As clinical neurologists, we hardly can pick up a neurology journal without finding one or two articles on Alzheimer’s disease. In the last few years, you have likely noticed a flurry of articles on frontal temporal dementia (FTD). Just since October of 2008, I have counted 10 articles in the journal *Neurology*. There is now even an international conference exclusively devoted to frontal temporal dementia.

Although currently there is no specific treatment for frontal temporal dementia, these articles provide much more insight into the disease and will hopefully soon lead to the development of animal models and targets for effective drug therapy.

It is important that clinical neurologists are up-to-date about frontal temporal dementia because much of this information affects day-to-day evaluation of cognitively impaired patients. A frequent dilemma for the clinical neurologist is determining whether their patient has Alzheimer’s disease, a form of frontal temporal dementia, or an Alzheimer’s variant of frontal temporal dementia. Implications of genetics and genetic counseling and specific treatment and prognosis vary in these disorders.

**FTD Classification**

If you look up frontal temporal dementia in the index of the first few editions of *Baker’s Clinical Neurology* (which I used as my bible in my neurology residency in the early 70’s), you will not find it listed. The subject is only referenced under the category of dementia as Pick’s disease, and it is covered in only one page of information. The book states that Pick’s disease (lobular cerebral atrophy) is a rare progressive dementia, and it may be hard to separate from Alzheimer’s disease. It usually begins in the fifth and sixth decade and is characterized by personality change, apathy, loss of concern for others and normal memory. It may cause speech impairments and gait and motor function impairments late in the disease.

Familial cases have been described, but no clear-cut genetic pattern has been determined. Pathology shows atrophy of the frontal and temporal lobes with cytoplasmic neuron inclusions called Pick bodies in some cases, but not all. Senile plaques and amyloid deposits were not seen.

Alzheimer’s research has gained momentum much more quickly in the last 25 years, because it is the more frequent cause of dementia and because of the development of the cholinergic hypothesis. The latter has led to the development of pharmacologic agents and put Alzheimer’s disease in the treatable dementia category.

Over the last 10 years it has been slowly realized that FTD can take on different clinical presentations, different pathologies, and different genetic variations. It is now recognized as the third most common cause of degenerative dementias, after Alzheimer’s disease and Lewy Body disease and the second most common cause of pre-senile dementia (in those ages 50 to 64).

With the help of international experts, a classification of FTD was suggested in 2001 with some suggested modifications since then:

1. **Frontal temporal dementia behavioral variant.** FTD behavioral variant initially characterized by personality change, apathy, inappropriate behavior, normal memory storage, and impaired executive function. Later in the disorder memory storage is impaired, as well as a disturbance in gait. The disease initially affects bilateral dorsal lateral prefrontal lobe and inferior frontal lobe. Later, the temporal lobes become affected.

2. **Primary progressive non-fluent aphasia.** This is characterized by aggramatic aphasia with marked apraxia of speech and normal comprehension. This is characterized by atrophy in the left frontal and insular region of the brain, which later becomes bilateral.

Note that there is another form of language disorder called the logopenic variant of primary progressive aphasia. These
cases have hesitant speech anomia, spared word comprehension, and impaired repetition. These cases have evidence of a focal left inferior parietal, and posterior temporal atrophy eventually becoming bilateral. This kind of speech disturbance resembles a conduction aphasia that often occurs in stroke. These cases have been found to actually have pathology of Alzheimer’s disease with amyloid plaques and neurofibrillary tangles.  

3. Semantic dementia. This is characterized by progressive fluent aphasia, anomia, and impaired sentence repetition. It may also have impaired object semantics (inability to use tools and utensils appropriately) and visual agnosia. This category mimics stroke-induced Wernicke’s aphasia. The pathology is localized to the left inferior and anterior temporal lobe with atrophy. The parietal lobe is normal. 

4. FTD with amyotrophic lateral sclerosis/motor neuron disease. 

Note: The above clinical descriptions are for very early disease. As the dementia progresses, clinical symptoms and pathology begin to overlap, hence the importance of a good history.

Genetic Defects
Aside from the important clinical description of these disorders, the emerging genetic information has been of major importance and only discovered in the last two to 10 years. The two genetic defects responsible for many cases of familial FTD are:

a.) Abnormal gene coding for microtubule associated protein tau (MAPT), which has been found on chromosome 17. The MAPT mutation produces an abnormal form of tau that produces the deposits in the brain cells.

b.) In the last two years, gene coding for progranulin (PGRN) has also been mapped to chromosome 17. Progranulin is known to be a growth factor involved in regulating tumor genesis, wound repair, and inflammation and may have a neurotrophic effect, as it promotes cortical and motor neuron survival.

The progranulin and gene defect is unlike other gene defects, because this genetic defect does not produce an abnormal protein but instead allows progranulin to become deficient. Unlike Alzheimer’s disease, which overall has the same pathology (amyloid plaques and neurofibrillary tangles),
regardless of the genetic defect, FTD has varied pathology depending on the genetic defect type. The abnormal MAPT gene pathologically leads to abnormal neuronal and glial tau inclusion with formation of Pick bodies. Clinically this MAPT gene defect is responsible for the familial behavioral variant of FTD, but it may also be associated with FTD and Parkinson’s, primary progressive non-fluent aphasia variety, and a dementia type that looks like frontal temporal dementia but has Alzheimer’s pathology. The abnormal progranulin (PGRN) gene on chromosome 17 leads to neuronal ubiquitin positive inclusions containing TDP-43 protein and occurs in the pathology of semantic dementia and FTD with ALS/MND.

Now that we know more about the genetic defects and the types of FTD, what percentage of patients do we suspect with FTD have these genetic defects? Seelaar, et al, studied a cohort of 364 patients with FTD. Twenty-seven percent had a positive family history suggesting autosomal dominant inheritance. In those cases they found 11 percent with MAPT and six percent with PGRN mutations (autopsy studies). In the remaining 10 percent, the genetic defect has yet to be found. The main age of onset in the PGRN group was 10 years older (62 +/- 9 years) than the MAPT group (52 +/- 5 years).

It seems from this detailed study and is suggested by others that we now know the cause of 17 percent of FTD familial cases. Also of importance was that one FTD sporadic case was found to have a PGRN mutation. However, the cause of FTD in 73 percent of patients without a family history is a mystery. These sporadic cases have shown the same aberrant protein accumulation (abnormal tau and ubiquitin TDP-43) as the known genetic types.

At a 2003 consensus conference, mild cognitive impairment (MCI) was classified into amnestic single and multiple domain and non-amnestic single and multiple domain types. Studies have suggested that non-amnestic single or multiple domain MCI showing language, attention and executive dysfunction were more likely to develop a non-Alzheimer’s dementia such as FTD or multi-infarct dementia. Where visual spatial dysfunction was one of the abnormalities in the nonamnestic MCI patients, Lewy body dementia was more likely to develop. Close follow-up of these patients and appropriate testing may well detect FTD early.

There has been a long recognized association between FTD and ALS. In one dementia clinic, of patients with FTD, 15 percent had definite ALS and 30 percent had possible ALS. This association has been shown in pathology, structural imaging, PET and SPECT scanning, and neuropsychological testing. ALS patients without dementia have shown executive function deficits in 35 percent of cases studied. Verbal fluency loss is also very common with and without dementia. The cause of both these disorders is unknown, but a genetic defect on chromosome 9 has been found in some cases of FTD and ALS. The precise gene defect in these cases is not known. A recent study found ubiquitin TDP-40-43 pathology in the brain stem and spinal cord of a subgroup of patients with FTD and ALS. The mutation was found in the gene coding for TDP-43 on chromosome 1.

**Practical Implications**

Some very practical clinical points arise from this increasing knowledge about FTD:

1. FTD is a disease with a very wide clinical spectrum and pathology with different ages of onset and various genetic forms.

2. PGRN and MAPT screening should be done in suspected familial cases, and PGRN screening should be considered in sporadic cases.

3. Alzheimer’s disease can mimic many of the forms of frontal dementia, especially the behavioral variant. It is very important, since the medications for Alzheimer’s disease (cholinesterase inhibitors and memantine) so far have not been shown to help FTD.

4. It has always been clinically taught that early FTD has normal memory as compared to Alzheimer’s disease, which...
has early memory impairment. Patients and families of patients with suspected FTD will often complain that memory is not normal and give you some examples. It is important to remember that working (immediate) memory is usually impaired in early FTD patients due to inattention and loss of focus. Delayed memory (memory storage) is usually normal.

Early Alzheimer’s disease has normal working memory with impaired delayed (storage) memory. This can be missed in standard office cognitive testing and often requires a thorough neuropsychological evaluation to recognize this.

5. Patients with early logopenic variant of PPA, which mimics conduction aphasia, are likely to have Alzheimer’s disease pathology. This form can be at times confusing with the language disturbance in the non-influent aphasia type of FTD and also semantic dementia.

Careful evaluation of comprehension, speech output and repetition will help sort these different forms of speech and language impairment in these cases.

6. Further studies are needed in sporadic FTD, some familial FTD and especially finding the genetic defect in FTD with ALS.

7. The current FTD information should help speed up animal model studies and identify biomarkers and lead to future drug therapies.

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Genetic Defects and the Types of FTD

Seelaar, et al, studied a cohort of 364 patients with FTD and found:

- 27% had a positive family history suggesting autosomal dominant inheritance.
- 11% had MAPT mutations.
- 6% PGRN mutations (autopsy studies).
- In the remaining 10 percent, the genetic defect has yet to be found.

In the PGRN group:

- Mean age of onset was 10 years older (62 +/- 9 years) than the MAPT group (52 +/- 5 years).
- One FTD sporadic case was found to have a PGRN mutation.

The cause of FTD in 73 percent of patients without a family history is a mystery.


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8. Closely follow non-amnestic MCI patients who have language and/or executive function disturbance, since they are possible future FTD patients.

9. FTD patients who come for the first time later in their disease may have symptoms and signs that overlap with the various types. Early history of onset is very important and will also help the clinician to decide if Alzheimer’s is a more probable diagnosis, especially if the neurological workup is inconclusive. **PN**

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