Neurodegenerative Disorders of Aging: The Down Side of Rising Longevity

by John C. Morris, MD

The exact causes of neurodegeneration remain the focus of much investigation, but as nerve cells have some of the highest metabolic rates in the human body, one possibility links the lifetime “wear and tear” on these cells.

The United States (U.S.) population is undergoing a demographic revolution, with ever-growing numbers of adults living to age 65 and beyond such that the proportion of older adults in our society will increase from 13% in 2010 to 20% by 2040. All-race U.S. life expectancies, also increasing, already are 81 years for women and 76 years for men. There thus not only are many more older adults, they are living longer. Longevity brings increasing risk for neurodegenerative disorders, in which nerve cells (neurons) deteriorate and die.

AD already is a public health menace of the highest order, as the disease costs over $200 billion a year in the U.S. to care for its victims. It is by far the most common cause of dementia and, alone among the leading causes of death, lacks any effective therapy to materially slow or halt its course or to prevent its occurrence. It is a disorder unique to humans, as the most highly developed brain cells in higher order association cortex are most vulnerable to the disease process. As synapses and neurons gradually degenerate and die, their brain functions become gradually impaired and eventually lost.

Hence, the clinical presentation of the illness is reflected in the gradual onset and inevitable progression of the clinical manifestations of the deteriorating function of higher order association cortex: impaired memory, insight, attention, reasoning, language, and personality. As the disease progresses over the typical 7-10 years from onset to death (AD is universally fatal), eventually other brain areas are affected and the individual loses the ability to control sphincters, swallow, talk, or walk. It is so feared because the affected individual gradually but
steadily loses their autonomy and their very personhood, becoming ever more dependent and disabled.

Alzheimer disease currently is diagnosed based on its dementia syndrome: the gradual onset and progression of memory and other cognitive impairment, representing a decline for that individual from previously attained abilities, which is sufficient to interfere with the performance of accustomed activities. However, this diagnostic process is time-consuming and inexact; it is estimated that 50% of all individuals with AD dementia remain to be diagnosed by their physicians. Our faculty outpatient group, the Memory Diagnostic Center at Washington University Medical Center in St. Louis, is working to improve dementia diagnosis and management and to translate these improvements to our clinician colleagues throughout Missouri. In addition, our Knight Alzheimer’s Disease Research Center (ADRC) is conducting translational research to not only enhance the tools needed to accurately identify persons with AD but also to develop and evaluate mechanism-based therapies that one day may provide truly effective therapy for this disorder.

The accompanying series of articles is contributed by members of the Memory Diagnostic Center and the Knight ADRC. The article written by Erik Musiek and Suzanne Schindler is focused on a high level but very practical approach to the clinical diagnosis and management of AD dementia. The paper from Suzanne Schindler, Jonathan McConathy, Beau Ances, and Marc Diamond extends the current clinical approach to the coming era of diagnostic testing for AD using molecular imaging and fluid biomarkers, which in the very near future are expected to allow us to move from a syndromic diagnosis to one that is supported by objective test results.

Not all dementia is caused by AD. In older adults, Parkinson disease also is a leading cause of dementia. The article by Allison Willis summarizes the most modern clinical approach to Parkinson disease and its management, and points to its role as another important neurodegenerative dementing disorder. In younger adults (e.g., <60 years), frontotemporal dementia (FTD) is equal to AD as a cause of dementia. The paper by Nupur Ghoshal and Nigel Cairns reviews this fascinating and informative group of disorders and illustrates how specific clinical disease phenotypes reflect the specific brain regions involved. Taha Bali and Timothy Miller link the FTD disorders to the spectrum of neurodegenerative motor neuron diseases (e.g., amyotrophic lateral sclerosis) and discuss a new genetic basis for this linkage. Finally, the previously under-recognized conditions that are characterized by rapidly progressive dementia (in contrast to the gradual onset and progression of neurodegenerative dementias) are reviewed by Robert Bucelli and Beau Ances as more state-of-the-art diagnostic tools are available for their recognition. The importance of this group of disorders is that some are responsive to selected therapies and thus the dementia potentially is reversible.

We provide these articles in hope that they will benefit the readers of Missouri Medicine with a better appreciation of the neurodegenerative dementing disorders and related diseases. Better recognition ultimately will translate to better management, and better management will lead to better understanding of the responsible etiologies. In this way, we hope together to develop the clinical infrastructure that will result in truly effective treatments for these devastating diseases.

Acknowledgments

This series of articles would not have been accomplished without the organizational and editorial efforts of Krista Moulder, PhD, who expertly oversaw the entire conceptual and writing process. Linda Krueger provided excellent editorial assistance. Dr. Morris, Dr. Moulder, and Ms. Krueger are supported by National Institute on Aging grants P50AG05681, P01AG03991, P01AG026276, and U19AG032438.
Alzheimer Disease: Current Concepts & Future Directions

Erik S. Musiek, MD, PhD & Suzanne E. Schindler, MD, PhD

Abstract

Alzheimer disease (AD) is the most common cause of dementia in individuals over age 65, and is expected to cause a major public health crisis as the number of older Americans rapidly expands in the next three decades. Herein, we review current strategies for diagnosis and management of AD, and discuss ongoing clinical research and future therapeutic directions in the battle against this devastating disease.

Introduction and Epidemiology

Alzheimer disease (AD) is a major public health problem in the United States and throughout the world. AD is the most common cause of dementia in people over the age of 65 and affects well over five million people in the United States (U.S.), including 110,000 people in Missouri. As the population ages, the number of American AD cases is projected to explode to 16 million by 2050, with an estimated annual cost of 1 trillion dollars. Aside from its devastating effect on affected individuals, AD also takes an enormous toll on caregivers, as caring for an Alzheimer’s patient has been associated with financial stress, depression, and increased risk for other medical problems. Moreover, while the numbers of deaths caused by the other major killer diseases in the U.S., such as heart disease, cancer, and HIV, have declined in the past decade, deaths caused by AD continue to increase (See Figure 1). While no curative therapies have yet been developed, diagnosis of AD early in the disease course is important in that it allows for optimal initiation of symptomatic therapy and lifestyle modification, provides the opportunity for the patient to make plans for her own future, and may someday facilitate the preservation of cognition through disease-modifying therapy.

Alzheimer disease is characterized clinically by an insidious onset and progressive decline of cognitive function, usually beginning with impairment of short term memory. The classic neuropathologic hallmarks of AD are amyloid plaques, which are formed by aggregation of the amyloid-beta (Aβ) peptide, and neurofibrillary tangles, which consist of misfolded tau protein (See Figure 2). Autopsy data demonstrate that amyloid plaques begin forming in the brain many years before the onset of any symptoms. Amyloid plaques likely initiate a pathological cascade of events, including tau misfolding, oxidative stress and synaptic injury that eventually lead to neuronal death.
and brain dysfunction. The medial temporal lobe, which plays a critical role in short term memory, is particularly affected in AD, explaining the early characteristic deficits in short term memory.

Age is the strongest risk factor for the development of AD. At age 65, 13% of Americans have AD and by age 85 over 45% are affected. Family history impacts AD risk, as individuals with an affected first degree relative (parent or sibling) have a two-three fold increased risk of developing AD. The vast majority of AD cases (99%) are sporadic, following no clear Mendelian genetic inheritance pattern. For sporadic AD, Apolipoprotein E (APOE) genotype is the major genetic susceptibility factor. APOE ε3 is the most common genotype in the overall population. In comparison to ε3, the ε2 allele imparts a decreased risk of AD, while the ε4 allele is associated with an increased risk. Two copies of the ε4 allele increase the risk of AD by 12-fold, and about half of all AD patients harbor at least one APOE ε4 allele. Recent evidence suggests that APOE is important in Aβ metabolism and amyloid plaque formation. Several other genes have recently been identified which modulate the risk of sporadic AD, and ongoing research is investigating their functions. In less than 1% of cases, a dominantly inherited familial form of AD is caused by mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2). Disease-causing mutations have been shown to influence production of Aβ peptide. Most patients with dominantly inherited AD present with symptoms between age 30-50.

Proposed environmental risk factors for AD include traumatic brain injury, low educational attainment, diabetes, obesity, and cardiovascular risk factors such as high cholesterol and coronary artery disease. Women have a significantly higher lifetime risk of AD than men, due in part to their longer average lifespan. Caucasians have lower rates of AD than do African Americans or Hispanic Americans, though the reason for this is unknown. Exercise, healthy diet (including high intake of fish, fruits, and vegetables), and remaining cognitively involved and stimulated are all associated with lower risk of AD, although it has not been proven that any specific food or activity can prevent AD or slow its course. While a variety of over the counter agents have been purported to bolster cognition or prevent AD, most of these have not been rigorously tested, and none have been proven efficacious in randomized controlled clinical trials in humans.

### Phenotype

The typical clinical course of AD dementia is characterized by an insidious onset and slow progression of symptoms over years. The initial symptoms are often related to short term memory deficits, such as repeating questions or statements, forgetting appointments, misplacing items, or forgetting important details about events. In the early stages, these symptoms can be very subtle, and can manifest simply as slight decline in the patient’s ability to perform complex tasks. Problems with orientation, including confusion about the date or getting lost, are often seen early in AD dementia. As the disease progresses, patients often require assistance managing finances, shopping, driving, and keeping track of their schedule. In moderate AD dementia, patients depend heavily upon a caregiver and often require assistance.
maintaining their hygiene. At the end stages of AD dementia, patients are completely dependent on others, may forget the identities of their closest friends and family members, and may become bed-bound. The proximate cause of death is usually aspiration or infection.

**Diagnostic Methods**

The goals of the initial history, exam, laboratory work-up and imaging are 1) to rule-out causes of cognitive dysfunction not related to neurodegenerative disease and 2) to diagnose the presence or absence of a neurodegenerative disease based on the history, exam, any available psychometric data, labs and imaging data.

**History and exam**

The majority of the history should be obtained from a collateral source familiar with the patient’s daily life, as patients with cognitive impairment often have poor insight into their condition. The focus of the history should be on changes in the patient’s memory and thinking over time, as individuals vary greatly in their baseline abilities and habits. For example, are there certain abilities the patient has lost because of a decline in memory or thinking? Although most people can describe occasional lapses in memory, the history should probe for problems that are consistent and worsening over time. The AD-8 Dementia Screening Interview can be helpful, as it is sensitive to early cognitive changes associated with dementia and is brief, reliable, and available at no cost.

Common causes of cognitive dysfunction, particularly in the elderly, include depression and cognitive side effects of medications. It is important to directly ask the collateral source and patient about symptoms of a possible mood disorder because this information is often not immediately offered. The patient’s medication list should be scrutinized for psychoactive medications, such as benzodiazepines, anti-cholinergics, pain medications, and sleep aids that can cause or exacerbate cognitive dysfunction. Any association between the patient’s symptoms and alcohol consumption should be assessed. A family history of dementia can suggest the patient is at higher risk, especially in cases of early onset dementia. Finally, it is helpful to screen for obstructive sleep apnea (OSA), as OSA is associated with a higher rate of developing dementia and is often treatable. In patients with dementia, disrupted sleep-wake cycles are common and may be a major cause of caregiver stress.

The patient should undergo a screening neurological examination. Verbal fluency should be noted, as certain dementias are associated with prominent language difficulties. A neurologic exam should be performed to exclude focal signs, which might suggest stroke, demyelination, or a mass lesion. The examiner should also evaluate for increased muscle tone, tremor, slowness, abnormal gait, or poor balance, which may indicate a Parkinsonian syndrome. Most patients presenting with AD dementia have normal neurological exams except for evidence of cognitive impairment.

Psychometric testing can be helpful in some circumstances: 1) Quantifying a subtle deficit 2) Identifying which cognitive domains are affected 3) Providing a baseline against which future testing can be compared. In addition to the informant-based AD8, short instruments that can be administered to the patient in an office setting include the Mini Mental State Exam (MMSE), the Short Blessed Test and the Montreal Cognitive Assessment (MOCA, available at [www.mocatest.org](http://www.mocatest.org)). Interpretation of the tests must take into account educational level and any other factors that could affect the result, including decreased vision or hearing. A poor result on a test does not definitively diagnose dementia, but may lend support to the diagnosis. Complete evaluation performed by a licensed clinical neuropsychologist can be helpful in complex or atypical cases.

**Laboratory work-up and imaging:**

Since cognitive dysfunction may be caused by a large number of medical and neurological causes, a thorough evaluation to rule-out potentially treatable causes of dementia is needed. Blood tests to be ordered include...
blood chemistries (including liver function test and creatinine), complete blood count, thyroid stimulating hormone (TSH) and vitamin B12 level. In patients with early onset dementia, atypical dementia, or risk factors for sexually transmitted infections, it is also appropriate to check a rapid plasma reagin (RPR) and HIV antibody. At this time, it is not recommended that patients routinely be tested for APOE isoform or mutations associated with autosomal dominant Alzheimer’s disease.11

Practice parameters developed by the American Academy of Neurology recommend that brain imaging be performed on all patients with cognitive decline.12 A brain MRI both with and without contrast and including diffusion sequences is the most sensitive test. In patients with renal dysfunction the MRI can be performed without contrast. In patients who cannot undergo an MRI because of contraindications such as an implanted pacemaker, a head CT is acceptable but may not visualize more subtle findings. In cases of early onset dementia, atypical dementia or dementia of uncertain diagnosis, cerebrospinal fluid (CSF) and advanced imaging techniques may help clarify the diagnosis. These methods, including recently-developed tests for CSF Aβ and tau and PET-based imaging of brain amyloid plaques (amyloid imaging) allow for more specific and earlier diagnosis of AD. These tests are described further in the article entitled, “Advances in Diagnostic Testing for Alzheimer Disease.”

Patients with onset of dementia prior to age 60, rapid progression of dementia over months, or atypical forms of dementia may benefit from seeing a dementia specialist for further evaluation. Symptoms of atypical dementias may include early and prominent changes in behavior, language, visuospatial function or movement.

Management

Two classes of medications are FDA approved for the treatment of AD. Acetylcholinesterase inhibitors, including donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) are approved for symptomatic treatment of mild to moderate AD, and are intended to support memory by increasing the amount of available acetylcholine in the synaptic cleft by preventing its breakdown. All of these agents are available in generic forms for oral administration. These drugs can cause gastrointestinal side effects including nausea, vomiting, and diarrhea, as well as cardiovascular effects such as bradycardia. Donepezil is the most commonly prescribed, and is usually initiated at 5 mg daily for four to six weeks, then increased to 10 mg daily if tolerated. A 23mg dosage has been approved that may impart slight increases in efficacy, but it is associated with significantly higher risks of gastrointestinal side effects. Rivastigmine is available as a patch (not yet available as a generic), which may have lower incidence of nausea and can be helpful in more advanced AD patients who have difficulty remembering to take their pills.

The second class of FDA approved AD medication is N-methyl-D-aspartate (NMDA) glutamate receptor antagonists. Memantine (Namenda®) has been approved for use in moderate to severe AD. The initial postulated mechanism of action was reduction in glutamatergic excitotoxicity, but several studies have shown this is not the case. Memantine is also a non-competitive antagonist of serotonin 5HT3 and nicotinic acetylcholine receptors, and activates dopamine D2 receptors, though it is unclear if these actions mediate its effects. Side effects from memantine are quite rare, but can include confusion, drowsiness, headache, agitation, insomnia, and hallucinations.13 Generic memantine is not yet available in the U.S. Generally, memantine is added to the regimen after the patient has already reached a stable dose of an acetylcholinesterase inhibitor, though it can be used as monotherapy in patients who do not tolerate acetylcholinesterase inhibitors.

In more advanced disease, patients can become aggressive and violent. Atypical antipsychotic medications are sometimes indicated, but should be used carefully because of studies showing that antipsychotics increase mortality in elderly dementia patients. Benzodiazepines should also be used with great caution, as they can cause paradoxical increases in agitation, as well as dependence and withdrawal. Non-pharmacologic strategies for behavioral management include keeping the environment consistent, non-threatening, and calm, avoiding cues which may precipitate agitation, and simplifying the daily routine. Depression and anxiety are very common in AD patients, and physicians and caretakers must be vigilant for these conditions and treat them appropriately. The Alzheimer’s Association (www.alz.org) provides a wealth of valuable resources for both patients and caregivers, and in many areas provides a variety of informational sessions, support groups, and referral services.

Regarding safety, assessment of driving skills by a professional is recommended for any individuals with notable cognitive impairment, and restricting or eliminating driving is encouraged if there is substantial concern. Firearms in the home should be secured. Patients may need oversight with meals and with their medications, as well as
with personal finances, and in some cases access to banking and investment accounts must be restricted. Patients with moderate disease may not be safe to leave unattended at home, as dangerous situations such as leaving water or a gas stove on are quite common. As the disease progresses, patients are likely to wander, and may need constant supervision, as well as a SafeReturn® bracelet, available through the Alzheimer’s Association.

Future Directions

It is an exciting time for research in AD and other dementias, as over 70 clinical trials of experimental therapies are ongoing. Large-scale clinical studies of dementia and healthy aging, including the Memory and Aging Project at Washington University and the nationwide Alzheimer's Disease Neuroimaging Initiative, have provided critical insights into how AD begins and progresses, and have shown that the pathological process leading to clinical AD begins at least a decade prior to the onset of any cognitive symptoms. With the advent of new biomarkers, very early and even presymptomatic diagnosis is now possible. Unfortunately, at this point in time, all efforts at therapeutic intervention in the symptomatic disease course have failed. Thus, it appears that treatment strategies for AD must be initiated as early as possible in the disease course, to prevent ongoing neurodegeneration. Ideally, asymptomatic individuals could be screened and treated presymptomatically, thereby preventing or delaying dementia. At present, there is no such therapeutic “prevention” option and thus presymptomatic screening cannot be encouraged.

The majority of current experimental therapeutic strategies for AD focus on eliminating Aβ, as Aβ accumulation appears to precede neurodegeneration and symptom onset by years, and likely initiates the pathogenic cascade in AD. Passive immunization with antibodies that bind Aβ is an attractive paradigm, and a number of monoclonal antibodies are in various stages of clinical trials in humans. Small molecule inhibitors of beta- and gamma-secretases, enzymes which play critical roles in the generation of Aβ, have also been developed, and several are in late stage clinical trials. As mentioned above, there have been several well-publicized failures of anti-amyloid therapies in phase III clinical trials in the past few years, including both Aβ antibodies and gamma secretase inhibitors. It is likely that these failures were due to multiple issues including poor efficacy of the drug in reducing Aβ levels, treatment too late in the disease process, and dilution of the trial population with non-AD dementias. A second generation of therapeutics is now entering phase III trials, and clinical trial methodology is being refined, so there is hope that an effective Aβ-targeted therapy will be identified. The first clinical trials providing presymptomatic therapy for rare early onset familial AD patients are beginning this year, including the Dominantly Inherited Alzheimer’s Network (DIAN) treatment trial.

Table: 8-item Informant Interview to Differentiate Aging and Dementia

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<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>1. Is there repetition of questions, stories, or statements?</td>
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<td>2. Are appointments forgotten?</td>
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<td>3. Is there poor judgment (e.g., buys inappropriate items, poor driving decisions)?</td>
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<td>4. Is there difficulty with financial affairs (e.g., paying bills, balancing checkbook)?</td>
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<td>5. Is there difficulty in learning or operating appliances (e.g., television remote control, microwave oven)?</td>
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<td>6. Is the correct month or year forgotten?</td>
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<td>7. Is there decreased interest in hobbies and usual activities?</td>
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<td>8. Is there overall a problem with thinking and/or memory?</td>
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TOTAL AD8 SCORE

*Adapted from Galvin et al, “The AD8: A Brief Informant-Interview to Detect Dementia”, Neurology. 2005;65:559-564.
and the Alzheimer’s Prevention Initiative (API). The DIAN trials will employ two distinct anti-AB antibodies and API will use another AB antibody.17, 18 While they focus on rare autosomal dominant AD, success of these trials may set the stage for future preventative trials in sporadic (late onset, non-familial) AD. Indeed, a third trial, entitled the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) study, will evaluate presymptomatic therapy with anti-AB antibodies in 70+ year old participants with no cognitive symptoms, but with amyloid imaging evidence of presymptomatic AD. Thus, the era of presymptomatic anti-amyloid experimental therapy is at hand (but far from ready for clinical use), and these important trials likely will have major impact on the AD field for years to come.

While these initial trials all employ therapies targeting AB, non-AB therapies are also in development, including agents which aim to reduce tau aggregation, suppress neuroinflammation, prevent oxidative injury, augment neuronal metabolism, and modulate APOE levels. Small molecule activators of γ7 nicotinic acetylcholine receptor and nasally-inhaled insulin have entered clinical trials, both of which have been show to enhance cognition in AD in smaller studies, providing new possible avenues of symptomatic therapy.19, 20 Intravenous immunoglobulin (IVIG) has shown promise in stabilizing cognition in small cohorts of symptomatic AD patients, though the mechanisms are unclear, and a larger trial has reportedly failed. Preclinical studies in mouse models have identified dozens more potential therapeutic targets, which await validation in humans but will hopefully keep the drug development pipeline stocked for years to come.

Conclusion

Alzheimer disease is a devastating neurodegenerative disease which affects millions of people, and threatens to become a public health crisis in coming years. Great strides have been made in our understanding of the underlying disease mechanisms and in early diagnosis, and the first experimental efforts to treat AD presymptomatically are beginning, potentially heralding a new era of AD management.

References

Advances in Diagnostic Testing for Alzheimer Disease

by Suzanne E. Schindler, MD, PhD, Jonathan McConathy, MD, PhD, Beau M. Ances, MD, PhD & Marc I. Diamond, MD

Abstract
The diagnosis of Alzheimer disease (AD) dementia is based primarily on the clinical history and examination, but advances in understanding the pathophysiology of AD have led to new diagnostic methods. When used appropriately, the tests can provide strong positive or negative evidence AD dementia. This article described which patients may benefit from additional testing using Cerebrospinal Fluid (CSF) biomarkers, amyloid imaging, quantitative structural magnetic resonance imaging (MRI), and fluoro-deoxyglucose positron emission tomography (FDG-PET).

Introduction
The development of biomarkers and imaging techniques for the diagnosis of Alzheimer disease (AD) has progressed considerably in the last several years. This article will describe the advanced diagnostic methods for AD that are currently available in clinical practice and when they are helpful.

A clear diagnosis of AD dementia can be helpful to patients in many ways. The diagnosis validates and explains the difficulties that patients have been experiencing and that caregivers have been noticing. Patients and caregivers may find comfort and support in educating themselves about the disease. Confirming diagnosis encourages patients and caregivers to join organizations, such as the Alzheimer’s Association, that offer resources to manage the illness. Knowledge of their loved one’s diagnosis may help caregivers to make plans that include choosing an appropriate living situation, completing legal paperwork and making a plan for supportive care. Patients with a clear diagnosis may also be more likely to start medications that help with the symptoms of disease.

Despite advances in diagnostic testing, AD dementia remains a clinical diagnosis. The available tests are not perfect and should be used by a clinician to help choose between diagnoses or, in some cases, to provide greater confidence in the diagnosis of AD dementia. There is no indication for testing in asymptomatic dementia.
individuals, particularly because we have no effective preventative therapy. A positive result also has not been demonstrated to inevitably result in dementia, and even if it did, it cannot predict the time frame within which the individual may develop symptoms, i.e. whether he or she will develop dementia in 1 year or 20 years. An asymptomatic individual who tests positive is likely to experience anxiety about developing dementia, but cannot significantly change their risk of dementia or predict when they will first manifest symptoms. Therefore, testing is not offered to asymptomatic individuals.

Indications for Referral and/or Advanced Diagnostic Testing

Alzheimer disease is a progressive neurodegenerative disease characterized neuropathologically by amyloid plaques, neurofibrillary tangles, and loss of neurons. The clinical syndrome of cognitive decline that accompanies AD pathology is termed AD dementia.1 Practice parameters developed by the American Academy of Neurology,2 as described by an article in this issue entitled “Alzheimer disease,” allow accurate diagnosis in many cases. The work-up consists of a detailed history from someone who knows the patient well, a screening neurological examination, routine laboratory testing, and brain imaging. The evaluation focuses on ruling out reversible causes of dementia and establishing a clinical history typical of AD dementia.

After a complete initial evaluation, it is still sometimes unclear whether a patient has AD dementia or some other cause of cognitive dysfunction. A referral to a dementia specialist may be indicated for a patient with unusual or complex cognitive problems, particularly if primary care physicians do not have the time or resources to perform a very detailed evaluation. A patient that falls into the following categories may particularly benefit from an evaluation by a dementia specialist and/or advanced diagnostic testing:

1. Early Onset Dementia

A patient younger than 65 with symptoms of dementia and no additional conditions explaining his or her cognitive decline may benefit from either cerebrospinal fluid (CSF) testing or an amyloid-PET scan to help support the diagnosis. Since AD dementia is unusual in patients before age 65,3 and because the diagnosis of AD dementia will likely have a more devastating impact on a younger patient’s life, a supporting laboratory test can reassure both the patient and clinician that the diagnosis is correct. Additionally, in patients with a strong family history of AD dementia and a very early age of onset (before age 55), genetic testing may be considered in cases with an appropriate pedigree demonstrating autosomal dominant inheritance over several generations.

2. Prominent Behavioral or Language Problems

A patient who develops prominent behavioral changes and/or language problems early in the course of disease may have a frontotemporal dementia (FTD). Additional history of the patient’s behavioral changes and a detailed examination of the patient’s language function are important. FDG-PET is sometimes used to evaluate patterns of regional hypometabolism and to help discriminate between dementia caused by FTD or by other diseases, including a rare “frontal variant” of AD4. When indicated, the presence of AD pathology can be established using either CSF testing or an amyloid-PET scan.

3. Prominent Visuospatial Dysfunction

A rare form of AD dementia, posterior cortical dysfunction, presents with prominent visuospatial problems.5 The patient’s eye exam may appear normal, but the patient may have deficits in processing visual information that can render him or her functionally blind. A detailed neurological examination is required to evaluate the extent of the visual deficits. A positive CSF test or an amyloid-PET scan supports the diagnosis of AD. Other causes of posterior cortical dysfunction include Parkinson disease and Creutzfeldt-Jakob disease.

4. Rapidly Progressive Dementia

Alzheimer disease dementia usually causes a very slowly progressive decline in memory and thinking and rarely results in an appreciable change from one week to the next or even one month to the next. When cognition rapidly worsens in a patient with pre-existing AD dementia, it may indicate a medical problem such as an infection. In a patient without pre-existing dementia, a sudden decline in memory and thinking over weeks to months may be caused by a number of different etiologies, some of which may be treatable. The work-
up is often complex and may require hospitalization (see article in this series on rapidly progressive dementia).

5. Uncertain Dementia

A patient with very mild memory changes consistent with AD dementia and no complicating factors usually has incipient AD dementia. Further testing is typically not necessary; instead, following the patient clinically over the next year or two usually provides information leading to a diagnosis. In a patient with very mild but consistent cognitive decline who has medical or psychiatric problems that complicate the diagnosis, further testing can help establish whether AD-related brain pathology is present. Positive CSF testing or amyloid-PET supports the diagnosis of AD, but does not rule out other contributors to cognitive dysfunction. Quantitative MRI allows evaluation for disproportionate cortical or hippocampal atrophy suggestive of AD or another neurodegenerative disease.

6. Individual Factors

Some patients may need a more certain diagnosis. For example, high functioning individuals with very mild AD symptoms may request confirmatory tests because an AD diagnosis would precipitate irreversible career changes (e.g. retiring, selling a company, etc.). The clinician must consider the degree of additional certainty that would be contributed by the test, and whether the results would definitely change an individual’s decisions. To date, insurance companies and Medicare usually do not cover such additional studies.

The new diagnostic tests for AD dementia have resulted from advances in our understanding of AD. We have learned that deposition of amyloid-β (Aβ) protein into neuritic plaques begins many years prior to the onset of symptoms and is accompanied by decreases in the 42 amino acid form of Aβ (A42) in CSF. Tau, a protein involved in neuronal structure, increases in the CSF prior to the onset of symptoms, possibly reflecting neuronal injury. Radiolabeled chemicals that bind amyloid in the brain have been developed that allow measurement of the total amount of amyloid in the brain via a PET scan. FDG-PET, which images the metabolism of the brain, can be used to evaluate the pattern of brain hypometabolism. Quantitative structural brain MRI can be used to evaluate for cortical and hippocampal atrophy.

Figure 1
Athena Diagnostics® is a commercial laboratory that performs the assays that provide a graphical interpretation of the results as consistent with AD.
due to neuronal death, which also begins prior to the onset of dementia.

**Cerebrospinal Fluid Biomarkers**

Cerebrospinal Fluid (CSF) biomarkers for AD require collection of the CSF via a lumbar puncture (spinal tap), a procedure which is very safe and reliable when performed by experienced personnel. CSF levels of three AD-related proteins are measured: Aβ42, tau, and tau phosphorylated at position 181. Patients with AD have low levels of CSF Aβ42 and high levels of CSF tau and phospho-tau, leading to elevated ratios of tau:Aβ42 and phospho-tau:Aβ42. Most patients with even very mild AD dementia have elevated ratios of tau:Aβ42 and phospho-tau:Aβ42. Athena Diagnostics® is a commercial laboratory that performs the assays (http://www.athenadiagnostics.com/content/test-catalog/find-test/service-detail/q/id/310) and provides a graphical interpretation of the results as consistent with AD (See Figure 1), not consistent with AD, and borderline. Some private insurance companies and Medicare may cover the costs of the lumbar puncture and CSF testing.

**Amyloid Imaging**

Several positron emission tomography (PET) tracers have been developed to non-invasively image fibrillary beta-amyloid plaques in the brain. One of these PET tracers, florbetapir (Amyvid™), is currently FDA-approved and commercially available and others are likely to be approved soon. The levels of radioactivity in the cerebral cortex measured through florbetapir-PET are correlated with the frequency of neuritic amyloid plaques at autopsy. Following intravenous injection of florbetapir, a PET scan is performed that is interpreted as either positive, indicating moderate to frequent neuritic amyloid plaques, or negative, indicating no to sparse neuritic amyloid plaques (See Figure 2).
positive scan supports the diagnosis of AD dementia, but is not diagnostic because a substantial number of older individuals have neuritic plaques but are cognitively normal. A negative scan makes the diagnosis of AD less likely, but does not completely rule it out. Florbetapir-PET is not currently reimbursed by the Centers for Medicare and Medicaid Services (CMS) or by most private insurance companies. Imaging centers that provide Amyvid-PET are listed at the following website: https://www.amyvidimagingcenterlookup.com/.

Quantitative Structural MRI

Nearly all patients evaluated for AD undergo structural brain imaging, usually MRI. Patients with AD usually have cortical and hippocampal atrophy. A number of commercially available software packages exist that can perform quantitative volumetric imaging analysis to determine whether an individual’s regional or whole brain volume is within the range of age- and education-matched normal older adults. Some neuroradiologists perform quantification of the degree of atrophy versus established norms using commercial packages or methods developed within the institution. Serial MRI also may be instructive, as AD is associated with progressive cerebral atrophy.

Fluorodeoxyglucose (FDG)-PET

The relative rates of glucose metabolism of different brain regions can be measured non-invasively with PET using the fluorine-18 labeled glucose analogue 2-deoxy-2-fluoro-D-glucose (FDG). FDG is intravenously injected and a PET scan is performed. Brain regions that are metabolically active preferentially take up FDG while brain regions with neuronal loss or synaptic dysfunction do not. The reader evaluates the scan to determine whether the metabolic activity is normal or whether some brain regions show evidence of hypometabolism. AD typically has a pattern of posterior temporal and parietal hypometabolism while FTD usually has frontal and anterior temporal hypometabolism. FDG-PET is used routinely for oncologic and neurologic imaging and is available at many PET imaging centers. Brain-FDG/PET is usually reimbursed by Medicare and private insurers when the clinical indication is to help differentiate between AD and FTD.

References


Disclosure

None reported.
Unravelling the Mysteries of Frontotemporal Dementia

by Nupur Ghoshal, MD, PhD & Nigel J. Cairns, PhD

Abstract

Frontotemporal dementia (FTD) is a clinical term that encompasses the neurodegenerative diseases that selectively affect the frontal and anterior temporal lobes of the brain. FTD, which is underdiagnosed in clinical settings, presents with behavioral changes or deficits in language. The last two decades have seen tremendous advances in the appreciation of the clinical assessment, genetics, and molecular pathology of this group of enigmatic diseases, thus offering hope for the development of rational therapeutic strategies.

Introduction

In 1892, Arnold Pick, a Czech neurologist, described a 71-year-old patient with progressive language and behavioral difficulties. Neuropathologic examination of the brain revealed focal atrophy of the frontal and anterior temporal lobes and characteristic inclusion bodies, called Pick bodies. Pick’s disease subsequently has been recognized as a prototypical form of what now is known as “frontotemporal dementia” (FTD), but because of the rarity of Pick’s disease there were minimal advances in the understanding of this family of disorders until the work of Arne Brun and colleagues in the 1980s. Since that time there have been tremendous advances in our understanding of the clinical features, genetics and molecular pathology of FTD. Although caused by several distinct pathological entities, they all have a predilection for involvement of the frontal and temporal lobes of the brain and thus have similar clinical phenotypes.

FTD is the second most common cause of dementia in individuals under age 65, after Alzheimer disease (AD). About one-third of all cases of FTD appear to be familial. Typical age at onset of symptoms is between 45-65 years, but may be as young as 30 and as old as 80 years. Men and women are both affected. The FTDs have a worldwide distribution.

In the last decade there have been huge strides made in the classification of these clinically and neuropathologically heterogeneous diseases (See Figure 1). Of particular note, it is now appreciated that there is an overlap between amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease, and FTD such that ALS and FTD represent different
ends of an FTD spectrum (see ALS paper by Drs. Bali and Miller in this Science of Medicine Series). Many individuals with ALS will develop the clinical features of FTD, and persons with FTD are at greater risk of developing ALS. The most common cause of FTD/ALS is a mutation in the C9ORF72 gene. Salient features of these FTD disorders are focal atrophy of the frontal and anterior temporal lobes, neuronal loss, gliosis, and the pathological aggregation of misfolded proteins, either in neurons or glial cells, or both. Although it now is possible to determine the underlying pathology in nearly all cases of FTD, there currently is no effective treatment of this group of diseases.

Clinical Phenotypes

In contrast to AD where cognitive deficits (particularly memory loss) predominate, FTD is characterized by language dysfunction or by a behavioral syndrome (See Table 1). There are three clinical subtypes of FTD:

1) behavioral variant FTD (bvFTD)
2) Semantic Dementia (SD)
3) Progressive Nonfluent Aphasia (PNFA)

PNFA affects women 2-to-1 over men while for bv FTD and SD, men are affected 2-to-1 over women. The bases for these gender differences are unknown.

Behavioral variant FTD (bvFTD) individuals have florid personality changes and a dramatic loss of insight into their behaviors early in the disease course. They are socially inappropriate and may be disinhibited (hyperorality and sexual disinhibition), apathetic, and less empathetic. Mental rigidity, obsessions, and compulsions are also seen in these patients. While language dysfunction may develop, there is relative sparing of memory, at least early in the disease course. Structural imaging usually reveals focal atrophy of both the frontal and temporal lobes.

Semantic dementia (SD) is primarily a language disorder in which patients have fluent speech, but display word finding difficulty and experience the loss of word meaning. For example, if asked “Can a fork eat a lion?”, they may answer affirmatively, indicating that they do not appreciate the meaning of “fork”, “eat”, “lion”, or all three. Memory changes occur later in the disease. Structural imaging often reveals focal atrophy of the anterior left temporal lobe with relative sparing of the frontal lobes; bitemporal atrophy also may be present.

Progressive nonfluent aphasia also (PNA) is a language disorder and can be considered a “dementia” of the language system. Patients with PNFA have nonfluent and hesitant speech but they retain knowledge about word meaning. Their speech and writing are agrammatical (i.e., stripped of modifying and connecting words) and may display increased spelling errors. The neural substrate of PNFA involves the left superior temporal lobe, the left inferior frontal lobe, and the left anterior insula. With disease progression, the parietal lobe also is affected.

Although other neurodegenerative disorders have histopathological phenotypes that are distinct from the FTDs and usually have a different topography of cerebral involvement, rarely they may preferentially affect frontal and temporal lobes and thus present as FTD:

1) Corticobasal Degeneration (CBD)
2) Progressive Supranuclear Palsy (PSP)
3) Frontal variant of AD

<table>
<thead>
<tr>
<th>Frontotemporal dementia subtypes</th>
<th>Features</th>
</tr>
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<tr>
<td>Behavioral variant FTD</td>
<td>Personality changes, Lack of insight, Socially inappropriate</td>
</tr>
<tr>
<td>Semantic dementia</td>
<td>Language predominant deficit, Fluent speech, loss of word meaning</td>
</tr>
<tr>
<td>Progressive nonfluent aphasia</td>
<td>Language predominant deficit, Nonfluent, hesitant speech, Retain word meaning, Agrammatical speech and writing</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Asymmetric rigidity, Difficulty with learned movements and actions (apraxia), Visuospatial deficits</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Symmetric, rigidity of trunk&gt;limbs, Impairment ability to look down, Falling backwards</td>
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</table>
Corticobasal degeneration (CBD) is a condition in which asymmetric rigidity is present as is seen in Parkinson disease (PD); however, patients are typically less responsive to standard PD treatment. These individuals may have difficulties with learned motor tasks (apraxia). Frontotemporal Dementia-like features may also be present in CBD, including executive dysfunction and visuospatial and number processing deficits. They may have a PNFA-like language deficit as well.

Progressive supranuclear palsy (PSP) is a condition in which symmetric rigidity is present and also is less responsive to standard PD treatment. These individuals have difficulties with looking up and down (supranuclear palsy), resulting in marked propensity to fall backwards. PSP-like features may also be present in PSP, such as impulsivity and executive dysfunction (i.e., impaired reasoning).

Frontal variant AD individuals initially present with social disinhibition, emotional blunting, stereotyped verbal utterances and therefore are often diagnosed with FTD. However, at autopsy these individuals may have a particularly heavy burden of AD pathology in their frontal lobes. Presumably their atypical clinical presentation is due to the topographical distribution of pathology in their frontal lobes.

Finally, another “variant” is dominantly inherited FTD, representing up to one third of all FTD. A careful interview and ascertainment of family history for the presence of FTD should prompt the consideration of dominantly inherited FTD. Causative mutations resulting in FTD have been identified (See Figure 1); the most commonly occurring are in the C90RF72, MAPT, and GRN genes (see the Neuropathologic Phenotypes section in this article). The earlier the age of symptomatic onset, the greater risk that an underlying autosomal dominant mutation is responsible. In the appropriate context, including a suggestive family history for dominantly inherited dementias, genetic counseling and genetic testing may be considered.

Management

Currently, there are no FDA-approved medications for the treatment of FTD.\textsuperscript{11,12} The bulk of FTD management speaks to providing supportive care and symptomatic treatment. Initial management should focus on minimizing polypharmacy, especially centrally acting prescription and non-prescription drugs as well as herbal supplements. Many centrally acting medications such as stimulants, sedatives, and anxiolytics may have paradoxical effects and result in exacerbated behavioral or cognitive symptoms.
Selective serotonin reuptake inhibitors (SSRIs) have been shown to improve behavioral disinhibition, perseverative behavior, hyperorality, and compulsions. Antipsychotics have been shown to address behavioral disinhibition as well. Stimulants may either reduce or increase compulsive risk taking behavior depending on the mechanism of action.

Frontotemporal dementia patients are not uncommonly treated off-label with approved AD medications. Studies of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) in FTD have yielded no conclusive evidence for cognitive or behavioral benefit. However, these agents are still often prescribed in the absence of FDA-approved medications for FTD and in some cases to minimize caregiver stress. NMDA antagonists (memantine) were initially thought to be beneficial in FTD based on small studies, but the benefit was not found in a rigorous multicenter, randomized, double-blind, placebo-controlled trial. SD and PNFA patients may benefit from speech therapy with the goal of providing them with assistive devices such a communication board or laptop to allow them to maintain or extend their language capabilities.

With recent advances in understanding the molecular underpinnings of FTD and its subtypes (See Figure 1), it is anticipated that protein-specific, disease-modifying therapies will emerge that will target one mechanistic pathway or another.

Neuropathologic Phenotypes FTD-Tau

The recognition of distinct misfolded proteins within neurons and glial cells has transformed the classification of FTD entities within recent years. About half of FTD cases have abnormal intracellular cytoplasmic accumulations of the microtubule-associated protein tau (MAPT) (See Figure 3). The term “tauopathies” has been applied to this family of apparently unrelated group of diseases which includes: Pick’s disease (PiD), corticobasal degeneration...
CBD), progressive supranuclear palsy (PSP), other rare entities, and familial FTD with mutations in the MAPT gene. Several families with FTD with and without movement disorder have been identified with mutations in the MAPT gene on chromosome 17. MAPT gene mutations account for up to 10% of all FTD cases. Microscopically, neuronal loss, astrocytosis, microvacuolation, and swollen neurons are found in affected areas together with a spectrum of tau pathology including intraneuronal neurofibrillary tangle (NFT)-like inclusions, neuronal globose tangle-like inclusions, intraneuronal Pick body-like inclusions, astrocytic tangle-like inclusions and oligodendroglial inclusions resembling coiled bodies and dystrophic neurites (See Figure 3). An extraordinarily wide-range of tau pathology has been observed in these familial cases.2,14

FTD-TDP
Frontotemporal dementia with ubiquitinated inclusions accounts for roughly the remaining half of FTD cases. The identification of two RNA-binding proteins within the ubiquitinated inclusions, TDP-43 (TDP)18 and the fused-in sarcoma (FUS) proteins,19 led to a further expansion in the number of distinct FTD entities. The majority of FTD with ubiquitin inclusion cases contain inclusion bodies made up largely of TDP-43 protein; a very small proportion (less than 5%) contain the protein FUS. FTD-TDP has been observed in both sporadic cases and dominantly inherited FTD cases with mutations in either an expansion in a hexanucleotide repeat in the C9ORF72 (10% of FTD) gene or in the GRN (10% of FTD) gene.20 Mutations in other genes including VCP and TARDBP are very rare causes of FTD. The neuronal and glial inclusions containing TDP are indistinguishable from those seen in most patients with ALS who later develop dementia, suggesting that FTD and ALS are two ends of the same spectrum of FTD-TDP proteinopathy.

FTD-FUS
Mutations have been identified in the FUS gene in rare cases of familial ALS and FTD.20 The inclusion bodies in these cases contain variable amounts of FUS protein (See Figure 4). Also, FUS has been identified as a component of the inclusions of some less frequent FTD entities, including neuronal intermediate filament inclusion disease (NIFID), atypical FTD with ubiquitin-immunoreactive inclusions (aFTD-U), and basophilic inclusion body disease (BIBD).2,3

Future Directions
In an effort to determine the mechanisms by which neurons and glial cells die in FTD, in vitro and in vivo transgenic models have been generated by over-expressing human tau, TDP or FUS proteins in mice. However, these mice only variably show the features of the human disease they are designed to model.22 In one more successful model, a mutation (P301L) in the human MAPT gene, led to the development of transgenic mice that develop age- and gene dose-dependent accumulation of tau tangles in the brain and spinal cord with associated nerve cell loss and gliosis as well as behavioral abnormalities. The tau inclusions were composed of only mutant human tau, thus implicating the P301L mutation in the aggregation of mutant tau. Various aspects of human tauopathies, TDP-43 and FUS proteinopathies, have been modelled which show some features of the human disease. Recently, in vivo models, it has been shown that small protein aggregates may be taken up by neurons and hijack the machinery of the cell to generate more misfolded protein, similar to that seen in prion diseases.23 Thus, a spectrum of models is being developed that recapitulates various features of human pathology and these models will facilitate understanding of the molecular mechanisms underlying neurodegeneration in FTD. These data also indicate how abnormal proteins may propagate throughout the brain, potentially providing a promising target for therapeutic intervention.

The Importance of Autopsy
An autopsy, even when limited to examination of the brain, is essential to determine the underlying cause of the clinical symptoms. Although DNA may be obtained to identify genetic causes in about one-third of FTD cases, neuropathology remains the ‘gold standard’ diagnosis. Neuropathology is essential to determine the underlying cause and the contribution, if any, of other pathologies including vascular disease or co-existing AD. Academic research centers can coordinate and manage the autopsy in those patients who participate in on-going studies. This is an option that should be considered in any patient who shows symptoms of an FTD-like disorder. Support organizations and information on brain donation are listed in this article.
When to consider FTD and refer patients? Initial symptoms: behavioral changes and language difficulties with or without Parkinsonian features. Age at onset: under the age of 65. Family history of young onset dementia with or without Parkinsonian features. Imaging: focal, not global, atrophy of the brain predominantly involving frontal and temporal lobes.

Support Groups
- Association for Frontotemporal Dementias (866) 507-7222 (toll free) [http://www.theaftd.org](http://www.theaftd.org)
- Alzheimer’s Association (800) 272-3900 (toll free) [http://www.alz.org](http://www.alz.org)

Research, Including Brain Donation
- Knight Alzheimer’s Disease Research Center at Washington University in St. Louis [Research, Participation, and Questions (314) 286-2683 http://www.adrc.wustl.edu/]

Acknowledgments
Support for this work was provided by grants from the National Institute on Aging of the National Institutes of Health, USA (P01 AG003991 and P50 AG005681). We would also like to thank the staff of the Knight Alzheimer’s Disease Research Center Neuropathology Core, Washington University School of Medicine, for their technical support, and the many patients studied and their families for making the research reviewed here possible.

References

Disclosure
N Cairns has no disclosures. N Ghoshal has participated, or is currently participating, in clinical trials of anti-dementia drugs sponsored by EliLilly and Company, Wyeth, Pfizer, Novartis, and Bristol-Myers Squibb.
A thorough, systematic approach is needed to evaluate an RPD patient in order to rule out possible treatable disorders.

Abstract

While the most common dementia is Alzheimer disease (AD), a detailed history is needed to rule out rapidly progressive dementias (RPDs). RPDs are less than two years in duration and have a rate of progression faster typical neurodegenerative diseases. Identification of RPDs is important as some are treatable. This review focuses on the spectrum of RPDs, with special emphasis on paraneoplastic disorders and Creutzfeldt-Jakob disease (CJD).

Introduction

While most causes of dementia are neurodegenerative and are characterized by a gradually progressive course, it is increasingly recognized that less common causes may have a more rapid course. In some instances, an apparent rapid course in fact represents the failure of observers to recognize subtle but progressive cognitive impairment that has been present for several years. Commonly, an evaluation in these instances is precipitated by crisis or a specific event (e.g. motor vehicle accident). The most common etiology is Alzheimer’s disease (AD) and a careful history will assist in the diagnosis (Please see previous article on AD). It is extremely important to rule out more common etiologies before considering other rare causes.

However, rare sources of dementia that may have rapid progression, moving from asymptomatic to severe stages in the course of weeks to months are increasingly recognized. It is important to be aware of these more rapidly progressive dementias (RPDs) because some are treatable (e.g. autoimmune encephalopathies) while others are not [e.g. Creutzfeldt-Jakob disease (CJD)]. This review focuses on the spectrum of RPDs, with emphasis on those that are potentially treatable. In contrast, CJD is an inevitably fatal, irreversible disease that requires public health reporting.

Rapidly Progressive Dementias

While no formal diagnostic criteria have been established to define RPDs, most experts use clinical criteria similar to those proposed for CJD. In general, the course of RPD is two years or less in duration and the rate of progression is much faster than observed for more common neurodegenerative diseases. Typically the mode of onset is more acute to subacute (i.e. days to weeks), in stark contrast to many neurodegenerative disorders where an exact date of onset is often difficult to identify. Beyond
this duration requirement, no unifying features exist that are common to all RPDs. A simple pneumonic for helping organize a framework for possible etiologies of RPD is “VITAMIN C”

- V = Vascular
- I = Infectious
- T = Traumatic
- A = Autoimmune
- M = Metabolic
- I = Idiopathic/Iatrogenic
- N = Neoplasms
- C = Congenital

These multiple potential etiologies engender a broad differential diagnostic approach (Please see websites listed at the end of the article). At Washington University in St. Louis (WUSTL) we use a systematic, multi-tiered, approach to evaluate RPD (See Figure 1). In this review we focus on two primary etiologies of RPD, the autoimmune dementing disorders and CJD. The former represents a treatable form of dementia and the latter is of significant importance from a public health perspective.

**Autoimmune Dementias**

Immune-mediated dementias represent a variety of disorders, ranging from neuropsychiatric lupus to paraneoplastic encephalopathies associated with anti-neuronal antibodies to neural antigens. These disorders can affect patients of all ages and until recently were considered a relatively rare cause of RPDs. Cognitive impairment in a young individual (< 50 years old) with a history of a dementing disorder should warrant an extensive evaluation for possible autoimmune disorders. Despite being less common, autoimmune etiologies should also be considered in the elderly population when there is a history of RPD. Some clues that may suggest an autoimmune encephalopathy include a history of an acute/subacute onset of symptoms, new onset seizures, sudden psychosis, respiratory impairment, concurrent involvement of other portions of the nervous system (e.g. peripheral neuropathy, myelopathy), or recently diagnosed cancer. The history of present illness is the cornerstone of the clinical diagnosis. As detailed a history as possible should be obtained from the patient, when possible, and from collateral source(s). In the absence of a reliable history or an available collateral source, the physician should have a low threshold for considering an autoimmune encephalopathy as this class of disorders is treatable and cognitive impairment may be reversed.

When considering paraneoplastic etiologies a defining feature of these disorders is that the signs/symptoms cannot be attributed to toxicity of chemotherapy or radiation therapy, infection, coagulopathy or other toxic or metabolic causes. While various mechanisms are likely responsible for the nervous system pathology in paraneoplastic syndromes (beyond the scope of this review), the general pathophysiology is associated with an immune-mediated injury to the nervous system due to a shared antigen, expressed on both tumor cells and within the nervous system. The immune system therefore attacks both the cancer cells and the nervous system in its attempt to clear the antigen. The term “paraneoplastic” is commonly applied to any syndrome associated with anti-neuronal antibodies. While many of these disorders occur in the central nervous system (CNS), auto-autoantibodies can also develop in the peripheral nervous system (PNS).
This review will focus on disorders of the CNS. Antibodies that are more likely to be associated with an underlying malignancy relative to others are presented in Table 1.

Antibody testing often involves analysis of panels of antibodies and any positive result needs to be interpreted within the appropriate clinical context as it may not always be of clinical significance. How to interpret a “positive” result and how the presence of an antibody will be incorporated into the patient’s care are important questions to consider before sending these tests as false positive results are not uncommon. The diagnosis of many of the autoimmune etiologies of RPD can be made using a combination of blood tests (See Figure 1), systemic imaging studies to screen for malignancy (including body computerized tomography (CT) and whole body positron emission tomography (PET)), cerebrospinal fluid analysis including glucose, protein, cell count, flow cytometry and cytology, pertinent microbiologic studies and polymerase chain reaction studies (PCRs) for specific viruses, an immunology profile (evaluation for oligoclonal bands and quantitative IgG relative to serum) and biomarkers for neurodegeneration including quantitation of the 14-3-3 antigen and total tau levels, and neuroimaging using magnetic resonance imaging (MRI) to evaluate for abnormalities characteristic of infectious, autoimmune or neurodegenerative etiologies. In some instances, repeat evaluations may be required every six months to detect malignancies that are suspected but not yet confirmed. It is

### Table 1. Paraneoplastic disorder etiologies

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Most Frequent Tumors</th>
<th>Associated Antibodies</th>
</tr>
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<tbody>
<tr>
<td>Limbic encephalitis and</td>
<td>Small cell lung cancer, testicular cancer,</td>
<td>Anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ri (ANNA-2), ANNA-3,</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>thymoma, teratoma</td>
<td>anti-Ma1, anti-Ma2, anti-amphiphysin, anti-CRMP5, anti-</td>
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<tr>
<td></td>
<td></td>
<td>NMDA (and other neuropil antibodies), anti-VGKC, nicotinic</td>
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<tr>
<td></td>
<td></td>
<td>ganglionic AChR autoantibody</td>
</tr>
<tr>
<td>Cerebellar degeneration</td>
<td>Breast cancer, ovarian cancer, small cell</td>
<td>Anti-Yo (PCA-1), anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-</td>
</tr>
<tr>
<td></td>
<td>lung cancer, Hodgkin disease</td>
<td>mGluR1, anti-VGCC, anti-Ma1, anti-CRMP5(CV2)</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>Neuroblastoma, small cell lung cancer, breast</td>
<td>Anti-Ri (ANNA-1), anti-Yo (PCA-1), anti-Hu (ANNA-1), anti-</td>
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<tr>
<td></td>
<td></td>
<td>Ma1, anti-Ma2, anti-amphiphysin, anti-CRMP5(CV2)</td>
</tr>
<tr>
<td>Stiff-person syndrome/PERM</td>
<td>Breast cancer, small cell lung cancer, Hodgkin</td>
<td>Anti-amphiphysin, anti-GAD, anti-glycine, anti-Ri (ANNA-2)</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>Lymphoproliferative disorders, small cell</td>
<td>Anti-Hu (ANNA-1), anti-Yo(PCA-1), anti-SGPS, anti-gangliosides</td>
</tr>
<tr>
<td></td>
<td>lung cancer, breast</td>
<td>GM1, GM2, GD1a and GD1b</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Small cell lung cancer, thymoma, lymphoproliferative disorders</td>
<td>Anti-Hu (ANNA-1), anti-CRMP5(CV2), anti-SGPS, anti-gangliosides GM1, GM2, GD1a and GD1b</td>
</tr>
<tr>
<td>Neuromyotonia</td>
<td>Thymoma, Hodgkin disease</td>
<td>Anti-VGKC, anti-Hu (ANNA-1)</td>
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<tr>
<td>Lambert-Eaton syndrome</td>
<td>Small cell lung cancer</td>
<td>Anti-P/Q VGCC</td>
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CRMP = collapsin response mediator protein; NR, NMDA= N-methyl-D-aspartate; ANNA= antineuronal nuclear antibody; PCA= purkinje cell autoantibody; VGCC= voltage-gated calcium channels; GAD= glutamic acid decarboxylase; TULP1= tubby-like protein 1; PTB= poly pyrimidine-tract binding; MAG= myelin-associated glycoprotein; SGPS= sulfated glucuronic acid paragloboside; VGKC= voltage-gated potassium channels; PERM = progressive encephalomyelitis with rigidity and myoclonus; AChR = acetylcholine receptor

*Modified from Toothaker and Rubins, Neurologist, 2009.*
not uncommon for the paraneoplastic syndrome to predate the detection of an underlying malignancy by months to years.6

Treatment for autoimmune dementias varies based on the underlying etiology, the patient’s medical comorbidities and the presence or absence of a possible underlying malignancy.2 Treatment regimens include oral or intravenous steroids, intravenous immunoglobulin, plasma exchange, or other immunomodulatory agents (e.g. rituximab, cyclophosphamide, azathioprine, mycophenylate mofitil, or methotrexate).5,7 For paraneoplastic disorders, the main priority is to identify and treat the possible underlying malignancy. While some paraneoplastic syndromes may initially respond to immunomodulatory therapies, for the vast majority this response will not persist unless definitive cancer treatment is pursued. With few exceptions, anti-neural antibodies directed against cell surface antigens are often responsive to immunomodulatory therapies, while those directed against intracellular antigens are unlikely to respond to treatment. Examples include antibodies (Ab) directed against the voltage-gated potassium channel complex (VGKC), a cell surface antigen.

In fact, the majority of patients with anti-VGKC syndromes do not have an underlying cancer and these patients usually respond very well to immunomodulatory therapies. In contrast, syndromes associated with antibodies against neuronal nuclear antigen 1 (ANNA-1, also known as Hu) are almost always associated with an underlying malignancy and do not respond to treatment unless the underlying cancer is identified and treated.2 Prognosis for paraneoplastic dementias varies and is primarily based on the underlying cancer. For non-paraneoplastic dementias and other autoimmune dementias, the prognosis is often quite good if recognized early. In fact, as the name suggests, steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT, also known as Hashimoto’s encephalopathy) is defined by its marked improvement after administering steroids.

**Creutzfeldt-Jakob Disease**

In contrast to autoimmune etiologies, Creutzfeldt-Jakob Disease (CJD) is a fatal RPD without known treatment.8 Most CJD cases are sporadic (sCJD) (85%) in nature but familial (15%) and acquired (≤ 1%) forms exist. The pathogenesis of sCJD remains poorly characterized but is believed to be due to a conformational change in the normal prion protein (PrP to an abnormal form (PrPSc) that is resistant to degradation. The term “prion” was initially coined by Stanley Prusiner in 1982 to describe proteinaceous infectious particles. Prusiner hypothesized once the abnormal PrPSc (for PrP scrapie, a spongiform encephalopathy in sheep) is formed, it acts as a template that subsequently converts normal surrounding PrP to PrPSc. This leads to an exponential growth in PrPSc and subsequent widespread propagation of neuronal degeneration.9 Of note, there is growing evidence that prion-like mechanisms play a role in not only CJD but other, more common, neurodegenerative disorders such as Alzheimer disease, amyotrophic lateral sclerosis, and Parkinson disease.10

**Figure 2**

Characteristic magnetic resonance imaging (MRI) findings of a patient with Creutzfeldt-Jakob disease (CJD). Striking diffusion restriction is present in the cortical ribbon on multiple axial slices using (a) fluid level attenuated inversion recovery (FLAIR) and (b) diffusion weight imaging (DWI).
The resistance of prions to typical sterilization procedures makes exposure to affected brain tissues (particularly dura mater grafts and human growth hormone preparations) a major public health issue, perhaps best exemplified by the marked increase in iatrogenic CJD in Japan, France, the United Kingdom and the United States that started in 1974 and peaked around the year 2000. Fortunately, with increased awareness the number of iatrogenic CJD cases (∼ 450 in total worldwide) has dramatically decreased since 2000, a public health feat that would not have been possible without the work of physicians to recognize this rare form of dementia. While definitive diagnosis of CJD often requires tissue confirmation, brain biopsy of a patient with suspected CJD is often precluded by for both financial and safety reasons. Many institutions choose to dispose of all instruments used during a biopsy surgery of a suspected CJD patient, a cost prohibitive practice in most circumstances. While strict precautions are used, the theoretical risk of iatrogenic transmission from surgical patients to health care personnel due to direct contact with contaminated tissue are also taken into consideration when considering a biopsy. Accordingly, more recent criteria for the diagnosis of CJD include less invasive methods.

Currently, the incidence (the number of new cases) of CJD in the United States is estimated to be 1-1.5 per million per year. Rates have not changed over the past two decades despite increased public awareness and a substantial increase in the number of referrals to the National Prion Disease Surveillance Center (NPDSC). The typical age of onset of sCJD is 55-75 years of age (median = 68 years old) with males and females equally affected. The median duration of survival is approximately 4.5 months from time of onset of symptoms to death with around 90% of patients living less than one year. We provide more recent guidelines developed at the University of California San Francisco (See Table 2A). It is important to note that cognitive changes may not be the initial presenting symptom but may occur somewhat later in the course. Other common initial signs and symptoms are listed in Table 2B. Noninvasive diagnostic tests outlined in the guidelines may help differentiate CJD from other more treatable RPD disorders. Currently the work-up of possible CJD at our institution includes a structural MRI, electroencephalogram (EEG), and cerebrospinal fluid (CSF) and serum analyses (See Figure 1).

Brain MRI has had the greatest impact on improving the accuracy of an antemortem diagnosis of CJD. Characteristic changes on fluid level attenuated inversion recovery (FLAIR) images and diffusion weight imaging (DWI) are extremely helpful for diagnosing CJD. We present characteristic MRI findings from a patient at initial presentation of symptoms (Figure 2). MRI alone has a sensitivity and specificity of 70-95% and 80-100%, respectively.

Cerebrospinal fluid analysis can also assist in the diagnosis. In particular, CSF should be evaluated for elevated levels of 14-3-3 (a non-specific marker
of neuronal death) and tau (a non-specific marker of neuronal degeneration). In particular, we have observed a marked elevation in tau in CJD patients (See Table 3). Differences exist concerning the sensitivity and specificity of each of these CSF measures for the diagnosis of CJD. Finally, EEG assessment for periodic sharp and wave complexes may also assist in the diagnosis of CJD. However, the accuracy of this measurement may vary on when in the time course of the disease it is performed. At best (even at specialty centers like ours) the sensitivity and specificity of each of these tests is approximately 90%. From our own previous experience with confirmed CJD patients we have seen significant improvement in the diagnosis using a combination of these tests.

Recent advances in using real-time quaking induced conversion (RT-QUIC) testing of CSF may allow for reliable antemortem diagnosis. Researchers have more recently demonstrated that RT-QUIC was capable of detecting femtogram amounts of PrPSc present in CSF of patients with CJD. While this method has great promise it has not been used in large clinical settings. Overall, diagnosis of CJD continues to remain very difficult and can be missed. Often the diagnosis of CJD is made at a tertiary referral center such as ours only after an extensive evaluation has been performed.

Unfortunately, no disease modifying therapies exist for CJD. To date, there have been two clinical trials, both of which failed to show any significant benefit with respect to cognitive function or survival in sCJD non-opioid analgesic, failed to show any improvements in cognitive function or survival in CJD patients receiving this medication. Currently there are no clinical trials for sCJD planned. However, ongoing interest in developing novel therapies for this rare disorder exists and treatments may also be relevant for more common neurodegenerative disorders.

While efficacious therapies do not exist for CJD, the role of the clinician remains extremely important in not only identifying possible treatable mimics of CJD but also providing supportive care to not only patients with sCJD but their families. The importance of identifying treatable mimics of CJD has been well illustrated by a large study by Chitravas and colleagues who demonstrated that from 2006 through 2009 the NPDSC received 1106 tissue specimens for diagnostic confirmation of CJD suspected on clinical grounds. Three hundred and fifty two (32%) of these specimens showed evidence of an alternative diagnosis and 71 out of these 352 (7% of the total cohort) specimens showed treatable disorders that had gone undiagnosed. The treatable disorders included immune mediated (n=26), neoplastic (n=25), infectious (n=14), metabolic/toxic (n=6).

Patterson and colleagues have also noted a similar percent misdiagnosis in regards to cases that were initially identified with other dementias but were subsequently shown at autopsy to be sCJD. To this end we concur with the approach of Dr. Michael patients. The PRION-1 study was a partially randomized, patient-preference clinical trial using the antimalarial drug quinacrine, a drug selected based on in vitro evidence of prion elimination from a cell culture prion model. An earlier study using flupirtine maleate, a
Geschwind who regards CJD as “the great mimicker of other diseases. It can look like anything (and vice versa).” As emphasized above, a thorough, systematic approach is needed to evaluate an RPD patient in order to rule out possible treatable disorders. We encourage all clinicians, if unsure, to contact our center to ensure that these patients undergo the thorough testing necessary to make this diagnosis. All patients and their families should be encouraged to consider pathologic confirmation of suspected disease. In addition, we provide our contact information as well as the CJD Foundation information for families and patients, and the NPDSC for pathological evaluation at autopsy.

References

Financial Disclosure
Supported by the National Institute of Mental Health (K23MH081786 to B.M.A.) and National Institute of Nursing Research (R01NR012907, R01NR012657, and R01NR014449 to B.M.A.).