

Ware AL, Glass L, Crocker N, et al. Effects of prenatal alcohol exposure and attention-deficit/hyperactivity disorder on adaptive functioning. *Alcohol Clin Exp Res*. 2014; 38:1439–1447.

Ware AL, O'Brien JW, Crocker N, et al. The effects of prenatal alcohol exposure and attention-deficit/hyperactivity disorder on psychopathology and behavior. *Alcohol Clin Exp Res*. 2013;37:507–516.

## ▲ 2.14 Neuropsychiatry of Neurometabolic and Neuroendocrine Disorders

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Metabolic and endocrine disturbance can have wide-ranging effects on the CNS. Neurons, because of their high metabolic level of activity and demand, are often acutely sensitive to derangements in more systemic metabolic processes. As a result, disorders affecting systemic metabolism often have a very high rate of associated CNS disturbance, ranging from the severe—with gross neurodevelopmental disruption, delirium, and/or coma—to the mild, with subtle cognitive and behavioral disturbance. However, a number of these disorders cause recognizable and significant psychiatric illness, including psychotic disorders, affective disturbance, anxiety disorders, attention-deficit disturbance, and other behavioral disturbance such as apathy, dysexecutive syndromes, and catatonia. For the purposes of this section, those disorders of metabolism and endocrine function associated with significant CNS disturbance will be referred to as *neurometabolic* and *neuroendocrine* disorders, respectively, and those associated with major neuropsychiatric syndromes will be highlighted.

The relevance of recognition of neuropsychiatric comorbidity in neurometabolic and neuroendocrine syndromes extends to both diagnostic and treatment issues. A number of these disorders can produce an accurate *phenocopy* of psychiatric illness, where illness presentation carries most or all the characteristic features of a psychiatric diagnosis. For example, a schizophrenia-like psychosis may develop in metachromatic leukodystrophy (MLD) that is otherwise indistinguishable from “typical” schizophrenia, at least until other features more typical of the primary neurometabolic illness supervene. Awareness of the types of disorders that may present as psychiatric illness phenocopies, and their associated physical, cognitive, or neurological concomitants, allows for the appropriate recognition and diagnostic confirmation of an underlying metabolic or endocrine illness. In some circumstances, this may mean medical treatment of an endocrine illness, enzyme replacement, or substrate reduction therapy for a metabolic illness. Failure to recognize the underlying illness while focusing on psychiatric treatment alone can delay the institution of appropriate management and result in potentially irreversible CNS changes.

Most clinicians will undertake a routine set of investigations for underlying “organic” causes of psychiatric illness at first presentation, including screening for thyroid illness, infective disease, electrolyte disturbance, and renal and kidney function, in addition to brain imaging and/or electroencephalography (EEG). Although these tests are relatively high yield and detect a number of illnesses producing secondary psychiatric syndromes, less common but no less significant conditions are often missed. Literally hundreds of

metabolic disorders have been described, and only a very limited number of these are screened for in the neonatal period (usually less than ten in most centers). This may provide the clinician with a false assurance that any significant and/or serious metabolic disorders will already have been detected. This situation is further complicated by the fact that the age of onset and presentation, in addition to disease expression, vary greatly across and within these disorders, and disorders that present later or in a less severe form are often missed by screening processes during the neonatal and childhood periods.

Those metabolic disorders that present initially, or predominantly, with neuropsychiatric syndromes generally have their onset in the period of the life cycle associated with the onset of the majority of psychiatric illnesses, that is, adolescence or early adulthood. The disorders that present in this stage will commonly be inborn errors of metabolism, affecting cellular function in the CNS. A wide range of phenotype–genotype correlations occur in such disorders, as differing mutations in the gene for the protein serving a key function in metabolism will result in different structural or conformational changes to the protein product and differential metabolic effects. For example, some mutations in the gene encoding for the NPC1 protein in Niemann–Pick disease type C are associated with an early onset or illness, severe mental retardation, and death in childhood, whereas others are associated with a less significant protein defect, a reduced effect on NPC1’s role in intracellular cholesterol metabolism (even falling into the “normal” range), and a presentation in adolescence or early adulthood. The adult-onset forms of these diseases often form a minority of cases of these disorders, although they will generally respond as favorably to primary treatments for the disorder. In addition, some carriers with autosomal recessive disorders who were previously considered asymptomatic (such as female carriers with adrenomyeloneuropathy) have been shown to have “borderline” syndromes often involving subtle psychiatric disturbance. For most of these disorders, gross metabolic disturbance results in severe impairment of CNS function (such as delirium or coma), with moderate impairments often resulting in dementia (or mental retardation in children) and movement disorders. More subtle impairments, however, are less likely to disrupt these core vegetative and functional systems of the brain, but rather disrupt higher-order functions that are much more dependent on highly synchronous corticocortical and subcortical connectivity, with the result being disturbance to higher cognitive functions and a predisposition toward major mood and psychotic disorders. As these systems tend to mature later in the brain’s neurodevelopmental trajectory, those disorders that alter or interrupt late neurodevelopment are more likely to cause neuropsychiatric syndromes. For progressive disorders, it is not uncommon for these disorders to present initially with a neuropsychiatric syndrome, which may be diagnosed and treated as a primary psychiatric illness. As the pathological effect of the metabolic derangement impinges further on the CNS and begins to result in degenerative change, frank neurological illness and dementia often supervene.

In addition to those metabolic disorders that impact on neurodevelopment, some metabolic disorders are associated with episodic but reversible metabolic disturbances (such as the acute porphyrias). As opposed to impacting late-maturing developmental networks, these disorders impact metabolically on presumably mature or normally developed brain systems. Those disorders that show a predilection for neuropsychiatric disturbance are more likely to affect brain regions (such as the frontal or temporal cortical regions) or transmitter systems (particularly dopaminergic and serotonergic systems) that are strongly associated with psychiatric illness. Similarly, the majority of major endocrine disorders that are associated with psychiatric disturbance do so in the setting of an otherwise intact

CNS. These endocrine systems are crucially involved in energy metabolism, cell turnover, and downstream metabolic effects. Disorders associated with elevated rates of psychiatric disturbance act via a direct effect of the altered hormonal system on particularly vulnerable cellular populations or neurotransmitter systems such as the effects of elevated cortisol levels on hippocampal neurons, or thyroid hormone on serotonin turnover.

## NEUROMETABOLIC SYNDROMES

### Lysosomal Disorders

The lysosome is a subcellular organelle that is manufactured by the Golgi apparatus and contains a number of hydrolytic enzymes such as proteases, lipases, nucleases, and polysaccharidases. They function as the “garbage disposal” system of the cell, via phagocytosis (digestion of extracellular material), endocytosis (digestion of cell surface proteins), and autophagy (digestion of old or damaged intracellular organelles or structures). Macromolecules (proteins, glycoproteins, lipids, and phospholipids) transported to lysosomes are degraded by enzymatic “factories,” which then pass out their monomeric components for reutilization. Impairment in function of a lysosomal enzyme occurs if it is structurally altered, alteration occurs to a cofactor protein, or enzyme transport is affected. Each enzyme is specific for breaking a particular chemical bond, as opposed to a particular substrate macromolecule. Over 70 lysosomal enzymes are known, and more than 40 disease syndromes involving defective enzyme function have been characterized. Many of these disorders present both in childhood and adulthood, and for those that present in adolescence or early adulthood—the period of onset of most major mental disorders—the rate of major mental illness is not unexpectedly elevated, whereas childhood presentations commonly result in major intellectual disability and older-adult presentations in dementia, in addition to frank neurological disturbance. Of those lysosomal storage disorders (LSDs) that present in adult life, those strongly associated with neuropsychiatric presentations include those involving defective breakdown of sphingolipid components (MLD, Fabry disease, GM2-gangliosidosis/Tay–Sachs disease [TSD], Niemann–Pick type C disease [NPC]), glycoproteins ( $\alpha$ -mannosidosis), and cholesterol and lipids (neuronal ceroid lipofuscinosis (NCL) or Kuf disease).

### Metachromatic Leukodystrophy

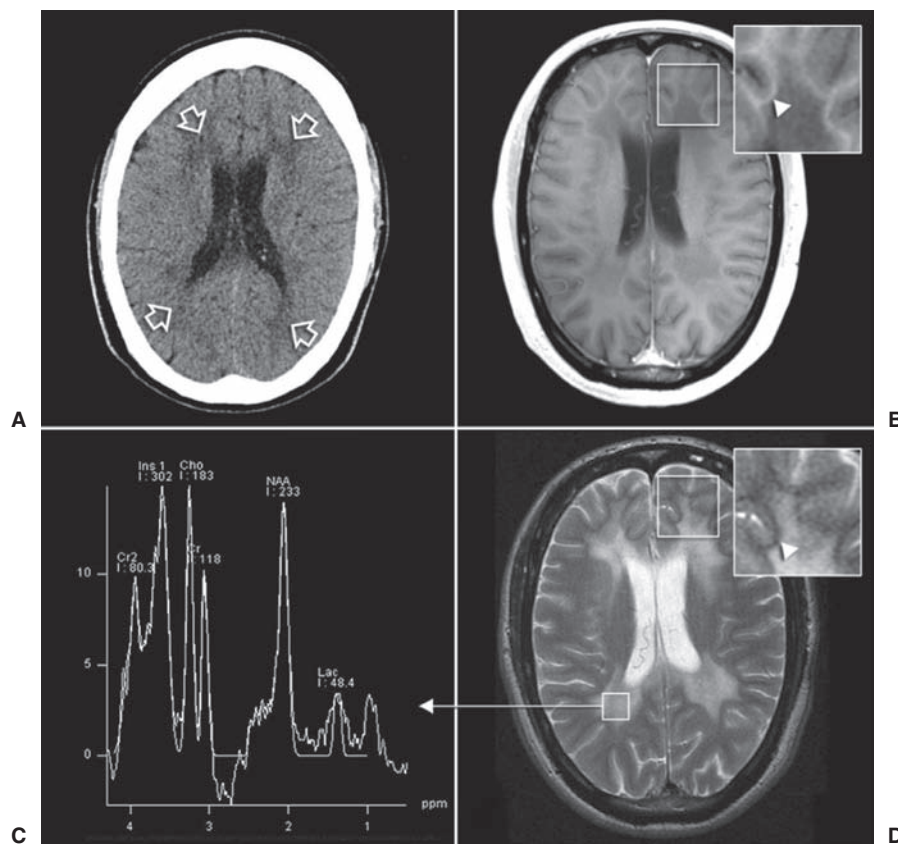
MLD is an autosomal recessive, incompletely penetrant genetic deficiency of the lysosomal enzyme arylsulfatase A (ASA). ASA hydrolyzes various sulfatides, including sulfate-containing lipids of the CNS. Lysosomal sulfatide accumulates in brain, peripheral nerves, kidney, and gallbladder, but particularly in myelinated structures, seen as metachromatic granules on histological examination and widespread loss of myelin. MLD is protean in its presentations such that in younger patients, seizures and motor symptoms predominate with psychiatric manifestations and dementia occurring frequently prior to the onset of motor symptoms in adult patients, particularly those with the I179S mutation. The adult form appears to cleave into two distinct phenotypes, one with a predominantly motor cerebellopyramidal presentation, and the other with a predominantly psychiatric presentation. Up to half of patients with illness onset between 10 and 30 years of age present with psychotic symptoms, including auditory hallucinations, systematized delusions, formal thought disorder, catatonic posturing, and inappropriate affect. As the illness progresses, other neurological symptoms supervene, such

as seizures, chorea, or dystonia. Dementia is an inexorably progressive component of the illness, initially presenting as attentional disturbance, reduced speed of processing and executive impairment, and may present as a phenocopy of frontotemporal dementia; if disinhibition is a prominent feature, it may present as a phenocopy of hypomania. Diagnosis is made by demonstrating reduced enzyme activity in leukocytes or skin fibroblasts. MRI generally demonstrates typical periventricular white matter changes sparing subcortical U-fibers, and often shows pathology with a frontotemporal preponderance (Fig. 2.14–1).

Treatment is generally symptomatic, although bone marrow transplantation has shown benefit in some patients, and enzyme replacement therapies are currently being investigated. Adolescent/adult MLD provides an intriguing model for the understanding of the neurobiology of psychosis, as it interrupts myelinative processes that occur during this critical period of neurodevelopment, in particular frontotemporal myelination. As frontotemporal connectivity is known to be impaired at both functional and structural levels in schizophrenia, MLD appears to have an almost uniquely psychotogenic propensity in this age group, and suggests that a neuropathological process that interrupts the normal development of connectivity between these cortical regions in this crucial late neurodevelopmental window can result in psychosis. It has also been shown that some treatment-refractory schizophrenia patients have ASA pseudo-deficiency or intermediate ASA levels, suggesting that this may be a disease modifier or potentially an independent risk factor for the development of psychosis.

### Fabry Disease

Fabry disease is an X-linked recessive disorder of the lysosomal enzyme  $\alpha$ -galactosidase A, resulting in accumulation of the glycolipid globotriaosylceramide (Gb3) in blood vessels and other tissues (Fig. 2.14–2). It particularly affects hemizygous males, with females varying from asymptomatic to severely affected because of X inactivation. The major clinical manifestations of Fabry disease reflect the particular impact of the disorder on vascular endothelium. Early clinical features with onset in childhood or adolescence include angiokeratomas and acroparesthesias. Angiokeratomas are dark, punctate vascular lesions most prevalent between the umbilicus and the knees but also seen on the oral mucosa and conjunctiva. Acroparesthesias are acute episodes of severe pain in the fingers and toes lasting days to weeks precipitated by exercise, fatigue, or fever, which are very disabling. Chronic pain syndromes associated with acroparesthesias may continue into adulthood and account for much of the associated psychiatric comorbidity. Corneal or lenticular opacities and hypohidrosis are also early manifestations. Disease progression is marked by vascular disease, resulting in kidney impairment, cardiovascular disease, and stroke in adulthood. MRI often demonstrates subcortical changes, in periventricular white matter, and the basal ganglia, thalamus, and brainstem. Cognitive impairment may be detected via formal neuropsychological testing, and often presents as impaired processing speed, attention, and executive functioning, likely reflecting the impact of subcortical vascular ischemia. Depressive disorders, often meeting criteria for a severe clinical depression, occur in up to half of all sufferers and is most strongly associated with the degree of peripheral pain and anhidrosis, suggesting that it reflects the burden of disease rather than being a poststroke phenomenon or associated with subcortical vascular change. Anxiety is also commonly reported; other psychiatric syndromes appear relatively rare. The degree of depression and anxiety also appears to predict the degree of social and occupational dysfunction. Symptomatic treatment of depression



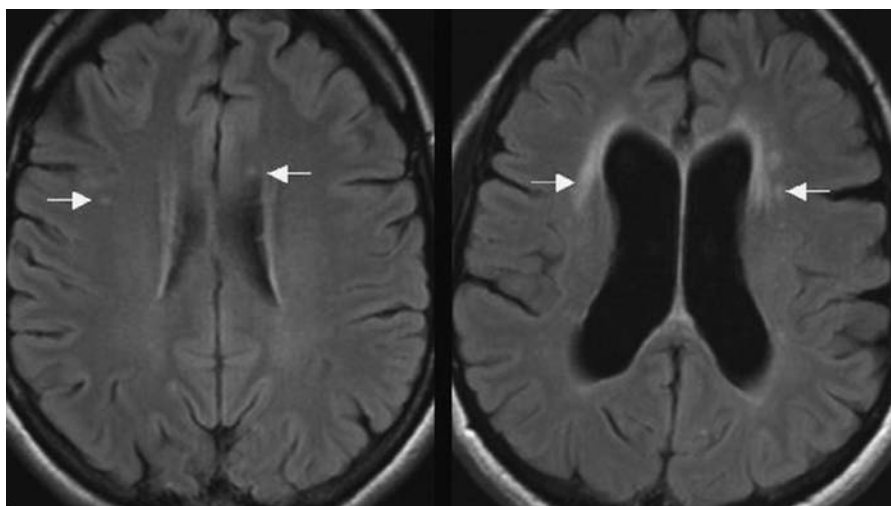
**FIGURE 2.14-1.** Typical imaging findings of MLD. **A:** Noncontrast CT brain demonstrates confluent bilateral periventricular deep white matter hypodensity (arrows) which is hypointense on T1 imaging without contrast enhancement (**B**) and hyperintense on T2 imaging (**D**). The abnormality spares the subcortical U fibers (arrowheads, inset **B,D**). Spectroscopy trace (**C**) demonstrates elevated myo-inositol, reduced N-acetylaspartate and increased lactate.

is often effective; however, enzyme replacement therapy has recently become available and may prevent some of the physical manifestations of Fabry disease that appear to be causally related to depression in this disorder.

### Gaucher Disease

Gaucher disease (GD) is the most common hereditary LSD, due to a deficiency in  $\beta$ -glucocerebrosidase (GBA1) which results in the accumulation of glucocerebroside in macrophage lysosomes. GD carrier status has more recently been shown to be the most common genetic risk factor for Parkinson disease, because of the molecular

relationship between glucocerebroside and  $\alpha$ -synuclein. These are deposited in a variety of tissues, including marrow, liver, spleen, and brain. Type 1 GD is “nonneuropathic” as the brain and spinal cord are thought to be spared; this presents with hepatosplenomegaly, anemia, leukopenia, and thrombocytopenia in addition to skeletal bone lesions. Types 2 and 3 affect the CNS, with type 2 causing progressive severe disease in infancy and type 3 being more indolent and often associated with survival into adulthood, with the development of seizures, ataxia, and gaze palsy being common neurological presentations. It is known however that even GD1 patients have some neuronal involvement, with astrogliosis and  $\alpha$ -synuclein deposition occurring in neuronal populations, but with only type 1 patients being



**FIGURE 2.14-2.** Fluid-attenuated inversion recovery magnetic resonance image demonstrating mild (left) white matter lesions (arrows) in a 39-year-old woman with Fabry disease, and more significant (right) white matter lesions in a 41-year-old woman with the same disease. (From Fellgiebel A, Müller MJ, Mazanek M, Baron K, Beck M, Stoeter P. White matter lesion severity in male and female patients with Fabry disease. *Neurology*. 65[4]:600, Figure 1, with permission.)



spared neuronal loss. GD1 patients may demonstrate subtle cognitive deficits, largely in attention and memory; in GD3 patients, cognitive function can vary widely—from severe impairment to normal functioning—according to the severity of the disease. Depression and anxiety are not uncommon in GD1 patients, at approximately three times the rate of the normal population. Depression in GD patients is known to respond to antidepressant medication. Enzyme replacement therapy in GD is associated with significant improvement in mood and psychological functioning, with similar improvements reported in quality of life.

### GM2 Gangliosidosis (Tay–Sachs Disease)

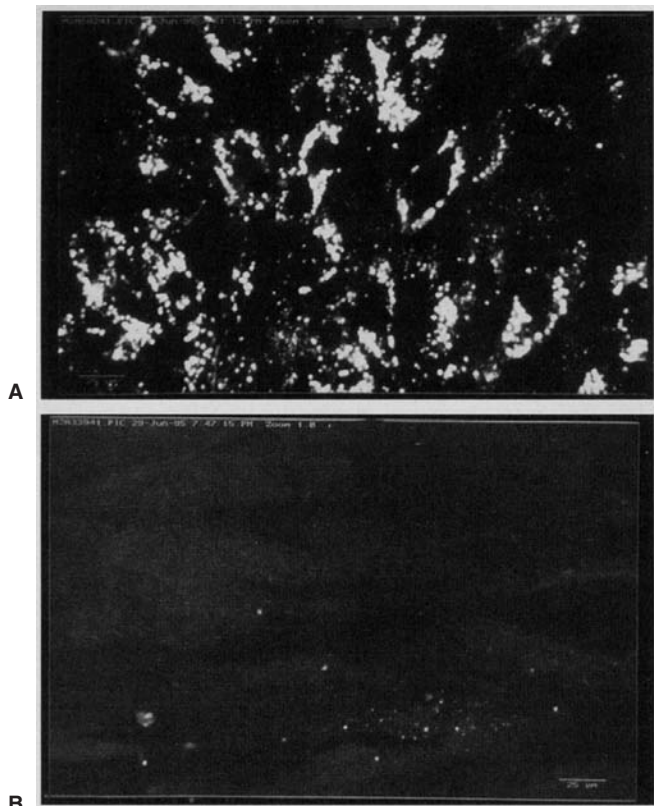
TSD is an autosomal recessive lipid storage disorder caused by the accumulation of GM2-gangliosides within neurons due to a deficiency in  $\beta$ -hexosaminidase A (HEX-A). HEX-A deficiency in lysosomes impairs the catabolism of gangliosides from the neuronal cell membrane, resulting in accumulation of lysosomal gangliosides (Fig. 2.14–3). This leads to secondary axoneuronal changes, particularly axon hillock outgrowth to form “meganeurites” with ectopic dendritogenesis and focal axonal enlargements known as *axonal spheroids*, both of which may alter neuron-to-neuron microconnectivity. In addition, ganglioside accumulation results in direct neurotoxicity, altered neuronal electrical properties, inappropriate apoptosis, or an inflammatory response. In infantile or childhood forms, severe neurological impairment usually results in death within 3 to 10 years. A later, or adult-onset, form of TSD

has been described and may be associated with having at least one allele (most commonly the G269S mutation) associated with residual enzyme activity. In this late-onset form, psychiatric symptoms may copresent with or predate the development of neurological disturbances in early adulthood. Patients present with speech disorder, gait disturbance, and tremor most commonly, with normal or near-normal cognitive function, although subtle deficits in executive function, processing speed, and memory may be present in up to half of patients. MRI often shows significant cerebellar atrophy, although cortical atrophy may also be seen. Neuropsychiatric presentations occur in up to half of late onset TSD patients, predominantly psychosis, which may occur in 30 to 50 percent of adult patients, marked by disorganization, auditory and visual hallucinations, and catatonia. Affective disorders including mania and depression have been occasionally reported. Patients only partially respond to neuroleptics or lithium (Eskalith), and are often very sensitive to motor side effects of these drugs. Importantly patients with psychotic illness appear to respond to ECT.

50% des formes tardive

### Neuronal Ceroid Lipofuscinosis

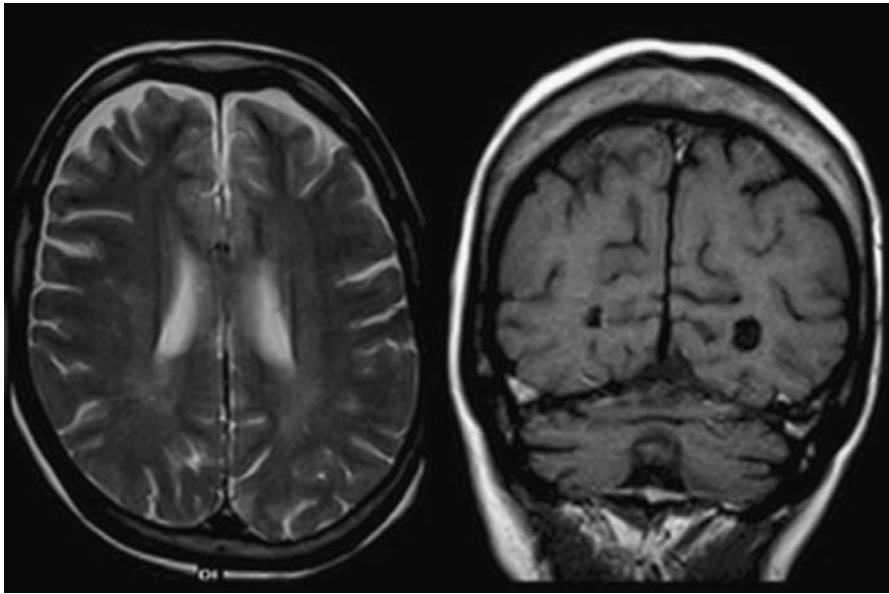
The NCLs are a group of neuronal storage disorders, one of which is Batten disease, the most common neurodegenerative disorder in childhood. Accumulation of lipofuscin-like material in lysosomes, particularly in neuronal tissue, characterizes NCL. Mutations in ten genes that encode for a range of proteins, all involved in lysosomal catabolism and recycling of proteins and lipids, have been shown to be responsible for this group of disorders. Adult neuronal ceroid lipofuscinosis (ANCL), Kuf and Parry diseases may be inherited in a recessive or dominant fashion, respectively, and make up between 2 and 10 percent of all NCLs. Dominant pedigrees have been shown to have mutations in the DNAJC5 gene, and recessive pedigrees by mutations in PPT1, CLN5, and SGSH genes. Lipofuscinosis diffusely affects cortical and subcortical neurons, but particularly the hippocampus and entorhinal cortex, and is associated with significant glial activation that precedes rather than follows neuronal loss. Alteration in axonal and synaptic function due to ultrastructural change occurs across the CLNs. Symptoms most commonly appear at the beginning of the fourth decade, but may be present early in the second decade. Two clinical forms of ANCL have been described: a progressive myoclonic epilepsy form, and a neuropsychiatric/cognitive form characterized by dementia, psychiatric disturbance, and dyskinesia. Psychosis occurs in up to 20 percent of patients, particularly in adolescent and early adult patients, with characteristic hallucinations, delusions, and thought disorder, and occasionally catatonia. Mood disturbance is particularly common. Patients present cognitively with slowing, attentional disturbance, and impaired new learning; older patients may present with a frontotemporal dementia-like picture or a Kluver–Bucy-type syndrome. Diagnosis rests on identification of characteristic inclusions in skin punch biopsy or leukocytes. MRI often shows cerebral and cerebellar atrophy and callosal thinning whilst SPECT shows regional cortical hypoperfusion. Treatment is symptomatic, although these patients are very sensitive to extrapyramidal side effects such as dystonia and neuroleptic malignant syndrome, as NCL patients may have muscle membrane pathology comorbid with changes in the CNS.



**FIGURE 2.14-3.** Indirect immunofluorescence staining of cultured fibroblasts with an anti-GM2 antibody in a patient with Tay–Sachs disease (**top**), showing significant accumulation of GM2 gangliosides compared to a healthy control (**bottom**). (From Sakuraba H, Itoh K, Shimmoto M et al. GM2 gangliosidosis AB variant: Clinical and biochemical studies of a Japanese patient. *Neurology*. 1999;52[2]:372, Figure 1, with permission.)

### $\alpha$ -Mannosidosis Type II

$\alpha$ -Mannosidosis (AM) is a recessively inherited LSD that results from deficiency of AM, which causes lysosomal accumulation or undigested oligosaccharides. AM is characterized by mild to moderate intellectual



**FIGURE 2.14-4.** Magnetic resonance imaging scan on a patient with psychosis and  $\alpha$ -mannosidosis. **Left:** T2-weighted imaging shows parietal and occipital white matter hyperintensities and frontal atrophy. **Right:** Coronal T2-weighted imaging at the level of the cerebellum shows atrophy of the cerebellar hemispheres. (From Gutschalk A, Harting I, Cantz M, Springer C, Rohrschneider K, Meinck H-M. Adult  $\alpha$ -mannosidosis: Clinical progression in the absence of demyelination. *Neurology*. 2004;63[9]:1744, Figure 1, with permission.)

disability, hearing loss, skeletal changes, and recurrent infections, with an indolent form (type II) occurring in the minority of patients who survive to adulthood. Deficiency of AM results in the intralysosomal accumulation of mannose-rich oligosaccharides and the formation of storage vacuoles in neuronal and glial cells, which impairs myelin formation. Neuropathologically, AM appears to initially affect myelinated structures before progressing to involve the neuronal body. In type II AM, the predominant clinical features are cerebellar ataxia, hearing loss, neuropsychological impairment, and retinopathy. Diagnosis rests on the demonstration of a pattern of urinary oligosaccharides and reduced enzyme activity in leukocytes or fibroblasts. MRI scanning shows periventricular T2 hyperintensities and cortical and cerebellar atrophy (Fig. 2.14-4), and may show iron accumulation in the basal ganglia. Like many LSDs, bone marrow transplantation is the only current viable treatment option. Up to 25 percent of type II AM patients over the age of 15 develop clear mental illness, predominantly a psychotic disorder characterized by delusions, hallucinations, and confusion. Generally, psychosis presents with neurological manifestations, although it may rarely present as a prelude to frank neurologic disturbance.

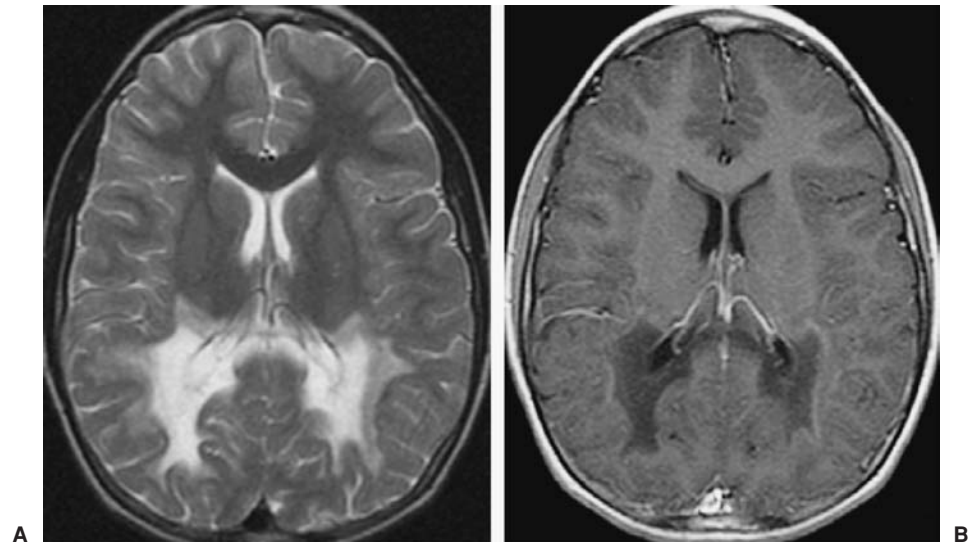
### Peroxisomal Disorders

The peroxisome is a subcellular organelle that plays a role in the breakdown of fatty acids, the degradation of hydrogen peroxide (released via oxidation of fatty acids), membrane phospholipid and cholesterol synthesis, and the metabolism of amino acids. Unlike lysosomes, the peroxisomes bud off from the endoplasmic reticulum. Disorders of biogenesis (formation) of the peroxisome are generally fatal during infancy. Defects in single enzymes of the peroxisome may also cause disease compatible with survival well into adult life, and at least one of these, X-linked adrenoleukodystrophy (X-ALD), the most common peroxisomal disorder, is known to be associated with psychiatric illness.

**X-linked Adrenoleukodystrophy.** X-ALD is an X-linked recessive disorder occurring in 1 in 20,000 births and is caused by mutations to *ABCD1*, the gene for a peroxisomal membrane protein that  $\beta$ -oxidizes very long-chain fatty acids (VLCFAs). This leads to the accumulation of saturated VLCFAs in brain white matter and

adrenocortical cells predominantly, which impairs membrane stability. It predominantly affects males, although some female carriers can be affected. In adults, it presents in either a predominantly cerebral form (5 percent of cases), marked by an inflammatory demyelinating process, or an adrenomyeloneuropathic (AMN) form (45 percent of cases), in which neuronal dysfunction is predominantly a distal axonopathy affecting the dorsal columns and corticospinal tract. The majority of other presentations are of the childhood cerebral form, which is rapidly progressive over 2 to 3 years. Both adult forms also present with adrenocortical insufficiency, often indistinguishable from primary Addison disease. The adult cerebral form shows a predilection for neuropsychiatric presentations, although the neurobiology of this is unclear. Demyelinative changes are most prominent in parietal and occipital cortex as well as the thalamus, callosum, and brainstem (Fig. 2.14-5), although more anterior cortical regions may be involved. MRI frequently shows symmetrical white matter hyperintensity that begins in the splenium of the corpus callosum and spreads into neighboring posterior regions on T2-weighted imaging. At presentation, the majority of adult-onset patients present with psychiatric disturbance, most commonly behavioral changes. Mania and affective psychosis appear to be the most common neuropsychiatric presentations, more so than schizophreniform illnesses, although the latter do occur. When white matter changes occur in a more anterior distribution, patients may show a frontotemporal dementia-like presentation. Psychiatric presentations may precede motor or cognitive changes by some years; and as in other organic psychiatric illnesses, patients often show treatment-resistance. In the AMN form, the most common form of ALD amongst adults, was thought to affect only the peripheral nervous system; however, subtle cerebral manifestations of the disorder are often present, and the rate of depressive illness appears to be elevated at least twofold. Some patients may present with mood changes subsequent to adrenal insufficiency, which reverse with appropriate corticosteroid replacement therapy. AMN patients may also show subtle neuropsychological changes that affect speed of processing and executive functioning. There is no primary treatment for X-ALD, although bone marrow transplantation has provided some stabilization in younger patients with early disease, and the oral administration of 4:1 glyceryl trioleate and glyceryl trierucate (“Lorenzo’s Oil”) normalizes plasma VLCFA levels but does not improve neurologic function in already symptomatic or adult patients.

**FIGURE 2.14-5.** T2-weighted (A) and T1-weighted (B) axial magnetic resonance images (MRI) from an adolescent with adrenoleukodystrophy who presented with confusion and psychosis. Symmetrical and confluent hyperintensity is seen in the posterior white matter of both hemispheres, a typical MRI finding. (From Hesselink JR. Differential diagnostic approach to MR imaging of white matter diseases. *Top Magn Reson Imaging*. 2006;17[4]:243, Figure 19, with permission.)



### Other Enzyme Deficiency Disorders

**Acute Intermittent Porphyria.** Acute intermittent porphyria (AIP) is one of the porphyria disorders group, where defects in heme biosynthesis result in excessive secretion of urinary porphyrins and their precursors; a number of heme synthesis pathway intermediates are neurotoxic. Most of the porphyrias are inherited in a dominant fashion. The incompletely penetrant, autosomal-dominant AIP results from defects in the enzyme porphobilinogen (PBG) deaminase, which speeds the conversion of PBG to hydroxymethylbilane. Deficient activity of this enzyme results in accumulation of porphyrin precursors PBG and amino-levulinic acid (ALA), which are thought to be neurotoxic. This enzymatic deficit becomes apparent in situations that require an increase in heme synthesis, including fasting, menstruation, intercurrent medical illness, and drugs that induce the cytochrome P450 system such as alcohol, estrogens, barbiturates, and sulfonamides, and presents most commonly in women of child-rearing age. Coproporphyrin, a dominantly inherited deficiency of coproporphyrinogen oxidase, can present identically to AIP in addition to cutaneous findings (bullous lesions, skin fragility, and scarring).

The periodic “madness” of King George III has in recent decades been considered to be secondary to AIP, in addition to being implicated as illnesses affecting the work of van Gogh and Soren Kierkegaard. AIP has been shown to be significantly overrepresented in a sample of 4,000 psychiatric inpatients (1 in 500 compared to a community rate of 1 in 100,000). The “classical triad” consists of abdominal pain, psychiatric disturbance, and peripheral neuropathies (mostly motor, and often mimicking Guillain-Barré syndrome) during episodes, although psychiatric symptoms alone may be the single presenting feature. Of clinically symptomatic cases, psychiatric disturbance occurs in up to half of all cases, half of which are psychotic episodes, although depression, anxiety, and delirium may also be the main presenting symptoms. The intermittent “attacks” of neuropsychiatric disturbance may result in a misdiagnosis of schizophrenia; in addition, the high likelihood of abdominal pain during attacks can result in a diagnosis of a somatoform disorder. More chronic porphyrias have been associated with elevated rates of anxiety and depression. How PBG and ALA accumulation causes neuropsychiatric disturbance is unclear. Explanatory hypotheses have included oxidative stress, vascular change, and demyelination, although it may be that ALA’s structural similarity to  $\gamma$ -aminobutyric acid (GABA) results in impaired release of GABA from synapses of GABAergic

inhibitory neurons, and reductions in heme-dependent enzymes causing increased serotonin turnover and reduced nitric oxide activity.

Diagnosis of AIP rests on the demonstration of elevated urinary ALA and PBG, red cell PBG deaminase activity; for coproporphyrin, urinary coproporphyrin levels should be assessed. Gross elevations of urinary ALA and PBG will often turn urine amber or purple in direct sunlight; it is imperative to collect specimens carefully (such as a 24-hour collection of urine, in light-protected containers and correctly preserved). Management involves correct identification and avoidance of precipitants if possible. During an attack, treatment includes the reversal of contributing illnesses, intravenous hydration, carbohydrate loading to inhibit heme synthesis, and hematin or heme arginate to provide negative feedback to the heme synthetic pathway. Psychopharmacological management of AIP involves judicious use of medication that will not worsen the biochemical deficit, which for psychosis includes chlorpromazine (Thorazine) and droperidol (Inapsine), fluoxetine (Prozac) for depression, lithium for mania, and lorazepam (Ativan), triazolam (Halcion), and temazepam (Restoril) for anxiolysis and sedation.

**Phenylketonuria.** Phenylketonuria (PKU), an autosomal recessive disorder with an incidence of 1 in 10,000 to 20,000 is caused by mutations in both alleles of the chromosome 12 gene for phenylalanine hydroxylase (*PAH*) that converts the amino acid phenylalanine to tyrosine. Mutations in both copies of the gene for *PAH* result in inactive or deficient enzyme levels, and accumulated phenylalanine (Phe) is converted to phenylketones, which are detectable in the urine. Resultant low levels of tyrosine, the precursor for the monoamines dopamine and serotonin, causes monoaminergic depletion in the CNS and severely disrupts normal neurodevelopment. In addition, reduced large neutral amino acid (LNAA) availability causes reduced protein and cholesterol synthesis, impaired synaptogenesis and myelination, and altered glutamatergic neurotransmission. Hypomyelination occurs in untreated and early-treated patients; increased T2 signal on MRI scanning is seen in most patients in frontal and parieto-occipital zones with MRS demonstrating increased cerebral Phe that tightly correlates with serum Phe levels. Functional MRI demonstrates altered connectivity within and between prefrontal cortical regions; DTI has also demonstrated impairments in white matter integrity, and these appear to underpin the executive deficits seen in PKU patients.

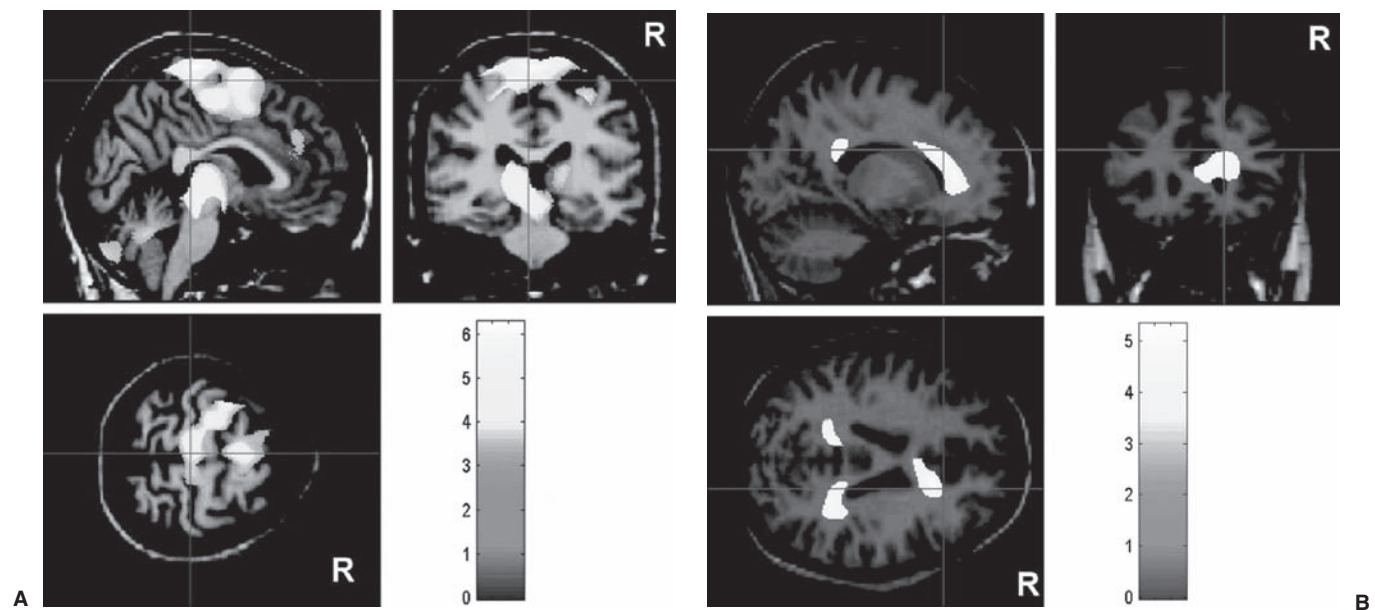
PKU sufferers require an individually tailored diet of foods low in phenylalanine and supplemented with tyrosine. Routine screening



of newborns and the universal initiation of dietary restriction within the first 3 months of life have essentially eliminated the severe, irreversible cognitive deficits and behavioral disturbance associated with untreated PKU. A reduced-phenylalanine diet maintained for the first decade of life is associated with essentially normal cognitive outcomes, although some controversy exists as to whether relaxing dietary restrictions in the preadolescent phase (“early treated” patients) is associated with greater psychiatric disturbance than in PKU sufferers in whom dietary control is not relaxed (“consistently treated” patients). Early treated patients are described as showing elevated rates of depression, anxiety disorders (particularly agoraphobia), attention-deficit disorder, and more nonspecific psychosocial adjustment issues in adolescence when compared to matched healthy individuals. Compared to individuals with chronic illnesses such as diabetes, they show elevated rates of anxiety disorders, suggesting that this is unlikely to be an effect of adjustment to chronic illness. Elevated rates of psychiatric and cognitive illness appear to directly negatively affect psychosocial outcomes, with a higher proportion of PKU patients remain unmarried, childless and/or living with their parents than their unaffected peers. Cognitive impairment also relates directly to the degree of past treatment, with untreated patients showing mental retardation and developmental delay; early-treated patients may show subtle reductions in IQ and executive and attentional impairment. Prefrontal dopaminergic neurons are particularly vulnerable to decreased tyrosine availability, and mild elevations in phenylalanine to tyrosine ratios (a marker of dopamine availability) in these patients in whom dietary restriction is not maintained are associated with executive impairment and may underpin the adolescent and early adulthood psychiatric disturbance seen in these patients. Acute tyrosine depletion in healthy adults is associated with depression, anxiety, and executive disturbance and may provide a model for psychiatric and cognitive disturbance as a result of a prefrontal hypomonoaminergic state as a result of elevated phenylalanine. In addition, impairment of oligodendrocyte function may impair myelination in PKU (Fig. 2.14–6). Frontotemporal myelination, in

addition to the dopaminergic innervation of the prefrontal cortex, peaks during adolescence, and the disruption of these processes may result in neuropsychiatric illness in this patient group. Animal models show that hypomyelination has been partially restored with dietary control, and limited human studies show a reversal of T2 signal abnormalities. However, perhaps less than 20 percent of adults maintain dietary control throughout adulthood, with the impact of diet on social interactions being the most commonly reported impediment for patients; discontinuation in adulthood is associated with poorer social, educational and health outcomes, but re-engagement of “lost” patients may allow for some reversal.

**Maple Syrup Urine Disease.** Maple syrup urine disease (MSUD) is an autosomal recessive disorder caused by a defect in the branched-chain  $\alpha$ -ketoacid dehydrogenase enzyme complex, with resultant abnormalities in branched-chain amino acid (BCAA) catabolism. In adult-presenting disease, altered leucine metabolism results in impaired glial function, reduced synaptogenesis and dendritic arborization, impaired myelination and the induction of neuronal apoptosis. In addition, elevated leucine reduces transport across the blood–brain barrier of LNAAs, including most monoamine precursors, which results in disruptions to dopaminergic, noradrenergic, histaminergic and serotonergic transmission. Altered BCAA metabolism also results in depletion of glutamate, GABA and aspartate, which alters excitatory/inhibitory transmission throughout the CNS. Although quite rare, incidence is significant (1 in 200) in Amish and Mennonite populations. Clinical manifestations include body fluid odor that resembles maple syrup and overwhelming illness in the first week of life, beginning with vomiting and lethargy, and progressing to seizures, coma, and death if untreated. In milder forms of the disease, the illness may manifest symptoms only during stress (such as infection or following surgery). MSUD is diagnosed by elevated plasma BCAAs, particularly leucine, and profound ketosis and acidosis. Long-term management is via restriction of dietary BCAAs, although small amounts are required for normal metabolic function. Like PKU, the advent of



**FIGURE 2.14–6.** Results of voxel-based analysis of magnetic resonance image changes in phenylketonuria. **A:** Statistical parametric map of grey matter volume reduction of phenylketonuria (PKU) patients compared to controls, in motor and prefrontal cortex and thalamus. **B:** White matter volume reductions in the same comparison, in anterior and posterior forceps of the corpus callosum. R, right side. (From Pérez-Dueñas B, Pujol J, Soriano-Mas C, et al. Global and regional volume changes in the brains of patients with phenylketonuria. *Neurology*. 2006;66[7]:1074, Figure 1, with permission.)

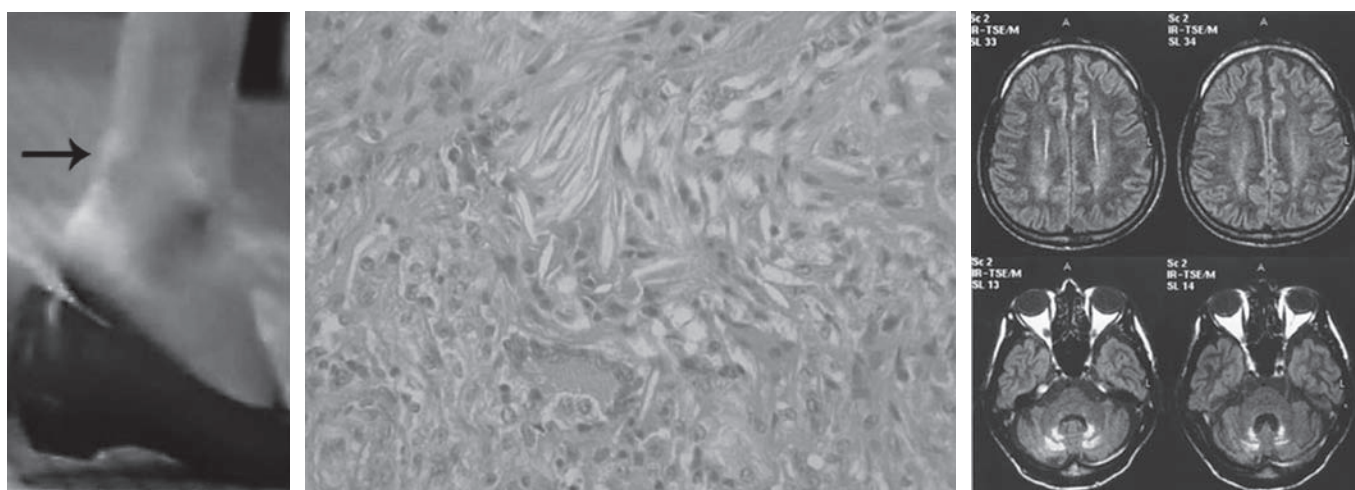
dietary restriction has modified the illness course significantly, and MSUD patients who survive into adulthood have demonstrated subtle cognitive deficits and an elevated rate of some neuropsychiatric disorders. Like PKU, adult neuropsychological impairment appears more related to age at institution of, and adherence to, treatment rather than persistent BCAA levels. Whereas in PKU the relative tyrosine deficiency results in altered myelination and monoaminergic transmission, in MSUD the BCAA-restricted diet results in chronic cerebral valine deficiency, which itself may impair neuronal and oligodendrocyte function. Despite strict metabolic control, many children suffer from attention-deficit disorders, whereas adolescents and adults commonly present with depression and anxiety. These are described as responding to psychostimulants and antidepressants, respectively. Cognitive impairment is usually seen in executive and attentional domains.

**Cerebrotendinous Xanthomatosis.** Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of cholesterol metabolism caused by mutations in the sterol-27 hydroxylase gene (*CYP27A1*) on chromosome 2. CTX was first described in 1937 and is also known by the eponymous name of van Bogaert disease. Since then over 300 patients with CTX have been described and about 50 mutations have been identified in the *CYP27A1* gene, just under half the mutations being missense mutations. Deficiency of the mitochondrial enzyme sterol 27-hydroxylase leads to reduced hepatic production of bile acid and reduced chenodeoxycholic acid (CDCA) production. The absence of CDCA-driven negative feedback on bile acid synthesis results in the accumulation of cholesterol precursors, increased cholesterol, and 7-hydroxycholesterol production. Accumulation of cholesterol and cholesterol in the eyes, tendons (often the Achilles, but also elbow/hand extensor tendons, patellar and neck tendons), and brain—particularly the cerebellar hemispheres (Fig. 2.14–7) leads to the classic clinical triad of juvenile cataracts, adult tendinous xanthomas, especially of the Achilles tendon, and progressive neurological impairment. The neurological manifestations are due to deposition of large granulomatous lipid deposits in basal/cerebellar nuclei and cerebral white matter or to demyelination and include peripheral neuropathy, mental retardation, seizures, cer-

ebellar ataxia, pyramidal signs, and dementia. Psychiatric symptoms usually accompany the dementing phase of the illness and include depression, psychosis, and personality or behavioral change. Two case series of CTX patients with psychiatric disturbance have been reported. In one, 3 of 35 cases suffered a neuroleptic-responsive psychotic disorder. A further series found psychiatric disturbance, predominantly agitation and psychosis, in seven of ten CTX patients. Depression has also been reported. A further series of 13 patients and review of all published CTX cases presenting with psychiatric syndromes suggests that younger patients present with behavioral and personality disturbance associated with learning difficulty, whereas older patients present with frontal–subcortical behavioral and cognitive syndromes associated with mood or psychotic disorders. Arteriosclerosis and osteoporotic fractures are often seen later in adult life with disease progression.

A 47-year-old woman with a 2-year history of treatment-resistant depression, unusual behavior, and memory problems was referred for neuropsychiatric assessment. On admission she fluctuated between periods of withdrawal and noncommunicativeness and periods of joviality associated with child-like comments and fatuous affect. She was unable to provide a detailed history and responded in a stereotyped way with single sentences: “I am confused,” “This is what I am like at the moment.” Cognitive assessment was not possible. The past history included cataracts and a hip fracture. Physical examination revealed enlarged, thickened Achilles tendons bilaterally (Fig. 2.14–7). Neurological examination revealed primitive reflexes and clonus in the right ankle, together with a right plantar response. A diagnosis of cerebrotendinous xanthomatosis was made on the basis of the clinical picture and elevated cholesterol levels. Treatment with chenodeoxycholic acid was instituted.

The diagnosis of CTX in adults should be suspected when the clinical picture includes cataracts, xanthomas, and progressive neurological or cognitive impairment. In the presence of the typical clinical picture the identification of elevated plasma cholesterol levels with



**FIGURE 2.14–7.** Cerebrotendinous xanthomatosis. **Left:** Image of left ankle of woman described in text demonstrating Achilles tendinous xanthoma. **Middle:** Hematoxylin and eosin stain of xanthoma of 42-year-old woman with early onset dementia and behavioral changes, showing cholesterol crystals. (From Wang Z, Yuan Y, Zhang W, Zhang, Y, Feng, L. Cerebrotendinous xanthomatosis with a compound heterozygote mutation and severe polyneuropathy. *Neuropathology*. 2007;27[1]:62, with permission.) **Right:** Transverse fluid-attenuated inversion recovery magnetic resonance imaging on two adult cerebrotendinous xanthomatosis patients showing mild hyperintensity of subcortical white matter and significant hyperintensity of the dentate nucleus of the cerebellum. (From De Stefano N, Dotti MT, Mortilla M, Federico A. Magnetic resonance imaging and spectroscopic changes in brains of patients with cerebrotendinous xanthomatosis. *Brain*. 2001;124:121, with permission.)



low or normal cholesterol levels plus reduced urinary excretion of bile alcohols is usually sufficient to confirm the diagnosis. MRI using FLAIR sequences can identify bilateral hyperintensities of the cerebellar dentate nuclei that mirror the known neuropathological site of disease involvement (Fig. 2.14–7), usually associated with folia atrophy, and lesions in the brain stem and periventricular regions. Global grey and white matter volume is frequently reduced. Treatment consists of lifelong replacement of CDCA (750 mg per day, often combined with a statin) and is aimed at limiting the long-term damage caused by cholestanol and cholesterol deposition, which improves neurological and neuroradiological markers of disease, particularly when initiated at an early stage. Treatment with CDCA alone has also been shown to result in an improvement in psychiatric symptoms and cognition in CTX patients.

**Tetrahydrobiopterin Deficiency.** Tetrahydrobiopterin deficiency (THD) is an extremely rare recessive disease (1/500,000 to 1,000,000 newborns) caused by the mutation of several genes, in particular GCH1, PCBD1, PTS, and QDRP, which encode enzymes involved in the production and recycling of tetrahydrobiopterin. Mutations in MTHFR and DHFR genes can also cause a mild deficiency. Impaired enzymatic function leads to altered levels of phenylalanine and central monoamines. PAH, tyrosine hydroxylase, and tryptophan hydroxylase all require tetrahydrobiopterin (BH4) as a cofactor. Inherited defects that reduce the concentration of BH4, therefore, lead to PKU and to reduced CNS levels of dopamine and serotonin, as tyrosine hydroxylase and tryptophan hydroxylase are enzymes required for the synthesis of these neurotransmitters.

Classical symptoms are progressive and include intellectual disability (IQ between 60 and 90 in most patients), movement disorder, dysphagia, seizures, developmental delay, and behavioral disturbance in younger patients. BH4 deficit has been associated with depression, and reduced BH4 levels have been demonstrated in both schizophrenia and schizoaffective disorder, and supplementation with the BH4 analogue sapropterin is being investigated as a potential therapeutic agent in psychotic disorders.

**Hyperprolinemia.** Hyperprolinemia (HP) is a recessive disease caused by mutation of either of the two genes *ALDH4A1* and *PRODH*. These genes coding for pyrroline-5-carboxylate dehydrogenase and proline oxidase, respectively, which are implicated in the degradation of proline. HP, which has no definitive treatment, is divided into two subtypes based on the severity of biochemical deficit; HP2 (with proline blood levels elevated ten to fifteen times) is considered more severe with patients presenting in childhood with seizures and mild intellectual disability. In HP1 (proline levels elevated three to ten times) patients have few symptoms or may be asymptomatic. There has long been a speculative association between HP1 and psychosis; the 22q11 deletion, known for its strong association with schizophrenia, results in a hemizygous deletion of the *PRODH* gene and up to 50 percent of patients with the 22q11 deletion have elevated plasma proline levels. In a recent study, schizophrenia patients demonstrated a mild to moderate increase in serum levels of proline when compared to sex and gender matched controls.

**Propionic Acidemia.** Propionic acidemia (PA), also called ketotic glycinemia and propionic aciduria, is a recessive disorder, affecting 1:100,000 births, caused by the deficiency of activity of the enzyme propionyl CoA carboxylase, a mitochondrial biotin-dependent enzyme which is essential for the catabolism of the amino acids threonine, methionine, isoleucine, valine, as well as

cholesterol and some fatty acids. This results in a buildup of organic acids in blood and tissues, in particular propionic acid. Patients with early-onset PA present with acute metabolic decompensation in childhood. Late-onset PA, still largely a childhood disorder, is more heterogeneous and may fluctuate (particularly in times of increased metabolic demand), with symptoms including vomiting and feeding difficulties with impairment in psychomotor development and movement disorder such as choreoathetosis and dystonia. Acute acidosis with encephalopathy and hyperammonemia may occur. It may rarely present in the third or fourth decade of life. Diagnosis requires urine organic acid analysis and a plasma or blood spot acylcarnitine profile, and treatment is largely symptomatic. PA has been associated with adolescent or young-adult psychosis associated with metabolic decompensation; and with autism spectrum disorder (ASD) in preadolescent patients. Treatment with antipsychotics may require careful consideration as patients may have long QT syndrome (LQT).

**$\alpha$ -Methylacyl-CoA Racemase Deficiency.**  $\alpha$ -Methylacyl-CoA racemase (AMACR) deficiency is a recently discovered recessive disorder caused by mutations in the *AMACR* gene, and has no specific treatment. The AMACR enzyme is found in mitochondria and peroxisomes. In peroxisomes, lack of AMACR leads to elevation of pristanic acid, a fatty acid, usually supplied from meat and dairy foods in the diet. The role of AMACR in mitochondria is felt to relate to the breakdown molecules derived from pristanic acid. Accumulation of pristanic acid influences functions of brain cells, leading to neuronal and glial cell death, and leads to alterations of brain structure with encephalopathy, progressive demyelinating neuropathy and xanthomas with sterol storage in the CNS. Diagnosis is made by demonstrating elevated pristanic acid in plasma. The disorder usually presents in early adulthood with cognitive decline, seizures, and migraine; acute decompensations may present as stroke-like episodes. More chronic neurological signs, such as ataxia, spasticity, and sensorimotor neuropathy may also present, and it has been associated with a late-onset ataxia presenting in the fifth decade. MRI tends to demonstrate increased T2 signal in cerebello-thalamic pathway structures.

Disturbances in fatty acid and oxidative phosphorylation pathways have been described in brain regions of patients with schizophrenia, including the prefrontal cortex. The AMACR gene is also located on chromosome 5p13, a locus which has been shown to be a putative schizophrenia susceptibility locus in a large sample of patients from Puerto Rico with three missense variants segregating with schizophrenia.

**Cerebral Creatine Deficiency Syndrome.** The cerebral creatine deficiency syndromes (CCDS) encompass two autosomal-recessive creatine biosynthesis disorders: guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine:glycine amidinotransferase (AGAT or GATM) deficiency, and the X-linked creatine transporter (SLC6A8) deficiency. Intellectual disability and seizures are common to all three CCDS. Creatine plays a key role in cellular energy availability through the regeneration of ATP, and is partly synthesized endogenously and supplemented by dietary intake. Creatine is synthesized from L-arginine, glycine, and methionine through a two-step process involving arginine:glycine amidinotransferase (AGAT) and GAMT. When synthesized, creatine is then transported to tissues with a high energy demand via the creatine transporter (SLC6A8). A diagnosis is suggested by a reduction or absence of the creatine peak visualized by proton MRS and increased urinary creatine excretion. Creatine monohydrate is the key treatment for GAMT and AGAT deficiency, but no treatment exists for SLC6A8 deficiency.

Almost all patients with GAMT deficiency have a behavioral disorder that may include autistic behavior and self-mutilation associated with pyramidal and extrapyramidal signs, with onset usually between the ages of 3 months and 3 years. Patients present mild intellectual disability and speech delay to severe intellectual disability, seizures, and behavioral disorder that may become more marked during the course of the disease. AGAT deficiency usually presents as mental retardation, autistic behavior and severe language disorder, without epilepsy. Autistic behavior is also a common feature in SLC6A8, although presentation tends to occur later in childhood or even in adulthood. SLC6A8 deficiency is the cause of approximately 2 percent of X-linked intellectual disability. Clinical characteristics include psychomotor and expressive speech delay, autism, epilepsy, and muscle hypotonia and hypotrophy. Semantic pragmatic language disorders and oral dyspraxia have been described.

**Glycine Encephalopathy.** Glycine encephalopathy, also known as nonketotic hyperglycemia (NKH), is caused by mutation of the GLDC (80 percent of NHK) or AMT genes (10 to 15 percent); its prevalence is estimated between 1:55,000 and 1:63,000 newborns. These genes produce to proteins implicated in the glycine cleavage enzyme complex that is responsible for breaking down glycine into smaller pieces. A dysfunction in this complex leads to an excess of glycine reaching a level toxic to various tissues. As glycine, an amino acid, is also a neurotransmitter, the brain is a key site of this damage. The classical form of the glycine encephalopathy appears shortly after birth presenting with lethargy, feeding difficulties, hypotonia, abnormal movements, and breathing and is not infrequently fatal. Outside the neonatal period, individuals may present with profound intellectual disability and treatment resistant seizures. The chief clinical phenotype is intellectual deficiency and childhood ADHD. Due to the intrinsic role glycine plays in excitatory neurotransmission by modulating the activity of the NMDA subtype of glutamate receptors, it has been suggested that NKH theoretically could present with psychosis in older patients, although there are no published reports associating psychosis and NKH. Biological diagnosis is made by glycine measurement in the CNS and confirmed by mutation analysis of the GLDC and AMT genes.

**Succinic Semialdehyde Dehydrogenase Deficiency.** Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare recessive metabolic disorder with a nonspecific and variable phenotype characterized by reduced activity of the enzyme SSADH, involved in the degradation of GABA leading to an accumulation of  $\gamma$ -hydroxybutyric acid (GHB) and coded for by the ALDH5A1 gene. GABA is the major inhibitory neurotransmitter in the brain (although is excitatory in the embryo), and is derived from glutamate, the major excitatory neurotransmitter. Impairments to SSADH activity result in an alteration of the balance between excitatory and inhibitory neurotransmission. Diagnosis rests on demonstration of elevated urinary GABA and leukocyte SSADH assay. MRI commonly shows T2 hyperintensity in basal ganglia, dentate nucleus and white matter.

Patients with SSADH deficiency present intellectual disability with deficits in expressive language, hypotonia, choreoathetosis, nonprogressive ataxia, and hyporeflexia. Neuropsychiatric symptoms are prominent and include sleep disorders, inattention, hyperactivity, autism-like behavior and anxiety or obsessive-compulsive symptoms. Symptoms occur before the age 4 years in most cases, although diagnosis has been made as late as the third decade. Developmental delay is present in all cases and 10 percent of patients will present movement disorders such as chorea, myoclonus, and dystonia. Delayed language is very common and frequently associated

with mental retardation. A recent study on a sample of transcortical sensory aphasia (TSA) patients ( $n = 187$ ) found two patients with SSADH deficiency, suggesting enrichment of this disorder in some clinical populations. In a review of 37 cases with of SSADH deficiency with psychiatric symptoms (70 percent of 53 patients), hyperactivity was present in 40 percent of patients, inattention in 50 percent, obsessive-compulsive disorder (OCD) in 35 percent, and aggressive behavior in 15 percent. Four patients in this sample also had hallucinations. The majority of neuropsychiatric presentations were seen in older children and adults, and these symptoms tended to respond to stimulants, serotonergic medication and antipsychotics. The enzyme deficiency itself has no specific treatment, although trials of vigabatrin, an irreversible inhibitor of GABA transaminase, has improved some patients but worsened others.

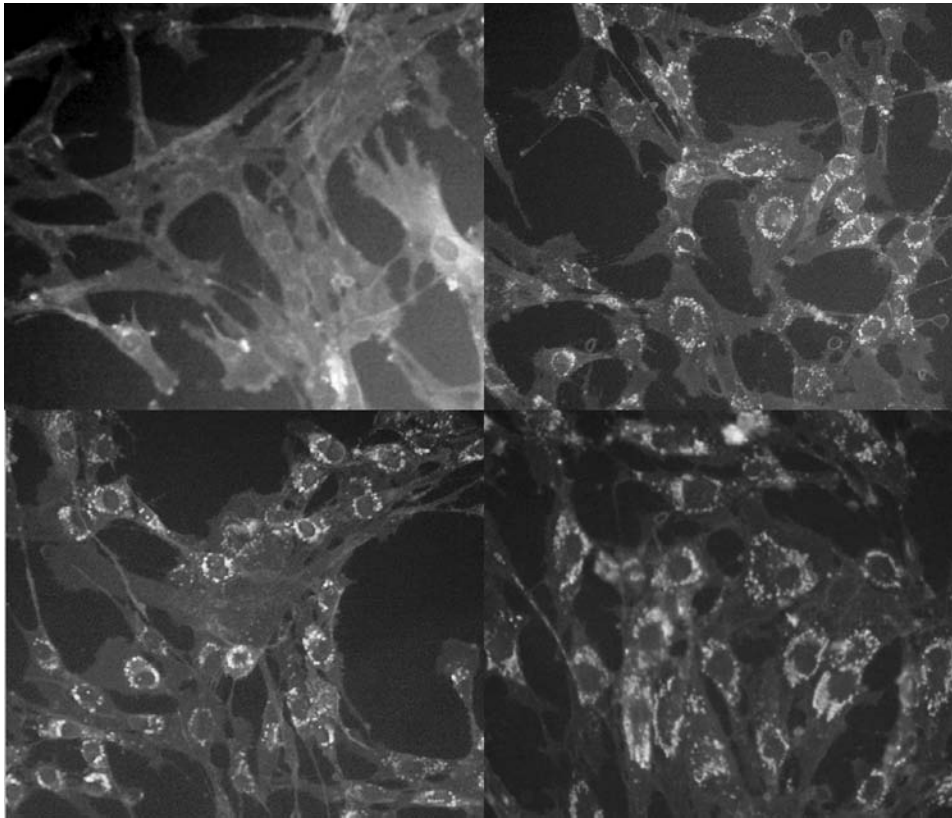
**Serine Deficiency Syndrome.** Serine deficiency syndromes (SDSs) are a group of three diseases implicating disturbance in the L-serine synthesis pathway. Three serine-deficiency syndromes have been described: 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency, 3-phosphoserine phosphatase (3-PSP) deficiency, and phosphoserine aminotransferase (PSAT) deficiency. L-serine plays a key role in the development of the CNS. Its conversion to glycine provides a source of one-carbon units for methylation processes, nucleotide and phospholipid synthesis, and cell proliferation; it also facilitates the role of glycine and D-serine in excitatory neurotransmission through activation of NMDA receptors.

PSAT deficiency patients present with acquired microcephaly, psychomotor retardation, treatment-resistant seizures, and hypertension. PSH deficiency patients have congenital microcephaly and intra-uterine growth retardation, feeding difficulties, and psychomotor retardation, and has been associated with Williams syndrome. The infantile form of 3-PGDH deficiency presents akin to PSH deficiency, whereas the juvenile form is more insidious with absence seizures, moderate developmental delay and abnormal behavior. This last clinical form may be seen by child psychiatrists in adolescence with developmental delay and aggressive behavior with no clinical neurological signs.

Diagnosis is made by demonstration of low plasma and CSF serine; treatment with L-serine (+/- glycine) improves seizures and behavioral disturbance but not developmental delay.

**Cerebral Folate Deficiency.** Cerebral folate deficiency (CFD) is defined as any neurological syndrome where CNS levels of 5-methyltetrahydrofolate in the presence of normal extra-CNS levels of folate. The two main causes are autoantibodies to the folate receptor that transports folate (also known as vitamin B9) into the CSF, or a mutation in the gene encoding this receptor; it has also been described in Aicardi and Rett syndromes, and mitochondrialopathies. Folate plays a key role in myelination, in the generation of biogenic amines and pterins, and is involved in the production and repair of DNA and gene expression. CFD is generally treated with folinic acid ameliorates symptoms if initiated early.

Cerebral folate transport deficiency (CFTD) is rare recessive disorder caused by a mutation in the *FOLR1* gene encoding for the folate receptor FR1 that allows folate to enter the cell, and is found on the basolateral endothelial surface of the choroid plexus. Impaired function of (or antibodies blocking) this receptor prevent the receptor-mediated endocytosis of folate and thus its entry into the CSF. Symptoms of CFTD do not begin until late infancy as until this period folate receptor FR2 is responsible for folate transport before birth and in early infancy. Affected children have classically onset of the disease around age 2 with psychomotor delay and regression, speech



**FIGURE 2.14-8.** Filipin staining on fibroblasts for three patients with Niemann–Pick disease type C. **Top left:** Stain on healthy control reveals lack of filipin staining of accumulated cholesterol; on three other cases, each of whom presented with psychosis, punctate perinuclear accumulation of cholesterol is identified.

difficulties, seizures and ataxia; leukodystrophy is usually apparent on MRI scanning secondary to marked impairment of myelination.

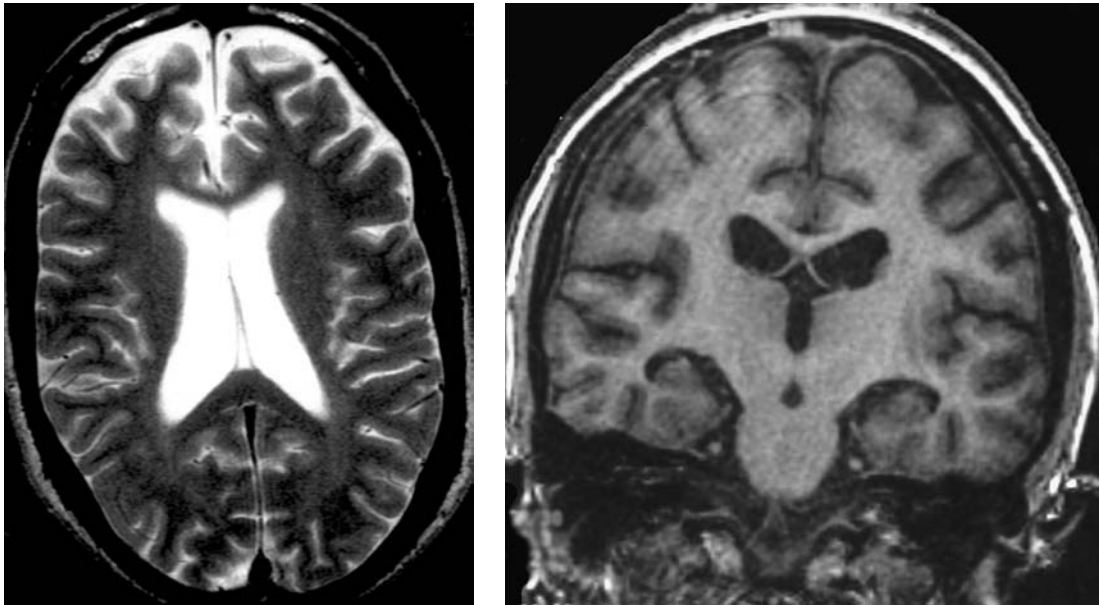
Autoimmune cerebral folate deficiency (ACFD) is an acquired disorder, with a wider spectrum of age of onset of disease and has been reported in children, adolescents, and rarely adults, although the vast majority are infants who develop symptoms after 4 months of age with irritability, sleep disturbance and then dyskinesia, ataxia and seizures. A number of patients present with autistic behavioral features, and in adolescents it has been associated with catatonic schizophrenia. In these patients, FR1 and FR2 receptor encoding is normal, but autoantibodies develop to the receptors. It has been suggested that this may develop via induction by soluble folate-binding proteins in cow's milk in infants, or by sensitization by other similar epitopes in older patients. In one sample of ASD patients, FR1/2 autoantibodies were found in almost 75 percent of patients, and folinic acid treatment improved one-third of patients. Similarly, FR1/2 autoantibodies were detected in 80 percent of a small sample of treatment-resistant schizophrenia patients, a number of whom showed symptomatic improvement to treatment with folinic acid.

### Other Neurometabolic Disorders

**Niemann–Pick Disease Type C.** NPC is an autosomal recessive neurovisceral disorder of lipid storage with a frequency of 1 in 100,000 live births, with 95 percent of sufferers having aberrations on the *NPC1* gene (18q11–12) and 5 percent on the *NPC2* gene (14q24.3). It is biochemically and phenotypically distinct from Niemann–Pick diseases types A and B, which result from a deficiency of lysosomal sphingomyelinase. *NPC1* and *NPC2* are involved in cyclical movement of sterols within cells and impairment results in late endosomal accumulation of cholesterol and gangliosides; excess

GM2 and GM3 gangliosides cause ultrastructural change to neurons, and disrupted cholesterol metabolism results in altered  $\tau$ - and  $\beta$ -amyloid processing (with Alzheimer-like neurofibrillary tangles), and disrupted calcium and metal metabolism. Axonal structures are particularly vulnerable and are affected early with subsequent involvement of cerebellar Purkinje cells, basal ganglia, and thalamic neurons followed by hippocampal and neocortical regions later (Fig. 2.14–8). The most fulminant neuronal loss occurs in the cerebellum, causing early cerebellar signs. Diagnosis is usually confirmed by demonstrating a low esterification rate of exogenous cholesterol in fibroblasts or by testing for lysosomal accumulation of free cholesterol by filipin staining (Fig. 2.14–9); more recently, oxidized cholesterol levels in plasma and/or direct *NPC1* sequencing has been utilized. NPC may present in infancy, adolescence, or adulthood with a clinically variable picture, although its core features include dementia, dysarthria, ataxia, vertical supranuclear ophthalmoplegia, and hepatosplenomegaly. Seizures, dysphagia, and pyramidal signs may appear with disease progression. Psychosis occurs in 25 to 40 percent of adolescent and adult-onset cases and may precede motor and cognitive disturbance by many years. Some cases have been described with onset in middle age associated with cognitive impairment alone. MRI often shows diffuse cerebral and/or cerebellar atrophy, and atrophy of striatum, hippocampus and thalamus, and thinning of the callosum. Executive function is impaired early in adults, before memory impairment and speed of processing becomes impaired. The co-occurrence of vertical gaze palsy and psychosis should prompt the clinician to consider NPC, so that appropriate treatment can be instituted. Psychosis may require higher doses of antipsychotics and may require treatment with a combination of neuroleptics and mood stabilizers or ECT. The development of substrate reduction therapy using the imino sugar miglustat (Zavesca), which penetrates the blood–brain barrier





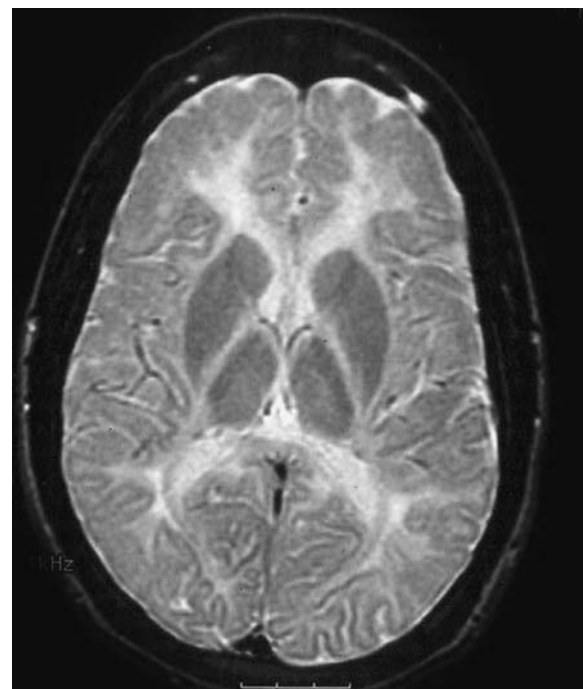
**FIGURE 2.14-9.** Magnetic resonance image scans on two individuals with Niemann–Pick disease type C who presented with major mental disorders. **Left:** T2-weighted axial image of a young adult male who presented with psychosis at age 16 prior to the onset of neurological disturbance at age 25, showing frontal atrophy, ventricular enlargement, and a cavum septum pellucidum. **Right:** A coronal T1-weighted image of a young male who presented with a rapidly cycling bipolar disorder in his early twenties. Note the disproportionate hippocampal atrophy in comparison to subtle global cerebral atrophy.

and reduces ganglioside accumulation, has shown promise in reversing the motor and cognitive deficits in NPC, and may also reduce or prevent psychiatric disturbance in this disorder.

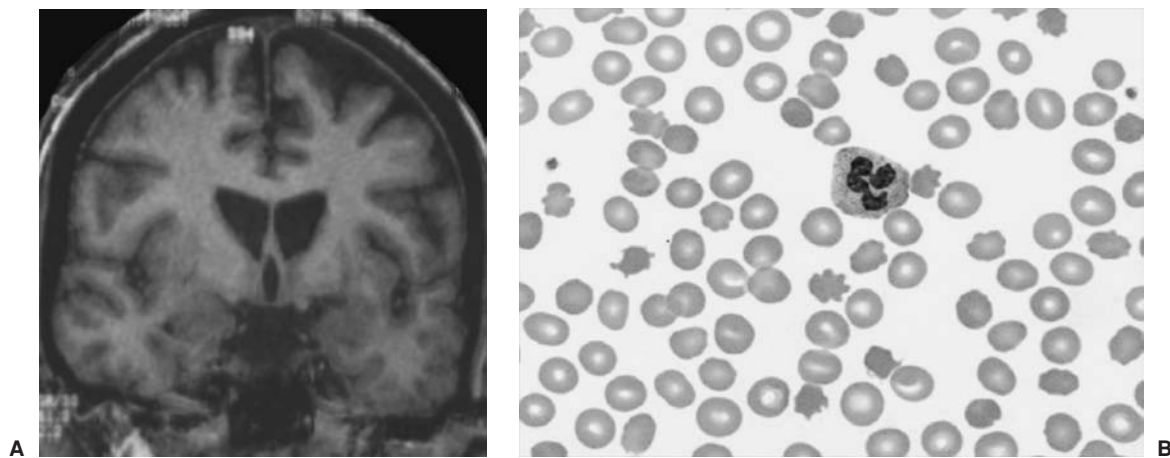
PLP has been reported in schizophrenia and in animals treated with NMDA antagonists in experimental models of schizophrenia, implicating abnormal formation of myelin in psychosis. Treatment of PMD is symptomatic and supportive.

A 26-year-old man presented with movement disturbance and dysarthric speech following a 10-year history of a treatment-resistant psychotic disorder. He suffered persistent auditory hallucinations and referential and persecutory delusions, which only abated when treated with olanzapine (Zyprexa) 60 mg per day and valproic acid (Depakene) 2,000 g per day. On examination, he showed dysarthric speech, gait ataxia, and disturbed eye movements with jerky saccades and grossly impaired downgaze. He was cognitively rigid with significant memory and executive impairment. Tests for TSD and other enzyme disorders were negative. Filipin staining of cultured fibroblasts showed an elevated number of cells, demonstrating perinuclear filipin staining of cholesterol (60 to 70 percent, normal less than 5 percent), and cholesterol esterification rate was mildly abnormal (2.9 pmol/h/mg; less than 2 abnormal, 2 to 3 equivocal, greater than 3 normal). Mutation analysis of the *NPC1* gene revealed a compound heterozygote status of G992R/R1186H, genetically confirming the diagnosis of Niemann–Pick’s disease type C.

**Pelizaeus–Merzbacher Disease.** Pelizaeus–Merzbacher disease (PMD) is an X-linked recessive disorder due to abnormalities in the gene encoding for the proteolipid protein (PLP), the major structural protein of CNS myelin, resulting in patchy myelin loss as a result of oligodendrocyte apoptosis and/or axonal damage. PMD is also variable in its onset and clinical manifestations, with childhood-onset PMD resulting in mental retardation, nystagmus, and spastic paraparesis, and adult-onset cases most commonly associated with mild, adult-onset lower limb spastic paraparesis. Dementia and psychiatric dysfunction, including psychosis, are common in adult-onset cases, often associated with subtle or partial interruption to myelination (Fig. 2.14–10), although adult-onset PMD is rare. Psychosis, when reported, occurs in the fourth or fifth decade. PLP has been implicated in schizophrenia. Downregulation of the gene encoding



**FIGURE 2.14-10.** T2-weighted magnetic resonance image scan in 20-year-old individual with Pelizaeus–Merzbacher disease, demonstrating abnormally high signal in the internal capsule and posterior corpus callosum. The “mottled” frontal white matter represents “islands” of normally formed myelin. (From Koeppen AH, Robitaille Y. Pelizaeus–Merzbacher disease. *J Neuropathol Exp Neurol.* 2002;61[9]:747, with permission.)



**FIGURE 2.14–11.** A 38-year-old woman with neuroacanthocytosis who first presented with adolescent obsessive–compulsive symptoms prior to adult-onset seizures and chorea. **A:** T1-weighted coronal magnetic resonance image showing almost total loss of the caudate head. **B:** Blood smear showing characteristic red cell acanthocytes. (See color plate.)

**Chorea-Acanthocytosis.** Chorea-acanthocytosis (ChAc) is a form of neuroacanthocytosis, a group of disorders that presents with neurological and psychiatric manifestations secondary to changes in the basal ganglia, and acanthocytes: spiculated red blood cells. ChAc is an autosomal recessive disorder associated with mutations or deletions in the *VPS13A* gene on chromosome 9q, which codes for the membrane protein chorein, a protein expressed in all tissues but particularly in brain, skeletal muscle, and erythroid cell precursors. The loss of function of chorein, which interacts with the membrane cytoskeletal proteins adducin and actin, causes destabilization of the membrane skeleton in red blood cells and neurons; in addition, adducin and actin are also crucially involved in synaptic function and plasticity, and synaptic vesicle trafficking. Cell loss and astrocytic gliosis then in the basal ganglia in ChAc patients, most particularly the caudate, but also the ventrolateral substantia nigra and globus pallidus (Fig. 2.14–10). The onset of neurological disturbance in ChAc is usually between the third and fifth decades, commonly with limb and orobuccal chorea that may be indistinguishable from Huntington chorea. It can be differentiated from the other main neuroacanthocytosis disorder, McLeod syndrome, by the absence of Kell antigens in red blood cells and the presence of cardiomyopathy in the latter. Patients with ChAc frequently present with mutilation of the tongue, lips, and cheeks, which is generally not a feature of Huntington chorea and can help to clinically distinguish the two disorders. Seizures, dystonia, and denervation atrophy occur in up to half of patients. Significant psychopathology is common in ChAc patients, occurring in up to two-thirds, and may precede the onset of frank neurological disturbance by up to a decade. In the original series of 19 individuals described by Hardie and colleagues (of a mixed ChAc-dominant group of neuroacanthocytosis patients), the most prominent psychiatric feature was behavioral and cognitive change (apathy, disinhibition, and poor judgment and planning) consistent with hypofrontality in more than half the patients, with OCD-like symptoms occurring in two patients. When psychiatric symptoms precede frank neurological disturbance, an overrepresentation of OCD-type disorders occurs, in addition to behavioral syndromes secondary to frontal lobe disturbance. These both appear to be the result of the predilection of neuropathology in ChAc for the head of the caudate nucleus, which is a key relay in a basal ganglia–thalamo–cortical loop known as the lateral orbitofrontal loop. This circuit integrates information from the anterior cingulate, orbitofrontal, and dorsolateral prefrontal cortex to determine behavioral and motor programs that occur to

resolve conflict or facilitate decision making. Disruptions to this circuitry lead to apathy, disinhibition, and poor judgment and planning. The motor compulsions seen in many ChAc sufferers may be secondary to behavioral dysregulation of motor acts through a loss of motor inhibition. Less commonly, patients with ChAc have been known to present with a schizophrenia-like psychosis. When compulsive disorders occur in ChAc, they have been known to respond to both SSRIs and TCAs. The disorder itself usually responds to antiepileptic medication, and dopamine blockers/depleters for chorea, in addition to deep brain stimulation and botulinum toxin treatment.

A 38-year-old woman with a history of complex partial seizures with secondary generalization since the age of 21 presented with a history of movement disorder. She first presented at age 16 with contamination fears and compulsive picking at her skin, which responded to antidepressant treatment. At the age of 27, she developed involuntary movements of the limbs, head, and neck, which were severe at the time of assessment. MRI demonstrated gross bilateral caudate atrophy, particularly affecting the head of the caudate, and a blood film showed 5 percent acanthocytes (Fig. 2.14–11). A Western blot on peripheral blood demonstrated the absence of normal chorein, confirming the diagnosis of neuroacanthocytosis. Her cognitive function deteriorated, and she remained on antidepressant medication while haloperidol (Haldol) was added, which significantly improved her worsening chorea. Her cognitive and behavioral decline continued over subsequent years, and she died of an unrelated medical illness 2 years later.

## Cysteine and Homocysteine Disorders

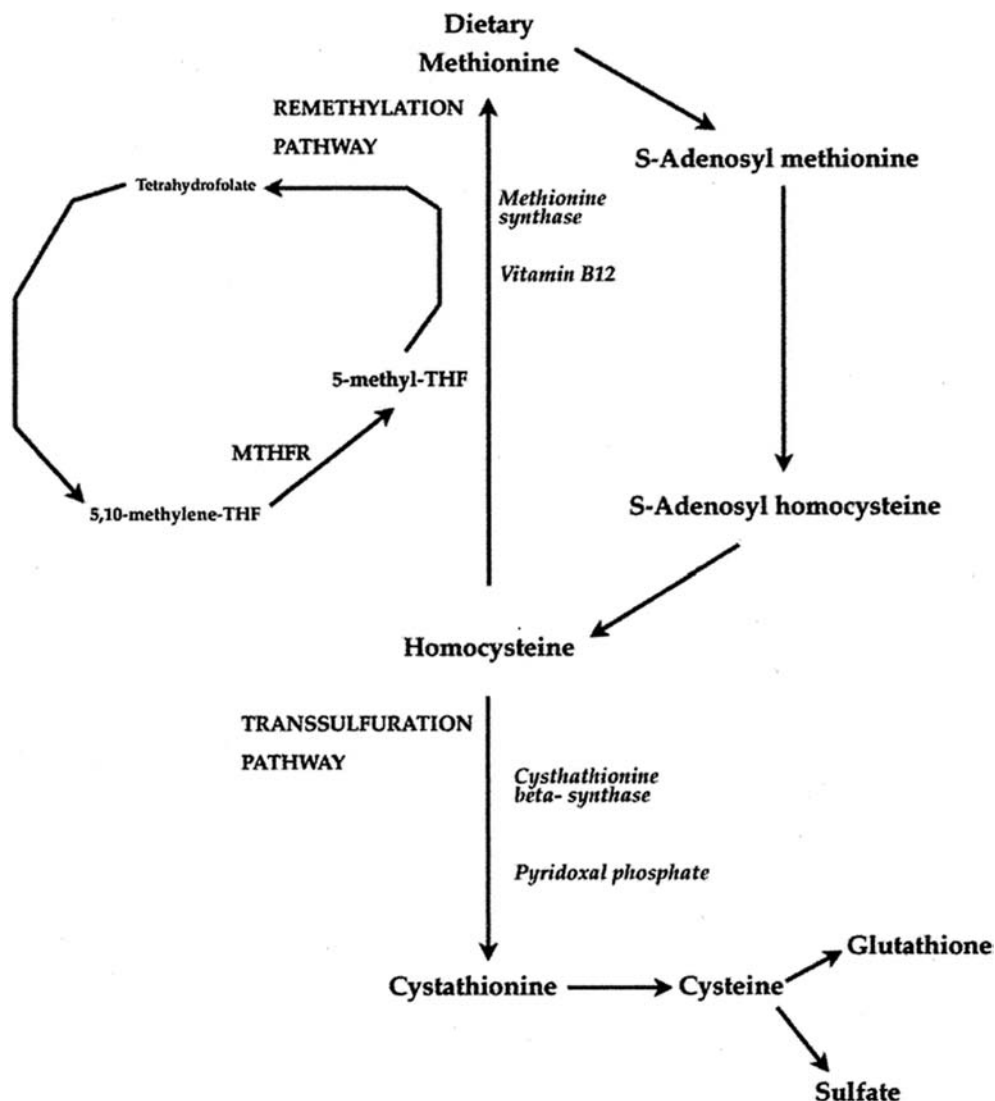
**Homocystinuria.** Disorders that lead to increased blood and urinary levels of homocysteine are grouped under the term homocystinurias. The classic form of homocystinuria is an autosomal recessive disorder caused by a defect in the chromosome 21 gene coding for cystathionine  $\beta$ -synthase, an enzyme that converts homocystine and serine into cystathionine. This leads to the accumulation of homocystine and methionine. Excessive homocystine disrupts the structure of fibrillin-1, an extracellular matrix protein, and leads to damage of collagen and elastic fibers; this leads to significant arterial and venous disease such as stroke, myocardial infarction, or venous thrombosis. In neurons it alters the release of monoamines, and may potentiate neurotoxicity through NMDA receptor agonism; it can also induce DNA strand breakage and cellular apoptosis. The

primary clinical effects of the disorder reflect this pathology. The presenting features are usually with developmental delay or mental retardation associated with optic lens dislocation within the first 10 years. Optic lens dislocation is seen in almost 100 percent of patients older than 10, and other ophthalmological complications may ensue such as cataracts, glaucoma, and optic nerve atrophy. Mental retardation is seen in about half of the patients, and intellectual decline tends to be slowly progressive. Patients may appear Marfanoid with a long narrow head, arachnodactyly, kyphoscoliosis, and pectus excavatum. Patients will often have pale, pink skin together with fine fragile, light-colored hair, and malar rash. Abnormalities in the clotting cascade and increased platelet adhesiveness lead to occlusion of and thromboembolism from arterial and venous vessels, with very high mortality. Other neurological complications include seizures and dystonias. Although early case reports identified patients with psychosis and homocystinuria, studies investigating large case series of patients have reported that personality disorder, behavioral disturbance (such as aggression), depression, and OCD are the most common psychiatric findings, and that aggression and behavioral disturbances were more common in patients with mental retardation. The diagnosis of classic homocystinuria is made on the basis of elevated plasma methionine, and elevated plasma and

urine homocysteine. Brain imaging may show the effects of cerebrovascular accidents, atrophy, or venous occlusions. Treatment with methionine restriction and cysteine supplementation will generally prevent any long-term sequelae if the disorder is diagnosed at birth. Oral pyridoxine (vitamin B<sub>6</sub>), which remethylates homocysteine to methionine, leads to a reduction in levels of methionine and homocystine in about half of patients, while the addition of folic acid and B<sub>12</sub> may be of further benefit.

The metabolic pathway that converts homocystine and serine to cystathionine is the most common pathway for the metabolism of homocystine (Fig. 2.14–12). Other autosomal recessive homocystinurias are caused by defects in an alternative remethylation pathway in which homocystine is catalyzed to methionine by either methionine synthetase or methylenetetrahydrofolate reductase (MTHFR). An inherited defect in methylcobalamin (methyl-B<sub>12</sub>) that acts as a cofactor for methionine synthetase will also result in homocystinuria, together with methylmalonic aciduria. Deficiencies in these enzymes will lead to high levels of homocystine, but, in contrast to cystathionine synthase deficiencies, low levels of methionine. The clinical picture in these enzyme defects is one of mental retardation, seizures, and hypotonia, while megaloblastic anemia is an additional feature of the disorder of methionine synthetase deficiency. The less

**FIGURE 2.14–12.** Metabolism of homocysteine in vivo. THF, tetrahydrofolate. (From Kelly PJ, Furie KL, Kistler JP, et al. Stroke in young patients with hyperhomocysteinemia due to cystathionine beta-synthase deficiency. *Neurology*. 2003;60[2]:275, with permission.)





severe form of MTHFR deficiency has been strongly associated with psychosis in adolescents and adults; this may be underpinned by alterations to dopamine synthesis and myelination. The C677T variant of the MTHFR gene, which causes a 35 percent reduction in enzyme function has been shown to be an independent risk factor for the development of psychosis. The clinical course and MRI findings can resemble that seen in childhood leukodystrophies in these two disorders. Neuropsychiatric symptoms figure most prominently in the presenting symptoms of patients with methyl-B<sub>12</sub> deficiency, with delays of up to 13 years between the onset of neuropsychiatric symptoms and the ultimate diagnosis.

## Mitochondrial Disorders

Mitochondrial disorders are characteristically multisystem disorders that overlap clinically and should be considered as a differential diagnosis across a range of neurological and neuropsychiatric presentations. The genetic and phenotypic complexity of these disorders can be best understood in the context of a description of the mitochondrial genome, which is inherited maternally. Each human cell has up to several thousand copies of the mitochondrial genome, which is organized into a circular double-stranded structure. Human mitochondrial DNA was first sequenced in 1981 and consists of 37 genes, with no introns and a small noncoding portion. Thirteen proteins are translated from mitochondrial DNA and all are involved in the respiratory chain/oxidative phosphorylation system. The mitochondrial respiratory chain consists of five enzyme complexes made up of polypeptides encoded by nuclear and mitochondrial genes, except for complex II, which is entirely encoded in the cell nucleus. As a result, the mitochondrion is under the genetic control of both nuclear and mitochondrial DNA, and mitochondrial disorders can result from mitochondrial or nuclear DNA mutations. These enzyme complexes participate in a chain of metabolic processes that lead to ATP production, the overall process being referred to as oxidative phosphorylation. ATP is used in the vast majority of cellular metabolic processes as an energy source, and the respiratory chain responds to the energy needs of cells, which in some cases may be quite stable while in others (e.g., muscle), they may vary dramatically over time. Other functions of the mitochondria include cellular homeostasis, fatty acid oxidation, the urea cycle, intracellular signaling, apoptosis, and the metabolism of amino acids, lipids, cholesterol, steroids, and nucleotides.

The genetics of mitochondrial disorders are complex but the following principles can be generally applied:

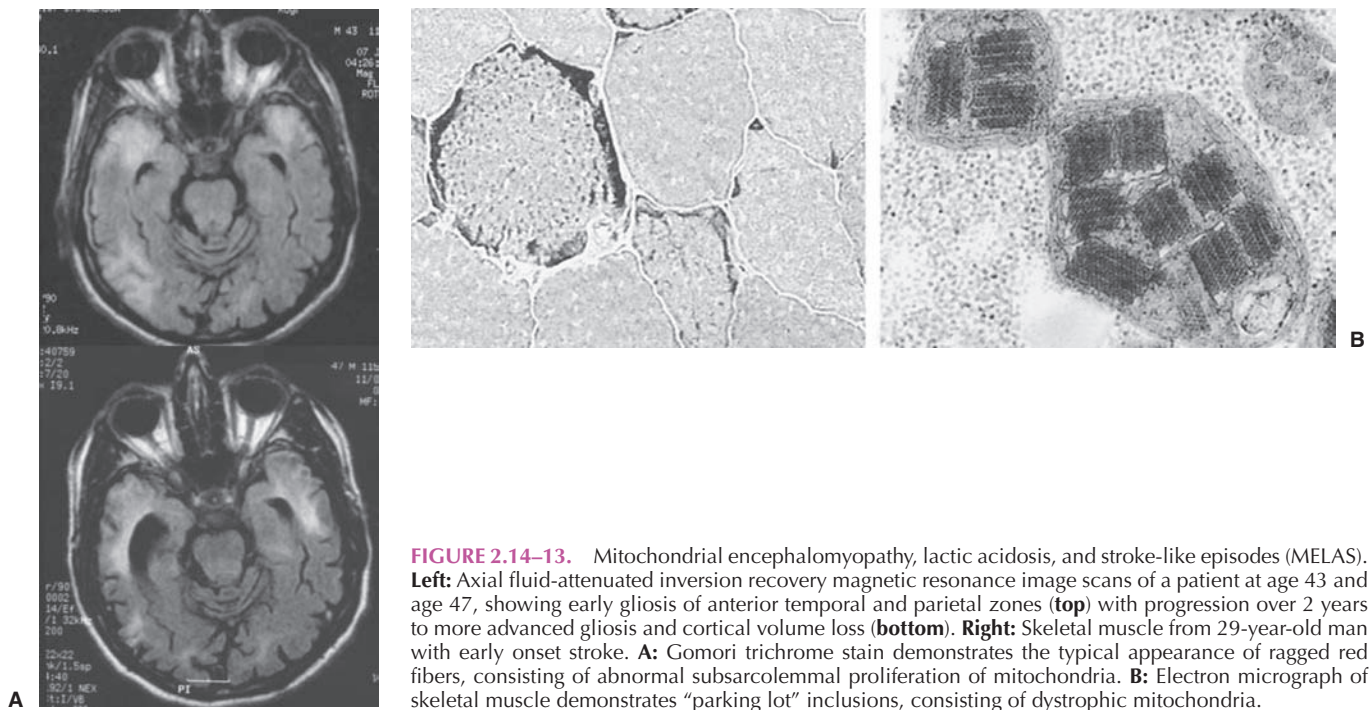
1. Mitochondrial disorders may be sporadic, maternally inherited, or inherited in an autosomal pattern.
2. Due to the polyploid nature of the mitochondrial genome, the one cell may include normal and mutated mitochondrial DNA (heteroplasmy), and thus siblings may show a very broad range of clinical variability due to differences in the inheritance of such heteroplasmic mitochondria. Mitochondrial function will generally begin to fail once the proportion of mutated mitochondrial DNA has crossed a threshold of 70 to 80 percent.
3. Mitochondrial respiratory chain disorders will most affect tissues with high metabolic needs (e.g., muscle, central and peripheral nervous system, heart, endocrine, and eye).
4. The clinical expression of mitochondrial disorders may vary widely from individual to individual with the same mutation depending on the proportion of mitochondria affected in different tissues, the interaction of that individual with the environment, and the differential metabolic energy needs of different tissues within the one individual.

Diseases caused by defects of mitochondrial oxidative phosphorylation are the most common inborn errors of metabolism, accounting for 1 in 5,000 live births. For the reasons outlined above, there is no clear genotype–phenotype relationship for the mitochondrial genome disorders. Clinical features common to all mitochondrial disorders include dysfunction of endocrine (short stature, diabetes, thyroid, and adrenal disorders), neurological (deafness, myopathy, peripheral neuropathy, retinopathy, optic atrophy, ophthalmoplegia, seizures, ataxia, dementia), and cardiac (cardiomyopathy, cardiac block) systems. The patterns of clinical presentation vary significantly with regard to age of onset, the temporal order of symptoms and conditions, and the progress of the disorders. The combination of a maternal history, multisystem involvement, and a progressive course should arouse clinical suspicion of a mitochondrial disorder. In patients with atypical psychiatric presentations, physical signs such as muscle weakness, hearing loss, seizures, short stature, diabetes, Wolff–Parkinson–White syndrome, or migraines should alert clinicians to the possibility of a mitochondrial disorder.

**Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes.** Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), the most common of the mitochondrial disorders, presents before early adulthood after a period of normal development. The majority (about 80 percent) of MELAS cases are due to an A to G substitution at nucleotide 3243 of tRNA leucine (A3243G tRNA<sup>Leu(UUR)</sup>). A further 10 percent of mutations are in other regions of this same gene, while the remaining 10 percent of mutations occur in six other mitochondrial genes. The characteristic features of MELAS are stroke-like episodes whose lesions do not conform to vascular territories and may involve gray or white matter. They typically occur in temporo–parieto–occipital regions, basal ganglia, brainstem, and cerebellum and lead to hemiparesis, hemianopia, and cortical blindness. Vomiting and migraine-like headaches are often associated clinical symptoms. Lactic acid levels are elevated and have been correlated with the level of neurological symptoms. The course of the disorder is highly variable, ranging from single stroke-like episodes through to a progressive course characterized by one or more of multiple strokes, deafness, diabetes, retinopathy, seizures, and cardiac abnormalities. Cases of schizophrenia or schizophrenia-like psychosis associated with MELAS have been reported. Such cases typically show an onset in the third decade, several years to a decade before the clinical diagnosis of MELAS is made. Similar cases of depression, OCD, bipolar disorder, and borderline personality disorder have been reported, but like the schizophrenia cases the course of the illness is not typical. Retrospective review of the patient's history will often reveal previously unappreciated features of MELAS such as short stature, diabetes, or unexplained somatic symptoms. The development of neurological signs or symptoms, cognitive decline, and evidence of strokes on imaging usually leads to the definitive diagnosis.

A 42-year-old man with deafness and diabetes was admitted with a confusional episode and found to have extensive posterior cortical and subcortical changes on MRI. The diagnosis of MELAS was confirmed by genetic testing. Five years later he was rereferred due to altered behavior, aggression, and having become very “fixed” in his ideas. He performed poorly on bedside executive function tests. Repeat MRI revealed extensive inferior frontal and parietotemporal atrophy (Fig. 2.14–13).

The diagnosis of MELAS is based on the clinical syndrome, elevated serum lactic acid levels, muscle biopsy showing ragged red



**FIGURE 2.14-13.** Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). **Left:** Axial fluid-attenuated inversion recovery magnetic resonance image scans of a patient at age 43 and age 47, showing early gliosis of anterior temporal and parietal zones (**top**) with progression over 2 years to more advanced gliosis and cortical volume loss (**bottom**). **Right:** Skeletal muscle from 29-year-old man with early onset stroke. **A:** Gomori trichrome stain demonstrates the typical appearance of ragged red fibers, consisting of abnormal subsarcolemmal proliferation of mitochondria. **B:** Electron micrograph of skeletal muscle demonstrates “parking lot” inclusions, consisting of dystrophic mitochondria.

fibers and molecular genetic testing. Ragged red fibers are muscle fibers, exhibiting mitochondrial proliferation in response to mitochondrial failure. MRI scanning typically shows cerebral stroke-like lesions. There is currently no available treatment for MELAS, although antioxidants, respiratory chain substrates, and cofactors have been studied in trials with varying results. Symptomatic treatments for MELAS may include cochlear ear implants for deafness, anticonvulsants, antipsychotics, and diabetic treatments. Antipsychotics with a higher risk of glucose intolerance (e.g., olanzapine) should be avoided or used with caution.

**Myoclonic Epilepsy with Ragged Red Fibers.** Myoclonic epilepsy with ragged red fibers (MERRF) typically begins in middle adulthood with photosensitive myoclonic seizures and is associated with limb-girdle weakness, dementia, cerebellar ataxia, cardiac abnormalities, and neuropathy. Muscle biopsy reveals ragged red fibers and the EEG is usually abnormal. In 90 percent of cases the causative mutation is an A8344G transition in the tRNA *lysine*. There is no specific treatment, but appropriate management of the epilepsy is critical to clinical outcome.

**Other Mitochondrial Disorders.** Kearns–Sayre syndrome (KSS) is a sporadic mitochondrial deletion disorder characterized by a triad of progressive external ophthalmoplegia, pigmentary retinopathy, plus one of the following: Heart block, cerebellar ataxia, or elevated CSF protein. Muscle biopsy reveals ragged red fibers, and serum lactate is often elevated. MRI will often show diffuse central white matter abnormalities and basal ganglia calcification. Maternally inherited Leigh syndrome (MILS) is an infantile encephalomyopathy characterized by seizures, heart block, dystonia, and optic atrophy. Leber hereditary optic neuropathy (LHON) is a maternally inherited disorder presenting as bilateral visual neuropathy in young adults. Although usually confined to the optic nerve, it has been described together with white matter pathology. “Overlap syndromes” have been described that include features typical of MELAS plus one of the other syndromes (e.g., LHON/MELAS, MELAS/MERRF, Leigh/MELAS).

**Wolfram Disease Type 1 and Type 2.** Wolfram disease type 1, an autosomal recessive disorder caused by a mutation on the short arm of chromosome 4 (4p16.1) in the *WFDS1* (wolframin) gene. The wolframin protein acts to regulate cellular calcium. Wolfram disease type 2 is caused by a mutation in the *CISD2* gene (on 4q24) that codes for a mitochondrial membrane protein. It has been identified only in a small number of families to date. Wolfram disease is also known by the acronym DIDMOAD (*d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, *o*ptic atrophy, *d*eafness) and often displays characteristic atrophy of the optic tract and loss of signal of the neurohypophysis on MRI (Fig. 2.14–14). Patients with *CISD2* mutations do not develop diabetes insipidus but may exhibit gastrointestinal ulcers and bleeding problems. In the largest study of this disorder 68 patients



**FIGURE 2.14-14.** Wolfram syndrome. Sagittal T1-weighted magnetic resonance image scan on a 32-year-old female with deafness and depression. Evident are frontal atrophy, thinning of optic chiasm and tracts, and atrophy of the brainstem and vermis and absence of physiological high signal of the neurohypophysis. (From Pakdemerli E, Karabulut N, Bir LS, Sermez Y. Cranial magnetic resonance imaging of Wolfram (DIDMOAD) syndrome. *Australas Radiol.* 2005;49[2]:189, with permission.)

with Wolfram disease were reviewed. Sixty percent (41 of 68) had had psychiatric symptoms and 25 percent (17 of 68) were classified as showing severe mental illness. Eleven (16 percent) patients had a history of psychotic symptoms. Heterozygous family members exhibited a high rate of psychiatric illness, approximately eight times greater than for noncarriers of the wolframin gene. The high rate of schizophrenia-like psychosis in this disorder is similar to that seen in some other adult-onset neurological disorders, such as velocardio-facial syndrome, MLD, and Niemann–Pick disease type C, each of which shows rates of psychosis in the 25 to 40 percent range.

### Disorders of Metal Metabolism

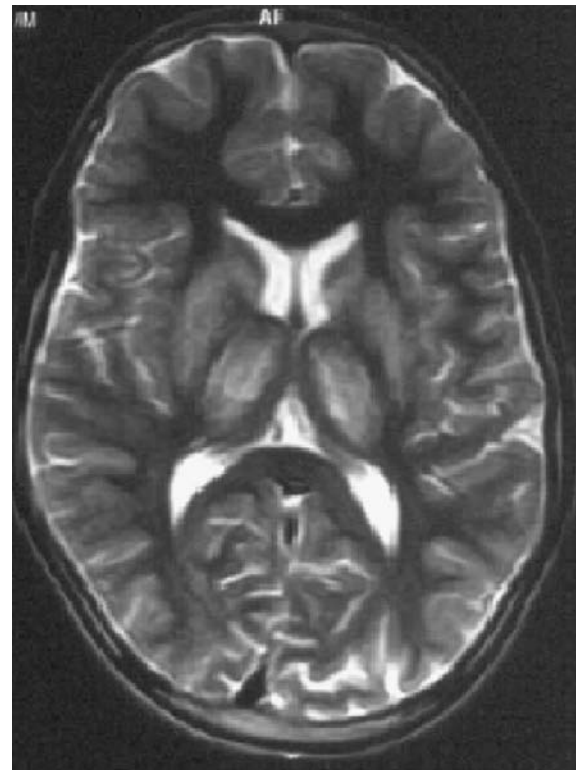
**Wilson Disease.** Wilson disease is an autosomal recessive disorder caused by mutations in a copper transporting ATPase encoded by the *ATP7B* gene on chromosome 13q14.3. About 1 percent of the population carries an *ATP7B* mutation, of which over 500 have been identified. The frequency of the disorder is estimated to be about 1 in 40,000. The gene defect leads to the accumulation of copper in the liver through impaired copper excretion and impaired binding of copper to ceruloplasmin. The subsequent catabolism of ceruloplasmin leads to low ceruloplasmin plasma levels and increased free copper. Free copper then accumulates in the brain and leads to the neurological and neuropsychiatric manifestations of this disorder. Copper deposition occurs in astrocytes but not neurons or the extracellular matrix, and is particularly evident in the basal ganglia.

The most common presentation of Wilson disease is with hepatic disease anywhere between the first and fourth decades. About 50 percent of patients are symptomatic by age 15. Up to two-thirds of patients will present with neurological disease in the second or third decade without clinical evidence of liver disease. The *dystonic* form is the commonest presenting neurological syndrome with dysarthria, dysphagia, drooling, and a rigid open mouth. In the *pseudosclerotic* form patients present with incoordination, clumsiness, unsteadiness of gait, or dysarthria. As the illness progresses patients may exhibit features of both forms with rigidity, tremor, choreic, athetoid, or dystonic movements. Such movements may be exacerbated by stress in the early stages of illness and be interpreted as functional. In particular, the tremor associated with Wilson disease, so-called wing beating, may be interpreted as a hysterical movement disorder. This tremor is characteristically absent at rest and develops after a short period of the arm extension. The arms beat in a wide violent arc, and the tremor may be altered by the position of the arms.

Wilson's original description in 1912 emphasized the importance of mental changes in the disease. Since then many authors have described the high prevalence of psychiatric symptoms with estimates ranging from 30 to 100 percent of symptomatic patients experiencing psychiatric symptoms at some point during their illnesses. Up to two-thirds of patients present with psychiatric symptoms and one-third will have received psychiatric treatment prior to the diagnosis being made. The most common reasons for psychiatric referral are behavioral and personality changes, with disinhibition, bizarre, or impulsive behavior being present in about a quarter of patients and depression in about one-fifth. Personality and behavioral changes, but not depression, correlate with the degree of neurological impairment. Although early reports suggested that psychotic presentation was a feature of Wilson disease, more recent investigations have shown that psychotic symptoms are relatively rare. The importance of recognizing the early psychiatric presentations of Wilson disease lies in the proven benefits of early treatment intervention. Diagnostic delays

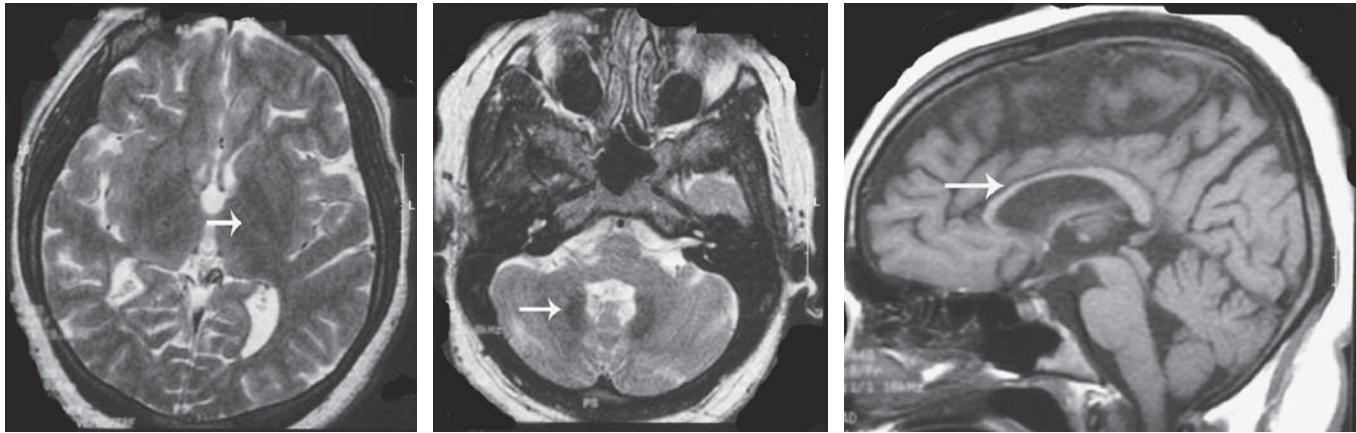
may be exacerbated if extrapyramidal movements are attributed to psychotropic medications or interpreted as functional. Patients with neurological involvement show a subcortical pattern of cognitive impairment with frontal executive deficits that correlate with the extent of cerebral involvement.

The presence of Kayser–Fleischer (KF) rings (copper deposits in the outer rim of the cornea that are brown or gray-green) on slit-lamp examination is the single most important clinical diagnostic sign and is observed in about half of patients with hepatic presentation and almost all patients with a neurological or psychiatric presentation. Of lesser diagnostic value are low serum levels of ceruloplasmin, which may be normal in 10 percent of patients and high urinary copper excretion. The gold standard test for Wilson disease is liver biopsy with staining for copper. MRI shows reduced T1 signal and increased T2 signal in basal ganglia, thalamus, and brainstem (Fig. 2.14–15). The aims of treatment are to remove accumulated copper and to prevent reaccumulation through maintenance treatment. Treatment with d-penicillamine (Cuprimine) combined with pyridoxine has been the mainstay of initial treatment, but concerns that neurological symptoms are worsened by the treatment have led to calls that it be replaced with the less toxic copper chelators, trientine (Syprine) or ammonium tetrathiomolybdate. Zinc acetate therapy has been used as a preventative treatment in patients who are presymptomatic and for maintenance treatment. It acts by inducing an intestinal protein which binds copper and is not absorbed into blood. Neurological and psychiatric symptoms will improve with copper chelation over 1 to 2 years, with regression of MRI lesions on serial imaging. In patients with neurological forms of Wilson disease, the best outcomes are



**FIGURE 2.14–15.** T2-weighted axial magnetic resonance image of an adolescent patient with Wilson disease, showing characteristic bilateral hyperintensity of the thalamus, caudate and putamen. (From Das M, Mirsa UK, Kalita J. A study of clinical, MRI and multimodality evoked potentials in neurologic Wilson disease. *Eur J Neurol.* 2007;14[5]:498, with permission.)





**FIGURE 2.14–16.** Scans of a 22-year-old woman patient with aceruloplasminemia and a schizophrenia-like psychosis. Reduced intensity of the basal ganglia (**left**) and dentate nucleus of the cerebellum (**middle**) on axial T2-weighted imaging representing iron deposition (*arrows*), and T1-weighted sagittal scan demonstrating anterior callosal thinning (**right, arrow**).

seen in patients with the pseudosclerotic form (82 percent symptom free), with lesser outcomes in patients with chorea (75 percent), parkinsonism (63 percent), and dystonia (53 percent).

**NEURODEGENERATION WITH BRAIN IRON.** The collective term neurodegeneration with brain iron (NBIA) refers to a number of genetic disorders associated with accumulation of iron in the brain. Aceruloplasminemia and neuroferritinopathy are caused by mutations in iron metabolism genes, while pantothenate kinase-associated neurodegeneration (PKAN) is caused by a mutation that disrupts several metabolic pathways, including iron metabolism.

**Aceruloplasminemia.** Aceruloplasminemia is an autosomal recessive disorder associated with reduced or absent levels of ceruloplasmin and tissue iron deposition. It can be caused by about 40 mutations in the ceruloplasmin gene on chromosome 3q25 and occurs in 1 per 2 million births. There are two types of ceruloplasmin. Serum ceruloplasmin is predominantly synthesized in the liver but does not cross the blood–brain barrier while a second form (GPI-anchored form) is produced by astrocytes in the CNS. Ceruloplasmin promotes the loading of iron onto transferrin, allowing  $\text{Fe}^{3+}$  efflux out of cells and preventing oxidative damage caused by  $\text{Fe}^{2+}$ . GPI-anchored ceruloplasmin plays a key role in regulating iron levels in the CNS and in preventing free radical injury. The disease leads to the deposition of iron in the CNS, retina, pancreatic cells, liver, spleen, and ovaries. The major sites of CNS iron deposition in ceruloplasmin are similar to the sites of greatest iron concentration in healthy individuals: The basal ganglia, cerebellar dentate nuclei, red nucleus, thalamus, and hippocampus. Aceruloplasminemia presents with diabetes mellitus, retinal degeneration, and neurological symptoms. Neurological signs may be preceded for many years by diabetes mellitus and anemia due to inefficient iron delivery. Ataxia and extrapyramidal movements such as blepharospasm, dystonia, dyskinesia, grimacing, and parkinsonism usually develop in the fifth decade. A subcortical picture of cognitive decline then follows with personality change, amotivation, psychomotor slowing, and executive deficits. Psychosis has been reported, although psychiatric symptoms have not been commonly described in aceruloplasminemia due to the rarity of the disorder. MRI findings typically show marked T2 hypointensity in the regions of maximal iron deposition, posterior white matter tract hyperintensity, and superficial cerebral and cerebellar cortical hypointensity.

A 21-year-old woman on treatment for aceruloplasminemia was referred for neuropsychiatric assessment. There was a family history of aceruloplasminemia and the diagnosis was made 12 months earlier after she was found to have abnormal liver function tests. She now presented with an 18-month history of schizophrenia-like psychosis and declining function in the absence of neurological signs. Neuropsychological testing showed significant dominant hemisphere deficits. MRI showed bilateral iron deposition in the cerebellar dentate nuclei and thalami, frontal atrophy, and periventricular white matter hyperintensities (Fig. 2.14–16).

The diagnosis of aceruloplasminemia can be made biochemically with findings of absent ceruloplasmin, low serum copper, normal serum total iron binding capacity, and moderately elevated ferritin. Treatment with the iron chelating agent desferrioxamine can decrease serum ferritin, reduce brain and liver iron stores, and can prevent the progression of neurological disease.

**NEUROFERRITINOPATHY.** Neuroferritinopathy is an extremely rare autosomal dominant disorder with fewer than 100 reported cases. It is caused by a mutation in the FTL gene on 19q13.33 with 7 mutations identified to date. The FTL gene codes for the ferritin light chain, a subunit of ferritin, which plays a role in the storage and release of iron from cells. In neuroferritinopathy ferritin is unable to store iron and excess iron is deposited in brain cells especially the globus pallidus, putamen, and dentate nuclei of the cerebellum. The clinical phenotype begins in the third or fourth decade with extrapyramidal symptoms and signs including chorea, ataxia, dystonia, tremor, dysphagia, and dysarthria. The presence of an orofacial action specific dystonia is characteristic of this disorder. A recent review of the neuropsychiatric features of neuroferritinopathy described 22 cases. This review identified that subcortical type cognitive changes began about 4 years after the onset of motor symptoms (mean onset age 47.2). Individual cases of OCD, psychosis, emotional lability, and aggression are noted.

The clinical diagnosis of neuroferritinopathy should be suspected in cases of adult onset movement disorder, MRI findings of excess iron deposition in basal ganglia or cystic degeneration on T2\* MRI images. The presence of cystic degeneration may help distinguish neuroferritinopathy from aceruloplasminemia. Serum ferritin may be low. The genetic diagnosis is based on identification of a mutation in

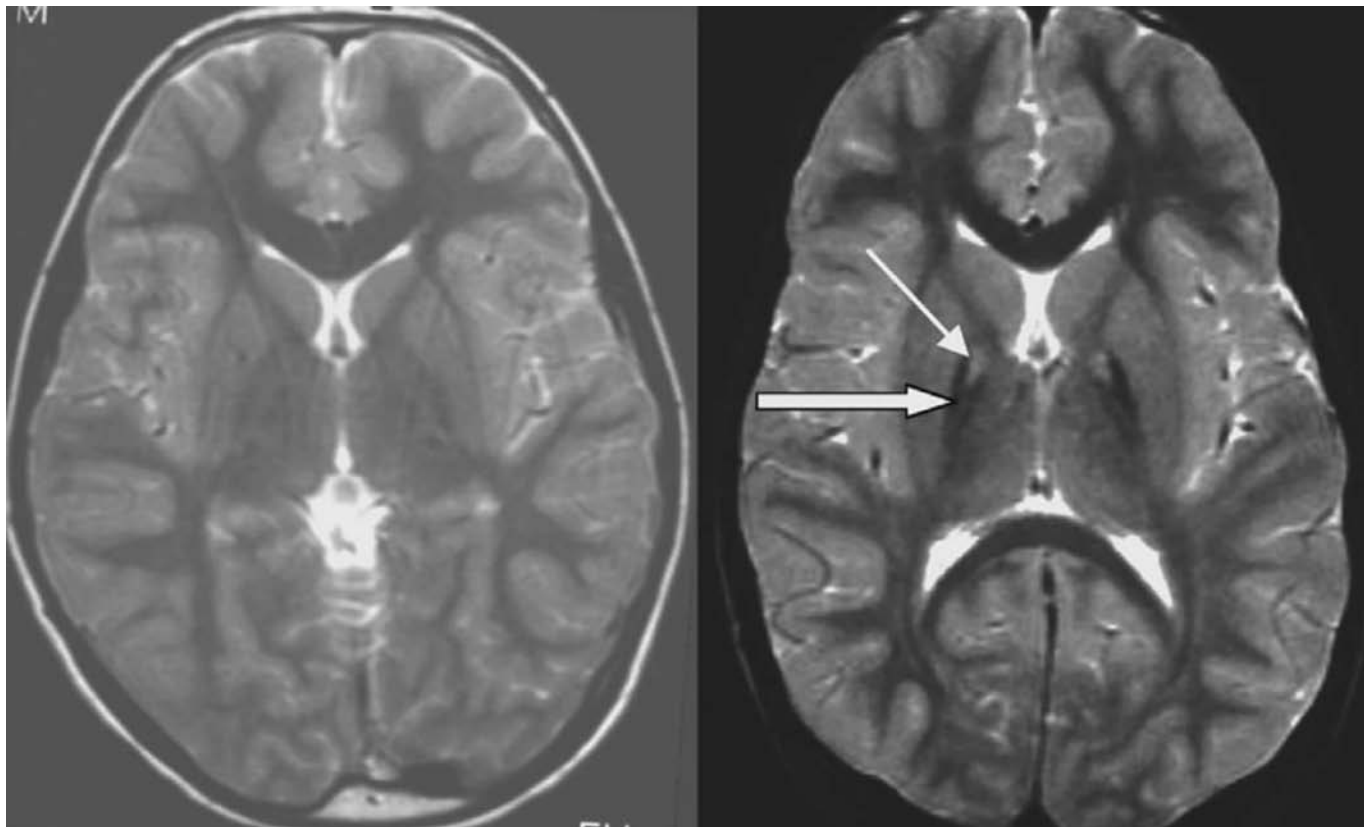
the *FTL* gene. There are no specific treatments available. Symptomatic treatment of the movement disorder is indicated though conventional treatments (tetrabenazine, benzhexol, l-dopa, benzodiazepines) are variably successful. Botulinum toxin may be of benefit in dystonias.

#### Pantothenate Kinase-Associated Neurodegeneration.

PKAN, an autosomal recessive disorder, is one of several disorders that had been previously described as Hallervorden–Spatz syndrome but are now collectively grouped under the term NBIA (neurodegeneration with brain iron accumulation). Common to these disorders is the accumulation and deposition of iron in the brain in association with clinical, radiological, and pathological evidence of neurodegeneration. The identification of mutations in the gene *PANK2* on chromosome 20p13 led to the descriptive term “pantothenate kinase-associated neurodegeneration” for what is recognized as the most prevalent form of NBIA. Pantothenate kinase 2 regulates the mitochondrial synthesis of coenzyme A (CoA), which is involved in energy and fatty acid metabolism. *PANK2* catalyses the phosphorylation of pantothenate (vitamin B<sub>5</sub>) to phosphopantothenate, which condenses with cysteine in the next step of CoA biosynthesis. Mutations in *PANK2* lead to an accumulation of cysteine, which binds iron and leads to free radical production, which triggers cell membrane damage and death. The retina and basal ganglia appear particularly sensitive to these effects of PKAN mutations, and the primary clinical features are those of retinopathy and basal ganglia syndromes.

The clinical phenotype of *PANK2* mutations can be divided into three types: the classic syndrome, the atypical syndrome, and HARP

(hypobetalipoproteinemia, acanthocytosis, retinopathy, and pallidal degeneration). The *classic* syndrome first described by Hallervorden and Spatz consisted of the early childhood (3 to 4 years) onset of dystonia, dysarthria, rigidity, pyramidal signs, pigmentary retinopathy, and cognitive decline, and with a progressive fulminant course such that patients became nonambulatory by their mid- to late teens. All patients with this classic phenotype have been found to have a *PANK2* mutation. The *atypical clinical phenotype* (about 25 percent of PKAN) is characterized by presentation in the early to mid-teenage years with palilalia, tachylalia, dysarthria, and psychiatric symptoms, including depression, emotional lability, personality changes, and cognitive decline. Extraparamidal rigidity, dystonia, and pyramidal spasticity develop subsequently and result in progressive loss of mobility over 15 to 40 years. About one-third of this *atypical clinical phenotype* exhibit *PANK2* mutations. Interestingly, the patients with *PANK2* mutations and late onset appear to be more likely to exhibit speech and psychiatric symptoms at onset. The third clinical phenotype, previously termed HARP, has now been identified as being caused by a *PANK2* mutation. Together with a strongly suggestive clinical picture, the finding of the characteristic MRI “eye of the tiger” sign (a low signal intensity region caused by iron deposition and a high signal area that corresponds to axonal spheroid formation, as seen in Fig. 2.14–17) is almost pathognomonic of a *PANK2* mutation and should lead to genetic testing. No treatment has been identified for PKAN and management remains symptomatic, with trials of iron chelation and antioxidants generally proving unsuccessful (Table 2.14–1).



**FIGURE 2.14–17.** Pantothenate kinase-associated neurodegeneration. **Left:** T2-weighted axial magnetic resonance image of a normal control shows isodense globus pallidus. **Right:** *PANK2*-mutation-positive patient with neurodegeneration with brain iron accumulation (NBIA) shows hypointensity (*thick arrow*) with a central region of hyperintensity (*thin arrow*) in the medial globus pallidus, known as “the eye of the tiger” sign. (From Hayflick SJ. Unraveling the Hallervorden-Spatz syndrome: Pantothenate kinase-associated neurodegeneration is the name. *Curr Opin Pediatr.* 2003;15[6]:572, with permission.)

**Table 2.14-1.**  
**Metabolic Disorders Presenting as Neuropsychiatric Syndromes, with Pattern of Inheritance, Gene Location, and Product, Prevalence, Onset, and Neuropsychiatric Features**

Disorder	Inheritance	Location	Gene	Gene Product	Stored or Altered Substance	Prevalence per Million
Metachromatic leukodystrophy	AR	22q13.31	ARSA	Arylsulfatase A	Cerebroside sulfate	5-25
Fabry disease	X-linked recessive	Xq22	a-Gal	$\alpha$ -galactosidase A	globotriaosylceramide	25 (males)
Tay-Sachs Disease	AR	15q23-q24	HEXA	$\beta$ -hexosaminidase A	GM2-gangliosides	150-400 (Jewish) 3 (general population)
Neuronal ceroid lipofuscinosis (Kufs)	AD/AR	Not yet identified	CLN4	Unknown—more than one may be involved (CLN1&2 – lysosomal thioesterase & protease; CLN3&8 are membrane proteins of unknown function)	Unknown	1-2
$\alpha$ -mannosidosis	AR	19q13.1	MANB	$\alpha$ -mannosidase	Oligosaccharides	2
X-linked adrenoleukodystrophy	X-linked recessive	Xq28	ABCD1	ALDP peroxisomal membrane protein	saturated very long chain fatty acids	50 (males)
Acute intermittent porphyria	AD	11q23.3	HMB	porphobilinogen-deaminase	porphobilinogen/amino levulinic acid	40-100
Phenylketonuria	AR	12q23.2	PAH	phenylalanine hydroxylase	phenylketones	50-100
Maple syrup urine disease	AR	19q13.1-13.2	BCKDHA BCKDHB	branched chain ketoacid dehydrogenase	branched chain amino acids	5
NPC	AR	1p31 18q11-12	DBT NPC1 NPC2		cholesterol and gangliosides	10
Pelizaeus-Merzbacher Disease	X-linked recessive	14q24.3	PLP1	proteolipid protein	n/a	2-5
Cerebrotendinous xanthomatosis	AR	Xq22	CYP27A1	sterol 27 hydroxylase	cholestanol and cholesterol	300 reported cases
Cystinosis	AR	17p13	CTNS	cystin	cystine	5
Homocystinuria	AR	21q22.3	CBS	cystathione synthase	homocystine and methionine	3-5
Tetrahydrobiopterin deficiency	AR	Multiple	GCH1 PCBD1 PTS	Multiple	BH4	2
Hyperprolinemia	AR	1p36	QDRP		Proline	<1
Propionic acidemia	AR	13q32, 3q21-22	ALDH4A1 PCCA PCCB	Pyrrroline-5-carboxylate dehydrogenase Propionyl-CoA carboxylase	Propionic acid	10
AMACR deficiency	AR	5p13	AMACR	$\alpha$ -methylacyl-CoA racemase	Pristanic acid	<1
CCDS	AR & XL	19p13.3, 15q21.1, Xq28	GAMT AGAT	Guanidinoacetate N-methyl transferase, Glycine amidinotransferase, Sodium and chloride-dependent creatine transporter	Creatine	<1
NKH	AR	9p22, 3p21.31	SLC6A8 GLDC	Glycine dehydrogenase, aminomethyltransferase	Glycine	20
SSADH deficiency	AR	6p22	ALDH5A1	Succinic semialdehyde dehydrogenase	GABA, GHB	<1
Serine deficiency	AR	1p12, 7p11.2, 9q21.2	PHGDH PSPH	Phosphoglycerate dehydrogenase, phosphoserine phosphatase,	Serine	<1
CFD	AR, autoimmune	11q13.3	PSAT1	phosphoserine aminotransferase	Folate	<1
MELAS	Maternal	mtDNA	FOLR1		n/a	60
Wolfgram disease	AR/Maternal	4p/ mitochondrial	MT-TL1 WFS1	mitochondrial tRNA leucine 1 wolframlin	n/a	170 reported cases
Wilson disease	AR	13q14.2-q21	ATP7B	copper transporting ATPase	copper	25
Aceruloplasminemia	AR	3q25	CP	ceruloplasmin	iron	.5
Pantothenate kinase associated neurodegeneration	AR	20p13	PANK2	pantothenate kinase	cysteine	1



Disorder	Onset	Neuropsychiatric Features
Metachromatic leukodystrophy	Childhood–adulthood	Psychosis in adolescent onset/chorea/seizures/dementia
Fabry disease	Childhood–adulthood	Depression
Tay–Sachs Disease	Childhood–adulthood	Psychosis in adult onset, speech, gait disorder, tremor
Neuronal ceroid lipofuscinosis (Kufs)	Adult (Kufs)	Psychosis/depression/myoclonic epilepsy/dyskinesias
$\alpha$ -Mannosidosis	Childhood–adulthood	Psychosis in adult onset/ataxia/deafness/retinopathy
X-linked adrenoleukodystrophy	Childhood–adulthood	Affective psychosis in adult onset/demyelination
Acute intermittent porphyria	Adulthood	Psychosis/delirium/depression/peripheral neuropathy
Phenylketonuria	Childhood	Mental retardation
Maple syrup urine disease	Childhood–adulthood	Depression and anxiety in adults
Niemann–Pick disease Type C	Childhood–adulthood	Mental retardation in childhood onset/psychosis in adolescent onset/dementia in adult onset
Pelizaeus–Merzbacher Disease	Childhood–adulthood	Mental retardation in childhood onset/psychosis and dementia in adult onset
Cerebrotendinous xanthomatosis	Adulthood	Psychosis/agitation/depression
Cystinosis	Childhood	Cystinosis encephalopathy
Homocystinuria	Childhood	Mental retardation/seizures/dystonias/personality change/behavioral disturbance/depression/OCD
Tetrahydrobiopterin deficiency	Childhood–adulthood	Behavioral disturbance, mental retardation; adult mood and psychotic disorders
Hyperprolinemia	Childhood–adulthood	Mental retardation, psychosis
Propionic acidemia	Childhood–adulthood	Encephalopathy, mental retardation, autism, psychosis
AMACR deficiency	Early adulthood	Cognitive decline, psychosis
CCDS	Childhood	Autism, self-mutilation, mental retardation
NKH	Childhood	Mental retardation, attention deficit
SSADH deficiency	Childhood–adulthood	Mental retardation, autism, OCD, psychosis
Serine deficiency	Childhood	Aggression, mental retardation
CFD	Childhood–adulthood	Mental retardation, autism, psychosis
MELAS	Adolescence/early adulthood	Stroke-like lesions/psychosis/depression
Wolfram disease	Childhood–adulthood	Schizophrenia
Wilson disease	Adolescence/early adulthood	Extrapyramidal movements/psychosis/parkinsonism/dysphagia/dyarthria
Aceruloplasminemia	Adolescence/early adulthood	Ataxia, dystonia, dyskinesia, subcortical dementia
Pantothenate kinase associated neurodegeneration	Childhood–adulthood	Childhood dystonia, rigidity/adolescent pallidus, dysarthria, depression, lability, personality change, cognitive decline

AR, autosomal recessive; AD, autosomal dominant; tRNA, transfer ribonucleic acid; ATP, adenosine triphosphate; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; OCD, obsessive–compulsive disorder.

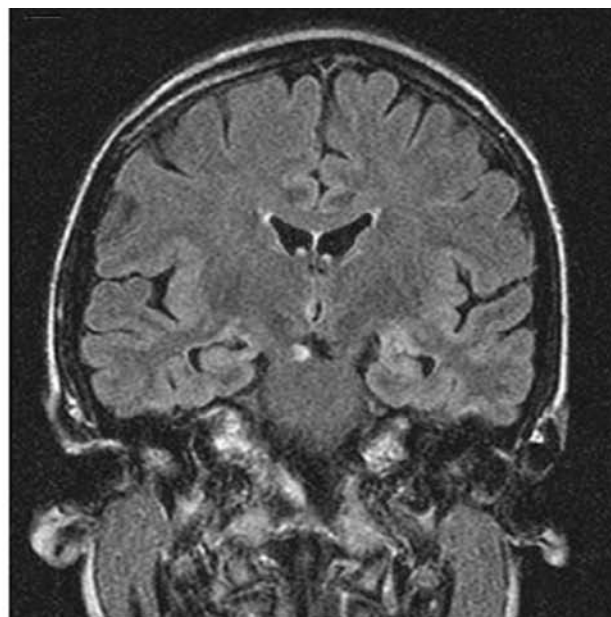
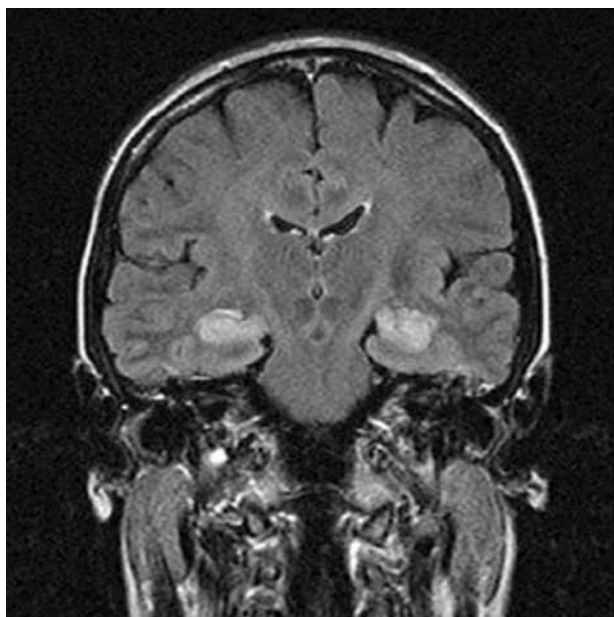
## Ion Channel Disorders

Disorders of ion channels, or channelopathies, have become an increasingly recognized group of disorders affecting cellular ion channels involving  $\text{Na}^+$ ,  $\text{Ca}^{++}$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  in electrically excitable tissue, such as heart, muscle, and brain. A number of genetic ion channel diseases have now been well-described, such as the LQT, periodic paralysis, and a range of monogenic seizure syndromes. The cardinal feature of ion channel disease is the disturbance of rhythmic function, best illustrated by epilepsy, with an abnormally synchronous discharge causing a seizure; other rhythmic CNS disturbances such as ataxia, paralysis, and sensorineural deafness. Additionally, the possibility of developing an *acquired* abnormality of ion channel function has been recognized, particularly in autoimmune disorders.

### Voltage-Gated Potassium Channel Encephalopathy.

VGKC antibodies are linked to a group of rare disorders characterized by abnormal neuromuscular excitability and CNS manifestations. These disorders form part of a larger group of CNS autoimmune disorders involving antibodies directed against targets on the neuronal surface. Isaac syndrome (acquired neuromyotonia) is associated with thymoma and VGKC antibodies but has no CNS manifestations. Morvan syndrome is a very rare disorder characterized by neuromyotonia, severe insomnia, excessive sweating, hyper-salivation, and a subacute encephalopathy commonly accompanied by psychotic features including delusions and hallucinations. High titers of VGKC of antibodies are also detected. A group of patient with nonparaneoplastic limbic encephalitis have high titers of VGKC antibodies. This group presents with complex-partial seizures and a progressive amnesic syndrome with sleep disturbance as well as fluctuating conscious state, personality change and variable psychotic symptoms. MRI frequently demonstrates bilateral high signal in the hippocampal region. These symptoms are steroid responsive, including reversal of cognitive deficits and MRI changes, once the

[AQ1] diagnosis has been made (Fig. 2.14–18).



**FIGURE 2.14–18.** Voltage-gated potassium channel antibodies causing limbic encephalitis. **Left:** Coronal fluid-attenuated inversion recovery magnetic resonance image shows bilateral mesial temporal hyperintensity. **Right:** Identical coronal slice 3 months later, after treatment, shows resolution of hyperintensities but resultant hippocampal atrophy.

**Timothy Syndrome.** Timothy syndrome is a relatively recently recognized multisystem  $\text{Ca}^{++}$  channelopathy in which autism-spectrum disorders occur in 80 percent of affected individuals, alongside cardiac arrhythmias and syndactyly. The affected  $\text{Ca}_v1.2$  gene is widely expressed, particularly in heart, brain, smooth muscle, and pituitary and adrenal glands. In the CNS, highest expression is in the granular layer of the dentate gyrus of the hippocampus, and cerebellum. It is not clear how changes to neuronal tissue excitability contribute to the development of autism, but it is likely to represent the endpoint of the interaction between tissue excitability and normal neurodevelopment. A greater understanding of the pathophysiology of this disorder may open up new avenues of research into the possible contribution of ion channel disturbance to polygenic neuropsychiatric disorders.

## NEUROENDOCRINE DISORDERS

### Hypothalamic Disorders

The relationship between the hypothalamus and pituitary gland is complex. In brief the release of six anterior pituitary hormones prolactin (PRL), growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropin (ACTH), and thyrotropin or thyroid stimulating hormone (TSH) is under the tonic influence of hypothalamic neuropeptides which travel from hypothalamic neurons via the portal system of the anterior pituitary to influence pituitary hormone producing cells. AVP (vasopressin or ADH, antidiuretic hormone) and PRL are produced in the hypothalamus and stored in the posterior pituitary. As a consequence of this relationship endocrine abnormalities of the hypothalamus are largely manifest as abnormalities of pituitary function as described below. However, the hypothalamus also has a number of nonendocrine functions that when disturbed may manifest as neuropsychiatric disorders.

The hypothalamus contains a number of unique neurons that create two neuropeptides known as *orexins* (formerly *hypocretins*). They are synthesized only in the hypothalamic neurons, and share

some homology to the gut hormone secretin. Orexinergic neurons project from the hypothalamus to a number of monoaminergic centers including the locus coeruleus, raphe nuclei, and ventral tegmentum. A number of these monoaminergic systems are involved in the regulation of sleep, in which the hypothalamus is now recognized as a key center. The contribution of the hypothalamus is via sleep-promoting GABAergic neurons of the ventrolateral preoptic area (VLPO) and the wakefulness-promoting orexinergic neurons in the lateral hypothalamus. These pathways are closely linked to the circadian pacemaker in the suprachiasmatic nuclei and the regulation of other hypothalamic functions such as temperature, food intake, metabolism, and hormone secretion.

The orexinergic system is also important in the regulation of food intake and energy expenditure. Orexin production can increase food craving, but is also inhibited by leptin, a hormone produced by adipocytes, and stimulated by ghrelin. Ghrelin is secreted by the stomach just prior to a meal and is known to stimulate caloric intake. This provides a biochemical basis for the well-demonstrated phenomenon of sleep-deprivation related catabolism despite adequate caloric intake described in animal models.

### Narcolepsy

Narcolepsy is a sleep disorder characterized by excessive daytime somnolence, cataplexy (a sudden loss of muscle tone, often triggered by strong emotional reactions) and manifestations of disordered REM sleep such as hypnagogic hallucinations, automatic behavior, and sleep paralysis. Although narcolepsy in dogs is linked to mutations in hypocretin-related genes, no such mutations have been described in humans, although in approximately 90 percent of patients, orexin levels in the CSF are low or nonexistent. Strong links to the human leukocyte antigen (HLA) system suggest an autoimmune basis. HLA-DR15 and HLA-DQ6 have been described in up to 85 percent of patients but only 20 percent of controls, and DQB1\*602 allele has been detected in 98 percent of patients with cataplexy. A gene-environment interaction is likely given the <25 percent concordance rate between monozygotic twins. Depression has been described in up to 25 percent of patients in some series, although others suggest a rate no higher than that in the healthy population. Whether narcolepsy is associated with psychosis is very controversial. It has been suggested that some psychoses are “narcoleptic” in origin and respond to treatment with stimulants, and that REM-intrusion into wakefulness may be misdiagnosed as schizophrenia. The vast majority of psychoses associated with narcolepsy do appear to relate to stimulant use/misuse, as historically dopaminergic agents such as dexamphetamine have been used to promote wakefulness. Newer agents such as modafinil may be less psychotogenic. Neuroleptics however worsen narcoleptic somnolence, as dopamine outflow is central to cortical wakefulness.

A 23-year-old man was referred for assessment of psychotic symptoms occurring in the setting of narcolepsy. At age 13, narcolepsy was diagnosed on the basis of daytime somnolence, cataplexy, sleep paralysis, and hallucinations. He showed an HLA-DR15 haplotype. He had begun dexamphetamine 2 years prior to assessment and started to experience auditory hallucinations, thought broadcasting, and a complex persecutory delusional system (whereby he was being studied through a device implanted in his head) within 6 months. His family described a precipitous psychosocial decline over 12 months, as the patient became unemployed, socially withdrawn, and increasingly disorganized. On mental

state, he presented as fatuous and inappropriate, with clear thought disorder. After commencing fluphenazine 4 mg and ceasing dexamphetamine, the hallucinations and delusions diminished, although he remained fatuous and amotivated. A diagnosis of narcolepsy-related psychosis secondary to dexamphetamine treatment was made, with a differential diagnosis of schizophrenia.

### Hypothalamic Lesions

Hypothalamic obesity has been associated with lesions of the ventromedial nucleus, and may initially involve aggressive behavior and hyperphagia until a new set weight is reached, at which time reduced appetite and activity may manifest. Rage reactions are also well described in animals with lesions in this region of the hypothalamus, although less so in humans with such lesions. Lateral lesions have been reported to result in an apathetic state. Thirst may also be impaired if ADH production is reduced by a hypothalamic lesion. Short-term memory dysfunction has been reported, particularly in lesions of the ventromedial and premamillary areas of the hypothalamus. Extensive hypothalamic lesions may produce features consistent with a dementing illness.

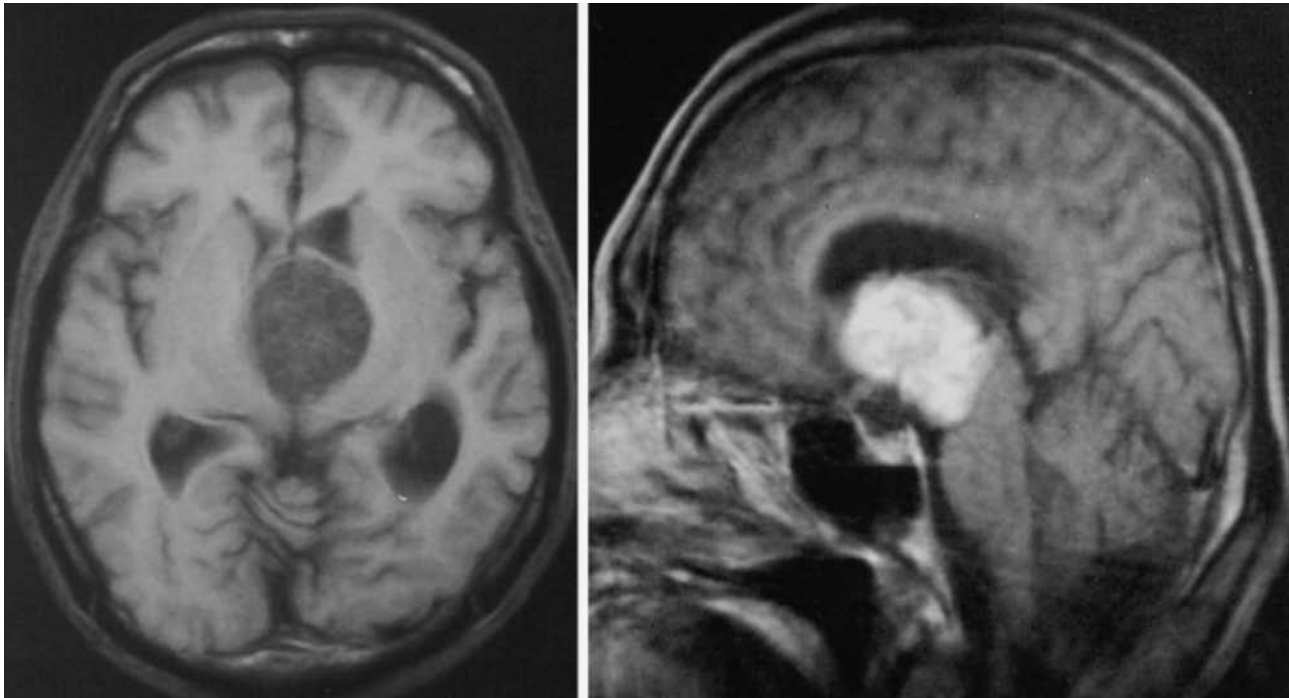
Hypothalamic disease may also result in abnormalities of thermoregulation. Temperature sensitive neurons are located in the anterior hypothalamus, whereas the posterior hypothalamus mediates heat loss mechanisms. Acute lesions such as hemorrhage, infarction or those from surgical procedures may result in acute and paroxysmal hypothermia. Conversely, posterior hypothalamic lesions may result in paroxysmal hyperthermia with associated fevers and rigors.

Childhood tumors invading the anterior and basal hypothalamus such as gliomas, midline cerebellar astrocytomas, and suprasellar ependymomas may result in the diencephalic syndrome which is manifest as motor hyperactivity, euphoria or inappropriate affect, increased alertness, and emaciation despite normal caloric intake. If death does not ensue the clinical picture may change to one of obesity and intermittent rage reactions. In adulthood, slower growing tumors usually result in a dementia syndrome, endocrine dysfunction, and food intake dysregulation. More rapid or destructive processes present with disturbances of consciousness, temperature, and autonomic dysregulation. Craniopharyngiomas, germinomas, and gliomas are the most frequently reported tumors. Craniopharyngioma, remnants of the embryonic Rathke pouch can manifest in both childhood (most common) and adulthood, usually involving the posterior hypothalamus. As most are suprasellar, patients usually present with visual abnormalities and headaches. Hypogonadism, hyperprolactinemia, diabetes insipidus, and weight gain are common as is cognitive deterioration and personality change without evidence of psychosis (Fig. 2.14–19).

### Pituitary Disorders

The pituitary gland, or *hypophysis*, is an endocrine structure that sits in the midline sella turcica at the base of the brain in the middle cranial fossa, and is covered by a dural fold (the *diaphragma sellae*). It secretes hormones regulating homeostasis, and through the release of trophic hormones, stimulates other distal endocrine structures. Its anterior lobe, the *adenohypophysis*, is under direct functional control of the hypothalamus, via the hypophyseal-portal vascular connection in the pituitary stalk, through which stimulatory and inhibitory signals are sent to control the five distinct endocrine cell types that release pituitary hormones. The posterior lobe, the *neurohypophysis*,





**FIGURE 2.14–19.** Craniopharyngioma causing the diencephalic syndrome. T1-weighted magnetic resonance imaging scans of a patient who presented with emaciation and features of the diencephalic syndrome. **Left:** Axial image demonstrating a slightly hypointense tumor within the third ventricle accompanied by moderate dilation of the lateral ventricles. **Right:** Sagittal image obtained after the administration of gadolinium revealing that the tumor is homogeneously enhanced and is entirely confined within the third ventricle. (From Miyoshi Y, Yunoki M, Yano A, Nishimoto K, Kononov AN. Diencephalic syndrome of emaciation in an adult associated with a third ventricle intrinsic craniopharyngioma: A case report. *Neurosurgery*. 2003;52[1]:224, with permission.)

is predominantly a collection of axons from the supraoptic and paraventricular nuclei of the hypothalamus that secretes peptide hormones into the hypophyseal circulation. The posterior lobe is connected by the infundibulum in the pituitary stalk, and the release of oxytocin and vasopressin is controlled through the tuberoinfundibular pathway. Given the complex nature of the hypothalamic–pituitary axis, it is not surprising that clinical manifestations of pituitary disease are protean. Pituitary dysfunction may result from pituitary tumors or destructive disease processes.

### Pituitary Tumors

Pituitary tumors are found in up to 20 percent of adults at autopsy and are frequent incidental findings at neuroimaging. They may result in increase or decrease of hormone levels and produce symptoms by invading surrounding structures such as the hypothalamus.

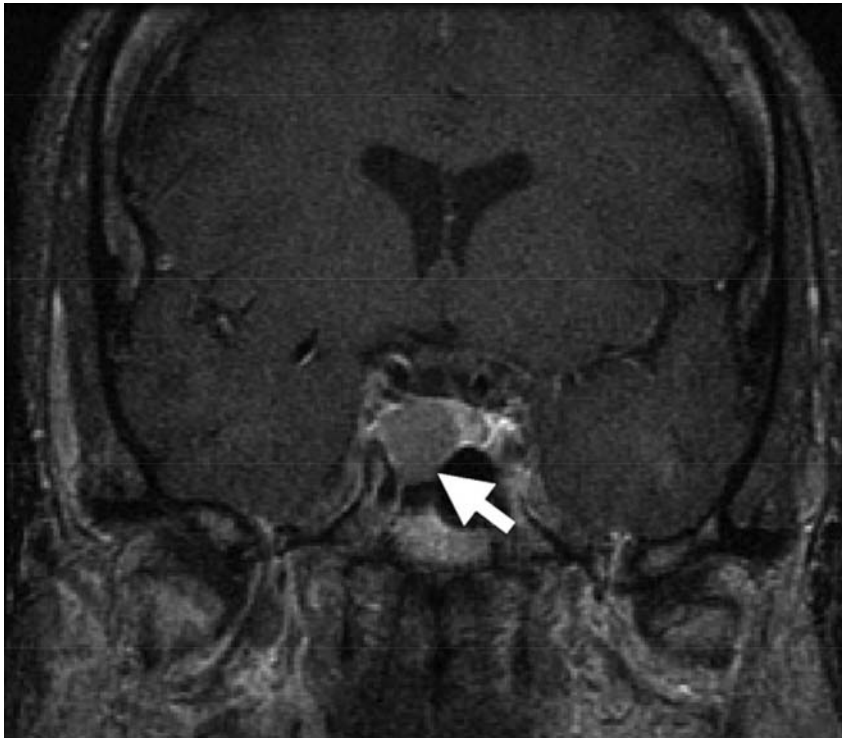
**Prolactinomas.** The most common secretory tumors are prolactinomas. Dysregulated secretion of PRL results in amenorrhea, infertility, and galactorrhea in women and impotence and occasionally galactorrhea or gynecomastia in men. Data regarding the neuropsychiatric manifestations of hyperprolactinemia is lacking. There is some evidence of increased aggression in lactating animals associated with elevated PRL levels, and in hyperprolactinemic human subjects. Depression and anxiety symptoms also occur with greater frequency in this group of patients, which may respond to treatment with the dopamine agonist bromocriptine. Psychotic symptoms have been described in neuroleptic naive patients with hyperprolactinemia at a case report level. Treatment with antipsychotic agents may then result in further elevation of PRL. Psychotic symptoms have also been described in patients receiving bromocriptine for the treatment

of a prolactinoma, with both delusions and hallucinations recorded. The incidental finding of a pituitary adenoma on neuroimaging can complicate the assessment of patients with a psychotic illness stabilized on an antipsychotic agent with hyperprolactinemia. Impulse control disorders such as pathological gambling have also been reported in patients receiving cabergoline (a potent Dopamine type 2 receptor agonist) therapy for pituitary adenomas.

**Growth-Hormone Secreting Tumors.** These are the second most common functional pituitary adenomas (Fig. 2.14–20). In adults they result in *acromegaly* with soft tissue and bone enlargement, particularly involving the hands, feet, jaw, and tongue with a characteristic overall coarsening of facial features. There may be associated hypertension, congestive cardiac failure and obstructive sleep apnea, and hypersomnolence. A number of psychiatric symptoms have been associated with acromegaly, largely at the case report level. Acromegalic patients appear to have a lifetime increased risk of affective disorders when compared with control subjects with and without chronic somatic disease. There is no evidence of a preponderance of psychotic symptoms although these are well described when acromegalic patients are treated with bromocriptine resulting in delusional symptoms, schizophrenia-like presentations, and visual hallucinations.

**Adrenocorticotrophin Secreting Tumors.** ACTH secreting tumors are the next most common pituitary tumor type, resulting in excessive cortisol production or Cushing disease. The neuropsychiatric manifestations of increased cortisol release are discussed below in the description of adrenal disease.

**Other Pituitary Tumors.** Clinical symptoms resulting from tumors producing LH or FSH are very rare. Increased TSH production



**FIGURE 2.14–20.** Pituitary adenoma causing acromegaly. Gadolinium-enhanced magnetic resonance imaging of the brain showing a well-defined mass in the right lateral aspect of the sella with lack of enhancement compared with the normal pituitary gland. Endocrinologic evaluation revealed elevated human growth hormone and insulin-like growth factor levels consistent with acromegaly. (From Koo CW, Bhargava P, Rajagopalan V, Ghesani M, Sims-Childs H, Kagetsu NJ. Incidental detection of clinically occult pituitary adenoma on whole-body FDG PET imaging. *Clin Nucl Med.* 2006;31[1]:42, with permission.)

can occasionally result in hyperthyroidism, the psychiatric aspects of which are discussed below. As many as 30 percent of pituitary tumors are nonsecretory, and are often larger at diagnosis because of the lack of endocrine manifestations. If large enough pituitary tumors may impinge on surrounding structures resulting in the classic visual field defect of bitemporal hemianopia, oculomotor palsies headache, and occasionally hypothalamic syndromes (see above). Visual hallucinations in the context of visual field defects related to pituitary tumors impinging the optic chiasm have been reported. More often these are of the simple, nonformed type and can be exacerbated by treatment with bromocriptine.

### Hypopituitarism

Deficiency or dysfunction of one or more of the pituitary hormones is referred to as hypopituitarism. In adulthood, this is usually caused by an acquired destructive process that may be traumatic (related to head injury), inflammatory, immune mediated, vascular, or as the result of compression from an adjacent tumor. Clinical manifestations are dependent on the hormones involved. GH is often first affected followed by the gonadotropins with associated amenorrhea and infertility in women and reduced libido and body hair loss in men. Low TSH can result in hypothyroidism, ACTH deficiency in fatigue, reduced appetite, weight loss, and impaired stress response. Vasopressin deficiency may also ensue, resulting in polyuria and thirst. A number of neuropsychiatric manifestations have been described in hypopituitarism in the absence of a delirium. Memory impairment, sleep disturbance, and personality change are commonly but variably reported. Visual and auditory hallucinations have been described at a case report level, and several observers have reported an absence of affect on mental state examination. A systematic study of psychiatric comorbidity in hypopituitarism found more psychiatric symptoms than those expected in chronic disease such as diabetes mellitus, most particularly depression and anxiety. Psychosis is uncommon.

More specific symptoms are attributable to particular hormone deficiencies. GH deficiency may result in reduced energy, depressed mood, anxiety, emotional lability, and impulsivity or impaired self-control. Testosterone deficiency has been associated with depression irritability and insomnia. Fatigue, social withdrawal, and negativism have been reported when ACTH is low. Lastly, as in hypothyroid states fatigue, depression, insomnia or hypersomnia, and psychotic symptoms have been described when TSH levels are low. There can be considerable variation in the type of psychotic symptoms described. In general, appropriate correction of the hormone deficiency and addressing the underlying cause results in resolution of these features.

### Thyroid and Parathyroid Disorders

Normal thyroid function involves the production of the two thyroid hormones, L-thyroxine ( $T_4$ ) and 3,5,3'-triiodo-L-thyronine ( $T_3$ ), which are required for the regulation of a number of metabolic processes. Increased thyroid hormone production results in hypermetabolism or increased caloric utilization and the other clinical features of hyperthyroidism. Hypometabolism and the features of hypothyroidism (sometimes referred to as myxedema) results from reduced hormone production. Psychiatric symptoms that accompany either of these states have been subject to more systematic study than those associated with pituitary disorders, as primary thyroid disorders have a much higher incidence in the population.

**Hyperthyroidism.** Hyperthyroidism is the result of excessive production of thyroid hormones. This may result from a toxic multinodular goiter, a single functioning adenoma, or from the presence of a thyroid stimulator, such as a thyroid stimulating antibody in Grave disease. Exogenous thyroid hormone can produce a similar picture as can disorders of thyroid hormone storage consequent to autoimmune thyroiditis.

Depressive symptoms are not only the most common psychiatric features seen in hyperthyroidism, occurring in up to 30 percent of

patients, but frequently occur prior to the onset of the other physical features. This includes lowering of mood as well as neurovegetative disturbance such as insomnia, reduced libido, weight loss, and fatigue. However, as distinct from depression, appetite is invariably increased in hyperthyroidism. The severity of the depressive symptoms have not been found to be related to the severity of hyperthyroidism as measured by subsequent thyrotoxic features and the extent of the biochemical abnormalities.

Elderly patients with thyrotoxicosis may present with predominantly apathy, depression, and weight loss rather than increased psychomotor activity. Typically this presentation is of slower onset, the neurological and ophthalmological features are less prominent, but cardiovascular events such as exacerbation of angina cardiac failure and atrial fibrillation are more prevalent. Anxiety symptoms presenting as generalized anxiety are also common, with a prevalence of between 10 and 20 percent, but panic and agoraphobia are relatively uncommon. Like depressive symptoms, anxiety may occur prior to the other features of hyperthyroidism, but more often correlates with the severity of the thyrotoxic features. Anxiety and depressive features are often comorbid. Manic symptoms are less common in hyperthyroid states with a prevalence between 2 and 5 percent, but may be difficult to distinguish from psychomotor agitation and anxiety. Psychotic symptoms including paranoid delusions and auditory hallucinations, while historically reported as common, have a true prevalence of between 2 and 5 percent. The depressive syndrome seen in hyperthyroidism rarely requires treatment other than that which is used to restore the euthyroid state; however, some features, such as anxiety, fatigue, and loss of function may persist for as long as 12 months after a euthyroid state has been achieved.

Cognitive dysfunction is reported between 5 and 10 percent of patients with thyrotoxicosis, but to a lesser degree than that seen in hypothyroidism. Patients may present with slow processing speeds, impairments in immediate memory, defective higher-level problem solving, or frank delirium. Mild disorders of attention and concentration are common, but their severity do not always correlate with the severity of thyrotoxicosis. These deficits invariably respond to reversal of the thyrotoxic state.

**Hypothyroidism.** The most common cause of hypothyroidism in adults is primary autoimmune hypothyroidism related to antithyroid antibodies. Other causes include treatment for hyperthyroidism, drug-related effects, and iodine deficiency. Supra-thyroid causes (hypothalamic or pituitary dysfunction) account for less than 5 percent of cases. The symptoms of hypothyroidism may include fatigue, lethargy, weight gain, constipation, cold intolerance, stiffness and cramping of muscles, hair loss, cognitive slowing, and depression. Signs include, hypothermia, bradycardia, dry skin, sparse hair, periorbital swelling, thickening of the tongue, coarsening and deepening of the voice, and a characteristic prolonged relaxation phase of deep tendon reflexes. This clinical picture is often referred to as *myxedema*. Hypothyroid patients may present with a variety of psychiatric symptoms ranging from mild cognitive slowing and depression to frank encephalopathy which often predates other physical features. Functional neuroimaging studies have demonstrated global hypometabolism and more specific areas of hypoperfusion in the posterior cingulate, insula, fusiform gyrus, and right parieto-occipital and primary motor cortex.

Cognitive deficits are the most common neuropsychiatric features of hypothyroidism, occurring in up to 50 percent of cases. Psychomotor speed, memory, and visual-perceptual skills are

often impaired. Difficulties with constructional skills, reduced performance in trail-making and maze tasks also suggest prominent executive deficits. The severity of these disorders is correlated with the degree of biochemical abnormality, and although largely corrected by return to a euthyroid state, some cognitive deficits may remain, particularly in the elderly or those with reduced cognitive reserve. Severe disturbance of consciousness, including coma and delirium may be encountered, but may be associated with other metabolic changes related to the hypothyroid state such as hyponatremia. Depression is only slightly less common than cognitive disturbance, reported in approximately 40 percent of patients, but appears less closely related to the severity of biochemical hypothyroidism. Low mood, fatigue, anhedonia, reduced concentration, and hypersomnolence are the most commonly described features of the depressive syndrome in hypothyroidism. These features predictably respond to treatment of the hypothyroid state. The origin of depression in hypothyroidism appears to relate to the role of thyroxine in serotonergic transmission, such that reduced thyroid input reduces serotonergic tone and lowers the threshold toward the development of depressive symptoms. Conversely, thyroid replacement restores central serotonin activity in concert with improvement in depressive symptoms. This may also underpin the adjunctive antidepressant effect of thyroxine.

In contrast, manic and hypomanic symptoms have been infrequently reported in association with hypothyroidism. However, hypothyroidism may be a risk factor for the development of bipolar disorder, particularly the rapid cycling form and treatment of otherwise refractory mood disorders with thyroid hormones has occasionally been shown to be effective. Generalized anxiety symptoms are described in up to 30 percent of patients and are strongly correlated with depressive symptoms but not with biochemical severity. Psychotic symptoms including paranoid ideas, misidentification, visual and auditory hallucinations, and thought disorder, were originally thought to be common (and described as “myxedematous madness”), but likely occur in less than 5 percent of all patients with hypothyroidism and tends to emerge after the onset of physical symptoms. Although these symptoms also respond to appropriate thyroid hormone treatment, rapid titration of hormone doses may exacerbate psychosis. Careful addition of a low dose of antipsychotic to thyroxine has been reported to be well tolerated and result in an earlier remission of psychosis.

**“Subclinical” Hypothyroidism.** Thyroid hormone abnormalities may occur without overt functional hypothyroidism. Designated *subclinical hypothyroidism*, these scenarios can be further classified into elevated TSH without changes in thyroid hormones (Grade II hypothyroidism), abnormal TSH response to stimulation with TRH (Grade III), and the presence of antithyroid antibodies with no thyroid hormone system abnormalities (Grade IV). Grade II hypothyroidism has been associated with depressive disorders. Patients with major depressive disorders have an increased incidence of Grade II hypothyroidism, and some studies show these patients respond poorly to conventional treatment. Grade II hypothyroidism may be a risk factor for major depressive disorders. Cognitive disturbance, particularly memory and psychotic symptoms have also been reported in Grade II hypothyroidism. Although there is some evidence of improvement in cognition, mood, and psychosis, treatment of subclinical hypothyroidism is controversial.

**Hashimoto Encephalopathy.** Hashimoto encephalopathy (HE), also described as steroid-responsive encephalopathy associated



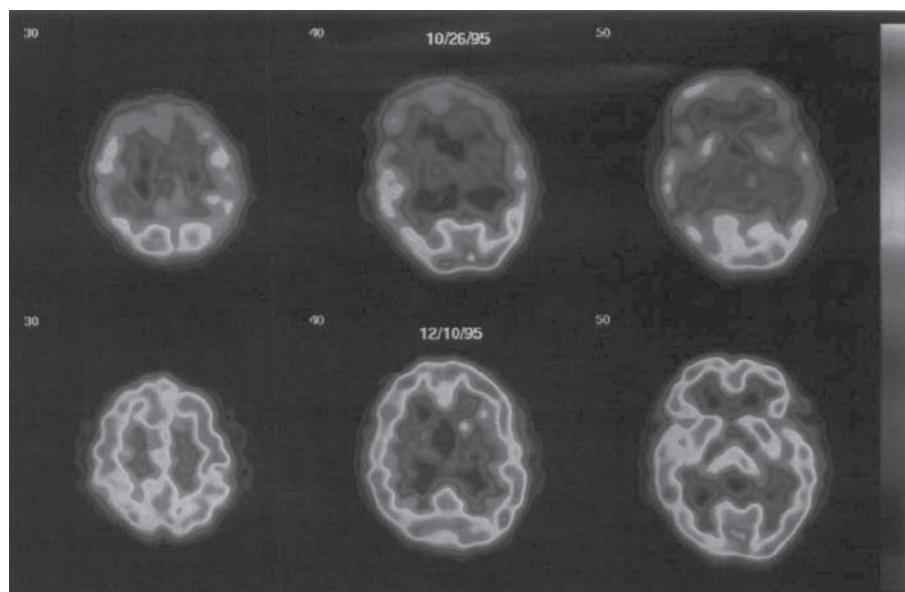
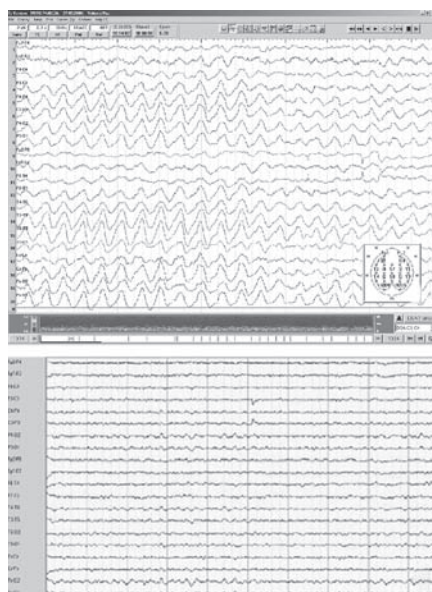
with autoimmune thyroiditis (SREAT) is best defined as an uncommon autoimmune encephalopathy of unknown etiology associated with high titers of serum antithyroid (usually antithyroid peroxidase  $\pm$  antithyroglobulin) antibodies. The role of antithyroid antibodies is controversial. There is no direct evidence that these auto-antibodies exert direct effects on CNS tissue, and they may be epiphenomena of another autoimmune process. In addition, the base rate of elevations of these auto-antibodies in the population is as high as 10 percent. Elevated serum antithyroid antibodies are associated with other thyroid disorders (Grave disease, de Quervain thyroiditis, primary hypothyroidism, and colloidal goiter) and other auto-immune disorders (including diabetes mellitus, Addison disease, and pernicious anemia).

HE is more common in women with a mean age of onset between 45 and 50 years. There may be a history of other autoimmune disease. The clinical picture is one of encephalopathy with progressive cognitive decline although the course may also be relapsing and remitting. Common features include seizures (>95 percent of cases), stroke-like episodes (>65 percent of cases), and memory dysfunction. Neuropsychiatric features include agitation and restlessness, apathy, social isolation. Visual hallucinations are frequently reported (>90 percent), as are other disorders of perception and delusions. Patients with a more typical presentation of psychiatric illness, such as depression, in the setting of mildly elevated antithyroid peroxidase antibodies are unlikely to have HE. However, when antithyroid peroxidase levels are very high (>1,000 IU/L), the likelihood of them being associated with neuropsychiatric HE is much greater.

Routine investigations are often normal, although patients will often show slowing on EEG, with the degree of slowing being proportional to clinical severity of the syndrome, and some patients may show triphasic waves (Fig. 2.14–21). The majority of patients

respond to corticosteroid treatment of with complete resolution of the neuropsychiatric symptoms.

A 66 year old woman presented with a four month history of cognitive decline including short-term memory and language deficits. She had a generalised tremor and developed a delusional belief that her husband wished to harm her. She became agitated and disoriented, particularly at night, and also described visual hallucinations of small animals in her room. No neurological features, including myoclonus, were described. At this time all routine blood investigations (including complete blood count, serum urea, electrolytes, creatinine, liver enzymes, thyroid hormone assays, folate and B<sub>12</sub> level and CT brain) were normal. One month later she suffered a generalized tonic-clonic seizure. Routine blood investigations and examination of the CSF were normal. Angiography of the anterior and posterior cerebral circulation was normal. MRI scan was normal and EEG was unremarkable. On mental state examination she was disoriented with impaired attention and markedly poor short-term memory (particularly nonverbal memory). Her speech was characterized by impaired verbal fluency and word finding problems. There was a concrete thinking style with reduced abstract reasoning as well as poor judgment. There were no depressive or psychotic features at this time. Her then mental state rapidly deteriorated. She became virtually mute, with poor concentration and attention and required assistance with all aspects of personal care. She had bilateral grasp and pout reflexes as well as diffuse hyperreflexia. She also had bilateral and multifocal myoclonus. In the face of previously normal investigations, the diagnosis of Hashimoto's encephalopathy was considered. Thyroid hormone (TSH, T4, T3) levels were within normal limits. Anti thyroid peroxidase antibodies (anti-TPO) were raised in titre (640 IU/ml, normal <50I U/ml) consistent with this diagnosis. A course of prednisolone 60 mg was commenced with marked improvement in her mental state within 2 weeks.



**FIGURE 2.14–21.** Reversibility in Hashimoto encephalopathy. **Left:** Electroencephalogram (EEG) before and after treatment in a 38-year-old woman with psychosis and an antithyroid peroxidase antibody titer of 779. **Top:** Pretreatment with corticosteroids showing general slowing with high voltage (2 to 3 Hz)  $\delta$  biphasic and triphasic waves. **Bottom:** EEG after corticosteroid treatment showing  $\alpha$  frequency, with occasional  $\theta$  waves (5 to 6 Hz), mainly in posterior regions. (From Sporis D, Habek M, Mubrin Z, Poljakovic Z, Hajnssek S, Bence-Zigman Z. Psychosis and EEG abnormalities as manifestations of Hashimoto encephalopathy. *Cog Behav Neurol*. 2007;20[2]:138, with permission.) **Right:** Single photon emission computed tomography (SPECT) showing gross global hypoperfusion in all nonoccipital regions in a 59-year-old woman with rapidly progressive cognitive impairment and myoclonus, with Mini-Mental State Examination (MMSE) score of 20 (**top**) and after significant clinical improvement 6 weeks later, when MMSE score was 27 (**bottom**). (See color plate.) (From Forchetti CM, Katsamakis G, Garron DC. Autoimmune thyroiditis and a rapidly progressive dementia: Global hypoperfusion on SPECT scanning suggests a possible mechanism. *Neurology*. 1997;49:623, with permission.)

## Parathyroid Disorders

The parathyroid glands are small accessory glands that are anatomically associated with but functionally distinct from the thyroid gland. Their sole function is to maintain serum calcium levels within a narrow range to permit optimum functioning of the nervous and muscular systems, through the release of parathyroid hormone (PTH). The release of PTH increases serum calcium via stimulating osteoclasts in bone to release calcium, and through increasing its absorption in the gut and kidneys.

**Hyperparathyroidism.** Hyperparathyroidism is usually diagnosed after an incidental finding of hypercalcemia on routine blood tests, and 50 percent of patient with hyperparathyroidism are asymptomatic. Increased PTH release is usually caused by a single functioning adenoma, although multiple adenomas may occur as part of multiple endocrine neoplasia syndrome (MENS). Symptoms are principally those secondary to hypercalcemia. These include fatigue, general malaise, proximal muscle weakness, renal colic, abdominal pain, and cognitive decline. There is often little to find on examination although renal calculi, nephrocalcinosis, or bone changes (osteitis fibrosa cystica, now rare) may be seen on radiological investigations ordered for other reasons. Although a number of psychiatric symptoms have been described in hyperparathyroidism (as part of the symptomatic tetrad of “bones, stones, moans, and psychic groans”), the prevalence overall is likely to be less than 10 percent. These symptoms correlate with both duration and severity of the associated hypercalcemia. Affective disorders predominately of the depressive type are the most frequently recorded, with anxiety often comorbid. Psychotic disorders are reported, although infrequent, with persecutory and paranoid delusions predominating. Cognitive changes, usually related to short-term memory loss, disorders of attention and acute confusional states often occur, and severe derangement of calcium metabolism may present with somnolence and coma. Neuropsychiatric symptoms are often the initial presentation in the elderly, or those with limited cognitive reserve. The more severe the hypercalcemia, the more severe the psychiatric disturbance, but symptoms generally respond to appropriate treatment such as parathyroidectomy. When PTH levels are mildly raised in the setting of normocalcemia (most commonly due to vitamin D insufficiency, increasingly prevalent in developed countries), psychiatric disturbance is uncommon.

**Hypoparathyroidism.** The most common cause of impaired PTH production in adults is inadvertent surgical removal during thyroid surgery or excessive removal for hyperparathyroidism. Clinical features relate to hypocalcemia, particularly symptoms of neuromuscular excitability including paresthesias, muscle cramps, carpal spasm, facial grimacing progressing to laryngeal spasm, and convulsions. Examination may reveal features of tetany, reduced or absent deep tendon reflexes, papilledema, and QT interval prolongation on ECG. Delirium is now understood to be the most common neuropsychiatric manifestation. One large study available demonstrated cognitive impairment in 39 percent of patients, affective or neurotic symptoms in 12 percent, psychotic symptoms in 11 percent, and non-specific affective disturbance in 21 percent of patients. Again, severity of symptoms directly relate to the degree of hypocalcaemia and appropriate normalization results in resolution of these symptoms, although persistent psychosis has been noted when associated hypomagnesemia was not addressed.

## Adrenal Disorders

The adrenal glands produce both adrenal steroids from the cortex and catecholamines from the medulla. The adrenal cortex produces

glucocorticoids, principally cortisol under the stimulatory effects of ACTH from the anterior pituitary controlled by a negative feedback loop. Aldosterone, a mineralocorticoid, originates from the adrenal cortex but is controlled by the renin–angiotensin system influenced by body volume and potassium balance. Adrenal androgens, predominately dehydroepiandrosterone (DHEA) are also regulated by the ACTH system and undergo peripheral conversion to sex-determining androgens. Hyperfunction or hypofunction of these adrenal systems result in distinct clinical syndromes with complex physical and neuropsychiatric manifestations.

**Hyperadrenalism.** Hyperadrenalism (Cushing syndrome) occurs when the adrenal gland produces excess corticosteroids, usually as a result of ACTH overproduction from the anterior pituitary secondary to a pituitary adenoma (Cushing disease). Other causes include ACTH production from a nonendocrine tumor, an adrenal neoplasm or most commonly, exogenous steroids, usually prescribed for treatment of a steroid-sensitive medical condition. Patients with Cushing syndrome present with the classic features of hypertension, muscle weakness and fatigue, osteoporosis, cutaneous striae, and easy bruising. A characteristic pattern of obesity is seen involving the upper face (resulting in a “moon face”), back (“buffalo hump”), and mesentery resulting in truncal obesity. Women may experience hirsutism, acne and amenorrhea, men, decreased libido and impotence. Neuropsychiatric features are well-described, with depression the most frequently noted psychiatric symptom in up to 70 percent of patients. Anxiety is commonly comorbid with depression, in up to 50 percent of sufferers. Depressive symptoms may present prior to physical symptoms. They respond to treatment of the underlying cause and the response correlates with lowering of plasma cortisol levels. Elevated mood is infrequently reported in Cushing syndrome, reported in less than 10 percent in most case series. Delirium is also relatively uncommon and is usually a marker of a supervening infection or other metabolic disorder such as metabolic alkalosis. Although dramatic case reports of Cushing syndrome presenting with psychosis and obfuscating the underlying condition are reported, this form of presentation is rare. When present, psychotic symptoms are almost always mood congruent delusional beliefs and derogatory auditory hallucinations associated with a depressed mood. Cognitive impairment occurs in over 50 percent of patients, presenting as deficits in verbal memory, attention, and visuomotor and visuospatial function. The degree of memory impairment, and its reversibility, appears to correlate with hippocampal volume, suggesting that cognitive impairment is partially driven by the effect of excess glucocorticoids on hippocampal neurons.

With exogenous administration of steroids, manic symptoms are most frequently reported, followed by delirium, depression, and psychotic symptoms. Mixed affective states also appear over-represented. The severity of these symptoms may be dose related, reproducible in the individual, and minimized with use of divided doses of steroids. Manic symptoms may respond to both cessation of the exogenous steroid administration and pharmacotherapy with mood stabilizing agents such as lithium and valproate, or treatment with antipsychotics.

**Hypoadrenalism.** Primary hypofunction of the adrenocortical system may result from a primary process at the level of the gland such as destruction by autoimmune process, referred to as Addison disease (most common), other inflammatory or destructive processes, or an inborn failure of enzyme function. It may also arise secondary to dysfunction of the hypothalamic–pituitary axis or withdrawal of exogenous steroids. The onset of symptoms is usually insidious with progressive fatigue, weakness, anorexia, nausea,



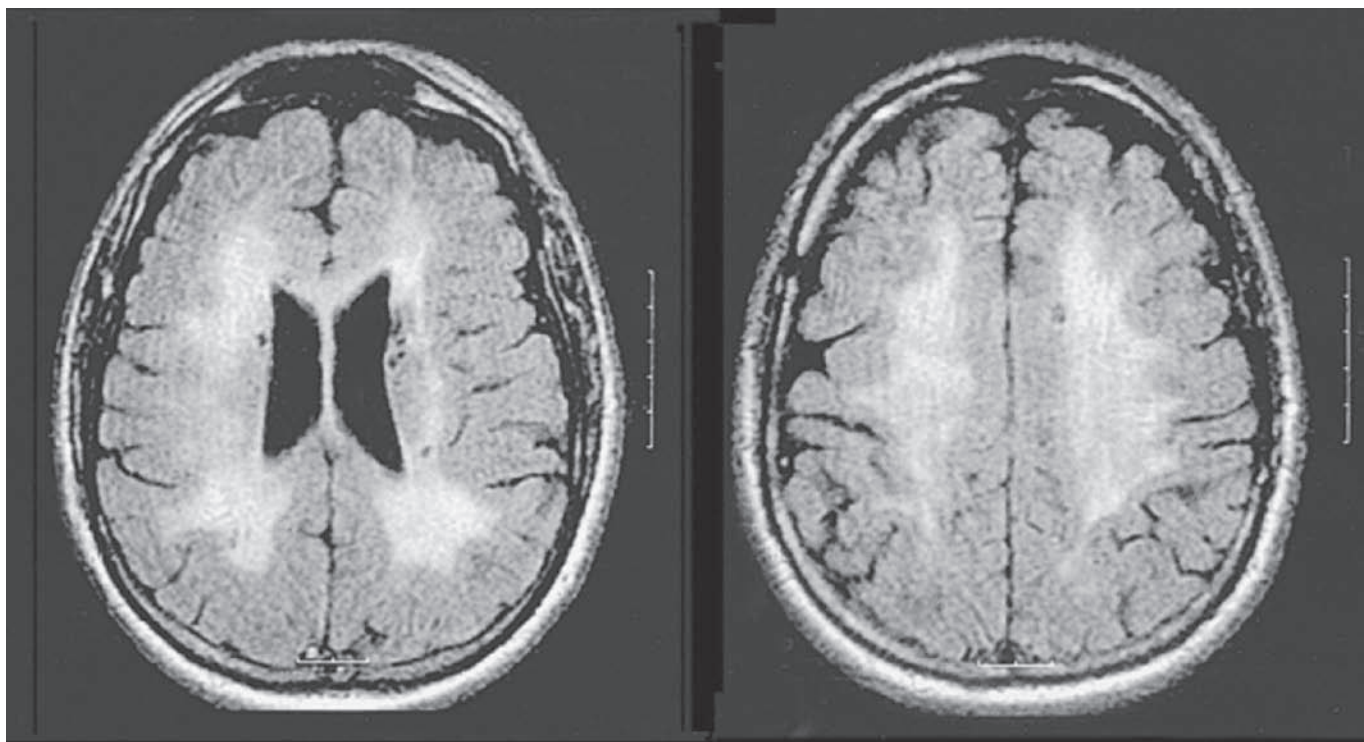
abdominal pain, weight loss, cutaneous and mucosal pigmentation, hypotension, and hypoglycemia. Other findings include hyponatremia, hyperkalemia, and metabolic acidosis. Reports of neuropsychiatric symptoms in Addison disease are uncommon, although the true prevalence is uncertain due to probable under-reporting. Depression, reduced motivation, and energy and behavioral changes predominate. Memory dysfunction is the most common form of cognitive disturbance. Paranoid symptoms and delusions are less common. Catatonia and self-mutilation are rare but dramatic presentations. Auditory and visual hallucinations, changes in conscious state, irritability, insomnia, and nightmares often herald an Addisonian crisis with frank delirium, coma, and seizures. Hyponatremia and metabolic acidosis may contribute to the delirium and cognitive deficits. These symptoms appear to largely resolve, including those of adrenal crisis, when treatment with adequate doses of corticosteroids is commenced. Use of other psychotropic agents is rarely indicated.

**Hyperaldosteronism.** Excess of the major adrenal mineralocorticoid aldosterone can arise from the adrenal gland (primary aldosteronism) or from an extra-adrenal site (secondary aldosteronism). Primary aldosteronism is usually due to an aldosterone producing adenoma (Conn syndrome) or bilateral cortical hyperplasia. Secondary aldosteronism relates to disturbance of the renin-angiotensin system and hypovolemia. The characteristic features of Conn syndrome are hypokalemia, hypertension, muscle weakness, fatigue, polyuria, and polydipsia. Metabolic alkalosis and hypomagnesemia may also occur and edema is characteristically absent. Depression has been identified as one of the major features but more recent studies have demonstrated features of generalized anxiety with individual cases of associated depression, features of OCD and panic without specific gender differences. Untreated primary hyperaldosteronism, and resulting severe hypertension, can result in

a vascular dementia if left untreated. Although treatments, such as surgical excision of a functioning adenoma are effective in reversing the physical symptoms of hyperaldosteronism, the effect on anxiety and other symptoms are unknown.

A 48-year-old man with no past psychiatric history had raised family concerns following 3 years of unusual behavior, social withdrawal, and poor self-care. He lost contact with friends, began to gamble heavily, had a number of car accidents, and was disinhibited and socially inappropriate. He had recently started a fire in his residence with one of many discarded cigarettes. On examination, he was hypertensive (240/120 mm Hg) and had signs of left ventricular hypertrophy, but no neurological abnormalities. On cognitive assessment, he had a marked dysexecutive syndrome. Serologically he had a mild metabolic alkalosis and hypokalemia (3.2 mmol/L). Serum cortisol, ACTH, and vasculitic screen were normal. ECG showed first-degree heart block and left ventricular hypertrophy, which was confirmed on echocardiography. There was failure of aldosterone suppression with saline challenge and bilateral adrenal hyperplasia on abdominal CT. Brain MRI showed extensive severe periventricular and subcortical white matter disease (Fig. 2.14–22). He was diagnosed with Binswanger's dementia secondary to hypertension associated with hyperaldosteronism.

**Pheochromocytoma.** Pheochromocytomas are tumors which secrete catecholamines and most commonly originate in the chromaffin cells of the adrenal medulla, but may rarely arise from similar cells in sympathetic ganglia. Familial forms are associated with MENS types 2a and 2b and von-Recklinghausen neurofibromatosis. Secretion of catecholamines may be continuous or sporadic, sometimes resulting in characteristic paroxysmal symptoms



**FIGURE 2.14–22.** Subcortical dementia due to hyperaldosteronism in a 48-year-old man with untreated hyperaldosteronism. Axial fluid-attenuated inversion recovery images show bilateral extensive periventricular and subcortical white matter hyperintensity with multiple lacunar infarcts in the basal ganglia, consistent with long-standing untreated hypertension.



of headache, profuse sweating, palpitations, Raynaud phenomenon, tremor, nausea vomiting, and abdominal and chest pain. The triad of palpitations, headache, and profuse sweating are the most sensitive and specific for pheochromocytoma. Clinical findings include hypertension, pallor, postural hypotension, and signs of chronic hypertension such as retinopathy. Paroxysmal symptoms occur in 40 percent of pheochromocytomas and may present as a phenocopy of anxiety symptoms, particularly a panic episode, and are often diagnosed as such. These may occur spontaneously or may be precipitated by exercise, postural change, raised intra-abdominal pressure, or emotional excitement or shock. The severity of the episodes may also vary and anxiety may persist for some time after the attack. Psychosis and cognitive deficits have not been described, although there are several case reports of a secretory pheochromocytoma causing relapse of a previously treated or quiescent psychotic disorder. Diagnosis is by detecting increased urinary secretion of catecholamines or catecholamine metabolites. Location of the underlying tumor and surgical excision with  $\alpha$ -adrenergic blockade is effective in resolving most anxiety symptoms if paroxysmal episodes are terminated.

### Neuroendocrine Tumors

While the term “neuroendocrine” is commonly used to refer to the interaction of the endocrine and nervous systems, histologically it refers to a particular type of cell. Neuroendocrine cells are cells that release a hormone or regulatory peptide into the circulation in response to a neural stimulus. The most extensive neuroendocrine system is in the gastrointestinal tract and associated organs, and when these tissues release excess hormones, a range of neuropsychiatric syndromes can occur.

**Carcinoid Syndrome.** A carcinoid is a neoplasm of neuroendocrine cells that synthesize and secrete serotonin in the respiratory system and gastro-intestinal tract. The main symptoms are flushing (often severe facial flushing with bronchial tumors), diarrhea, wheezing, and hypotension. Although peripherally secreted serotonin does not cross the blood–brain barrier, a number of psychiatric symptoms have been described. These include depression (in up to half of patients), anxiety, sleep disorders and, rarely, psychosis. A series of 23 patients found that over half experienced personality change consisting of increased irritability and impulsive aggressive thoughts or behavior, some meeting criteria for impulse control disorder. These changes often preceded the other physical symptoms. Depression was far less common and psychotic symptoms were not detected.

**Insulinoma.** Insulinomas are functioning  $\beta$ -islet cell tumors of the pancreas which result in unregulated insulin secretion at times with abrupt fluctuations. Clinical features include fasting hypoglycemia (relieved by glucose ingestion) and weight gain. Hypoglycemia is characterized by hunger, restlessness, palpitations, flushing, and ataxia but may also include malaise, anxiety, depersonalization, and derealization. A more subacute syndrome characterized by clumsiness, disinhibited or aggressive behavior (and associated amnesia for these episodes) may mimic alcohol intoxication. Global and irreversible cognitive deficits may result if hypoglycemia is long standing. Surgical therapy is the most definitive treatment, but hyperglycemic treatment with the somatostatin analogue octreotide can be helpful.

**Glucagonoma.** This is a rare pancreatic islet cell which secretes glucagon. The presenting features are of impaired glucose tolerance and diabetes and a severe migratory and necrolytic erythema. Anxiety and agitation may accompany these features.

### FUTURE DIRECTIONS

An awareness of the relationship between neurometabolic and neuroendocrine disease and psychiatric illness by psychiatrists and other physicians provides for more diagnostic precision, in addition to allowing for improved treatment of psychiatric comorbidity in these disorders. Psychiatric symptoms can have a profound effect on long-term quality of life, and the recognition of a comorbid mental illness in these disorders can improve health outcomes and quality of life for both patient and caregiver alike. As psychiatrists are best placed to manage major psychiatric disturbance, the involvement of a psychiatrist in the care of these patients is crucial, whether psychiatric illness is the first or only presentation of illness, or if it develops later in the course of the illness.

Recognizing, understanding, and exploring the links between neurometabolic and neuroendocrine disorders and major psychiatric syndromes can also provide insights into the neurobiological basis of mental illness. For example, the recognition of the elevated rates of schizophrenia-like psychosis in MLD has highlighted the possible role of myelinated structures as a possible anatomical substrate for the functional disconnectivity that has been well described in schizophrenia. Following a group of publications by Hyde and Weinberger on the links between schizophrenia and leukodystrophies, a large body of research in the subsequent 20 years has produced real insights into the role of white matter structures in schizophrenia at the genetic, developmental, and structural levels. In addition, the emerging data on the exceedingly rare movement disorder ChAc suggesting significantly elevated rates of OCD and its unique predilection for neuropathology in the caudate and putamen, has further highlighted the role of disturbed prefrontal–subcortical circuitry in OCD “proper.” Further delineation of the neurobiological link between the cellular and metabolic deficit in these syndromes and the psychiatric disturbance they are commonly associated with may yet yield further insights into the neurobiological basis of those disorders that present most commonly in psychiatric practice but that have only yet afforded limited insights into their underlying pathophysiology.

### SUGGESTED CROSS-REFERENCES

[AQ2]

The reader is referred to Section 11.13 on Anabolic-Androgenic steroid abuse; Section 24.7 on endocrine and metabolic disorders; Section 31.30 on Thyroid hormones; and Section 31.37 on Applied reproductive hormonal treatment (sex steroids).

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## H1A 2.14 Neuropsychiatry of Neurometabolic and Neuroendocrine Disorders

AQ1: Please check whether the inserted Fig. 2.14-18 cross-citation is correct here.

AQ2: Please confirm whether the Section numbers mentioned in “SUGGESTED CROSS-REFERENCES” are as intended.