

REVIEW

Rapidly Progressive Dementia: Is it Alzheimer's or Not?

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ABBREVIATION LIST

AD: Alzheimer's disease
APP: Amyloid precursor protein
CBD: corticobasal degeneration
CDR: Clinical Dementia Rating Scale
CJD: Creutzfeldt-Jakob disease
CSF: cerebrospinal fluid
DLB: dementia with Lewy bodies
FLTD: frontotemporal lobar degeneration
MMSE: Mini- Mental State Examination
LPA: logopenic progressive aphasia
PNFA: progressive non-fluent aphasia
rpAD: rapidly progressive Alzheimer's disease
RPD: rapidly progressive dementia
PSP: progressive supranuclear palsy
SD: semantic dementia
VD: vascular dementia
VITAMINS: vascular, infectious, toxic/metabolic/traumatic, autoimmune, metastatic/neoplastic, iatrogenic/inborn disorders of metabolism, neurodegenerative, seizures/systemic

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ABSTRACT

Alzheimer's disease is a chronic progressive disease, which accounts for 60% of all dementias. Sometimes 10-30% of Alzheimer's disease cases have a more fulminant course, but this subtype is not the only cause of rapidly progressive dementia. There exists a variety of entities presenting as rapidly progressive dementias, a number of which are reversible or treatable. It is imperative that accurate and prompt diagnosis be made, since it is crucial for neuronal survival. Some of these rapidly progressive manifestations concern vascular, infectious, toxic-metabolic, autoimmune, metastatic-neoplastic, iatrogenic, neurodegenerative or systemic diseases, which can be arranged in a list using the mnemonic "VITAMINS". This review summarizes the major aetiologies of rapidly progressive dementia. Differential diagnostic algorithms are also presented.

INTRODUCTION

Dementia, a clinical syndrome which encompasses a variety of diseases, is characterized by a cluster of symptoms and signs manifesting as loss of executive functioning, concerning the ability of decision making, cognitive decline, memory impairment, language disturbances, psychiatric and psychological changes leading to impaired performance in daily living activities. Usually of a gradually progressive course, dementia is considered one of the major causes of disability and dependency. Its prevalence is rising rapidly, especially after the seventh decade of life. The total number of people in 2010 was estimated to be about 35.6 million and is expected to reach 115.4 million by 2050.¹⁻³

Alzheimer's disease (AD) is considered the most common type of dementia, followed by vascular dementia (VD). The combination of AD and VD (mixed dementia) has been considered by some studies as not only a subtype of dementia, but also the most frequent. There seems to be a gender difference in the prevalence of dementia subtypes. Women in the older age group (85 years and more) are more likely to develop AD, while men vascular dementia, atherosclerotic cardiovascular diseases or stroke. In 2011 the National Institute on Aging- Alzheimer's Association (NIA-AA), led by the vast evolution of neuroimaging and biomarkers, presented new criteria for all cause dementia and AD, definite diagnosis being made only post-mortem (Tables 1a, b, c,

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RAPIDLY EVOLVING DEMENTIAS

TABLE 1A. Criteria for all-cause dementia as quoted from and according to the 2011 recommendations of the NINCDS-ADRDA^{4,5}

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities;
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
 - a) Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
 - b) Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
 - c) Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
 - d) Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
 - e) Changes in personality, behavior, or comporment

TABLE 1B. Criteria for Alzheimer’s Disease as quoted from and according to the 2011 recommendations of the NINCDS-ADRDA.^{4,5}

AD is classified in: (1) Probable AD dementia, (2) Possible AD dementia, and (3) Probable or possible AD dementia with evidence of the AD pathophysiological process

1. Probable AD Dementia: Meets criteria for dementia described in section I, and in addition, has the following characteristics:
 - A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
 - B. Clear-cut history of worsening of cognition by report or observation; and
 - C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
 - a) Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
 - b) Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
 - D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

TABLE 1C. Criteria for Possible and Pathophysiologically proven AD dementia as quoted from and according to the 2011 recommendations of the NINCDS-ADRDA.^{4,5}

<p>2. A. Possible AD dementia</p> <ul style="list-style-type: none"> • Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline. • Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.
<p>B. Pathophysiologically proven AD dementia</p> <p>The diagnosis of pathophysiologically proved AD dementia would apply if the patient meets the clinical and cognitive criteria for AD dementia outlined above, and the neuropathological examination demonstrates the presence of the AD pathology.</p>
<p>Dementia unlikely to be due to AD</p> <p>1. Does not meet clinical criteria for AD dementia.</p> <p>2. a. Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington’s disease, or others that rarely, if ever, overlap with AD.</p> <p>b. Regardless of meeting clinical criteria for possible AD dementia, both Aβ and neuronal injury biomarkers are negative</p>

d).^{4,5} AD demonstrates a clinical heterogeneity. Different subtypes have been verified, such as late and early-onset, familial, sporadic and rapidly progressive (rpAD).^{6,7} In the following review the rapidly progressive subtype of AD is discussed and differential diagnosis from other similar entities presented.

TABLE 1D. Criteria for Probable and Possible AD dementia with evidence of the AD pathophysiological process as quoted from and according to the 2011 recommendations of the NINCDS-ADRDA.^{4,5}

<ul style="list-style-type: none"> • Probable AD dementia with evidence of the AD pathophysiological process Major AD biomarkers that have been widely investigated and may be broken into two classes based on the biology which they measure. Biomarkers of brain amyloid-beta (Aβ) protein deposition are low CSF Aβ₄₂ and positive PET amyloid imaging. The second category is that of biomarkers of downstream neuronal degeneration or injury. The three major bio-markers in this category are elevated CSF tau, both total tau and phosphorylated tau (p-tau); decreased ¹⁸fluorodeoxyglucose (FDG) uptake on PET in temporo-parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex. In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. Biomarker test results can fall into three categories—clearly positive, clearly negative, and indeterminate. • Possible AD dementia with evidence of the AD pathophysiological process This category is for persons who meet clinical criteria for a non-AD dementia but who have either biomarker evidence of AD pathophysiological process, or meet the neuropathological criteria for AD. Examples would include persons who meet clinical criteria for dementia with Lewy bodies or for a subtype of frontotemporal lobar degeneration, but who have a positive AD biomarker study or at autopsy are found to meet pathological criteria for AD. In the biomarker table, we indicate that both categories of biomarkers must be positive for an individual who presents clinically with a non-AD phenotype to meet criteria for possible AD.

RAPIDLY PROGRESSIVE ALZHEIMER’S DISEASE

Classical AD’s duration ordinarily varies from a few years

to two decades with a mean 8 year survival rate. There is about a 3 Mini- Mental State Examination (MMSE) point decline in cognition per year. Attempts have been made to define the diverse types of AD by specifying the cognitive disorder features (frontal, cortical, subcortical), the cerebrospinal fluid (CSF) biomarker profiles, genetic testing and neuroimaging findings for each one. Despite the multiversity of AD and the different biological aetiologies of its subgroups, in the end there is a similar evolution. This is characterized by accumulation of β -amyloid ($A\beta$) plaques and neurofibrillary tangles, composed of tau fibrils, with subsequent synapse and neuronal loss. Amyloid precursor protein (APP), which is a membrane bound protein, normally undergoes endoproteolytic cleavage by enzyme α -secretase forming soluble fragments. When there is abnormal APP cleavage by β - and γ -secretases, accumulation of $A\beta$ peptide is observed, thus launching the pathogenic self-sustaining cascade. Other proteins such as presenilin 1 and 2 also participate in $A\beta$ protein production.⁶⁻⁸

Concerning the more rapidly evolving type of AD, it has been the object of dispute mainly regarding the term "rapid". The term rapid has been used to describe not only cognitive decline, evaluated by MMSE or Clinical Dementia Rating Scale (CDR), but survival rate as well. Reaching a consensus rapidly progressive Alzheimer's disease (rpAD) has been defined as a six -point decline in cognitive performance as evaluated by MMSE or survival rate of less than two years. RpAD patients represent 10-30% of AD cases according to the different definitions given.^{6,8}

The factors contributing to the rapid progression of AD continue to be under investigation. Rapid cognitive deterioration has been related to high ratio of total tau to β - amyloid 1-42 ($A\beta$ 1-42) protein (≥ 81), high levels of total tau protein or phosphorylated tau (ptau) and low $A\beta$ 1-42 (≤ 411 pg/mL) in the CSF. CSF protein 14-3-3, usually detected in patients with Creutzfeldt-Jakob disease, is sometimes detected in fast evolving AD cases.⁹

Genetic factors have also been associated with rpAD, though occasionally controversial, as in the case of the presence or not of the Apolipoprotein E ϵ allele or the polymorphisms of the G51S purine nucleoside phosphorylase, presenilin/rs3025780 (T6 genotype) and others.¹⁰⁻¹⁴

Comorbidities also seem to play an important role in the progression of AD. Among these are the pre-existing cognitive reserve, diabetes mellitus, atherosclerosis, hypertension, atrial fibrillation, hypercholesterolemia, myocardial infarction and others.^{15,16} Proof for the above is the fact that hyperglycemic conditions and impaired glucose metabolism in general have been known to provoke accumulation of α -ketoaldehyde methylglyoxal (MG). MG, a reactive intermediate of cellular metabolism, has been correlated with oxidative stress in AD. It is formed endogenously as a by-product of the glycolytic pathways and is able to induce cellular damage by linking proteins and glycation. MG furthermore induces tau hyper-

phosphorylation by reducing phosphatase levels and enhancing kinase activities.¹⁷

Another crucial issue arising is the differential diagnosis of rpAD. Are all rpAD patients with a condemned at present diagnosis?

RAPIDLY PROGRESSIVE DEMENTIAS

A considerable number of nosologies other than rpAD have a rapid cognitive deterioration of which a numerous amount are reversible and some are not. It is imperative in the event of treatable causes to make a swift and accurate diagnosis in order to minimize neuronal or synaptic loss. Aiding in this is the use of a mnemonic table of disorders featuring as rapidly progressive dementias (RPDs) "VITAMINS" (V= vascular, I= infectious, T= toxic/metabolic/traumatic, A= autoimmune, M= metastatic/ neoplastic, I= iatrogenic/inborn disorders of metabolism, N= neurodegenerative, S= seizures/systemic) (Table 2).¹⁸⁻²⁰

RPDs have a course, usually subacute, ranging between weeks, months up to two years. Conditions commencing as an acute confusional state, which evolve within hours or days, for instance acute infectious or metabolic encephalopathies, are excluded from this diagnosis.²⁰ Prevailing etiologies differ analogous to the investigation's point of view, like the referral centre or age group. According to the referral center, for example at the University of California, San Francisco, Memory and Aging Center, prion diseases (all types) are the most prominent rpd cause, while in a Greek tertiary referral centre secondary-potentially treatable nosologies are more often.^{19,21} In young patients, secondary dementias (vasculitis and autoimmune inflammatory brain diseases) are more common. Concerning prion disorders the variant Creutzfeldt- Jakob disease is typically observed in this age group.²²

Strategies to best assess the vast number of entities, which manifest initially as rapidly progressive dementias are depicted in following algorithm (Table 3a, b). First it involves a meticulous history taking (time of onset, duration, associated features, co morbid conditions, evidence of systemic disease, exposure to toxic substances or blood products, family history, rashes, psychiatric symptoms, workplace, previous hospital admissions, etc.). This is succeeded by a thorough physical examination (neuropsychological testing, inspection for signs or symptoms pertaining to neurological, cardiovascular, pulmonary, rheumatological, dermatological, gastroenterological disorders), laboratory (serum, CSF, urine) analysis, cerebral and whole body imaging studies, electroencephalographic evaluation and finally brain biopsy.^{19,22-24}

Neuroimaging plays an important role in the differential diagnosis of dementia inducing conditions. Concerning cerebral MRI characteristic is the "humming bird" or "penguin" sign noted in T1- weighted midsagittal images due to atrophy

TABLE 2. Differential Diagnosis of Rapidly Progressive Dementias with the aid of the mnemonic list “VITAMINS”¹⁸⁻²⁰

Vascular	Multi-infarct vascular dementia, strategic infarct dementia, inflammatory cerebral amyloid angiopathy, primary CNS angiitis, cerebral venous sinus thrombosis, hyperviscosity syndromes
Infectious	Viral encephalitis (including HSV), HIV dementia, progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis, fungal and parasitic infections, treponema pallidum, mycobacterium tuberculosis, Whipple’s disease, Lyme disease
Toxic-Metabolic	Vitamin B1, B12 and niacin deficiency, folate deficiency, uremia, electrolyte imbalances, hypothyroidism, hyperparathyroidism, severe liver disorders, inherited metabolic disorders (leukodystrophies, Wilson’s disease, lysosomal and mitochondrial), lead, aluminum, mercury, arsenic and bismuth toxicity
Autoimmune	Paraneoplastic limbic encephalitis (anti-Hu, anti-CV2, anti-NMDA), Anti- VGKC and Anti-GAD encephalitis, Hashimoto encephalopathy, Systemic Lupus Erythematosus, Sjogren’s syndrome, primary or secondary CNS vasculitis, Coeliac and Behcet’s disease, neurosarcoidosis
Metastases/Neoplasm	Metastatic tumors, primary CNS lymphoma, gliomatosis cerebri
Iatrogenic	Lithium, valproic acid, anticancer drugs, benzodiazepines
Neurodegenerative	CJD (sporadic, genetic, variant), Alzheimer’s disease, Lewy Body Dementia, behavioral variant frontotemporal dementia, corticobasal syndrome, progressive supranuclear palsy
Systemic/seizures/other	Hypertensive encephalopathy, eclampsia, chemotherapy, normal pressure hydrocephalus, non-convulsive status epilepticus, psychiatric disorders

Abbreviations: CNS: central nervous system; HSV: herpes simplex virus; NMDA: N-methyl D-aspartate; GAD: glutamic acid decarboxylase; VGKC: voltage-gated potassium channel.

TABLE 3A. Diagnostic Algorithm for initially evaluating Rapidly Progressive Dementias according to Patterson RW et al modifications.¹⁹

Basic panel of tests			
Blood tests	CSF	Imaging	Urine/Other
Complete blood count, basic metabolic panel (including Ca, Mg and P), Liver and renal function tests, rheumatology screen (ESR, ANA, RF, CRP, C-ANCA and P-ANCA), thyroid function, B12, homocysteine, anti-thyroglobulin and anti-thyroperoxidase antibodies, HIV, Lyme, paraneoplastic and autoimmune antibodies, rapid plasma reagin	Cell count and differential, protein, glucose, IgG Index, Oligoclonal bands, VDRL, 14-3-3 protein, neuron-specific enolase, tau protein	Cerebral MRI [including FLAIR, DWI (diffusion weighted images) and ADC (apparent diffusion coefficient) sequences] with and without contrast	Urine Analysis and cultures, Collect 24-hour urine for heavy metal screen including: arsenic, lead, mercury, copper, aluminum and bismuth (relative to history of exposure). Electroencephalogram

TABLE 3B. Diagnostic Algorithm for initially evaluating Rapidly Progressive Dementias according to Patterson RW et al modifications.¹⁹

Tests to consider under various conditions			
Blood tests	CSF	Imaging	Urine/ Other
Lyme disease, cancer screen, blood smear, coagulation profile, copper, ceruloplasmin, hypercoagulability tests, further rheumatologic examination (complement, dsDNA, anti-SM, anti-RNP, anticardiolipin, anti-SCL 70, anti-Jo, anti-centromere antibodies)	Bacterial, fungal, acid-fast bacilli cultures and stains, flow cytometry, cytology, Whipple and viral PCRs, cryptococcal antigen, viral cultures	Cancer screen: CT of chest, abdomen, pelvis (with and without contrast), mammogram, body PET scan Brain angiogram or MR angiography, MR spectroscopy, Carotid ultrasound, Echocardiogram	24h urine screen for porphobilinogen, delta-aminolevulinic acid, copper and heavy metals Nerve conduction studies/ EMG Brain biopsy

of the midbrain tegmentum, considered a classical sign in progressive supranuclear palsy. Another is the “hot cross bun” sign caused by bilateral symmetric hyperintensity of the atrophic middle cerebellar peduncles observed in multiple system atrophy shown in T2- weighted MR images. In prion diseases, the “pulvinar” or “hockey stick” sign is indicative of variant CJD. It is formed by confluent hyperintensities within the dorsomedial thalamus and posterior thalamus (pulvinar). Diffusion weighted imaging (DWI) sequences and apparent

diffusion coefficient (ADC) maps aid in the differentiation of CNS lymphoma, glioblastoma and metastatic lesions. While infectious aetiologies can be distinguished by combining serology tests and brain thalium-201 single-photon emission tomography (SPECT). Malignant and non-malignant cerebral lesions have also been accurately recognized by positron-emission tomography (PET). The main neuroimaging findings in RPDs are demonstrated in Tables 4a and 4b.^{19,25-29}

In the succeeding descriptions, the various types of

TABLE 4A. Neuroimaging findings in Rapidly Progressive Dementias caused by Neurodegenerative Disorders.^{19,25-29}

Disease	Neuroimaging investigation
Alzheimer’s disease	Cerebral MRI: higher magnitude of atrophy in the occipital and parietal lobes MR spectroscopy: decrease in N-acetylaspartate (NAA) and increase in myo-inositol and choline
Dementia with Lewy Bodies	Cerebral MRI: relative preservation of the medial temporal lobe (MTL), may be normal or non-specific atrophy MR spectroscopy: preservation of NAA-to-creatine ratios 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane SPECT: reduced dopamine transporter levels
Frontotemporal Lobar Degeneration	Cerebral MRI: “knife edge” sign, which is due to focal atrophy within the anterior temporal lobe at the level of the temporal horn of the lateral ventricle
Progressive Supranuclear Palsy	Cerebral MRI: “humming bird or penguin” sign caused by atrophy of the midbrain, pons, thalamus, superior cerebellar peduncle, striatum T2-weighted images very specific, but not always present, are hypointensities of the putamen and hyperintensities of the tegmentum DWI sequences: possible demonstration of putaminal ADC value increase
Multiple System Atrophy	Cerebral MRI: “hot cross bun” sign in the pons DWI demonstrates increased diffusivity and ADC within the affected middle cerebellar peduncles, with a matching decreased fractional anisotropy and putaminal ADC increases (not observed in Parkinson)
Corticobasal Syndrome	Cerebral MRI: Asymmetric parietal or frontal lobe atrophy

TABLE 4B. Indicative Neuroimaging findings in Rapidly Progressive Dementias caused by Vascular, Prion, Inflammatory and other Nosologies.^{19,25-29}

Disease	Neuroimaging investigation
Vascular Diseases	Cerebral MRI: multiple regions of T2/FLAIR hyperintensities in vascular territories(Multi-Infarct Vascular Dementia), multiple grey or white matter T2 hyperintensities (primary CNS angiitis). In inflammatory CAA there are microbleeds on T2 with confluent hyperintensities (hypointensities on T1)
Infectious	Cerebral MRI: may be normal or shows non-specific atrophy in neurosyphilis, normal versus hyperintensities in MTL, midbrain and diencephalon in Whipple disease, normal in Lyme, cortical atrophy and nonspecific white matter changes in HIV Dementia, MTL hyperintensities on FLAIR sequences followed by asymmetric hemorrhagic necrosis in herpetic meningoencephalitis
Toxic-metabolic	Cerebral MRI: T2 hyperintensities in medial thalamus and mammillary bodies in Wernicke syndrome, nondiagnostic in B12 deficiency, PallidalT1 hyperintensities with normal T2 in acquired hepatocerebral degeneration
Autoimmune	Cerebral MRI: T2 hyperintensities in cerebral/ cerebellar cortex with meningeal contrast enhancement in NMDAR encephalopathy, MTL hyperintensities on FLAIR or normal in encephalopathy with VGKC antibodies, MTL hyperintensities on FLAIR and T2 or normal in Limbic encephalitis
Prion Disease	Cerebral MRI: Flair and DWI sequences depict in sCJD the “cortical ribboning” sign (hypersignals delineating the cortex), hypersignals in the striatum and thalamus. In the vCJD the “pulvinar” sign is observed due to marked hyperintensity of the anterior putamen
Metastasis/ neoplasia	Cerebral MRI: focal hypo- or hyper T2 lesions with contrast enhancement in primary CNS lymphoma
Normal Pressure Hydrocephalus	Cerebral MRI: enlargement of ventricular system

RPDs are discussed, the relatively more often, somewhat more extensively. More rapidly progressive dementias have been observed with neurodegenerative diseases, prion diseases, notably Creutzfeldt-Jakob disease (CJD), autoimmune and infectious diseases, toxic, vascular and metabolic disorders, neoplastic, paraneoplastic, systemic nosologies and seizures.

NEURODEGENERATIVE DISORDERS

A large number of neurodegenerative diseases that usually progress gradually can also present as RPD. AD, as aforementioned, is the most common cause of dementia with a median survival rate of approximately 8-12 years. It can rarely present a rapid deterioration course, mimicking CJD, especially when combined with amyloid angiopathy. AD represents a major non-CJD RPD cause in some centres, while in others a much less common.^{6,20} Among other neurodegenerative diseases that can more likely portray a fulminant evolution are frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP).²⁴

FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) concerns pathologies that have a predilection to the frontal and/or temporal lobes early. The varying clinical and pathological presentations of this group of syndromes contributed to an extensive spectrum of referring terms. Briefly the term “frontotemporal lobar degeneration (FTLD)” is used when addressing the pathological entity and “frontotemporal dementia” (FTD) in referral to the clinical one. Pick’s disease is the original term for frontotemporal degeneration. The term Pick’s disease is used at present for a specific pathology with Pick bodies, which are abnormal collections of the protein tau in the brain. These neuronal cytoplasmic inclusions stain slightly basophilic on routine hematoxylin-eosin staining. Though they are strongly argyrophilic after Bielschowsky or Bodian silver staining, pick bodies do not stain with Gallyas silver stain. Pick bodies by immunohistochemistry testing are revealed to be tau, RD3, p62, and ubiquitin immunoreactive and RD4, α -synuclein, and transactive response DNA-binding

protein of 43 kDa (TDP-43) negative. Their cortical distribution typically involves neurons in the dentate gyrus, but also and other cortical areas, which include the cornu Ammonis of the hippocampus, presubiculum, cingulate gyrus, insula, inferior temporal lobe, and the inferior parietal lobule. Pick bodies are less prominent in the subcortical and brainstem area. Pick cells, pertaining to swollen chromatolytic neurons, are also typically found. Glial cell inclusions (often showing atypical 3R and 4R positivity) are less pronounced in Pick disease than in other tauopathies.^{20,30-32}

Regarding the initial pathology, when it affects the frontal lobes, the main changes are in personality and behaviour (Behavioral-variant FTD). Individuals with predominant temporal lobe involvement present with loss of language skills (Progressive Non-fluent Aphasia, Semantic Dementia). Frontotemporal lobar degeneration (FTLD) can be divided into various types according to histopathological findings or symptomatology.

The histopathology of FTLD in general is characterised by linear spongiosis in layers II and III of the cortex, with predominant neuronal loss and gliosis. The tau protein, transactive response DNA-binding protein of 43 kDa, and “fused in sarcoma” protein are proteins involved in pathologic processes that represent the basis for frontotemporal lobar degeneration classification. From the histopathological point of view the FTLD can be classified into 4 groups based on the presence of aggregates or deposits in neurons or glial cells: tauopathies, ubiquitinopathies, neuronal intermediate filament inclusion disease, and those with no data specifically pertaining to any of the above types. There are types of FTLD with tau inclusions (FTLD-tau) and others containing TAR DNA-binding protein 43 (FTLD-TDP). On the basis of the number of microtubule-binding repeats in the tau protein (a consequence of differential mRNA splicing), FTLD-tau pathologies are further classified into 3R, 4R, or combined 3R/4R subtypes. Overlapping FTLD–motor neuron disease and FTLD–parkinsonism syndromes are relatively frequent. These nosologies predispose to a fast progression of the disorder.^{20,30-32}

Clinically, FTD is divided into the following categories: behavioral variant of FTD (bvFTD), concerning executive function and behaviour (as bvFTD progresses disinhibition develops, and there is a remarkable loss of restraint in personal relationships and social life); primary progressive aphasia (PPA), a progressive language disorder, and its three subtypes: a) progressive non-fluent aphasia (PNFA), b) semantic dementia (SD), c) logopenic progressive aphasia (LPA). In PNFA the ability to generate words is lost, and speech becomes halting and ungrammatical. The ability to read and write also may be impaired. SD is marked by easy speech, but the words conveyed have less and less meaning. There is a tendency

to use broader general terms. Also language comprehension declines. The third PPA subtype, logopenic progressive aphasia (LPA), represents an atypical language presentation of AD-neuropathology.

In FTD the clinical presentation varies, depending on whether the frontal or temporal lobe is affected first. It is also noted that a considerable phenotypical overlap exists between FTD and amyotrophic lateral sclerosis (ALS). 30% of FTD patients develop clinical symptoms of motor neuron dysfunction. FTD represents a common cause of RPD, with an incidence and prevalence in some studies similar to that of AD and in which it is considered the second most often. SPECT or FDG-PET scans have aided in distinguishing between FTD and AD. There exists a pattern of hypometabolism in frontal association cortex, anterior temporal cortex, and anterior cingulate cortex in FTD as to a pattern of hypometabolism in posterior cingulate and posterior association cortex in AD. Cerebral MRI in CBS reveals asymmetric atrophy of the perirolandic cortex and basal ganglia, whilst PSPS has been associated with atrophy of the midbrain, superior cerebellar peduncle and frontal white matter, with lesser involvement of the frontal cortex.^{20,30-32}

CORTICOBASAL DEGENERATION

Corticobasal degeneration (CBD) is considered a 4R tauopathy, portrayed as an atrophy of the corpus callosum, but not so prominent in subcortical regions. Characteristic asymmetric focal atrophy of the frontal and parietal lobes is depicted, with a relative sparing of the brainstem and cerebellum. There is some loss of pigmented neurons in the substantia nigra. Pick-like inclusions, which are spherical corticobasal bodies may be found in neurons, mostly in the frontal and parietal cortex. They are tau-4R immunoreactive and can be stained with Gallyas. Some distinctive features of CBD are the numerous Gallyas- and tau-immunoreactive threads in the neuropil of affected gray matter structures and adjacent white matter as well as the swollen chromatolytic neurons (sometimes called “ballooned neurons”) and the presence of astrocytic lesions called “astrocytic plaques” with typical peripheral Gallyas- and tau-4R-immunoreactive inclusions in astrocytes.³¹

Progressive loss of the ability to control movement is noted, typically beginning around age 60. The most prominent symptom is apraxia (inability to use the hands or arms to perform a movement despite normal strength). Symptoms may appear first on one side of the body, but eventually both sides are affected. Sometimes language problems or trouble orienting objects in space are the first presenting symptoms with the movement disorders developing later.³¹

PROGRESSIVE SUPRANUCLEAR PALSY

As noted in other tau-related pathologies, progressive supranuclear palsy (PSP), also called Steele-Richardson-Olszewski syndrome, may progress as RPD. PSP is usually sporadic, even though autosomal dominant cases have been described. High PSP risk has been associated with the H1 haplotype of the tau gene (MAPT). Furthermore some of the MAPT mutations linked to chromosome 17, which have been known to be associated with familial frontotemporal dementia with parkinsonism (FTDP-17 and/or FTLT-tau) cause phenotypes resembling PSP. The motor symptoms associated with this pathology can easily be misdiagnosed as CJD. Cardinal symptoms are inability to coordinate the eyes in order to look up or down. Some patients experience this visual deficit as blurring. Loss of balance and gait instability resulting in increased likelihood of falls, slowness and stiffness of movements, similar to that seen in Parkinson disease, dysphagia, dysarthria, immobile, “masked face” and forced laughing or crying are also observed. The most characteristic gross finding in PSP is atrophy of the superior cerebellar peduncle due to loss of neurons in the dentate nucleus. Also the subthalamic nucleus is often atrophied and the substantia nigra is depigmented. The rest of the gross cerebral examination is unremarkable or may demonstrate mild cortical and midbrain atrophy with mildly dilated ventricles. Concerning the pathology of the lesions there are typical findings of “pretangles”, which are diffuse granular cytoplasmic inclusions immunoreactive for tau and also cytoplasmic, globose 4R-tau-immunoreactive inclusions. Tufted astrocytes, containing argyrophilic and tau-immunoreactive inclusions located toward the center of astrocytes, and oligodendroglial coiled bodies, which constitute tau-immunoreactive, rounded, cytoplasmic inclusions are found in glial lesions.^{20,31,33,34}

ARGYROPHILIC GRAIN DISEASE

Argyrophilic Grain Disease (AGD) is usually a sporadic entity, which may manifest with dementia and behavioral abnormalities such as emotional and mood imbalance. Tau pathology (silver stained or argyrophilic grains) at hippocampal formation and amygdala regions, as well as involvement of anterior medial temporal lobe regions with further extension to limbic cortices, certain subcortical nuclei, and brainstem tegmentum, are thought to be responsible for AGD symptomatology. These characteristic argyrophilic grains can be demonstrated with Gallyas silver stain, Bodian and Bielschowsky stains, and by a positive immunohistochemical reaction for tau protein, its 4R isoform, and p62 and are scattered throughout the neuropil in both cortical and subcortical areas. Most susceptible as aforementioned, are limbic structures,

mainly transentorhinal and entorhinal cortex. Non-specific pathologies can also be found in AGD, such as Gallyas- and tau-immunoreactive oligodendroglial coiled bodies (found also and in other tauopathies) and ballooned neurons (mainly in the limbic lobe). MRI findings are usually unremarkable, although mild medial temporal lobe atrophy may be seen. AGD is considered a distinct neuropathologic entity, which can present with Alzheimer disease-like pathologic changes (AT8-immunoreactive neuronal cytoplasmic inclusions) and may frequently coexist with another neurodegenerative disease.^{31,35,36}

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies (DLB) the second most common type of neurodegenerative dementia after AD, with estimated prevalences of 0.7% in individuals aged 65 and older. In addition to dementia, central features of DLB include fluctuations in attention, alertness or cognition, visual hallucinations, and parkinsonism. DLB patients also exhibit severe sensitivity to neuroleptic medications and autonomic dysfunction. Lewy bodies, the pathologic hallmark of DLB, consist of eosinophilic cytoplasmic inclusion bodies containing ubiquitin, α -synuclein neurofilament and other proteins distributed throughout the cortical and subcortical structures of the central nervous system (CNS) as well as in peripheral, and autonomic nervous systems.²²

PRION DISEASE

Prion diseases (PrDs) are a group of transmissible neurodegenerative disorders belonging to the category of transmissible spongiform encephalopathies. They are caused by infectious proteins called prions. PrDs occur in humans and many other species (scrapie in sheep and goats, bovine spongiform encephalopathy in cattle). There exists a variety of subgroups of human PrDs, which can be classified into three categories: sporadic (85–90%), genetic (10–15%), and acquired (1–3%). The sporadic form is represented by sporadic Creutzfeldt-Jakob (sCJD). The genetic types are subdivided into genetic CJD (gCJD), Gerstmann-Strüssler-Scheinker disease (GSS), and familial fatal insomnia (FFI). The acquired forms include variant CJD (vCJD) disease, Kuru and iatrogenic CJD (iCJD). The most common human phenotype of human PrDs is Creutzfeldt-Jakob disease (CJD). Concerning the pathophysiology of PrDs it is believed to be due to the propagation of abnormally conformed infectious proteins, the prions. This abnormal protein is named PrP^{Sc}, which is a mostly β -pleated sheet structure. In PrP^{Sc} the superscript Sc comes from scrapie and it is considered a conformational isoform of the normal cellular prion-related, α -helical struc-

tured, protein referred to as PrP^C. The normal PrP^C is a membrane-bound protein that is predominantly expressed in nervous tissue. It is thought to take part in neuronal development and function although its physiologic function is not entirely known. It has been shown that PrP^C participates in immunological homeostasis by regulating T cell receptor-mediated T cell activation. The pathogenic PrP^{Sc} acts as a template to convert PrP^C into PrP^{Sc} by misfolding it as PrP^C comes into contact with the abnormal protein. It is through this mechanism that prion infectivity takes place. In turn this new PrP^{Sc} becomes a new template for conversion of existing PrP^C, initiating a autocatalytic cascade reaction, that leads to neuronal destruction. Prions do not need nucleic acids or other co- factors to transmit disease. PrP^{Sc} is also characterized by resistance to nucleic acid destroying procedures and protease K. Diagnosis is definitely made neuropathologically. Tests assisting in the diagnosis are the electroencephalogram (EEG), cerebrospinal fluid (CSF) examination and cerebral MRI. The EEG findings consist of periodic sharp wave complexes (PSWCs), observed in approximately two-thirds of patients, but vary depending on disease phase. From the CSF examination, the presence of the 14-3-3 protein points to CJD, but this protein is a nonspecific index of neuronal injury, since it has been also detected in CSF of patients with non-CJD nosologies (metabolic encephalopathies, cerebrovascular disease, CNS infections, neurodegenerative dementias). Signal abnormalities in the basal ganglia and/or cortical ribbon on diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences as featured in the brain MRI aid in the diagnosis. This has been added to the differential criteria of probable CJD. Clinically, CJD patients demonstrate rapidly progressing mental decline and within a few weeks to several months there is onset of dementia, ataxia, and visual disturbances, while myoclonus occurs with disease progression.³⁷⁻⁴³

SPORADIC CREUTZFELDT- JAKOB

The incidence of sCJD is found to be about 1 to 1.5 per million per year. Officially reported national incidence rates vary from 0.48 to 2.23/million population/year. The age of onset has a large range that of 12 to 98 years with a peak age of about 68. In individuals younger than 30 years Creutzfeldt-Jakob disease is rare, and mostly is either acquired or genetic. In sCJD subgroup there is no gender predilection, although there seems to be a female preponderance. Sporadic PrD is probably the result of spontaneous folding of PrP^C into PrP^{Sc} or a somatic mutation in the prion protein gene (PRNP gene). The PRNP gene is located on the short (p) arm of chromosome 20. There are currently more than 30 known mutations in this gene.

GENETIC PRION DISORDERS

Genetic prion disorders include various subtypes, such as genetic Creutzfeldt-Jakob (gCJD), Gerstmann-Straussler-Scheinker disease and fatal familial insomnia (FFI). The genetic Creutzfeldt-Jakob (gCJD) has an autosomal dominant pattern of inheritance with a high age-dependant penetrance. Among mutation carriers of Libyan Jewish heritage the penetrance was calculated to be around 1% at age 40, only to reach close to 100% after the ninth decade of life. PRNP polymorphisms can also influence a patient's susceptibility to develop disease. Sometimes this group of disorders is called familial. Genetic CJD is associated with younger ages and a longer survival. Gerstmann-Straussler-Scheinker disease, usually appearing in the fourth to six decade, has a subacute progressive ataxic symptomatology. Parkinsonian features, cognitive decline, pyramidal signs, areflexia and dysesthesia also set in later. Fatal familial insomnia, with an onset at the fifth and sixth decade of life, manifests as severe, progressive insomnia, accompanied by dysautonomia, cognitive decline and motor signs.^{20,40}

ACQUIRED HUMAN PRION DISORDERS

Under the acquired human prion disease category are three main types of disorders; Kuru, variant Creutzfeldt-Jakob and iatrogenic CJD. Kuru and most cases of vCJD are orally acquired forms of PrD. The prions are uptaken through the intestinal epithelium and then accumulate in lymphoid tissue before being transported via sympathetic and parasympathetic nerves to the central nervous system. Variant CJD is different from sCJD. vCJD occurs in the younger age groups (mean age 27 years) and has a longer course with psychiatric symptoms being the first presentation of the disorder. It has been associated with bovine spongiform encephalopathy, which is believed to be the only directly transmissible animal encephalopathy to humans. Characteristic cerebral MRI finding of vCJD is the "pulvinar sign", which is due to a brighter posterior thalamus than the basal ganglia on T2-weighted sequences. Iatrogenic CJD has been caused by injection of growth hormone and gonadotrophin extracted from contaminated cadaveric pituitaries, dural grafts, corneal transplants, blood products or surgical instruments.^{40,42,43}

AUTOIMMUNE DEMENTIAS

Autoimmune RPDs encompass an enormous spectrum of pathologies, which display potentials for therapeutic intervention, in contrast to neurodegenerative diseases that have very limited treatment options. By promptly using immunomod-

latory agents or treatment for the underlying etiology, there exists a possibility of responsiveness and remission. The immunologically mediated dementias can be divided into two main categories depending upon the finding or not of specific antigens and antibodies. In the first category are paraneoplastic syndromes (limbic encephalitis) and nonparaneoplastic syndromes, such as anti-voltage-gated potassium channel encephalopathy (anti-VGKC-E), anti-glutamic acid decarboxylase (anti-GAD) syndrome, Hashimoto's encephalopathy (HE), systemic lupus erythematosus (SLE), and Sjögren's encephalopathy. The second autoimmune dementia group includes diseases, which are not associated with known specific antigens or antibodies (sarcoidosis, Behçet's disease, primary angiitis of the central nervous system).^{18,19,22,44}

In paraneoplastic syndromes the immune-mediated injury to the cerebral system is caused by shared antigens, which are expressed both in the nervous system (NS) and on tumor cells. Most of these syndromes do not respond to immunomodulatory treatments and persist unless the underlying neoplasm is treated. Patients with limbic encephalitis associated with anti-Hu antibodies usually have small cell lung carcinoma, while those with anti-CV2 antibodies (anti-collapsin response mediated protein 5) exhibit thymoma and with anti-Ma2 antibodies testis germ-cell tumors, breast and non-small cell lung cancer. Frequently, in younger women presenting with anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibody-associated encephalopathy ovarian teratoma is the underlying tumor. Anti-Ri (anti-neuronal nuclear antibody-2 (anti-ANNA-2) antibodies are related to breast cancer, ovarian malignancy, and small cell lung cancer.^{18,24,44}

Concerning non-paraneoplastic syndromes, the anti-voltage-gated potassium channel encephalopathy can be easily mistaken for CJD because of overlapping symptoms, biochemical testing results and neuroradiological findings. It is responsive to immunotherapy, so early diagnosis is imperative. Hashimoto's encephalopathy, which responds to high-dose corticosteroids, is correlated with increased circulating antithyroperoxidase or antithyroglobulin antibodies. It has a prevalence estimated at 2.1 in 100,000 subjects and female preponderance.^{44,45}

VASCULAR RPDS

Vascular disorders, such as bilateral thalamic infarcts, cerebral amyloid angiopathy, dural arteriovenous fistulas, cerebral venous sinus thrombosis and hypertensive encephalopathy, may present as a rapidly evolving dementia. More rare and usually fatal causes of vascular rpd are cerebrotretinal microangiopathy and subacute diencephalic angioencephalopathy. The latter being considered a deleterious type of posterior reversible encephalopathy.²⁴

POTENTIALLY REVERSIBLE RPDS

Reversible rapidly progressive dementia can be caused by a number of conditions such as bismuth, lithium, mercury and arsenic toxicity, alcoholic dementia, vitamin B₁, B₁₂ deficiency, niacin and folate deficiency, uremia, electrolyte abnormalities, normal pressure hydrocephalus, hyperviscosity syndromes. Infectious diseases may have a subacute course and appear as rpds. Among these are syphilis, fungal/viral meningoencephalitis (e.g., aspergillosis, herpes encephalitis), Whipple's disease (a *Tropheryma whippelii* infection), parasitic infections and Lyme disease.^{20,22}

CONCLUSION

Rapidly progressive dementias are not only a subtype of Alzheimer's disease, but a diverse compilation of heterogeneous entities, which warrant meticulous investigation, since some disorders can be treated, showing full remission, if therapeutic intervention is commenced immediately. This review touched only the "tip of the iceberg" of rapidly progressive dementias in an effort to increase awareness of these challenging conditions.

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