

Dementia:

A Brief Review

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Abstract

Dementia is an increasingly common diagnosis in our aging population, and the numbers are expected to rise exponentially in coming years. Alzheimer's disease alone now affects 4.5 million people in the US, while millions more are currently affected by vascular dementia, Lewy Body disease and frontotemporal dementia. Each of these is a distinct entity, though overlapping symptoms and comorbidities occur frequently. Within the past two decades research has progressed rapidly on multiple fronts, including epidemiology, etiology, pathology, diagnosis and treatment. It is important for clinicians to recognize early signs and symptoms of dementia, and to note critical differences among them. Dementia research has moved beyond description of symptoms and clinicopathological correlation to the elucidation of risk factors, the pathobiology of the disease process, and most important, to the first generation of dementia treatments. Our purpose here is to review the current state of knowledge and directions of research for the four major dementias noted above. We are entering an era of dementia care that will be based upon the identification of potentially modifiable risk factors and early disease markers, and the application of new disease-specific diagnostic tools and treatment modalities.

Key Words: Aging, dementia, diagnosis, treatment, pathology, Alzheimer's disease, vascular dementia, Lewy Body disease, frontotemporal dementia.

Introduction

THE CLINICAL PICTURE OF DEMENTIA as a deterioration in cognition in later years has been recognized for centuries but understood in its current formulation only for the past three decades. In the late 19th and early 20th centuries the shift in the conceptualization of mental illness away from moral causation towards disease etiologies extended to dementia, which was then conceived as an effect of aging and related to arteriosclerosis. Alzheimer's disease (AD) did not emerge as a distinct disease until the mid-20th century, which led to the recognition of multiple diseases of cognition with different etiologies.

The dementias can be categorized according to clinical presentation, neuropathology and/or etiol-

ogy. Research criteria have defined four major dementia groupings: Alzheimer's dementia; the Parkinson's group (including Lewy Body disease, dementia of Parkinson's and Alzheimer's dementia with Parkinson's); the frontotemporal group (including Pick's disease and Semantic dementia); and the vascular group (including large and small vessel disease). This review will focus on these four major categories of dementia.

Alzheimer's Disease

AD is the most common type of dementia in this country in clinical and autopsy surveys. Plaques and tangles had been observed by others prior to Alzheimer's investigations in the early 20th century. What intrigued Alzheimer about his original case, Auguste D. was the clinical presentation of paranoid delusions, and marked and progressive cognitive deterioration in a young patient (in her 50s) coupled with unusual pathological findings of "a clotting of fibrils...in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex." In the following decades efforts were focused on determining the biochemical composition of the plaques and tangles, their specificity and their correlation with the clinical picture. The advent of electron mi-

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This work was supported by grant NIH P50-AG005138, PI: M. Sano (all authors) and the VA Special Fellowship Program in Psychiatric Research/Neurosciences (CB).

croscopy in the 1960s ultimately revealed that amyloid, a substance familiar to pathologists since the 19th century, formed the central core of the plaque and that the tangles were neurofilaments.

Epidemiology

The current prevalence of AD in the U.S. is estimated at 4.5 million, a number expected to rise three-fold over the next 50 years as the population ages (1). Age is the strongest risk factor for AD. In Rochester, Minnesota the incidence of new AD cases between 1960 and 1975 was 66/100,000 per year at age 60–69, 409/100,000 per year at age 70–79, and 1,479/100,000 per year age 80 and older (2).

Risk Factors

In large population studies lower education has repeatedly been identified as a risk factor for the development of AD, while higher education correlates with older age at onset and possibly with lower overall risk (3). This pattern has been attributed to brain and cognitive reserve. Gender, marital status and living in an urban area have been suggested as possible risk factors for Alzheimer's, though further studies are needed.

There are three so-called "Alzheimer genes," autosomal dominant genes responsible for many familial cases of AD: Presenilin I, Presenilin II, and APP, which are thought to work through increased production of A β peptides. These genes are relatively rare, accounting for only 5% of cases, usually the early-onset variant. Most AD cases, particularly with onset after the age of 65, are "sporadic," i.e., occur in the absence of one of the causative genes and without an identified family history. The major susceptibility gene associated with sporadic late-onset AD cases is apolipoprotein e4 (APOe4). By age 85 those homozygous for the APOe4 allele (2% of the population) have a 50–90% chance of developing AD, and those heterozygous for the APOe4 allele (15% of the population) have a 45% chance, in contrast to the 20% chance in the general population (4).

Lifestyle, too, appears to play a role. Patients with more and more varied activities, including intellectual, physical, recreational and social activities, are less likely to develop AD (5). Social network size seems to modify the effect of brain pathology on cognition, as suggested in one clinicopathological study in which cognitive function remained higher for subjects with larger social networks (6). Medical risk factors for AD include head trauma as remote as several decades prior to onset of dementia, diabetes mellitus and clinical depression (7–9).

Pathobiology/Etiology

AD at the outset was identified by its unique pathology, the plaques and tangles that Alzheimer referred to as "a clotting of fibrils.... in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex." These pathological findings have driven the etiologic search through the identification of the biochemical and ultrastructural composition of the plaques and tangles. Several theories of pathogenesis are in debate. The amyloid cascade hypothesis (10), first articulated in 1992, is the dominant explanation for Alzheimer disease development. This hypothesis derives from what has been learned regarding plaque composition and AD pathogenesis over the past three decades. The fundamental abnormality is an excess of A β peptides brought about through either overproduction or diminished clearance. Patients with missense mutations in the APP, Presenilin 1 and Presenilin 2 genes are lifelong overproducers. It is postulated that late-life onset AD (aka "typical" or "sporadic" AD) results from a failure of metabolism and degradation rather than overproduction of A β . Secondary protective responses such as microglial activation, an inflammatory response and free radical formation are part of the toxic cascade induced by amyloid accumulation, which ultimately contributes to neuronal death, leading to the clinical manifestations of dementia.

Initially it was thought the plaque was necessary to initiate this toxic cascade, but it is now considered more likely that the A β monomers and oligomers initiate the process, long before organizing into plaques. These small molecules are thought to disrupt synaptic function even in apparently healthy neurons, accounting for the affected neurons' degeneration.

Signs and Symptoms

The clinical hallmark of Alzheimer's disease is memory impairment. A sense of memory failure, detected by the patient or a close relative, is usually the presenting symptom. Motor and sensory symptoms are absent until late in the course of the disease. However, other cognitive domains, such as language, praxis and recognition skills, are affected even early in the presentation.

Course

AD has a gradual and progressive course, typically 10 years from diagnosis to death. The advent

of cholinesterase inhibitors has had some effect on the course of disease for individual subjects, though population trends have been harder to demonstrate (11, 12).

Diagnosis

The diagnosis of AD remains a clinical diagnosis. A history of insidious onset with subtle and gradual progression, the presence of characteristic symptoms such as problems with retaining recent information or struggles to come up with words are suggestive of AD. Neuropsychological testing demonstrating a pattern of lower than expected performance on memory tasks and (usually) language, often with more semantic than phonemic difficulties (meaning that the patient has more difficulty generating words in specific categories, such as animals, than in generating words that begin, for example, with the letter F) is particularly informative in the earliest stages. The neurological exam shows lack of focal findings. Examination of blood or cerebrospinal fluid (CSF) is typically normal, with no evidence to suggest another etiology. Genetic testing is not part of the diagnostic work-up, since the most common susceptibility gene, APOe4, is not diagnostic. There are no biomarkers or imaging scans that are diagnostic or reliably predictive of who will develop AD. Imaging serves the clinical function of ruling out other etiologies that are visible on scan (e.g., stroke, tumor or rare dysgenesis). Structural imaging can provide evidence of atrophy, which is seen in virtually all cases of AD but is not specific to AD. Imaging of amyloid in live patients using radioactive ligands visualized on positron-emission tomography (PET) scan has been demonstrated at several sites. This has the potential to develop into a preclinical diagnostic marker, but is still in experimental stages.

CSF is not routinely obtained in the evaluation AD. There is a characteristic pattern of elevated CSF A β and hyperphosphorylated tau and total tau, but specificity is inadequate for this to serve as a diagnostic marker.

Treatment

A decade ago there was no treatment for Alzheimer's disease. Early treatment studies were predicated on the role of cholinergic neurotransmitters in memory function. Tacrine, the first cholinesterase inhibitor, introduced in 1992, proved too hepatotoxic for widespread use, but it did help create a paradigm shift for perceiving AD as a treatable disease. The first wave of Alzheimer's treat-

ment that began with Tacrine was followed by three other cholinesterase inhibitors with better safety and tolerability profiles: donepezil, rivastigmine and galantamine. All of these agents were approved for the treatment of mild-to-moderate severity AD after demonstrating the ability to forestall decline for 6–12 months. In 2003, memantine, an *N*-methyl-D-aspartate (NMDA) antagonist, was approved for the treatment of moderate severity AD. There are currently over 70 compounds in human trials, most targeting steps in the toxic amyloid cascade. These include interfering with A β aggregation, enhancing its metabolism, diminishing the production of toxic A β peptides and enhancing the enzymatic formation of non-soluble A β peptides. Other approaches interfere with tau hyperphosphorylation or target downstream responses to or byproducts of amyloid cascade: inflammation, oxidation and apoptosis.

In tandem with treatments, better measurement tools are being developed. Future treatment of AD will involve an assessment of risk factors and specific strategies aimed at ameliorating specific risks. Treatment efficacy will be monitored *in vivo* through amyloid imaging and serum/CSF biomarkers.

Vascular Dementia

Epidemiology

Vascular dementia is the second most common form of dementia after Alzheimer's disease among the elderly. Pooled prevalence from eight European countries was 1.6% for vascular dementia in subjects older than 65, compared to a prevalence of 4.4% for AD (13). A meta-analysis of the European studies on the incidence of dementia showed vascular dementia constituted 17.6% of all incident dementia (14).

Diagnosis

Vascular dementia may be the result of a single strategic infarct, multiple cortical or lacunar infarcts or a microvascular insult in which neither clinical symptoms of stroke nor infarcts by imaging are evident. Conversely, the mere presence of multiple (or strategic single) infarcts on imaging does not automatically imply vascular dementia. No specific pattern of cognitive deficits defines vascular dementia and neuropsychological testing cannot differentiate vascular dementia from Alzheimer's disease (15).

The impact of computed tomography (CT) and magnetic resonance imaging (MRI) on the diagno-

sis of vascular dementia is still undetermined. Number of infarcts, location, size and unilateral vs. bilateral distribution make quantification of lesions for the diagnosis of vascular dementia very difficult. A strategically placed infarct in the thalamus, caudate or hippocampus, however small, can cause marked cognitive decline. Some patients can be amazingly resilient despite having extensive infarcts on imaging: 20% of cognitively normal elderly had clinically silent lacunar infarctions on MRI (16). However, many such subjects had lower scores on neuropsychological testing and a higher risk of future dementia than their counterparts without lacunae (17).

Risk Factors

There is an elevated risk for subsequent dementia in patients who have had a stroke in comparison to controls without any evidence of a stroke (18). Diabetes and hypertension are stronger risk factors for vascular dementia than for Alzheimer's disease (19). The apolipoprotein e4 genotype is a risk factor for vascular dementia as well as AD (20).

Pathology

Dementia is a clinical syndrome that does not directly correlate with size, location or type of ischemic infarct. Microvascular pathology, including foci of pallor, neuronal loss and gliosis, has been found to play a causal role in dementia (21). Dementia was also found to be better correlated with the amount of hippocampal and cortical atrophy than with the volume of the lacunae (22). The role of microvascular ischemic changes in the white matter in cognitive decline is still an open question (23).

A British study found 11% of autopsied dementia cases had pure vascular dementia and another 20% had a combination of vascular dementia and AD (24). There is compelling evidence that vascular pathology and AD pathology are additive, and patients with a combination of both pathologies have a clinically more severe dementia.

Treatment

Cholinesterase inhibitors have been used successfully in patients diagnosed with vascular dementia (25). Galantamine and donepezil improved cognition in patients with probable and possible vascular dementia in comparison to placebo (26). Several clinical trials have shown that antihypertensive therapy prevents the onset of vascular dementia (27).

Dementia With Lewy Bodies

Dementia with Lewy bodies primarily affects the basal ganglia. Lewy bodies and Lewy neurites are pathologic aggregations of alpha-synuclein, a ubiquitously expressed synaptic protein that has been implicated in vesicle production (28). Lewy bodies also contain chaperone proteins and elements of the ubiquitin-proteasome system; however, these features are non-specific, in that they are also found in other neuronal inclusions, such as the neurofibrillary tangles found in AD. Immunohistochemical staining for alpha-synuclein has been shown to be the most sensitive and specific method for detecting Lewy bodies and can be used in a semiquantitative grading of severity of Lewy-related pathology (29).

Dementia with Lewy bodies is thought to be the third most common type of dementia in the elderly, accounting for 10–15% of cases at autopsy. In population-based studies of subjects aged 65 and older, the prevalence of dementia with Lewy bodies was found to be 0.7%, which is consistent with its rate of 10–15% of hospital-based cases at autopsy (30). The epidemiology of dementia with Lewy bodies is sparse; age and gender distribution and potential risk factors have yet to be defined.

Many patients with dementia with Lewy bodies also have Alzheimer's disease pathology, which alters the clinical presentation. Dementia with Lewy bodies' patients who also have many neurofibrillary tangles display more core clinical features of AD (31). Conversely, Lewy bodies also occur in more than half of all patients with sporadic and early-onset AD (32). The number of cortical Lewy bodies correlates only weakly with severity and duration of the dementia, whereas Lewy neurites are more closely linked with clinical symptoms (33).

Strong similarities have been found between dementia with Lewy bodies and Parkinson's disease dementia, both of which are clinically defined syndromes. The use of an arbitrary 1-year rule has been used to separate the disorders: onset of dementia within 12 months of parkinsonian symptoms qualifies as dementia with Lewy bodies; and dementia that begins more than 12 months after the onset of parkinsonian symptoms as Parkinson's disease dementia. However, there are no definite pathological criteria that distinguish the disorders.

Signs and Symptoms

The essential feature for a diagnosis of possible or probable dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude

to interfere with normal social or occupational function.

Fluctuations (waxing and waning of cognition, functional abilities and arousal from almost normal to markedly confused or hypersomnolent) are a core feature of dementia with Lewy bodies. Another core feature is visual hallucinations that are usually vivid, colorful and well-formed false perceptions of animals or people. Visual illusions and delusions, which typically have a paranoid quality, are also common. Auditory, tactile or olfactory hallucinations are rare. Other common neuropsychiatric features include depression, apathy and anxiety. Agitation and aggressive behavior tend to occur late in the course of the illness, if at all. Spontaneous parkinsonism unrelated to dopamine antagonist exposure is also a core feature of dementia with Lewy bodies. Signs and symptoms include tremor, bradykinesia, rigidity, shuffling gait, masked facies, stooped posture and retropulsion. Rapid eye movement (REM) sleep behavior disorder is common in dementia with Lewy bodies, as well as in Parkinson's disease (34). Affected patients act out their dreams by screaming and kicking, which can cause injuries to themselves and their bed partners. The dreams often have a chasing or attacking theme, and their content tends to match the exhibited behavior. Interestingly, REM sleep behavior disorder often begins years to decades before any other cognitive or motor symptoms develop.

Imaging

Functional imaging of the dopamine transporter yields information on the integrity of the nigrostriatal dopaminergic system and is abnormal in dementia with Lewy bodies and Parkinson's disease, but is normal in Alzheimer's disease (35). Low dopamine transporter uptake in the basal ganglia by PET or single-photon emission-CT (SPECT) imaging is therefore a suggestive feature of dementia with Lewy bodies. Currently there are no specific findings for dementia with Lewy bodies on laboratory testing of blood or CSF.

Treatment

Several studies have shown improvement of cognitive functioning and neuropsychiatric symptoms with cholinesterase inhibitors (36, 37). Theoretically, cholinergic stimulation should worsen parkinsonism, but in practice use of cholinesterase inhibitors rarely causes an increase of parkinsonian symptoms. Cholinesterase inhibitors have been shown to also help improve visual hallucinations,

but if they are not frightening to the patient, reassurance may be sufficient. Psychostimulants, levodopa/carbidopa and dopamine agonists have also been reported to improve cognition, apathy and psychomotor slowing. Management of fluctuations has been difficult.

Atypical neuroleptics like clozapine, quetiapine, risperidone or olanzapine have been slightly effective with delusions and agitation (38, 39). Depression and anxiety respond to selective serotonin reuptake inhibitors (SSRIs), and electroconvulsive therapy can be effective in some patients without affecting cognition. Many of the parkinsonian symptoms of dementia with Lewy bodies respond to levodopa/carbidopa and the dopamine agonists.

Clonazepam is the mainstay of therapy for REM sleep behavior disorder, with melatonin alone or as add-on therapy effective as well. Mirzapine and trazodone may improve insomnia. Continuous positive airway pressure (CPAP) therapy can be tolerated well by dementia patients and sometimes significantly improves alertness and cognition.

Frontotemporal Dementia

Signs and Symptoms

Frontotemporal dementia (FTD), also known as Pick's disease, encompasses a diverse group of clinical and pathological disorders. There are several distinct clinical presentations, most commonly behavioral changes, but a language disorder, usually in form of a progressive non-fluent aphasia, can be the main presenting sign. The most common clinical presentation of FTD is characterized by profound changes in personality and social conduct, including a decline in manners and social skills that are incongruent with the patient's premorbid behavior. Active antisocial and disinhibited verbal, physical and sexual behavior (e.g., tactlessness, offensiveness, disinhibited speech and gestures, incontinence and sexual exposure) are usually present at the initial presentation of the patient. Affected patients lack emotional warmth, empathy and sympathy and are indifferent to others. There is usually a quantitative change in customary behavior ranging either from profound apathy, inertia or passivity to overactivity or increased talking, laughing, singing, sexuality or aggression. Patients are typically unaware of or unconcerned about the social, occupational and financial consequences of their behavioral alterations. Cognitive deficits occur in the domains of attention, abstraction, planning and problem solving, reflecting an executive problem, whereas

memory, language and spatial functions are well preserved. Speech output may become spontaneous and limited to short phrases or stereotyped utterances. Echolalia is often observed. There often is a decline in personal hygiene and grooming. Overeating, altered food preferences and oral exploration of inanimate objects are frequently seen in patients with FTD.

It is increasingly recognized that varying degrees of frontal lobe dysfunction are present in motor neuron disease/amyotrophic lateral sclerosis (40), and 15% of cases of FTD have signs of motor neuron disease (41).

Pathology

At autopsy markedly gross atrophy of the frontal and temporal lobes is seen in FTD. On histologic examination the salient features include neuronal loss, micro-vacuolization and astrocytic gliosis centered on cortical layer II. The microtubule-associated protein tau has been found to be mutated in a family with FTD with parkinsonism (42). Immunohistochemical and biochemical techniques are now used to distinguish tau-related forms of FTD from non-tau forms, which mainly contain ubiquitin-positive intraneuronal inclusions (43).

Unfortunately, there is only moderate correlation between clinical and pathological findings: the same clinical syndrome can arise from two different pathologies and a single pathology can present as different clinical syndromes.

Imaging

MRI of patients with FTD often shows atrophy in the frontal and temporal lobes, which may be asymmetric (44). Functional imaging (PET or SPECT scans) have shown abnormalities in the ventromedial frontal cortex (often asymmetric) occur earliest (45). A longitudinal PET scan study showed that in the earliest stages FTD atrophy is limited to the frontal lobes and in later stages spreads into temporal and parietal cortices.

Epidemiology

Prevalence studies of FTD are inconsistent, giving ranges of 3.6–15.0 per 100,000 (46). There is a high familial occurrence of FTD (47). Some affected families from Great Britain, Australia and the U.S. have been traced to a common founder in North Wales (48). Genetic factors, specifically different alleles of apolipoprotein E, have been inconsistently linked to sporadic FTD (49, 50). The

distribution of FTD is equal between men and women. Age at onset is typically between 45 and 65, and does not differ between familial and sporadic cases (51). The mean duration of illness from onset to death is 4–6 years, with a range of 2–20 years. Patients with tau-positive frontotemporal lobar degeneration survive significantly longer on average than those who are tau-negative (52). Progression to death in FTD is much more rapid than in AD (average of 4.2 years and 6.0 years, respectively), a pattern repeated in the rate of cognitive decline on Mini-Mental State Examination (MMSE) (53). FTD with motor neuron disease has been shown to be a much more aggressive disease process than FTD without motor neuron disease (54).

Biomarkers

Total tau in CSF is increased in AD and other dementias, and is considered a general marker of neurodegeneration. There are conflicting results on the diagnostic accuracy of CSF total tau and A β ₄₂ for the diagnosis of frontotemporal dementia (55, 56). Recently developed immunoassays for the detection of CSF tau that is phosphorylated at specific epitopes (e.g., threonine 231) can distinguish well between Alzheimer's disease and FTD (57).

Treatment

There have been no large-scale double-blind, placebo-controlled clinical trials for the treatment of FTD, although several smaller trials (30 subjects at most) have been carried out. In these studies the use of the anticholinergic medication rivastigmine and other antidepressants have consistently been shown to improve behavioral symptoms but not cognition (58, 59).

Delirium: A Cautionary Note

Delirium and rapidly progressive dementia are easily confused with each other since they share many clinical features. Core clinical features of delirium include acute and fluctuating course, reduced level of consciousness, inattention and disorganized thinking. Delirium is thought to be caused by non-specific alterations in neurotransmitter and endocrine pathways, which subsequently alter cerebral metabolism. Changes in cognition, such as memory deficits, language disturbances or disorientation, are commonly seen in delirium. Some cases of delirium may evolve in a subacute time course and are often misdiagnosed as dementia. Delirium may be multifactorial and can be caused by almost any disease that affects

the brain. Its causes may include toxic-metabolic disturbances and traumatic, vascular, infectious, neoplastic, epileptic, nutritional or psychiatric pathophysiologic entities. In-hospital delirium complicates up to 20% of all admissions (60), and its likelihood increases with each decade of age. Full recovery can be expected in most cases, although reversal of delirium can take weeks. Persistent deficits in memory or other cognitive skills may remain in some cases. Abrupt behavioral decline in patients with Alzheimer's disease or other dementias is more often caused by a secondary process than by an abrupt acceleration of the degenerative process. Almost any systemic or neurologic illness can cause a superimposed delirium in a patient with preexisting dementia. Very common causes are urinary tract infections with or without sepsis, pneumonia, unwitnessed trauma with related pain or medication errors. Less common are stroke, seizures, meningitis or subdural hematoma.

Conclusion

The past two decades have witnessed a fundamental shift in our appreciation of the aging mind, away from the inevitability of "senility" and towards an appreciation of distinct diseases of late life that can impinge upon cognition. This shift in intellectual mindset has led to the identification of clear-cut dementia syndromes, etiologies and, most important, the first generation of treatments. The benign neglect of the dementia patient that characterized care for most of the past century has been pushed aside by the contemporary focus on diagnosis and treatment. Our purpose here is to review the current state of knowledge of the dementias most commonly encountered in clinical practice and provide an update on where current research is heading. In an aging population, clinicians will encounter increasing numbers of patients with dementia. In the 21st century these patients can now be approached with the hallmarks of clinical care identifying symptoms and syndromes, elucidating the underlying pathobiology and treating the etiologies.

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