Motor Sequela of Dementia

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Introduction: Consideration of motor disorders in patients with dementia is of clinical importance in establishing the etiopathogenesis of dementia in affected patients, and in many instances, in determining disease progression and prognosis. The motor manifestations may vary from mild extrapyramidal rigidity to paralysis depending on the type and the stage of the dementia. For example, patients with Alzheimer disease (AD) develop parkinsonian features and motor difficulties later in their illness; such symptoms at onset should prompt consideration of dementia due to Lewy bodies (DLB) or another type of dementia[1,2]. An alternative reason would be a more aggressive type of AD, often associated with a worse prognosis[3,4].

This chapter addresses motor disorders early and late in the course of dementia of various causes along with the epidemiology, pathophysiology and available treatments. The dementias associated with acquired immunodeficiency syndrome, normal pressure hydrocephalus, and motor neuron diseases are covered elsewhere.

Alzheimer Disease: While the pathology is identical, AD can be divided into two clinically different phenotypes defined by different genotypes, namely early onset AD (EOAD), with age at onset prior to the age of 60, and late onset AD (LOAD), with an onset after 60 to 65 years[5,6].

About 5% of cases of AD are of the EOAD type. Autosomal dominant mutations in the presenilin 1 gene on chromosome 14 (the most common type), in the presenilin 2 gene on chromosome 1 or the APP gene on chromosome 21, as seen in patients with trisomy 21, account for about half of the cases of EOAD[5,6]. Patients with EOAD typically manifest myoclonus, parkinsonism, and psychiatric features early in their course with rapid progression to infirmity and death[7,8]. They may be misdiagnosed by virtue of their relative youth.

In one kindred[9], the proband developed depression at 29 followed by dementia one year afterward, and dysarthria, aphasia and myoclonus four years later. He developed seizures by age 36 and died at 38. His brother developed cognitive impairment at age 27, and by 30 had aphasia, myoclonus and generalized seizures, followed by limb rigidity at 32 and death a year later. The father had mood swings from age 35 followed by violent temper, dementia, generalized seizures and myoclonus from age 38. A clinical diagnosis of Creutzfeld-Jakob disease was made, although brain pathology subsequently revealed AD. This family, with an exceptionally early age of onset and a virulent course characterized by early motor disturbances, was found to have a mutation in the PS1 gene on chromosome 14[9].

The molecular pathogenesis of EOAD reflects acceleration of abnormal accumulation of beta amyloid and tau protein. Genetic screens are commercially available to screen for the commonest mutations. However, as it appears that many families have a 'private' mutation unique to that family, a negative genetic screen for common mutations for EOAD does not preclude the diagnosis[10]. While the response to treatment in EOAD has been less well studied than late onset AD, treatment with acetylcholinesterase inhibitors and N-methyl D-aspartate (NMDA) antagonists such as memantine is warranted.

The course of LOAD is more indolent than that of EOAD, with a prevalence of 9% above the age of 65, rising to between 35% and 50% in persons above the age of 85[11,12]. Women are at a higher risk than men even after controlling for greater longevity, although this issue is controversial[13]. In contrast to EOAD, LOAD manifests a multi-factorial etiology with contributions from genetics and the environment[14,15]. The presence of the E4 isoform of the apolipoprotien E gene on chromosome 19, as well as alpha-2-macroglobulin polymorphisms significantly increases the risk for the disorder[16]. Other associations with variants in the sortilin-

related receptor 1 (SORL1), complement component (3b/4b), clusterin and phosphatidylinositol-binding clathrin assembly protein have been reported. [17], [18]

Environmental factors are of equal or greater importance in determining development of LOAD including antecedent head trauma, early hysterectomies, lower educational levels, cardiovascular disease and low levels of physical activity[14]. The neuropathological changes of AD commence in the third decade and a higher premorbid intellect correlates with protection from dementia in later life [19].

Motor manifestations in LOAD are uncommon early in the course of the condition when the disease is confined to the temporal cortex. As the illness progresses, the earliest motor symptom is extrapyramidal rigidity, which if present early, implies another diagnosis or a poor prognosis[3,4]. Five to ten years into LOAD, patients may develop geggenhalten, apraxia and other frontal release phenomena as well as left hemibody neglect[20]. Myoclonus, seizures, and spasticity occur in the later terminal stages.

Magnetic resonance imaging (MRI) of the brain reveals hippocampal and general cortical atrophy[21]. Brain proton emission tomography (PET) shows hypometabolism of the temporal and parietal lobes[219]. There are new techniques available to image β−amyloid plaque burden and distribution further assisting in confirming the antemortem diagnosis[22].

Treatment is directed at the cognitive symptoms and the psychiatric disturbances. Therapy of the cognitive disorder includes the use of cholinesterase inhibitors including donepezil, rivastigmine and galantamine in the early stages of the condition[23]. These treatments can be continued well into the disease as long as they are tolerated although data regarding efficacy of these agents after the first two to three years is inconsistent[231]. The NMDA receptor antagonist memantine reduces glutamate-mediated neurotoxicity of vulnerable neurons, and has

been approved for the treatment of moderate to severe AD[24]. Patients treated with a combination of a cholinesterase inhibitor and memantine fared better than those given either drug alone[25]. Atypical antipsychotic agents such as quetiapine are effective for associated psychotic symptoms and agitation and have fewer side effects, while serotonin reuptake agents are efficacious in treating depression in AD.

Dementia due to Lewy Bodies: This is the second most common dementia accounting for 10 to 15% of cases at autopsy[26]. Subcortical and cortical Lewy bodies are associated with a variable combination of cognitive, psychiatric, and extrapyramidal features. Men are more affected than women with prevalence at autopsy of 1.5:1. The course was first considered to be far more rapid than AD with a survival of 2 to 5 years from presentation to death, but the current view is that for the majority of both DLB and AD patients, survival is about 12 years[1,27]. The clinical definition of DLB includes fluctuation of cognition and early prominence of psychiatric symptoms, especially visual hallucinations, in up to 75% of patients, and parkinsonian features that lead to frequent falls, rigidity, gait impairment; resting tremor infrequently occurs[1,28]. Symptoms of restless leg syndrome can precede the diagnosis of DLB by several decades and rapid-eye-movement sleep behavior disorder is a parasomnia frequently associated with DLB[29]. While a quarter of patients demonstrate rigidity and bradykinesia, the frequency varies depending upon patient selection bias and the confounding effects of neuroleptics. Postural instability, falls and syncope occur in up to a third of patients and should prompt consideration of DLB. Autonomic phenomena are more common in patients with DLB than in AD, particularly orthstatic hypotension and carotid-sinus hypersensitivity[30]. Urinary incontinence is an early phenomenon in DLB compared with AD[31].

In contrast to AD, cortical Lewy bodies are preferentially deposited in the cingulate gyrus, insular cortex and temporal lobe with sparing of the hippocampus in cases of DLB, and neocortical neurofibrillary tangles are sparse or absent reflecting the difference in tau processing. Beta-amyloid protein levels are equally increased in both disorders. Patients with DLB and an excess of tangles demonstrate a clinical pattern more akin to AD, while those with fewer tangles present with the classical features of DLB[1,32].

Brain MRI of patients with DLB shows preservation of the volume of hippocampal and medial temporal lobes and SPECT demonstrates occipital hypoperfusion[33]. Electroencephalography may show slowing of the background and posterior dominant rhythms. Dopamine transporter loss in the caudate and putamen as demonstrated on fluoropropyl brain SPECT confers a diagnostic sensitivity of 83% and a specificity of 100%[34].

There are differences in the neuropsychological profile of DLB compared to AD. Patients with DLB perform quantitatively worse on learning and memory tasks when compared with AD patients of the same degree of dementia severity, and manifest differences in focal attentional ability on visual search tasks[1,35].

Treatment of the cognitive loss with cholinesterase inhibitors is associated with a consistently more robust response in DLB than in AD[1,36]. Extrapyramidal symptoms may respond to anti-parkinsonian agents, although dopamine agonists, monoamine oxidase-B inhibitors and anticholinergic medications also have the potential to exacerbate psychiatric symptoms[36]. Neuroleptics that are used to treat psychiatric symptoms can result in acute extrapyramidal reactions in up to one half of patients due to loss of substantia nigra dopaminergic neurons and the failure of up-regulation of post-synaptic striatal D_2 receptors in response to the nigrostriatal deficit and the neuroleptic challenge[37]. The atypical neuroleptic

clozapine, which exerts its antipsychotic effects via the D_4 receptors is generally better tolerated and very low doses are sufficient for symptom control. DLB should be considered in patients with the clinical diagnosis of idiopathic Parkinson's who develop psychotic symptoms in response to anti-parkinsonian drugs[38].

Parkinson Disease Dementia: About 10% to 40% of patients with PD develop dementia (PDD) and a large number of patients with PD also develop mild cognitive impairment. About 15% to 20% of patients in movement disorders clinics, and a quarter of those in one autopsy series diagnosed with idiopathic PD had another neurodegenerative condition such as AD[39]. Since the pathology of PDD and DLB are similar, the clinical designation should conform to an arbitrary "1-year rule", which requires that parkinsonian features antedate dementia by more than a year to evoke the diagnosis of PDD, whereas dementia within 12 months of the onset of parkinsonism should lead to the designation of DLB[40]. Clues to accurate diagnosis include the presence of rest tremor, which is seen in up to 90% of clinical series, and 76% to 100% of pathologically confirmed cases of Parkinson's disease, and a favorable response to levodopa[41]. The occurrence of PDD is associated with a worse prognosis and a less favorable response to anti-parkinsonian medication than PD without dementia[42].

Thirteen kindred with autosomal dominant, progressive frontotemporal dementia and Parkinsonism have been mapped to chromosome 17[43]. Accompanying findings included disinhibition, apathy, poor impulse control, psychosis, alcoholism, dystonia, eye movement abnormalities, eyelid opening and closing apraxia, and upper and lower motor neuron dysfunction. Neuropathological features include tau-positive cytoplasmic inclusions and

ballooned neurons in some but not all kindreds. PDD may be treated with the available anti-cholinesterase medication[44].

Frontotemporal Lobe Dementia: Patients with frontotemporal lobe dementia (FTLD) have selective although differential involvement of frontal and temporal lobe cortices, depending on the type of FTLD. Of the three types of FTLD, the most common is behavioral variant frontotemporal dementia (bvFTD), followed by semantic dementia (SD) and progressive non-fluent aphasia (PNFA)[45,46]. The onset is generally before age 65[47], with nearly one-half of patients having an affected first-degree relative. About 30-50% of FTD cases are familial and mutations of the microtubule associated protein tau and progranulin genes, both on chromosome 17, account for about half of the familial cases. (ref46),[48] Most patients have evidence of frontal lobe involvement with frontal release signs including grasp, snout or sucking reflex[49]. Motor neuron signs can accompany clinical syndromes of lobar degeneration[50].

The bvFTD type of FTLD, also known as Pick disease, is associated with a dramatic change in personality and social conduct, with apathy, loss of volition, social disinhibition and distractibility, and preservation of memory, while both PNFA and SD, previously known as primary progressive aphasia, are associated with significant language difficulties[51,52]. The differentiation of bvFTD, PNFA, and SD forms of FTLD, as well as the more recently described logophenic phonological variant is summarized in Table 1.

All three lack a significant spatial disorder, as manifested by intact diagram copying and dot counting; and intact perception as tested by naming challenges, functional object descriptions, and pantomime object use. FTD patients perform poorly on tests of frontal lobe function including the Wisconsin card sort, Stroop and Trail making tests[52,53].

Brain MRI and PET and SPECT imaging demonstrate concordant atrophy and abnormal tracer uptake in frontal and anterior temporal cortices, which may be bilaterally symmetric or asymmetric, affecting the left or right hemisphere disproportionately[54]. In FTD, there is prominent bilateral and symmetric atrophy of the frontal lobes. The slowing of the background often seen on EEG in AD is not generally seen in the FTLD syndromes. Asymmetric atrophy of the left frontal and temporal lobes is seen in forms of PNFA and SD is associated with symmetrical atrophy of bilateral anterior temporal neocortex, and inferior and middle temporal gyri. Microscopically, all forms of FTLD are associated with microvacuolar change without specific histological features and severe astrocytic gliosis with or without ballooned cells and Pick-type inclusions[52,55]. There are currently no effective treatments for the FTLD syndromes.

Vascular Dementia: Vascular dementia (VaD) is a heterogeneous category of dementia, encompassing lesions due to embolism, hemorrhage, and ischemia; affliction of vessels of differing caliber, large and small, both named and unnamed, with involvement of cortical and subcortical structures. Strategic large vessel strokes of the right posterior cerebral artery and anterior cerebral artery territories can result in a clinical dementia, as may single lacunes in the genu of the capsule, intralaminar thalamic nuclei, and head of the caudate[56,57]. Subcortical ischemic VaD is due to lacunar infarction and periventricular leukoariosis that spares U fibers as in Binswanger disease[57]. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is due to mutations in the Notch3 gene on chromosome 19[58]. The three elements that are required for the clinical diagnosis of VaD include cognitive loss; cerebrovascular etiopathogenesis inferred by history, examination, and neuroimaging; and onset of dementia within 3 months of a symptomatic stroke[57,59]. The latter criterion is not necessary

for the diagnosis of subacute VaD. Clinical and motor manifestations will vary depending on the site of the lesion.

A careful history may reveal memory loss antedating the stroke in 10% to 15% of patients suggesting underlying AD worsened by stroke[60]. Binswanger subcortical pathology was found in a third of normal subjects age 65 and older, and in about 50% of those with AD, leading one expert to cite it as an ongoing 'silent epidemic'[61]. A longitudinal study of nuns found that the presence of one or more lacunes increased the risk for AD 20-fold and reduced the plaque and tangle burden required for clinical signs to appear[62]. The importance of the vascular component in dementia needs to be specifically recognized and treated. Patients with AD and seemingly trivial vascular lesions warrant treatment to control cerebrovascular risk factors and to promote stroke prevention. Antihypertensive therapy is associated with a 28% reduction in the risk of recurrent stroke, and a 38% to 55% reduction in the risk of dementia[63], [64]. Such therapy also may delay the development of clinical symptoms of dementia in patients with pathological signs of disease.

Cholinesterase inhibitors are useful in the management of VaD[65]. All the available cholinesterase agents approved for the treatment of AD have been efficacious in treating patients with VaD. It is suggested that calcium channel blockers may be beneficial in VaD and AD by improving calcium dysregulation and conferring neuroprotection[66].

Corticobasal degeneration: Corticobasal degeneration (CBD) presents generally around the age of 63 years. Dementia occurs in the course of the disease[67]. Proposed clinical diagnostic criteria include the presence of predominant basal ganglia and cortical signs at onset, with limb rigidity and either apraxia, cortical sensory loss, or alien limb phenomenon[68]. An

alternative nosology delineates rigidity, limb dystonia, and focal reflex myoclonus as the predominant features[69].

The earliest sign of CBD in up to one half of patients is asymmetric, progressive, limb clumsiness, with or without rigidity. Akinesia, rigidity, and apraxia occur in over 90% of cases within about three years of disease[70]. There may also be a gait disorder, postural instability, dysarthria, orofacial dyspraxia, blepherospasm, hypomimia, painful paresthesias, corticospinal tract signs, behavioral problems, loss of two-point discrimination and extinction to double simultaneous stimulation, and action and postural tremors of 6-8 Hz. This tremor is more irregular and jerky than the slower rest tremor of PD. There may be superimposed myoclonus elicited by percussion. Asymmetric limb dystonia is observed in a vast majority of patients with superimposed choreoathetosis of limb and face muscles[71]. The upper limb is the most affected region in choreoathetosis, leading to flexion of the arm and hand, and adduction of the shoulder[72].

Eye movement abnormalities include bilateral horizontal saccades with slowed extraocular movements appearing to require multiple steps to reach a target. Vertical saccades are usually normal, helping to differentiate CBD from progressive supranuclear palsy[73,74]. Depression occurs commonly in CBD, followed by apathy, irritability and agitation. Delusions and obsessive-compulsive behavior are less common.

Formal cognitive and neuropsychological testing shows particular affliction of executive function, with better performance on tests of immediate recall and attention in CBD as compared to patients with AD and extrapyramidal disease, but more impairment in tests of praxis, digit span, and unimanual and bimanual motor series. Recognition memory is generally spared, with impairment of encoding and recall strategies[75].

Neuroimaging is typically normal early in the disease, but with progression, MRI shows asymmetric posterior frontal and parietal cortical atrophy with ventricular dilatation. Focal atrophy of the corpus callosum correlates well with impaired cognition[76]. Brain PET shows a global reduction of oxygen and glucose metabolism in the cerebral hemisphere contralateral to the most affected limb, and in the thalamus with dysfunction of the nigrostriatal dopaminergic system[77]. A characteristic pattern of asymmetrically reduced frontoparietal cerebral cortical metabolism and cerebral blood flow in conjunction with bilaterally reduced F-dopa uptake in the caudate and putamen supports the diagnosis of CBD[78,79]. The parkinsonian syndrome of CBD responds poorly to levodopa, which aids in differentiating it from idiopathic PD. The pathology of CBD can be associated with bvFTD, semantic dementia and progressive nonfluent aphasia (ref68).

Neuroacanthocytosis: Acanthocytes are irregularly spaced erythrocytes with a thorny surface and terminal bulbs, and a valuable clue to the presence of neuroacanthocytosis. The three syndromes of neuroacanthocytosis include abetalipoproteinemia, McLeod syndrome, and chorea-acanthocytosis (ChAc)[80]. Subcortical dementia is a pervasive feature of ChAc. An autosomal recessive disorder due to a mutation on the gene encoding the protein chorein on chromosome 9, ChAc has a mean age at onset of 35 years, with a range from the first to seventh decade[81].

Psychiatric symptoms include cognitive impairment, personality changes and depression with alteration of frontal lobe function. The chorea resembles Huntington disease (HD) with involuntary movements of the tongue and lips, vocalizations, dysarthria, dysphagia, and involvement of the legs[82,83]. Repetitive motor tics are present and dystonia may be presenting features. Hyperkinesis can progress to parkinsonism, and orofacial movements can lead to

feeding disturbances. Areflexia is typically noted on examination. Seziures can occur in some patients. Increased liver enzymes and reduced haptoglobin levels are noted in the majority of patients, along with circulating acanthocytes, some of which may be mistaken for echinocytes. Electrophysiological testing shows peripheral neuropathy in all patients. Atrophy of the caudate nucleus is demonstrated on MRI along with abnormal increased T2 signals in the caudate and putamen[84]. Brain PET studies shows dysfunction of dopaminergic neurons in the ventrolateral substantia nigra with reduced uptake in caudate, putamen and frontal cortex.

In McLeod syndrome, cognitive and psychiatric impairment occur in up to 45% of patients typically late in the disease course[85]. It demonstrates X-linked inheritance with a clinical presentation similar to ChAc but distinguished by the presence of the Kell antigen, which is present in all cases and is the third most important blood group after ABO and Rhesus. Acanthocytes are present in 3% to 40% of patients.

Abetalipoproteinemia presents with fat malabsorption, pigmentary retinal degeneration, progressive ataxia, neuropathy and acanthocytosis, but without dementia. There is a recently described syndrome of chorea, dementia, parkinsonism and acanthocytes, without linkage to the ChAc locus[86].

Wilson Disease: This is an autosomal recessive disorder of copper metabolism due to dysfunction of a copper transporting protein encoded on chromosome 13. A quarter of patients demonstrate hepatic and neuropsychiatric symptoms at the time of first presentation. Affected patients demonstrate dysarthria, drooling, clumsiness of the hands, and personality change. Presentation later in life is associated with parkinsonism, dystonia and chorea. The etiopathogenesis is associated with the disturbed metabolism of copper that leads to it's

accumulation in the liver with reduced serum ceruloplasmin, and increased hepatic and urinary copper levels[87,88].

Hepatic dysfunction is the most common manifestation in younger patients aged 10 to 13 years, while neurological symptoms initially present in older patients in the fourth to fifth decades[89]. Nearly all patients show evidence of cirrhosis. The deposition of copper in Descemet membrane of the cornea is recognized on slit lamp examination, and may be absent in younger patients or early in the course of the disease, prompting a liver biopsy for a conclusive diagnosis[87,88]. Because of the currently over 200 different mutations present in the gene coding for the condition, a direct mutational analysis remains elusive.

The treatment of choice has been chelation with d-penicillamine or trientine, although zinc is safer as a long-term, life-long therapy because it blocks copper absorption from the diet. Liver transplant may be attempted in fulminant advanced cases[90].

Kuf Disease: This disorder belongs to neuronal ceroid-lipofuscinosis, a group of hereditary neurodegenerative disorders primarily of childhood that share the presence of storage inclusions in lysosomes of neurons and other cells[91]. Cognitive impairment is a common feature of all affected patients. Kuf disease differs in that onset is in adulthood and there is no retinal degeneration and blindness. Up to 70% of patients manifest autosomal recessive inheritance. Type A patients have a clinical course that includes generalized tonic-clonic seizures, myoclonus, ataxia, and dysarthria[92]. Type B patients exhibit dementia, neuropsychiatric involvement, extrapyramidal and cerebellar dysfunction[92]. Dementia may be the presenting symptom of Kuf disease and may remain quiescent until the seventh decade of life. The typical presentation of Kuf disease is the gradual onset and progression of deficits in episodic memory,

executive function, and visuospatial ability, otherwise suggestive of AD. The presence of seizures and motor disturbances assist in the differentiation from AD early in the course of dementia[93].

Urinary sediment dolichol levels are elevated in both types suggesting defective intracellular processing of lysosomes inclusions present in ultra structural tissues, and in biopsies of apocrine and eccrine secretory cells of the skin, rectum, conjunctiva, and muscle. There is currently no treatment for this condition.

Huntington Disease: Huntington disease (HD) is a phenotypically heterogeneous motor and neuropsychiatric disorder that is inherited in an autosomal fashion due to an unstable CAG trinucleotide repeat sequence encoding the protein huntingtin on chromosome 4[94]. The length of the trinucleotide repeats appears to be directly correlated with an earlier age of onset, a cognitive behavioral presentation and an accelerated disease progression[95].

Symptoms generally begin in the third or fourth decade of life, with a triad of psychiatric changes, cognitive loss and a movement disorder. Psychiatric symptoms are present in up to 98% of patients with HD and include depression, apathy, aggression and disinhibition with a four-fold increased risk for suicide[96,97]. Delusions and hallucinations are less common. The chorea of HD involves axial and limb musculature along with facial grimacing and parakinesias. Younger patients present with dystonia while older patients demonstrate more of a chorea and exhibit a clinically more virulent form of the disease[98]. There is reduced saccades and smooth pursuit movements. The sub-cortical dementia of HD is associated with visuospatial deficits, significant memory impairment and disturbed executive function[99].

Brain PET demonstrates reduced striatal glucose metabolism and dopamine receptor binding in patients and half of all asymptomatic adult carriers[100]. The brain MRI shows caudate

atrophy, especially with longer CAG repeat lengths[101]. Microscopically, there is a selective loss of medium spiny neurons in the striatum, along with reduced levels of substance P, GABA and dynorphin.

The chorea may be treated with dopamine blockers or with agents such as riluzole[102]. Treatment is aimed primarily at treating depression and psychosis.

Whipple Disease: This is a rare multisystemic disease caused by *T. whippelii* infection, a commensal gut organism that leads to clinical disease in immunocompromised individuals. Patients generally present in the fifth decade of life with fever, arthralgia, lymphadenopathy, and diarrhea. Neurological involvement occurs later with confusion, dementia, psychiatric disturbances, supranuclear ophthalmoplegia, meningoencephalitis, and uveitis. Less common manifestations include myoclonus, seizures, oculomasticatory movements, cranial and peripheral neuropathy. Neurological involvement confers a more severe prognosis[103,104,105].
The brain MRI may be normal or may demonstrate abnormal high signal intensity on T2 weighted images affecting the frontal cortex, basal ganglia, periventricular white matter, hypothalamus, temporal and the parietal cortex in decreasing order of frequency. Cerebrospinal fluid (CSF) may reveal the diagnosis using light microscopy with PAS staining and PCR assay[106].

The optimal treatment of Whipple disease remains controversial both as to the most effective agent and the duration of treatment. Currently recommended therapy for patients without neurological involvement includes procaine penicillin G 1.2 million units with streptomycin 1 g daily intramuscularly for 14 days followed by oral trimethoprim sulfamethoxazole (TMP-SMX) for 1 year. Neurological symptoms may develop or persist on

this regimen. Alternatively patients can be treated with 2 grams of ceftriaxone twice daily for 14 to 30 days, followed by oral TMP-SMX or cephalosporin for 1 to 2 years[106]. The addition of gamma interferon can be considered in antibiotic resistant cases.

Creutzfeldt - Jakob disease: Creutzfeldt-Jakob disease (CJD) is a prion disease that leads to accumulation of PrP^{Sc} in the brain, an abnormal, insoluble and protease-resistant form of the normal cellular protein, PrP^{C}. Accumulation of PrP^{Sc} leads to the clinical syndrome of CJD with characteristic spongiform changes in the brain[107].

There are two types CJD, each with a different clinical course. A classic endemic form (cCJD) is typified by motor features of ataxia, dysarthria, incoordination, and myoclonus[108]. A variant form (vCJD) is caused by consumption of infected beef with bovine spongiform encephalopathy. vCJD usually begins in the third decade of life, with a course of about 14 months until death in contrast to cCJD which typically presents in the seventh decade of life with death in about six-months[109110]. Involuntary movements, depression, anxiety and painful paresthesias are common in vCJD. The EEG features of periodic sharp wave complexes seen in cCJD are not observed in vCJD. A unique pathological feature of vCJD is the accumulation of PrP^{Sc} in florid or daisy-like plaques. Diffusion weighted imaging on MRI may show abnormalities as early as 3 weeks after onset of symptoms[111]. The presence of scrapie associated protein 14-3-3 in the CSF of affected patients is associated with CJD and tau concentrations in CSF of greater than 1300 pg/ml is associated with a diagnostic sensitivity of 87% and specificity of 97%[112]. There are no effective treatments available for this condition.

TABLE 1

Characteristics of the three types of FTLD

Behavioral variant frontotemporal dementia	Progressive non-fluent aphasia	Semantic Dementia	Logophenic or phonologic variant
Frontal tests poor, No severe amnesia, no aphasia, no severe perceptuospatial disorder	Reduced verbal fluency. Apraxia of speech. Impaired motor speech. Normal visual memory. Comprehension affected later.	Fluent empty speech, loss of word meaning. Also prosopagnosia, misuse of objects, preserved ability to read aloud, but without comprehension is a key feature. Able to remember autobiographical events.	Agrammatism, slow output; motor speech spared. Repetition impaired. Impaired comprehension.

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