

CONNECTIONS

Frontotemporal Dementia: Growing Interest in a Rare Dementia

Editor's Note: This special reprint of *Connections* focuses on a group of rare diseases called frontotemporal dementia (FTD). These diseases are characterized by an accumulation in the brain of abnormal forms of *tau* protein. To view the complete issue of *Connections*, including an illustration of the brain and a graphic showing how mutations of the *tau* gene disrupt the neuron's microtubule transport system, visit www.alzheimers.org/pubs/conv09n4.html.

Dementia is frequently equated with Alzheimer's disease. While it is true that AD is the most common cause of dementia, scientists and clinicians have identified a number of additional progressive neurodegenerative conditions that cause dementia, including vascular dementia, dementia with Lewy bodies, and a much rarer group of diseases called frontotemporal

dementia. Scientists are showing growing interest in understanding the similarities and differences among these neurodegenerative diseases. Though much is still unknown, the more we learn about these diseases, the more patients and families will benefit. New knowledge about these rarer forms of dementia also may shed light on AD.

What is FTD?

FTD primarily affects the frontal and anterior temporal lobes of the brain. These areas control "executive functions" such as reasoning, personality, social behavior, movement, speech, language, and certain aspects of memory. FTD usually develops between the ages of 35 and 75, and affects men and women about equally. Patients generally live with the disease for 2 to 10 years after

diagnosis. FTD appears to be quite rare; researchers believe that FTD accounts for perhaps 3 percent of all dementia cases. The disease appears to have a strong genetic component, for in 20-40 percent of the cases, the person had a family history of dementia. A major scientific breakthrough occurred in 1998 with the discovery that a mutation in the *tau* gene causes a form of FTD called frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (see following article on tauopathies for more on the genetic links to FTD).

What are the Clinical Characteristics of FTD?

FTD is characterized by a gradual onset of changes in personality, social behavior, and language ability. Particular changes depend on whether the damage has

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Tauopathies: New Discoveries, New Knowledge

A central characteristic of many neurodegenerative diseases is aggregation of abnormal proteins in the brain. For example, a protein called alpha-synuclein is known to accumulate in Parkinson's disease, and a protein called huntingtin accumulates in Huntington's disease. These abnormal proteins likely play a key role in the dysfunction and death of neurons and the resulting clinical characteristics of the diseases. In the last couple of decades, considerable attention has been focused on one such

abnormal protein—beta-amyloid—and the resulting plaques that may lead to AD.

Within the last few years more attention has been focused on the other hallmark feature of AD—the "tangles" of abnormal *tau* protein. We are learning more about *tau* and what happens to change it in the AD process. Scientists are discovering that these *tau* tangles, along with extensive neuron loss and gliosis (a kind of tissue scarring in the brain), are the major feature

of a number of neurodegenerative diseases. A consensus is emerging that these diseases should be called "tauopathies." Tauopathies include frontotemporal dementia (see related article on FTD), Pick's disease, corticobasal degeneration, familial FTDP-17, progressive supranuclear palsy, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, and motor neuron disease.

Tau's Vital Role

Tau is a protein commonly found throughout the central nervous system. Six forms of *tau* are found in the adult human brain and each

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primarily affected the right or left side of the front of the brain (language deficits predominate when the left side is primarily affected; behavioral problems develop with right-sided disease). Symptoms include one or more of the following:

- uninhibited and socially inappropriate behaviors (people begin to do things they never would before, such as stealing or drinking out of the punch bowl at a party)
- inappropriate sexual behavior
- loss of awareness of or concern about the changes in behaviors
- loss of concern about personal appearance and hygiene
- major increase in appetite that leads to constant eating and weight gain
- apathy, loss of drive, social withdrawal, lack of concern and empathy for others
- loss of speech and language (many become completely mute by the middle to late stages)
- compulsive or repetitive behaviors, such as pacing, collecting things, or handwashing

- oral fixation (people begin to put objects as well as food into their mouths); this occurs more in the late stages
- memory loss, although this is not one of the first signs and is less severe relative to other symptoms

People with FTD also have motor difficulties like those seen in Parkinson's. These include rigidity, lack of balance, and stiffness of movement, but not the trembling of arms and legs at rest that are characteristic of Parkinson's. One major difference between FTD and AD is that people with FTD do not suffer memory loss to the same degree as those with AD. People with FTD also remain oriented to time and place and are able to recall information about the past and present. Even in the late stages, people with FTD, unlike those with AD, are able to negotiate their surroundings and know where they are.

What Pathologic Changes Can Occur in FTD?

Though scientists don't yet know the cause of the destructive changes of FTD, they have a fairly good understanding of the changes themselves. One of the most characteristic pathologic changes is an accumulation of abnormal *tau* inside nerve cells in the brain. *Tau* is a protein that plays an essential role by supporting the internal structure of the nerve cell and serving as a part of the transport mechanism for nutrients and other molecules. In FTD, *tau* becomes abnormal and aggregates into tangles. This disrupts normal nerve cell processes and ultimately leads to the death of the cells (see the article on tauopathies for more on the process). Other changes include a progressive loss of nerve cells in the frontal and temporal regions of the brain. Gliosis, a form of tissue scarring in the central nervous system, also occurs, as does vacuolation, a process in which "holes" form in the outer layer of the brain. In Pick's disease, Pick bodies, which are

Frontotemporal Dementia and Alzheimer's Disease: Similarities and Differences

<i>Features</i>	<i>Frontotemporal Dementia</i>	<i>Alzheimer's Disease</i>
<i>age at which disease generally occurs</i>	<ul style="list-style-type: none"> • usually after age 40 and before 65 	<ul style="list-style-type: none"> • usually after 65
<i>brain areas affected</i>	<ul style="list-style-type: none"> • frontal and temporal lobes 	<ul style="list-style-type: none"> • starts in the medial temporal area, usually in the hippocampus • spreads to other areas of the brain
<i>pathologic features</i>	<ul style="list-style-type: none"> • loss of nerve cells • no amyloid plaques • <i>tau</i> tangles seen in certain FTDs 	<ul style="list-style-type: none"> • loss of nerve cells • amyloid plaques • <i>tau</i> tangles
<i>clinical features</i>	<ul style="list-style-type: none"> • begins with personality and behavior changes; some may be hyperactive while others seem apathetic • loss of empathy toward others; lack of insight into proper social conduct • memory is preserved early on • language difficulty • compulsive eating and oral fixations • repetitive actions • later, loss of motor skills, speech and muscle movement 	<ul style="list-style-type: none"> • begins with memory loss • patients lose ability to learn new information • patients become unable to orient themselves to time and place • later, personality and behavior problems develop • possible hallucinations and delusions in later stages

abnormal cell inclusions, begin to form in the brain.

How is FTD Diagnosed?

Because of its symptoms, FTD is often misdiagnosed as a psychiatric problem or as AD (see chart for a summary of similarities and differences between AD and FTD).

However, a trained and experienced health care professional can look for features that rule out other diagnoses as well as those that pinpoint FTD. Diagnosis generally involves:

- a careful medical history and examination of behavioral changes—because patients lack the ability to recognize changes that have occurred or that their current behavior is problematic, information from family members and others close to the patient is crucial;
- neuropsychological examination, which helps assess language, memory, executive functioning, visual-spatial skills; and
- neuroimaging to determine where and how extensively brain regions have atrophied.

What Treatments are Available for FTD?

Currently, no treatments are available to slow or stop the disease process. However, available psychiatric medications can be used to treat some of the behavioral problems. For example, selective serotonin reuptake inhibitors (SSRIs) or small doses of newer antipsychotic medications, can help to alleviate some of the more difficult behavioral symptoms. Practical strategies can blunt the impact of behavioral symptoms. These strategies include making sure that the person with FTD does not drive and avoids situations that call for financial decisions or those in which judgment is important.

In treating FTD, an accurate diagnosis is crucial. Some medications commonly used to treat other dementias, such as cholinergic drugs and antipsychotic drugs that

contain dopamine blockers, are ineffective or could be harmful in a person with FTD. As with other types of progressive neurodegenerative diseases, caring for people with FTD is stressful and challenging. Therefore, providing caregivers with educational materials and sources of support is critical.

The Outlook

Scientists are still grappling with many unanswered questions about frontotemporal dementia and other dementias. They are actively researching all aspects of these disorders to obtain a better understanding of the causes and risk factors. It is hoped that with a better understanding of abnormal *tau* formations, more effective methods of diagnosis and treatment will be found.

Tauopathies: New Discoveries, New Knowledge

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is maintained in a constant proportion. *Tau* binds and helps stabilize microtubules, a component of the nerve cell's internal support structure or skeleton. In the healthy cell, microtubules form structures like train tracks, which guide nutrients and other molecules from the cell body down through the axon. *Tau*, therefore, plays a vital role in ensuring a nerve cell's survival by supporting its structure and facilitating transport.

What Goes Wrong?

Tau normally undergoes a process called phosphorylation in which molecules called phosphates are added to the protein. Scientists have found that *tau* in the tangles that characterize AD and other neurodegenerative diseases is composed of overly and abnormally phosphorylated *tau*. They speculate that this process causes the *tau* to aggregate into tangled filaments instead of attaching itself to the microtubules, thereby destabilizing the microtubules.

Starting in 1998, scientists took a major step forward when they found that mutations in the gene that directs the production of *tau* cause one particular tauopathy—frontotemporal dementia with parkinsonism linked to chromosome 17, or FTDP-17. These mutations appear to lead to problems in two ways—by forming mutant *tau* proteins in cells or by changing the proportion of the forms of *tau* normally expressed in the brain. These changes promote *tau* aggregation into filaments and harm the ability of *tau* to bind to microtubules.

Scientists have a growing body of clues, evidence, and facts about *tau* tangles and what goes wrong. The puzzle is that this pathologic process gives rise to such a wide range of disorders and diseases. These diseases share a number of characteristics, but they also each have distinct features that set them apart from each other, and from AD. This suggests to scientists that environmental and other genetic factors also must play a role in the cause and development of tauopathic conditions.

Transgenic Mouse Models

In 1999, scientists produced several transgenic mouse models that express *tau* tangles. These animals are not complete models of tauopathies, but they will allow researchers to explore normal *tau* function more fully and to study and measure the accumulation of abnormal *tau* deposits in the brain. The models enable investigators to move ahead on several genetic fronts, including determining how known mutations lead to the death of neurons and studying how other mutations may be involved.

Questions Persist

Investigators hope that growing knowledge about *tau* will answer questions about tauopathies as well as lead to further insights about Alzheimer's disease. They want to know, for example:

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- What roles do environmental and other genetic factors play in the development of tauopathies, and how do they contribute to the clinical characteristics of these diseases?
- In what different ways does the abnormal *tau* expressed in AD and tauopathies contribute to the development of these diseases?
- Which feature of AD is responsible for the dysfunction and death of neurons—beta-amyloid plaques, or *tau*-containing tangles? If they both play a role, what are those roles and how might they interact? How is the process of plaque formation related to tangle formation?

Progress is being made, however, giving rise to hopes that someday we will have effective treatments and perhaps even preventive measures for these devastating diseases.

Recent Paper Classifies Criteria for FTD

An international team of scientists is proposing guidelines for classifying diseases with certain characteristics under the collective, umbrella term, frontotemporal dementia. Writing in the November 2001 issue of the *Archives of Neurology*, well-known dementia disease researchers Guy M. McKhann, M.D., Marilyn S. Albert, Ph.D., Murray Grossman, M.D., Ph.D., Bruce Miller, M.D., Dennis W. Dickson, M.D., and John Q. Trojanowski, M.D., Ph.D., present a summary of conclusions reached by a larger group of experts on proposed clinical and neuropathological criteria for FTD.

To help general physicians, neurologists, neuropathologists, and psychiatrists understand the heterogeneous diseases that make up FTD, the group proposes 5 distinct neuropathological categories, based on presence of abnormal *tau* inclusions, neuron loss and gliosis, 3R *tau* and/or 4R *tau*. Among the diseases which the group recommends classifying as FTD are Pick's disease, FTD with parkinsonism

linked to chromosome 17, corticobasal degeneration, progressive supranuclear palsy, and neurofibrillary tangle dementia,

This paper clarifies the demographics of FTD; the core clinical phenotypes of FTD, including the behavioral and language presentation of FTD; and imaging and laboratory data in FTD. Because these diseases are often misdiagnosed as a psychiatric disorder, and many general physicians believe almost all dementia is AD, the group hopes that this classification system will promote greater understanding in the medical community. The authors hope to improve early and accurate diagnosis of FTD and to continue research to discover effective treatment strategies.

Reference: McKhann et. al. (2001) Clinical and Pathological Diagnosis of Frontotemporal Dementia: Report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Archives of Neurology*, Nov., 58(11), 1803-1809.

<i>Characteristics of Selected Frontotemporal Dementias</i>	
Disease	Clinical Characteristics
Pick's Disease	<ul style="list-style-type: none"> ◆ personality and behavioral changes: disinhibition, inappropriate social behaviors, loss of mental flexibility and empathy; development of obsessive-compulsive behaviors, compulsive overeating, food cravings, putting any object in mouth ◆ language problems: use of wrong words, echoing what others say, mutism can develop ◆ difficulties in thinking, concentrating, paying attention; gradual emotional apathy, loss of moral judgment; generalized dementia
FTDP-17	<ul style="list-style-type: none"> ◆ behavioral changes: loss of initiative, disinhibition, obsessive-compulsive behavior, restlessness, verbal aggressiveness ◆ psychiatric symptoms: delusions, visual or auditory hallucinations ◆ cognitive decline: word finding difficulties, other language difficulties though comprehension remains preserved; executive functions, attention, and abstract reasoning become impaired; mutism eventually develops
Supranuclear Palsy	<ul style="list-style-type: none"> ◆ motor difficulties: problems with balance and gait; problems controlling eye movement, involuntary closing of the eyes, inability to maintain eye contact with others; difficulties with swallowing ◆ personality/behavioral changes: apathy, increased irritability, angry outbursts, depression, progressive dementia
Corticobasal Degeneration	<ul style="list-style-type: none"> ◆ signs of parkinsonism: poor coordination, rigidity, impaired balance ◆ cognitive and visual-spatial impairments, loss of ability to make familiar and purposeful movements ◆ hesitant and halting speech ◆ sudden contractions of muscles or muscle groups ◆ difficulty swallowing