Biomarkers of Alzheimer Disease: Current and Future Applications to Diagnostic Criteria


Abstract

ABSTRACT:

Purpose of Review:

This article reviews recent advances in imaging and fluid biomarkers for Alzheimer disease (AD) and their application to newly proposed diagnostic criteria across the continuum of AD.

Recent Findings:

There have been remarkable developments in neuroimaging markers for AD over the past decade, most notably the advent of positron emission tomography (PET) amyloid imaging using radiotracers that label fibrillar forms of amyloid-β (Aβ). Similarly, new research in CSF markers suggests CSF levels of Aβ1–42 and phosphorylated tau may be useful in the early diagnosis of AD and prediction of cognitive decline. The National Institute on Aging and the Alzheimer’s Association recently convened three workgroups to develop joint recommendations for new diagnostic guidelines across the spectrum of AD. These recommendations incorporate biomarkers and propose updated criteria for the previously recognized stage of AD dementia, the evolving definition of mild cognitive impairment, and a newly proposed concept of stages of preclinical AD.

Summary:

Recent advances in AD biomarkers have increased the ability to detect evidence of early AD pathology in vivo. These biomarkers have been incorporated into new diagnostic recommendations, but a number of challenges remain for the biomarkers to become widely applied in clinical practice.

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Key Points

- Biomarkers are conceptualized into two broad categories: (1) markers of amyloid-β accumulation and (2) markers of neuronal injury or neurodegeneration.
- Paradoxically, Alzheimer disease is associated with a decrease in CSF amyloid-β$_{1-42}$ that is generally thought to represent evidence that amyloid-β is polymerizing and depositing as fibrillar plaques. PET imaging of amyloid-β utilizes derivatives of histopathologic stains, such as thioflavins, that bind to fibrillar forms of amyloid-β.
- Recent studies suggest that amyloid PET is likely equivalent to demonstration of amyloid plaque pathology at autopsy.
- A negative amyloid PET study signifies few or no amyloid deposits and indicates that the likelihood of cognitive impairment due to Alzheimer disease is low.
- The most important concept to recognize in considering the high image-to-pathology correlation is that amyloid positivity does not reliably distinguish clinical diagnoses.
- Increased levels of CSF tau and phosphorylated tau have also been demonstrated to predict progression to dementia in subjects with mild cognitive impairment and are already elevated in clinically normal mutation carriers in autosomal dominant familial Alzheimer disease.
- The characteristic pattern of fluorodeoxyglucose abnormalities associated with Alzheimer disease is bilateral temporoparietal hypometabolism.
- Convergent studies suggest that atrophy begins years before the diagnosis of dementia.
- Atrophy is not specific to Alzheimer disease.
- Amyloid might be necessary but not sufficient to result in Alzheimer disease dementia.
- The most common presentation of Alzheimer disease dementia is the amnestic form, which involves impairment in episodic memory (ie, the ability to learn and retain new information). However, some patients have initial involvement of other cognitive domains, such as language or visuospatial or executive functioning.
- Alzheimer disease is increasingly recognized as a continuum.

Alzheimer Disease Pharmacologic Treatment and Treatment Research


Abstract

ABSTRACT:

Purpose of Review:

This article reviews marketed pharmacologic treatments for Alzheimer disease as well as their efficacy, effectiveness, adverse effects, and issues involved in their use, including duration of treatment, adverse events, and controversies. Current experimental drug development, including challenges to developing successful drugs for Alzheimer disease, are also reviewed and assessed.

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Recent Findings:

Cholinesterase inhibitors and memantine are the available pharmacologic treatment options. They show limited clinical effects over the shorter term for some patients, mild to moderate cholinergic adverse effects in a minority of patients, and potentially underappreciated toxicity over the longer term. No subsequent experimental drug in development has been successful thus far; there has not been a new drug marketed for Alzheimer disease since 2003.

Summary:

Cholinesterase inhibitors and memantine are marketed for the treatment of Alzheimer disease. Drug development programs aimed at new targets, including the amyloid-β cascade, have been unsuccessful thus far despite their designs to detect very small or minimal clinical effects from the experimental drugs. Marked advances in preclinical science nevertheless support a basis for considerable optimism that effective interventions will be found soon.

Key Points

- The cholinergic hypothesis of memory impairment implies that cholinergic deficits are responsible for cognitive and behavioral changes in patients with dementia and age-related memory impairment, and that augmentation of central cholinergic function will improve cognitive function.
- Historically, the targeted cholinergic treatment approaches have included using (1) acetylcholine precursors; (2) direct cholinergic agonists; and (3) cholinesterase inhibitors.
- The most common adverse events due to cholinesterase inhibitors include nausea, diarrhea, vomiting, anorexia, and weight loss. Muscle cramps are common with donepezil.
- Early cholinergic effects are frequently related to the initial dosing and titration of the medications.
- Anorexia varies in incidence from 8% to 25% at higher doses of cholinesterase inhibitors compared with 3% to 10% in patients on placebo and may be dose related. The proportion of patients with weight loss in clinical trials ranges from 10% to 24% in patients taking higher doses compared to 2% to 10% of placebo-treated patients.
- An analysis of Canadian medical and prescription records showed that patients on cholinesterase inhibitors were hospitalized for syncope nearly twice as often as people with dementia who did not receive these drugs.
- Despite differences in mechanism of action and dosing levels, no evidence exists for efficacy differences between the three cholinesterase inhibitors. In a Cochrane review, the drugs are associated with an overall mean 2.4 points effect over placebo on the Alzheimer Disease Assessment Scale—Cognitive Subscale.
- A 23-mg extended release formulation of donepezil is intended to be used after a patient has been treated with 10 mg/d for at least 3 months and when the clinician is uncertain whether the patient is benefiting from the 10-mg dose.
- Cholinesterase inhibitors are not indicated for mild cognitive impairment, yet their use may be common practice. Clinical trials of cholinesterase inhibitors in MCI were not positive on their primary outcomes and showed an excess in adverse events.
- Memantine was approved by the US Food and Drug Administration in late 2003 for moderate to severe Alzheimer disease. The basis for approval was positive outcomes on two 6-month-long placebo-controlled clinical trials. In one trial cholinesterase inhibitors
were not allowed, and in another, patients had been taking donepezil for at least 6 months (over 2 years on average). A third trial did not show significant effects.

- Only one of three trials of memantine in mild to moderate Alzheimer disease showed significant improvement on the Alzheimer Disease Assessment Scale—Cognitive Subscale and global assessment. Memantine has not been approved by the US Food and Drug Administration for patients with mild Alzheimer disease.
- A Cochrane review concluded that memantine had a small beneficial effect in moderate to severe Alzheimer disease and was well tolerated.
- Adverse events with memantine are infrequent but can include headache, dizziness, confusion, somnolence, and infrequent hallucinations. In clinical trials, the frequency of gastrointestinal symptoms is less than placebo; diarrhea occurred half as often.
- Extracts from leaves of the *Ginkgo biloba*, or maidenhair, tree are widely sold in the United States as food supplements for which health claims are not permitted. A specific standardized extract, EGB 761, is approved by the formularies of Germany and France.
- *G. biloba* extract is also used as a memory enhancer in people without Alzheimer disease; however, clinical trials in older and younger adults who do not have cognitive impairment show mixed results at best.
- A Cochrane review that included 35 clinical trials reported inconsistent evidence that *G. biloba* had clinically significant benefits for dementia or cognitive impairment.
- A medical food is a food formulated for the dietary management of an illness that has distinctive nutritional requirements, and is intended to be used under medical supervision.
- A formulation of medium-chain triglycerides is marketed as a medical food for Alzheimer disease in the United States. Another medical food, marketed in late 2012 in Europe and Brazil, is a combination of compounds including uridine, choline, omega-3 fatty acids, phospholipids, B vitamins, and antioxidants, intended to enhance synaptic function and neurotransmitters, presumably improving cognitive function. Controlled trials of these two medical foods have not been positive.
- It is difficult to identify the individual patient who benefits from cholinesterase inhibitors or memantine because the outcome measures and mean changes on scale scores do not identify responders.
- Discontinuation of cholinesterase inhibitors has been associated with worsening of cognition and confusion in some patients in trials. Yet worsening of behavior and confusion do not appear common when the drugs are stopped in clinical practice. In clinical practice, 19% to 23% of patients continued to take donepezil or rivastigmine for more than 1 year, and about one-third discontinued the drugs within 2 months.
- In a withdrawal trial after maintenance treatment with donepezil for 2 to 3 years in severely impaired patients with Alzheimer disease, continuing donepezil was associated with better cognitive scores and activities of daily living. Many patients discontinued donepezil without difficulty, and only half of the patients assigned to continue donepezil actually continued treatment beyond the 1-year follow-up. Thus, the outcomes support decisions either to continue medication or to taper and discontinue it when physicians are uncertain of continuing benefit.
- Only three of 14 trials showed significant effects for cholinesterase inhibitors improving behavior; none of these effects was large. Trivial effects were reported in the more mildly cognitively impaired patients, but no effect was reported in the more severely impaired.
- Regulatory criteria for marketing symptomatic and disease-modifying therapies require demonstrating improvements in cognition and activities of daily living, overall improvements compared to placebo, and adequate safety.
- The gist of the amyloid cascade hypothesis is that amyloid-β deposition drives tau phosphorylation, tangle formation, and neuron death.

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There are several amyloid-β–targeted experimental approaches, including modulation of amyloid-β production, inhibition of amyloid-β aggregation, enhancement of amyloid-β degradation, and use of passive and active immunization to raise antibodies that target and remove amyloid-β.

The range of anti-tau therapeutic approaches under development include inhibiting tau kinases; enhancing phosphatase activity in an effort to enhance microtubule stability; blocking or inhibiting tau hyperphosphorylation, tau aggregates, and filament formation; and enhancing clearance of aggregates with drugs or antibodies.

Challenges to developing effective treatments for Alzheimer disease include the uncertainty and lack of validated drug and molecular targets and the ability to conduct efficient clinical development programs. Establishing validated drug targets requires greater understanding of the pathogenic processes leading to illness.

New Genes and New Insights from Old Genes: Update on Alzheimer Disease


Abstract

ABSTRACT:

Purpose of Review:

This article discusses the current status of knowledge regarding the genetic basis of Alzheimer disease (AD) with a focus on clinically relevant aspects.

Recent Findings:

The genetic architecture of AD is complex, as it includes multiple susceptibility genes and likely nongenetic factors. Rare but highly penetrant autosomal dominant mutations explain a small minority of the cases but have allowed tremendous advances in understanding disease pathogenesis. The identification of a strong genetic risk factor, APOE, reshaped the field and introduced the notion of genetic risk for AD. More recently, large-scale genome-wide association studies are adding to the picture a number of common variants with very small effect sizes. Large-scale resequencing studies are expected to identify additional risk factors, including rare susceptibility variants and structural variation.

Summary:

Genetic assessment is currently of limited utility in clinical practice because of the low frequency (Mendelian mutations) or small effect size (common risk factors) of the currently known susceptibility genes. However, genetic studies are identifying with confidence a number of novel risk genes, and this will further our understanding of disease biology and possibly the identification of therapeutic targets.

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Key Points

- Although cases of Alzheimer disease inherited in a Mendelian fashion are rare (accounting for approximately 1% of cases), genetic factors are likely to play an important role in all forms of the disease.
- Studying large populations with sensitive techniques has allowed the identification of several new genes consistently associated with Alzheimer disease risk. However, the overall magnitude of the risk conferred by each of these is small, and therefore the clinical relevance of these findings is as yet undefined. Nonetheless, study of the pathways through which these genes contribute to Alzheimer disease pathology is an avenue toward the identification of potential therapeutic targets.
- Although substantive disease-modifying interventions do not yet exist, these advances have enabled definitive diagnosis of familial Alzheimer disease and therefore can have significant effects on patients and their families in terms of understanding the illness, its inheritance, and its prognosis. Furthermore, this progress allows for the possibility of presymptomatic testing in unaffected at-risk subjects. Therefore, clinicians should have a thorough understanding of the phenotypes and of testing that is available.
- The existence of these groups of familial Alzheimer disease families of specific ethnic and geographic origins indicates that inquiring about patients’ ancestral origins can be informative.
- In a retrospective chart review comparing clinical features between 32 patients with familial Alzheimer disease due to PSEN1 mutations and 81 patients with nonfamilial early-onset Alzheimer disease, those with PSEN1 mutations tended to be younger (42 versus 56 years of age at onset), more likely to have memory complaints as the presenting feature (84% versus 58%, with nonfamilial cases frequently presenting with visuospatial and language deficits) and more likely to experience significant headaches, myoclonus, gait abnormalities, and pseudobulbar affect. The presence of such features in a young-onset case of Alzheimer disease when the family history is unavailable should prompt the clinician to consider genetic testing.
- Because the pathogenicity of identified variants in PSEN2 (and other familial Alzheimer disease genes) is not always clear, caution needs to be exercised when interpreting results of genetic testing with patients and their families.
- Trials to prevent familial Alzheimer disease by administering experimental medications to asymptomatic mutation carriers are in development and should commence in 2013.
- In humans, APOE is highly polymorphic; the APOE*E3 allele is the most common, followed by the *E4 allele, which is in turn more common than the *E2 allele. The *E3, *E4, and *E2 alleles, which differ in only one or two amino acids, have been reproducibly shown to have differential effects on risk of late-onset Alzheimer disease, with *E4 conferring a greater risk than *E3, which in turn confers a higher risk than the *E2 allele, with odds ratios between approximately 4 for heterozygous and approximately 15 for homozygous carriers of the *E4 allele.
- There is ample convergent evidence for ApoE as a potential therapeutic target for disease-modifying interventions in Alzheimer disease.
- The prevalence of the *E4 allele in the population varies depending on ethnicity but is typically in the range of 15% to 20%. Among people with Alzheimer disease, the prevalence is around 50%, again depending on the specific population being studied. The increased risk conferred by the *E4 allele is generally thought to be a three- to fourfold
increase, and the lifetime risk of developing Alzheimer disease in someone with this polymorphism is 50% among those who live to be 80 years of age.

- Although hundreds of genes have been implicated or studied at some point over the past 20 years in relationship with Alzheimer disease, only recent, large-scale studies and rigorous statistical analyses (including correction for population stratification) have allowed the identification of robust and replicable genetic risk factors for Alzheimer disease.
- Ten Alzheimer disease–associated variants explain approximately 20% of the total variation of risk and approximately 33% of the risk attributable to genetic effects.
- Because of the small effect size (for common variants) and low frequency (for rare variants), the advances in genetics still have very limited clinical utility.

Nonpharmacologic Treatment and Prevention Strategies for Dementia

Yaffe, Kristine MD; Hoang, Tina MSPH. CONTINUUM: Lifelong Learning in Neurology. Volume 19(2) Dementia. April 2013: p 372–381.

Abstract

ABSTRACT:

Purpose of Review:

Epidemiologic studies can provide critical evidence to inform the timing and duration of nonpharmacologic interventions. Although more studies are needed to further determine long-term efficacy, the evidence supporting modifiable risk factors for prevention is compelling, and prevention strategies that incorporate multidomain nonpharmacologic factors may have the most impact.

Recent Findings:

Epidemiologic studies have identified a number of promising nonpharmacologic factors that have the potential to lower the risk of developing dementia.

Summary:

Potential modifiable strategies for dementia prevention include cardiovascular risk factors; lifestyle risk factors such as physical, cognitive, and social activity as well as nutrition, smoking, and alcohol use; and sleep quality. Results of randomized controlled trials for the treatment of cardiovascular risk factors have not been consistent, while interventions that increase physical, cognitive, and social activity have demonstrated protective effects for dementia risk. Trials of single-nutrient dietary supplementation have also been conflicting, but focus on multinutrient supplementation shows promise. Observational data also indicate that sleep quality may be a modifiable risk factor for dementia prevention.
Key Points

- Cardiovascular risk factors (including hyperlipidemia, hypertension, obesity, and diabetes) are associated with increased risk of dementia.
- Results of previous treatment trials for hyperlipidemia and hypertension have been mixed, but additional randomized controlled trials are needed to understand the potential impact for dementia prevention.
- Epidemiologic studies indicate that physical activity may delay cognitive decline, and evidence from early randomized controlled trials supports these findings.
- Interventions that increase a patient’s cognitive and social activity may have the potential to serve as a buffer against the neuropathologic damage associated with dementia.
- Nutrient deficits have been associated with increased risk of dementia. Single-nutrient supplementation trials have not consistently demonstrated benefits, but results from multinutrient trials are promising.
- Smoking is associated with increased risk of dementia, whereas moderate alcohol use may have a protective effect.
- The evidence for sleep quality as a modifiable risk factor is preliminary, but observational studies support a possible role for treatment of sleep disturbances and sleep-disordered breathing.
- Epidemiologic studies can provide critical evidence to inform the timing and duration of nonpharmacologic interventions.
- Nonpharmacologic interventions could play a major role in reducing dementia prevalence, especially when their effects are considered collectively.
- The latest nonpharmacologic randomized controlled trials will test the efficacy of targeting multiple modifiable risk factors, and future interventions may incorporate both pharmacologic and nonpharmacologic methods.

The Clinical Problem of Neuropsychiatric Signs and Symptoms in Dementia

Burke, Anna MD; Hall, Geri PhD, ARNP, GCNS, FAAN; Tariot, Pierre N. MD.

Abstract

ABSTRACT:

Purpose of Review:

This article reviews behavioral signs and symptoms of dementia that can lead to increased mortality, excessive cognitive and functional disability, early institutionalization, and increased caregiver burnout.

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Recent Findings:

Almost all patients with a dementia will develop significant behavioral disturbances at some point over the course of their illness. These behavioral signs and symptoms rarely fit into usual diagnostic classifications or meet full criteria for a formal major psychiatric disorder.

Summary:

Treatment of behavioral signs and symptoms of dementia should include both pharmacologic and nonpharmacologic interventions. There are currently no treatments for these disturbances approved by the US Food and Drug Administration. Best judgment should be used in identifying dominant target symptoms and matching them to the most relevant drug class. Implementing nonpharmacologic interventions before the development of neuropsychiatric symptoms may prevent triggers related to a progressively lowered stress threshold and therefore is key in the treatment of all patients with a dementia.

Key Points

- Neuropsychiatric signs and symptoms in dementia are common, morbid, and distressing and occur in predictable clusters.
- The Neuropsychiatric Inventory trigger questions may be useful for detecting and tracking neuropsychiatric signs and symptoms in dementia.
- Neuropsychiatric signs and symptoms in dementia occur more readily as dementia progresses because of progressively lowered stress threshold.
- A systematic approach to help evaluate, manage, and treat neuropsychiatric signs and symptoms in dementia is helpful.
- No medication for treatment of neuropsychiatric signs and symptoms in dementia is approved by the US Food and Drug Administration, although this does not preclude clinician judgment regarding clinical necessity.
- Cholinesterase inhibitors and memantine are approved by the US Food and Drug Administration for treatment of dementia due to Alzheimer disease and may mitigate neuropsychiatric signs and symptoms in dementia.
- There is no first-line recommendation for medications to treat agitation without psychosis.
- Atypical antipsychotics may be first-line treatment for clinically significant psychosis but should be discontinued if ineffective.
- Predictable triggers for neuropsychiatric signs and symptoms in dementia can be identified.
- Refer to basic precepts for care of people with dementia.

The Diagnostic Evaluation of a Patient With Dementia


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Abstract

ABSTRACT:

Purpose of Review:

This review outlines a practical approach to the history, mental state, neurologic examination, and laboratory tests in the diagnosis of dementia.

Recent Findings:

Proposed new diagnostic criteria for Alzheimer disease recognize that nonamnestic presentations with symptoms that predominantly affect language, visuospatial abilities, or executive function may occur, particularly with onset before the age of 65. New criteria assign greater likelihood to diagnosis if progressive cognitive decline is documented through serial assessment, or if biomarkers are supportive. In patients aged 80 or older, more than one cause of dementia is often present, for example, Alzheimer disease plus vascular dementia. Clinical diagnostic criteria for non-Alzheimer dementias are evolving, particularly in areas such as frontotemporal dementia. Imaging and CSF biomarkers have been proposed in recent diagnostic criteria for Alzheimer disease. Although biomarkers can provide a higher level of certainty that Alzheimer pathology may or may not be present, biomarkers for non-Alzheimer dementias are lacking.

Summary:

The availability of biomarkers does not replace or diminish the need for a thorough clinical evaluation. A structured clinical approach helps to define the diagnosis and collects information essential for establishing a comprehensive care plan for patients with dementia and their families.

Key Points

- It is useful to determine the patient’s degree of insight into problems, because this will influence his or her acceptance of elements of a care plan.
- Symptoms that point to a major memory problem include asking questions repeatedly; forgetting details of conversations, appointments, and plans; not paying bills on time; and not recalling the details of TV shows or movies. These types of problems need to be distinguished from complaints that are usually blamed on memory but reflect age-associated cognitive changes.
- The clinician should always inquire about activities that could pose significant safety risks in the setting of dementia.
- Behavioral symptoms are common in patients with dementia, may provide diagnostic clues, and should be considered when formulating a treatment plan.
- The goals of cognitive testing are to document performance of memory and other key cognitive domains, to define areas of strength and weakness that may support a diagnosis, and to help stage the severity of dementia.
- The term “memory impairment” is often used loosely in relation to Alzheimer disease. The major feature of memory impairment in Alzheimer disease is episodic memory, which depends on the structural integrity of the hippocampus and allows us to encode and remember where or when something happened.
- Focal findings consistent with stroke, or a gait disorder not explained by other factors, may support a cerebrovascular contribution to dementia.

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In cases in which a decision about dementia could substantially alter the patient’s life (eg, a patient who is still working) or in which there are legal questions (eg, competency to manage assets), detailed neuropsychological evaluation can strengthen the clinical diagnosis and provide sensitive indices of the degree of impairment.

Mild Cognitive Impairment


Abstract

ABSTRACT:

Purpose of Review:
The term mild cognitive impairment (MCI) is used to describe older subjects with demonstrable cognitive impairment who have not crossed the threshold for dementia. Because patients with MCI have an increased risk of developing dementia, especially Alzheimer disease (AD), there is significant interest in the clinical characterization of these subjects and in understanding the pathophysiology of the transition from MCI to AD.

Recent Findings:
The MCI syndrome, as an expression of an incipient disorder that may lead to dementia, is extremely heterogeneous and may coexist with systemic, neurologic, or psychiatric disorders that can cause cognitive deficits. Recent clinical criteria were designed to take into account the different forms of clinical presentation of the syndrome, and introduced the possible contribution of biomarkers to the clinical diagnosis. Bedside diagnosis of MCI can be difficult, since patients who report having cognitive problems may have normal scores in global cognitive scales or in brief neuropsychological instruments.

Summary:
This article presents the evolution of the clinical concept of MCI, the operationalization of its current definitions, the development of biomarkers that can help to identify an underlying neurodegenerative process as the etiology of the syndrome, and its proposed treatments.

Key Points

- Patients with mild cognitive impairment are at risk of developing dementia, especially Alzheimer disease.
- The mild cognitive impairment syndrome is not restricted to memory deficits, and these patients can present with a much broader cognitive syndrome, which may not include memory impairments.
- The prevalence of mild cognitive impairment in the general elderly population ranges from 2% to more than 20%.

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The mild cognitive impairment syndrome with memory-only deficits is less prevalent than mild cognitive impairment with a much broader cognitive syndrome in the general population.

The mild cognitive impairment syndrome, as an expression of an incipient neurodegenerative disorder that may lead to dementia, is extremely heterogeneous and may coexist with systemic, neurologic, or psychiatric disorders that can cause cognitive deficits.

Approximately 20% of patients with diagnosis of mild cognitive impairment return to normal cognition on follow-up examination.

Patients with mild cognitive impairment can present with mild deficits in instrumental activities of daily living.

Increased CSF phosphorylated tau and decreased Aβ-42 protein levels increase the short-term risk of conversion to Alzheimer disease in mild cognitive impairment patients.

Decreased metabolism in temporal-parietal regions, including the precuneus (detected with fluorodeoxyglucose-PET), and increased amyloid deposition (detected with amyloid ligands) increase the risk of conversion to Alzheimer disease.

Biomarker studies should be interpreted with caution. Although they indicate that Alzheimer disease pathology is present, they do not provide information about when the patient will progress to an Alzheimer disease clinical dementia.

There are no therapies that can prevent the conversion from mild cognitive impairment to Alzheimer disease. However, studies conducted with cholinesterase inhibitors have shown a modest cognitive improvement in subjects with mild cognitive impairment treated with these medications compared to placebo.

Understanding and Treating Vascular Cognitive Impairment


Abstract

ABSTRACT:

Purpose of Review:

It is estimated that one in three people will experience a stroke, dementia, or both during their lifetime. The goal of this article is to assist clinicians in the identification and treatment of patients with vascular cognitive impairment (VCI). To that end, we will discuss the scope and definition of VCI; how this definition can be applied in clinical practice; VCI epidemiology and pathogenesis, its clinical features, and assessment; and prevention and treatment of this disorder.

Recent Findings:

During the past decade, we have gained a more complete understanding of clinical manifestations of VCI (eg, the importance of executive function and memory), what it looks like pathologically (eg, the role of cerebral amyloid angiopathy, microinfarcts, and “silent” strokes), and how VCI
relates to other disease processes (eg, co-occurrence with Alzheimer disease). A recent American Heart Association and American Stroke Association guidance statement clarified the construct of VCI, including the severity of cognitive and behavioral dysfunction contained under the definition of VCI and the presence of both “pure” and “mixed” VCI forms. VCI treatments approved by the US Food and Drug Administration are still lacking, and challenges remain regarding how to convert promising observational study findings that link stroke and coronary heart disease risk factors to cognitive impairment and dementia into evidence-based preventive methods.

Summary:

VCI is a common contributor to cognitive impairment in later life. Because the risk of Alzheimer disease may be heightened by the same risk factors that make us susceptible to stroke and coronary heart disease, these borderlands merit careful consideration as we strive to preserve cognitive function throughout the aging process.

Key Points

- Vascular cognitive impairment is defined as “a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain.” Vascular cognitive impairment therefore encompasses all of the potential levels of cognitive severity, from its mildest form detectable by neuropsychological assessment to full-blown vascular dementia.
- Strokes and Alzheimer disease often occur concomitantly and pose risks for one another.
- Vascular dementia has been considered the second leading cause of progressive and irreversible dementia after Alzheimer disease.
- Neuropathologic studies show an additive influence or correlation between Alzheimer disease pathology and cerebral infarction in the manifestation of cognitive impairment.
- Traditionally, survival in Alzheimer disease is longer than in vascular dementia or mixed dementia, but survival varies according to the patient’s age, race or ethnic group, and severity of cognitive impairment.
- Lowering blood pressure in patients who do not have cognitive impairment can reduce the risk of subsequent cognitive impairment, whereas lowering blood pressure to preserve cognition among patients who already have cognitive impairment remains unproven as a successful strategy.
- Risks for stroke, such as hypertension, hypercholesterolemia, hyperhomocysteinemia, elevated body mass index and fat intake, atrial fibrillation, diabetes mellitus, cigarette smoking, and metabolic syndrome, are now considered risks not only for vascular cognitive impairment but also for Alzheimer disease.
- In addition to clinically manifest strokes, vascular cognitive impairment may have an underpinning of subclinical cerebrovascular brain injury.
- At the microscopic level of the brain, the neurovascular unit is a conduit for neurovascular dysfunction.
- The most common form of vascular cognitive impairment is the subcortical type.
- Regional white matter integrity (whether on the side of a recent acute cerebrovascular brain injury or not) and thalamic density have been suggested as possible pathogenetic links for risk of vascular cognitive impairment based on diffusion tensor imaging and voxel-based morphometry study, respectively.
- The clinical picture of patients with vascular cognitive impairment may be linked with the volume and location of the underlying pathology.
Individual patients may show both focal neurocognitive deficits associated with the location of their stroke lesions and a more diffuse pattern, depending on the presence and extent of subcortical cerebrovascular brain injury. Given the lack of clarity from research studies and the fact that many elderly patients with dementia and cognitive impairment have multiple sources of brain pathology, clinicians should be cautious about basing their clinical diagnosis solely on the pattern of cognitive deficits. The pattern of memory impairment in vascular cognitive impairment can be qualitatively different from that of Alzheimer disease. It is important to screen for depressive symptoms in patients with suspected cerebrovascular brain injury. Reliably differentiating functional disability due to physical (eg, hemiparesis) versus cognitive and behavioral impairment is a specific difficulty in examining for impaired activities of daily living after stroke. There is reasonable evidence to suggest blood pressure–lowering therapy as a useful intervention for people who are middle-aged and younger elderly (Class IIa, Level of Evidence B); however, the usefulness of lowering blood pressure for those over 80 years of age for the prevention of dementia is not well established (Class IIb, Level of Evidence B). Further robust and consistent studies are necessary to provide clear, concise answers to important research questions regarding the role of vascular risks for cognitive impairment and dementia. Currently no drugs that have gained wide acceptance for use in practice have been approved by the US Food and Drug Administration for the treatment of vascular cognitive impairment. The failure of the cholinesterase inhibitors to successfully treat patients with vascular dementia on an across-the-board cognitive and functional basis has raised questions regarding whether there is an absence of cholinergic deficits in pure vascular dementia.

Incorporating New Diagnostic Schemas, Genetics, and Proteinopathy into the Evaluation of Frontotemporal Degeneration


Abstract

ABSTRACT:

Purpose of Review:

Within the continuously growing body of knowledge in the field of dementia, frontotemporal degeneration stands out in importance as the second most common cause of early-onset dementia.
after Alzheimer disease. Neurologists, neuropsychologists, and speech pathologists are particularly involved in the diagnosis and recognition of etiologies for patients with deficits in frontal lobe function and language.

Recent Findings:

The recent discovery of a novel mutant gene (C9ORF72) and the new nomenclature adopted for subclassification have significantly promoted our understanding of this disorder.

Summary:

This article relates the most recent consensus criteria for diagnosis of the two forms of frontotemporal degeneration (ie, behavioral and primary progressive aphasia variants) to basic neurologic principles and remind clinicians of the neuropsychiatric and neuroradiologic components that clarify frontotemporal degeneration diagnoses and guide management.

Key Points

- Diagnostic criteria now allow for a subclass of possible behavioral variant frontotemporal degeneration, which represents earlier stages of illness in which neuropsychological testing in high-functioning patients may not reveal executive deficits or in which neuroimaging does not yet support regional atrophy or regional dysfunction.
- Consultation with speech and language pathologists (especially in mildly affected cases) is invaluable, as some of the features of the primary progressive aphasias are difficult to identify without subspecialty training.
- Unlike probable behavioral variant frontotemporal degeneration, activities of daily living are maintained well into illness, except those related to language (eg, using the telephone).
- The description of logopenic progressive aphasia is new to the consideration of frontotemporal degeneration syndromes, and its inclusion remains somewhat controversial because of the Alzheimer disease pathology found in a fair number of logopenic variant cases.
- Semantic variant primary progressive aphasia (formerly known as semantic dementia) may be most easily distinguished by the loss of single-word meaning.
- Given the early age of onset of patients with frontotemporal degeneration, it is important to rule out neoplasm or other mass lesion.
- When structural imaging is inconclusive or the patient is still within the first few years of symptom onset, functional neuroimaging may help rule in the diagnosis (but cannot rule it out).
- Any unexpected or abrupt changes in symptomatology, new seizure onset, losses of consciousness, or falls with head trauma could warrant reimaging.
- It may be more helpful for the examiner to monitor the quality of performance for sustained attention; response variability, set shifting, and mental flexibility; monitoring and utilization of feedback; and sequencing than to concentrate on total scores for the instruments administered. Clinicians may wish to administer the Frontal Assessment Battery along with the Mini-Mental State Examination or the Montreal Cognitive Assessment as a fairly time-efficient way to glimpse the frontal lobe functions listed above.
- Symptoms of behavioral variant frontotemporal degeneration may precede, follow, or coincide with the onset of motor neuron symptoms.
- A referral to a genetics counselor should precede any collection of samples for genetic testing, unless the testing is done for research purposes and the results will not be disclosed to participants.
• Not all patients with family histories of similar symptoms, Parkinson disease, ALS, or primary psychiatric disorder have positive genetic testing.
• Positive family histories are most commonly elicited from patients with behavioral variant frontotemporal degeneration and frontotemporal degeneration with ALS and infrequently from patients with semantic dementia.
• The most common clinical phenotype associated with both MAPT and GRN mutations is behavioral variant frontotemporal degeneration, although a more varied clinical spectrum has been associated with GRN mutations, including diagnoses such as primary progressive aphasia and corticobasal syndrome.
• A major recent discovery identified C9ORF72, which appears to be the most common genetic abnormality both in familial behavioral variant frontotemporal degeneration (11.7% of cases) and ALS (23.5%).
• There is no CSF biomarker specific for the diagnosis of frontotemporal degeneration.
• The clinical trial yielding the highest level of evidence (through a randomized, double-blind, placebo-controlled crossover trial) in frontotemporal degeneration used trazodone at a dose of 100mg orally three times a day.
• One challenge for the clinician is to determine whether the behavioral and psychiatric symptoms of dementia are a manifestation along the anxiety spectrum (including obsessive-compulsive features) or represent agitation.
• Acetylcholinesterase inhibitors developed to improve symptoms of Alzheimer disease do not seem to be effective in managing symptoms of frontotemporal degeneration, perhaps because the cholinergic neurons in the nucleus basalis of Meynert are relatively spared in frontotemporal degeneration.
• Regardless of the medication prescribed, it behooves the clinician to make sure that the caregiver understands the symptoms targeted by the medication so that there can be an ongoing dialogue about whether the medication is working or is still indicated.
• One of the most influential changes in behavioral management has been the shift away from medical models of treatment for behavioral and psychiatric symptoms of dementia toward the reconceptualization of behavioral and psychiatric symptoms of dementia as responsive behaviors.
• Because patients with early-onset dementia may have children with a wide range of ages who are active informal caregivers, there is a need for groups that support children and emphasize balance between growing up and caregiving.

Dementia in the Oldest Old


Abstract

ABSTRACT:
Purpose of Review:
This article discusses some of the unique features of dementia in the oldest old, including some of the most common diagnostic challenges, and potential strategies to overcome them.

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Recent Findings:

Advances include new insight into the role of common risk factors and the effects of multiple underlying neuropathologic features for dementia in the oldest old. In addition, this article contains the latest age-specific normative data for commonly used neuropsychological tests for the oldest old.

Summary:

The oldest old—people aged 90 years and older—are the fastest-growing segment of society and have the highest rates of dementia in the population. The risk factors, diagnostic challenges, and underlying neuropathologic features of dementia are strikingly different in the 90-years-and-older population compared to younger elderly. Special consideration of these unique features of dementia is necessary when evaluating oldest-old subjects with cognitive impairment.

Key Points

- The oldest old—people aged 90 years and older—are the fastest-growing segment of the society. By 2050, the oldest old will account for 2% of the US population.
- The oldest old have the highest incidence and prevalence rates of dementia in the population. Women have a higher prevalence of dementia than men. The incidence of dementia is similar in men and women and doubles approximately every 5 years after the age of 90.
- Risk factors for cognitive decline and dementia appear to change with age. In the oldest old, some risk factors are no longer relevant (eg, the apolipoprotein E ε4 allele) and some may have a protective effect (eg, hypertension).
- Cognitive performance declines with age even in subjects who are cognitively intact. Using age-specific normative data is crucial to avoid overestimation of cognitive impairment in oldest-old subjects.
- Vision and hearing impairment, frailty, and fatigue are common in oldest-old patients and can easily affect cognitive performance. Modifications to neuropsychological testing to accommodate these limitations are important to avoid misdiagnosis of dementia in oldest-old subjects.
- Alzheimer disease remains the most common pathology underlying dementia. However, the relationship between Alzheimer disease pathology and cognitive impairment weakens in the oldest old. Alzheimer disease pathology is also common in nondemented oldest old; about half of nondemented subjects have high levels of Alzheimer disease pathology at death.
- Vascular pathology is the second most common pathologic feature in the oldest old. Although the number of large-vessel infarcts decreases in the 90-years-and-older population, the prevalence of microinfarcts increases significantly in the oldest old.
- Accumulation of multiple neuropathologic features is common in the oldest old. The odds of dementia increase with increasing number of pathologies.
- Approximately a quarter of oldest-old people develop dementia without obvious underlying pathology.
- The oldest old are particularly susceptible to the unwanted side effects of pharmacotherapy; therefore, the “start low, go slow” approach and nonpharmacologic alternatives are important in the treatment of dementia.