CHAPTER 1

Introduction

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This book was developed in order to provide a clinically relevant review of non-Alzheimer's and atypical dementia syndromes. Specifically, we felt there was a need for a broad but comprehensive overview of the differential diagnoses for atypical dementia that could be utilized by health-care providers who encounter these patients in their clinical practice, including neurologists, primary care providers, psychiatrists, neuropsychologists, nurses, social workers, etc. Where relevant, we have included clinical case studies in each chapter to help illustrate key or unique diagnostic features of each disorder and to provide a "real-world" view of how each disorder might present in the clinic.

Multidisciplinary evaluation of the atypical dementia patient

In this chapter, the editors review a framework for the clinical evaluation of the patient with a suspected atypical dementia syndrome. In particular, we focus on the benefits of a multidisciplinary evaluation with a team that includes a combination of a neurologist, neuropsychologist, psychiatrist, nurse, and social worker. Each team member brings a unique set of skills to the evaluation, which enables an in-depth and comprehensive assessment of a variety of domains, including relevant history, neurological function, cognitive abilities, mood and behavior, and daily function. Obtaining information from both the patient and a close family member or friend is essential as many atypical syndromes lead to loss of insight, and thus, more accurate reporting might come from someone other than the patient themselves. We have found that a case conference approach, where all team members meet after seeing the patient to review all relevant findings and discuss the case in detail, leads to a more accurate differential diagnosis, which can then be relayed to the patient and their family members in a timely fashion.

Atypical Alzheimer's disease

In this chapter, Sharon Sha and Gil Rabinovici review the atypical presentations of Alzheimer's disease (AD), which by definition present with symptoms other than memory loss and therefore might not meet most standard diagnostic criteria for AD. These patients tend to be younger than "typical" AD cases and might present with visuospatial complaints, executive dysfunction, behavioral changes, or language impairment. Additionally, often, patients meet diagnostic criteria for posterior cortical atrophy (PCA, a visual dysfunction syndrome), corticobasal syndrome (CBS, executive dysfunction or behavioral syndrome), and/or primary progressive aphasia (PPA, language syndrome) disorders that have not historically associated with AD pathology; however, recent research has demonstrated that a significant portion of these clinical syndromes are ultimately found to have AD pathology at autopsy. Neuropsychological testing and atrophy patterns on MRI often are very helpful in the differential diagnosis of the clinical syndrome. PET imaging with amyloid binding agents such as Pittsburgh compound B (PiB) or flurbetapir F18 might provide additional, if not even more convincing, evidence of underlying AD pathology. The recognition of AD pathology as a causative factor in these atypical syndromes is important because of available symptomatic treatments and ongoing clinical trials for AD. Future diagnostic criteria for AD will need to incorporate the possibility of atypical presentations in order to increase sensitivity.

Vascular cognitive impairment: Diagnosis and treatment

In this comprehensive chapter, Helena Chui and Liliana Ramirez Gomez first review the complex history and terminology of vascular contributions to cognitive impairment. They postulate that the physiological effects of vascular brain impairment (VBI) lead to variable vascular cognitive impairment (VCI), depending on the location, extent, and severity of injury. White matter imaging methods including structural (i.e., white matter hyperintensities) and functional (diffusion tensor imaging) techniques provide the most useful information regarding the extent of VBI. VCI usually involves slowed processing speed and executive dysfunction but can vary widely depending on the location of pathology. The effect of VBI is additive and might be worsened by the presence of other underlying neuropathological conditions (i.e., AD). Risk factors for VBI/VCI include hypertension, hyperlipidemia,
and diabetes, which suggest that the risk profile for cognitive impairment in many individuals could be lowered via lifestyle modifications. Current pharmacological treatments (i.e., cholinesterase inhibitors, NMDA receptor blockers) are symptomatic in nature, and firm evidence regarding their utility is lacking.

**Frontotemporal dementia**

In this chapter by David Perry and Howard Rosen, the clinical syndrome of frontotemporal dementia (FTD) and its underlying pathological etiologies (frontotemporal lobar degeneration (FTLD)) are reviewed. Newly developed diagnostic criteria for FTD have been developed, which identify three core clinical syndromes: (i) behavioral variant FTD (bvFTD), (ii) semantic variant primary progressive aphasia (svPPA, also called semantic dementia), and (iii) nonfluent variant primary progressive aphasia (nfvPPA). The most common presentation is bvFTD, with initial symptoms that might include apathy, disinhibition, loss of empathy, and other personality changes and MRI revealing relative atrophy of the fronto-insular cortex and underlying white matter. Cognitive testing often reveals relative deficits in executive function, although cognition might be relatively preserved early in the disorder. The hallmark features of svPPA include word-finding deficits and loss of semantic knowledge for words and objects, with MRI usually revealing relative atrophy in the left anterior temporal lobe. Bilateral temporal lobe atrophy becomes more prevalent over the course of the disease with additional frontal lobe involvement and behavioral symptoms including loss of empathy, and compulsions might appear (although they are not usually a presenting feature as in bvFTD). Slow and effortful speech is a classic feature of nfvPPA, with frank mutism being common over the course of the disease. MRI typically reveals asymmetric atrophy of the left inferior frontal cortex. Other clinical syndromes, including motor neuron disease (i.e., amyotrophic lateral sclerosis (ALS)), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), can overlap significantly with FTD syndromes and are referred to as FTD spectrum disorders. The underlying neuropathology of FTD is complex, and research in this field is evolving rapidly. As a general guideline, svPPA tends to be associated with TDP-43 pathology, nfvPPA tends to be associated with tau pathology, and bvFTD is associated with a variety of pathologies (TDP-43, tau, FUS, PSP, and CBD). Treatments for these disorders are currently symptomatic, although clinical trials are in development.

**Lewy body dementias**

In this chapter, dementia with Lewy bodies (DLB) and Parkinson’s disease with dementia (PDD) are reviewed by Carol Lippa and Katherine Possin. Both disorders feature a parkinsonian motor syndrome (i.e., rigidity, bradykinesia, tremor), cognitive impairment (visuospatial dysfunction, fluctuations in attention/arousal, and executive dysfunction), and neuropsychiatric symptoms (depression, anxiety, visual hallucinations). DLB is usually associated with relatively simultaneous onset of cognitive and motor symptoms, while PDD is associated with cognitive impairment in the setting of an established PD diagnosis (usually occurring >1 year after motor symptoms). Both syndromes are disorders of alpha-synuclein and are associated with underlying Lewy body pathology. Concomitant AD pathology is often present. Structural MRI findings are often grossly normal for age, while clinical symptoms associated with alpha-synuclein disorders (i.e., REM sleep behavior disorder, anosmia, autonomic dysfunction) might provide additional confirmation of a suspected DLB or PDD diagnosis. The treatment of the motor symptoms is usually with standard dopaminergic therapies utilized in PD, while acetylcholinesterase inhibitors often improve attention deficits and visual hallucinations. Neuropsychiatric symptoms might require SSRIs or low doses of newer antipsychotic agents such as quetiapine. These patients are susceptible to delirium, and exposure to anesthetics, anticholinergics, and antipsychotics should be closely monitored.

**Corticobasal degeneration and progressive supranuclear palsy**

Suhee Lee and Bruce Miller define the terms in the title of their chapter as reflecting the neuropathological entities of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), which are both disorders of tau. They move on to discuss the typical clinical presentations of CBD as (i) nonfluent variant PPA (nfvPPA), (ii) an executive motor (EM) syndrome, and (iii) behavioral variant FTD (bvFTD). The clinical syndromes of nfvPPA and bvFTD have been reviewed in Chapter 5. EM syndrome typically presents with early executive dysfunction and motor impairment, often including axial rigidity and dystonia. MRI findings might include relative atrophy in the left frontal cortex. The clinical syndrome associated with pathological PSP is labeled PSP syndrome (PSP-S), which typically presents with oculomotor abnormalities (reduced saccade velocity and restricted vertical downgaze), axial rigidity and falls, executive dysfunction, and behavioral changes including apathy and disinhibition. Many individuals with PSP-S during life, however, are found to have other neuropathological disorders at autopsy, such as CBD. Conversely, clinical syndromes other than PSP-S are sometimes associated with pathological PSP at autopsy (i.e., CBS, bvFTD). Treatment of both CBD and PSP remains symptomatic, but several anti-tau agents are currently in the early stages of clinical trials.

**Repeat expansion diseases and dementia**

This chapter by Praveen Dayalu, Roger Albin, and Henry Paulson reviews DNA repeat expansion disorders that cause cognitive impairment, the most common of which is Huntington’s disease.
Prion disorders

This chapter, written by Leonel Takada and Michael Geschwind, discusses the three basic forms of human prion disease (PrDs): sporadic (spontaneous), genetic, and acquired. PrDs are uniformly fatal, often rapidly progressive, neurodegenerative dementias. They are caused by the transformation of a normal prion protein into a misshapen form called the prion (pre-ahn). Prions then act as templates, causing nearby prion proteins to also change shape into the disease-causing, misshapen form, the prion. As sporadic Creutzfeldt–Jakob disease (sCJD) is by far the most common type of human PrD, much of the chapter focuses on this form, including the importance of diffusion-weighted brain MRI, and the shortcomings of relying on CSF biomarkers alone for diagnosis. The most common clinical features of sCJD are rapid-onset (weeks to months) dementia, ataxia, behavioral/personality changes, and other motor features (parkinsonism, myoclonus, etc.). Although myoclonus sometimes occurs in DLB and CBD, its presence in a patient with rapid progression should suggest CJD. A minority of sCJD patients present with prominent vision and visuospatial abnormalities (Heidenhain variant). Brain MRI should include FLAIR, DWI, and ADC sequences, which have the highest diagnostic utility for sCJD, showing restricted diffusion in the cortex (cortical ribboning) and/or deep nuclei, particularly the striatum. The use of CSF biomarkers, such as 14-3-3, neuron-specific enolase (NSE), and total tau (t-tau), is somewhat controversial. Many feel that these are merely markers of rapid neuronal injury and thus not specific, but sometimes they can be helpful for CJD diagnosis. Several conditions mimic sporadic CJD, some of which are currently untreatable, such as rapid forms of other common neurodegenerative diseases, such as DLB, AD, CBD, and PSP (discussed in other chapters), and treatable, reversible conditions, such as autoimmune dementias (Chapter 10). Genetic prion diseases (gPrDs), comprising about 15% of human PrDs, are due to autosomal dominant mutations in the prion gene, PRNP. These forms may present identically to sCJD with a rapid course or present as other neurodegenerative diseases, with prolonged courses of a few years to more than a decade, sometimes with prominent psychiatric features. Often, patients with gPrDs do not have a known positive family history, although further investigation often reveals neuropsychiatric disorders, which likely were misdiagnosed. Although the most notorious, acquired prion diseases are the least common form of PrD. They can occur from iatrogenic exposure, consumption of bovine spongiform encephalopathy (BSE), blood transfusion from variant CJD (vCJD), or other causes. Despite ongoing research, presently there are no cures or disease-modifying treatments for PrDs.

Autoimmune dementias

This chapter, written by Andrew McKeon and Sean Pittock, reviews autoimmune etiologies of cognitive impairment or encephalopathy. Clinical features suggestive of an autoimmune disorder include acute or subacute presentation with fluctuating symptoms, CSF or laboratory results suggestive of autoimmunity, and positive response to immunotherapy. Past medical and family history is important to review for a history of cancer, familial autoimmune disorders or cancers, smoking history, and constitutional symptoms. Neuropsychological testing sometimes provides evidence of cognitive dysfunction in those with subtle complaints. MRI may demonstrate T2 abnormalities in the mesial temporal lobe, and EEG sometimes demonstrates generalized and/or focal slowing or epileptiform discharges. An elevated CSF protein, oligoclonal bands, and elevated IgG are all potentially suggestive of an autoimmune disorder, although not diagnostic. Antithyroid and antinuclear antibodies (ANA) tend to be nonspecific but should prompt further autoimmune workup, while neural antibodies (i.e., anti-Hu, CV2, NMDAR, VGKC) should prompt further evaluation for cancer as a paraneoplastic etiology should be high on the differential. Acute treatment of suspected autoimmune illness usually involves high-dose corticosteroids, IVIG, or plasma exchange for 6–12 weeks, with subsequent evaluation to determine improvement. If there is a positive response to treatment, an autoimmune diagnosis is more likely. Maintenance therapy may be required, as many individuals will relapse once treatment is discontinued. Unfortunately, long-term treatments can be associated with a variety of negative side effects, and the relative risks and benefits should be weighed accordingly.
**Toxic and metabolic dementias**

In this chapter, Michelle Mattingly, Katie Osborn and Leon Prockop review toxic and metabolic causes of dementia. Although rare, many of these etiologies are treatable, which emphasizes the need for accurate identification and appropriate intervention. The fluctuating alterations in consciousness associated with delirium can often masquerade as a dementia, but delirium typically is more acute in onset and often associated with toxins or underlying medical illnesses (i.e., cancer, liver disease, thyroid problems). A list of common toxic agents that can cause dementia is provided, with detailed descriptions of the effects of ethanol, carbon monoxide, and lead exposure; these toxins can cause cognitive, neuropsychiatric, and/or movement symptoms that can range from mild to severe with heterogeneous presentations. MRI is not only helpful in some cases of carbon monoxide exposure, with abnormalities in the globus pallidus and white matter, but also may be normal. Treatments include cessation of alcohol intake, hyperbaric oxygen therapy for carbon monoxide, and chelation therapy for lead exposure. Metabolic causes of dementia are broad, and this chapter reviews three common presentations, including thyroid disease, hepatic dysfunction, and disorders of glucose metabolism. Both hypo- and hyperthyroidism can lead to cognitive impairment and psychiatric symptoms, with resolution of symptoms often observed after appropriate medication is administered and euthyroid laboratory values are obtained. Hepatic encephalopathy can range from mild to severe and may be chronic in individuals with severe hepatic disease; treatment involves the use of nonabsorbable disaccharides and antibiotics. Both hypo- and hyperglycemia can lead to cognitive impairment. Individuals with diabetes are at a higher risk for cognitive decline and dementia, which may be due to secondary effects in the vascular system of the brain or may modify the effects of Alzheimer’s disease pathology. Consideration of potential toxic or metabolic contributions to cognitive and neuropsychiatric dementia syndromes is important because of the possibility of treatment and reversal of symptoms.

**Leukoencephalopathies/leukodystrophies**

Authors Gregory Pastores and Swati Sathe review adult-onset leukoencephalopathies, a diverse group of disorders of white matter that cause cognitive decline. A distinction between acquired (i.e., inflammatory, vascular, toxic) causes and hereditary forms is made. The chapter largely focuses on these hereditary causes, termed leukodystrophies. Although many of these disorders have onset in childhood, there are also late-onset presentations that are often misdiagnosed as multiple sclerosis. Symmetric white matter changes on MRI should raise suspicion for leukodystrophy. CADASIL typically presents in the 30s and involves migraine with aura, recurrent strokes, seizures, cognitive impairment, mood changes, and apathy, with progressive episodes of decline over decades. It is an autosomal dominant disorder associated with mutations in the Notch3 gene. Treatment is largely symptomatic for migraine prevention and control of vascular risk factors. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a term that encompasses other syndromes (hereditary diffuse leukoencephalopathy (HDLS) and pigmentary orthochromatic leukodystrophy (POLD)), in which individuals present in their 40s with behavioral changes and motor impairment (i.e., parkinsonism, ataxia) and are often suspected to have a frontotemporal dementia syndrome. In an exciting development, the gene CSF1R has recently been identified as the cause for both POLD and HDLS, further supporting that they are a spectrum of the same disease entity. Several other leukodystrophies are reviewed, including adult-onset autosomal dominant leukodystrophy with autonomic dysfunction, adult polyglucosan body disease, and adult-onset Alexander disease. Mitochondrial disorders that can have significant white matter involvement and can cause dementia are reviewed, including mitochondrial encephalopathy, lactic acidosis, and strokes (MELAS); myoclonic epilepsy with ragged-red fibers (MERRF); Leigh syndrome; Kearns–Sayre syndrome (KSS); nevropathy, ataxia, and retinitis pigmentosa (NARP); Leber hereditary optic neuropathy (LHON); or Mucr–Torre syndrome (MTS). Treatment of these disorders may involve ketogenic diet, physiotherapy, metabolite administration, and avoidance of stress. Lysosomal storage disorders are multisystemic, but can have cognitive impairment as a feature, and may include late-onset forms of metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy (Krabbe disease) and Fabry disease. Treatment may involve hematopoietic stem cell transplant, dietary therapy, enzyme replacement therapy, or adrenal hormone replacement therapy. Although often confused with multiple sclerosis, identifying the cause of a leukoencephalopathy or leukodystrophy is important to consider in order to ensure appropriate diagnosis, genetic counseling, and management.

**Infectious causes of dementia**

This chapter, written by Cheryl Jay, Emily Ho, and John Halperin, reviews the subacute and chronic infections that may lead to a dementia syndrome. HIV-associated dementia is less common in the era of combination antiretroviral therapies (cART) but may involve apathy, slowed thinking, and motor symptoms, along with generalized cognitive dysfunction. The effects of concomitant infections (e.g., hepatitis C, cryptococcal meningitis), substance abuse, and other associated syndromes (e.g., primary CNS lymphoma, progressive multifocal leukoencephalopathy) must be ruled out. Treatment with appropriate cART for HIV and appropriate treatment of any other contributing infections or syndromes is recommended. Subacute sclerosing panencephalitis (SSPE) occurs long after an acute measles infection and is relatively rare in locations
with adequate measles vaccination programs. Myoclonus is common, along with cognitive and behavioral impairment and seizures developing over months. Treatment is largely symptomatic with progression to death typically over one to two years from diagnosis. Acute presentations of hepatitis C and viral encephalitis may also cause long-lasting cognitive impairment. Bacterial causes of dementia include neurosyphilis, Lyme disease, and Whipple's disease. Acute bacterial meningitis may also be associated with cognitive impairment, which continues to stabilize or improve over many years. Fungal infections such as cryptococcal meningitis can cause cognitive impairment, most often in the context of concomitant HIV infection. Intensive antifungal treatment is required. Dementia may also occur in the context of parasitic infection such as neurocysticercosis (NCC), related to tapeworm infection. CNS cysts can be observed on MRI or CT. Seizure and neuropsychiatric symptoms are common presentations. Treatment involves cysticidal drugs and steroids. Although many of these disorders are responsive to therapy, many cognitive deficits will be long-lasting, and some cases are, unfortunately, fatal.

Rheumatologic and other autoimmune dementias

In this chapter by Laura Julian and Christopher Filley, the intersection between neurology and rheumatology is discussed, with a particular focus on systemic lupus erythematosus (SLE). SLE is an autoimmune disease that may affect any organ system and is frequently associated with cognitive and neuropsychiatric symptoms. MRI findings are often notable for white matter hyperintensities. Antiphospholipid syndrome (APS) can lead to stroke or transient ischemic attack (TIA) and thus secondary cognitive and neuropsychiatric dysfunction. Sneddon's syndrome also causes early strokes and TIAs that has a more severe clinical course and greater extent of cognitive impairment in comparison to APS. Treatment may involve anticoagulation and immunosuppressive drugs. Sjögren's syndrome can be associated with a variety of CNS manifestations, although the underlying causes are less well understood. Various vasculitides (blood vessel inflammation) can also cause CNS symptoms and frequently require blood vessel biopsy for confirmation. These syndromes include Wegener's granulomatosis, Churg–Strauss syndrome, Behcet's disease, and giant cell arteritis. Systemic sclerosis or scleroderma may have white matter lesions in the absence of severe neurological symptoms or patient's cognitive complaints. Sarcoidosis in the CNS is frequently associated with cranial neuropathy but may also be accompanied by cognitive and behavioral symptoms, depending on brain lesion location. With neurosarcoidosis, there are typically profound MRI abnormalities, often around the brainstem. Immunosuppressive drugs are typically used for treatment. Celiac disease, an inflammatory reaction to wheat, may lead to CNS complications in 10–20% of individuals with this disorder, most typically an ataxia. A gluten-free diet is appropriate for treatment. The link between rheumatological disorders and cognitive impairment is still in its relative infancy, and further studies with large numbers of patients are needed to more fully understand this phenomenon.

Comprehensive management of the patient with an atypical dementia

This chapter, written by Jennifer Merrilees, Cynthia Barton, Robin Ketelle, and Amy Kuo, provides a framework for clinical management of patients with atypical dementia. These patients often have unique challenges relative to older, more typical dementia patients, including younger age, greater behavioral disturbance, inability to work, and increased caregiver strain. These disorders are underrecognized and caregivers and families may have seen multiple health-care providers before being accurately diagnosed, which can lead to high levels of familial stress. Environmental modifications and behavioral strategies are recommended for a first line of defense in managing mood and personality changes, prior to pharmacological intervention. Caregiver training can be a crucial tool in helping keep the patient at home and delay placement within a facility, which can be difficult as many facilities are not equipped or trained to deal with severe behavioral or motor symptoms.