NEURODEGENERATIVE DISORDERS

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Overview

Recent advances in neurogenetics, molecular biology, and immunocytochemical staining methods have expanded the spectrum of neurodegenerative disorders now known to cause dementia +/- parkinsonism and motor neuron disease. A subset of these disorders tend to evolve from onset to death rather rapidly over 1-3 years, and the differentiation of these disorders (with no established disease-altering therapies) from the prion disorders and the autoimmune encephalopathies can be very challenging, particularly early in the course of symptoms. In this brief review, we will present case examples of many of these disorders and discuss the clinical and radiologic features that may evolve from onset to death within 3-4 years.

The nomenclature regarding the syndromes and disorders associated with dementia is confusing, and a few distinctions should be emphasized. Most clinicians use the term “clinically probable Alzheimer’s disease” (pAD) or Alzheimer’s disease dementia (ADem) for the dementia syndrome typically associated with the disease of AD. Lewy body disease (LBD) refers to the histopathologic disorder that typically underlies the syndromes of dementia with Lewy bodies (DLB), Parkinson’s disease (PD), and Parkinson’s disease with dementia (PDD). Behavioral variant frontotemporal dementia (bvFTD) refers to a dysexecutive-behavioral syndrome, whereas frontotemporal lobar degeneration (FTLD) refers to the pathologic state that often underlies the syndrome of bvFTD. The histopathologic findings of neuronal loss and gliosis without any additional specific features are characteristic of dementia lacking distinctive histopathology (DLDH), but also sometimes termed FTLD. These disorders and terms are reviewed further in the discussion that follows.

The most important issue for any clinician is to determine in whom with a rapidly progressive encephalopathy has a potentially treatable disorder (e.g., an infectious, autoimmune/inflammatory, or metabolic process) versus a disorder with limited or no effective therapies currently available (e.g., a paraneoplastic process, a prion disorder, or a neurodegenerative disorder). In most cases, an accurate diagnosis can be made following a comprehensive evaluation including blood and urine tests, CSF studies, EEG, and MRI +/- SPECT or PET scans. Cerebral angiography may be enlightening in select cases. Brain biopsy is most useful when directed toward a lesion on neuroimaging studies, but even “blind” biopsy of moderately involved tissue can be informative.

Most neurodegenerative disorders can be diagnosed with relative confidence when certain clinical features are present and additional diagnostic studies fail to reveal an alternative explanation. If biopsy is deemed appropriate, a wedge biopsy should be performed which would include ample meninges, neocortex, and subcortical white matter. Routine stains should be carried out to look for evidence of infectious and vasculitic/inflammatory processes. A full panel of immunocytochemical techniques should be employed to adequately evaluate the spectrum of prion and neurodegenerative disorders. Immunostains directed toward the following usually leads to a diagnosis: β-amyloid, tau, α-synuclein, neurofilaments, α-internexin, ubiquitin, TDP-43, and prion protein Preparing for brain biopsy requires adequate communication between the neurologist, neurosurgeon, and neuropathologist.

In this syllabus, several case examples are presented with a particular focus on non-Alzheimer's disease etiologies. In the slides for this course, these disorders as well as Alzheimer's disease will also be presented.

Dementia with Lewy Bodies

Case example. A male with 18 years of formal education, retired engineer, began exhibiting dream enactment behavior at night around age 65, in which he would scream and flail his limbs on 3 nights per week on average. He had sustained multiple bruises over several years, and his wife had been struck with punches and kicks a few times as well. When he awoke immediately after experiencing such an episode, he would relate to his wife the content of the dream, which often had a chasing or attacking theme with him being the one being chased or attacked. There was no snoring and no observed apnea. He developed cognitive and behavioral changes at age 72. He was mildly forgetful, was not able to perform sequential tasks (e.g., programming their VCR to record a TV show which he had previously done without any difficulties), was easily distractable, and had become lost on a couple of occasions while driving. He often experienced visual hallucinations in which deceased relatives would be present in rooms of his home. Capgras syndrome with associated delusions also developed, in which his wife Linda could be viewed as one of several "Lindas" – one was his true wife, another was a mean imposter trying to poison him, another was a boring imposter who seemingly sat aimlessly in a couch at home but tried to steal from him when he was elsewhere in the house. His wife observed some periods lasting several hours in which he would think and behave almost normally, but most of the time he was slow to think and move, was confused, and made bizarre comments. His initial neurologic examination was notable for an MMSE of 26/30 with his greatest difficulties being present in drawing the intersecting pentagons. He recalled 2/3 items on delay. He also had a masked facies, decreased eyeblink frequency, mild low amplitude and high frequency tremor of the limbs when outstretched or performing some activity but not at rest, mildly increased tone in both arms, and a tendency to shuffle when walking. Neuropsychological testing revealed deficits that were most prominent in attention/concentration, cognitive set shifting, verbal fluency, and constructional praxis, whereas his verbal memory and confrontation naming was preserved. He was diagnosed with clinically probable dementia with Lewy bodies (DLB) as well as probable REM sleep behavior disorder (RBD).

He was commenced on donepezil with mild improvement in his cognitive abilities but no change in his neuropsychiatric features. Quetiapine was added and his visual hallucinations and delusions decreased minimally despite 200 mg/day, and this agent was discontinued and olanzapine was commenced. Re-evaluation three months later showed a MMSE score of 20/30 and a marked increase in his parkinsonism. His hallucinations and delusions were much better. Carbidopa-levodopa was initiated with an impressive improvement in his motor skills but orthostatic hypotension developed. Three months later his agitation and aggression particularly directed toward "the mean Linda" led to his admission to an inpatient psychiatric unit. MMSE score at that time was 13/30, and mild orthostatic hypotension and parkinsonism were present. Mutliple changes in his medication regimen were attempted, but no conventional neuroleptics were ever used. He developed increasing abdominal pain which was later determined to be a bowel obstruction. A plethora of other medical problems developed over the ensuing two weeks and he was ultimately treated sufficiently that dismissal to home with appropriate nursing care was feasible. He died two days later for unclear reasons.

Diagnosis. The diagnostic criteria for DLB include dementia plus some combination of parkinsonism, visual hallucinations, cognitive fluctuations, and REM sleep behavior disorder.[1-4] Neuropsychological testing typically shows impairment maximal in attention/concentration/set shifting (eg, Trailmaking Test, Stroop, Digit Symbol, etc.), verbal fluency (COWAT), and visuospatial functioning (WAIS-R or WAIS-III Block Design, Picture Completion, Object Assembly, or Rey-Osterreith Complex Figure Test) with relative preservation in verbal memory and confrontation naming.[5-8] The hippocampi are less atrophic on MRI in DLB compared to AD,[9, 10] and functional neuroimaging studies have tended to show abnormalities in parieto-occipital cortices.[11, 12] The so-called "posterior cingulate island sign," in which the posterior cingulate metabolism is relatively preserved and appears like an "island" surrounded by hypometabolic tissue, is a relatively consistent finding in DLB patients.[13] It should be noted that clinical experience using FDG-PET scans in patients with typical DLB features is variable, and one should not base a diagnosis of DLB primarily on the FDG-PET findings. Dopamine transporter imaging using ioflupane SPECT is now available in the United States and Europe – studies in Europe have shown that reduced dopamine transporter uptake in the basal ganglia in those with dementia is highly suggestive of underlying Lewy body disease.[14] RBD is often present in DLB and this may be a particularly specific feature in the setting of dementia.[15-19] Early reports on DLB suggested that the disease course was more rapid than in AD, and the duration of symptoms in the case described above was indeed rapid. Yet recent survival analyses indicate that the mean duration of symptoms between DLB and AD are similar.[20] A recent overview of DLB can be found in this reference.[21]

Management. Cholinesterase inhibitors are the mainstay of management,[12] although treatment directed toward the neuropsychiatric (e.g., atypical neuroleptics), motor (e.g., carbidopa/levodopa or dopamine agonists), sleep (e.g., CPAP for obstructive sleep apnea, clonazepam or melatonin for RBD), and autonomic (e.g., physical therapy measures, midodrine) manifestations are often necessary.[3, 4, 21, 22]

Neuropathology. Most neuropathologists now characterize Lewy body pathology by the topography and frequency of Lewy bodies and Lewy neurites using ubiquitin and particularly α-synuclein immunocytochemistry. The syndrome of DLB is often associated with limbic- or neocortical-predominant Lewy body disease (LBD).[1, 2, 4] A recent clinicopathologic analysis validated the proposed clinical and pathologic diagnostic schemes proposed in the 2005 McKeith criteria.[23] The similar distribution of pathology is also present in patients with Parkinson's disease with dementia (PDD).[24] The wrinkle in this pathologic classification scheme is that many patients with Parkinson's disease *without* dementia have limbic +/- neocortical Lewy bodies at autopsy.[25] Clearly further work in this area is necessary to better understand the pathologic substrate for the dementia syndrome associated with LBD.

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 with a Mutation in the Gene Encoding *Microtubule Associated Protein Tau* (*MAPT*)

Case example. This right-handed man began experiencing speech articulation problems and stating yes – no reversals at age 24, and by age 25 he wasn't able to follow complex instructions and was more distractible, perseverative, and socially withdrawn. Memory also was declining. He lost control of his car which resulted in a crash. There was no disinhibited or inappropriate behavior exhibited, no motor symptoms, and no fasciculations nor dysphagia.

His parents and sister were alive and well, with no known relatives having any neurodegenerative disorder. On his initial examination, he scored 25/38 on the Kokmen Short Test of Mental Status (roughly equivalent to 24/30 on the MMSE), with difficulties in digit span, learning, calculations and abstractions. His delayed recall was intact. On language testing, he had mild difficulties with repetition, fluency, and naming, with comprehension relatively preserved. He occasionally would reverse yes for no, and he had mild apraxia of speech. The remainder of the examination was normal. Neuropsychological testing showed impairment in executive functioning, attention/concentration, and verbal fluency, with memory and visuospatial functioning relatively preserved. CSF analysis showed no abnormal findings. He was diagnosed with very early-onset sporadic FTD. Brain biopsy was contemplated but not performed.

He was re-evaluated 8 months later. His cognitive impairment progressed, and he now exhibited moderately disinhibited and socially inappropriate behavior. His MRI showed significant progression in bilateral frontal>temporal atrophy (representative images will be shown in the slides for this presentation). Brain biopsy was again considered. Because of his young age and marked progression over less than a year, despite his negative family history, he underwent genetic counseling and genetic testing for mutations in the microtubule associated protein tau (*MAPT*), and the G389R mutation in exon 12 was identified. Brain biopsy was obviously then considered unnecessary. By age 27, he was living in a nursing home, incontinent, did not recognize his family. He expired at age 31, and at autopsy there was marked frontotemporal cortical atrophy associated with numerous tau-positive inclusions.

Diagnosis. The initial diagnostic criteria for the clinical diagnosis of FTD[26] have been updated,[27] and focus on the striking behavioral features of disinhibition, loss of empathy, apathy, perseveration, etc. The clinical features, profile of impairment on neuropsychological testing, and frontal and/or temporal abnormalities on structural and functional neuroimaging studies make diagnosis relatively easy in most individuals. CSF analyses are typically normal except for the occasional patient with elevated protein, and phospho-tau and total tau are often elevated, but these values are not diagnostic. In this case, the clinical, neuropsychological, and radiologic features and absence of any CSF abnormalities made the diagnosis of FTD straight-forward, but this case is notable for his very early age of onset, rapid rate of progression, and presence of a mutation in the *MAPT* gene despite an absence of a family history of any neurodegenerative disorder. This case exemplifies how genetic testing in early onset dementia cases can be enlightening (again despite a negative family history), and negates the need for brain biopsy. More details on genetic testing are in the final paragraph of this section of the syllabus.

Management. The inappropriate, disinhibited, and aggressive behaviors often exhibited by FTD patients are challenging to manage. A few studies have been carried out demonstrating efficacy with selective serotonin reuptake inhibitors (SSRIs) and trazodone in this patient population.[28, 29] Atypical neuroleptics (e.g., quetiapine, olanzapine), anticonvulsants (e.g., carbamazepine, valproic acid), and beta blockers can also be effective. Occasional patients with prominent apathy may benefit from cholinesterase inhibitors, dopamine agonists, or psychostimulants.[30]

Neuropathology. While all cases with mutations in *MAPT* have tau-positive neuronal and/or glial inclusions, the specific histopathologic features can vary, even among relatives with the same mutation. Some cases have findings indistinguishable from sporadic Pick's disease, sporadic corticobasal degeneration (CBD), sporadic progressive supranuclear palsy (PSP), or sporadic argyrophilic grain disease (AGD). There are six isoforms of tau, three of which are so-called "3 repeat" due to 3 binding domains for associating with microtubules, and three "4-repeat" isoforms due to 4 binding domains.[31-33] Specific immunostains for 3-repeat

(3R) and 4-repeat (4R) tau have been developed, which has revealed Pick's disease is associated with predominantly 3R tau while CBD, PSP, and AGD are associated with predominantly 4R tau (Alzheimer's disease is associated with roughly equal proportions of 3R and 4R tau). Thus, the specific neuropathologic diagnosis not only rests on the specific findings using tau and other immunostains, but also genotyping *MAPT*. Astute neuropathologists may even suggest, based on the neuropathologic findings, that a mutation in *MAPT* is likely, and such testing can be done for clinical or research purposes in these instances.

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 with a Mutation in the Gene Encoding *Progranulin* (*PGRN*)

Case example. This right-handed woman developed personality/behavior changes and forgetfulness at age 56. She developed difficulties recalling people's names and a tendency to repeat herself in conversations. She had difficulties balancing their checkbook, resulting in several overdrafts, and she had forgotten items on the stove several times. She had minimal insight and reported her deficits as "a little forgetfulness." Her initial examination at our institution at age 56 found impairments in calculation, construction and learning. She was fluent, but she did make some paraphasic errors. She had significant difficulty following multi-step commands, and her general neurological examination was also notable for motor impersistence. She did not have any signs of parkinsonism or motor neuron disease at this time. Neuropsychological testing revealed impairments in language, memory, and executive functions. Initial MRI demonstrated mild temporal atrophy and subcortical white matter changes, greater on the right than the left**.** She was diagnosed with bvFTD and managed symptomatically.

Over the next year, she developed infrequent hallucinations and became progressively more forgetful. She would suspiciously look out of a door in their house 20 or more times per day. She began eating anything that was put in front of her, and gained 20 pounds over a couple of months. By age 58, she was dependent on others for her care, and her activities of daily living were limited to managing her personal effects and using the bathroom independently most of the time. Very mild rigidity was noted in her left arm and leg at this visit. Annual MRI evaluations documented progression of this atrophy, most prominently in the temporal lobes (greater on the right) as well as progression of the deep white matter T2 changes as well (representative images will be shown in the slides for this presentation). Over the next year rigidity progressed to the degree that her left arm was held in flexion and her gait was disturbed due to left leg rigidity. She was entirely dependent upon others for her needs.

Two of her brothers and her father all had a very similar disorder, with motor features most evident on the left. Her brothers had pathologic findings of FTLD-U with neuronal intranuclear inclusions.[34] *PGRN* analysis in her and one of her brothers revealed a single base pair deletion in exon 9 (c.1145delC).[35, 36] The effect of this mutation is to cause a frameshift (p.Thr382SerfsX30), creation of a premature termination codon, and, likely, create a null allele through nonsense-mediated decay.[35, 36] The mechanism for progranulin mutations is therefore presumed to be mediated through a haploinsufficiency mechanism whereby approximately 50% of the normal amount of progranulin in produced and secreted; how this haploinsufficiency leads to focal brain degeneration is still not clear.

Diagnosis. The clinical phenotypes associated with mutations in *PGRN* are varied, and includes mild cognitive impairment, probable Alzheimer's disease, Parkinson's disease, Parkinson's disease with dementia, and DLB in addition to FTD +/- parkinsonism and one of the progressive aphasia syndromes. The corticobasal syndrome has also been particularly frequent in the cases reported thus far[35-46] The diagnosis is made on testing for mutations in *progranulin* (also called "granulin" and abbreviated *"GRN"*). More details on genetic testing are in the final paragraph of this section of the syllabus.

Management. See section under FTD associated with *MAPT* mutation.

Neuropathology. Upon histologic exam, the consistent finding is FTLD-U with neuronal intranuclear inclusions.[35, 36, 38, 39, 41-45] Immunostaining directed against progranulin stain normal structures and not the ubiquitinated protein(s) that is(are) presumed to be pathogenic[47]; rather, TAR DNA-binding protein 43 (TDP-43) was recently discovered to be the ubiquitinated protein in FTLD-U, FTLD with motor neuron disease, and in those with clinical ALS.[48] All *PGRN* mutations identified thus far cause premature termination codons, inducing nonsense mediated decay or a related mechanism to result in a 50% reduction in progranulin production, or haploinsufficiency – a true loss of function.[35, 36, 38]

Frontotemporal Dementia Associated With a Mutation in the *C9ORF72* Gene

Case example. This right-handed male with 16 years of formal education began exhibiting personality changes at age 33, initially manifested by lack of interest and aggressive tendencies directed toward his children. He also became hyper-religious and started to purchase many religious rock CDs which was a theme very different from his usual musical interests. He was described as selfish, hypervigilant at times, and he tended to cram food into his mouth while eating (ie, gluttony). Hypersomnolence also evolved, in which he might sleep for 18-20 hours on some days. His memory and organizational skills also declined, and by age 34 he was also exhibiting changes in his speech output. He was released from his place of employment. His family history was

only notable for alcohol dependence in his maternal uncle and late onset dementia in his paternal grandfather. He was treated with over a dozen different psychotropic medications for presumed bipolar disorder and schizophrenia.

His initial neurologic examination at MCR revealed impulsivity, tendency to pace, poor comprehension and failure to follow any commands. He was entirely mute. There was reduced upgaze on eye movement testing. His tone, strength, and deep tendon reflexes were all normal, and pyramidal tract signs, frontal release signs, and fasciculations were all absent. He underwent a comprehensive work-up, with blood/urine/CSF studies all normal, but his MRI showed moderate bilateral frontal cortical atrophy and subtle R>L amygdale atrophy. He was diagnosed with rapidly progressive FTD.

His wife and parents sought a clear diagnosis, and the patient proceeded to undergo biopsy of the right frontal meninges, neocortex, and white matter. The findings showed marked gliosis, diffusely positive staining in axons for neurofilament, and rare ubiquitin-positive inclusions in neurons. Beta-amyloid, tau, α-synuclein, and prion protein immunocytochemistry were all negative. These findings were considered most consistent with frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U). Although this disorder was not treatable, the family greatly appreciated the fact that a neurologic disorder was underlying his symptoms, and a specific disease process was identified. His former employer and insurance provider finally approved full and permanent disability, with all appropriate legal and financial repercussions granted to the patient's family. The patient continued to rapidly decline, culminating in his death at age 35, only 2 years after the onset of his symptoms. Neuropathologic examination revealed ubiquitin-positive inclusions (much more frequent than on brain biopsy) diffusely scattered in the frontal, temporal, and parietal neocortex. There was also marked degeneration of the substantia nigra. With the advent of TDP-43 immunohistochemistry becoming available in late 2006, the tissue was re-examined and indeed the ubiquitin-positive inclusions also stained positively to TDP-43.

Following the discovery of the GGGGCC hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (*C9ORF72*) gene in 2011,[49, 50] we performed genetic analysis on stored frozen tissue and confirmed that this patient indeed carried the mutation. We subsequently learned that the patient's father had developed ALS in his 60's, and he undoubtedly had the same mutation as his son.

Diagnosis. This patient exemplifies the challenge of establishing an accurate diagnosis in a previously healthy young adult with a rapidly progressive neuropsychiatric disorder. At the time of his assessments, he had no obvious significant family history for any neurodegenerative or primary psychiatric disorder, yet his father's development of ALS exemplifies the wide range of age of onset associated with the *C9ORF72* mutation. While bipolar disorder and particularly schizophrenia were certainly reasonable considerations in this case, his prominent executive dysfunction, development of mutism, lack of delusions and hallucinations, and atrophy on his MRI, along with his other features, were highly consistent with FTD. Because the course was so rapid and the family sought a clear diagnosis, the clinicians involved in this case and his family chose to proceed to brain biopsy. The primary reason for performing brain biopsy in cases like this is to look for evidence of a potentially-treatable non-degenerative disorder, and no such findings were present. Interpretation of the biopsy findings in cases like this can also be troubling, since most of the neurodegenerative and prion disorders that can underlie rapidly progressive FTD have distinctive histopathology revealed by immunocytochemistry, yet scattered and rare ubiquitin-positive inclusions can be seen in a variety of disorders. Dementia lacking distinctive histopathology (DLDH) is a pathologic diagnosis of exclusion, and sampling error can suggest this disorder even though a disorder *with* distinctive histopathology could be the underlying process. Immunostains directed toward TDP-43 are critical to perform when evaluating patients with early-onset dementia in whom brain biopsy is performed. Since the *C9ORF72* mutation is now known to be the most common cause of familial FTD and familial ALS, and numerous cases of apparently sporadic disease have been identified associated with this mutation, consideration of genetic testing in sporadic as well as familial FTD has been heightened.

Management. See section under FTD associated with *MAPT* mutation.

Neuropathology. More recent consensus criteria for the pathologic diagnoses of this and related disorders have been published – readers are encouraged to obtain and refer to these updated papers for all FTLD-related matters.[51-53]

DLDH has been the most frequent pathologic diagnosis in some series of autopsied FTD patients.[54] Almost all such cases that have been re-examined and found to have TDP-43 pathology.

The rapid evolution in our understanding of c9FTD/ALS, and apparent frequency among sporadic and familial FTD and/or ALS, underscores the worthiness of readers to review several key papers on this entity. [53, 55-62]

Frontotemporal Dementia Associated With Frontotemporal Lobar Degeneration With Ubiquitin-Positive but TDP-43-Negative Inclusions

Case report. A right handed gentleman began exhibiting cognitive and behavior changes at age 50. He had difficulties keeping score when he and his wife played golf. He had a history of significant alcohol intake, and

he suddenly and dramatically decreased his intake of alcohol. He became less motivated to maintain hygiene, tends to laugh at inappropriate times, his recent memory was very impaired, and he was quite impatient and disinhibited. For example, he tended to stare at young female neighbors, also would bring a toy gorilla to the carnival and at work. He would pick up rocks stating it was for his fish tank when he had none. He took great pleasure in stepping on ants whenever possible. He avoided cracks in the sidewalk and told others not to step on them. His intake of liquids greatly increased, and he sought sweets whereas before he was very meticulous in eating a good diet. Thioridazine was instituted with minimal change. Two siblings had chronic mental illness, but there was no definitive family history of any neurodegenerative disorder.

On examination, he was a hypervigilant gentleman who appeared his stated age, went to use the bathroom three times during an hour long visit, was often walking around the room and tinkering with shells and other items in the examiner's room as well as art work that the examiner's daughter had made, made comments such as his brother is "queer", and he touched the examiner's hair, stating that it was very curly, and commented that the lenses of the examiner's glasses are quite thick. (Note – for those clinicians with an atypical hair style, spontaneous comments about hair, or touching/grabbing an examiner's hair without asking for permission, is an obvious sign of disinhibition and highly typical of those with FTD). He was fully oriented, had good recall of recent events in the news. Palmomental reflex was significantly present bilaterally, snout was also but less obvious, as was a subtle glabellar reflex. There were no signs of motor neuron disease nor parkinsonism, and no tremor or myoclonus.

On neuropsychological testing, his primary domains of impairment were in executive functioning, verbal fluency, and learning, with relative preservation on delayed recall and visuospatial functioning. His laboratory studies, including CSF, was only notable for a mildly increased protein at 78. His EEG was normal during the wake state. MRI showed impressive bifrontal cerebral cortical atrophy as well as mesial temporal lobe atrophy and hippocampal atrophy, right more so than left. There was obvious caudate atrophy. The inferior lateral and anterior temporal lobes were actually quite preserved. He was diagnosed with bvFTD and commenced on valproic acid with mild improvement in his behavior. Months later he developed muscle cramps and sparse fasciculations, and subsequently dysphagia, resulting in aspiration and death at age 52, only 2 ½ years after onset of symptoms. Neuropathologic examination initially was characterized as dementia lacking distinctive histopathology (DLDH). We have since re-examined this case with ubiquitin and TDP-43 immunohistochemistry, and have found numerous ubiquitin-positive inclusions but none are TDP-43 positive. Severe neuronal loss and gliosis of the caudate was also present.

Diagnosis. The diagnosis of FTD was also straight-forward in this case. This patient exemplifies how modern immunohistochemistry can redefine older cases.

The newly appreciated entity of FTLD-U but TDP-43 negative appears to have some important differences compared to the far more common FTLD-U/TDP-43 cases and FTD cases associated with tau pathology. These cases tend to be younger, tend NOT to have any family history of neurodegenerative disease, and tend to have imaging and pathologic evidence of severe caudate atrophy.[63-65]

Management. See section under FTD associated with *MAPT* mutation.

Neuropathology. Additional details on the neuropathologic characteristics can be found in references.[63-65]

Considerations on Genetic Testing

In patients with dementia – regardless if there is a positive family history of dementia/parkinsonism/motor neuron disease or not – genetic testing sometimes provides a definitive diagnosis and obviates the need for invasive tests such as brain biopsy. Although there are many circumstances when genetic testing would not be ideal (e.g., rapidly progressive course making a 3-6 week wait for results unattractive, limited financial resources, troublesome insurance issues or family dynamics, etc.), there are instances when genetic testing would be reasonable. Ideally, patients and their relatives should formally meet with genetics counselors for appropriate pre- and post-test counseling. In some circumstances, a formal psychiatric consultation may be indicated to ensure that the patient is mentally fit to consent to testing and to deal with the results if testing reveals a mutation.

Additional resources on genetics issues pertinent to the material covered in this section can be found in these references[56, 66, 67] and the websites below; the GeneTests site is particularly helpful to identify centers around the world which perform research and/or clinical testing for various syndromes and mutations:

GeneTests
http://www.genetests.org/

On-Line Mendelian Inheritance in Man – *Microtubule Associated Protein Tau*
http://omim.org/entry/157140

On-Line Mendelian Inheritance in Man – *Progranulin (*or *Granulin)*
http://omim.org/entry/607485

On-Line Mendelian Inheritance in Man – *C9ORF72 (or C9orf72)*
http://omim.org/entry/105550

Alzheimer Disease & Frontotemporal Dementia Mutation Database
http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=0&ML=0&Page=Home

Education, Support and Research

For patients/families interested in research participation, as well as considerable information pertaining to diagnosis, management and support, some key sites are listed below:

Dementia With Lewy Bodies
Contact the ***Lewy Body Dementia Association***: www.lbda.org

Frontotemporal Dementia
Contact the ***Association for Frontotemporal Degeneration***: www.theaftd.org

Advancement of Research in Frontotemporal Lobar Degeneration Research (ARTFL)
https://clinicaltrials.gov/show/NCT02365922

Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)
https://clinicaltrials.gov/show/NCT02372773

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