Imaging Dementia

Essentials for Clinical Practice

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Nomenclature

Advanced neuroimaging This term refers to neuroimaging techniques, which rely on materials and/or image post-processing available only in specialized centers, such as, for example, diffusion tensor MRI, resting state functional MRI, or PET imaging using experimental **tracers.**

Amyloid PET This is a biomarker used to demonstrate in vivo the presence of amyloid plaques in the brain, one of the main features of AD pathology. PET radioligands currently approved for clinical use include ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol [1].

Conventional neuroimaging This term refers to standard neuroimaging techniques that are commonly used in a clinical context, either for the assessment of structural (i.e., compute tomography [CT], morphologic magnetic resonance imaging [MRI]) or functional (i.e., ^{18}F-Fluorodeoxyglucose Positron Emission Tomography [FDG-PET], dopamine transporter single-photon emission computed tomography [DaT-SPECT]) brain features.

Dementia Dementia, as defined in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [2], is an acquired condition marked by impairment in at least one cognitive domain that is severe enough to cause significant limitations in social and/or occupational functioning. Causes of dementia are categorized by their neuropathology, clinical features, and/or presumed etiology. The most common causes encountered in middle-aged and older individuals are Alzheimer's disease (AD), vascular, Lewy body, and frontotemporal dementia.

Diffusion-weighted (DW) MRI Diffusion-weighted (DW) MRI is a quantitative technique that exploits the diffusion of water within biological tissues [3]. The diffusion coefficient measures the ease of this translational motion of water. In biological tissues, this coefficient is lower than that in free water because the various structures of tissues (membranes, macromolecules, etc.) impede the free movement of water molecules. For this reason, the measured diffusion coefficient in biological systems is referred to as the "apparent diffusion coefficient" or ADC [3].

Diffusion tensor (DT) MRI Because some cellular structures (e.g., axons) impede movement to a greater degree in some directions than others (e.g., across as opposed to along the axon cylinder), the measured ADC also depends upon the direction in which the diffusion is measured. A full characterization of diffusion can be provided by the so-called tensor, which is a 3×3 matrix that characterizes the measured diffusion in three orthogonal directions [4]. From the diffusion tensor (DT) matrix, two scalar measures are derived. The first is the mean diffusivity (MD), which reflects the average diffusion in all three directions. The other measure, the fractional anisotropy (FA), measures the extent to which diffusion is nonuniform in the three orthogonal directions. DT MRI is typically used to assess the integrity of white matter tracts, as alterations of its parameters suggest axonal pathology and loss of structural connectivity within the brain [4].

Dopamine transporter (DaT) scan This term indicates single-photon emission computed tomography (SPECT) measurement of the striatal uptake of [^{123}I]ioflupane (or FP-CIT), a dopamine transporter (DaT) radioligand. It reflects the integrity

of terminal fields of nigrostriatal neurons [5]. Loss of striatal DaT occurs in parkinsonian syndromes [5].

FDG-PET The most common radioligand used to assess brain function in PET studies is 2-[fluorine-28]fluoro-2-deoxy-D-glucose (FDG) [6], which is an analog of glucose, the main energy substrate of the brain. FDG, after uptake, is trapped within metabolically active cells so that signal emission mostly depends on cell metabolic activity. Synaptic dysfunction or loss, which is a main feature of brain damage and dementia, will induce a reduction in cell metabolism and energy demand, which is detected by FDG-PET studies.

Gray matter atrophy assessment T1-weighted MRI sequences are widely used to investigate alterations of gray matter structure, as they allow to visually assess and measure the overall brain volume, the pattern and rate of atrophy, and the volumes of specific regions of interest. Several post-processing analytical techniques can be applied to T1-weighted imaging, providing semi-automated measurements of gray matter volume loss at the voxel level (e.g., voxel-based morphometry) or cortical thinning.

Mild cognitive impairment (MCI) The term refers to the predementia symptomatic phase. In this phase, the cognitive impairment is both neither normal for age nor severe enough to affect subject's independence in functional abilities [7]. Affected cognitive domain is typically memory, and also language, executive, or other functions show an initial impairment.

Resting state functional MRI (RS fMRI) fMRI is able to measure brain activity by detecting changes associated with blood flow, based on the assumptions that cerebral blood flow and neuronal activation are coupled, and brain regions that are co-activated establish networks fundamental to maintain normal brain function [8]. The analysis of synchronous low-frequency (<0.1 Hz) fluctuations seen on fMRI scans at rest (i.e., in the absence of external stimulations) has demonstrated the presence of so-called resting-state networks of the human brain, which display synchronous variations of the blood-oxygenated-level-dependent signal. Assessing variations in the activity of resting state networks has provided important pathophysiological insights in normal aging [9] and several neurological conditions [10].

Subjective cognitive decline (SCD) SCD is defined as self-perceived cognitive decline among cognitively normal individuals. Some studies have suggested that SCD may be associated with an increased risk of incident MCI or dementia [11].

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Introduction

Dementia is a syndrome characterized by the development of multiple cognitive deficits and behavioral changes that lead to impairment of functional activities. Dementia is a common condition in the elderly, especially the very elderly, and the absolute number of cases will continue to grow as the population ages. Every patient with cognitive decline deserves an assessment. There are potentially reversible conditions that may cause or mimic dementia, including brain tumors, normal pressure hydrocephalus, metabolic changes, infections, thyroid dysfunction, nutritional deficiencies (vitamin B_{12} being the most common), and dysimmune disorders (Table 1). Toxins, including chronic alcohol abuse, drugs or medication, may cause confusion and cognitive decline (Table 1). Sleep disorders and psychiatric diseases, such as depression, can be associated with cognitive deficits (Table 1). If detected and treated early, these cognitive problems can be reversed or their progress halted. However, the majority of cases of dementia are associated with primary degenerative, progressive, and irreversible diseases. An early accurate diagnosis of irreversible dementia is essential, too, to allow the disease to be tackled with available or experimental intervention, lifestyle changes, or logistical arrangements, before disability develops.

In the early and differential diagnosis of diseases leading to irreversible dementia, clinical history, which needs to be supplemented by an informant, should focus on the affected cognitive domains, the course of the illness, the impact on activity of daily living, and any associated noncognitive symptoms. Past medical history, comorbidities, family and education history are all important. A general and neurological physical examination should be performed in all patients. Neuropsychological assessment is central to diagnosis and management of disorders associated with cognitive impairment and should be performed, preferably, at an early stage of the disease. Laboratory tests should be used to explore whether the patient has comorbidity, risk factors for cognitive decline, or has a treatable cause for dementia (Table 1). Following clinical, neuropsychological, and laboratory evaluation, the diagnosis of irreversible dementias can be improved by the use of biological measures. Biomarkers of functional impairment, neuronal loss, and protein deposition that can be assessed by neuroimaging (i.e., magnetic resonance imaging [MRI] and positron emission tomography [PET]) or cerebrospinal fluid analysis are increasingly being used to diagnose Alzheimer's disease (AD) and other neurodegenerative

Table 1 Treatable causes of cognitive impairment and dementia

Etiology		Main features	Treatment	Typical neuroimaging findings
Toxic disorders	Drugs	Mainly due to drugs with anticholinergic properties, in elderly patients and during polipharmacotherapy (antihistamines, tricyclic antidepressants, antipsychotics, antimuscarinics)	Drug discontinuation	None
	Alcohol abuse	Anterograde and retrograde memory, apathy, intact sensorium, and relative preservation of long-term memory and other cognitive skills	Alcohol cessation	CT and MRI: enlargement of cerebral ventricles and sulci
Vitamin deficiencies	B_{12}	Most frequent, due to malabsorption of decreased intake. Associated with macrocytic anemia and neuropathy	Deficit correction	Not typical
	Folate	Associated with macrocytic anemia	Deficit correction	Not typical
	B_6	Associated with normocytic anemia, angular cheilitis, and glossitis	Deficit correction	Not typical
	B_1	Wernicke-Korsakoff syndrome: ataxia and ophthalmoplegia associated with confusion with acute onset. Related to alcohol abuse	Deficit correction	MRI—T2-weighted/FLAIR: symmetrically increased signal intensity in the mammillary bodies, dorsomedial thalami, tectal plate, periaqueductal gray matter, around the third ventricle MRI—T1-weighted (Gd): contrast enhancement can be seen in the same regions, most commonly the mammillary bodies

Endocrine disorders	Thyroid diseases	Hyper- and hypothyroidism	Hormone replacement/ antithyroid agents	Not typical
Structural disorders	Tumors	Both benign or malignant tumors, primitive or secondary	Surgery, radiotherapy, chemotherapy	CT and MRI—T1-weighted, T2-weighted, FLAIR: mass with altered signal with different features according to the tumor type; enhancement in T1-weighted with Gd
	Normal pressure hydrocephalus	Hakim's clinical triad: 1. Urinary incontinence 2. Deterioration in cognition (dementia) 3. Gait disturbances	Ventriculo-peritoneal shunt	• Marked dilatation of ventricles • Wide appearance of Sylvian and parasagittal CSF fissures • Wide aqueduct with a significant signal void in it from high-speed flow on MRI T2-weighted images • Lack of downward bending of the third ventricle floor • Periventricular edema • Narrow callosal angle of less than 90° • Increased Evans' ratio, more than 0.3
	Chronic subdural hematoma	Cognitive impairment, apathy, somnolence, and occasionally seizures	Neurosurgery	CT hypodensity and MRI hyperintensity—FLAIR is the most sensitive sequence
Infections	HIV	• Direct consequence of the HIV virus • Opportunistic infections • Neoplasm • Treatment-related complications	Anti-retroviral therapy, antimicrobic therapy, drug therapy monitoring	• Symmetric periventricular and deep white matter T2 hyperintensity on MRI • Confluent or patchy • No mass effect • No contrast enhancement
	Syphilis	Dementia with marked personality changes and tabes dorsalis	Antimicrobic therapy	Leptomeningeal enhancement, cerebral vasculitis, ischemic stroke, cerebral atrophy, and spinal cord atrophy

(continued)

Table 1 (continued)

Etiology		Main features	Treatment	Typical neuroimaging findings
Dysimmune disorders	Autoimmune encephalitis	Acute onset of cognitive deficits, seizures, acute onset of psychiatric disorders, dyskinesia (mainly in the face district)	High-dose steroids, intravenous immunoglobulin, plasma exchange	CT: negative MRI inconsistent findings: T2-FLAIR hyperintense demyelinating areas and Gd + areas in different regions. MRI often negative
	Paraneoplastic encephalitis	Acute onset of cognitive deficits, seizures, acute onset of psychiatric disorders	Treatment of the primitive tumor May be useful: high-dose steroids, intravenous immunoglobulin, plasma exchange	CT: negative MRI inconsistent findings: T2/FLAIR hyperintense demyelinating areas and Gd + areas in different regions. MRI often negative
Sleep disorders	Obstructive sleep apnea syndrome	Daytime sleepiness, memory and attention impairment, frequently associated with obesity and snoring	Continuous positive airway pressure, surgery	Not typical
Psychiatric disorders	Depression	Pseudodementia and associated cognitive dysfunction can be reversible	Antidepressants, psychotherapy	Not typical

Abbreviations: *CSF* cerebrospinal fluid, *CT* computed tomography, *FLAIR* fluid attenuated inversion recovery, *Gd* gadolinium (contrast agent), *HIV* human immunodeficiency virus, *MRI* magnetic resonance imaging

diseases in research studies and specialist clinical settings. However, the practical value of various neuroimaging techniques in clinical routine practice is not well defined yet and their potential future development is not fully appreciated.

The aim of this book is to guide the physicians in the choice of the available neuroimaging tools for a correct and cost-saving diagnosis and management of common primary, irreversible dementias. The book, which is concise in its content but profuse in its illustrative, tabular, and clinical case material, wishes to provide some practical and useful algorithms and rules to be used in the clinical setting.

AD is the most prevalent form of dementia: it accounts for 60% of cases of progressive cognitive impairment in aged individuals, age being the single most important risk factor. Thus, it is fitting that a chapter on an update on neuroimaging in AD kicks off this book. Chapter 2 is on vascular cognitive impairment (VCI), which is the second most common form of dementia after AD in terms of incidence and prevalence. Even though VCI is a common disorder, the diagnosis of pure vascular dementia is uncommon. Vascular pathology alone causes less than 10% of dementia cases, while it is an important contributive factor in multiple-etiology (also termed "mixed") dementia, mainly associated with AD pathology, accounting for approximately 30–40% of all dementia cases.

Chapter 3 of the book is focused on frontotemporal lobar degeneration (FTLD)—a devastating, relentlessly progressive, young onset, neurodegenerative disorder. FTLD typically shows a relatively focal and progressive atrophy involving the frontal or temporal lobes, or both. FTLD is less common than AD, with estimates of population prevalence ranging from 4 to 22 per 100,000 before age 65 years in Europe and the USA. However, this disease group is of incommensurate importance as a cause of young onset dementia and/or motor deficits, with all the global societal economic costs that this implies. Only in the past few decades has the clinical and pathological complexity of these diseases as paradigm of selective brain degeneration been fully appreciated.

In recent years we have increasingly recognized that Parkinson's disease (PD) and other parkinsonian syndromes do not simply feature disturbance of the motor function. Rather, patients with PD and other parkinsonisms also experience a multitude of non-motor symptoms commonly including cognitive impairment. Non-motor symptoms become increasingly prevalent over the course of the illness and are a major determinant of impaired quality of life and progression of disability.

In a later chapter, rapidly progressive dementias (RPD) are discussed. In contrast to most dementing conditions that take years to progress to death, RPD can be quickly fatal. It is critical to evaluate the RPD patient without delay to identify some peculiar features of specific diseases, as well as to rule out several treatable etiologies (i.e., tumors, autoimmune disorders). The chapter will discuss the general diagnostic workup of RPD, focusing on neuroimaging findings in prion diseases, which represents the main single etiology.

Dementia is becoming a major challenge for global health and social care. Neuroimaging is now considered as standard-of-care in the initial clinical assessment of patients with dementia. We hope that this book will be of practical relevance and assistance to practicing neurologists and radiologists in their daily activity and will also be an educational framework for trainees and researchers.

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