Published in final edited form as:

Handb Clin Neurol. 2018 ; 154: 129–149. doi:10.1016/B978-0-444-63956-1.00008-4.

The neuropathology of the adult cerebellum

ARNULF H. KOEPPEN*

Research, Neurology, and Pathology Services, Veterans Affairs Medical Center and Departments of Neurology and Pathology, Albany Medical College, Albany, NY, United States

Abstract

This chapter summarizes the neuropathologic features of nonneoplastic disorders of the adult cerebellum. Gait ataxia and extremity dysmetria are clinical manifestations of diseases that interrupt the complex cerebellar circuitry between the neurons of the cerebellar cortex, the cerebellar nuclei (especially the dentate nuclei), and the inferior olivary nuclei. The cerebellum is a prominent target of several sporadic and hereditary neurodegenerative diseases, including multiple system atrophy, spinocerebellar ataxia, and Friedreich ataxia. Purkinje cells display selective vulnerability to hypoxia but a surprising resistance to hypoglycemia. A classic toxin that damages the cerebellar cortex is methylmercury, but the most common injurious agent to Purkinje cells is ethanol. Many drugs cause ataxia, but doubts continue about phenytoin. Ischemic lesions of the cerebellum due to arterial thrombosis or embolism cause a spectrum of symptoms and signs, depending on the territory involved. Large hemorrhages have an unfavorable prognosis because they displace critical brainstem structures or penetrate into the fourth ventricle. Fungal infections and toxoplasmosis of the cerebellum, and cerebellar progressive multifocal leukoencephalopathy, have become rarer because of improved control of the acquired immunodeficiency syndrome. Ataxia is a prominent feature of prion disease. Adultonset Niemann–Pick type C1 disease and Kufs disease may have a predominantly ataxic clinical phenotype. The adult cerebellum is also vulnerable to several leukodystrophies. A rare but widely recognized complication of cancer is paraneoplastic cerebellar degeneration.

CEREBELLAR CIRCUITRY AND CLINICOANATOMIC CORRELATION

The motor abnormalities caused by the diseased cerebellum are ataxia and dysmetria (see Chapters 9 and 10), the former generally applied to gait disability, the latter to loss of coordinated extremity movements. Among the cerebellar nuclei, the main output stations of the cerebellum are the dentate nuclei (DN), and clinicians have known for a long time that dysmetria, dysarthria, and dysphagia due to lesions of the DN are more disabling than those due to damage of the cerebellar cortex. Magnetic resonance imaging now can visualize in vivo abnormalities of cerebellar gray and white matter in remarkable detail, and clinicoanatomic correlation has become very precise.

The study of cerebellar pathology must consider in particular the reciprocal circuitry that includes Purkinje cells and their corticonuclear connections, the neurons of the DN, the

*Correspondence to: Arnulf H. Koeppe, MD, Research Service (151), VA Medical Center, 113 Holland Avenue, Albany NY, 12208, United States. Tel: +1-518-626-6377, arnulf.koeppen@med.va.gov.

dentato-olivary fibers, the inferior olivary nuclei (ION), and the olivocerebellar (climbing) fibers (CF) (Koeppen et al., 2011). Figure 8.1 illustrates these way stations, and immunohistochemistry of glutamic acid decarboxylase (GAD) and vesicular glutamate transporters 1 and 2 (VGluT1, VGluT2) also allows the identification of inhibitory and excitatory transmission. The dendritic tree of Purkinje cells consisting of primary and secondary branches and spiny branchlets (Fig. 8.1A) receives abundant input from glutamatergic parallel fibers that originate from granule cells (Fig. 8.1D). This excitatory input is modified by inhibitory synapses arising from surrounding stellate and basket cells (Fig. 8.1A and B) that use g-aminobutyric acid (GABA) as their transmitter. The well-known terminal baskets about Purkinje cells are also GABAergic (Fig. 8.1B). Purkinje cells themselves display pale GAD reaction product (Fig. 8.1B) as an indicator of their inhibitory GABAergic function on the DN (Fig. 8.1F). The availability of antibodies to VGluT1 and VGluT2 has made it possible to study glutamatergic fibers in the molecular layer that arise from granule cells (Fig. 8.1D) and as CF originating from the ION (Fig. 8.1C). VGluT1 and VGluT2 reaction products are also good markers of mossy fiber terminals in the granular layer Fig. 8.1C and D).

The DN contains large, intermediate-size, and small neurons (Fig. 8.1E). Small neurons are GAD-reactive (Fig. 8.1F), though the DN also contains small glycinergic nerve cells (Koeppen et al., 2015). The small GABAergic neurons in the DN provide most, if not all, GABAergic input to the ION (Fig. 8.1H). The organization of the ION includes interdigitating dendrites (Fig. 8.1G) that receive synaptic clusters and form gap junctions (King, 1980). GABAergic terminals mirror the elaborate spherical dendritic expanse of ION neurons. Glutamatergic CF arising from the ION bypass the granular layer, ascend to Purkinje cells, and establish synaptic connections with the proximal dendrites on the contralateral side, thus closing the circuit (Fig. 8.1C). CF also send sparse collaterals to the nerve cells of the DN (Koeppen et al., 2011). In addition to the described principal participants in the circuitry, cerebellar cortical physiology utilizes intrinsic neurons, such as the inhibitory Golgi neurons and their GABAergic axonal plexuses (Fig. 8.1B), and several other “nontraditional” nerve cells in the granular layer (Ambrosi et al., 2007; Mugnaini et al., 2015).

SPORADIC AND HEREDITARY ATROPHY OF THE CEREBELLUM

Multiple system atrophy (MSA)

For the clinical practice of neurology, MSA remains a sporadic disease, but it is important to rule out dominant ataxias that share the morphologic phenotype of “olivo-pontocerebellar atrophy” by taking a family history, and, in selected cases, obtaining genetic testing. Patients with MSA may show slow saccades that strongly resemble a similar disturbance in spinocerebellar ataxia (SCA) types 2 and 7. A consensus conference in 2008 defined two categories of MSA based on the predominance of parkinsonian (MSA-P) or cerebellar signs (MSA-C) (Gilman et al., 2008).

In the clinical experience of the author, MSA progresses rapidly, and neuropathologic examination shows lesions in all structures that are the pathologic substrates of parkinsonism and ataxia. They include severe atrophy of the substantia nigra, the posterolateral putamen,

the basis pontis, and the cerebellar cortex (Fig. 8.2A and B). Neurons of the DN are often well preserved (Fig. 8.2C, inset), but GABAergic afferents are sparse (Fig. 8.2C). The ION displays the expected retrograde atrophy that is commensurate with Purkinje cell loss (Fig. 8.2D). The glial response in the ION is of small-cell type, which is consistent with retrograde degeneration. A hallmark of the disease is the presence of ubiquitin- and α -synuclein-reactive glial cytoplasmic inclusions (gci) (Fig. 8.2E and F, respectively). It is peculiar that gci are more readily found in the white matter of the basis pontis, the cerebral peduncles, and the internal capsule. While neurons may also display inclusion bodies, their presence does not explain the damage of the cerebellar cortex (Fig. 8.2B). The immunoreactivity of gci with antibodies to α -synuclein has prompted the assignment of MSA to the “synucleinopathies,” and the disease may involve a prion-like spread of α -synuclein aggregates (Jellinger and Wenning, 2016). Protein aggregation in gci involves multiple other proteins, and α -synuclein constitutes only 11.7% of the total protein (McCormack et al., 2016).

Spinocerebellar ataxia

The diagnosis of SCA now generally implies autosomal dominant transmission. The number of defined SCA has surpassed 40, and the Neuromuscular Center of Washington University, St. Louis, MO, United States, maintains a comprehensive list (2016) of names, clinical features, and mutations. Dentatorubropallidoluysian atrophy (OMIM 125370) is on the list of SCA, but because of its rarity outside Japan (Dubourg et al., 1995), the disorder will not be described in this review of the neuropathology in SCA. SCA-1 (OMIM 164400), SCA-2 (OMIM 183090), SCA-3 (Machado-Joseph disease) (OMIM 109150), SCA-6 (OMIM 183086), SCA-7 (OMIM 164500), and SCA-17 (OMIM 607136) are caused by pathogenic cytosine-adenine-guanine (CAG) trinucleotide repeat expansions in coding regions of their respective genes. SCA-12 is also due to a CAG trinucleotide repeat expansion, but the mutation is noncoding. Coding CAG trinucleotide repeat expansions generate abnormally long polyglutamine stretches that can be detected on Western blots of proteins extracted from frozen tissues. It is for this reason that the CAG-related SCA are often listed among the polyglutamine (or polyQ) diseases. The neuropathologic analysis of SCA has benefited greatly from a monoclonal antibody, commonly termed “1C2,” that detects polyglutamine in nuclei or cytoplasm of neurons in CAG-related SCA (Trottier et al., 1995) (Fig. 8.2K and P; Fig. 8.3E and J) and other polyQ diseases.

The neuropathology of the SCA is diverse, and Koeppen et al. (2013) presented a semiquantitative analysis of polyQ-related SCA and Friedreich ataxia (FA), as these disorders affect the stations of the reciprocal cerebellar circuitry. Figures 8.2 and 8.3 illustrate these lesions in SCA-1, SCA-2, SCA-3, SCA-6, and FA.

Loss of cell bodies and dendritic trees of Purkinje neurons is characteristic of SCA-1, SCA-2, and SCA-6. In terms of severity, SCA-2 displays the most serious cerebellar cortical atrophy (Fig. 8.2M). In SCA-6, Purkinje cell loss is often less serious (Fig. 8.3B). Retrograde degeneration of the neurons in the ION matches the degree of Purkinje cell loss, and, as expected, is less severe in SCA-6 (Fig. 8.3D) than in SCA-1 (Fig. 8.2J) and SCA-2 (Fig. 8.2O). The destruction of Purkinje cells also deprives the DN of GABAergic afferents, and

transsynaptic degeneration is a possible explanation for atrophy of DN neurons. The voids of neurons created by immunohistochemistry with anti-GAD in the normal DN (Fig. 8.1F) are no longer visible in SCA-1 (Fig. 8.2I), SCA-2 (Fig. 8.2N), and SCA-6 (Fig. 8.3C), and the GAD-reactive terminals appear disorganized. In SCA-6, showing relative preservation of DN neurons, the GAD-reactive terminals are sparse but not as disorganized as in SCA-1 and SCA-2 (Fig. 8.3C). Granular neurons of the cerebellar cortex may be affected by SCA, especially in cases of long duration. It is of note that Golgi neurons in the granular layer appear to be resistant to atrophy in SCA and MSA.

The neuropathology of SCA-3 differs greatly from that in SCA-1, SCA-2, and SCA-6. The cerebellar cortex is normal (Fig. 8.3G), and, as expected, ION neurons show no sign of retrograde atrophy (Fig. 8.3I). The DN, however, is a critical target of SCA-3, displaying characteristic grumose reaction (Fig. 8.3H). The author prefers grumose “reaction” over the more widely used term “degeneration” because the GAD-reactive clusters (Fig. 8.3H) also react strongly with antisynaptophysin, supporting proliferation of synaptic terminals (Koeppen et al., 2015). While neurons in the DN must still have intact dendrites to present sites for proliferation of axon terminals, the clusters ultimately disappear. In SCA-3 cases of long duration, the DN shows total loss of large nerve cells, and grumose reaction is absent. By a process of exclusion, large neurons in the DN are thought to be glutamatergic. Small neurons are GABAergic (Fig. 8.3H) or glycinergic. The selective destruction of large neurons in SCA-3 does not cause transsynaptic degeneration of the ION because the dentato-olivary pathway, originating from small GABAergic DN neurons, remains intact. Patients with SCA-3 do not develop palatal myoclonus that would be expected from destructive lesions of the DN, in which the smaller DN neurons are not spared (Guillain and Mollaret, 1931; Lapresle and Ben Hamida, 1970).

The distribution of neuronal inclusion bodies is similar in SCA-1, SCA-2, and SCA-3 (Fig. 8.2K and P; Fig. 8.3J). They are readily visualized in the neurons of the basis pontis. The abundance of neuronal inclusions does not correlate well with the extent of tissue damage, and their role in the pathogenesis has remained poorly understood. In SCA-6, inclusions are more often localized to the cytoplasm of neurons rather than to nuclei (Fig. 8.3E), and their distribution is more widespread. In SCA-17, inclusions occur in many graymatter regions of the brain, and this distribution may explain the complex motor and psychiatric manifestation in this SCA (Rolfs et al., 2003).

Friedreich ataxia

The cerebellar lesion in FA (OMIM 229300) is largely restricted to the DN, though in some long-standing cases, the cerebellar cortex may show reduced numbers of Purkinje cells or bizarre modifications of their dendrites. On gross dissection, the DN may be difficult to see, but thinning of the superior cerebellar peduncle is evident (Fig. 8.3K). Atrophy of the DN may be highlighted by a macroscopic stain for iron (Fig. 8.3K). It is noteworthy that the reaction product does not coincide with the graymatter ribbon of the DN due to the accumulation of the metal in ferritin of oligodendroglia of DN fleece and hilum (Koeppen et al., 2012). As in SCA-3, the ION remains intact (Fig. 8.3N) due to the integrity of Purkinje cells (Fig. 8.3L) and survival of the small GABAergic neurons in the DN (Fig. 8.3M).

(Koeppen et al., 2011). Grumose reaction and neuronal loss in the DN of FA (Fig. 8.3M) also resemble SCA-3 (Fig. 8.3H).

HYPOXIA, HYPOGLYCEMIA, AND TOXIC LESIONS OF THE CEREBELLUM

Hypoxia

The human brain is vulnerable to even brief interruptions of oxygen supply, and cerebral hypoxia occurs on a background of arrested circulation (ischemic or stagnant hypoxia), insufficient oxygen saturation of hemoglobin in circulating red blood cells (pure anoxia), or toxicity that interferes with oxygen transport or delivery. In experimental animals, hypoxia with sustained cerebral blood flow does not cause neuronal necrosis, whereas hypoxia combined with ischemia causes gray-matter necrosis (Miyamoto and Auer, 2000). In clinical practice, lack of brain perfusion such as in the course of profound hypotension or cardiac arrest is the most common cause of brain hypoxia. Since cardiac resuscitation is practiced widely, ischemia and reperfusion of the hypoxic brain are the rule rather than the exception. Hippocampus and cerebellar cortex share selective vulnerability to hypoxia, but no gray or white-matter region in the brain is entirely resistant to the lack of oxygen (Auer and Benveniste, 1997).

A characteristic tinctorial property of neurons, including Purkinje cells, exposed to hypoxia and reperfusion, is intense eosinophilia, or more appropriately, loss of basophilia of the cytoplasm (Fig. 8.4A, and inset). These changes occur within a few hours after restoration of blood flow (Hausmann et al., 2007), and the number of Purkinje cells declines progressively over an irregular gradient, with survival ranging from minutes to days or weeks (Hausmann et al., 2007). Granular layer and DN also show evidence of hypoxia (Fig. 8.4C and D). Figure 8.4D and inset illustrate the microglial response after ischemic hypoxia and survival of 6 days. After longer survivals, such as weeks or months, the sequelae of cerebellar hypoxia become visible on gross examination (Fig. 8.4E and H). (Figure 8.4F and G show total loss of neurons in the molecular and granular layers and hypertrophy of Golgi epithelial cells ("Bergmann gliosis") (Fig. 8.4G). The prominent white color of the middle cerebellar peduncle in this case is due to gliosis (Fig. 8.4E). The cases illustrated in (Figure 8.4A–D represent ischemic hypoxia due to circulatory collapse. The case of near drowning (Fig. 8.4E–G) represents "pure" anoxic hypoxia. The unsuccessful suicide attempt by hanging (Fig. 8.4H and I) probably represents mixed stagnant and anoxic hypoxia. It is peculiar that neuronal depletion of the cerebellar granular layer is more severe in the case of survived near drowning (Fig. 8.4F and G) than in the longer survival after unsuccessful suicidal hanging (Fig. 8.4I).

Hypoglycemia

The human brain is vulnerable to low glucose in the circulating blood (see review in Auer and Benveniste, 1997), and lesions of the cerebral cortex are similar to those of hypoxia (Fig. 8.5A). The cerebellum generally remains intact, even after extended survival following iatrogenic, accidental, suicidal, or homicidal hypoglycemia (Auer et al., 1989) (Fig. 8.5B). Patrick and Campbell (1990) reported modest cerebellar lesions in 3 diabetic patients with hypoglycemic coma who died 17, 17, and 13 days, respectively, after hospital admission.

While the injection of insulin in incorrect doses is the most common cause of hypoglycemia, oral antidiabetic medications and, on occasion, an insulin-producing tumor of the pancreas may be responsible (Terbrüggen, 1932). Auer and Benveniste (1997) proposed that the exemption of the cerebellum from hypoglycemic damage is due to more efficient glucose uptake. Preservation of the cerebellar cortex is of obvious importance in the forensic analysis of unexplained coma (Fig. 8.5).

Toxins and the cerebellum

ETHANOL

Alcoholic cerebellar degeneration is a classic example of clinicoanatomic correlation in neurology. The selective involvement of superior vermis (Fig. 8.6A) and hemispheres translates into disabling gait ataxia and leg dysmetria while coordinated movements of the arms and speech remain intact. Reasons for the regional selectivity of the lesion remain elusive. Dar (2015) recently summarized the complex effects of ethanol on the cerebellum, and it is evident that ataxia after short exposure is due to disturbances of synaptic transmission at many levels of the cerebellar circuitry. While human drunkenness may be equivalent to the described animal experiments, the destruction of Purkinje cells must involve different factors. Two considerations add to the uncertainty about the pathogenesis, namely, the common malnutrition of alcoholics and the consumption of cheap liquor that may contain nonethanol alcohols with potential direct toxic effects.

The prevalence of alcoholic cerebellar degeneration varies greatly among the world's populations where alcohol consumption reaches the level of "alcoholism" (see review by Yokota et al., 2006). The cited authors reported a low prevalence of alcoholic cerebellar degeneration in Japanese people (0.4% of 1509 unselected autopsies; 10.9% of autopsies conducted on 55 established alcoholics). These figures are low compared to those obtained in Norway on a larger number of autopsies (1.8% of 6964 unselected autopsies and 27.6% of 126 autopsies on established alcoholics).

Alcoholic cerebellar degeneration may also be present in patients who suffer from Wernicke–Korsakoff encephalopathy, but it may no longer be justified to state that these conditions are closely related (Victor et al., 1989). Beyond Wernicke–Korsakoff encephalopathy, lack of thiamine also causes beriberi polyneuropathy, and even very low doses of thiamine are effective against acute ataxia and ophthalmoplegia of Wernicke disease and beriberi neuropathy. Korsakoff amnesic "psychosis" is more resistant to vitamin therapy and may remain a lifelong problem for the patient. Thiamine also does not reverse established alcoholic cerebellar degeneration in the short term, but ataxia improves after prolonged abstinence. The likely reason for the recovery is the integrity of the DN.

When the regional selectivity of the lesion is discounted, Purkinje cell loss (Fig. 8.6B), empty baskets (Fig. 8.6C), and torpedoes (Fig. 8.6C) are similar to parenchymatous cerebellar atrophies that are unrelated to alcoholism.

MERCURY

In a now classic paper, Hunter and Russell (1954) established the remarkable cerebellar pathology of mercury toxicity in a single case. The toxic form of the metal was methyl mercury, and the route of entry was exposure to dust, presumably causing inhalation or a combination of inhalation and ingestion. Mercury is toxic in any of its forms (metallic, inorganic, and organic) (Carocci et al., 2014; Caito and Aschner, 2015), but the lipid solubility of organic mercury is critical for the neurotoxic properties of the metal. Metallic mercury and mercury salts may be converted to organic mercury compounds, and ultimately all forms of mercury may become neurotoxic.

Conversion of inorganic mercury salts in industrial waste to methyl mercury by microorganisms, accumulation to high levels in fish and shellfish, and human consumption of tainted seafood were the cause of Minamata disease (Tsubaki and Irukayama, 1977). Hunter and Russell (1954) illustrated extensive modifications of Purkinje cell dendrites with the formation of “witch’s brooms,” depletion of granular neurons, loss of Golgi neurons and basket fibers, and torpedoes. It was peculiar that the lesion was more severe in the depth between the cerebellar folia. The cerebellar pathology in Minamata disease is similar (Eto, 1997). The microphotographs in (Figure 8.6D and E were taken after the restaining of slides that were generously provided by Professor F. Ikuta (Niigata, Japan). Toxicity in the illustrated case occurred through contamination of fish in the Agano River (not Minamata Bay). (Figure 8.6D shows the depletion of granule cells beneath the Purkinje cell layer. Basket fibers remain intact ((Fig. 8.6D, inset). Though Hunter and Russell (1954) reported that the DN in their case was normal, (Figure 8.6E shows modest numeric reduction of neurons and grumose reaction (Fig. 8.6E, inset).

DRUGS AND CEREBELLAR DAMAGE

In 2000, Spencer et al. listed only six drugs that are strongly associated with a “cerebellar syndrome”: cytarabine, fludarabine, 5-fluorouracil, lithium, metronidazole, and phenytoin. Since then, the list of therapeutic agents causing ataxia has grown enormously (Manto, 2012; van Gaalen et al., 2014). While the unfavorable effects are generally transient and disappear after dose reduction or discontinuation, some agents may cause lasting damage to the cerebellar cortex or DN. Fortunately, autopsy confirmation of drug-induced damage is rare. Phenytoin is of interest to neurologists and neuropathologists because the drug was widely used for the control of epilepsy, and neuroimaging studies strongly supported cerebellar atrophy. It proved difficult, however, to distinguish the effects of phenytoin from damage caused by epilepsy itself (Gessaga and Urich, 1985). Also, patients with intractable seizures were more likely to receive larger doses of the anticonvulsant, and serum levels probably became toxic. Nevertheless, in selected cases, long-term phenytoin therapy may indeed be the cause of cerebellar cortical degeneration (Ghatak et al., 1976).

In some patients on metronidazole, cerebellar ataxia is most likely due to a structural lesion of the DN, and magnetic resonance imaging shows a remarkable hyperintense signal in the DN on T2-weighted images (Heaney et al., 2003; Moosa and Perkins, 2010). Symmetric T2hyperintense signal in the central tegmental tracts and ION supports transneuronal degeneration due to interruption of the GABAergic dentato-olivary fiber tract, but palatal

myoclonus has not been reported (Moosa and Perkins, 2010). Cerebellar ataxia due to metronidazole may be reversible after discontinuation of the drug, and signal hyperintensity of the DN on T2-weighted images or fluid attenuation recovery may disappear (Woodruff et al., 2002; Simonetta et al., 2013).

VASCULAR LESIONS OF THE CEREBELLUM

Spontaneous hemorrhages in the cerebellum are less common than hematomas in the cerebral hemispheres (Nilsson et al., 2002). The hemorrhage illustrated in Figure 8.7A is relatively small. Hematomas may be much larger, displace the brainstem, and penetrate into the fourth ventricle. Brainstem displacement conveys an unfavorable prognosis (Nilsson et al., 2002; Witsch et al., 2013; Chang et al., 2015). Most recent reports on prevalence, therapy, and outcome appeared in the neurosurgical literature, and it is uncommon that large hematomas resolve without surgical intervention. The cerebellum does not differ from other regions of the brain in the slow conversion of heme to hemosiderin. The most common etiology of cerebellar hemorrhage is arterial hypertension, but thrombocytopenia and other bleeding diatheses are well-recognized factors.

Due to the smaller caliber of arteries supplying the cerebellum, embolism is less common than in the cerebral hemisphere, but hemorrhagic infarctions are not rare (Fig. 8.7C). The lesion illustrated in (Figure 8.7D and E shows a combination of hypoxia of the cerebellar cortex (Fig. 8.7D) and a vigorous macrophage response to the presence of red cells and necrotic tissue (Fig. 8.7E).

Bland cerebellar infarctions cause cystic necrosis of the tissue (Fig. 8.7F), and the lesion is restricted to the supply territory of the involved artery, such as the right superior cerebellar artery (Fig. 8.7F). Necrosis affects the entire thickness of the cerebellar cortex though Golgi epithelial cells and their processes, the Bergmann glia, show a measure of resistance to the necrotic process (Fig. 8.7G). Smaller macrophages are characteristic of older cystic infarctions (Fig. 8.7H), and hemosiderin in these cells is a tell-tale sign of the hemorrhagic nature of the original infarction.

Transsynaptic hypertrophic degeneration of the ION (Fig. 8.7J) is the anatomic substrate of palatal myoclonus. When the lesion is present in the central tegmental tract, olivary hypertrophy is ipsilateral. When the responsible lesion is located in the DN (Fig. 8.7I), hypertrophy occurs in the contralateral ION (Fig. 8.7J–L). It remains unknown how the deafferentation of the ION causes the involuntary arrhythmic movements of the soft palate.

A little more is known about the pathogenesis of olivary hypertrophy. If the cerebellar cortex is also involved, retrograde olivary atrophy precludes hypertrophy. However, when transsynaptic changes of the ION antedate cortical cerebellar atrophy, olivary hypertrophy persists (Koeppen et al., 1979). Based on recent work, it is likely that loss of trophic input by GABAergic dentato-olivary fibers is the critical trigger for olivary hypertrophy (Koeppen et al., 2011). Swelling of nerve cells appears to be due to retention of proteinaceous material in the rough endoplasmic reticulum of olivary neurons (Koeppen et al., 1980; Barron et al., 1982). It should also be noted that the glial response to transsynaptic degeneration of the

ION differs greatly from that of retrograde degeneration. Astrocytes in transsynaptic olivary degeneration are peculiarly large and bizarre.

INFECTIONS OF THE CEREBELLUM

Leptomeningitis

The subarachnoid space over the cerebellum and brainstem is a conduit for rapid spread of bacterial infection, similar to the brain convexities (Fig. 8.8A), but certain infections, such as tuberculosis, tend to involve the posterior fossa structures more than the cerebral hemispheres (Fig. 8.8H). In purulent meningitis of recent onset, such as in the case of *Streptococcus pneumoniae* infection illustrated in Figure 8.8A–D, the inflammatory exudate appears confined to the subarachnoid space, and sections reveal abundant polymorphonuclear leukocytes (Fig. 8.8C). The cerebrospinal fluid of this patient, who died within 24 hours of diagnosis and initiation of therapy, contained protein of 364 mg/100 mL, glucose of 28 mg/100 mL, and 7800 white cells/ μ L. After centrifugation of the cerebrospinal fluid, a Gram stain showed polymorphonuclear leukocytes and encapsulated extracellular “cocci-in-pairs” (Fig. 8.8D). The introduction of polyvalent pneumococcal conjugate vaccine has brought about a remarkable decline in the incidence of invasive pneumococcal disease, including leptomeningitis, especially in children (Moore et al., 2015). A similar positive trend is true for vaccination against *Haemophilus influenzae* and *Neisseria meningitidis*.

Fungal infections of the central nervous system, especially by *Cryptococcus neoformans*, were very common during the epidemic of acquired immunodeficiency syndrome (AIDS) due to infection by the human immunodeficiency virus (HIV). Before AIDS/HIV, steroid use for a number of indications was the usual reason for immuno-suppression. In the illustrated case of *Aspergillus* sp. leptomeningitis (Fig. 8.8E–G), the 65-year-old patient received high doses of dexamethasone to control brain edema due to metastatic tumors. The diagnosis of leptomeningitis was not made during life.

Antiviral therapy of AIDS/HIV has brought about a decline of death rates from 8.3/100,000 in 1990 to 1.1/100,000 in 2014 (National Center for Health Statistics, 2016), and autopsies showing fungal meningitis have become much rarer. The danger of steroids, however, was recently highlighted by cases of leptomeningeal and parameningeal fungal infections following local injections of contaminated methylprednisolone solutions (Centers for Disease Control and Prevention, 2012). The classic monograph by Fetter et al. (1967) remains a valuable resource for the tissue diagnosis of fungal infections in the brain.

Incidence and prevalence of tuberculosis have also declined, and fatal tuberculous meningitis is now rare. The specimen illustrated in (Figure 8.8H–J derived from a 37-year-old woman who died from the mass effects of a thalamic tuberculoma that was not diagnosed during life. At autopsy, the patient also had tuberculous meningitis over the base of the brain and cerebellum (Fig. 8.8H). Sections showed granulomatous inflammation with multinucleated Langhans giant cells (Fig. 8.8I) and scattered acid-fast bacilli (Fig. 8.8J).

Infections of the cerebellar parenchyma

Immunosuppression by steroids, chemotherapeutic agents, anti-inflammatory antibodies, and AIDS/HIV has caused a spectrum of opportunistic infections of the cerebellum. (Figure 8.9A–J illustrates cerebellar toxoplasmosis (Fig. 8.9A–C), cytomegalovirus infection (Fig. 8.9D–G), and progressive multifocal leukoencephalopathy (PML) (Fig. 8.9H–J). The introduction of highly active antiretroviral therapy (HAART) has caused a remarkable decline in incidence and prevalence of *Toxoplasma gondii* brain infection in patients with HIV/AIDS (Antinori et al., 2004; Riveiro-Barciela et al., 2013; Hernandez et al., 2017), but the benefit also relates to the prompt therapy with specific anti-*Toxoplasma* drugs (Hernandez et al., 2017). Similarly, the incidence of cytomegalovirus and other herpetic infections declined after the introduction of HAART for the control of AIDS/HIV (Schwarcz et al., 2013).

PML lesions due to JC virus infection of the cerebellum are generally small and nonconfluent and may not cause ataxia or dysmetria. When present, their histopathology does not differ substantially from the foci of demyelination in the subcortical white matter of the cerebral hemispheres (Fig. 8.9H–J). The prognosis of AIDS/ HIV-related PML has improved with the introduction of HAART (Bowen et al., 2016), though a new concern, immune reconstitution inflammatory syndrome, has arisen (Vendrey et al., 2005; Bauer et al., 2015).

Encephalitis caused by the sudden invasion of cytotoxic T cells presents a major therapeutic challenge, and steroids may not be effective. As the natural immunosuppression due to AIDS/HIV is now reversible, PML due to the emerging use of monoclonal antibodies for a number of inflammatory diseases, including multiple sclerosis (MS), may become more frequent. Bauer et al. (2015) listed 13 medications that have caused PML, among which natalizumab accounted for 563 of 799 cases.

The identification of protein infectious particles (prions) (Prusiner, 2001) allows the conclusion that Jakob–Creutzfeldt disease is a parenchymatous infection of the cerebellum (Fig. 8.9K–M). Ataxia may be a major clinical feature of the disease, and rapid progression is the rule, such as 2½ months from onset to death in the case illustrated in Figure 8.9K–M. The lack of grossly visible cerebellar atrophy is not surprising. Low brain weights, cerebral, and cerebellar atrophy are generally present only in cases of longer duration. While most cases of prion disease are sporadic, a family history is present in over 10%. As of 13 December 2016, the National Prion Disease Pathology Surveillance Center in Cleveland, OH, United States, reported 368 familial cases among a total of 3633 cases, spanning a period of 20 years. In comparison, cases of iatrogenic and variant Jakob–Creutzfeldt disease are rare (a combined percent-age of 0.44) (National Prion Disease Pathology Surveillance Center, 2016).

MULTIPLE SCLEROSIS IN THE CEREBELLUM

Plaques of MS are relatively uncommon in the cerebellum due to the paucity of white matter compared to the cerebrum. Nevertheless, discrete plaques do occur in efferent and afferent myelinated fiber tracts, and it is not surprising that they are most common in the middle

cerebellar peduncles (Fig. 8.10A). When a demyelinating lesion is located strategically in the superior cerebellar peduncle or the hilum of the DN, the patient may have limb dysmetria, palatal myoclonus, or both. The pathology of MS in the cerebellum does not differ from that in other parts of the central nervous system. Figure 8.10A shows the gross specimen of a 74-year-old man with well-established MS of long duration. The myelin stains shown in Figure 8.10B–D are characteristic of MS; and the paucity of axons (Fig. 8.10E) is consistent with MS as an axonal disease (Dutta and Trapp, 2007). The junction of plaque and intact white matter reveals the proliferation of microglia (Fig. 8.10F) and astrocytes (Fig. 8.10G). The autopsy experience of MS is changing as the prognosis has improved after the introduction of immunomodulatory therapy (Ziemssen et al., 2016). Autopsy cases of acute and relapsing relapsing MS were always rare, and most neuropathologists now see only specimens of chronic MS.

THE CEREBELLUM IN LIPID STORAGE DISEASES AND LEUKODYSTROPHY

While lipid storage diseases are mostly childhood disorders, adult-onset lipidoses may affect the neurons of the cerebellar cortex and DN. Figure 8.11A–F displays the findings in archival specimens of a 54-year-old man who suffered from ataxia and progressive cognitive decline. The gross specimen of the cerebellum shows smallness of the DN but no gross cortical cerebellar atrophy (Fig. 8.11A). Sections of the cerebellar cortex display loss of Purkinje cells (Fig. 8.11B), lipid storage in Golgi neurons (Fig. 8.11B and C), and torpedoes (Fig. 8.11D). Based on the presence of neurofibrillary tangles (Fig. 8.11E), the retrospective diagnosis of adult-onset Niemann–Pick disease type C1 (OMIM 257220) was made (Distl et al., 2003). Autofluorescence was present in lipid-storing neurons (Fig. 8.11F) but was not as widespread as in Kufs disease (see below). In this case, a mutation in the NPC1 gene (chromosome 18q11.2) could not be established. Sections shown in Figure 8.11G–I, however, came from a 37-year-old woman with ataxia in whom genetic analysis of deoxyribonucleic acid extracted from frozen cerebellum and the lymphocytes of her parents confirmed a compound heterozygous mutation in the NPC1 gene. Lipid storage in Golgi neurons and Lugaro cells (Fig. 8.11G, arrows; Fig. 8.11H) and DN (Fig. 8.11I) was similar to that shown in the archival case (Fig. 8.11B and C). Neurofibrillary tangles were also present (not illustrated), and fixed vibratome sections confirmed filipin-reactive cholesterol deposits (Distl et al., 2003).

Adult-onset neuronal ceroid-lipofuscinosis (Kufs disease) (OMIM 601780) should now be defined as an autosomal-recessive disease caused by a mutation of the CLN6 gene (Arsov et al., 2011). The pathologic diagnosis still relies on widespread neuronal autofluorescence (Goebel and Braak, 1989). Figure 8.11 illustrates loss of Purkinje cells (Fig. 8.11J), a bizarre expansion of a Purkinje cell dendrite (Fig. 8.11K), and autofluorescence in Purkinje cells (Fig. 8.11L and M).

Heritable leukodystrophies with adult onset may present with ataxia, and neuropathologic examination may disclose characteristic lesions of the cerebellar white matter in adrenoleukodystrophy (OMIM 300100) (Ogaki et al., 2016), Alexander disease (OMIM

203450) (Spalke and Mennel, 1982; Stumpf et al., 2003), metachromatic leukodystrophy (OMIM 250100) (Guseo et al., 1975), Krabbe globoid cell leukodystrophy (245200) (Shao et al., 2016), and adult-onset dominant leukodystrophy (OMIM 169500) (Coffeen et al., 2000; Alturkustani et al., 2013).

Figure 8.12 shows the neuropathologic phenotype of the cerebellum in adult-onset dominant leukodystrophy. The demyelinating process is remarkable for the retention of oligodendroglia (Fig. 8.12E) (Eldridge et al., 1984; Coffeen et al., 2000), lack of astrogliosis that would be expected given the degree of myelin loss, and the presence of bizarre large astrocytes (Fig. 8.12G). The demyelinating process stimulates the proliferation of microglia (Fig. 8.12F), but macrophages are rare. Damage to axons is conspicuous and involves the formation of end bulbs in the transition zone between normal and depleted white matter (Fig. 8.12C and D). Lack of gliosis was also confirmed by direct assay of the glial fibrillary acidic protein (Coffeen et al., 2000). The failure of a more vigorous glial response to active demyelination has not been explained by the mutation, a duplication of a nuclear envelope protein gene, lamin B1 (Padiath et al., 2006).

CEREBELLAR DEGENERATION IN MALIGNANCY

The prevailing nomenclature is paraneoplastic cerebellar degeneration (PCD), and most investigators have accepted the interpretation that destruction of Purkinje and granule cells is immunemediated. The number of antibodies to cerebellar antigens has grown to 20, though anti-Yo (in gynecologic cancers), antiHu (in small-cell lung cancer), and anti-Tr (in Hodgkin disease) account for 73% of cases (Mitoma et al., 2015). The first neuro-pathologic description of PCD should be attributed to Brouwer (1919), whose patient, a 60-year-old woman, died after a 7-monthlong course of progressive and disabling ataxia. Her autopsy discovered an incidental “polymorphcellular pelvic sarcoma.” The lesion of the cerebellar cortex consisted of severe loss of Purkinje cells and an abundance of empty baskets.

Brouwer (1919) specifically commented on the surprising integrity of the ION, which, in retrospect, may be due to the rapid pace of Purkinje cell atrophy. PCD is an uncommon disease with variable clinical features, disease duration, and prognosis (see review in DeAngelis and Posner, 2009), and most neuropathologic reports are based on small series of cases. It became clear, however, that in some autopsy specimens cerebellar cortical atrophy was associated with inflammatory infiltration (Henson and Urich, 1982; Scaravilli et al., 1999; Venkatraman and Opal, 2016). In their comprehensive review of PCD, Henson and Urich (1982) pointed out that paraneoplastic encephalomyelitis may also affect the cerebellum. In these cases, PCD may be part of the cerebral inflammatory disease. It is appropriate to recall that not all patients with PCD reveal antibodies to identifiable antigens in serum or cerebrospinal fluid, and the cerebrospinal fluid may not show an increase in white cells.

ACKNOWLEDGMENTS

For this work, the author has received financial support from several sources: Friedreich’s Ataxia Research Alliance, Downingtown, PA, United States; National Ataxia Foundation, Minneapolis, MN, United States; Neurochemical Research, Inc., Glenmont, NY, United States, National Institutes of Health, Bethesda, MD, United States

(R01NS069454); and Alexander-von-Humboldt Foundation, Bonn, Germany. Some of the archival cases were made available by the Pathology and Laboratory Medicine Service of the Veterans Affairs Medical Center and the Department of Pathology of Albany Medical College, Albany, NY, United States. The author gratefully acknowledges the expert technical assistance of Ms. Alyssa B. Becker.

REFERENCES

- Alturkustani M, Sharma M, Hammond R et al. (2013). Adult-onset leukodystrophy: review of 3 clinicopathologic phe-notypes and a proposed classification. *J Neuropathol Exp Neurol* 72: 1090–1103. [PubMed: 24128683]
- Ambrosi G, Flace P, Lorusso L et al. (2007). Non-traditional large neurons in the granular layer of the cerebellar cortex. *Eur J Histochem* 51 (Suppl 1): 59–64.
- Antinori A, Larussa D, Cingolani A et al. (2004). Prevalence, associated factors, and prognostic determinants of AIDS-related toxoplasmic encephalitis in the era of advanced highly active antiretroviral therapy. *Clin Infect Dis* 39: 1681–1691. [PubMed: 15578371]
- Arsov T, Smith KR, Damiano J et al. (2011). Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in CLN6. *Am J Hum Genet* 88: 566–573. [PubMed: 21549341]
- Auer RN, Benveniste H (1997). Hypoxia and related conditions. In: Graham DI, Lantos PL (Eds.), *Greenfield's neuropathology* Oxford University Press, New York, pp. 263–314.
- Auer RN, Hugh J, Cosgrove E et al. (1989). Neuropathologic findings in three cases of profound hypoglycemia. *Clin Neuropathol* 8: 63–68. [PubMed: 2721042]
- Barron KD, Dentinger MP, Koeppen AH (1982). Fine structure of neurons of the hypertrophied human inferior olive. *J Neuropathol Exp Neurol* 41: 186–203. [PubMed: 7062087]
- Bauer J, Gold R, Adams O et al. (2015). Progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome (IRIS). *Acta Neuropathol* 130: 751–764. [PubMed: 26323992]
- Bowen LN, Smith B, Reich D et al. (2016). HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. *Nat Rev Neurol* 12: 662–674. [PubMed: 27786246]
- Brouwer B (1919). Beitrag zur Kenntnis der chronischen diffusen Kleinhirnerkrankungen. *Neurol Centralbl* 38: 674–682.
- Caito S, Aschner M (2015). Neurotoxicity of metals. In: Lotti M, Bleecker ML (Eds.), *Handbook of clinical neurology* vol. 131 Elsevier, Amsterdam, pp. 169–189. [PubMed: 26563789]
- Carocci A, Rovito N, Sinicropi MS et al. (2014). Mercury toxicity and neurodegenerative effects. *Rev Environm Contam Toxicol* 229: 1–18.
- Centers for Disease Control and Prevention (2012). Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy—United States, 2012. *MMWR Morb Mort Wkly Rep* 61: 839–842.
- Chang C-Y, Lin C-Y, Chen L-C et al. (2015). The predictor of mortality within six-months in patients with spontaneous cerebellar hemorrhage: a retrospective study. *PLoS ONE* 10 (7): e013297 1–9.
- Coffeen CM, McKenna CE, Koeppen AH et al. (2000). Genetic localization of an autosomal dominant leukodystrophy mimicking chronic progressive multiple sclerosis to chromosome 5q31. *Hum Mol Genet* 9: 787–793. [PubMed: 10749986]
- Dar MS (2015). Ethanol-induced cerebellar ataxia: cellular and molecular mechanisms. *Cerebellum* 14: 447–465. [PubMed: 25578036]
- DeAngelis LM, Posner JB (2009). *Neurologic complications of cancer*, 2nd edn. Oxford University Press, New York, pp. 585–593.
- Distl R, Treiber-Held S, Albert F et al. (2003). Cholesterol storage and tau pathology in Niemann-Pick type C disease in the brain. *J Pathol* 200: 104–111. [PubMed: 12692848]
- Dubourg O, Dürr A, Chneiweiss H et al. (1995). La forme ataxo-choreique de DRPLA existetelle en Europe? Recherche de la mutation dans 120 familles. *Rev Neurol (Paris)* 151: 657–660. [PubMed: 8745629]
- Dutta R, Trapp BD (2007). Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology* 68 (suppl 3): S22–S31. [PubMed: 17548565]

- Eldridge R, Anayiotos CP, Schlesinger S et al. (1984). Hereditary adult-onset leukodystrophy simulating chronic progressive multiple sclerosis. *N Engl J Med* 311: 948–953. [PubMed: 6472420]
- Eto K (1997). Pathology of Minamata disease. *Toxicol Pathol* 25: 614–623. [PubMed: 9437807]
- Fetter BF, Klintworth GK, Hendry WS (1967). *Mycoses of the central nervous system*, Williams and Wilkins, Baltimore, MD.
- Gessaga EC, Urich H (1985). The cerebellum of epileptics. *Clin Neuropathol* 4: 238–245. [PubMed: 4075636]
- Ghatak NR, Santoso RA, McKinney WM (1976). Cerebellar degeneration following long-term phenytoin therapy. *Neurology* 26: 818–820. [PubMed: 821007]
- Gilman S, Wenning GK, Low PA et al. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 71: 670–676. [PubMed: 18725592]
- Goebel HH, Braak H (1989). Adult neuronal ceroid-lipofuscinosis. *Clin Neuropathol* 8: 109–119. [PubMed: 2663281]
- Guillain G, Mollaret P (1931). Deux cas de myoclonies synchrones et rythmiques velo-pharyngo-laryngo-oculo-diaphragmatiques: le problème anatomique et physio-pathologique de ce syndrome. *Rev Neurol (Paris)* 2: 545–566.
- Guseo A, Deák G, Szirmai I (1975). An adult case of metachromatic leukodystrophy. Light, polarization and electron microscopic study. *Acta Neuropathol* 32: 333–339. [PubMed: 1180011]
- Hausmann R, Seidl S, Betz P (2007). Hypoxic changes in Purkinje cells of the human cerebellum. *Int J Legal Med* 121: 175–183. [PubMed: 17031692]
- Heaney CJ, Campeau NG, Lindell EP (2003). MR imaging and diffusion-weighted imaging changes in metronidazole (Flagyl)-induced cerebellar toxicity. *AJNR Am J Neuroradiol* 24: 1615–1617. [PubMed: 13679281]
- Henson RA, Urich H (1982). Cancer and the nervous system. In: *The neurological manifestations of systemic malignant disease*, Blackwell Scientific, London, pp. 346–367.
- Hernandez AV, Thota P, Pellegrino D et al. (2017). A systematic review and meta-analysis of the relative efficacy and safety of treatment regimens for HIV-associated cerebral toxoplasmosis: is trimethoprim-sulfamethoxazole a real option? *HIV Med* 18: 115–124. [PubMed: 27353303]
- Hunter D, Russell DS (1954). Focal cerebral and cerebellar atrophy in a human subject due to organic mercury compounds. *J Neurol Neurosurg Psychiatr* 17: 235–241. [PubMed: 13212411]
- Jellinger KA, Wenning GK (2016). Multiple system atrophy: pathogenic mechanisms and biomarkers. *J Neural Transm* 123: 555–572. [PubMed: 27098666]
- King JS (1980). Synaptic organization of the inferior olivary complex. In: Courville J, de Montigny C, Lamarre Y (Eds.), *The inferior olivary nucleus* Raven Press, New York, pp. 1–33.
- Koeppen AH, Barron KD, Cassidy RJ (1979). Transneuronal degeneration of the inferior olivary nuclei in system atrophy. *Acta Neuropathol* 47: 155–158.
- Koeppen AH, Barron KD, Dentinger MP (1980). Olivary hypertrophy in man In: Courville J, de Montigny C, Lamarre Y (Eds.), *The inferior olivary nucleus* Raven Press, New York, pp. 309–314.
- Koeppen AH, Davis AN, Morral JA (2011). The cerebellar component of Friedreich's ataxia. *Acta Neuropathol* 122: 323–330. [PubMed: 21638087]
- Koeppen AH, Ramirez RL, Yu D et al. (2012). Friedreich's ataxia causes redistribution of iron, copper, and zinc in the dentate nucleus. *Cerebellum* 11: 845–860. [PubMed: 22562713]
- Koeppen AH, Ramirez RL, Bjork ST et al. (2013). The reciprocal cerebellar circuitry in human hereditary ataxia. *Cerebellum* 12: 493–503. [PubMed: 23389921]
- Koeppen AH, Ramirez RL, Becker AB et al. (2015). Friedreich ataxia: failure of GABA-ergic and glycinergic synaptic transmission in the dentate nucleus. *J Neuropathol Exp Neurol* 74: 166–176. [PubMed: 25575136]
- Lapresle J, Ben Hamida M (1970). The dentato-olivary path-way. Somatotopic relationship between the dentate nucleus and contralateral inferior olive. *Arch Neurol* 22: 135–143. [PubMed: 4188259]
- Manto M (2012). Toxic agents causing cerebellar ataxias. In: Subramony SH, Dürr A (Eds.), *Handbook of clinical neurology Third series Ataxic disorders*. Elsevier, Amsterdam, pp. 201–213.

- McCormack A, Chegeni N, Chegeni F et al. (2016). Purification of a-synuclein containing inclusions from human post mortem brain tissue. *J Neurosci Methods* 266: 141–150. [PubMed: 27039974]
- Mitoma H, Hadjivassiliou M, Honnorat J (2015). Guidelines for treatment of immunemediated cerebellar ataxias. *Cerebellum Ataxias* 2: 14. [PubMed: 26561527]
- Miyamoto O, Auer RN (2000). Hypoxia, hyperoxia, ischemia, and brain necrosis. *Neurology* 54: 362–371. [PubMed: 10668697]
- Moore MR, Link-Gelles RE, Schaffner W et al. (2015). Impact of 13-valent pneumococcal conjugate vaccine used in children on invasive pneumococcal disease in children and adults in the United States: analysis of multisite, population-based surveillance. *Lancet Infect Dis* 15: 301–309. [PubMed: 25656600]
- Moosa ANV, Perkins D (2010). MRI of metronidazole induced cerebellar ataxia. *J Neurol Neurosurg Psychiatry* 81: 754–755. [PubMed: 20581140]
- Mugnaini E, Sekerková G, Martina M (2015). The unipolar brush cell: a remarkable neuron finally receiving deserved attention. *Brain Res Rev* 66: 220–245.
- National Center for Health Statistics (2016). Health. In: United States, 2015 National Center for Health Statistics, Hyattsville, MD, pp. 100–102.
- National Prion Disease Pathology Surveillance Center (2016) Available online at : <http://casesdu/med/pathology/centers/npdpssc/index/html>.
- Neuromuscular Center, Washington University, Saint Louis, USA (2016) Available online at: <http://neuromuscular.wustl.edu/ataxia/domatax/html>.
- Nilsson OG, Lindgren A, Brandt L et al. (2002). Prediction of death in patients with primary intracerebral hemorrhage: a prospective study of a defined population. *J Neurosurg* 97: 531–536. [PubMed: 12296635]
- Ogaki K, Koga S, Aoki N et al. (2016). Adultonset cerebello-brainstem dominant form of X-linked adrenoleukodystrophy presenting as multiple system atrophy: case report and literature review. *Neuropathology* 36: 64–76. [PubMed: 26227820]
- Padiath QS, Saigoh K, Schiffmann R et al. (2006). Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 38: 1114–1123. [PubMed: 16951681]
- Patrick AW, Campbell IW (1990). Fatal hypoglycaemia in insulin-treated diabetes mellitus: clinical features and neuropathological changes. *Diabet Med* 7: 349–354. [PubMed: 2140089]
- Prusiner SB (2001). Neurodegenerative diseases and prions. *N Engl J Med* 344: 1516–1526. [PubMed: 11357156]
- Riveiro-Barciela M, Falcó V, Burgos J et al. (2013). Neurological opportunistic infections and neurological immune reconstitution syndrome: impact of one decade of highly active antiretroviral treatment in a tertiary hospital. *HIV Med* 14: 21–30. [PubMed: 22726389]
- Rolfs A, Koeppe AH, Bauer I et al. (2003). Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (SCA17). *Ann Neurol* 54: 367–375. [PubMed: 12953269]
- Scaravilli FD, An SF, Groves M et al. (1999). The neuropathology of paraneoplastic syndromes. *Brain Pathol* 9: 251–260. [PubMed: 10219743]
- Schwarz L, Chen M-J, Vittinghoff E et al. (2013). Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. *AIDS* 27: 597–605. [PubMed: 23079812]
- Shao Y-H, Choquet K, La Piana R et al. (2016). Mutations in GALC cause late-onset Krabbe disease with predominant cerebellar ataxia. *Neurogenetics* 17: 137–141. [PubMed: 26915362]
- Simonetta F, Christou F, Vandoni RE et al. (2013). Walking unsteadily: a case of acute cerebellar ataxia. *BMJ Case Rep* <https://doi.org/10.1136/bcr-2012-007688>.
- Spalke G, Mennel HD (1982). Alexander's disease in an adult: clinicopathologic study of a case and review of the literature. *Clin Neuropathol* 1: 106–112. [PubMed: 6301723]
- Spencer PS, Schaumburg HH, Ludolph AC (2000). *Experimental and clinical neurotoxicology*, 2nd edn. Oxford University Press, New York.
- Stumpf E, Masson H, Duquette A et al. (2003). Adult Alexander disease with autosomal dominant transmission. A distinct entity caused by mutation in the glial fibrillary acid protein gene. *Arch Neurol* 60: 1307–1312. [PubMed: 12975300]

- Terbrüggen A (1932). Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome. *Beitr Pathol Anat Allg Pathol* 88: 37–59.
- Trottier Y, Lutz Y, Stevanin G et al. (1995). Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* 378: 403–406. [PubMed: 7477379]
- Tsubaki T, Irukayama K (1977). *Minamata disease*, Elsevier, Amsterdam, pp. 96–102.
- van Gaalen J, Kerstens FG, Maas RPPWM et al. (2014). Drug-induced cerebellar ataxia: a systematic review. *CNS Drugs* 28: 1139–1153. [PubMed: 25391707]
- Vendrey A, Bienvenu B, Gasnault J et al. (2005). Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol* 109: 449–455. [PubMed: 15739098]
- Venkatraman A, Opal P (2016). Paraneoplastic cerebellar degeneration with anti-Yo antibodies-a review. *Ann Clin Transl Neurol* 3: 655–663. [PubMed: 27606347]
- Victor M, Adams RD, Collins GH (1989). *The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition*, 2nd edn. FA Davis, Philadelphia, PA, pp. 121–122.
- Witsch J, Neugebauer H, Zweckberger K et al. (2013). Primary cerebellar haemorrhage: complications, treatment, and out-come. *Clin Neurol Neurosurg* 115: 863–869. [PubMed: 23659765]
- Woodruff BK, Wijdicks EFM, Marshall W (2002). Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 346: 68–69. [PubMed: 11778010]
- Yokota O, Tsuchiya K, Terada S et al. (2006). Frequency and clinicopathological characteristics of alcoholic cerebellar degeneration in Japan: a cross-sectional study of 1509 post-mortems. *Acta Neuropathol* 112: 43–51. [PubMed: 16622656]
- Ziemssen T, Derfuss T, De Stefano N et al. (2016). Optimizing treatment success in multiple sclerosis. *J Neurol* 263: 1053–1065. [PubMed: 26705122]

Fig. 8.1.

The neurons of the reciprocal cerebellar circuitry. (A–D) Cerebellar cortex; (E and F) dentate nuclei (DN); (G and H) inferior olivary nuclei (ION). Immunohistochemical stains: (A) class III b-tubulin; (B, F, and H) glutamic acid decarboxylase (GAD); (C) vesicular glutamate transporter 2 (VGLUT2); (D) vesicular glutamate transporter 1 (VGLUT1); (E), nonphosphorylated neurofilament protein; and (G) calbindin D28k. (A) The Purkinje cells of the cerebellar cortex show their well-known idioblastic tree. Small neurons in the molecular layer that also react with the antibody to class III b-tubulin represent basket and stellate cells. In the granular layer, a Golgi neuron is immunoreactive (arrow). (B) The GAD stain of the cerebellar cortex shows pale reaction product in the cytoplasm of Purkinje cells and more robust reaction product in terminal baskets. Anti-GAD also labels parallel fibers and basket and stellate cells in the molecular layer, and the axonal plexuses of Golgi neurons in the granular layer (arrow). (C) An antibody to VGLUT2 generates punctate reaction product in climbing fibers (arrow) as they abut Purkinje cell dendrites, and more intense labeling of mossy fiber terminals in the granular layer. (D) Anti-VGLUT1 labels mossy fiber terminals in the granular layer. Strong, finely granular, reaction product is distributed throughout the entire thickness of the molecular layer, generating negative images of

primary and secondary dendritic branches of Purkinje cells. **(E)** The neurofilament stain shows reaction product in large, intermediate, and small neurons of the dentate nucleus. **(F)** Anti-GAD generates reaction product in axon terminals of the DN and creates negative images of larger neurons **(N)**. The stain also visualizes GAD in the cytoplasm of small neurons at the perimeter of the DN (arrows). **(G)** Neuronal cell bodies and dendrites of the ION are strongly reactive with anticalbindin D28k. **(H)** Terminals abutting ION neurons are strongly GAD-reactive. Bars, 50 μ m.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 8.2.

The cerebellar and olivary lesions in multiple system atrophy (*MSA*), spinocerebellar ataxia types 1 (*SCA-1*) and 2 (*SCA-2*). (A–F) *MSA*; (G–K) *SCA-1*; (L–P) *SCA-2*.

Immunohistochemical stains: (B, H, and M) cerebellar cortex, class III b-tubulin; (C, I, and N) dentate nuclei (DN), glutamic acid decarboxylase (*GAD*); (C, inset) DN, neuron-specific enolase; (D, J, and O) inferior olivary nuclei (ION), calbindin D28k. (E) Neuron in the basis pontis, ubiquitin; (F) neuron in the basis pontis, a-synuclein; (K and P) neurons in the basis pontis, 1C2 for polyglutamine. The midline sections of the brains in *MSA* (A), *SCA-1* (G), and *SCA-2* (L) show small cerebella and, in *MSA* (A) and *SCA-2* (L), atrophy of the basis pontis (arrows). The cerebellar cortex displays thinning of the molecular layer, loss of Purkinje cells, and an impoverished dendritic tree. The DN shows low density of *GAD*-reactive terminals in *MSA* (C), though DN neurons are intact (C, inset). In *SCA-1* (I) and *SCA-2* (N), the DN displays a greater density of *GAD*-reactive terminals than in *MSA* (C).

Void spaces corresponding to large DN neurons are absent in MSA (**C**), SCA-1 (**I**), and SCA-2 (**N**). The ION in MSA (**D**), SCA-1 (**J**), and SCA-2 (**O**) reveal gaps. Shared features of MSA, SCA-1, and SCA-2 are Purkinje cell atrophy, loss of GABAergic afferents of the DN, and retrograde degeneration of the ION. MSA and SCA-2 share atrophy of the basis pontis. 1C2-positive intranuclear neuronal inclusion bodies indicate poly-glutamine expansions in SCA-1 (**K**) and SCA-2 (**P**). Bars: (**A**, **G**, and **L**) 1 cm; (**B–D**, **C**, inset, **H–J**, and **M–O**, 100 μ m; **E** and **F**, **K**, and **P**, 10 μ m (oil immersion).

Fig. 8.3.

The cerebellar and olivary lesions in spinocerebellar ataxia types 6 (*SCA-6*) and 3 (*SCA-3*), and Friedreich ataxia (*FA*). (**A–E**) *SCA-6*; (**F–J**) *SCA-3*; (**K–N**) *FA*. Immunohistochemical stains: (**B**, **G**, and **L**) cerebellar cortex, class III b-tubulin; (**C**, **H**, and **M**) dentate nuclei (*DN*), glutamic acid decarboxylase (*GAD*); (**D**, **I**, and **N**) inferior olivary nuclei (*ION*), D28k; (**E** and **J**) neurons of the basis pontis, 1C2 for polyglutamine. The midline section of the brain in *SCA-6* (**A**) shows atrophy of the upper vermis with wide spaces between folia. The pons is well preserved in *SCA-6* (**A**). Pontine atrophy, however, is present in the illustrated case of *SCA-3* (**F**, arrow). Collapse of the *DN* in *FA* is especially apparent on a macroscopic stain for iron (**K**). The cerebellar cortex in *SCA-6* (**B**) shows loss of Purkinje

cells whereas the cortex in SCA-3 (**G**) and FA (**L**) is normal. The DN in SCA-6 shows reduced density of GABAergic terminals (**C**). The DN in SCA-3 (**H**) and FA (**M**) displays grumose reaction (arrows). Voids representing large neurons are still visible in the DN of SCA-3 (**H**). The ION in SCA-6 (**D**) reveals minor gaps in the chain of neurons, but the spherical dendritic tree in the remaining nerve cells is intact. The ION is entirely normal in SCA-3 (**I**) and FA (**N**), reflecting the integrity of Purkinje cells (**G** and **L**). 1C2-positive neuronal inclusion bodies are cytoplasmic in SCA-6 (**E**, arrows) but intranuclear in SCA-3 (**J**, arrow). Bars: (**A**, **F**, and **K**) 1 cm; (**B–D**, **G–I**, and **L–N**) 100 μm ; (**E** and **J**), 10 μm (oil immersion).

Fig. 8.4.

The cerebellum in hypoxia. (A, B) Three-day survival after incomplete cardiorespiratory resuscitation (49-year-old man); (C, D) 6-day survival after a 20-minute-long episode of pulselessness and resuscitation (59-year-old man); (E–G) 3-week survival after near drowning (14-year-old girl); (H, I) 1-year-survival after unsuccessful suicide attempt by hanging (48-year-old man). Stains: (A, C, F, G, and I) hematoxylin and eosin stains of cerebellar cortex; (B and D), hematoxylin and eosin stain of the DN; (D, inset) IBA-1 immunostain for microglia in the dentate nuclei (DN). (E and H) gross specimens. Brief

stagnant hypoxia causes loss of basophilic staining of Purkinje cells (**A**, and inset) and DN neurons (**B**). The granular layer is intact. After longer survival, loss of Purkinje cells is complete (**C**). Neurons of the DN still show the acidophilia of hypoxia (**D**), but a microglial response is now also apparent (**D**, inset). In the case of near drowning (**E–G**), the cerebellar cortex becomes atrophic, and the white matter of the brachium pontis is peculiarly white. Sections show thinning of the molecular layer and total loss of Purkinje and granule cells (**F**). The Purkinje cell layer displays intense proliferation of Golgi epithelial cells (“Bergmann gliosis”) (**G**). The cerebellum in the case of stagnant hypoxia during an unsuccessful suicide attempt by hanging (**H**) shows gross cerebellar atrophy. Loss of Purkinje cells is complete, and the density of granule cells is reduced (**I**). Bars: (**A**, **C**, **F**, and **I**) 100 μm ; (**B** and **D**) 50 μm ; (**A** and **D**, insets, and **G**) 20 μm ; (**E** and **H**) 1 cm.

Fig. 8.5.

The cerebellum in hypoglycemia. **(A)** Parietal cortex; **(B)** cerebellar cortex. A forensic autopsy was conducted on a 27-year-old man who was found in an unexplained comatose state from which he did not recover over a period of 3 weeks. Blood glucose levels were low, and the diagnosis was accidental, suicidal, or homicidal injection of insulin. The deeper layers of the parietal cortex **(A)** show necrosis, proliferation of capillaries, and infiltration by macrophages. The subpial gray matter (to the upper right) displays reactive astrogliosis **(A)**. In contrast to the cerebral cortex, the cerebellar cortex is intact **(B)**. Stain: hematoxylin and eosin; bars: 50 µm.

Fig. 8.6.

The cerebellum in ethanol and mercury toxicity. (A–C) Alcoholic cerebellar degeneration; (D and E) cerebellar atrophy in methylmercury toxicity. The gross specimen of the cerebellum obtained from a 58-year-old man with alcoholic cerebellar degeneration reveals atrophy of the superior vermis (A). Stains: (B, D, E, and E, inset), hematoxylin and eosin; (C and C, inset) Bodian silver stain for axons; (D, inset) immunohistochemistry of phosphorylated neurofilament proteins. Sections show loss of Purkinje cells (B), empty baskets (C, arrow) and axonal expansions (torpedoes) in the granular layer (C, inset). The section of the cerebellum in chronic methylmercury toxicity shows depletion of granular cells immediately adjacent to the Purkinje cell layer (D, arrow). Basket fibers surround intact Purkinje cells or form empty baskets (D, inset). The dentate nucleus displays moderate neuronal loss (E) and regions of grumose regeneration (E, inset). Bars: (A) 1 cm; (B) 200 μ m; (D and E) 50 μ m; (C–E, insets) 20 μ m. (D and E courtesy of Professor F. Ikuta, Niigata, Japan).

Fig. 8.7.

Vascular lesions of the cerebellum. (**A** and **B**) Small spontaneous cerebellar hemorrhage in a 68-year-old man with cancer; (**C–E**) 7-day-old hemorrhagic infarction in a 71-year-old man with cerebral embolism arising from vegetations on the aortic valve; (**F–H**) perioperative thrombosis of the right superior cerebellar artery in a 68-year-old man (survival of 2 months). (**I–L**), small infarction of the dentate nucleus (*DN*) (**I**, arrow) and olivary hypertrophy (**J**, arrow) in an 88-year-old man. Stains: (**B**, **D**, **E**, **G**, and **H**) hematoxylin and eosin; (**I**) Weil stain for myelin; (**J–L**) Bodian silver stain. The acute cerebellar hemorrhage

(A) displaces the cerebellar cortex, but has not yet generated a cellular response (B). In contrast, the hemorrhagic infarction (C) causes hypoxia in Purkinje cells (D), extravasation of red blood cells (D, arrow), and a vigorous macrophage response (E) with erythrophagocytosis (E, arrow). The old cystic infarction (F) is due to thrombotic occlusion of the superior cerebellar artery (F, arrow). The infarction involves the full thickness of the cerebellar cortex though Bergmann glia and their parent cell bodies remain intact (G). The infarction is sharply demarcated from the intact tissue (G). Small macrophages are present in the cystic infarction (H), and some contain brown hemosiderin pigment. A small infarction of the DN (I, arrow) causes transsynaptic hypertrophy of the inferior olivary nucleus (J, arrow), characterized by nerve cell vacuolation (K) and a bizarre plaque-like dendritic expansion (L). Bars, (A, C, and I) 1 cm; (F) 2 cm; (J) 5 mm; (B, D, and G) 100 μ m; (E, H, K, and L) 20 μ m.

Fig. 8.8.

The cerebellum in leptomenigitis. (A–D) *Streptococcus pneumoniae*; (E–G) *Aspergillus* sp.; (H–J) *Mycobacterium tuberculosis*. (A) and (B) An inflammatory infiltrate fills the subarachnoid space over the cerebellar cortex of this 61-year-old man with *S. pneumoniae* leptomenigitis. On the gross specimen, the exudate is visible in perivascular spaces (A, arrow). Inflammatory cells are predominantly polymorphonuclear leukocytes (C). On a smear preparation of pelleted cerebrospinal fluid, the organisms occur as “cocci-in-pairs,” are surrounded by a capsule, and are mostly extracellular (D). In the case of incidental *Aspergillus* sp. leptomenigitis in a 65-year-old man with steroid-induced

immunosuppression (**E–G**), the subarachnoid exudate consists of lymphocytes and histiocytes (**E**). The vessel wall is also infiltrated (**E**). A Grocott methenamine silver stain shows abundant septate fungal hyphae (**F**) that display branching (**G**). (**H**) A thick exudate is present over brainstem and cerebellum of a 37-year-old woman with thalamic tuberculoma and tuberculous leptomeningitis. Note also the presence of tonsillar herniation. The exudate consists of epithelioid cells, lymphocytes, and Langhans multinucleated giant cells (**I**). Caseation is absent. A section stained for acid-fast bacilli shows a single red organism (**J**, arrow). Stains: (**B**, **C**, **E**, and **I**) hematoxylin and eosin; (**D**) Gram stain with safranin counterstain; (**F**, and **G**) Grocott methenamine silver stain for fungi; (**J**) Ziehl–Neelsen stain for acid-fast bacilli. Bars: (**A** and **H**) 1 cm; (**B**) 0.5 mm; (**E**, **F**, and **I**) 50 μ m; (**C** and **G**) 20 μ m; (**D** and **J**) 10 μ m (oil immersion).

Fig. 8.9.

Infections of the cerebellar parenchyma. (A–C) Cerebellitis and *Toxoplasma gondii* infection in acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV); (D–G) cytomegalovirus infection in AIDS/HIV; (H–J) progressive multifocal leukoencephalopathy in non-AIDS immunosuppression; (K–M) prion disease: sporadic Jakob–Creutzfeldt disease. (A) The cerebellar cortex of a 50-year-old man with AIDS/HIV shows microglial nodules in the molecular layer (A, arrows). (B) Multiple cysts of *T. gondii* are present in the dentate nucleus (DN). (C) This microphotograph shows an enlargement

of four cysts in **(B)** that lie adjacent to a DN neuron (arrow). **(D)** The cerebellar section of a 49-year-old man with AIDS/HIV shows a necrotizing disease process in the molecular and granular layers of the cerebellum with many large cells due to cytomegalovirus infection. **(E)** The necrotic cerebellar white matter in this case displays a large cell of unknown derivation with densely amphophilic cytoplasm and a Cowdry type A intranuclear inclusion (arrow). **(F and G)** These microphotographs show immuno-histochemical reaction product of cytomegalovirus-specific cytoplasmic protein in the molecular **(F)** and granular layers **(G)**. **(H–J)** The cerebellar white matter of a 76-year-old man with progressive multifocal leukoencephalopathy due to immunosuppression in the course of chemotherapy for leukemia shows a focus of myelin loss **(H)**, inflammatory infiltration by plasma cells and lymphocytes **(I)**, and a giant astrocyte **(I, arrow)**. **(J)** The nearby intact white matter displays a pan-nuclear inclusion body (arrow). **(K)** The gross specimen of a 70-year-old with a rapidly progressive fatal neurologic illness diagnosed as Jakob–Creutzfeldt disease does not show convincing atrophy of the cerebellum. Sections reveal sponginess of the molecular layer **(L)** and immunohisto-chemical reaction product of protease-resistant prion protein, termed PrPsc in analogy to scrapie (monoclonal antibody 3F4) **(M)**. Bars: **(A, L, and M)** 50 µm; **(D and H)** 100 µm; **(B, E, F, G, and I)** 20 µm; **(C and J)** 10 µm (oil immersion).

Fig. 8.10.

Multiple sclerosis (*MS*) in the cerebellum. (**A**) A transverse slice through brainstem and cerebellum reveals plaques of *MS* in the cerebellar white matter and the brachium pontis (arrows). Stains: (**B** and **C**) Luxol fast blue–periodic acid–Schiff (*LFB-PAS*) for myelin; (**D**) immunohistochemistry (*IHC*) for myelin basic protein (*MBP*); (**E**) *IHC* for phosphorylated neurofilament protein; (**F**) *IHC* for IBA1; (**G**) *IHC* for glial fibrillary acidic protein (*GFAP*). (**B** and **C**) The section stained with *LFB-PAS* reveals a relatively sharp transition from intact white matter to the plaque of *MS*. (**D–G**) The plaque is located in the upper right portion of the images. (**D**) A stain for *MBP* is similar to (**C**), showing abrupt ending of myelination. (**E**) Axons traverse the plaque, but their density is lower than normal, and their caliber is small. (**F**) The junction between plaque and normal white matter displays micro-glial proliferation. (**G**) At the junction between plaque and normal white matter, a *GFAP* stain reveals reactive astrocytes. Bars: (**A**) 1 cm; (**B**) 0.5 mm; (**C–G**) 50 μ m.

Fig. 8.11.

The cerebellum in adult-onset lipid storage disease. (A–I) Niemann–Pick disease type C1; (J–M) ceroid-lipofuscinosis (Kufs disease). Stains: (B, C, G–J) hematoxylin and eosin; (D, E, and K) Bodian silver stain; (F, L, M) autofluorescence. (A–F) An archival case of a 54-year-old man shows reduced bulk of the dentate nucleus; loss of Purkinje cells (B) and a torpedo (D); lipid storage in Golgi neurons (B and C, arrows); neurofibrillary tangles (E); and autofluorescence of lipid-laden neurons of the granular layer (F). (G–I) A genetically confirmed recent case of a 37-year-old woman with progressive ataxia shows loss of

Purkinje cells (**G**), lipid storage in a Lugaro cell (**G**, arrow), a Golgi neuron (**H**), and a dentate nucleus neuron (**I**). (**J–M**). The cerebellar cortex in Kufs disease reveals reduced numbers of Purkinje cells and neurons in the granular layer (**J**). Some Purkinje cells show unusual dendritic expansions (**K**). The Purkinje cell cytoplasm is autofluorescent (**L** and **M**). Bars: (**B**, **D**, **G**, and **K**) 50 μm ; (**C**, **E**, **F**, **H**, **I**, and **M**) 20 μm ; (**J** and **L**) 100 μm .

Fig. 8.12.

The cerebellum in adult-onset autosomal-dominant leukodystrophy. Immunohistochemical stains: (A, B) Myelin basic protein; (C) class III b-tubulin; (D) phosphorylated neurofilament protein; (E) hematoxylin and eosin; (F) IBA1 as a marker of microglia; (G) glial fibrillary acidic protein. (A) The subcortical white matter of the cerebellum in this 54-year-old man shows patchy loss of myelin. (B) In contrast to multiple sclerosis, the demarcation of depleted and intact white matter is not sharp, and axons at the transition zone display bulbous endings (C, D). (C) The stain for class III b-tubulin does not reveal axons passing into the demyelinated region. (D) In contrast to the tubulin stain, reaction product of phosphorylated neurofilament protein reveals delicate axons in the myelin-deficient area. (E) Despite extensive myelin loss, oligodendroglia persist. (F) Microglia are abundant in transition zones. (G) The depleted regions show large and bizarre astrocytes while fibrous gliosis is absent. Bars: (A) 0.5 mm; (B–G) 50 μ m.