AlzOnline.net
Caregiver Support Online
CAREGIVING TOPICS

Frontotemporal Lobar Degeneration (FTLD): Brief Discussion of Tau and Ubiquitin Proteins

Prepared by: Leilani Doty, PhD, CoDirector, University of Florida Memory Disorder Clinic (MDC),Box 100236, McKnight Brain Institute, Gainesville, FL 32610-0236, Office (352)273-5555; Memory Disorder Clinic Appointments: (352)265-8408. Partially supported by the Florida Department of Elder Affairs Alzheimer's Disease Initiative (2006)

PREFACE: *This session is a companion piece to two other sessions, 1)* ***Frontotemporal Lobar Degeneration (FTLD)*** *and 2)* ***Frontotemporal Lobar Degeneration (FTLD) with Movement Difficulties****, both available on the web site* ***www.AlzOnline.net****. The companion pieces contain more details about how people may act and function as a result of changes in the frontal lobes and temporal lobes of the brain. Essentially,* one of the *companion sessions,* ***Frontotemporal Lobar Degeneration,*** *covers frontotemporal dementia, primary progressive aphasia, and semantic dementia. The other companion session,* ***Frontotemporal Lobar Degeneration with Movement Difficulties*** *covers progressive supranuclear palsy, cortical basal degeneration, and frontotemporal dementia with motor neuron disease.*

The following session contains a brief discussion of tau and ubiquitin proteins and their

Frontotemporal Lobar Degeneration: Tau and Ubiquitin Proteins

Introduction

Frontotemporal Lobar Degeneration (FTLD) results from the decline of brain cells typically in the frontal lobes and the temporal lobes. Sometimes more internal parts and lower parts of the brain such as the basal ganglia and the brain stem are involved. The decline of the brain neurons leads to changes in personality and brain-controlled functions such as difficulty: remembering, understanding and talking, doing chores either on the job or at home, planning and enjoying leisure time such as a movie and dinner with a loved one, keeping up with personal care such as dressing, and moving the body to do all the activities that are part of one's daily life.[1-6]

In order to learn more about the disease process, to identify ways to stop diseas, and to discover a cure, researchers have examined the brain tissue of people with a clinical picture of Frontotemporal Lobar Degeneration (FTLD) who donated their brains for future study. In studies of the brain tissue, researchers found particles consisting of proteins that have undergone abnormal changes. Two of these proteins, the tau protein and the ubiquitin protein, are of major concern because they appear related to the brain cell changes of frontotemporal lobar degeneration as well as other progressive dementias.[7,8] For example, significant amounts of abnormal tau protein are related to Alzheimer's disease, called a tauopathy[9,10].

Tau and Ubiquitin Proteins

Tau and ubiquitin proteins were identified as distinctly different proteins in the 1980s and often were found bridged together[11]. The forming of tau and ubiquitin proteins occurs when signals in the genes direct steps to produce both the tau protein and the ubiquitin protein.

The tau ("tau" is the Greek letter for "t") protein helps in putting together the microtubules (tiny tubes) of cells. The microtubules help to transport chemicals in the cells and to support the structure of the cell. Thus the tau protein is important to maintain the shape of neurons (nerve cell) in the brain.[12]

Ubiquitin (from the word "ubiquitous" meaning being everywhere at the same time) lives up to its name; the protein seems to be everywhere in complex human cells such as neurons. One of the many functions of ubiquitin is housecleaning, that is to identify proteins that are considered "garbage" and need to be decomposed and eliminated. Ubiquitin serves also as "traffic officer"; it signals several activities within the cell including targeting proteins, such as receptors that need to move from the cell membrane.[13]

Abnormal Tau and Ubiquitin Proteins

When there is a change (called a mutation) in the genes that provide directions for producing tau and ubiquitin proteins, abnormal amounts of these proteins form in the brain or abnormal amounts of them build up into clumps. Various abnormal changes may occur to the different varieties of tau protein that exist[14]. When the abnormal proteins and clumps build up, the abnormal tau and ubiquitin proteins act in ways that are unhealthy for the neurons. The increased abnormal tau protein leads to problems with the structure of the neuron while the increased abnormal ubiquitin protein leads to poor regulation of cell activities including problems with disposal of "cell garbage".[12-14]

When abnormal *tau* proteins build clumps, they form tangles called neurofibrillary tangles. The neurofibrillary tangles interfere with cell function and may result in normal brain cells (neurons) becoming weak and dying. Significant amounts of tau protein changes lead to disease, called a tauopathy (from the words "tau" which, as mentioned before, is the "t" in the Greek alphabet and "pathology", the study of disease). A *tauopathy* is any form of progressive dementia that is associated with disease related to abnormal changes in the tau protein or abnormal build up of the tau protein in neurons. The abnormal tau leads to altered brain function, resulting in symptoms such as seen in FTLD.[14]

Non-tauopathy conditions with a build up of the protein *ubiquitin*, also important to nerve cells, may result in abnormal motor neuron diseases. Abnormal build up of ubiquitin leads to muscle weakness including difficulty with walking, fasciculations (which are twitches or flutterings in muscles), problems moving one's limbs, and struggles with swallowing.[15]

Tau abnormalities may occur alone, with ubiquitin abnormalities, and/or with other brain cell changes. Likewise, ubiquitin abnormalities may occur alone, with tau abnormalities, and/or with other brain cell changes.[16-24]

Developing a Test for Diagnosis

One important reason for learning about abnormal tau protein or abnormal ubiquitin protein rests in the continuing search to discover an easy way, early in the course of disease, to test for a specific type of progressive dementia. There is some indication that a study of the cerebrospinal fluid gathered from a spinal tap may indicate abnormal types of tau protein and/or abnormal ubiquitin protein and/or other abnormal cell inclusions[24]. Very high levels of these abnormal proteins may increase the accuracy (high sensitivity and specificity values) of a diagnostic test for a progressive dementia such as FTLD, semantic dementia, corticobasal ganglionic degeneration or one of the other related progressive dementias.

Need for Full Medical Evaluation
At this point in time a full medical evaluation (discussed in the companion text, Frontotemporal Lobar Degeneration (FTLD), available on www.AlzOnline.net) is the best means to achieve the most accurate diagnosis. If there is any question of changes in ability to remember, think, communicate, or do activities, a full medical evaluation is essential.

Value of Early, Accurate Diagnosis
An accurate early diagnosis may lead to early intervention and prevention. With early therapies, a person may reverse early signs of a progressive dementia because some conditions such as a vitamin B12 deficiency, thyroid imbalance or an anti-memory effect from medicines such as benedryl or other antihistamines, are treatable (which means the memory and thinking functions may return to normal or close to normal). Early diagnosis leading to appropriate care recommendations may result in the person being able to meet professional, personal, and relationship needs at normal levels of functioning.

Some of the FTLD conditions are difficult to distinguish early in the course of the disease. When the deficits are worse, the clinical picture may become clearer and more suggestive of the disease condition. If a specific test of blood, cerebrospinal fluid, etc. were available, the medical evaluation would be shorter and the diagnosis, therapy, and interventions quicker. Quicker intervention would, hopefully, help the patient function with more autonomy, more productively, and more fully for a much longer period of time.

Related Diseases

Tauopathy (Diseases)
A tauopathy is any progressive dementia with tau protein pathology and without (or with insignificant amounts of) ubiquitin protein pathology. Alzheimer's disease, frontotemporal lobar degeneration, progressive supranuclear palsy, and corticobasal ganglionic degeneration are considered to be tauopathies[9,10,25,26]. The Pick's bodies that are the hallmark of Pick's disease are made of round clumps of abnormal tau protein in the neurons.[14,15,27] The tauopathy from changes on Chromosome 17[16,28] result in the condition FTDP-17T (which stands for "**f**ronto**t**emporal lobar **d**egeneration with **p**arkinsonism on Chromosome **17** with **t**au abnormalities"), a specific tauopathy[15,29].

Although these conditions generally are considered tauopathies, significant amounts of ubiquitin (and minimal or no abnormal tau protein) have been identified in the brain cells of people diagnosed with some of these conditions, for example, Alzheimer's disease, FTLD (classic Pick's disease)[30] familial as well as sporadic FTLD[30-32] and semantic dementia a specific type of FTLD[10,20,23].

Non-Tauopathy (Diseases)
A non-tauopathy is any progressive dementia without (or with insignificant) tau protein pathology such as vascular dementia which may result from a series of small strokes or a large stroke. Another non-tauopathy is Creutzfeldt-Jacob disease, a rare progressive dementia that is a "distant cousin" of a progressive dementia called mad cow disease (bovine spongiform encephalopathy). Ubiquitin-positive findings have been linked to classic motor neuron disease, as well as motor neuron disease with dementia or with FTLD[33].

Some researchers conclude that non-tauopathies may account for 72% of cases of FTLD with 62% of these grouped as FTLD-U[17]. FTDP-17U stands for "**f**ronto**t**emporal lobar **d**egeneration with **p**arkinsonism on Chromosome **17** with ubiquitin abnormalities"[15,17-19,20,22,23,30.] Other researchers suggest a strong role in neurodegeneration associated with FTLD although the tissue of some brains they studied revealed no pathology including no abnormal ubiquitin[18].

Current Controversies about Tau and Ubiquitin

The inconsistent findings of researchers in studies of brain tissue reflect the many unknowns about the brain and brain disease. For example, research findings indicate significant abnormal ubiquitin protein in some brain tissue specimens of those diagnosed as FTLD with motor neuron disease while in other studies researchers find minimal or no abnormal ubiquitin protein in the brain tissue of people with that diagnosis. The researchers also differ in their findings of motor neuron disease-like inclusions in the cells they studied[7,9,10,18,19]. Some researchers have found no major differences regarding the progression of FTLD-U versus FTLD-T diseases[17] while other researchers have concluded that there is a shorter survival time when FTLD with motor neuron disease is the diagnosis[7,19].

There is a great deal of controversy in the research studies because there are many unanswered questions and so much not yet known about the brain, function of brain cells and brain systems, or brain disease[19]. There is also the factor of human differences; just as no two people are alike, no two presentations of the same disease in either clinical picture or tissue study are alike.

In order to keep up with the latest findings from research on abnormal tau and ubiquitin proteins, their impact on brain cells, ways to treat such conditions, and strategies to deal with long-term care management, it is essential that families maintain links to a wide network of loved ones, health and social service providers, community resources, and useful educational resources, such as those available on the internet. The following Table 1, Information on FTLD**,** lists resources for information and support specific to Frontotemporal Lobar Degeneration. The resources include web sites as well as toll-free telephone numbers, when they are available.

Table.1. Information on FTLD: Internet sites and Toll Free Phone Numbers
► **Association for Frontotemporal Dementias: www.ftd-picks.org** ► **National Aphasia Association: www.aphasia.org; (800)922-4622** ► **ALSA (Amyotrophic Lateral Sclerosis Association); www.alsa.org or info@alsa-national-org; (800)782-4747** ► **Society for Progressive Supranuclear Palsy: www.psp.org; (800)457-4777**

Other resources listed next in Table 2, General Resources, provide general information about progressive dementias and caregiver management that may be of help to people dealing with frontotemporal lobar degeneration. (These resources are listed also in the companion session ***Frontotemporal Lobar Degeneration,*** **www.AlzOnline.net**.)

Table 2. General Resources
► Alzheimer's Association (USA): **www.alz.org** or **www.alzheimers.com**; (800)272-3900 ► Alzheimer Society of Canada: **www.alzheimer.ca** ► Alzheimer's Society (United Kingdom): **www.alzheimers.org.uk** ► AlzOnline (at University of Florida): **www.AlzOnline.net** ► American Academy of Neurology: **www.aan.com; www.thebrainmatters.org** ► (National) Aphasia Association: **www.aphasia.org;** (800)922-4622 ► Family Caregiver Alliance: **www.caregiver.org;** (800)445-8106 ► Helpguide, Aging Issues: **www.helpguide.org/elder/lewy_body_disease.htm** ► Los Angeles Caregiver Resource Center: **http://geroweb.usc.edu/lacrc;** (800)540-4442 ► National Institute of Neurological Disorders and Stroke: **www.ninds.nih.gov/disorders**

References

1. Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., & Benson, D.F. (1998). Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. Neurology, 51(6), 1546-1554.

2. Kertesz, A., Hudson, L., MacKenzie, I.R., & Munoz, D.G. (1994). The pathology and nosology of primary progressive aphasia. Neurology, 44(11), 2065-2072.

3. Kertesz, A. & Munoz, D.G. (Eds.). (1998). Pick's Disease and Pick's Complex. NY: Wiley-Liss.

4. Association for Frontotemporal Dementias: www.ftd-picks.org (accessed 1/13/06)

5. The Lund and Manchester Groups. (1994). Clinical and neuropathological criteria for frontotemporal dementia. Journal of Neurology, Neurosurgery and Psychiatry, 57(4), 416-418.

6. Snowden, J.S., Neary, D., & Mann, D.M.A. (1996). Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia. New York: Churchill Livingstone.

7. van Swieten, J.C. & Rosso, S.M. (2006). Epidemiology of frontotemporal dementia. Advances in Clinical Neuroscience and Rehabilitation, 6(1), 9-10.

8. Kertesz, A., Kawarai, T., Rogaeva, E., St. George-Hyslop, P., Poorkaj, P., Bird, T.D., & Munoz, D.G. (2000). Familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusions. Neurology, 54(4), 818-827.

9. Chow, T.W., Miller, B.L., Hayashi, V.N., & Geschwind, D.H. (1999). Inheritance of frontotemporal dementia. Archives of Neurology, 56(7), 817-822.

10. Hutton, H., Lendon, C.L., Rizzu, P., Baker, M., Froelich, S., et al. (1998). Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature, 393(6686), 702-705.

11. Shaw, G. & Chau, V. (1988). Ubiquitin and microtubule-associated protein tau immunoreactivity each define distinct structures with differing distributions and solubility properties in Alzheimer brain. Proceedings of the National Academy of Sciences of the United States of America, 85(8), 2854-2858.

12. Wikipedia. Tau protein. http://en.wikipedia.org/wiki/Tau (protein) (accessed 3/2/06)

13. Wikipedia. Ubiquitin. http://en.wikipedia.org/wiki/Ubiquitin (accessed 3/2/06)

14. Kwon, J. (2006). Tau mutations directory. Alzheimer Research Forum. www.alzforum.org/res/com/mut/tau/default.asp (accessed 2/21/06)

15. Foster, N.L., Wilhelmsen, K., Sima, A.A., Jones, M.Z., D'Amato, C.J., & Gilman, S. (1997). Frontotemporal dementia and parkinsonism linked to Chromosome 17: A consensus statement. Annals of Neurology, 41, 706-715.

16. Goedert, M. & Spillantini, M.G. (2000). Tau mutations in frontotemporal dementia FTDP-17 and their relevance for Alzheimer's disease. Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease, 1502(1), 110-121.

17. Josephs, K.A., Holton, J.L., Rossor, M.N., Godbolt, A.K., Ozawa, T., Strand, K., Khan, N., Al-Sarraj, S., & Revesz, T. (2004). Frontotemporal lobar degeneration and ubiquitin immunochemistry. Neuropathology and Applied Neurobiology, 30(4), 369-373.

18. Katsuse, O. & Dickson, D.W. (2005). Ubiquitin immunohistochemistry of frontotemporal lobar degeneration differentiates cases with and without motor neuron disease. Journal of Alzheimer's Disease and Associated Disorders, 19(Supplement 1), S37-43.

19. Kersaitis, C., Halliday, G.M., Xuereb, J.H., Pamphlett, R., Bak, T.H., Hodges, J.R., & Krill, J.J. (2006). Ubiquitin-positive inclusions of pathology in frontotemporal dementia and motor neurone disease identifies a group with mainly early pathology. Neuropathology and Applied Neurobiology, 32, 83-91.

20. Kertesz, A., Kawarai,T., Rogaeva, E., St. George-Hyslop, P., Poorkaj, P., Bird, T.D., & Munoz, D.G. (2000). Familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusions. Neurology, 54(4), 818-827.

21. Nicholl, D.J., Greenstone, M.A., Clarke, C.E., Rizzu, P., Crooks, D., Crowe, A., Trojanowski, J.Q., Lee, V., & Heutink, P. (2003). An English kindred with a novel recessive tauopathy and respiratory failure. Annals of Neurology, 54(5), 682-686.

22. Rosso, S.M., Kamphorst, W., de Graaf, B., Willemsen,R., Ravid, R., Niermeijer, M.F., Spillantini, M.G., Heutink, P., & van Swieten, J.C. (2001). Familial frontotemporal dementia with ubiquitin-positive inclusions is linked to chromosome 17q21–22. Brain, 124(10), 1948-1957.

23. Rossor, M.N., Revesz, T., Lantos, P.L., & Warrington, E.K. (2000). Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. Brain, 123(2), 267-276.

24. Shoji, M., Matsubara, E., Murakami, T., Manabe, Y., Abe, K., Kanai, M., Ikeda, M., Tomidokoro, Y., Shizuka, M., Watanabe, M., Amari, M., Ishiguro, K., Kawarabayashi, T., Harigaya, Y., Okamoto, K., Nishimura, T., Nakamura, Y., Takeda, M., Urakami, K., Adachi, Y., Nakashima, K., Arai, H., Sasaki, H., Kanemaru, K., Yamanouchi, H., Yoshida, Y., Ichise, K., Tanaka, K., Hamamoto, M., Yamamoto, H., Matsubayashi, T., Yoshida, H., Toj, H., Nakamura, S., & Hirai, S. (2002). Cerebrospinal fluid tau in dementia disorders: A large scale multicenter study by a Japanese study group. Neurobiology of Aging, 23(3), 363-370.

25. Brito-Marques, P.R., Mello, R.V. & Montenegro, L. (2001). Classic Pick's disease types with ubiquitin-positive and tau-negative inclusions: case report. Arquivos de Neuro-Psiquiatria, 59(1),128-133.

26. Josephs, K.A., Petersen, R.C., Knopman, D.S., Boeve, B.F.,Whitwell, J.L., Duffy, J.R., Parisi, J.E. & Dickson, D.W. (2006). Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology, 66(1), 41-48.

27. Piao, Y.S., Tan, C.F., Iwanaga, K., Kahita, A., Takano, H., Nishizawa, M., Lashley, T., Revesz, T., Lees, A., deSilva, R., Tsujihata, M., & Takahashi, H. (2005). Sporadic four-repeat tauopathy with frontotemporal degeneration, parkinsonism and motor neuron disease. Acta Neuropathologica, 110(6), 600-609.

28. Martinaud, O., Laquerriere, A., Guyant-Marechal, L., Ahtoy, P., Vera, P., Sergeant, N., Camuzat, A., Bourgeois, P., Hauw, J.J., Campion, D., & Hannequin, D. (2005). Frontotemporal dementia, motor neuron disease and tauopathy: Clinical and neuropathological study in a family. Acta Neuropathologica, 110(1), 84-92.

29. Hardy, J., Momeni, P., & Traynor, B.J. (2006). Frontal temporal dementia: Dissecting the aetiology and pathogenesis. Brain, 129(4), 830-831.

30. Godbolt, A.K., Josephs, K.A., Revesz, T., Warrington, E.K., Lantos, P., King, A., Fox, N.C., Sarraj, S.A., Holton, J., Cipolotti, L.,Khan, N., & Rossor, M.N. (2005). Sporadic and familial dementia with ubiquitin-positive tau-negative inclusions. Archives of Neurology, 62(7), 1097-1101.

31. Piao, Y.S., Tan, C.F., Iwanaga, K., Kahita, A., Takano, H., Nishizawa, M., Lashley, T., Revesz, T., Lees, A., deSilva, R., Tsujihata, M., & Takahashi, H. (2005). Sporadic four-repeat tauopathy with frontotemporal degeneration, parkinsonism and motor neuron disease. Acta Neuropathologica, 110(6), 600-609.

32. Short, R.A., Graff-Radford, N.R., Adamson, J., Baker, M., & Hutton, M. (2002). Differences in tau and apolipoprotein E polymorphism frequencies in sporadic frontotemporal lobar degeneration syndromes. Archives of Neurology, 59(4), 611-615.

33. Mackenzie, I.R. & Feldman, H.H. (2005). Ubiquitin immunohistochemistry suggests classic motor neuron disease, motor neuron disease with dementia, and frontotemporal dementia of the motor neuron disease type represent a clinicopathologic spectrum. Journal of Neuropathology and Experimental Neurology, 64(8),730-739.