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Chapter 12

Nutritional and systemic metabolic disorders

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Abstract

Vitamin deficiency disorders display a wide variety of neurologic signs and symptoms, the pathogenesis of which is not clearly understood. Metabolic encephalopathies (hepatic, hypoglycemic, and uremic) have to be considered in the differential diagnosis of patients with cognitive impairment, motor disturbances, psychiatric symptoms, seizures, and neuropathies. Calcifications (vascular wall and parenchymal) occur in the normal aging brain and in neurodegeneration; some associated genes are already described.

VITAMIN DEFICIENCIES

Major vitamin deficiencies affecting the nervous system and their clinical sequelae are given in Table 12.1.

Thiamine (vitamin B_1) Wernicke encephalopathy

Wernicke–Korsakoff syndrome is one of the most frequently seen neurologic disorders associated with long-term and heavy alcohol abuse (Victor et al., 1971).

Clinical signs of Wernicke encephalopathy may present with acute or subacute onset. Ocular alterations consist of retinal hemorrhage, pupillary changes, extraocular muscle palsy, gaze palsy, and nystagmus. The site of pathology is the tegmentum of the brainstem. Autonomic changes include hypo- or hypertension, hypo- or hyperthermia, cardiac arrhythmias, and respiratory failure. The site of pathology is the hypothalamus and the dorsal nucleus of the vagus. Depression of consciousness, reduced alertness from obtundation to coma may exist. The site of pathology is the periaqueductal gray. Ataxia (vestibular and/or cerebellar dysfunction) is found, whereby the site of pathology is the vestibular region of the medulla and cerebellum.

Korsakoff amnestic syndrome is characterized by impairment of recent memory, including verbal and nonverbal material. It occurs after recovery from Wernicke encephalopathy. The sites of pathologic changes are the dorsomedial nuclei of the thalamus, mammillary bodies, and relay stations of the limbic lobe. Brain regions involved in Wernicke encephalopathy include the walls of the third ventricle, the mammillary bodies (atrophy in chronic cases), the dorsomedial nuclei of the thalami, the periaqueductal gray matter, and the floor of the fourth ventricle. Both conditions appear to have an identical neuropathology characterized by hemorrhages and other lesions around the ventricular system (Halliday et al., 1994).

Acute Wernicke encephalopathy is macroscopically characterized by soft consistency and yellow to brown discoloration of the tissue and petechial hemorrhages around the third and fourth ventricles, medial hypothalamus, thalamus, and periaqueductal gray matter. Microscopic changes consist of edema, hypertrophy of endothelial cells, extravasation of erythrocytes, and reactive astrogliosis. No apparent changes in neurons are seen.

Chronic Wernicke encephalopathy is macroscopically characterized by shrinkage and brown discoloration

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Table 12.1

The most important vitamins and neurologic features caused by their deficiency

Vitamin	Neurologic features
Vitamin B_1 (thiamine)	• Wernicke–Korsakoff encephalopathy • Cerebellar atrophy • Polyneuropathy
Vitamin B_3 (niacin)	• Pellagra • Beriberi • Polyneuropathy • Myelopathy • Encephalopathy • Chromatolysis of neurons in the cerebral cortex, brainstem, and spinal cord • Dementia
Vitamin B_6 (pyridoxine)	• Seizures in infancy • Polyneuropathy
Vitamin B_9 (folic acid, folate)	• Polyneuropathy • Myelopathy
Vitamin B_{12} (cobalamin)	• Degeneration of spinal cord • Polyneuropathy
Vitamin E (α-tocopherol)	• Spinocerebellar disorder • Degeneration of posterior and lateral columns of spinal cord • Axonal spheroids in cuneate and gracile nuclei of medulla

of the mammillary bodies. Microscopic findings include spongiform changes of the tissue, reactive astrogliosis, capillary endothelial hyperplasia, presence of lipid-laden macrophages, hemosiderin-laden macrophages as residues of microhemorrhages, deposition of hemosiderin pigments, fresh pericapillary hemorrhages, endothelial hypertrophy and proliferation, and destruction of myelin and axons. There is relative sparing of neurons (Torvik, 1987a, b).

Wernicke–Korsakoff syndrome is a very complex, multifactorial disorder where the interaction of multiple genes and environment plays an important role in the pathogenesis. The pathogenesis is due to deficiency of thiamine, a cofactor of several enzymes implicated in glucose metabolism, rather than a direct toxic effect of alcohol. The association of vitamin B_1 deficiency with intracellular and extracellular edema by glutamate (*N*-methyl-D-aspartate) receptor-mediated excitotoxicity seems to be an important mechanism (Torvik, 1987a, b). Genetic studies with controversial and nonconclusive results were undertaken on candidate genes like thiamine-dependent enzymes, alcohol-metabolizing enzymes, gamma-aminobutyric acid (GABA) receptors, and thiamine transporters (SLC19A2 and SLC19A3) (Guerrini et al., 2009). In a high-throughput proteomics study it was shown that each brain region reacts in a significantly different manner to chronic alcohol ingestion. Abnormalities in vitamin B_1 (thiamine)-related biochemical pathways as well as significant differences in protein expression profiles between uncomplicated and complicated alcoholics with hepatic cirrhosis were identified, suggesting that hepatic factors such as ammonia have significant additive influences on brain protein expression (Matsumoto, 2009).

Niacin (vitamin B_3): pellagra encephalopathy

Pellagra is characterized by a typical reddish and glossy rash on the dorsum of hands and feet and around the neck (sign called Casal's necklace) (Lopez et al., 2014). Pellagra is a disease of malnutrition involving deficiency not only of the B vitamin niacin (vitamin B_3), but also its tryptophan (Trp) precursor, and is compounded by deficiencies of other nutrients, notably other B vitamins and possibly also zinc (Badawy, 2014). Pellagra encephalopathy should still be considered in the differential diagnosis of acute psychotic disorders seen in the context of chronic alcoholism (Lopez et al., 2014).

Depression in pellagra may be due to a serotonin deficiency caused by decreased Trp availability to the brain. Anxiety and other neurologic disturbances may be caused by 5-aminolevulinic acid and the Trp metabolite kynurenic acid. Pellagra symptoms are resolved by niacin, but aggravated mainly by vitamin B_6. Alcohol dependence can induce or aggravate pellagra by inducing malnutrition, gastrointestinal disturbances, and B vitamin deficiencies, inhibiting the conversion of Trp to niacin and promoting the accumulation of 5-aminolevulinic acid and porphyrins. Alcoholic pellagra encephalopathy should be managed with niacin, other B vitamins, and adequate protein nutrition (Badawy, 2014).

Alcoholic pellagra encephalopathy as a result of nicotinamide deficiency is clinically characterized by confusion and/or clouding of consciousness, marked oppositional hypertonus, and myoclonus (Serdaru et al., 1988; Cook et al., 1998). No gross macroscopic changes are usually visible. Microscopically, the major finding is a central chromatolysis of neurons, predominantly in the brainstem and in the cerebellar dentate nuclei. The affected neurons are ballooned with a loss of Nissl substance and eccentrically located nuclei. Nuclei of cranial nerves, the reticular nuclei, arcuate nuclei, and posterior horn cells may also be affected. Glial cells, myelin, or blood vessels are not affected (Ishii and Nishihara, 1981; Hauw et al., 1988).

Folic acid (folate, vitamin B_9)

Folic acid (folate) is necessary for the production and maintenance of new cells, for DNA synthesis and RNA synthesis, and for preventing changes to DNA, and, thus, for preventing cancer. It is also essential for the formation of biogenic amines and pterins in the central nervous system. It is especially important during periods of frequent cell division and growth, such as infancy and pregnancy (Blom et al., 2006).

Folate deficiency produces a variety of neurologic symptoms, including neuropsychiatric disturbances and movement disorders in adults and neural tube defects in newborns. Cerebral folate deficiency (CFD) can be defined as any neurologic syndrome associated with low cerebrospinal fluid 5-methyltetrahydrofolate, the active folate metabolite, in the presence of normal folate metabolism outside the nervous system. CFD may result from either disturbed folate transport or from increased folate turnover within the central nervous system (Ramaekers and Blau, 2004; Ramaekers et al., 2013). Classic autoimmune CFD is characterized by normal early development followed by abrupt neurologic regression. At approximately 4 months, children develop marked irritability, decelerated head growth, psychomotor retardation, ataxia, spasticity, dyskinesia (choreoathetosis and ballism), visual loss, hearing loss, and myoclonic epilepsy (Ramaekers et al., 2002, 2005, 2013; Ramaekers and Blau, 2004).

The most common cause underlying CFD syndromes is the presence of serum autoantibodies of the blocking type directed against folate receptor-α attached to the plasma side of choroid plexus epithelial cells. Less frequent causes of CFD are FOLR-1 mutations, mitochondrial disorders, and inborn errors affecting folate metabolism (Ramaekers et al., 2013).

Cobalamin (vitamin B_{12})

Vitamin B_{12} deficiency results from its impaired absorption, leading to disturbed function of an intrinsic binding factor which is synthesized by parietal cells of the gastric mucosa and necessary for its intestinal absorption. Cobalamin takes part in a variety of methylation reactions during the synthesis of DNA, neurotransmitters, protein, and fatty acid, all necessary for myelin metabolism. Reduced amount of S-adenosyl-methionine, as found in cobalamin deficiency, leads to the synthesis of abnormally methylated phospholipids and may cause central myelin breakdown (Vry et al., 2005). Causes responsible for vitamin B_{12} deficiency include autoimmune gastritis, gastrectomy, enteritis, malabsorption diseases, and fish tapeworm infestation (Berger, 1997; Gilbert, 1997).

Clinical signs include: subacute paresthesias of the extremities, weakness and diminished or lost vibratory and position sensations in the lower extremities, positive Romberg sign, spastic ataxic gait, cerebral dysfunction, emotional lability, confusion, and intellectual decline.

On gross anatomic examination the spinal cord shows mild atrophy and grayish discoloration of the posterior and lateral columns. Histologic changes consist of myelin degeneration in the posterior and lateral columns with vacuolization and spongiform changes. A case of isolated and partially reversible leukoencephalopathy has been reported (Vry et al., 2005).

METABOLIC ENCEPHALOPATHIES

Hepatic encephalopathy

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver defined hepatic encephalopathy as a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurologic or psychiatric abnormalities ranging from subclinical alterations to coma (Vilstrup et al., 2014). Thus, hepatic encephalopathy is a complication of liver disease in alcoholics, particularly in the course of liver cirrhosis. The damaged liver can no longer clear neurotoxic substances from the blood and these subsequently enter the brain and damage neurons and astrocytes (Butterworth, 2016).

Clinical signs include cognitive, psychiatric, and motor changes encompassing deterioration in the level of consciousness accompanied by decreased (or occasionally increased) psychomotor activity; if left untreated, it leads to increasing drowsiness, stupor and eventual coma. As the encephalopathy progresses, signs of pyramidal tract dysfunction such as hypertonia and hyperreflexia are common, eventually being replaced by hypotonia as coma develops (Butterworth, 2003; Lewis and Howdle, 2003; Atluri et al., 2011). The prognosis of patients with overt hepatic encephalopathy is poor: the 1-year survival is about 40%, falling to about 15% after 3 years (Lewis and Howdle, 2003). The major causes of death in hepatic encephalopathy are brain edema and intracranial hypertension (Vaquero et al., 2003).

Autopsy revealed brain edema and astrocyte swelling in patients with fulminant hepatic failure where hepatic encephalopathy developed within 8 weeks after onset of liver disease (Blei and Larsen, 1999). In patients with liver cirrhosis and portosystemic shunts, the typical histologic finding is the presence of Alzheimer type II astrocyte (Norenberg, 1998) (Fig. 12.1). These astrocytes have a characteristic swollen shape with a large, pale nucleus, prominent nucleolus, and margination of chromatin. They are found in widespread regions of the brain,

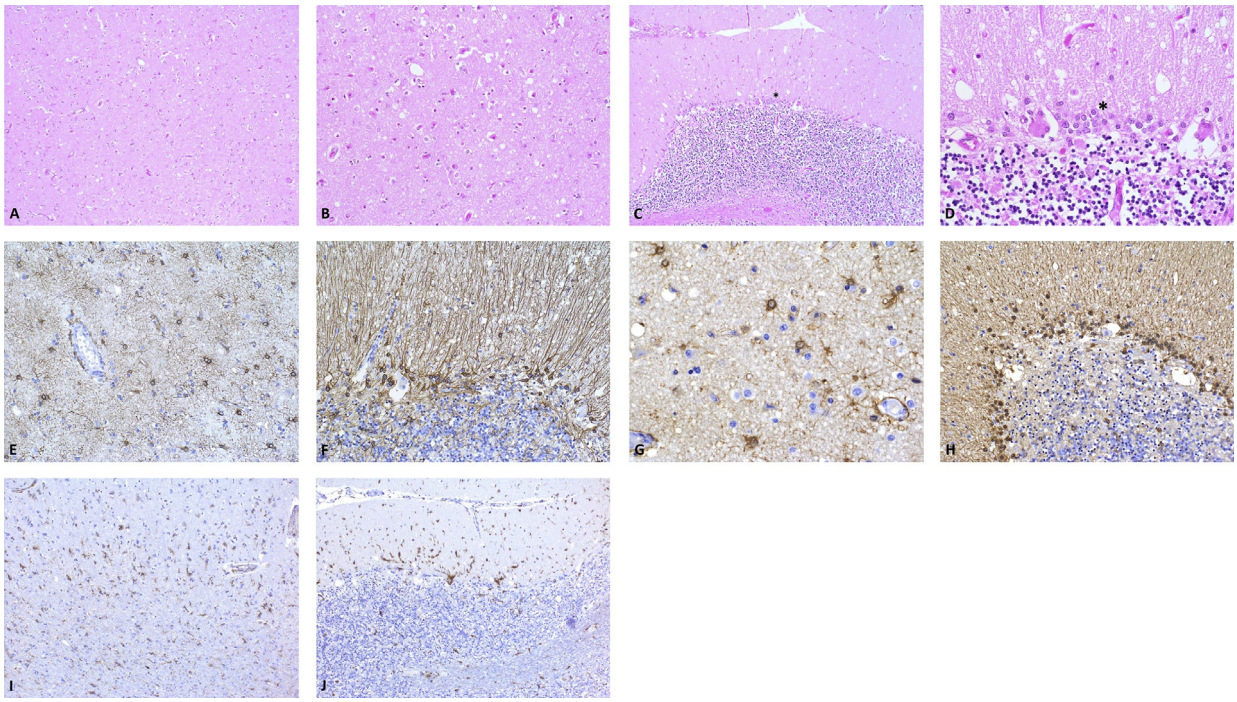

Fig. 12.1. Hepatic encephalopathy: spongiform changes and reactive astrogliosis in the cerebral cortex with presence of Alzheimer type II astrocytes (arrows) (**A**, **B**) and in the cerebellum with Bergmann gliosis (asterisk) (**C**, **D**), reactive astrogliosis (glial fibrillary acidic protein) in the cerebral cortex (**E**) and cerebellum (**F**), S-100-positive astrocytes in the cerebral cortex (**G**) and cerebellum (**H**) reactive microgliosis in the cerebral cortex (**I**) and in the cerebellum (**J**).

including the cortex and the lenticular, lateral thalamic, dentate, and red nuclei (Norenberg, 1998; Haussinger et al., 2000). The majority of these cells show prominent immunoreactivity for S100P but not for glial fibrillary acidic protein, especially in the gray matter (Kimura and Budka, 1986).

A major pathogenic factor consists of an ammonia-induced dysfunction of astrocytes. Inflammation, infection, and oxidative/nitrosative stress might modulate the pathophysiologic effects of ammonia on astrocytes (Seyan et al., 2010; Toris et al., 2011). Deficits in the uptake of glutamate by astrocytes from the extracellular space may lead to abnormal glutamatergic and GABAergic-mediated neurotransmission and subsequent neuronal excitotoxicity (Blei and Larsen, 1999; Haussinger et al., 2000). In addition, an altered blood–brain barrier permeability (Haussinger et al., 2000), a combined derangement of cellular osmolarity coupled with cerebral hyperemia (Vaquero et al., 2003), as well as excessive glutamine synthesis in ammonia-overloaded astrocytes (Zielinska et al., 2014) appear to be involved in the generation of the edema.

Hypoglycemic encephalopathy

A sudden drop in the blood glucose level to 30–40 mg/100 mL results in permanent brain damage within 1–2 hours. Causes of hypoglycemic episodes include insulin overdose in diabetic patients, insulinoma of pancreatic island cells, and liver, adrenal, pituitary, and thyroid diseases.

Clinical signs consist of headaches, perspiration, nervousness, tremulousness, confusion, myoclonic jerks, seizures, decerebrate rigidity, and coma.

The cerebral cortex is atrophic and the volume of the white matter reduced. Histologically, selective neuronal necrosis is seen affecting the hippocampus (CA1 sector), subiculum, neocortical regions, caudate nucleus, putamen, and Purkinje cells of the cerebellum.

Uremic encephalopathy

Patients with renal failure or hemodialysed patients may develop uremic encephalopathy clinically manifest as tremor, asterixis, myoclonic jerks, seizure, sleep disorders, peripheral nervous system involvement, autonomic neuropathy, mononeuropathies, myopathy, cognitive impairment, stupor, and coma (Brouns and De Deyn, 2004; Seifter and Samuels, 2011; Bansal and Bansal, 2014; Baumgaertel et al., 2014). Reversible parkinsonism with lentiform fork sign as an initial and dominant manifestation of uremic encephalopathy has been described (Park et al., 2015).

Brain examination shows signs of cytotoxic edema, neuronal loss in the cerebral and cerebellar cortex, deep gray-matter structures, and perivascular demyelination.

High levels of various uremic toxins (guanidino compounds), advanced glycation endproducts, excess of parathyroid hormones as well as pump activity of an abnormal Na-K-ATPase and inhibition of the organic anion transporter system are involved in the pathogenesis of acute uremic encephalopathy (Heidland et al., 2010).

CALCIUM METABOLIC DISORDERS

Calcium deposits

In elderly brains, deposits of calcium can be found in the basal ganglia, in the hippocampus, and in the cerebellar dentate nucleus within the vessel wall (capillaries and small arteries) (Fig. 12.2), as well as small extraparenchymal droplet-like, globular to mulberry-like basophilic structures.

Fahr disease (striato-pallido-dentate calcification)

Striato-pallido-dentate calcifications or Fahr disease are encountered in patients presenting with hypo- or hyperparathyroid disorders. The calcifications have the appearance as described above (Fig. 12.3).

Nowadays, Fahr disease is also named idiopathic basal ganglia calcification (IBGC). IBGC is characterized by mineral deposits in the brain, an autosomal-dominant pattern of inheritance in most cases, and genetic heterogeneity. Diagnosing IBGC necessitates the exclusion of other causes, including calcification related to normal aging, for which no normative data exist (Nicolas et al., 2013).

IBGC may be a phosphate imbalance disorder. Recently, genetic studies have identified several genes associated with IBGC, including *SLC20A2*, *PDGFRβ* (encodes a member of the platelet-derived growth factor receptor family type β), *PDGF* (the specific ligand of PDGFRβ), *ISG15*, and *XPR1*. Loss-of-function mutations in these genes have been associated with disturbance in phosphate homeostasis in brain regions, the dysfunction of blood–brain barrier, as well as enhanced interferon-α/β immunity (Lemos et al., 2013; Deng et al., 2015; Wang et al., 2015). Wang et al. (2012) identified seven novel mutations at the *SLC20A2* gene and showed that such mutations have an effect through haploinsufficiency (Wang et al., 2012). Clinical and radiologic diversity is confirmed, regardless of the genetic status. Quantification of calcification is correlated with the symptomatic status, but the location and severity of the calcifications do not reflect the whole clinical diversity (Nicolas et al., 2013). The mutations may suppress PDGFRβ autophosphorylation, result in partial loss of autophosphorylation, or involve reduced protein levels (Sanchez-Contreras et al., 2014). Arts et al. (2015) reported that one mutation had no kinase activity and failed to activate any of the pathways normally stimulated by PDGF. Another mutant activated Akt and MAP kinases, but did not induce the phosphorylation of signal transducer and activator of transcription 3 (STAT3). After PDGF stimulation, phosphorylation of phospholipase Cγ was decreased and a mutant was more rapidly degraded upon PDGF binding compared to wild-type PDGFRB (Arts et al., 2015).

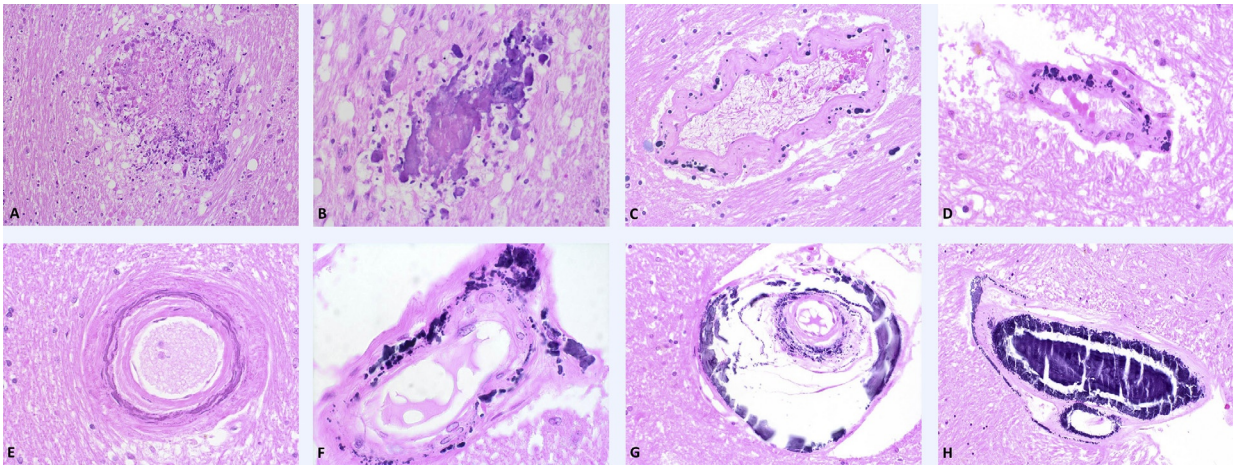

Fig. 12.2. Vessel wall calcifications. Calcium deposits in the form of dystrophic tissue calcifications (**A**, **B**); various developmental stages of vascular wall calcifications (**C–H**).

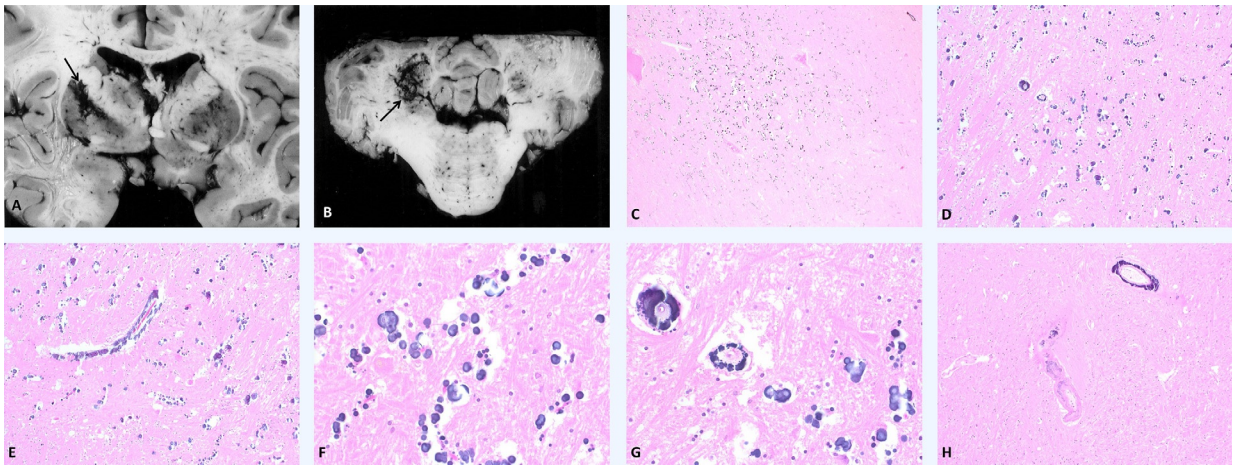

Fig. 12.3. Idiopathic basal ganglia calcification or Fahr disease. Gross anatomic appearance of calcium deposits in the basal ganglia and in the dentate nucleus of the cerebellum (arrows) (**A**). Calcium deposits in the basal ganglia (**B–H**), dentate nucleus (**G**), and vascular wall (**D**, **F**, **H**).

References

Arts FA, Velghe AI, Stevens M et al. (2015). Idiopathic basal ganglia calcification-associated PDGFRB mutations impair the receptor signalling. J Cell Mol Med 19 (1): 239–248. http://dx.doi.org/10.1111/jcmm.12443.

Atluri DK, Prakash R, Mullen KD (2011). Pathogenesis, diagnosis, and treatment of hepatic encephalopathy. J Clin Exp Hepatol 1: 77–86.

Badawy AA (2014). Pellagra and alcoholism: a biochemical perspective. Alcohol Alcohol 49: 238–250.

Bansal VK, Bansal S (2014). Nervous system disorders in dialysis patients. Handb Clin Neurol 119: 395–404.

Baumgaertel MW, Kraemer M, Berlit P (2014). Neurologic complications of acute and chronic renal disease. Handb Clin Neurol 119: 383–393.

Berger JR (1997). Cobalamine deficiency. Neurology 48: 295.

Blei AT, Larsen FS (1999). Pathophysiology of cerebral edema in fulminant hepatic failure. J Hepatol 31: 771–776.

Blom HJ, Shaw GM, den Heijer M et al. (2006). Neural tube defects and folate: case far from closed. Nat Rev Neurosci 7: 724–731.

Brouns R, De Deyn PP (2004). Neurological complications in renal failure: a review. Clin Neurol Neurosurg 107: 1–16.

Butterworth RF (2003). Hepatic encephalopathy. Alcohol Res Health 27: 240–246.

Butterworth RF (2016). Pathogenesis of hepatic encephalopathy in cirrhosis: the concept of synergism revisited. Metab Brain Dis 31: 1211–1215.

Cook CC, Hallwood PM, Thomson AD (1998). B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol Alcohol 33: 317–336.

Deng H, Zheng W, Jankovic J (2015). Genetics and molecular biology of brain calcification. Ageing Res Rev 22: 20–38.

Gilbert GJ (1997). Cobalamine deficiency. Neurology 48: 295.

Guerrini I, Thomson AD, Gurling HM (2009). Molecular genetics of alcohol-related brain damage. Alcohol Alcohol 44: 166–170.

Halliday G, Cullen K, Harding A (1994). Neuropathological correlates of memory dysfunction in the Wernicke–Korsakoff syndrome. Alcohol Alcohol Suppl 2: 245–251.

Haussinger D, Kircheis G, Fischer R et al. (2000). Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema? J Hepatol 32: 1035–1038.

Hauw JJ, De Baecque C, Hausser-Hauw C et al. (1988). Chromatolysis in alcoholic encephalopathies. Pellagra-like changes in 22 cases. Brain 111: 843–857.

Heidland A, Sebekova K, Klassen A et al. (2010). Mechanisms of acute uremic encephalopathy: early activation of Fos and Fra-2 gene products in different nuclei/areas of the rat brain. J Ren Nutr 20: S44–S50.

Ishii N, Nishihara Y (1981). Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases. J Neurol Neurosurg Psychiatry 44: 209–215.

Kimura T, Budka H (1986). Glial fibrillary acidic protein and S-100 protein in human hepatic encephalopathy: immunocytochemical demonstration of dissociation of two glia-associated proteins. Acta Neuropathol 70: 17–21.

Lemos RR, Ferreira JB, Keasey MP et al. (2013). An update on primary familial brain calcification. Int Rev Neurobiol 110: 349–371.

Lewis M, Howdle PD (2003). The neurology of liver failure. Q J Med 96: 623–633.

Lopez M, Olivares JM, Berrios GE (2014). Pellagra encephalopathy in the context of alcoholism: review and case report. Alcohol Alcohol 49: 38–41.

Matsumoto I (2009). Proteomics approach in the study of the pathophysiology of alcohol-related brain damage. Alcohol Alcohol 44: 171–176.

Nicolas G, Pottier C, Charbonnier C et al. (2013). Phenotypic spectrum of probable and genetically confirmed idiopathic basal ganglia calcification. Brain 136: 3395–3407.

Norenberg MD (1998). Astroglial dysfunction in hepatic encephalopathy. Metab Brain Dis 13: 319–335.

Park JW, Kim SU, Choi JY et al. (2015). Reversible parkinsonism with lentiform fork sign as an initial and dominant manifestation of uremic encephalopathy. J Neurol Sci 357: 343–344.

Ramaekers VT, Blau N (2004). Cerebral folate deficiency. Dev Med Child Neurol 46: 843–851.

Ramaekers VT, Hausler M, Opladen T et al. (2002). Psychomotor retardation, spastic paraplegia, cerebellar ataxia and dyskinesia associated with low 5-methyltetrahydrofolate in cerebrospinal fluid: a novel neurometabolic condition responding to folinic acid substitution. Neuropediatrics 33: 301–308.

Ramaekers VT, Rothenberg SP, Sequeira JM et al. (2005). Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med 352: 1985–1991.

Ramaekers V, Sequeira JM, Quadros EV (2013). Clinical recognition and aspects of the cerebral folate deficiency syndromes. Clin Chem Lab Med 51: 497–511.

Sanchez-Contreras M, Baker MC, Finch NA et al. (2014). Genetic screening and functional characterization of PDGFRB mutations associated with basal ganglia calcification of unknown etiology. Hum Mutat 35 (8): 964–971. http://dx.doi.org/10.1002/humu.22582.

Seifter JL, Samuels MA (2011). Uremic encephalopathy and other brain disorders associated with renal failure. Semin Neurol 31: 139–143.

Serdaru M, Hausser-Hauw C, Laplane D et al. (1988). The clinical spectrum of alcoholic pellagra encephalopathy. A retrospective analysis of 22 cases studied pathologically. Brain 111: 829–842.

Seyan AS, Hughes RD, Shawcross DL (2010). Changing face of hepatic encephalopathy: role of inflammation and oxidative stress. World J Gastroenterol 16: 3347–3357.

Toris GT, Bikis CN, Tsourouflis GS et al. (2011). Hepatic encephalopathy: an updated approach from pathogenesis to treatment. Med Sci Monit 17: Ra53–Ra63.

Torvik A (1987a). Brain lesions in alcoholics: neuropathological observations. Acta Med Scand Suppl 717: 47–54.

Torvik A (1987b). Topographic distribution and severity of brain lesions in Wernicke's encephalopathy. Clin Neuropathol 6: 25–29.

Vaquero J, Chung C, Cahill ME et al. (2003). Pathogenesis of hepatic encephalopathy in acute liver failure. Semin Liver Dis 23: 259–269.

Victor M, Adams RD, Collins GH (1971). The Wernicke–Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp Neurol Ser 7: 1–206.

Vilstrup H, Amidio P, Bajaj J et al. (2014). Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 61: 642–659.

Vry MS, Haerter K, Kastrup O et al. (2005). Vitamin-B12-deficiency causing isolated and partially reversible leukoencephalopathy. J Neurol 252: 980–982.

Wang C, Li Y, Shi L et al. (2012). Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet 44: 254–256.

Wang C, Xu X, Li L et al. (2015). Molecular mechanism of idiopathic basal ganglia calcification. Yi Chuan 37: 731–740.

Zielinska M, Popek M, Albrecht J (2014). Roles of changes in active glutamine transport in brain edema development during hepatic encephalopathy: an emerging concept. Neurochem Res 39: 599–604.