# A-Z of Neurological Practice

Second Edition

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**A Guide to Clinical Neurology**

Second Edition

Springer

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ISBN: 978-1-84882-993-0 e-ISBN: 978-1-84882-994-7
DOI: 10.1007/978-1-84882-994-7
Springer Dordrecht Heidelberg London New York

A catalogue record for this book is available from the British Library



First edition published in 2005 by Cambridge University Press, Cambridge, UK (ISBN 978-0-52162-960-8).



*Cover design:* eStudio Calamar, Figueres/Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

# Preface to the Second Edition

As with the first publication, the aim of this new, slimmer edition is to present information about neurological disorders in a structured and succinct way, following a "trickle down" principle: beginning with overviews and then moving on to specific disease categories. The latter address clinical features (i.e., information accessed by history-taking and physical examination), investigations, differential diagnosis, treatment, and prognosis. In this new edition, diagnostic criteria have been referenced where appropriate, but not included, both for fear of making the book too unwieldy and because this has already been done elsewhere.[1] Neurological signs are omitted and neuropsychology is not discussed in detail, since both these undertakings have been presented elsewhere.[2,3] Cross-references to the Online Mendelian Inheritance in Man (OMIM) database have been given where relevant.

George Orwell pointed out ("Why I write," 1946) that "writing a book is a horrible, exhausting struggle, like a long bout of some painful illness." It has sometimes seemed so with this book, but we hope that Orwell's other dictum, that "every book is a failure," does not prove entirely true and that our readers find something of use in these pages. We thank Manika Power at Springer for taking the book on, and for her unstinting encouragement in bringing it to fruition.

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1. Larner AJ. Diagnostic Criteria in Neurology. Totawa, NJ: Humana Press; 2006.
2. Larner AJ. A Dictionary of Neurological Signs. 3rd ed. New York: Springer; 2011.
3. Larner AJ. Neuropsychological Neurology: The Neurocognitive Impairments of Neurological Disorders. Cambridge, UK: Cambridge University Press; 2008.

# Contents

# A

## Abetalipoproteinemia [OMIM#200100]

### *Bassen–Kornzweig syndrome*

Bassen and Kornzweig first described the association of a progressive ataxic syndrome with fat malabsorption, atypical retinitis pigmentosa, and acanthocytosis with a lack of serum betalipoproteins in two siblings of consanguineous parents in the 1950s. Abetalipoproteinemia is a rare autosomal recessive condition characterized by the defective assembly and secretion of apolipoprotein-B-containing lipoproteins, which are required for secretion of plasma lipoproteins that contain apolipoprotein B. In consequence, there are very low plasma concentrations of cholesterol and triglyceride, and of fat-soluble vitamins, especially vitamin E, which produces the clinical features of peripheral neuropathy, retinitis pigmentosa, and cerebellar degeneration. The condition is caused by mutations in the gene coding for microsomal triglyceride transfer protein (MTP) on chromosome 4q22-24, a protein required for the assembly of lipoproteins which contain apolipoprotein B. A related condition, hypobetalipoproteinemia, is inherited in an autosomal dominant fashion, with a defect in the apolipoprotein-B gene in some cases, and in the homozygous state may be indistinguishable from abetalipoproteinemia.

### *Clinical features*

- Malabsorption: steatorrhea, with failure to thrive in children.
- Retinal degeneration: usually before the age of 10 years, with impaired night vision (nyctalopia) initially, and progressive retinitis pigmentosa; vitamin A deficiency may be significant. However, visual impairment is seldom severe.
- Peripheral neuropathy: a sensorimotor neuropathy with areflexia is often the presenting feature and is usually present by 10–30 years of age; vitamin E deficiency may be significant.
- Ataxic syndrome: with dysarthria, nystagmus, and head titubation. It results from a combination of peripheral neuropathy, spinocerebellar tract degeneration, and direct cerebellar damage (i.e., sensory and cerebellar ataxia); vitamin E deficiency may be significant.

A.J. Larner et al., *A-Z of Neurological Practice*,
DOI: 10.1007/978-1-84882-994-7_1,

- Dorsal column sensory loss and extensor plantar responses.
- Ophthalmoplegia in later stages.
- Skeletal abnormalities: pes cavus, scoliosis; may be secondary to the peripheral neuropathy.
- Subdural, retroperitoneal hemorrhages; excessive blood loss during surgery (vitamin K deficiency may be significant).
- No autonomic abnormalities, but cardiac involvement with cardiomegaly is found in the late stages of the disease.

## *Investigation*

Blood: low ESR; often a mild hemolytic anemia; acanthocytosis on blood film (which must be fresh to exclude false negatives), usually 50% or more of the red blood cells showing acanthocytic morphology; and low levels of apolipoprotein B (as demonstrated with immunoelectrophoresis), with very low plasma levels of chylomicrons, very low-, intermediate-, and low-density lipoproteins (VLDL, IDL, LDL). The plasma levels of cholesterol and triglycerides are very low, in the region of 1–2 and 0–1 mmol/L, respectively. The concentrations of fat-soluble vitamins, especially vitamin E, are also low. Neuroimaging (CT/MRI) shows no specific abnormalities. CSF is usually normal. Neurophysiology (EMG/NCS) shows peripheral sensorimotor neuropathy (axonal, demyelinating, or mixed); SSEPs may show abnormal posterior column function; VERs may be consistent with optic neuropathy; ERG may be consistent with retinal degeneration. Malabsorption tests may be required; jejunal biopsy reveals normal villi but the intestinal mucosal cells are vacuolated due to the presence of fat droplets that accumulate within them as they cannot be taken up by the chylomicrons.

## *Differential diagnosis*

- *Friedreich's ataxia*
- Vitamin E deficiency secondary to other malabsorption syndromes (e.g., *coeliac disease*, cystic fibrosis)
- Isolated vitamin E deficiency (*ataxia with vitamin E deficiency* [AVED])

## *Treatment and prognosis*

Treatment of the malabsorption syndrome is achieved by substitution and restriction of fat intake (i.e., low fat diet and medium chain triglycerides). Many of the neurological complications can be prevented by oral administration of vitamin E (1–10 g/day). Replacement of other fat-soluble vitamins (vitamins A, D, and K) is required. Untreated patients are usually

unable to stand or walk by the time they reach adolescence and rarely survive beyond the age of 40 years.

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Hardie RJ. Acanthocytosis and neurological impairment – a review. Q J Med. 1989; 71:291–306
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## Abscess: overview

An abscess is a focal suppurative process, which may occur within or adjacent to nervous tissue, with resultant neurological features as well as systemic disturbance (pyrexia) from infection.

- Cerebral abscess:
  - Focal suppuration within brain parenchyma may present with the symptoms and signs of a space-occupying lesion: headache, focal signs, impaired level of consciousness, and epileptic seizures. Fever is not universally present, so its absence should not rule out the diagnosis. Predisposing causes include penetrating head trauma, hematogenous spread (e.g., infective *endocarditis*), and immunosuppression (e.g., *HIV/AIDS*), but the most common cause is contiguous spread of infection, for example in the ear, paranasal sinuses, or teeth. Pulmonary fistulae in *hereditary hemorrhagic telangiectasia* (Osler–Weber–Rendu syndrome) predispose to cerebral abscesses. Fungal infections may also result in cerebral abscess formation (aspergillosis, blastomycosis, coccidioidomycosis, mucormycosis), as may filamentous bacteria (actinomycosis).
- Spinal cord abscess:
  - Abscess within the spinal cord is extremely rare; symptoms and signs are indistinguishable from epidural abscess.
- Epidural or extradural abscess:
  - These are located between dura and bone; they may be spinal or, less often, cranial.
    - Spinal: Spread of infection is from vertebral osteomyelitis or retroperitoneal, mediastinal, or paraspinal infection. Severe back +/– radicular pain; compressive spinal cord syndrome (myelopathy +/– radiculopathy) may develop (thoracic > lumbar > cervical), often with systemic features of infection. Bloods may show leucocytosis, elevated ESR. Plain radiographs may show narrowing of disc spaces and/or lytic changes but MRI is investigation of choice for visualization of abscess. CSF, which should

only be done if MR imaging shows there is spinal block, reveals raised white count (typically <100 cells/μl), raised protein, and normal glucose. Treatment is with surgical decompression with appropriate antibiotic cover: Staphylococcus aureus is the most common organism, but others include streptococci, enterobacteria, Mycobacterium tuberculosis, and various fungi and parasites. Prognosis is good if surgical intervention is early; delayed diagnosis is associated with a poor prognosis.

- Cranial: Almost always associated with an overlying osteomyelitis or local paranasal sinus infection. The features and management are similar to those of *subdural empyaema*. CSF may show pleocytosis (20–100 cells/μL) with normal glucose and protein. Treatment is with antibiotics; *Staphylococcus aureus* is the most commonly identified organism. Surgery has a place if there is significant mass effect or if an organism cannot be identified from peripheral cultures.

- Subdural abscess/empyaema:
  - These are located between dura and arachnoid. Spinal subdural abscess is clinically indistinguishable from epidural abscess.

**References**

Calfee DP, Wispelwey B. Brain abscess. Semin Neurol. 2000;20:353–360
Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. The rational use of antibiotics in the treatment of brain abscess. Br J Neurosurg 2000;14:525–530
Pradilla G, Ardila GP, Hsu W, Rigamonti D. Epidural abscesses of the CNS. Lancet Neurol. 2009;8:292–300

## Acanthamoeba

*Acanthamoeba* is one of the free-living amoebae, which, like *Naegleria*, may cause sporadic (primary amoebic) meningoencephalitis, spreading hematogenously from a cutaneous (skin ulcer) or pulmonary source, particularly in immunocompromised (e.g., *HIV/AIDS*, transplantation) patients. CSF shows pleocytosis; organisms are never cultured from CSF. Bacterial, fungal, and tuberculous meningitides could be considered in the differential diagnosis. Treatment with pentamidine is recommended and single cerebral *abscess* may be surgically removed. Mortality is very high.

**Reference**

Grunnert ML, Cannon GH, Kushner JP. Fulminant amebic meningoencephalitis due to *Acanthamoeba*. Neurology. 1981;31:174–177

## Aceruloplasminemia [OMIM#604290]

This rare, recessively inherited disorder, in which ceruloplasmin is absent from the plasma, is clinically similar to *Wilson's disease*, individuals presenting with cerebellar ataxia, dementia, and involuntary movements, although copper metabolism is normal. Diabetes mellitus may also be present. Iron deposition in the basal ganglia is thought to be the cause. Similar cases with raised serum ferritin (ceruloplasmin deficiency with hemosiderosis) are also reported from Japan. Oral iron chelation has been reported to improve symptoms.

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Logan JL, Harveyson KB, Wisdom GB, Hughes AE, Archbold GPR. Hereditary caeruloplasmin deficiency, dementia and diabetes mellitus. Q J Med. 1994; 87:663–670

Skidmore FM, Drago V, Foster P, et al. Aceruloplasminaemia with progressive atrophy without brain iron overload: treatment with oral chelation. J Neurol Neurosurg Psychiatry. 2008;79:467–470

## Achondroplasia [OMIM#100800]

### *Chondrodystrophy*

Achondroplasia is the most common form of bone dysplasia, inherited as an autosomal dominant condition, with an incidence of 1:25,000. Failure of normal endochondral bone formation, as a consequence of mutations in the fibroblast growth factor 3 gene, results in diminished vertebral body height and short stature. Such changes may be exacerbated with age due to further flattening and wedging of vertebral bodies, disc prolapse, and osteophyte formation. In 20–50% of cases, there are neurological complications, including the following:

Skull base compression with *hydrocephalus*, *syringomyelia*, +/– lower cranial nerve palsies, with myelopathy.

Spinal cord/root compression: can be anywhere, but typically in the cervicomedullary region (*foramen magnum syndrome*, causing progressive paraparesis or quadriparesis) or the cauda equina.

Respiratory disturbances, including *obstructive sleep apnea–hypopnea syndrome*.

Surgery for cord or root compression is often difficult due to the extent of the stenosis but seems to be most successful when done in young patients. However, in some cases decompression is ineffective and the stenosis continues to progress and is ultimately fatal.

**Reference**

Gordon N. The neurological complications of achondroplasia. Brain Dev. 2000;22:3–7

## Acromegaly

Pituitary disease, resulting in excessive secretion of growth hormone (hypersomatotropism) in adults, leads to acromegaly (*cf.* gigantism in children). This is a cause of secondary *diabetes mellitus*, so untreated acromegalics are at risk of all the potential neurological complications of diabetes. In addition, recognized neurological features of acromegaly include:

- Headache
- Acroparesthesia
- Visual disturbance (bitemporal hemianopia)
- Proximal myopathy (acromegalic myopathy; arthropathic > myopathic?)
- Thickening of the peripheral nerves +/– peripheral neuropathy (distal paresthesia, weakness, and areflexia, slowed nerve conduction velocities, soft tissue compression, nerve stretching?)
- *Carpal tunnel syndrome*
- Central sleep apnea syndrome

The myopathy may be accompanied by a raised creatine kinase, with myopathic features on EMG and muscle biopsy, variation in fiber size, type 2 fiber atrophy, and nonspecific increase in glycogen and lipofuscin on electron microscopy.

**References**

Khaleeli AA, Levy RD, Edwards RH, et al. The neuromuscular features of acromegaly: a clinical and pathological study. J Neurol Neurosurg Psychiatry. 1984;47:1009–1015
Woo CC. Neurological features of acromegaly: a review and report of two cases. J Manipulative Physiol Ther. 1988;11:314–321

## Actinomycosis

Actinomycosis is caused by various Gram-positive anaerobic or microaerophilic rods (filamentous bacteria) of the genus Actinomyces. The most common clinical manifestation is "lumpy jaw," cervicofacial abscess formation. Infection may spread to the brain by direct extension or hematogenous spread to cause cerebral *abscess*(es) and/or acute or chronic nonspecific *meningitis*. Organisms are seldom identified from the CSF, but culture from extraneural sites may be possible. Yellow exudates from cutaneous abscesses

contain "sulfur granules." Actinomycosis resembles *nocardiosis* as both may be a consequence of prolonged nonspecific immunosuppression; actinomycosis may occur, however, in immunocompetent patients.

**Reference**

Jacobson JR, Cloward RB. Actinomycosis of the central nervous system: a case of meningitis with recovery. JAMA. 1948;137:769–771

## Action myoclonus–renal failure syndrome (AMRF) [OMIM#254900]

Action myoclonus–renal failure syndrome is characterized by tremor, action myoclonus, cerebellar signs, epilepsy, and renal failure, with onset in teenage or the early twenties. It was initially reported in several French-Canadian kindreds in Quebec and presumed to be an autosomal recessive disorder. The neurological features do not seem to be related to renal failure per se in this condition, which is thought to result from an inherited metabolic defect.

### *Clinical features*

- Tremor of fingers, hands: onset age 17–18 years
- Proteinuria: onset age 17–18
- Action myoclonus: onset age 19–23; most disabling symptom
- Renal failure: onset age 20–22
- Cerebellar signs, ataxia, dysarthria: onset age 21–23; not severe
- Epilepsy (infrequent generalized seizures): onset age 21–23
- +/– Mild axonal degenerative neuropathy
- No extrapyramidal, pyramidal signs. Intelligence probably normal

### *Investigation*

Neuroimaging shows nonspecific cerebral or cerebellar atrophy. EEG may show spike wave complexes, slowing, and photoparoxysmal discharges. Brain pathology shows pigment granules in astrocytes. Renal biopsy shows a nonspecific nephritis.

### *Differential diagnosis*

Other causes of hereditary myoclonus, epilepsy, cerebellar syndrome, for example, sialidosis type I, neuronal ceroid lipofuscinosis (*Kuf's disease*), *neurodegeneration with brain iron accumulation*.

### *Treatment and prognosis*

Symptomatic treatment of myoclonus and epilepsy; renal dialysis +/– transplantation (no recurrence in transplanted organ).

**References**

Badhwar A, Berkovic SF, Dowling JP, et al. Action myoclonus-renal failure syndrome: characterization of a unique cerebro-renal disorder. Brain. 2004;127:2173–2182
Berkovic SF, Dibbens LM, Oshlack A, et al. Array-based gene discovery with three unrelated subjects shows SCARB2/LIMP-2 deficiency causes myoclonus epilepsy and glomerulosclerosis. Am J Hum Genet. 2008;82:673–684

## Acute disseminated encephalomyelitis (ADEM)

### *Acute hemorrhagic leukoencephalitis, acute necrotizing hemorrhagic encephalomyelitis, acute postinfectious encephalomyelitis (APEM), Hurst's disease*

Acute disseminated encephalomyelitis (ADEM) is a monophasic illness characterized by a meningitic and encephalomyelitic syndrome, usually following an infective illness or vaccination, with evidence of widespread demyelination within the CNS. In its less fulminant form, it may be difficult to distinguish from the first episode of *multiple sclerosis* (*MS*): because abnormalities in CSF, evoked potentials and MRI are similar in both conditions, continued follow-up may be the only way to make the distinction. ADEM typically occurs in children and young adults, is uncommon, and has a significant morbidity and mortality. Treatment with high-dose parenteral steroids is often tried, but is of unproven benefit.

### *Clinical features*

- ADEM is a clinical syndrome: there are currently no accepted diagnostic criteria.
- Preceding infection: measles, rubella, chickenpox; rarely mumps, influenza, *Mycoplasma pneumoniae*.
- Preceding vaccination: rabies, smallpox, rarely tetanus antitoxin.
- Prodromal phase: fever, malaise, myalgia.
- Rapid onset (hours, days) of:
  - Focal or multifocal signs and symptoms of white matter lesions: e.g., optic neuritis (may be bilateral), ataxia, and paraparesis (*transverse myelitis*) with varying degrees of bladder and bowel involvement.

- Focal cortical deficits (e.g., dysphasia, seizures, and hemiparesis) are more common in ADEM than in episodes of multiple sclerosis.
- Encephalopathy, ranging from confusion and somnolence to fits, stupor, and coma, may be seen in adults, but is more commonly seen in children.
- Meningism with headache, fever, and neck stiffness is classically associated with hemorrhagic ADEM.

## *Investigation*

Blood: usually unhelpful, but leukocytosis is not uncommon, especially in cases of acute necrotizing hemorrhagic encephalomyelitis, when there is also an elevated ESR. Neuroimaging: MRI demonstrates multifocal white matter lesions that are often more symmetric in their distribution, than those found in MS. As with MS the lesions enhance and persist, but in contrast with MS no new lesions develop beyond the time the disease typically evolves, which rarely extends beyond 2 weeks. New symptoms or signs, or new MRI lesions, appearing after 4 weeks from the start of the episode should be considered a second episode and raise the possibility of multiple sclerosis. Hence, interval scanning may help differentiate ADEM from MS. CSF usually shows increased protein and cells (lymphocytes) with a normal glucose concentration. This is most florid with the acute necrotizing hemorrhagic encephalomyelitis variant (which has all the same causes as the regular form of ADEM, although Mycoplasma is especially relevant) when there may be associated red blood cells in the CSF. Oligoclonal bands may be found, but usually do not persist; persistent oligoclonal bands are more suggestive of MS. Neurophysiology: evoked potentials and EEG may be abnormal, depending on extent and distribution of lesions. Pathology is rarely available. Perivascular inflammation with lymphocytes and mononuclear cells may be seen, with edema and microglial activation, and disseminated foci of demyelination throughout the brain and spinal cord centered on small- and medium-sized veins (peripheral nervous system spared). In its most severe form (acute hemorrhagic leukoencephalitis, Hurst's disease), there is necrosis of small blood vessels and brain tissue around the vessels; these lesions may coalesce and lead to almost complete hemorrhagic necrosis of whole hemispheres.

## *Differential diagnosis*

The major differential diagnosis is between ADEM and the first episode of MS. Other conditions that may enter the differential diagnosis include:

- Multiple emboli
- Viral encephalitis
- Granulomatous disease (e.g., *neurosarcoidosis*)
- *Vasculitis*

### *Treatment and prognosis*

Nearly 10–30% mortality rate; in the fulminant hemorrhagic form, death may occur in a few days. About 5% make a complete recovery, usually beginning within weeks. Recurrence may occur: multiphasic disseminated encephalomyelitis (MDEM). No treatment has been critically evaluated in ADEM, but there is some anecdotal evidence of benefit with intravenous methylprednisolone and plasmapharesis, with less compelling evidence for intravenous immunoglobulin. The development of more purified vaccines has greatly reduced the incidence of ADEM as a postvaccinial disorder. Rate of reclassification of ADEM as MS varies, but a recent large retrospective survey found that 35% of affected adults were reclassified as MS in 1 year.

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De Seze J, Debouverie M, Zephir H, et al. Acute fulminant demyelinating disease: a descriptive study of 60 patients. Arch Neurol. 2007;64:1426–1432
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Weinshenker B, O'Brien P, Petterson T, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46:878–886

## Adrenoleukodystrophy (X-ALD) [OMIM#300100]

### *Adrenomyeloneuropathy (AMN), Siemerling–Creutzfeldt disease*

X-linked adrenoleukodystrophy (X-ALD), the most common of the peroxisomal disorders, is characterized by a variable clinical phenotype, even within families, the spectrum of disease varying from an aggressive cerebral form of progressive demyelination with deafness, blindness, dementia, spasticity, as well as adrenal insufficiency, to an adult presentation (including carrier females) with a spastic paraparesis and a mild distal polyneuropathy, termed adrenomyeloneuropathy (AMN). X-ALD is due to mutations in a gene encoding a peroxisomal membrane protein ("ALD protein") that belongs to the ATP-binding cassette (ABC) protein family. This leads to accumulation of very long chain fatty acids (VLCFA) that characterizes the disease.

## *Clinical features*

Heterogeneity of expression is very common in X-ALD, including within families. It affects approximately 1:25,000 males.

- Childhood cerebral presentation: age of onset <10 years:
  - Progressive personality change and intellectual decline, leading to dementia.
  - Gait abnormalities that evolve into a spastic quadriparesis.
  - Development of hearing and visual impairments at a later stage, leading to deafness and blindness.
  - Epileptic seizures rare.
  - Adrenal insufficiency (hypotension, skin pigmentation) found in >90% of cases but to varying degrees, some clinically overt, some biochemical only. In 70–80% of cases, the neurological deficits precede the adrenal insufficiency.
  - Pathology is more inflammatory than in other varieties of leukodystrophy.
- Adolescent cerebral presentation: 10–21 years:
  - Same as for childhood presentation but with a slower or "stuttering" onset. Motor involvement and cortical blindness may be absent.
- Adrenomyeloneuropathy (AMN): age 28 ± 9 years:
  - Progressive spastic paraparesis
  - Mild distal polyneuropathy
  - Adrenal insufficiency
  - Hypogonadism
  - Perhaps 45% develop later cerebral involvement, including neuropsychiatric disturbances, typically schizophreniform psychosis; dementia occurs late and is slowly progressive.
- Adult cerebral: age >21 years:
  - Rapidly progressive cerebral disease, as in childhood form, without preceding AMN; dementia may be a presenting feature (rare).
- Addison's disease only; no neurological features.
- Asymptomatic: genetic abnormality only, without endocrine or neurological features.
- Female heterozygotes:
  - Twenty percent have an AMN-like illness of variable severity (mild spastic paraparesis to wheelchair bound); 1–3% develop dementia, behavioral disturbance, or visual failure.

## *Investigation*

Blood electrolytes, ACTH, and cortisol may demonstrate adrenal insufficiency. Very long chain fatty acids (VLCFA) are raised in serum, white cells,

or cultured fibroblasts (in particular, the C26:C22 ratio). Neurogenetic testing reveals mutations in an ATP-binding-cassette transporter gene; over 500 have been described. Neuroimaging: brain CT/MRI shows extensive white matter demyelination, predominantly parieto-occipital, with incomplete sparing of U-fibers; contrast enhancement at the advancing margin of demyelination is characteristic and may be predominantly posterior or anterior in distribution. MR spectroscopy shows reduced *N*-acetyl aspartate, increased choline. CSF may show nonspecific raised protein and increased cell counts. Neurophysiology (EMG/NCS) may show a demyelinating neuropathy.

## *Differential diagnosis*

Other *leukodystrophies*, especially *metachromatic leukodystrophy*, in adults. In adults, other conditions to consider include

- *Hereditary spastic paraplegia* (*HSP*)
- *Subacute combined degeneration of the cord*
- *Multiple sclerosis*
- CIDP with central demyelination

## *Treatment and prognosis*

Adrenal replacement therapy for adrenal insufficiency. Symptomatic treatments of spasticity.

Treatment of ALD per se:

- Dietary: Lorenzo's oil (a mixture of glycerol trioleate acid and trierucic acid in 4:1 ratio) normalizes plasma VLCFA, and if given early to asymptomatic boys, it reduces the risk of developing MRI abnormalities; its use may therefore be appropriate in asymptomatic boys with no MRI changes.
- Bone marrow transplantation: of no use in rapidly advancing disease, but may have a place in early disease to arrest, stabilize, and maybe even reverse early cerebral disease as measured by MR imaging and neuropsychology; no current indication in asymptomatic patients.
- Immunosuppressive therapy has no proven place.
- Gene therapy remains a hope.

Nearly two thirds of ALD patients escape the most severe phenotype.

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Moser HW, Raymond GV, Dubey P. Adrenoleukodystrophy: new approaches to a neurodegenerative disease. JAMA. 2005;294:3131–3134
Moser HW, Raymond GV, Lu SE, et al. Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. Arch Neurol. 2005;62:1073–1080
X-linked Adrenoleukodystrophy Database, www.x-ald/nl

## Albers–Schönberg disease

### *Osteopetrosis*

A condition characterized by increased bone density throughout the skeleton, which may occasionally lead to cranial nerve palsies or *hydrocephalus*.

## Alcohol and the nervous system: overview

Alcohol can have many effects on the central and peripheral nervous system. The pleasurable short-term effects are familiar to most people. However, adverse effects of alcohol consumption are common and may be classified as acute or chronic in nature. This distinction relates to the amount of and the period of time over which alcohol has been consumed. Many of the chronic complications of alcoholism are due to a combination of the toxic effects of alcohol coupled with the nutritional deficiencies commonly coexisting with excessive alcohol consumption (e.g., thiamine deficiency), along with some as yet unidentified genetic predisposition. Alcohol does not act at specific receptors but does appear to selectively stimulate chloride ion flux through the GABA/Barbiturate/Benzodiazepine receptor, with a particular anatomical preference for the brain stem.

Damage to the nervous system may possibly result from

- Direct toxic effects
- Oxidation to glutaraldehyde
- Nonoxidative metabolism to fatty-acid ethyl esters
- Malnutrition

Alcohol-induced pathology differs in different sites:

- Muscle: muscle fiber damage and myopathy, including an acute necrotizing myopathy (*rhabdomyolysis*) after an alcoholic binge
- Peripheral nerve/optic nerve: axonal loss (peripheral neuropathy; optic atrophy)
- Cerebellum: Purkinje cell loss, especially in anterior/superior vermis
- Cerebral hemispheres: cortical atrophy and possibly cholinergic deafferentation of cortex
- Brain stem: symmetrical pallor and hemorrhage around the third/fourth ventricles, aqueduct, and in the mammillary bodies and medial thalamus (*Wernicke–Korsakoff syndrome*)

### *Clinical features*

Not everyone who consumes excessive quantities of alcohol develops neurological complications. It is unclear why only certain individuals do, and why they should develop some of the neurological complications but not others.

- Alcohol intoxication:
  - Dependent on the plasma level of alcohol, although chronic consumption of alcohol leads to tolerance:
  - >5.4 mmol/L; mild intoxication: altered mood (usually excitement); impaired cognition and incoordination
  - >21.7 mmol/L; vestibular and cerebellar signs, autonomic dysfunction with hypotension and hypothermia, stupor, and eventually coma as the plasma level rises
  - >108.5 mmol/L; usually results in death from respiratory depression
  - In addition, heavy alcohol consumption over short periods of time may result in episodes of amnesia that cannot be accounted for by either a global depression of consciousness or coincident disorders, such as epileptic seizures.
- Alcohol withdrawal state:
  - Nausea, vomiting, perceptual difficulties, tremor, visual hallucinations, fits, delirium tremens (DTs). This latter condition is a severe confusional state that is usually seen within the first 4 days of stopping drinking alcohol, and usually lasts for 1–3 days. It consists of profound agitation, with insomnia, visual hallucinations and delusions, tremor, and autonomic hyperactivity. There may be associated hypophosphatemia.
- Nutritional deficiencies of the nervous system secondary to alcoholism:
  - Wernicke–Korsakoff syndrome (WKS): Wernicke's acute encephalopathy with (or without) ophthalmoplegia and ataxia precedes a chronic Korsakoff's syndrome, which is characterized by a profound anterograde and retrograde memory deficit, which may (or, more often, may not) be associated with confabulation. Thiamine deficiency is thought to be causative.
  - Pellagra.
  - Peripheral neuropathy: a painful axonal sensorimotor polyneuropathy.
  - Optic neuropathy (so-called tobacco– alcohol amblyopia): often occurs in association with heavy smoking. It presents with a painless bilateral visual loss that develops over weeks.
- Conditions of uncertain pathogenesis associated with excessive alcohol consumption:
  - Cerebellar degeneration: M > F, usually in association with peripheral neuropathy. It predominantly involves the rostral vermis, developing over weeks to years, and typically presents with walking difficulties secondary to truncal ataxia. Nystagmus, dysarthria, and intention tremor are uncommon. There may be some recovery on stopping the alcohol.
  - *Marchiafava–Bignami syndrome*: characterized by stupor, coma, fits, dementia, and emotional lability. Pathologically, there is demyelination,

predominantly of the corpus callosum. Said to affect, predominantly, drinkers of Italian Chianti, M > F.
  - *Central pontine and extrapontine myelinolysis (CPEPM)*: often correlated with rapid electrolyte changes associated with alcoholic liver disease. It typically presents with a rapidly progressive flaccid quadriparesis, with brain stem signs and bulbar failure.
  - Alcoholic myopathy and cardiomyopathy.
  - Alcoholic dementia (the differential diagnosis of cognitive decline in alcoholic patients includes traumatic subdural hematomas, which must actually be excluded, because they are potentially reversible).
  - Cerebral atrophy.
- Fetal alcohol syndrome (FAS):
  - Occurs in ~6% of alcoholic females. There is aberrant fetal neuronal and glial migration, with cerebellar dysplasia. Affected babies are microcephalic and have pre- and postnatal growth retardation, facial dysmorphology, neurological deficits, and other systemic abnormalities.
- Neurological disorders associated with alcoholic liver disease:
  - Hepatic encephalopathy.
  - Chronic hepatocerebral degeneration, or "non-Wilsonian hepatocerebral degeneration".
- Neurological disorders sometimes responsive to alcohol:
  - *Essential tremor*.
  - Alcohol-responsive *myoclonus–dystonia syndrome* (DYT11): autosomal dominant, starts early in life with combination of dystonia and myoclonic jerks; alcohol in small amounts affects dystonia to some extent but has a dramatic effect on the myoclonic jerks.

## *Treatment and prognosis*

Specific treatment depends on the particular syndrome, but general recommendations include

- Stop alcohol consumption in the context of an alcohol detoxification program.
- Treat with high-dose thiamine, initially intravenously, then orally.
- Replace any other vitamin deficiencies, normalize any electrolyte abnormalities (e.g., hyponatremia, hypophosphatemia) slowly.
- Check for any other treatable conditions (e.g., subdural hematoma).

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## Alexander's disease [OMIM#203450]

This rare disorder, classified with the *leukodystrophies* and first described in 1949, is typically a childhood condition characterized by megalencephaly, progressive neurological deterioration, and pathological findings of diffuse Rosenthal fiber formation. It has very rarely been described in adults. Autosomal dominant mutations in the gene encoding glial fibrillary acidic protein (GFAP) on chromosome 17 have been associated with the condition.

### *Clinical features*

- Infantile group: from birth to early childhood
  - Psychomotor retardation with failure to thrive.
  - Epileptic seizures.
  - Quadriparesis.
  - Megalencephaly: progressive head enlargement is a major (but not consistent) feature.
- Juvenile group: age 7–14 years
  - Progressive bulbar/pseudobulbar symptoms.
  - Spasticity.
  - Epileptic seizures and cognitive decline are less common.
- Adult group: age 20–60
  - Similar to juvenile group.
  - Occasionally present with a course resembling *multiple sclerosis*.
  - Occasionally asymptomatic.

### *Investigation*

Neuroimaging (CT/MRI) shows extensive white matter demyelination; large head in infants, may also have evidence of hydrocephalus; CSF usually normal; nonspecific protein elevation. Neurophysiology (EEG) may show some epileptiform features. Neurogenetic testing for mutations in the GFAP gene is diagnostic. This may supersede the need for brain biopsy: the pathological focus is in the white matter, with demyelination and morphological abnormalities in astrocytes, with the pathological hallmark of diffuse accumulation of Rosenthal fibers. These represent a gliotic reaction in which astrocytes appear to have been converted into hyalinized eosinophilic bodies. While not unique to Alexander's disease, Rosenthal fibers are characteristic of it, especially in the subependymal, subpial, and perivascular regions, more so in frontal white matter areas than occipitally. The later the onset of disease, the less severe is the demyelination.

### *Differential diagnosis*

Other leukodystrophies, especially Canavan's disease.

Enlarged head:

- Hydrocephalus (in juvenile cases)
- Canavan's disease
- Glutaric aciduria type I
- Gangliosidoses
- *Metachromatic leukodystrophy*
- *L-2-hydroxyglutaric acidemia*

### *Treatment and prognosis*

No specific treatment. Symptomatic measures for epilepsy, spasticity. The younger the onset, the worse the prognosis: survival in the infantile group is ~2.5 years; in the juvenile group, it is ~8 years.

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## Altitude illness

### *Acute Mountain Sickness, Chronic Mountain Sickness, Monge disease*

High altitude environments (i.e., greater than 5,300 ft) are characterized by a lower atmospheric partial pressure of oxygen and hence the risk of hypoxia in humans. All travelers to high altitude will experience varying degrees of acute mountain sickness (AMS), but only in a small percentage does this become life-threatening with acute pulmonary and/or cerebral edema. This most often occurs with rapid ascent to over 12,000 ft in unacclimatized individuals.

### *Clinical features*

- Acute mountain sickness (AMS):
  - Headache, insomnia, anorexia, nausea and dizziness; a syndrome of burning feet and burning hands is also described.
  - More serious manifestations: vomiting, dyspnea, muscle weakness, oliguria, peripheral edema and retinal hemorrhages; the latter may progress to visual

failure. In addition, the patient may develop ataxia, abnormal behavior, drowsiness, and hallucinations, which may progress to coma and death from severe pulmonary and cerebral edema.
  - Cerebral edema may first manifest with slight mental impairments or change in behavior, accompanied by headache, nausea, vomiting, and hallucinations, sometimes with epileptic seizures and ataxia, which may progress to coma and death.
  - Prolonged exposure to high altitude has been reported to cause some mild impairment of neurobehavioral function, especially memory.
- Chronic mountain sickness (Monge disease):
  - Pulmonary hypertension, cor pulmonale, and secondary polycythemia induced by hypoxia and the systemic effects of long-term habitation at high altitudes.
  - Neurological features may occur, such as mental slowness, fatigue, nocturnal headache, and sometimes papilledema.

### *Treatment and prognosis*

- Prevention:
  - Slow ascent with acclimization at around 6,000–8,000 ft.
  - Increased fluid intake; avoidance of alcohol.
  - Conditioning exercise before departure, especially if over 35 years old.
  - High carbohydrate, low fat, low salt diet.
  - Carbonic anhydrase inhibitors (acetazolamide or faster acting methazolamide), dexamethasone, and nifedipine have been shown to have a prophylactic role in AMS.
- Treatment:
  - In established cases, treatment is with supplemental oxygen, descent to lower altitude, and rest; dexamethasone is indicated in cases of cerebral edema.

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## Alzheimer's disease (AD)

### *Dementia of the Alzheimer type (DAT)*

Alzheimer's disease (AD) is a common neurodegenerative disease, first described by Alois Alzheimer in 1906. It characteristically affects the elderly

population and usually presents with episodic memory difficulties. Sporadic and familial cases are reported, the latter tending to occur earlier. As the disease progresses, there is increasing difficulty with memory, language, and orientation, leading to global impairment of cognitive faculties within 5–10 years from symptom onset. Death is usually from secondary causes such as bronchopneumonia. The neuropathological accompaniments of intellectual decline are

- Neurofibrillary tangles composed ultrastructurally of paired helical filaments, composed largely of the microtubule associated protein tau
- Plaques composed largely of amyloid protein, with various morphologies
- Dystrophic neurites containing paired helical filaments: surrounding some plaques, and in the cortical neuropil (neuropil threads, cortical neuritic dystrophy)
- Synaptic and neuronal loss

Abnormal cellular processing and subsequent aggregation of certain proteins may be the key pathophysiological process. The amyloid (cascade) hypothesis remains the most favored explanation of disease pathogenesis, largely because many of the genetic mutations identified as deterministic for AD (in the genes encoding amyloid precursor protein [OMIM#104300], presenilin 1 [OMIM#607822] and presenilin 2 [OMIM#606889]) lead to increased cellular production of the long variant (42–43 amino acids) of amyloid β-peptide (Aβ42) from its precursor molecule, amyloid precursor protein (APP). Apolipoprotein E (ApoE) genotype is a risk factor for the development of AD, the ε4/ε4 genotype carrying the greatest risk, although this is neither necessary nor sufficient for the development of AD. Extracellular amyloid brain burden is not sufficient to cause disease; disruption of intraneuronal cytoskeletal integrity leading to formation of neurofibrillary tangles and dystrophic neurites, with synapse loss and neuronal death, is also required for the development of dementia. Neurofibrillary pathology follows a predictable pattern of spread from transentorhinal cortex to neocortex. Gross atrophy of the cerebral cortex with extensive gliosis and neuronal cell loss, associated with atrophy of the cholinergic forebrain nuclei including the basal nucleus of Meynert, and cholinergic insufficiency is the end result.

## *Clinical features*

- Cognitive deficits: impairment of episodic memory is the most common presenting symptom, with relative preservation of working memory/sustained attention. It is advisable to obtain a history from other family members or carers, to help ascertain the nature, extent, and duration of the problems. The patient often makes light of difficulties or attempts to explain them away. Isolated amnesia, insufficient to fulfill diagnostic criteria for AD, may be labeled as mild cognitive impairment (MCI), a condition that may progress to AD.

- Cognitive deficits progress to involve other domains, e.g.,:
  - Language difficulties, including word finding and comprehension problems.
  - Visuospatial dysfunction: occasionally a presenting feature (*posterior cortical atrophy*, visual variant AD).
  - Dysexecutive syndrome.
- Impaired activities of daily living (ADL): initially operational (shopping, cooking, finances), but latterly basic (dressing, toileting, feeding).
- Behavioral features: depression may be common in the early stages, and it is sometimes difficult to differentiate cognitive deficits due to depression and dementia. Agitation, wandering, and psychosis may also occur. These are the features which most often lead to breakdown of care at home and necessitate institutionalization.
- Neurological features: there are no specific signs. Some patients develop extrapyramidal signs, but these are usually mild. Myoclonus and epileptic seizures may occur, with increasing frequency as the disease progresses and probably more common in familial than sporadic disease. A variant with spastic paraparesis associated with certain presenilin-1 gene mutations is described.

Clinical variants of AD that have been described include:

- Posterior cortical atrophy (PCA): patients present with progressive visual agnosia but with relative preservation of memory; may be associated with depression.
- Lewy body variant (LBV) of AD: this name has been applied to those patients with *dementia with Lewy bodies* (*DLB*), with additional pathology sufficient to meet standard pathological criteria for AD; this condition may be distinguished from "diffuse Lewy body disease" (DLBD), which lacks concomitant AD pathology.
- A frontal variant of AD (rare).
- *Mild cognitive impairment* (*MCI*) may in some instances be prodromal AD, especially the amnestic type of MCI.

Various forms of Familial AD (FAD) have been identified, and in certain cases deterministic genetic mutations identified:

- Mutations in the amyloid precursor protein (APP) gene on chromosome 21: rare families (ca. 25 worldwide) in which dominant mutations show complete penetrance by the age of 60, with most cases presenting from 30 to 60 years of age. (One of the amyloid angiopathies, hereditary cerebral hemorrhage with angiopathy, Dutch type [HCHWAD], also results from mutation within the APP gene.)
- Mutations in the presenilin-1 (PS-1) gene on chromosome 14, and in the presenilin-2 gene on chromosome 1: PS-1 mutations are the most common identified cause of FAD, over 170 different mutations are recorded. Mutations usually result in disease with the same age of onset within,

but not necessarily between, families; there are occasional cases of incomplete penetrance. These observations suggest a role for other genetic or epigenetic factors (but not ApoE). PS-1 FAD generally presents earlier and runs a more rapid course than sporadic cases of AD. In addition, myoclonus and epileptic seizures are more prominent than in sporadic AD.

- In trisomy 21 (*Down syndrome*), AD neuropathology usually develops before the age of 40 due to a gene dosage effect of APP.
- Polymorphisms in the gene encoding apolipoprotein E (ApoE) on chromosome 19 influence the risk of developing both sporadic and some familial AD (e.g., APP mutation families) in a dose-dependent manner; possession of two ApoE ε4 alleles increases risk by about eightfold; however, this is neither necessary nor sufficient for the development of AD. In contrast the ε2 allele may offer some protection against developing AD.

Other families have been described that do not map to any of the above loci.

## *Investigation*

Blood: usually all normal; should assay thyroid function, calcium, vitamin $B_{12}$, syphilis serology to identify potentially treatable causes of dementia (extremely rare). Neuropsychology is often helpful in defining the nature and extent of cognitive deficits. Earliest changes are typically in episodic memory, although some patients present with visuospatial problems. Difficulties in language and executive function also emerge with time. Often a global pattern of cognitive impairment is evident by the time of the patient's presentation. Islands of preserved ability may remain (e.g., reading, but without comprehension). Neuroimaging: Structural imaging (CT/MRI) may show cortical atrophy, but this may overlap with that seen in normal ageing. Longitudinal study of volumetric indices (e.g., hippocampal volume) may be helpful in showing progressive atrophy, but determining hippocampal volume on one-off standard clinical service MRI scans is rarely reliable. Functional imaging (SPECT/PET) changes may demonstrate hypoperfusion/hypometabolism in the parietotemporal regions. Magnetic resonance spectroscopy may show reductions in neuronal markers (*N*-acetyl-aspartate). CSF: regular indices are usually normal, but assay of tau protein (raised) and Aβ (lower) may be useful in diagnosis. Neurophysiology: EEG shows nonspecific changes only, such as slowing of background alpha rhythm; this may be helpful in distinction from *frontotemporal lobar degeneration*, where EEG remains largely normal. Pathological change remains the "gold standard" for diagnosis, but this is seldom present antemortem. Neurogenetic testing: for early onset AD with a family history suggestive of autosomal dominant transmission (= at least three affected individuals in at least two generations), searching for mutations in APP, PS-1, and PS-2 may be worthwhile.

## *Differential diagnosis*

- Normal aging
- *Mild cognitive impairment*
- Depression
- *Delirium*
- The differential diagnosis of *dementia* per se is broad; mixed pathology (AD + vascular change) is also common. *Vascular cognitive impairment*, *vascular dementia*

## *Treatment and prognosis*

Support and information for patients and families. Cholinesterase inhibitors, whose aim is to potentiate the central cholinergic network, are licensed for the symptomatic treatment of mild-to-moderate AD. Memantine, an antagonist at NMDA receptors, may also have a therapeutic effect. Behavioral features may require behavioral therapy and pharmacotherapy, although the latter may be associated with increased cerebrovascular mortality. Disease-modifying drugs are not yet available, but research into agents influencing amyloidogenesis and tau aggregation are ongoing. Institutionalization may eventually be necessary, often because of behavioral features or incontinence; early intervention may avoid the need for institutionalization. The disease is progressive and the median survival time from diagnosis to death is around 7–10 years.

### Diagnostic criteria

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