Importance of Biomarkers in FTLD

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In the Medical Advisory Council Update in the AFTD November 2007 Newsletter, I attempted to provide an overview of the confusing terminology, some of the key genes, and two of the important dysfunctional proteins pertinent to the frontotemporal lobar degeneration spectrum disorders (often abbreviated FTLD). In this newsletter, we will review the issue of “biomarkers” which is becoming increasingly important as we plan for some exciting clinical trials. Readers are encouraged to refer to the November 2007 newsletter (available on the AFTD website) as the terminology continues to be challenging to follow.

What is a biomarker? There are many definitions for the term “biomarker,” but for our purposes relating to FTLD a biomarker is any test result that provides clues about the underlying disorder or disease process.

What are some biomarkers pertinent to FTLD? You could consider any of the following as biomarkers:

- A certain profile of strengths and weaknesses on neuropsychological testing. An example would be weaknesses on tests of executive functions, social cognition, and attention/concentration but relatively normal performance on tests of memory, language, and visuospatial function characteristic of a patient with behavioral variant frontotemporal dementia (bvFTD).

- Detection of a protein from a blood sample being very high or very low, or simply being detectable at all. An example would be a low level of progranulin in the blood, which would suggest the presence of a genetic mutation in the progranulin gene.
• Detection of a protein from a sample of cerebrospinal fluid (CSF) being very high or very low, or simply being detectable at all. Examples would be very high or very low levels of tau, amyloid, progranulin, or TDP-43.

• Detection of an error in a gene (mutation), or a combination of genetic markers (haplotype), from a sample of blood. Examples would be a mutation in the microtubule associated protein tau (MAPT) gene, or a mutation in the progranulin (PGRN) gene, or the tau haplotype.

• A pattern of shrinkage or atrophy on an MRI scan. Examples would be right frontal atrophy consistent with bvFTD, or left anterior temporal lobe atrophy consistent with semantic dementia.

• The types of measurement possible using MRI technology is expanding, and includes magnetic resonance spectroscopy (MRS), voxel-based morphometry (VBM), tensor-based morphometry (TBM), and diffusion tensor imaging (DTI), to name a few.

• A pattern of metabolism decrease (hypometabolism) on brain fluorodeoxyglucose positron emission tomography (FDG-PET) scans.

• Detection of a certain protein using brain PET technology. A very important new example of this technology is the Pittsburgh Compound B (PiB) PET scanning, which detects the presence of amyloid in the brain, thereby suggesting Alzheimer’s disease.

Please note that most of the biomarkers described above are only being studied at research centers, and therefore they are not yet available for routine clinical use. The ones that are available for clinical use, and therefore any physician can order them, include neuropsychological testing, MRI scans, and FDG-PET scans. Genetic testing for mutations in the MAPT and PGRN genes also is available, but this is best ordered by a specialist in medical genetics since patients and families should undergo adequate counseling before and after testing.

**Why are biomarkers so important?** The only ways to know the underlying cause of a patient’s dementia with 100% certainty is examination of brain tissue either by a brain biopsy or autopsy, or by the detection of a disease-causing mutation in a gene known to cause dementia. Herein lies the problem – the vast majority of patients with an
FTLD disorder do not have a mutation in any of the known genes, and most patients (and their relatives) do not want to undergo brain biopsy surgery, particularly if no curative treatments are available yet. Plus, some patients who undergo a brain biopsy still do not obtain a clear-cut diagnosis. If we had one or more accurate biomarkers available, they would greatly improve our ability to 1) establish accurate diagnoses, 2) decide which treatments to use, and 3) monitor the effects of therapies.

**How could biomarkers help establish an accurate diagnosis?** As many who are reading this newsletter can attest, there is often a long and arduous journey that patients and their families endure until an accurate diagnosis of an FTLD spectrum disorder is made. There are many reasons for this, but in most instances it reflects these facts: 1) there are dozens of causes that can explain changes in cognition, behavior, and motor functioning and all must be investigated; 2) most clinicians have little or no experience in recognizing the FTLD disorders as they are rather rare; 3) there are some patients who have atypical features which makes establishing the diagnosis even more challenging; and 4) the diagnostic tests and biomarkers that we currently have available are imperfect. In other words, the diagnostic skills of the clinician, the clinical features, the laboratory results, the neuropsychological profile of impairment, and the results on MRI and PET scans allow most patients to be accurately diagnosed into a clinical syndrome such as bvFTD, primary progressive aphasia (PPA) or corticobasal syndrome (CBS). Accurate clinical diagnosis is very important to learn about the disorder, anticipate the future, and decide on patient management. But if we are to identify the underlying proteinopathy that causes the syndrome—and thus intervene in that disease process—we need improvements in biomarkers.

**How could biomarkers help clinicians decide which treatments are most likely to help individual patients?** As we prepare for treatments that impact tau and TDP-43—the two most important proteins involved in the FTLD-spectrum disorders—it will be critical to identify which is the key dysfunctional protein (proteinopathy) in individual patients. We will require accurate biomarkers to distinguish the patients who suffer from a problem with the tau protein (and thus could be included in a clinical trial testing an
agent that impacts the disease process caused by tau) from those who have a problem in the TDP-43 protein pathway (and could be appropriate for a trial that tests a TDP-43 agent.) Likewise, it will be extremely important to know that neither patient is actually suffering from atypical Alzheimer’s disease.

_How would biomarkers help monitor the effects of therapies_? Once we are into a clinical trial for a potential drug, it will be critical to have sensitive biomarkers to determine if therapies are actually working. Using these biomarkers we will first need to develop a profile of “normal” progression of disease. We will then be able to measure disease progression in a patient who is taking the new drug and know by comparison if that therapeutic agent does, indeed, slow or even stop the disease process.

An even more challenging task is preparing for trials in asymptomatic patients, as it is very difficult to predict when symptoms will begin, and hence how will we be able to tell if a medication is working or not? If we can identify biomarkers that change from year to year in asymptomatic patients, then commence a therapy, and then determine if those biomarkers are stable or actually improving, then we would be more confident that the drug might prevent or delay on the onset of symptoms. We have a way to go until we are ready for this type of trial, but be assured that the scientific community is preparing for this.

_How can I help?_ Advancing knowledge in FTLD so that effective treatments can be developed requires adequate funding and considerable effort by many groups of individuals. Patients and families can assist the clinicians and scientists in these efforts by participating in research. If you or a relative or friend is affected by FTLD, please stay in touch with research advances by checking the AFTD website frequently. Other options include discussing research with your primary physician who can then refer you to a reputable program close to where you live, or you can access the information on the website for Alzheimer’s Disease Centers in the United States: [http://www.nia.nih.gov/Alzheimers/ResearchInformation/ResearchCenters/](http://www.nia.nih.gov/Alzheimers/ResearchInformation/ResearchCenters/) Finally, become familiar with the government website [www.clinicaltrials.gov](http://www.clinicaltrials.gov), where you can search by disease name and see all of the approved drug trials for that condition,
including the sites participating the that trial, the types of patients who qualify for participation, and contact information on the coordinator for each trial. Our future success in developing treatments is in part reliant on enhancing our biomarkers, and identifying those biomarkers that are most helpful is critically dependent on research participation by those affected by FTLD.

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