy metabolism in the brain, which in the end results in cellular death.

The pathological changes symmetrically affect certain areas of the brain obviously very much dependent on a high rate of thiamine-related glucose and oxidative metabolism, such as the periaqueductal grey matter, thalamus, superior cerebellar vermis and mamillary bodies. Acute lesions show microhaemorrhages with spongiosis, but no interstitial infiltrations of macrophages or any capillary proliferation. Chronic lesions feature swelling of astrocytes, neuronal loss, activated microglia, demyelination, astrogliosis and vessel hyperplasia.

Neuroimaging Strategy and Findings

CT might be used in the acute clinical setting, but MRI is much more sensitive and the modality of choice, with a sensitivity of 53% and a specificity of 93% (Box 7.2). Due to the rather distinct involvement pattern, additional advanced MR techniques (e.g. ^{1}H-MR spectroscopy) are not necessary in a clinical routine setting (Fig. 7.25).

7.5.2.2 Vitamin B12 Deficiency

Synonyms
Cobalamin deficiency, subacute combined degeneration

History

The association between vitamin B12 deficiency and neuropsychiatric syndromes has been recognised since the first description of pernicious anaemia in 1849. In 1900, the term *subacute combined degeneration of the spinal cord* was introduced by Russell et al. Vitamin B12 (cobalamin) itself was discovered by George Whipple in 1920, who later shared the Nobel Prize with Minot and Murphy in 1934 for this discovery.

Epidemiology, Clinical Presentation and Treatment

The prevalence of B12 deficiency is probably underrated and might range up to 16% in developed countries. Reduced levels of vitamin B12 become more

Box 7.2 Neuroimaging findings in Wernicke encephalopathy (WE)

Typical MRI findings in WE may include:

- Increased signal on T2/FLAIR in characteristic areas
  - Medial thalamus
  - Mamillary bodies
  - Periaqueductal GM and colliculi
- Increased signal on T1 may occur, due to microhaemorrhages
- Contrast enhancement can be seen in the acute phase
  - May be absent in non-alcohol WE
- DWI may show reduced ADC in the acute phase of the disease

Atypical manifestations include symmetric changes in

- Cerebellum (hemispheres, vermis)
- Other deep GM nuclei: caudate, red nucleus, dentate and cranial nerve nuclei
- Splenium of the corpus callosum
- Cerebral cortex

^{1}H-MR spectroscopy

- Decreased levels of NAA in the thalami and cerebellum indicating axonal damage
- Increased lactate in the cerebellum indicating necrosis

Differential diagnosis

- Mitochondrial disease (e.g. Leigh syndrome)
- Other toxic disorders (hypophosphataemia, methyl bromide intoxication, bromvalerylurea intoxication)
- Posterior circulation ischaemia (e.g. top-of-the-basilar artery syndrome)
- Deep venous thrombosis
- CJD
- Paraneoplastic disease
- Metronidazole treatment (atypical distribution pattern)
- Neuromyelitis optica (NMO) due to aquaporin-4 antibodies

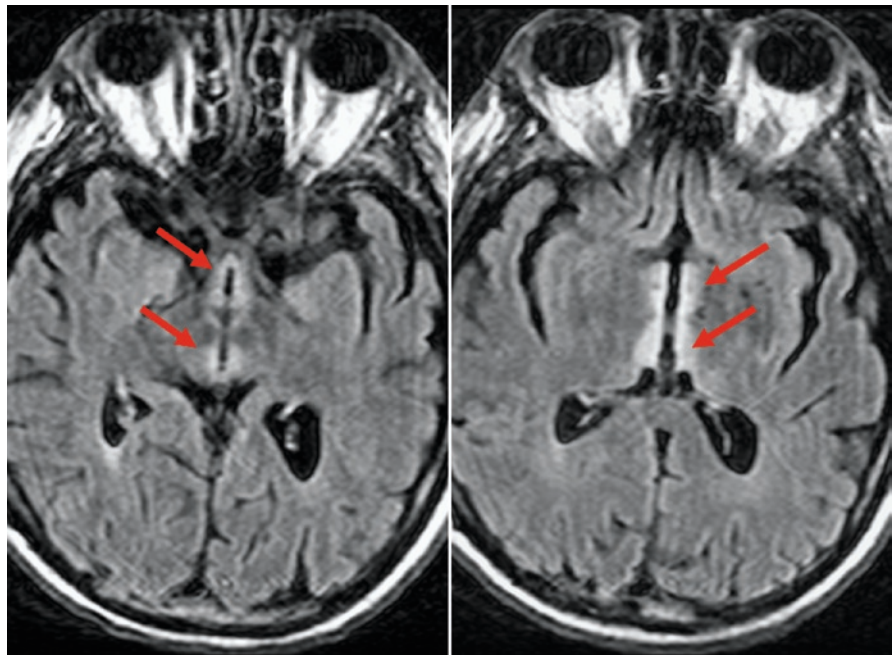

Fig. 7.25 Wernicke encephalopathy. FLAIR images show the characteristic distribution of high signal lesions (*red arrows*) around the third ventricle, affecting the medial thalamus and periaqueductal grey matter

prevalent with ageing, rising to 20% in subjects older than 70 years.

Due to the body storage of 2–5 mg in the liver, B12 deficiency from malabsorption only develops after several years. The early signs of B12 deficiency are often vague and non-specific, such as concentration deficits, memory complaints, irritability and depression. Besides haematological (megaloblastic anaemia) and gastrointestinal manifestations (atrophic glossitis, stomatitis, diarrhoea), chronic vitamin B12 deficiency results in a complex clinical syndrome affecting the peripheral (neuropathy with numbness and altered proprioception) and the central nervous system. CNS symptoms include progressive paraparesis, ataxia, visual changes (due to optic nerve involvement), sleep disturbances, depression, personality changes and memory impairment. The association of lower vitamin B12 with cognitive impairment (adjusted for other risk factors such as age, sex and smoking) is firmly established.

Vitamin B12 metabolism is linked to the metabolism of homocysteine. B-vitamins (B12, B6) are important cofactors for homocysteine catabolism. For example, the enzyme methionine synthase and its cofactor methylcobalamin mediate the remethylation of homocysteine to methionine. Therefore, hyperhomocysteinaemia may indicate B-vitamin deficiency. Similar to B12 deficiency, hyperhomocysteinaemia is more common in the elderly and is associated with an increased risk of cognitive dysfunction. Homocysteine plasma concentrations can predict memory decline with age in the elderly. In addition, high homocysteine plasma levels are an independent risk factor for vascular pathology and vascular dementia.

Supplementation of vitamin B12 (parenteral or oral cobalamin) at an efficient dose for several weeks (or even lifelong) is the only treatment option. Haematological and neurological symptoms can recover, as well as the MRI abnormalities. However, whether adequate cobalamin supplementation or treatment of hyperhomocysteinaemia also positively affects cognition is difficult to predict.

Aetiology and Pathophysiology

Vitamin B12 has an essential role in the functioning of the CNS, being involved in the cell metabolism in terms of DNA synthesis and regulation, as well as in the fatty

acid synthesis and energy production. Vitamin B12 is absorbed in the terminal ileum. An 'intrinsic factor' produced by the gastric parietal cells is also needed for its adsorption. Vitamin B12 deficiency can be caused by an impairment of absorption: surgical interventions, chronic gastro-intestinal diseases (e.g. atrophic gastritis, celiac disease), achlorhydria, bacterial overgrowth (e.g. blind loop syndrome), medication (e.g. metformin), chronic infections (e.g. giardiasis or other parasitic infections), medications (e.g. colchicine, neomycin); impaired intake: dietary imbalance (e.g. vegan diet); toxic (nitrous oxide exposure/ nitrous oxide anaesthesia) or hereditary causes such as MTHFR deficiency, homocystinuria and transcobalamin deficiency.

Cobalamin deficiency may lead to diffuse demyelination within the CNS, even though the pathophysiological mechanism remains poorly understood. Histopathologically, vitamin B12 deficiency is characterised by multifocal demyelination in the white matter of the brain and spinal cord. In the spinal cord, multiple areas of demyelination and vacuolisation with myelin breakdown, infiltration of foamy macrophages and axonal pathology can be observed in the posterior and lateral columns – the so-called *subacute combined degeneration*. Demyelination commences in the central parts of the posterior columns of the thoracic cord spreading laterally and cranially to the corticospinal tracts of the cervical spinal cord and medulla oblongata. The histopathological findings in the brain, in terms of demyelination, do not substantially differ from those observed in the spinal cord. In addition, degeneration of the optic nerves can be typically observed.

Neuroimaging findings in Vitamin B12 deficiency

Brain MRI findings

- Diffuse supratentorial areas of T2 hyperintensity in the periventricular and deep white matter
  - Usually bilateral, but not necessarily symmetrical
  - Large lesions may involve subcortical U-fibres
- Brain stem and the cerebellar white matter are relatively spared
- Blood–brain barrier disruption may occasionally be observed
- Broadening of the gyri due to swelling can be occasionally observed.
  - Atrophy might be present, but can be reversible during/ after treatment
- In patients with additional hyperhomocysteinaemia, silent infarctions may be observed.
- In infants/young children, delayed myelination or dysmyelination instead of demyelination

Spinal cord MRI may show a mild enlargement of the spinal cord and shows signal abnormalities (T2 hyperintense, T1 hypointense) in the dorsal and lateral columns. Contrast enhancement is not observed.

Differential diagnosis:

In general, the differential diagnosis includes toxic, metabolic, infectious and paraneoplastic conditions associated with diffuse demyelination of the central nervous system. Due to the involvement of the spinal cord, the differential diagnosis should particularly include HIV encephalomyelopathy and multiple sclerosis.

Neuroimaging Strategy and Findings

In general, CT is not recommended in the detection of vitamin B12 deficiency-related changes due to its low sensitivity. In particular, spinal cord abnormalities cannot be detected by means of CT. Therefore, multisequence MRI (including T2-weighted sequences) of the brain and spinal cord is the imaging modality of choice. Spinal cord T2-weighted MRI should be performed in sagittal and transverse orientations, in order to detect typical spinal cord manifestations in the posterior columns ranging from the thoracic spinal cord to the brain stem (Fig. 7.26). Administration of intravenous contrast media is not necessary to establish the diagnosis. However, it might be helpful for narrowing/ excluding differential diagnoses.

7.5.3 Chronic Kidney Disease and Dialysis

Synonyms
Chronic kidney disease (CKD), dialysis dementia, dialysis encephalopathy, dialysis dyspraxia, uremic encephalopathy, dialysis disequilibrium syndrome

History

The first reports linking neuropsychiatric symptoms and chronic renal disease were published in the late 1960s. In 1972 the first patients were reported with

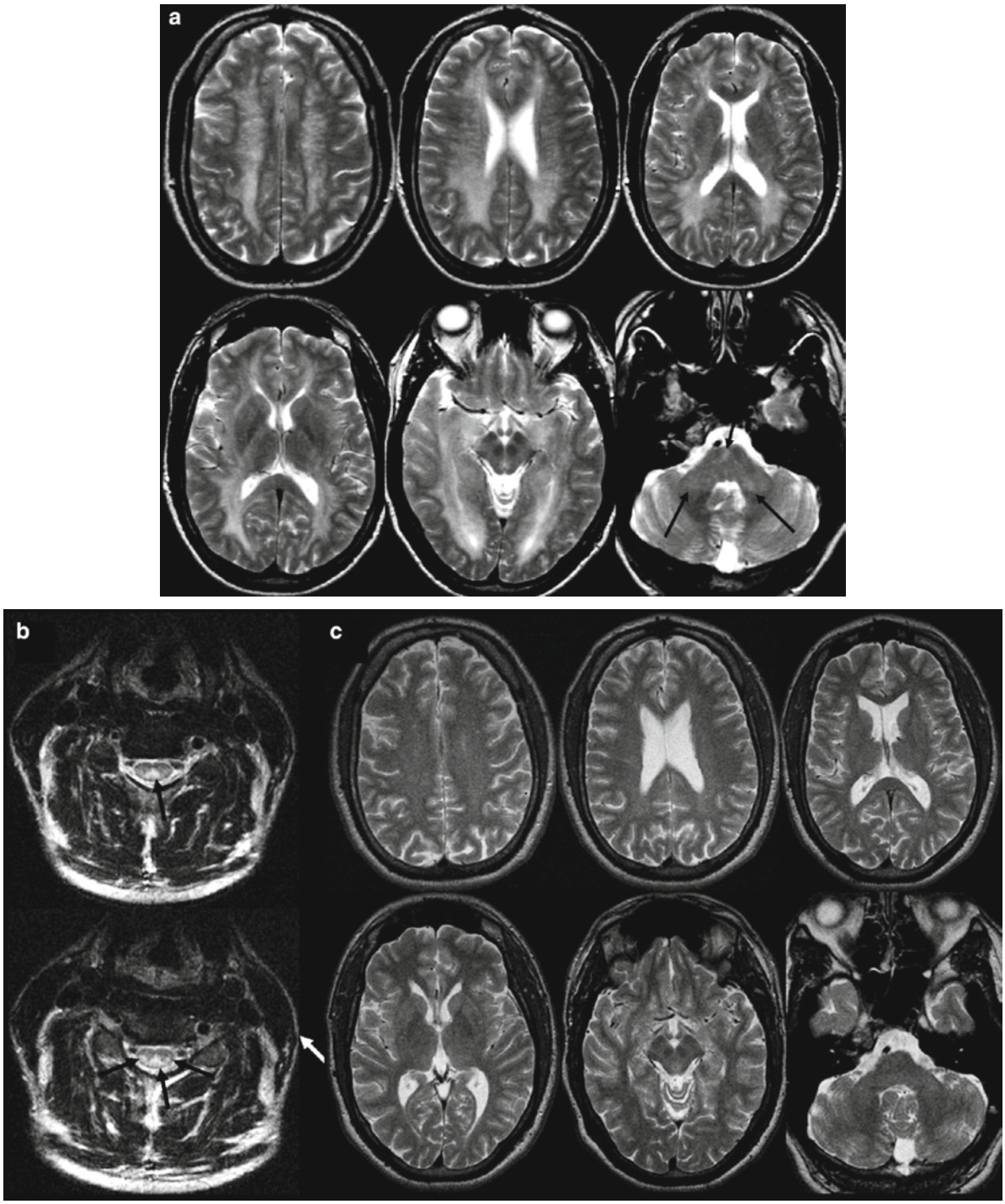

Fig. 7.26 CNS demyelination in vitamin B12 deficiency: A 39-year-old male who presented at a neurological outpatient clinic with progressive neurological complaints including ataxia, paraparesis and numbness of the legs, concentration deficits and memory complaints. The laboratory tests revealed a moderate vitamin B12 deficiency. Initial brain MRI (**a**): transverse T2-weighted images show diffuse confluent hyperintense areas, bilaterally, in the periventricular and deep white matter reaching (but not completely affecting) the U-fibres. The corpus callosum and the infratentorial white matter are relatively spared. However, subtle diffuse white matter changes can also be observed in the pons and the middle cerebellar peduncles (*arrows*). Spinal cord MRI (**b**) shows the typical involvement of *subacute combined degeneration* affecting the posterior and lateral columns (*arrows*) on transverse T2-weighted MR images. The 2-year follow-up MRI (**c**) after adequate supplementation of vitamin B12 shows a complete regression of the diffuse demyelination in the white matter

transient neurological symptoms, such as seizures and speech anomalies during haemodialysis. Subsequent observations confirmed even more fatal encephalopathic complications related to dialysis. A potential role of aluminium as a neurotoxic agent located in phosphorus binders and dialysis water related to chronic cognitive decline in dialysis patients was suggested. During the past decennia it became obvious that neurological complications, in general, and cognitive impairment, in particular, in patients with CKD are an important medical and socio-economic issue that needs further investigation.

Aetiology and Histopathology

Retention of metabolic and toxic waste products (e.g. urea, potassium) and metabolic imbalance reflected by insulin resistance, vitamin D deficiency and hyperparathyroidism are all considered to contribute to cerebral pathology. In particular, hyperparathyroidism might play a major role, since elevated parathyroid hormone levels have neurotoxic effects and secondarily lead to higher brain calcium concentrations, influencing neurotransmission in the CNS. In addition, CKD patients often have substantial (micro) vascular co-morbidity which contributes unfavourably to the clinical outcome as discussed below.

In patients with end-stage CKD undergoing dialysis treatment, rapid shifts in urea concentrations and fluid levels often lead to cerebral oedema during and/or immediate after the dialysis sessions. This pathophysiological process has been referred to as '*dialysis disequilibrium syndrome*', which was more frequently observed in the early days of dialysis treatment – currently rarer with newer dialysis regimens. However, acute metabolic disturbances (e.g. hypocalcaemia, hypophosphataemia, hyponatraemia), and fluid changes possibly leading to temporary cerebral hypoperfusion during and/or shortly after the dialysis sessions, are still causing acute cognitive disturbances occurring during the dialysis session. The current model of the complex pathophysiology of cognitive impairment in haemodialysis patients is based on a combination and interaction of vascular pathology (stroke, cerebral hypoperfusion), systemic factors (toxic metabolic, genetic, inflammatory etc.) and acute factors (during the dialysis process) leading to chronic cognitive impairment.

At the time that phosphorus binders and dialysis water contained aluminium, patients who underwent dialysis showed significantly higher concentrations of aluminium in the CSF and cerebral grey matter than non-dialysed subjects. The concentrations of iron can even be (ten times) elevated in patients who developed dementia. However, at present, the discussion about the association between aluminium concentrations and dementia is getting controversial again. The general association between dialysis and cognitive decline has been referred to as '*dialysis dementia*', a term still used to date.

Clinical Presentation, Epidemiology and Treatment

The prevalence of cognitive impairment in end-stage renal disease is more than double that of the general population. There is both a cross-sectional and a longitudinal relationship between renal function, as measured by the glomerular filtration rate (GFR), and cognitive function. In fact, the prevalence of cognitive decline rises with the severity/grade of kidney dysfunction. CKD reflects an independent risk factor for dementia and acts independently from accompanying risk factors: most patients with CKD have substantial cardiovascular co-morbidity sharing several cardiovascular risk factors including diabetes, hypertension, hyperlipidaemia, obesity etc. All of these are also risk factors for AD and vascular dementia. Additional non-vascular risk factors are often present, such as anaemia, hyperparathyroidism, aluminium, polypharmacy, sleep disturbances and depression. Reflective of that, subclinical vascular WMH on MRI are found in many CKD patients. However, a direct association between vascular factors and cognitive decline in CKD patients has not been established. Apparently, the cognitive deficits in CKD are primarily caused by several factors independent of vascular co-morbidity, which rather have a synergistic effect on clinical outcome measures.

Clinically, patients with CKD may present with deficits in the domains of memory and executive function consistent with a subcortical pattern of cognitive dysfunction. The impairment in terms of memory

Clinical manifestations:

- During/after dialysis procedure: (‘*dialysis disequilibrium syndrome*’)
  - Acute cognitive impairment – a delirium state
    - (Sub)acute disturbance of consciousness
    - Disorientation, attention deficit
    - Impaired cognitive function

In general, the symptoms resolve completely. Recurrent delirium state in haemodialysis patients is associated with higher risk of chronic cognitive decline and dementia.

- Chronic stage
  - Progressive neurological symptoms associated with dementia
    - Dysarthria-apraxia
    - Mutism
    - Myoclonus
    - Personality change, mood disorders
    - Seizures

Compared to patients undergoing classical haemodialysis, the clinical manifestations are less severe in patients undergoing peritoneal dialysis.

Treatment:

- Improve the renal organ function and optimise the dialysis procedure.
  - Renal transplantation
  - Reconstitution of metabolic changes

Neuroimaging strategy

CT shows a low sensitivity in the detection of abnormalities associated with CKD. Neuroimaging should include a multi-sequence MRI protocol, including FLAIR (WM changes and atrophy). T2 (infratentorial WM changes and thalamic lesions). T2* (microbleeds) and 3D-T1 with multi-planar reconstructions to evaluate the hippocampus. Optional: Diffusion-weighted imaging (DWI). The imaging findings are summarized below:

Neuroimaging findings in CKD

- No consistent and specific imaging findings have been reported concerning dementia associated with CKD and/or dialysis.
- High incidence of cardiovascular/cerebrovascular co-morbidity in CKD patients
  - Moderate to severe vascular white matter changes (in 50% of CKD patients)
  - Silent subcortical (lacunar) infarctions can be frequently observed
  - Neurodegeneration, reflected by global cortical atrophy
  - During haemodialysis cerebral oedema can be observed

The amount of the vascular white matter damage seems related to the degree of renal failure and is more pronounced in patients undergoing haemodialysis

capacity may resemble AD. In most of the cases, however, the deficits in memory functions reflects a synergistic pattern of Alzheimer pathology and vascular cerebral compromise.

Differential Diagnosis

Alzheimer’s disease, vascular dementia, normal ageing brain, metabolic/toxic encephalopathy, reversible posterior leukoencephalopathy syndrome (mimicking vasoenic oedema occurring during dialysis procedure).

7.5.4 Carbon Monoxide Poisoning

Synonyms, Abbreviations
Delayed encephalopathy, delayed neuropsychiatric syndrome

History

Carbon monoxide (CO) was identified by Cruikshank in 1800 and toxic effects on dogs were investigated by Claude Bernard around 1846.

Aetiology and Histopathology

CO is a colourless, tasteless, inodorous, and non-irritant toxic gas produced by incomplete combustion of hydrocarbons. As a result, CO poisoning is easily missed. Sources of CO poisoning include exhaust fumes, impaired heating systems, inhaled smoke and methylene chloride (a frequent component of solvents such as paint remover). CO is easily absorbed through the lungs, and binds to haemoglobin 200–250 times more effectively than oxygen, thus blocking its capacity to carry oxygen. In addition to cellular hypoxia, CO-mediated toxicity includes reoxygenation injury (particularly in the CNS) and peroxygenation of lipids leading to (transient) demyelination. CO also affects the mitochondrial respiratory enzyme chain by binding

to cytochrome oxidase. This leads to a substantial and prolonged impairment of the intracellular oxidative metabolism.

CNS damage in the delayed stage includes bilateral demyelination and necrosis of the white matter, globus pallidus, cerebellum, hippocampus and the cerebral cortex.

Clinical Presentation, Epidemiology and Treatment

CO poisoning is one of the most frequent causes of injury and death due to poisoning world wide. In the USA, more than 40,000 people per year are admitted to medical institutions for CO poisoning. The clinical symptoms of acute CO poisoning are non-specific (flu-like symptoms) and dominated by systemic reactions of cellular hypoxia such as tachycardia and tachypnea. As a result of cellular hypoxia and vasodilatation in the CNS, neurological symptoms including seizures and syncopes frequently occur. Chronic exposure to relatively low levels of CO can lead to persistent symptoms such as headaches, lightheadedness, depression, attention deficits, memory decline, nausea and vomiting. Up to 30% of patients may develop a delayed onset of neuropsychiatric symptoms (*delayed neuropsychiatric syndrome, delayed encephalopathy*) 3–240 days after the initial exposure – see Sect. 7.5.5.

Initial treatment in the acute setting of poisoning is the removal from the exposure. Immediate administration of oxygen significantly reduces the half life of CO. Hyperbaric oxygen therapy is used in order to support the dissociation of CO from HbCO and cytochrome oxidase. Further treatment options include the symptomatic treatment of seizures, cardiac complications, hypotension, pulmonary oedema and metabolic acidosis.

Neuroimaging findings in CO poisoning:

Necrotic and ischaemic lesions in the deep grey matter structures
- Globus pallidus, to a lesser extent putamen and caudate nucleus
  - Hippocampal atrophy may develop
- T2-hyperintense lesions surrounded by hypointense rim (haemosiderin)
  - CT hypodense
- Can show disruption of the BBB in terms of contrast enhancement

Less frequent the cerebral and cerebellar cortex may be involved:
- Diffuse hyperintensities on T2-weighted images particularly in the temporal lobe.

White matter demyelination in the subcortical white matter
- Bright on T2/FLAIR, sparing U-fibres
- Confluent aspect, predominantly located in the periventricular WM and centrum semi-ovale
- In delayed stages WM damage may extend to corpus callosum, internal/external capsule and subcortical U-fibres
- Might improve slightly during follow-up of several months.

In the acute stage of carbon monoxide poisoning, diffusion-weighted images show:
- Restricted diffusion (high signal on DWI, low ADC values)
- In the affected areas of the white and grey matter indicating cytotoxic oedema

In the chronic stage, the ADC values may gradually increase.

MR spectroscopy shows decreased levels of NAA (axonal damage) and increased lactate concentrations (hypoxia). SPECT shows areas of cerebral hypoperfusion, particularly in the temporal cortex.

Differential diagnosis:
Clinically, CO is one of the 'great mimickers' due to the diverse and non-specific presentation. The radiological DD includes:
- Metabolic diseases (Wilson disease)
- Japanese encephalitis
- Vascular lesions (small vessel disease)
- Creutzfeldt–Jackob disease (CJD)
- Leigh syndrome

Neuroimaging Strategy and Findings

Rapid initial evaluation involves CT in the acute setting. However, CT is less sensitive in detecting changes associated with carbon monoxide poisoning (Figs. 7.27). Further neuroimaging should include a more sensitive multi-sequence MRI protocol, including FLAIR/T2-weighted images, T1-weighted images (pre- and postcontrast administration) and DWI (Fig. 7.28). Optional: MR spectroscopy, MR perfusion, SPECT to evaluate cerebral perfusion status (see box above).

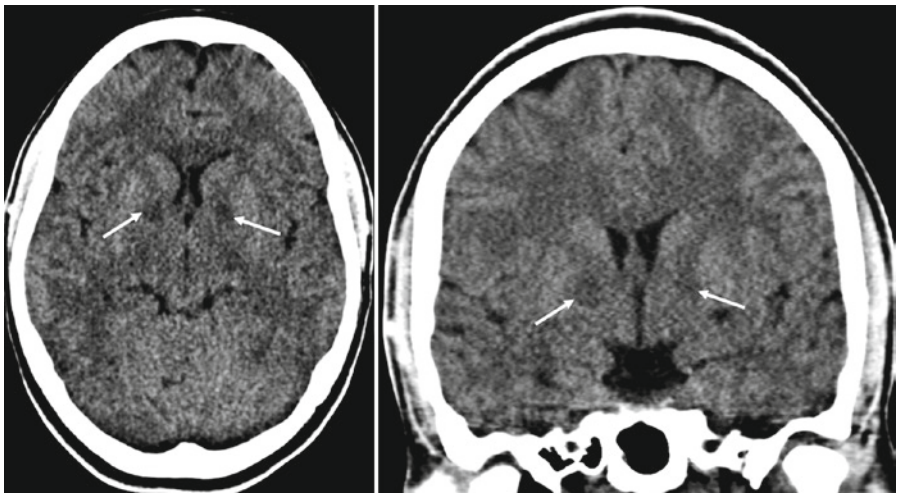

Fig. 7.27 A 21-year-old female fire victim who was found in a comatose state in her office. At the time of arrival the police was alerted by CO-alarm. The oxygen saturation at the emergency department was 65% and the percentage of HbCO was 32%. CT shows symmetric hypodense lesions in the globus pallidus (*arrows*) due to hypoxic grey matter damage

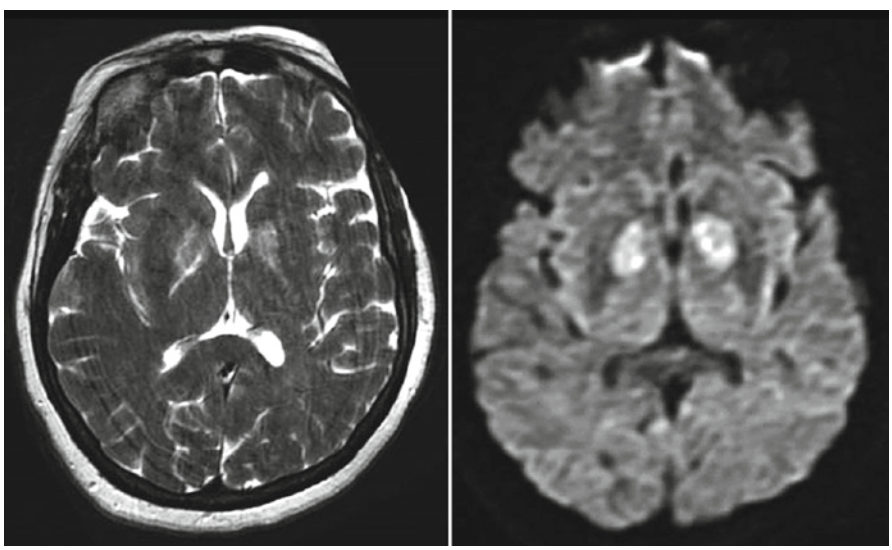

Fig. 7.28 A 51-year-old woman with drowsiness and instability that was diagnosed as accidental carbon monoxide poisoning caused by faulty domestic heating. (**a**) Axial T2-weighted image shows increased signal intensity of bilateral globus pallidi. (**b**) Corresponding diffusion-weighted image shows high signal due to restricted diffusion in bilateral globus pallidi. (Reprinted with permission from Pranshu Sharma, *Am J Roentgenol* 2009; 193: 879–886)

7.5.5 Delayed Post-hypoxic Demyelination

Synonyms
Delayed post-hypoxic leukoencephalopathy (DPHL), delayed anoxic leukoencephalopathy

Aetiology, Histopathology, Clinical Presentation and Treatment

Delayed post-hypoxic leukoencephalopathy (DPHL) develops typically 2–40 days after the initial hypoxic/anoxic event. Clinically, DPHL is characterised by cognitive deficits which are typically subcortical with problems of attention and speed of processing, frontal executive deficits are common – memory may appear to be affected but this may partly be due to the frontal and attentional problems. In addition, gait disturbance and hypo/akinetic motor syndromes are characteristic but psychotic syndromes, mutism, tremor, incontinence and speech disturbances can be observed. DPHL is connected to carbon oxide (CO) poisoning (see Sect. 7.5.4) since ~3% of patients with CO intoxication develop DPHL. DPHL is also frequently seen as a complication of drug overdose (heroin, benzodiazepine), surgical anaesthesia and cardiac arrest, etc.

The exact pathophysiologic mechanism is not completely understood. The reduced oxygenation of blood and oxygen delivery to the brain tissue probably results in a breakdown of ATP-dependent enzymatic pathways leading to demyelination. This is reflected in confluent areas of diffuse demyelination, particularly located in periventricular and subcortical deep white matter. The subcortical U-fibres and the infratentorial white matter are relatively spared.

Interestingly, only a subset of patients with the above risk factors will actually develop DPHL. The degree of hypoxia does not completely correspond to the risk of developing DPHL. Obviously, other markers must influence the clinical course and the severity of symptoms. Deficiency in arylsulphatase-A, an enzyme involved in the sulphatide metabolism, has been described to be a predisposing factor. A complete deficiency of arylsulphatase-A results in a metachromatic leukodystrophy, which is characterised by demyelination of the central and peripheral nervous system. An association between a partial deficiency of arylsulphatase-A and DPHL has been observed. However, a substantial number of patients developing DPHL have no impairment of arylsulphatase-A.

No proven treatment options exist. Recovery rates up to 75% have been reported but depend on the severity of the insult (Fig. 7.29).

Neuroimaging strategy and differential diagnosis in DPHL:
CT may be helpful as an initial imaging approach. MRI has a higher sensitivity and is the image modality of choice – no contrast material administration is necessary. Optional: ^{1}H-MRS, SPECT
CT: Confluent hypodense areas in periventricular and deep white matter In later stages, global cortical atrophy with ventricular enlargement is seen.

MRI findings:
- T2/FLAIR: diffuse/confluent hyperintensity in periventricular and deep white matter
  - Representing diffuse demyelination
- Subcortical U-fibres and white matter in the posterior fossa are spared
- No cavitation can be observed
- Generalised atrophy is a late finding
- DWI: restricted diffusion (up to 30 days after the anoxic/hypoxic event)
  - Much longer than in ischaemic stroke

^{1}H-MR spectroscopy: Low NAA and increased Cho in affected white matter; lactate mostly normal

Differential diagnosis:
- Toxic encephalopathy (heroin inhalation, inhalation of organic solvents)
- Chronic inflammatory disease (e.g. multiple sclerosis, PML)
- Metabolic diseases associated with demyelination (e.g. leukodystrophies)
- Radiation/chemotherapy-induced encephalopathy

7.5.6 Organic Solvent Inhalation

Synonyms
Organic solvents dementia, House Painter's dementia, toluene misuse

History

Organic solvents were introduced in the second half of the nineteenth century. The rapid increase of their use led to reports dealing with toxicity, in general, and neurotoxicity, in particular, in the 1920s. Organic solvents are a heterogeneous group of agents. Only a limited number of agents have been sufficiently tested for neurotoxic effects. Toluene (methyl-benzene) is one of the best investigated solvents in terms of toxicity and cognitive impairment.

Epidemiology, Clinical Presentation and Treatment

Organic solvent inhalation is a common form of substance abuse especially in children and young adults because of the low costs and easy availability. Besides substance abuse, chronic organic solvent inhalation may also result from occupational exposure in dry cleaning, aviation and chemical industries.

Organic solvents can be found in spray paint, paint thinner, pharmaceuticals, rubber, gasoline, varnishes and glue. Among the lipophilic organic solvents that might cause long-term damage, toluene is a frequently used industrial solvent which is a lipid soluble clear liquid aromatic hydrocarbon.

Acute intoxication states due to inhalation are characterised by transient symptoms including behavioural changes, euphoria, headache and ataxia.

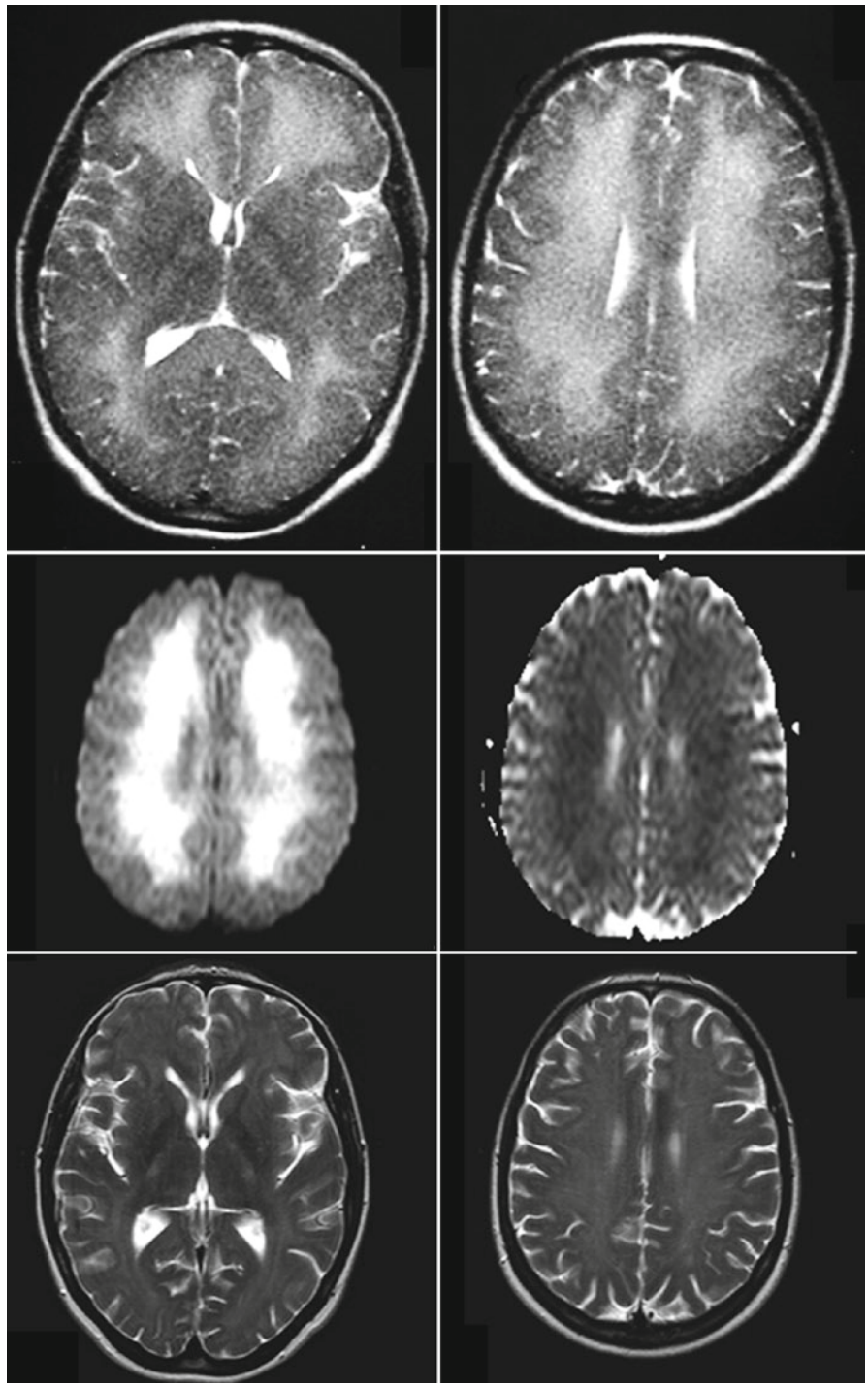

Fig. 7.29 Delayed post-hypoxic demyelination. A 40-year-old woman presented with a history of neurobehavioural disturbance beginning with confusion and decreased attention and distractability, progressing to include urinary and faecal incontinence. She had recently been resuscitated after an inadvertent overdose of morphine. On admission, there was massive swelling and T2 hyperintensity of the supratentorial white matter with sparing of the basal ganglia (*upper row*). She developed severe global cognitive impairment, with marked deficits in memory and verbal fluency. A second MRI after 3 weeks showed high signal on DWI due to restricted diffusion on the ADC map (*middle row*). Clinical improvement occurred with supportive care only. A third scan after 6 months showed almost complete normalisation of WM abnormalities (*bottom row*) without atrophy. This was mirrored by clinical improvement and she returned to work. (Reprinted with permission from Sophie Molley, *Am J Neuroradiol* 2006;1763–1765)

Persistent symptoms are usually related to chronic exposure. Cognitive deficits occur in 65–79% of patients with a history of chronic exposition to organic solvents. Patients may present with substantial cognitive impairment across many domains including learning and memory, visuo-spatial, attention/concentration, working memory, deficits in speed of information processing and executive abilities. Some patients

meet the criteria of dementia. Children or young adults show a significant decrease in IQ.

There probably is a relationship between the duration of solvent (toluene) abuse and degree of neuropsychological impairment as well as imaging findings in terms of white matter abnormalities (axonal damage and increased glial cell activity) measured by ^{1}H-MR spectroscopy. Clinical improvement may occur in patients with long-term abstinence. No other treatment options are available.

Aetiology and Histopathology

The histopathological mechanism of toluene-mediated damage to the CNS is not completely understood. Toluene enters the blood easily through the respiratory tract and reaches the brain tissue by passing the blood-brain barrier. Due its lipophilic nature, toluene has a high affinity to lipid-rich tissue components and therefore accumulates in the white matter, particularly in myelin. It is assumed that the storage of toluene in the white matter subsequently leads to activation of glial cells, demyelination and axonal damage. Of note, there is evidence that axonal pathology occurs independently from demyelination and that demyelination might occur secondary to axonal damage and loss. Neuropathologically, toluene-mediated brain damage is reflected by demyelination and gliosis mostly localised in the periventricular, subcortical and cerebellar white matter. Further neurodegenerative changes including a thinning of the corpus callosum, widening of the ventricles and atrophy of the brain and cerebellum can be observed in long-term toluene users.

Neuroimaging Strategy and Findings

CT may be an initial approach, but multi-sequence MRI (including T2-weighted sequences and DWI) is the image modality of choice (Fig. 7.30). Optional investigations include ^{1}H-MR spectroscopy, SPECT (see box on the next page). Neuroradiological changes are only observed in patients with chronic exposure to organic solvents. Neuroimaging studies in acute intoxications fail to show abnormalities.

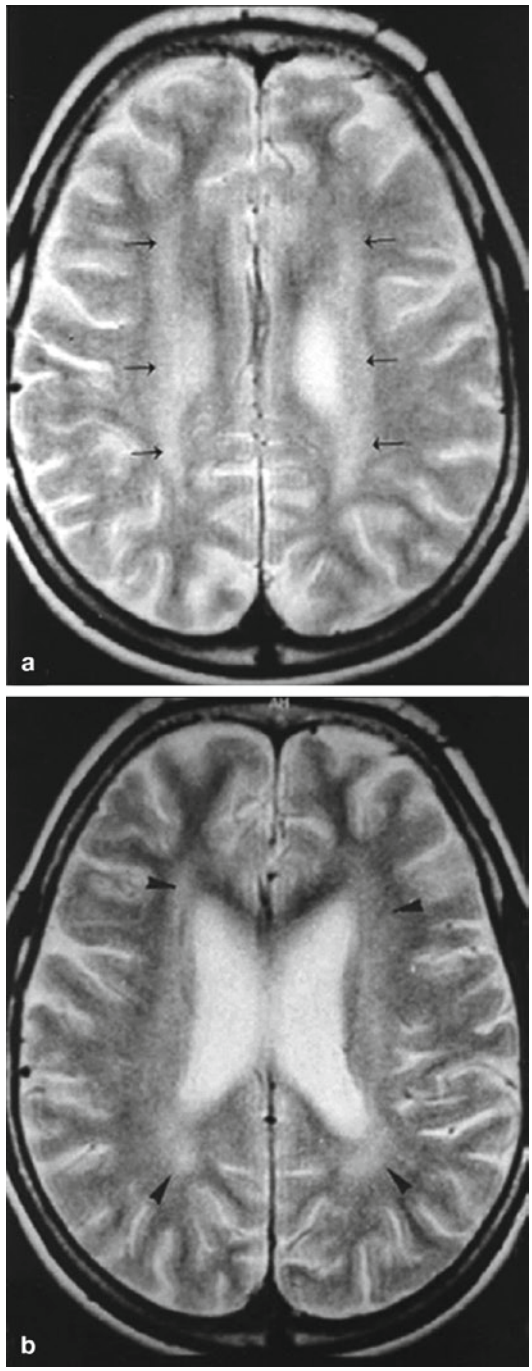

Fig. 7.30 Axial T2-weighted images in a 16-year old who had inhaled toluene for 6 years. (**a**) High signal intensity is seen in the centrum semi-ovale (*arrows*) on both sides. The peripheral cerebral white matter and grey matter–white matter differentiation are preserved. (**b**) High-signal-intensity changes involve the frontal and parietal periventricular white matter (*arrowheads*). Note that the lateral ventricles and cerebral sulci are enlarged. (With permission from Aydin et al., *AJNR* 2002)

Neuroimaging findings and differential diagnosis in Organic Solvent Disorders

CT may reveal global atrophy or areas of focal atrophy in the brain
- Particularly of the cerebellum, and brainstem
- Sulcal widening and ventricular dilatation
- Thinning of the corpus callosum (better seen on sagittal MRI)

MRI may reveal atrophy (as for CT) and white matter changes:
- Deep white matter, but particularly in the periventricular white matter
- Around the deep grey matter structures
- Decreased differentiation between the white matter–grey matter interface

Structural MRI abnormalities can be found in ~20–50% of patients with chronic toluene inhalation.

^{1}H-MR spectroscopy in the deep white matter, and cerebellum (but not in the thalamus):
- Low concentrations of NAA
- High concentrations of myo-inositol

indicating a combination of axonal damage and probable gliosis in the white matter

SPECT: Areas of low perfusion can be frequently (in up to 70% of cases) found in prefrontal, parietal and temporal brain regions.

Differential diagnosis:
Includes toxic, metabolic and infectious diseases with diffuse demyelination
- Delayed post-hypoxic demyelination
- Post-treatment demyelination (chemotherapy, radiation therapy)
- Osmotic demyelination syndrome
- CO-intoxication
- Post-hypoglycaemic encephalopathy

7.5.7 Heroin Vapour Inhalation

Synonyms
Heroin vapour inhalation-induced spongiform leukoencephalopathy, heroin-induced toxic leukoencephalopathy, 'chasing the dragon', 'chinesing', 'Chinese blowing'.

History

Inhalation of heated heroin or 'Chasing the dragon' gained popularity around 1950 in Hong Kong and more recently worldwide. Spongiform leukoencephalopathy related to heroin vapour inhalation was first described in 1982 in the Netherlands, when Wolters reported 47 patients with spongiform leukoencephalopathy due to inhalation of heroin pyrolysate. Since then, many similar reports and case series have been published.

Aetiology, Clinical Presentation and Treatment

Heroin powder (heroin pyrolysate) is usually heated on aluminium foil over a flame and the vapour is inhaled through a straw or pipe ('chasing the dragon'). The inhaled heroin is absorbed rapidly with high bioavailability and immediate central nervous effects. What is unclear is how and why damage to CNS structures (in particular oligodendrocytes and myelin) occurs in some cases. It has been suggested that toxicity may be related to additives/contaminants of heroin or to tin in the aluminium foil. However, no specific toxin has been definitively identified.

The clinical course is poorly defined. A latent period between exposure and manifestations of clinical symptoms ranges from several days to months. In general, clinical manifestations can be subdivided into three stages (see Table 7.4). The clinical course is variable and patients may remain in the initial or intermediate clinical stage. However, approximately 25% of the patients will enter the terminal stage, which is characterised by a mortality rate of up to 23%. There is no established treatment; and management is supportive aiming at preventing complications (e.g. aspiration pneumonia). In some case series experimental treatment with antioxidant therapy including coenzyme Q was associated with substantial improvement of symptoms.

Table 7.4 Clinical manifestations of heroin vapour inhalation-induced spongiform leukoencephalopathy

Initial stage	Speech problems (pseudobulbar), cerebellar ataxia, motor restlessness, apathy, bradyphrenia
Intermediate stage	Pyramidal signs (spastic paraparesis), extrapyramidal signs (tremor, choreathetoid movements, myoclonic jerks).
Final stage	Stretching spasms, hypotonic paresis, akinetic mutism, central pyrexia, death

Histopathology

Histopathologically, heroin-leukoencephalopathy involves spongiform degeneration of the white matter with vacuolisation of the myelin lamellae at the intraperiodic lines on electron microscopy. In addition, swelling of the mitochondria and a distension of the endoplasmatic reticulum is seen in oligodendrocytes.

Neuroimaging Strategy and Findings

In general, the imaging findings in patients with spongiform toxic leukoencephalopathy due to heroin vapour inhalation correlate well with the neuropathological findings. Hence, the pattern of involvement on structural neuroimaging is fairly specific for this leukoencephalopathy (Box 7.3). Imaging therefore may usefully point to the aetiology (heroin inhalation), which may not have been available (or not revealed) on history taking. CT is often used in the acute setting but may be normal in patients with mild manifestations. Multi-sequence MRI (including T2-weighted and /or FLAIR sequences) provides a higher sensitivity and represents the image modality of choice (Figs. 7.31 and 7.32). Optional image modalities: Diffusion-weighted imaging (DWI), ^{1}H-MR spectroscopy, SPECT, PET. Typical imaging findings and differential diagnosis and presented in Box 7.3.

7.6 Cognitive Dysfunction Associated with Cancer Therapy

Mike P. Wattjes

Synonyms, Abbreviations
Chemobrain, chemo fog syndrome, radiation-induced leukoencephalopathy, radiation necrosis

History

Compared to the effects of chemotherapy, the clinical consequences of radiotherapy for the CNS have been described several decades ago. Sheiline first described in 1977 a classification of different stages of radiation-induced encephalopathy which is still being used. Advances in cancer treatment, in particular the combination of different treatment modalities (chemo-,

Box 7.3 Neuroimaging findings and differential diagnosis in Heroin encephalopathy

CT and MRI findings
- CT may be normal in patients with only mild manifestations
- Confluent hypodense white matter changes suggestive of diffuse demyelination can be observed.
  - Infratentorial changes are located in the cerebellum, brain stem and cerebellar peduncles.
  - Supratentorial brain white matter confluent hypodense white matter lesions.
    - Posterior WM typically involving the posterior limb of the internal capsules.
    - The anterior limbs are classically spared.
- Deep GM structures, cortex and subcortical U-fibres are classically spared.
- Symmetric involvement of corticospinal tract, medial lemniscus and tractus solitarius (MRI).
- No disruption of the blood–brain barrier in terms of contrast enhancement can be observed.
- Findings on DWI may include increased diffusion (suggestive of vasogen oedema), but also decreased diffusion (due to vacuolisation and intracellular oedema).

Advanced neuroimaging
- ^{1}H – MR spectroscopy
  - Low NAA and choline in the affected areas indicating axonal damage
  - Increased levels of lactate reflecting abnormal energy metabolism
- SPECT: Low levels of perfusion can be observed bilaterally in the parietal and occipital cortex
- ^{18}F-FDG PET decreased uptake in the described affected white matter areas on MRI

Differential diagnosis
- Toxic encephalopathy due to other agents (e.g. inhalation of organic solvents)
- Chronic inflammatory disease (e.g. multiple sclerosis, PML)
- Metabolic diseases associated with demyelination (e.g. forms of leukodystrophy)
- Radiation-induced encephalopathy
- Chemotherapy-induced encephalopathy
- Post-hypoxic demyelination (e.g. due to carbon monoxide poisoning)
- Reversible posterior leukoencephalopathy syndrome (RPLS)

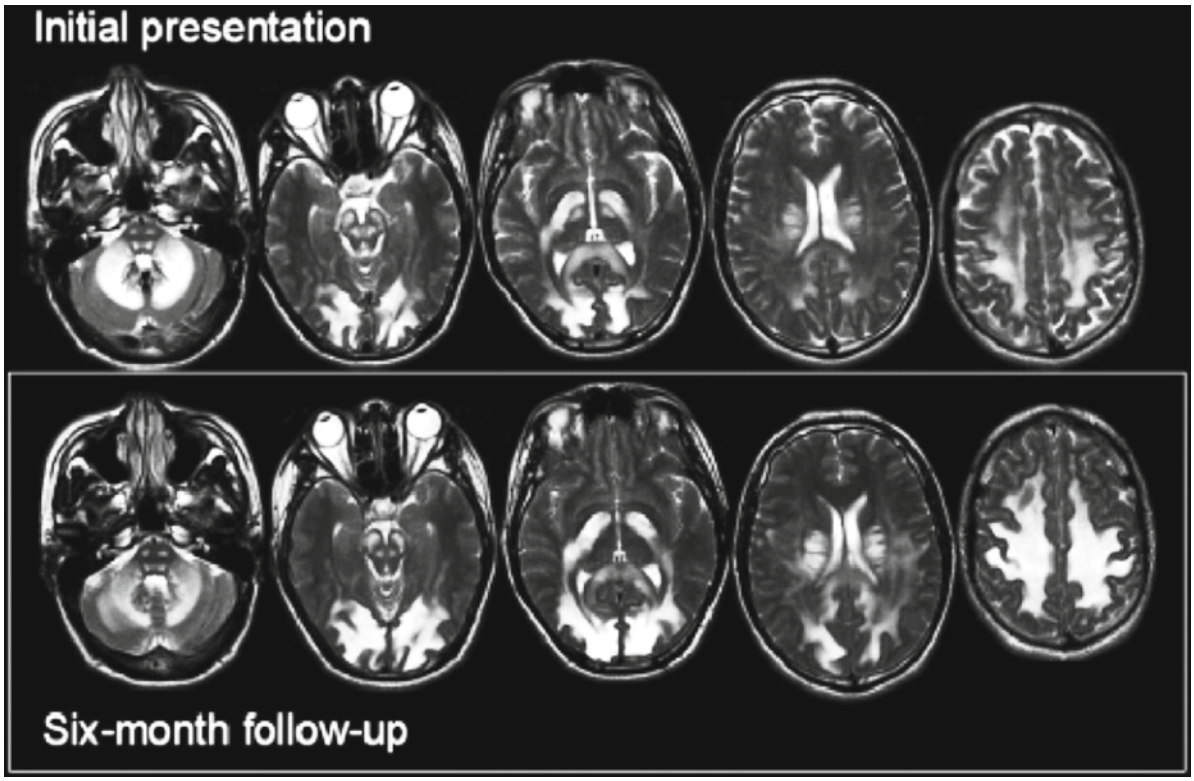

Fig. 7.31 Toxic leukoencephalopathy in 'chasing the dragon'. This 23-year-old HIV-negative male was admitted after a 2–3 week history of bilateral weakness, ataxia and dysarthria that progressed to an inability to speak. The patient later admitted to inhaling heroin vapour daily for the past 3 years. T2-weighted MR images at initial presentation (*above*) and at 6-month follow-up (*below*) show increased signal within the cerebellar white matter with some sparing of the dentate nuclei; involvement of the anterior horns (motor) of the brainstem grey matter and the corticospinal tracts; anterior thalami; posterior limb of the internal capsule, with sparing of the anterior limb; splenium of the corpus callosum; posterior corona radiata; and the white matter of the occipital, parietal, posterior-temporal and posterior-frontal lobes, with sparing of the sub-cortical white matter. (Reprinted with kind permission from *Br J Radiol* 2005;78:997–1004; Sophy Molloy, *AJNR* 2006)

hormone-, and radiotherapy), have led to further appreciation of the necessity to understand and investigate their accompanying toxic effects and clinical consequences.

Aetiology and Histophysiology

Radiotherapy

A combination and interaction of effects on different cell types (e.g. mature neurons, neural progenitor cells, oligodendrocytes and endothelial cells) is responsible for radiation-induced CNS damage, and may lead to cognitive decline. The degree and pattern of radiation-induced effects strongly depends on the time and dosage. The effect on oligodendroglia is characterised histopathologically by a time-dependent breakdown of myelin, apoptosis of oligodendroglial precursor cells and, finally, a loss of mature oligodendrocytes and myelin several months after the radiation exposure.

Radiation can have a dose-dependent direct effect on the function of mature neurons; more pronounced, however, are the effects on neural progenitor cells. These self-renewing cells are crucial for the neurogenesis (generation of neurons, astroglia, oligodendroglia, lineage-restricted precursor cells) in the post-natal and adult brain. This effect becomes most obvious in the hippocampus, where radiation can substantially decrease the production of neurons (Fig. 7.33). The decline in the neurogenic cell population after radiotherapy is probably the result of an

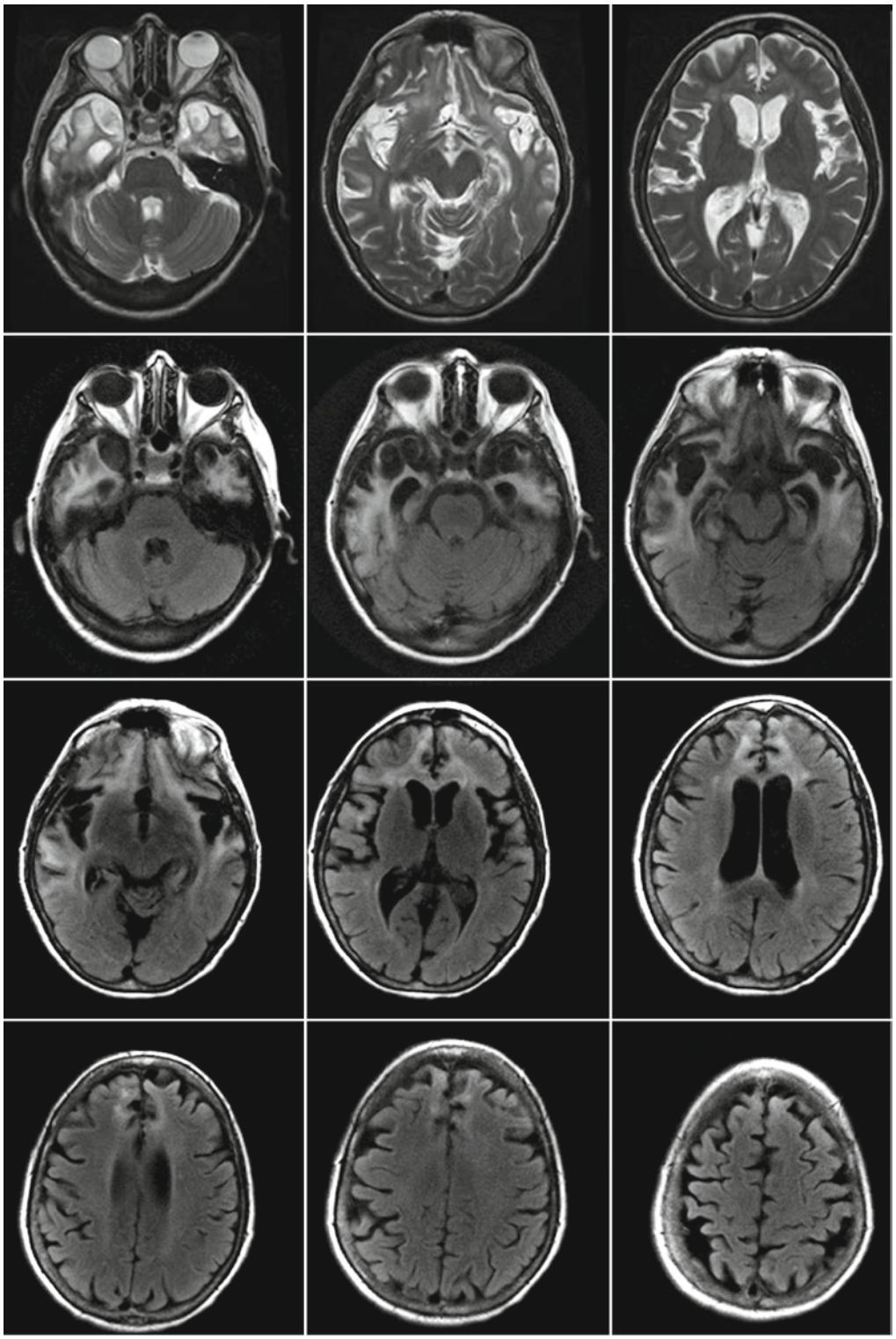

Fig. 7.32 Heroin intoxication. This 55-year-old lady with a vacuolising myelinopathy of the temporal lobes presented with dementia over the course of the last 4 years following extensive heroin inhalation approximately 10 years ago. She smoked heroin for more than 10 years on a regular basis. Images kindly provided by Timo Krings. Note high signal on T2-weighted (*top*) FLAIR (bottom three rows) images in the frontal and temporal lobes, with end-stage atrophy of the temporal lobes bilaterally, similar to FTLD

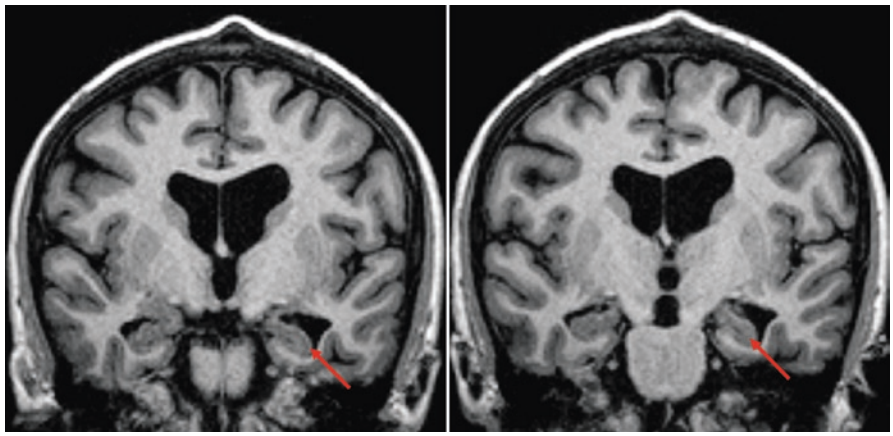

Fig. 7.33 Hippocampal atrophy after radiation therapy. This 31-year-old woman developed acute lymphoblastic leukaemia at the age of 14. She was treated with combination whole-brain radiation and chemotherapy (including vincristine, prednisone, l-asparaginase, 6-mercaptopurine methotrexate). She developed late neuropsychological deficits, including impairment of working memory, attention deficits, visual spatial deficits and impaired cognitive flexibility and eye-hand coordination. Her total IQ was 63 at time of MRI. Coronal T1-weighted images shows severe atrophy of especially the left hippocampus (*red arrows*), probably reflecting damage to neural progenitor cell population

impairment of proliferative activity in combination with direct cell damage (and death). The inhibition of neurogenesis is enhanced by changes in the neuronal microenvironment: radiation-induced microglial inflammatory reaction secondarily leading to neurovascular changes.

Time-dependent changes in blood-brain barrier permeability play a role in the pathophysiology of radiation-induced damage in the CNS. The early (transient) phase of blood-CNS barrier disruption is strongly associated with apoptosis of endothelial cells, which recovers within a few weeks. During the regeneration process endothelial proliferation occurs. The late (second) phase of blood-CNS permeability is associated with tissue necrosis, inflammatory reactions, vasogenic oedema and tissue hypoxia leading to cell damage and loss. This process is also referred to as radiation necrosis and occurs between 6 months and 10 years after therapy (see also Chapter 8.4.4).

Chemotherapy

The current pathophysiological concept of chemotherapy-induced damage is based on a variety of factors including direct vascular injury, oxidative damage, inflammation, autoimmune reactions, toxic neuronal injury, chemotherapy-induced systemic factors such as anaemia, and genetic factors (e.g. APOE-ε4 allele). The degree of neurotoxicity strongly depends on the type, dosage and combination of various chemotherapeutic agents. Due to toxic effects on vascular endothelial cells and release of free radicals, vascular damage occurs leading to alterations of cerebral blood flow, perfusion and metabolism. Chemotherapy-induced inflammatory responses are driven by cytokine-mediated cascades (including IL-1, IL-6, TNF-α) inducing glial cell activation with secondary axonal damage. Typical manifestations of this inflammatory process are vasculitis and allergic hypersensitivity responses. The direct neuronal injury is further characterised by an imbalance of neurotransmitters (particularly acetylcholine).

Chemotherapeutic agents may not only directly lead to neurotoxicity, but also indirectly by promoting conditions associated with cognitive decline, such as metabolic and hormonal abnormalities, anaemia, liver and renal dysfunction etc.

Combined Therapy

Combined therapeutic strategies including both chemotherapy and radiotherapy do have higher neurotoxic effects than single modality treatment (Fig. 7.34). The single pathological mechanisms are acting in a synergistic way but are also likely to interact with each other.

Clinical Presentation, Epidemiology and Treatment

Chemotherapy

The incidence of chemotherapy-induced cognitive dysfunction can reach up to 70%. The occurrence and severity of cognitive manifestations related to chemotherapy depends on different variables including the treatment protocol, patient's age, integrity of the blood-brain barrier, and the level of cognitive functioning before treatment. In general, chemotherapy broadly affects various domains of neuropsychological functioning including verbal and visual memory, mental flexibility, information processing, attention and concentration, visuo-spatial ability, language and motor function. Regarding memory function, patients may display impaired learning efficiency and problems with memory recall, due to damage in frontal and subcortical white matter networks (Fig. 7.35).

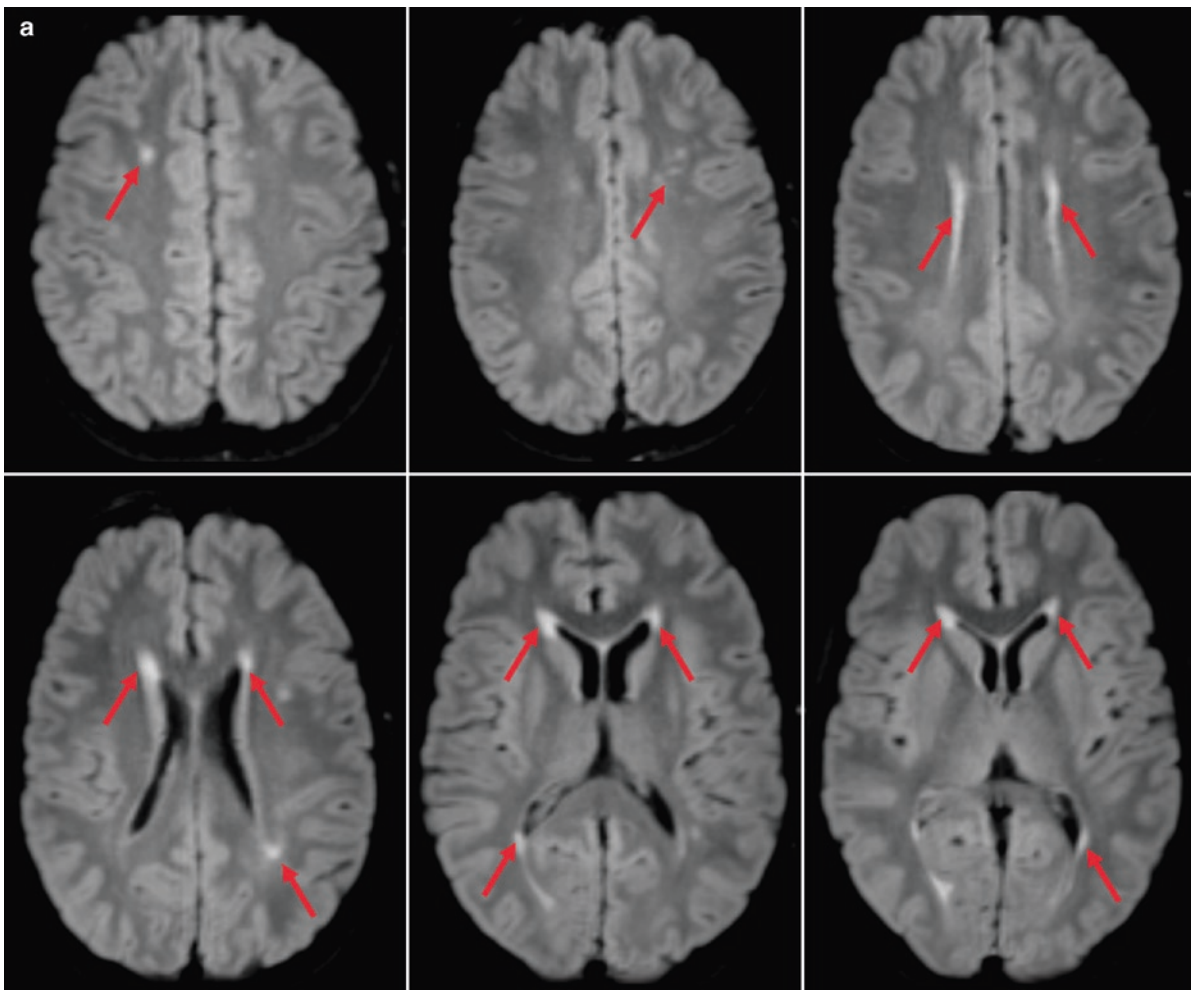

Fig. 7.34 Combined radio- and chemotherapy effects. This 31-year-old woman developed acute lymphoblastic leukaemia at the age of 13. She was treated with combination therapy of brain radiation and systemic and intrathecal chemotherapy (including vincristine, prednisone, l-asparaginase, 6-mercaptopurine methotrexate). She developed severe attention deficits (sustained attention) and impairment of cognitive flexibility. Axial FLAIR images (**a**) show focal WMH in the deep white matter and diffuse white matter changes in the periventricular white matter indicating treatment-induced leukoencephalopathy. Axial T2-weighted gradient-echo images (**b**) reveal microhaemorrhages (*arrows*) in the deep grey matter, neocortex, thalamus and white matter–grey matter junction, suggestive of radiation-induced vasculopathy (*continued on next page*)

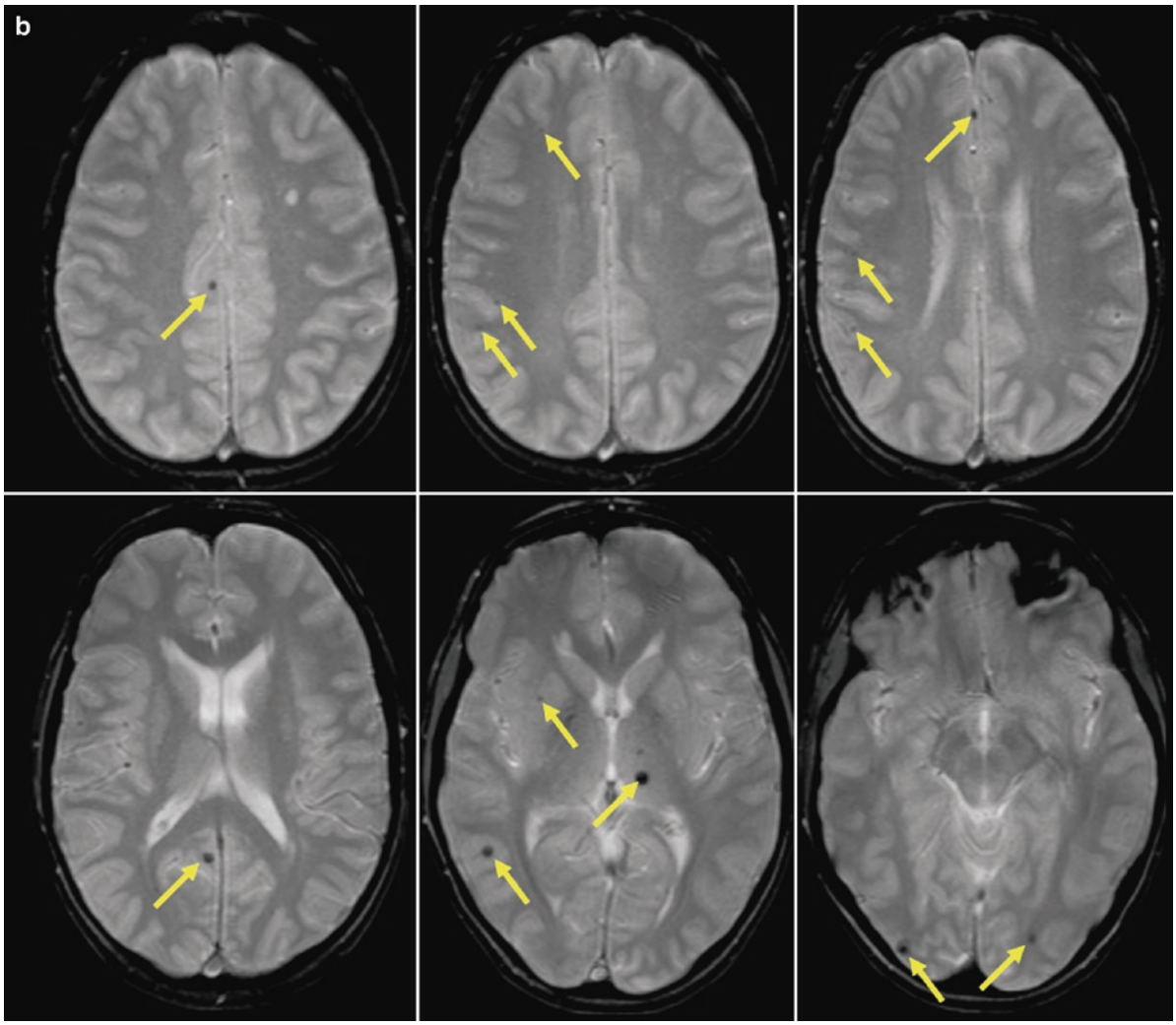

Fig. 7.34 (continued)

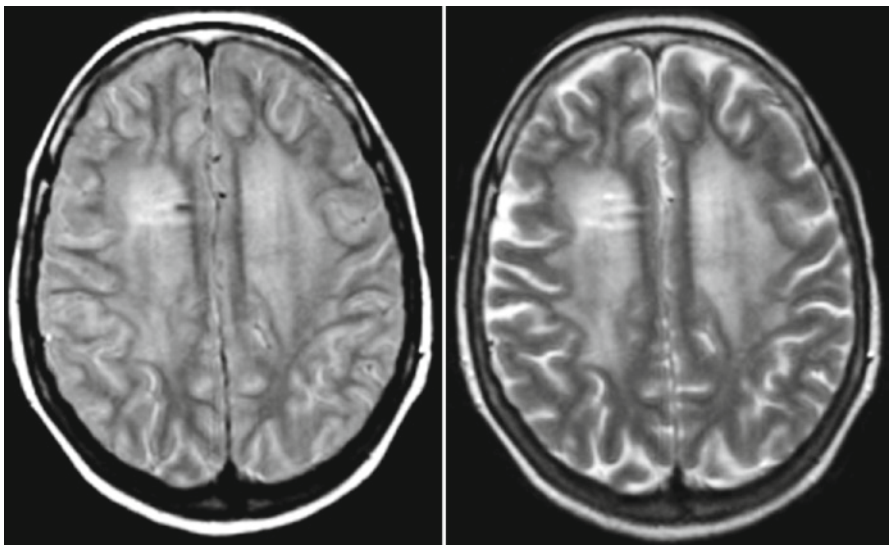

Fig. 7.35 Leukoencephalopathy after intrathecal methotrexate treatment. Note diffuse mild signal increase in white matter on proton-density-weighted (*left*) and heavily T2-weighted images, with sparing of the U-fibres

Due to the complex mechanisms and interactions of different chemotherapeutic agents no specific treatment exists. Current treatment strategies focus on antioxidant regiments such as vitamin E and the herb *Ginkgo biloba* in order to reduce the formation of free radicals. Other pharmacological interventions include recombinant human erythropoietin to increase the haemoglobin levels or use of the psychostimulant dexmethylphenidate to improve cognitive performance.

Radiotherapy

Cognitive impairment is one of the most common sequelae of radiotherapy in children and adults. The incidence can reach 86% and strongly depends on patient's age, dose per fraction, cumulative dose, target volume (Fig. 7.36), time interval, additional use of chemotherapy and co-morbidity (anaemia, renal failure, diabetes etc.). Radiation encephalopathy is traditionally subdivided into three different clinical stages: acute, early-delayed and late-delayed reaction:

1. During the *early stage* (first weeks) patients may remain asymptomatic or may develop self-limiting (sub) acute focal neurological deficits.
2. The *early-delayed stage* is characterised by somnolence, fatigue and symptoms of cognitive impairment suggestive of frontal network malfunction, with slowed information processing, decline in memory retrieval, attention deficits and decline in executive functioning.
3. The symptoms of *late-delayed* stage occur months to years after treatment and are linked to the hippocampus function. They are probably resulting from damage to neural progenitor cells. The main symptoms are impairment of memory function, attention deficits and visual motor processing. Most of the symptoms are irreversible or even progress over time.

Management of radiation encephalopathy (Fig. 7.37) includes treatment of oedema and increased intracranial pressure. No specific treatment of radiation-induced cognitive dysfunction exists. Several experimental in vivo studies focus on indometacin in order to repair the network of neurogenesis or try to use anti-inflammatory drugs and antioxidants.

Differential Diagnosis

The differential diagnosis should include the whole gamut of transient and/or persistent white matter changes associated with demyelination and gliosis such as post-hypoxic demyelination, metabolic disturbances, hereditary and inflammatory white matter diseases.

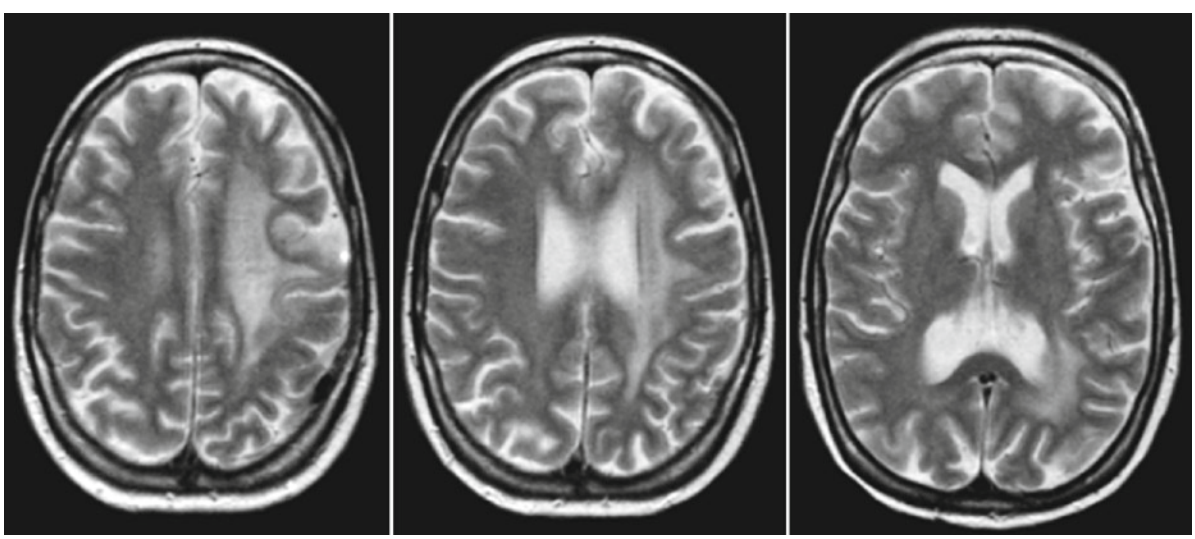

Fig. 7.36 Localised effects of radiotherapy. This patient was treated with radiotherapy applied to the left hemisphere only, resulting in unilateral diffuse leukoencephalopathy of the left hemispheric white matter, with sparing of the U-fibres

Neuroimaging Strategy and Findings after Chemotherapy and Radiotherapy

Neuroimaging should include a multi-sequence MRI protocol:

- Axial FLAIR: assessment of white matter changes and global and focal cortical atrophy
- Axial T2: assessment of infratentorial white matter changes and thalamic lesions
- Axial T2*: detection of vasculopathy in terms of microhaemorrhages/microbleeds
- Coronal 3D T1 with multi-planar reconstructions: evaluation of hippocampal structures
- Contrast-enhanced T1-weighted images: detection of blood–brain barrier disruption
- Optional: Diffusion-weighted imaging, MR perfusion, MR spectroscopy

Stage	*Chemotherapy*	*Radiotherapy*
Acute	Symmetric and focal or diffuse Deep and periventricular WMH Sparing the U-fibres, corpus Callosum, anterior commissure	Asymmetric, focal or diffuse Deep and periventricular WMH Sparing of U-fibres Initial phase: interstitial oedema, acute demyelination, transient disruption of the blood–brain barrier (contrast enhancement)
Early/late subacute	Contrast enhancement in necrotic areas ^{1}H-MRS: ↓ *tNAA* and ↑ *Choline*	Contrast enhancement and swelling (radionecrosis); Vasculopathy: microbleeds
Chronic	Global atrophy	Global *and* local atrophy (hippocampus) Secondary tumours (e.g. meningeoma) Cavernomas

Combined therapy

The combination of chemotherapy and radiotherapy can result in more severe manifestations in terms of acute changes (oedema) but also chronic white matter changes, vasculopathy, axonal damage and secondary neurodegeneration.

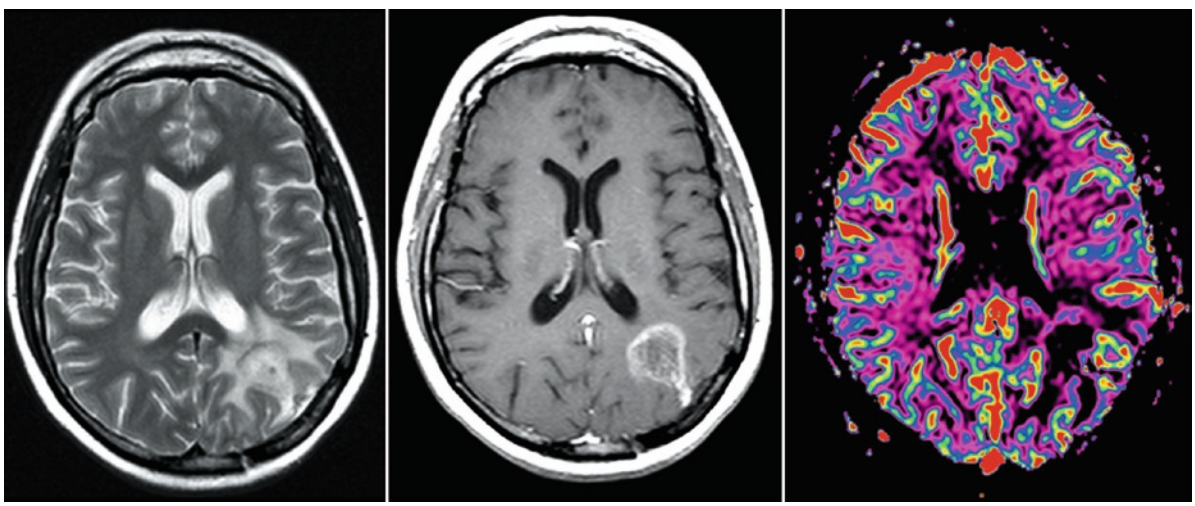

Fig. 7.37 Radiation necrosis. On the T2-weighted image (*left*), an area of oedema is seen, with central, partly patchy, enhancement after gadolinium administration (*middle*). Perfusion-weighted image (*right*) shows low CBV, consistent with the biopsy finding of radiation necrosis

7.7 Trauma

7.7.1 Dementia Associated with Traumatic Brain Injury

Mike P. Wattjes

Synonyms, Abbreviations
Traumatic brain injury (TBI), diffuse axonal injury (DAI)

History

The pathophysiological mechanism of traumatic brain injuries (TBI) has first been described in 1943 by Holbourn. Using 2D gelatine moulds he showed that rotational forces rather than linear and/or translational forces are causing shear injury in the brain, in particular at locations with substantial differences in tissue density.

Aetiology

TBI is caused by an outside force manifesting as a direct or indirect impact (coup or contre-coup) and/or acceleration leading to primary and secondary injury of the brain tissue. Diffuse axonal injury (DAI) in patients with TBI is a result of rapid rotational acceleration/deceleration of the brain due to unrestricted head movement. This results in shearing forces particularly occurring in areas of the brain containing tissues of different density such as the grey–white matter interface. The degree of injury depends on the distance from the centre of rotation, the arc of rotation and duration of the force.

Histophysiology

Following a traumatic event, acute neuronal pathology develops over a time interval of hours to days. The primary brain injury occurs in the acute trauma setting by stretching, compression and tearing the brain tissue and vascular structures. The subsequent axonal pathology is characterised by a damage of sodium channels in the cell membrane resulting in a pathological influx of sodium and subsequently increased intracellular calcium concentration leading to an activation of proteolytic activity and intracellular oedema. Neuronal/axonal swelling leads to elongated varicosities and bulb formation. Histopathologically, this results in 'retraction ball' formation at the terminal end of the axon followed by Wallerian degeneration and reactive gliotic changes and restructuring.

The concept of secondary brain injury is based on a complex interaction of inflammation, release of free radicals, excitotoxicity, oedema and changes in cerebral blood perfusion. It has been postulated that TBI may induce a molecular cascade of inflammation that leads to the formation of amyloid plaque formation. APOE-ε4, a protein which is involved in the transportation of produced β-amyloid peptide, seems to play a key role in this process. In fact, patients can show features of neurodegeneration and Alzheimer pathology after TBI in terms of an increase of *tau* and A-β-amyloid precursor protein levels in the CSF and amyloid-β plaque deposition in the temporal cortex. Another possibility is that TBI exhausts reserve capacities and thus lower the threshold for subsequent Alzheimer pathology to become manifest (stepping-stone theory), which could explain the association between brain trauma and AD.

Clinical Presentation, Epidemiology and Treatment

Traumatic Brain Injury

Cognitive impairment is one the most important and frequent long-term consequences of traumatic brain injury. The clinical outcome shows a relationship with the trauma severity and mechanism. In the acute trauma setting, patients can present with a wide range of symptoms ranging from focal cognitive deficits, amnesia to a vegetative state. At one year follow-up, patients with severe TBI frequently show slower information processing, decline of anterograde memory. However, also patients with mild to moderate TBI frequently present with cognitive complaints such as lack of concentration and memory deficits usually immediate after the traumatic event which usually recovers completely during short-term follow up. The manifestation of TBI is very heterogeneous. Depending on the localisation and severity of the traumatic lesions in the CNS (Fig. 7.38), different patterns of clinical manifestations

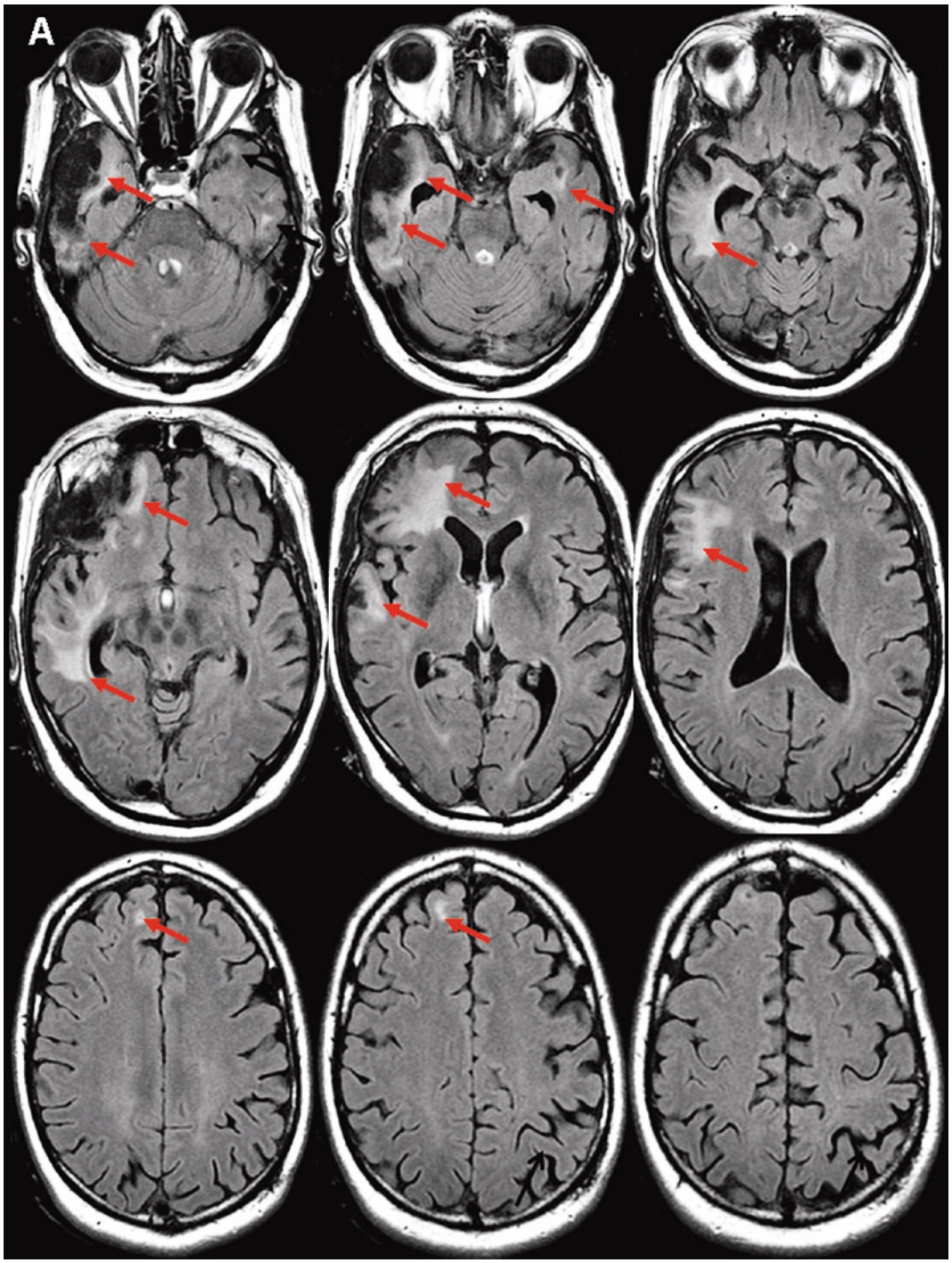

Fig. 7.38 Multifocal TBI and DAI. MRI images of a 57-year-old man who was involved in a car accident leading to a severe brain contusion. Subsequently he developed short term memory complaints and concentration deficits. The transverse FLAIR images (**a**) shows post-contusional changes in the right frontal en temporal lobe (including the medial temporal lobe) with focal loss of brain tissue (grey and white matter) and perifocal gliotic changes (*red arrows*). Please note also the slight asymmetry of the ventricles due to ex vacuo dilatation of the right lateral ventricle. This patient already presents with neurodegenerative changes of the brain suggestive of Alzheimer pathology on the coronal T1-weighted images (**b**) – disproportionate bilateral atrophy of the hippocampus (*white arrows*). Please not also the right temporal post-traumatic changes and the ex vacuo dilatation of the temporal horn. The susceptibility-weighted images (**c**) show haemosiderin deposits in the contusion area of the right frontal lobe but also microbleeds in the deep and juxtacortical white matter of the left parietal lobe (*red arrows*) indicating axonal injury grade 1 according to Adams classification (*continued on next page*)

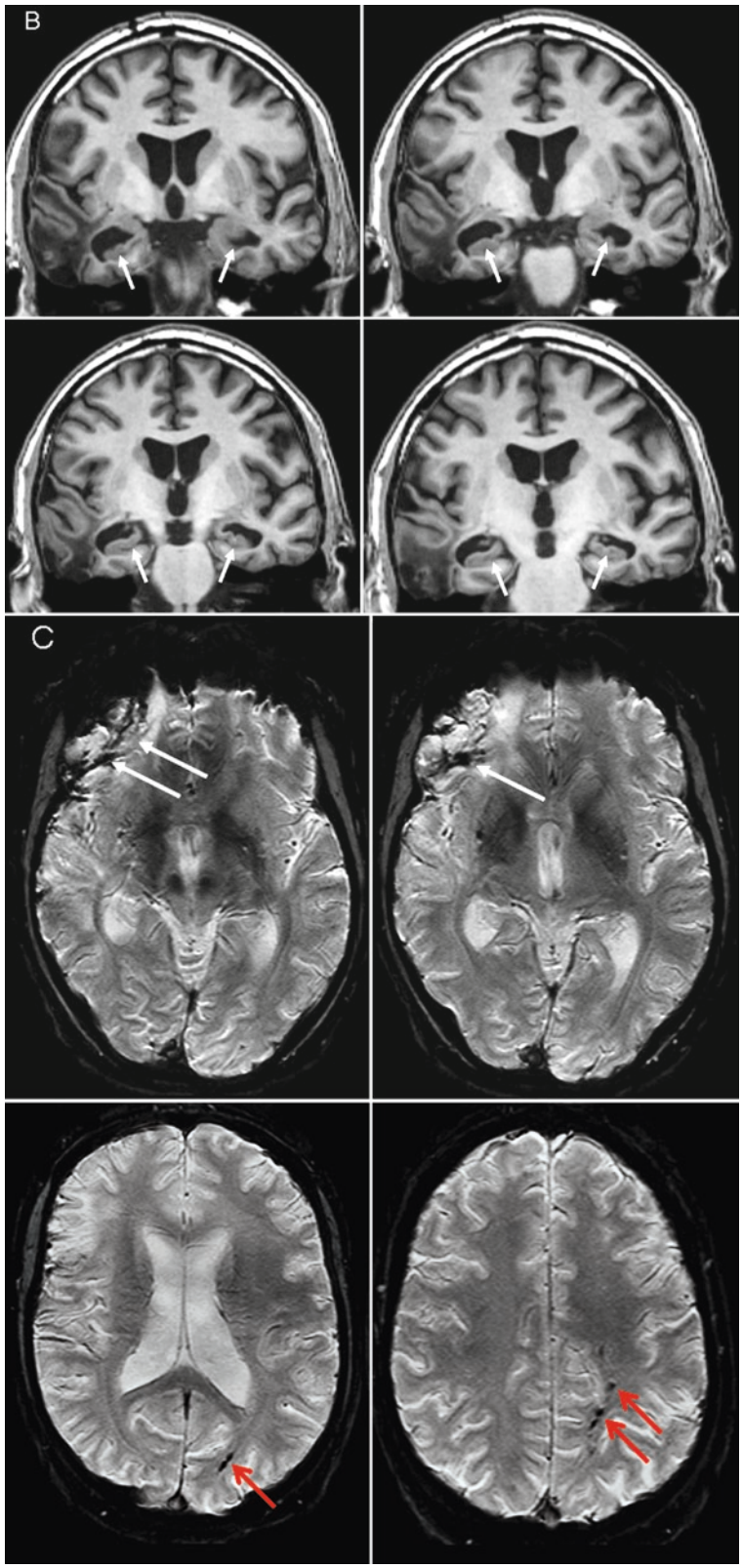

Fig. 7.38 continued (*see legend on previous page*)

can occur: *memory function* characterised by working memory impairment, *language* problems including fluent and non-fluent aphasia and high order language alterations and *executive functions*.

TBI in children can have even more consequences in term of clinical outcome and is therefore an important socio-economic issue (Fig. 7.39). TBI is a frequent cause of developmental disability involving intellectual, behavioural, attention, language and memory functions possibly leading to long-term cognitive impairment.

An association between chronic TBI and dementia showing neuropathological features of Alzheimer's disease referred to as the term *Dementia pugilistica* (see Sect. 7.7.2) has been reported. The crucial question whether TBI might increase the risk of developing dementia is still a matter of debate. Several retrospective and prospective studies have shown a positive association between a history of TBI and dementia (particularly AD) and have reported that TBI might be related to an earlier onset of dementia. However, the data of all performed studies are not completely conclusive since some other studies and meta-analysis failed to reproduce these findings. In addition, an effect of the APOE-ε4 allele on the clinical outcome in patients with TBI could not conclusively be demonstrated.

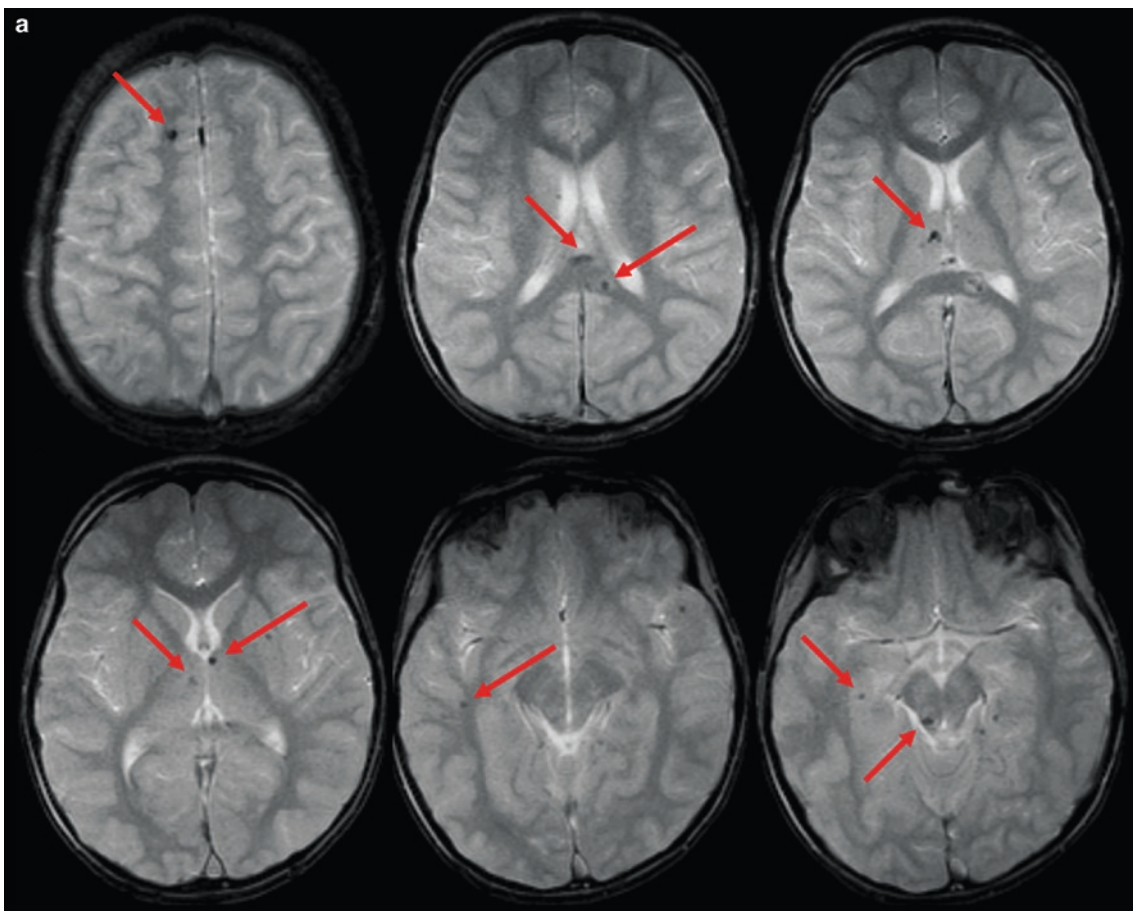

Fig. 7.39 Diffuse axonal injury (DAI). This 5 year-old child was involved in a car accident presenting with prolonged post-traumatic unconsciousness and a low Glasgow coma scale score. (**a**) Transverse T2* images show multiple focal hemorrhagic lesions (microbleeds) associated with DAI in typical anatomic locations such as in the grey–white matter junction of the supratentorial brain, the corpus callosum, the basal ganglia and the brain stem (*red arrows*). The distribution is consistent with grade 3 severity according to Adams classification. (**b**) Transverse T2-weighted turbo spin echo (*left*), DWI (*middle*) and corresponding AIDS dementia complex (ADC) map (*right*) demonstrate non-haemorrhagic lesions, with restricted diffusion due to intracellular oedema (*arrows*)

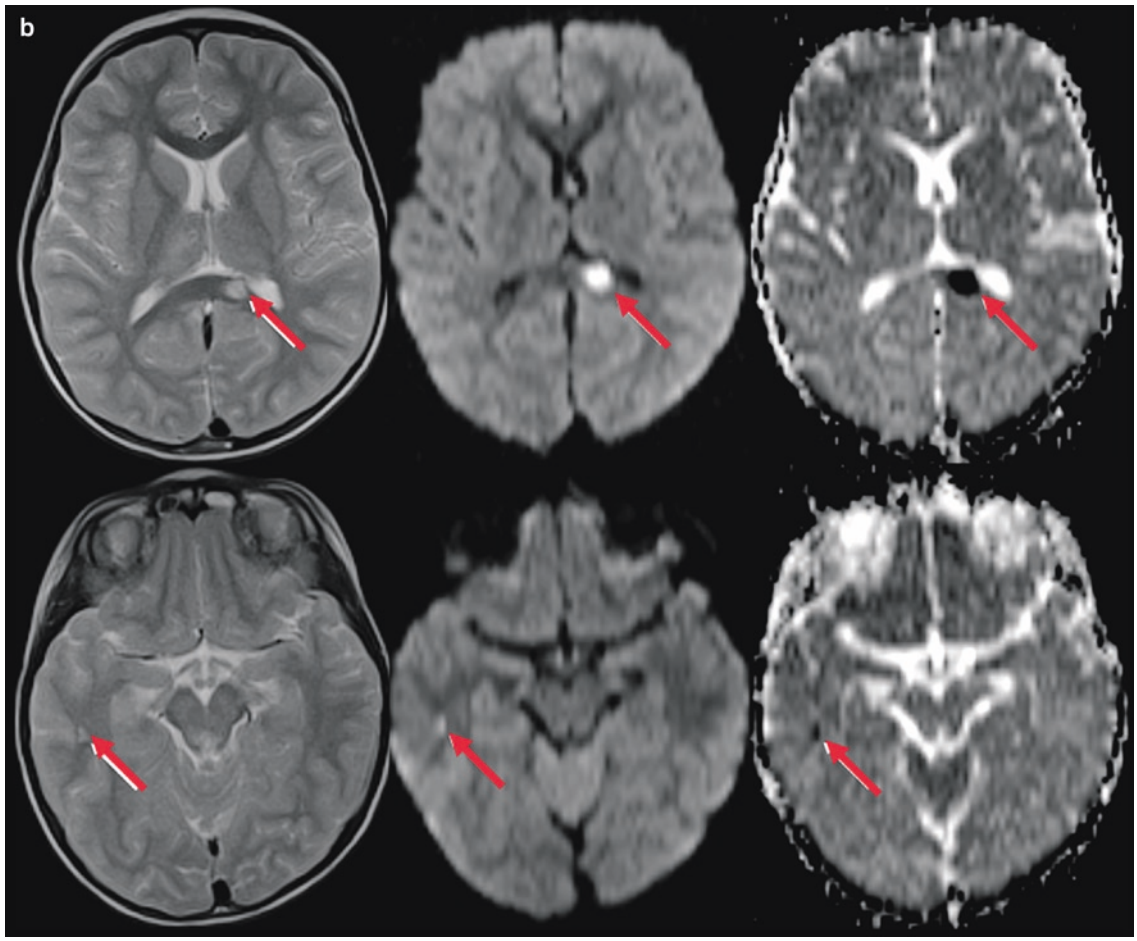

Fig. 7.39 continued (*see previous page for legend*)

Diffuse Axonal Injury (DAI)

A more severe manifestation of TBI is DAI, which is associated with a rather poor clinical outcome. DAI is one of the most frequent manifestations of rotational deceleration, classically resulting from high-speed motor vehicle accidents. Patients presenting with DAI can also show other traumatic changes of the central nervous system including epidural and subdural haematoma, traumatic subarachnoid haemorrhage and haemorrhagic brain contusion. However, DAI can occur independently from other traumatic lesions and be the sole traumatic manifestation in the brain.

In contrast to focal traumatic changes (e.g. epidural haematoma or cortical contusion) DAI does not always present clinically with focal neurological deficits or a lucid interval. Prolonged post-traumatic unconsciousness and coma are the most common clinical manifestation in patients with DAI. While rarely resulting in death, depending on the degree of involvement, DAI can result in a persistent vegetative state. Patients with TBI associated with DAI usually pass through an interval of global cognitive disturbance (post-traumatic amnesia) which potentially can recover. The clinical manifestation and prognosis correlates with the extent of involvement assessed by neuroimaging.

Anatomically, DAI most frequently occurs bilaterally in the supratentorial brain particularly at the grey-white matter junction, but also involving the corpus callosum, basal ganglia region (caudate nucleus thalamus, internal capsule) and the brain stem (mesencephalon) – see Fig. 7.39. The Adams classification recognises – according to the anatomic location – the following

three stages which has been used to classify DAI as mild, moderate or severe:

Stage 1. Supratentorial brain damage including the parasagittal regions of frontal lobes, periventricular temporal region, parietal and occipital lobes, internal capsule and cerebellum

Stage 2. In addition to stage 1, involvement of the corpus callosum

Stage 3. In addition to stage 2, involvement of the brain stem

The treatment of both common TBI and DAI includes established treatment schemes for TBI (stabilising the patient, treatment of increased intracranial pressure, neurosurgical treatment). However, TBI in general and DAI in particular currently lack specific treatment options.

Neuroimaging strategy and findings in TBI:

Acute setting
- CT: the image modality of choice
  - Spiral CT with multi-planar reconstructions (bone and soft tissue kernel)
  - Demonstrate haematoma and mass-effect
  - Cerebral contusions demarcate only after days
- MRI: if CT fails to explain clinical presentation
  - Imaging protocol: include FLAIR, T2*/SWI, DWI, T1-weighted images
  - T2*-weighted (microbleeds) and DWI (cytotoxic oedema) may reveal DAI
  - FLAIR and T2-weighted imaging for cortical contusion
  - T1-weighted imaging: detection of early subacute haemorrhage
- Cerebral hypoperfusion
  - HMPAO-SPECT and FDG PET: reduced perfusion/metabolism

Chronic setting
- Ventricular widening and communicating hydrocephalus (CT or MR)
- Focal cortical contusions with gliotic changes (esp. temporal and baso-frontal)
  - MRI (FLAIR) more sensitive than CT
  - MRI (T2*/SWI): detection of haemosiderine deposition
- Wallerian degeneration
  - Signal changes in the corticospinal tract
  - Hypertrophic degeneration of the olivary nuclei
- Neurodegenerative changes
  - Global cortical atrophy
  - Focal atrophy (particularly hippocampus) on coronal T1-weighted MRI
- DAI
  - Cerebral microbleeds only seen using T2*-weighted MRI
    - Differential diagnosis: CAA, cavernomata, vasculitis

7.7.2 Dementia Pugilistica

Synonyms
Chronic traumatic brain injury; post-traumatic Alzheimer's disease; chronic traumatic encephalopathy; chronic boxer's encephalopathy; traumatic boxer's encephalopathy; boxer's dementia; 'punch-drunk' syndrome

History and Histopathology

The repeated head trauma experienced by boxers can lead to the development of dementia pugilistica. The clinical symptom complex of this disorder was first described by Martland in 1928, and the neuropathology was first described in a classic report by Corsellis et al. in 1973. They describe the presence of numerous neurofibrillary tangles in the absence of plaques, in contrast to the profusion of tangles and plaques seen in AD. Later investigations found that there were diffuse plaques instead of neuritic plaques. Epidemiological studies have shown that head injury and ApoE 4 genotype are risk factors for AD. It is probable that dementia pugulistica and AD share common pathogenic mechanisms leading to tangle and plaque formation.

Clinical Presentation, Epidemiology and Treatment

Dementia pugulistica associated with boxing occurs in approximately 20% of professional boxers who suffered multiple concussions. Typical manifestations include problems with memory, or even dementia and Parkinsonism, or tremors and lack of coordination. Risk factors associated with chronic traumatic brain injury include increased exposure (i.e. duration of career, age of retirement, total number of bouts), poor performance, increased sparring and APOE genotype, notably the epsilon 4 allele. A recent report also demonstrated that dementia in retired boxers may be caused and/or exacerbated by other etiologic factors, such as multiple cerebral infarcts and Wernicke–Korsakoff syndrome. Clinically, boxers exhibiting dementia pugulistica will present with varying degrees of motor, cognitive and/or behavioural impairments. The diagnosis is dependent upon documenting a progressive neurological condition attributable to brain

trauma and unexplainable by an alternative pathophysiological process. There is no specific therapy.

Neuroimaging Strategy and Findings

The association between the finding of a cavum septi pellucidi and dementia in old boxers was first described by Ferguson and Mawdsley in 1965. Since then it has commonly been listed as one of the features of this condition ('born to box'). Fenestration of the septum pellucidum, with formation of a cavum, however, does not appear to correlate with neurological or physiological evidence of brain damage and should probably be classified as a chance finding, as documented in a large Swedish study. A number of imaging techniques have been used to investigate changes produced in the brain by boxing. The most commonly reported finding is diffuse cerebral atrophy with a non-specific pattern. Most morphological studies have failed to show significant correlations between putative abnormalities on imaging and clinical evidence of brain damage. Serial studies on large groups may be more informative but are not available to date. The link with AD, as denoted above, may lead to findings of bilateral hippocampal shrinkage.

Differential Diagnosis

Given that retired boxers are usually middle-aged and older, a comprehensive clinical and neuroimaging evaluation is necessary to exclude other causes of dementia. Actually, as the MRI findings are non-specific, a number of alternative diagnoses may be considered: Alzheimer's disease, Parkinson's disease with dementia, frontotemporal dementia being the most prevalent.

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