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Neurodegenerative Disease as A Potential Consequence of Aging in Cystic Fibrosis

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ABSTRACT

New therapies in cystic fibrosis (CF) have made a significant impact on the overall health of people with CF (pwCF). Because of the success of these therapies, it is anticipated that lifespans of pwCF will significantly increase. For the first time, the impacts of aging with CF need to be considered. Until now, relatively little has been done to evaluate neurological health in pwCF. In this review, we consider evidence for a potential prevalence of neurodegenerative disease in CF including our recent study examining tauopathy in an aged CF mouse model.

Introduction

CF is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR is a cAMP activated chloride channel that also regulates bicarbonate transport across epithelial cells, though CFTR expression has been observed in other cell types including immune cells and neurons[1,2]. Cystic fibrosis refers to fibrotic cysts of the pancreas and most pwCF initially succumbed to digestive issues and malnutrition at a very early age. As nutritional therapies and pancreatic enzyme therapies were developed, increasing life span revealed extensive pulmonary manifestations that have become the most common cause of morbidity and mortality in CF with life expectancies in the late 30s. The development of highly effective modulatory therapies (HEMT) that restore at least partial function of disease-causing mutations of CFTR has significantly improved pulmonary outcomes including better clearance of airway mucus, reduced airway blockage and reduced pulmonary exacerbations from chronic bacterial infections[3-5], significantly expanding the expected life spans of pwCF. This breakthrough has significantly extended life expectancy, transforming CF into a chronic condition and necessitating urgent research into aging-related complications previously not observed in this population. Emerging evidence highlights CFTR's direct role in neuronal function, with mouse models recapitulating key neurological phenotypes observed in pwCF, including growth dysregulation, anxiety, depression, and circadian dysregulation[6-8]. New evidence suggests that aging with CF has significant impacts on neuropathology and the decline of cognitive function in a mouse model of CF[9]. This review is the first to discuss the neurodegenerative aspects of CF.

Cognitive changes associated with cystic fibrosis

Aging is associated with increased risk of developing neurological disease, however, little neurological research has been pursued in the context of CF. There is evidence that cognitive decline may begin early in the context of CF. One study examined cognitive function in people with

CF (pwCF) in conjunction with neuroimaging. This study identified mild cognitive impairment in pwCF as early as 30 years of age[10]. T1 and T2 weighted images from pwCF and healthy age matched controls (average 29.7 years) reveal grey matter tissue damage in the hippocampus and prefrontal cortex and altered T2 relaxation in many brain regions associated with cognition. Functional assessments reveal increased depression in pwCF as determined by the Beck Depression Inventory (BDI), while cognitive function was significantly lower particularly on the visuospatial subscale using the Montreal Cognitive Assessment[10].

In a separate study by Chadwick et al, cognitive changes were assessed in pwCF with CF-related diabetes (CFRD), in pwCF without CFRD, and in non-disease controls[11,12]. Cognitive function was assessed using the Cambridge Neuropsychological Test A Battery (CANTAB). Compared to healthy controls, pwCF with and without CFND had deficits in Verbal Recognition Memory, Paired Associates Learning Test, and Spatial Span[12]. There were no statistical differences in Motor Speed and Rapid Visual Processing between groups, though the authors note that pwCF performed less well in each test. With the Attention to Switching Task, pwCF without CFRD had a 20% reduction in processing speed compared to non-disease controls, while pwCF with CFRD had a 40% reduction in processing speed. Based on these two studies, pwCF display some aspects of cognitive impairment compared to non-disease control. Although the reported cognitive impairment is relatively mild, these studies were conducted on young subjects, highlighting the need for cognitive assessment as pwCF age.

These cognitive changes in CF are recapitulated in mouse models of CF, an F508del model, the most common disease-causing mutation of CFTR, and a G542X model that does not produce CFTR protein. Both mouse models exhibit memory and learning deficits with age consistent with the human findings discussed above[9]. Neurological disease in these mouse models is discussed more below while describing neuropathology associated with CF.

Circadian regulation in cystic fibrosis

There are other neurological complications associated with CF, particularly with circadian rhythmicity and sleep regulation. Disordered sleep and sleep disturbances are widely reported in pwCF[13-16]. The type of sleep disturbances experienced by individuals with CF are associated with phase alterations in the circadian timing system (CTS)[17]. The CTS is a complex set of cyclic cellular mechanisms that serve to synchronize discrete cell groups across multiple organ systems to adapt the body's physiology to a (roughly) 24-hour clock. Sleep disturbances in CF have typically been attributed to be the result of CF-related pulmonary and GI disease[18,19]. However, children with CF exhibit similar nocturnal respiratory profiles to healthy controls, but still suffer from sleep disturbances. Additionally, no association between prevalence of disordered sleep and severity of CF lung disease as measured by FEV1 is shown[17]. Taken together, these findings suggest the presence of other factors leading to the disordered sleep experienced by this population. Jensen et al. established a delayed circadian phase of sleep onset as well as increased sleep latency and duration, that was not related to FEV1% predicted, prior acute pulmonary exacerbations, or weight, suggesting altered circadian timing of sleep is a primary manifestation of CF disease[17]. It has been reported that sleep disturbances experienced by individuals with CF are consistent with circadian system phase delays[17,20]. In CF mice, altered timing of the sleep wake rhythm as well as altered clock gene expression in brain and peripheral tissues have also been reported[21], suggesting that the CTS is alterd in both pwCF and animal models of the disease. This CF mouse model carries the F508del mutation which is the most common disease-causing mutation of CFTR. Circadian changes in this CF mouse model consist of earlier activity onset, sporadic activity throughout normal sleep periods, and altered responses to constant darkness exposure[6].

Anxiety and depression in cystic fibrosis

Anxiety and Depression are complex mood disorders understood to result from altered neurotransmission within the central nervous system (CNS). The increased prevalence of anxiety and depression in pwCF suggest that CFTR loss of function within the CNS contributes to this altered cognitive phenotype[22-25]. Mental health issues such as increased risk of anxiety and depression have become a forefront topic in the CF community, including how to identify and treat these conditions. CF researchers implemented The International Depression Epidemiological Study (TIDES), where they concluded that depression and anxiety were elevated in CF subjects, where 19% of adults reported depression and 32% of adults reported anxiety[26,27]. These levels are 2-3 times higher than community samples[26]. Two studies demonstrate anxiety- and depression-like behavior in two different CF mouse models, a knockout model and the F508del model. Importantly these mouse models circumvent the psychological complications humans with a chronic disease face, supporting that these phenotypes are an inherent property of CF neurological disease[7,28].

Neurodegenerative disease in cystic fibrosis mouse models

The above studies detail the presence of early mild cognitive impairment, circadian disruptions, and increased prevalence of anxiety and depression in pwCF. Each of these phenotypes, especially in combination, can be precursors to other neurological diseases such as Alzheimer's disease[29-33]. We hypothesized that aging in the context of CF would be associated with neurodegenerative pathology. There are no tissue banks of CF brain tissue and until recently, pwCF had shorter life expectancies making the study of progressive neurological disease difficult. Since mouse models of CF exhibit both circadian and anxiety/depression phenotypes[6,21], the effect of aging on neuropathology in this model was examined.

A recent study revealed a distinct neurodegenerative phenotype in CF mice[9]. An age- dependent decline in learning and memory was observed using both the spontaneous alternation (SA) and novel object recognition (NOR) tests. CF mice were indistinguishable from wild-type (WT) mice on both the SA and NOR tests at three months of age. However, by seven months of age, CF mice had a significant decline in SA performance compared to WT mice. CF showed a notable decline in NOR performance as well by 7 months of age, but this decline did not reach statistical significance. By 12-15 months of age, CF mice had significant declines in both the SA and NOR tests compared to WT controls in two separate cohorts of mice. Given the clear progression of deficits in learning and memory, long-term potentiation (LTP) which underlies learning and memory was examined in the oldest cohort. No differences between WT and CF mice were observed in short-term plasticity using paired-pulse facilitation. However, when theta-burst were applied to induce LTP, significant deficits were observed in the CF mice consistent with the observed decline in learning and memory performance.

The age-dependent deficits in learning and memory suggested the presence of progressive neuropathology. Microtubule changes related to tubulin acetylation and microtubule formation rates in CF cells were previously identified suggesting reduced microtubule stability[34,35]. Based on these previous findings, CF mouse hippocampal sections were assessed for hyperphosphorylated tau (pTau), a pathological posttranslational modification of the microtubule stabilizing protein tau[36]. At 9-months of age, CF mice showed a significant increase in pTau[37] levels in the anterior but not posterior dentate gyrus. By 15 months of age, however, pTau levels were significantly elevated in both the anterior and posterior dentate gyrus showing progressive tau pathology in CF mice. Direct measurement of NeuN positive neurons showed loss of neuronal density in 15-month-old CF mice compared to WT demonstrating that neuropathology associated with CF is likely neurodegenerative.

Evidence of neurodegenerative disease in pwCF

Though there is no CF brain tissue biobank, there were early autopsy studies that examined pathology in brain stem samples in pwCF. These studies showed that CF brain samples exhibited clear axonal dystrophy which is a swelling of neuronal axons and an early marker of neuronal degeneration[38-42]. The oldest subject in these studies was 32 years of age suggesting that this indication of early neurological pathology is occurring at young ages in CF. In general, axonal dystrophy is caused by impaired axonal transport mechanisms due to various lipid accumulation conditions[43-45], mitochondrial dysfunction leading to oxidative stress and axonal damage[46,47], improper iron transport[48,49], and cytoskeletal dysfunction[50-52]. The early occurrence of axonal dystrophy in the brains of pwCF is consistent with the tauopathy and neurodegeneration observed in CF mouse models and may offer insight into mechanisms leading to these neurological phenotypes in CF.

Potential mechanisms leading to neuropathology in CF

The observance of tauopathy and cognitive decline in aged CF mouse models coupled with the early observance of axonal dystrophy strongly support the idea of innate neuropathology associated with the loss of CFTR function. However, the mechanisms linking the absence of CFTR function to these pathological processes are not fully delineated. Mechanistically it is proposed that microtubule changes associated with CF are a likely initiation step in this process. Previous work has shown that inhibition or depletion of Hdac6 corrects these microtubule changes in CF and has *in vivo* efficacy. If circadian disruption and anxiety/depression phenotypes in CF are truly early precursors to this neurodegenerative process, then it has been shown that knocking Hdac6 expression out of CF mice corrects these phenotypes. Hdac6 KO completely corrects CF- related circadian changes and effectively reverses depression-like behaviors found in CF mice[6,7]. Hdac6 inhibition could be restoring microtubule regulation to CF cells and potentially preventing the neurodegenerative process from beginning in CF mice. It has also been shown that Hdac6 depletion or inhibition reduces inflammation in a CF context[34,53]. The efficacy of Hdac6 depletion in restoring circadian regulation in CF mice could be related to reduced neuroinflammation, though this mechanism in CF needs further exploration.

Finally, lipid accumulation is a clear cause of axonal dystrophy as discussed above. Altered cholesterol metabolism and accumulation of cholesterol in CF epithelial cells has been reported, however these phenotypes have not been explored in brain derived CF cell types[54-58]. A strong mechanistic link between microtubule regulation and this cholesterol processing phenotype in CF including through Hdac6 regulation[34,59]. A role of microtubule dysregulation in CF leading to axonal dystrophy and other neurological phenotypes is consistent with other reports showing the efficacy microtubule stabilizing agents in preventing the occurrence of axonal dystrophy in other disease models[50-52,60]. This specific mechanism needs to be further explored in a CF context.

The role of fat-soluble vitamin deficiency in neurological phenotypes should also be explored. Vitamin E deficiency specifically has been shown to be associated with neurodegenerative disease as summarized in these reviews[61,62]. This relationship is important as vitamin E deficiency has been seen in pwCF[63-66]. This deficiency has been associated with neurological phenotypes in CF and an early study by Sung et al showed that vitamin E supplementation had efficacy in improving axonal dystrophy in CF[41,65,67,68]. It is not clear if the CF mouse models exhibit vitamin E deficiency, but future studies should explore the impact of vitamin E supplementation to address CF neurological outcomes.

Other potential systemic mechanisms that could contribute to neurodegenerative disease in CF include CF related diabetes (CFRD) or chronic inflammation. Both diabetes and chronic inflammation have been strongly linked to the development of dementia[69,70]. However, there is a very distinct tauopathy and associated cognitive decline in the CF mouse model and there is limited evidence of either diabetes or systemic inflammation in this model. The occurrence of neuropathology in the CF mouse does suggest a more direct mechanism associated with the loss of CFTR function.

Potential impact of HEMT

As mentioned above, HEMT for pwCF has led to an expected increase in life span making the understanding of aging in the context of CF an important area of study. However, the impact of HEMT on neurological health in CF is unknown. Adverse events associated with HEMT associated with the CNS include anxiety, depression, and cognitive impairment[71-73]. Mechanistically, it is unclear if the compounds and or their metabolites are augmenting CFTR function in the brain leading to adverse consequences, or possibly potentiating other channels such as BK channels[74]. Key to the uncertainty over mechanisms is the question of whether HEMT compounds readily corss the blood brain barrier (BBB). One study in a CF rat model shows that HEMT compounds enter the brain freely in neonates and in utero, but not in adult rats once the BBB is formed[75]. Chronic inflammation which is experienced by many pwCF can lead to a more permeable BBB allowing these compounds in the CNS[76]. It is also possible that metabolites of HEMT compounds are more accessible to the CNS and causing adverse events in some pwCF. Also unclear is whether treatment with HEMT will prevent a neurodegenerative process in pwCF. If HEMT compounds can indeed cross the BBB, it is likely at very low doses and the efficacy on long-term neurological health is difficult to predict.

Exploring biomarkers of tauopathy in pwCF

As noted above, there are no brain biobanks for CF tissue, further obtaining CNS derived samples from pwCF is invasive. Other studies have shown that oral and olfactory cells from people with Alzheimer's disease show tau pathology[77,78]. There are available panels of primary human nasal epithelial (HNE) cells from pwCF and non-CF controls, these cells were used in a preliminary study to demonstrates that CF HNE cells have significantly elevated pTau levels compared to non-CF controls suggesting that the development of tau pathology is inherent to CF cell biology and that the progressive CF-related neurodegeneration (CFND) observed in the CF mouse model could be relevant to pwCF[9]. Only five samples from pwCF were examined, but all showed elevated pTau levels compared to non-CF controls warranting further study.

Conclusions

Further study of the neurological impacts of aging in CF are needed, particularly as newer treatments are effectively increasing the lifespans of pwCF. Longitudinal human studies employing neuroimaging, and cognitive assessment are required to evaluate the presence of this neuropathology in pwCF. Further it is necessary to assess the efficacy of these newer treatments in modulating the progression of neurological disease in the CF context. Evidence from a CF rat model suggests that HEMT drugs do not cross the blood brain barrier in adult animals[75]. If true, then HEMT in pwCF is unlikely to reverse these neurological CF phenotypes and supportive therapies will need to be developed highlighting the need for future mechanistic studies in addressing this novel manifestation of CF.

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