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Attention-Deficit/Hyperactivity Disorder in Older Adults: Prevalence and Possible Connections to Mild Cognitive Impairment

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Abstract

Attentional deficits are frequently seen in isolation as the presenting sign and symptom of neurodegenerative disease, manifest as mild cognitive impairment (MCI). Persistent ADHD in the geriatric population could well be misconstrued as MCI, leading to the incorrect assumption that such persons are succumbing to a neurodegenerative disease process. Alternatively, the molecular, neuroanatomic, or neurochemical abnormalities seen in ADHD may contribute to the development of de novo late life neurodegenerative disease. The present review examines the issue of causality vs confound regarding the association of ADHD with MCI, suggesting that both are tenable hypotheses.

Keywords

Attention-deficit/hyperactivity disorder; ADHD; Adult ADHD; Older adults; Mild cognitive impairment; MCI; Alzheimer's disease; Parkinson's disease; Dementia with Lewy bodies; DLB; Frontotemporal dementia; FTD; Genetics; Neurotransmitter systems; Neuroimaging; Pathogenesis; Treatment

Introduction

ADHD is considered the most prevalent cause of childhood learning disabilities [1, 2, 3•]. Most developmental disabilities are related to intrinsic molecular, neuroanatomic, and neurochemical disturbances, that persist throughout life, potentially predisposing to late-life cognitive decline. The strongest evidence for developmental disorders predisposing affected

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persons to the development of late-life cognitive decline involves Down syndrome, in which affected individuals inherit a triplication of the chromosome 21 region encoding for the amyloid precursor protein (APP) [4]. Persons with Down syndrome universally develop the pathological changes of Alzheimer's disease (AD) by age 40 [4, 5]. The evidence linking the molecular pathogenesis of Down syndrome to the precocious development of AD is irrefutable.

It is currently unclear if other developmental disorders such as ADHD also predispose to the development of late-life cognitive decline. Many genetic, molecular, and neuroanatomic/neurochemical alterations have been described in individuals with ADHD, that share some similarity and overlap with the neuroanatomic/neurochemical alterations implicated in the development of late-life dementias such as AD, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).

Inherent in the clinical pathogenesis of slowly progressive degenerative dementia is a prodromal state, referred to as mild cognitive impairment (MCI), where subtle signs and symptoms of cognitive, behavioral, and neuropsychiatric decline appear years before the development of functional decline sufficient to warrant the diagnosis of dementia [6–10]. Thus, one can envision 2 scenarios whereby ADHD could be linked to late life cognitive diagnoses, including (1) a true molecular/neuroanatomic/neurochemical predisposition to de novo late life neurodegeneration, or (2) non-pathologic, age-related cognitive decline superimposed on a fragile substrate, augmenting lifelong persistent learning disabilities, misdiagnosed as the development of MCI, or degenerative dementia distinct from the diagnosis of ADHD.

This review aims to explore the prevalence, clinical features, and molecular/neuroanatomic/neurochemical associations seen in ADHD in the adult population, focusing on comorbidities associated with ADHD and further examining a potential link between ADHD and mild cognitive impairment or the development of a late-life neurodegenerative dementia.

Prevalence of ADHD Across the Lifespan

Attention-deficit hyperactivity disorder (ADHD) is one of the most common behavior disorders in children. Studies have estimated that it affects 5 %–12 % of children in the United States [11]. Children with ADHD may show symptoms of inattention, hyperactivity, and impulsivity. Commonly believed to be a childhood disorder, it has been shown that up to one half of childhood ADHD cases persist into adulthood [12, 13]. While adult ADHD is not as well studied as childhood ADHD, the existing data suggest that the prevalence of ADHD is approximately at 4 % in the adult population [14]. Similar to other adult populations, a study using the Wender Utah Rating Scale to retrospectively diagnose ADHD in geriatric patients showed a 5 % prevalence rate in undiagnosed individuals [15••].

Diagnosing Adult ADHD

The *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) specifies that the symptoms of ADHD must have appeared before the age of 7 [16]. Therefore, it is often necessary to retrospectively analyze symptoms during childhood to diagnose the disorder in an adult, further confounding estimates of the prevalence of ADHD in the geriatric population.

ADHD can be reliably diagnosed in adults according to the DSM-IV if they currently have symptoms associated with ADHD and if their they can recount having their symptoms since before the age of 7 [16]. Retrospective diagnosis of ADHD in adults has been previously

validated [17, 18]. Several studies have also found significant correlations between self reported ADHD symptoms and symptoms reported by participants' spouses or other informants [18]. A variety of tests including the Wender Utah Rating Scale, Brown Attention-Deficit Disorder Scales, and Conner rating scales have been validated as a diagnostic aids for adult ADHD [17, 19, 20].

Adult ADHD-Associated Cognitive Impairment and Comorbidities

In children, ADHD is associated with a wide variety of comorbidities including mood and anxiety disorders [21]. When ADHD continues into adulthood, the manifestations of comorbid symptoms change. It has been shown that impulsivity and hyperactivity do not usually persist except for a feeling of restlessness [22]. In contrast, symptoms of inattention are present into adulthood and may continue into the geriatric years [15••, 23].

While cognitive deficits related to ADHD may persist into the geriatric years, when persons are at highest risk for the development of MCI or dementia, they are generally felt to represent static deficits that are seldom confused with a progressive dementing condition, although this hypothesis has not been studied to date and so any conclusions regarding the static nature of ADHD may be incorrect [3•, 24, 25]. In fact, some adults may feel like their symptoms of inattention have worsened over time potentially mimicking a degenerative condition [26].

In addition to cognitive deficits, adult ADHD tends to be associated with depression, anxiety, and alcohol/drug dependency [27]. Such comorbidities can directly lead to cognitive impairment, masquerading as MCI or dementia, and have also been strongly associated with both MCI and dementia as a result of underlying neurodegenerative condition [6, 9, 10].

Depression

Comorbid depression in ADHD is well documented in the literature [28, 29]. Alpert and colleagues found that around 16 % of patients with major depression also had ADHD [30]. Conversely, major depressive disorder is the most commonly associated comorbidity of ADHD. Approximately 50 % of participants with ADHD also suffer from depression [31]. ADHD is also associated with an earlier age at onset, longer duration, more severe depression-associated, and a higher rate of suicidal tendencies. [32].

Anxiety

Van Ameringen and colleagues found that 23 % of subjects with ADHD have a comorbid general anxiety disorder [31]. Agoraphobia, panic disorder, post-traumatic stress disorder, and social phobia have also been shown to occur at higher rates among ADHD adults [14].

Functional Consequences of Late-Life ADHD

Adult ADHD can have a profound effect on an affected person's everyday life. Deficits in attention can cause social and financial difficulties along with problems at work due to distractibility and poor time management. One study comparing ADHD adults with non-ADHD adults found that significantly more ADHD adults had experienced a suspension of their driver license and had performed poorly, quit, or been fired from their job [33]. In Kessler and colleagues' survey study, which analyzed sociodemographic correlates, adults with ADHD were more likely to be divorced, unemployed, or disabled [14]. Another study that used the Wender Utah Scale to assess ADHD in women recruited from the Rhode Island Department of Corrections found that women were more inconsistently employed, recently homeless, have been incarcerated for more than 90 days in their lifetime [34]. These

functional deficits can be easily mistaken for a late-life degenerative dementia in the geriatric population with ADHD.

Mild Cognitive Impairment (MCI) and Dementia

The prevalence of MCI and dementia increases steadily with advancing age in the geriatric population. Prevalence estimates for MCI range from 5 %–40 % across studies [6, 8, 35, 36]. This variability is related to both the age range for population studied and the precise criteria used to assess MCI across populations [6, 10, 37–39]. Recent advances and consensus recommendations for the diagnosis of MCI have led to more accurate estimates of the prevalence of MCI in the geriatric population at approximately 16 % [6, 10, 35, 36]. Current consensus recommendations for the diagnosis of MCI [10], taken from the 2nd International Working Group on MCI include:

1. A cognitive complaint, preferably corroborated by an informant or evidence for longitudinal decline on cognitive test performance (1.5 SD).
2. Generally intact global cognition.
3. No or minimal functional impairment (insufficient to meet current diagnostic criteria for the DSM-IV diagnosis of dementia).
4. Not demented by DSM-IV criteria.
5. Lack of medically identifiable cause for cognitive decline.

The first criterion (#1 above) specifies a need to establish longitudinal cognitive decline that should prevent persons with stable, lifelong cognitive impairment (as can be seen in ADHD) from being labeled with this diagnosis that has been designed as a predictor of early or prodromal degenerative dementia. The last criteria item (#5 above) is designed to eliminate non-degenerative causes of decline including disorders such as ADHD that meet DSM-IV criteria. Despite these safeguards, persons with ADHD could be included in prevalence estimates for MCI if this condition was not screened for (criteria #5), or if progressive decline is reported (criteria #1), as can be seen in many cases of adult ADHD [26]. Thus ADHD may remain a confound in many studies of MCI depending on the rigor with which the current criteria were applied.

The longitudinal cohort at the University of Kentucky has been used to study this issue in incident MCI, as well as in prevalent cases with longitudinal follow up that appear “unstable”, as they fluctuate between states of cognitive impairment and normal cognitive function across annual evaluations. Medically reversible causes of incident MCI are common (31 % of all incident cases) and often discovered only after the diagnosis of MCI has been applied and rigorous workup for medical or psychiatric causes of cognitive decline are sought [40]. Further longitudinal study of prevalent MCI cases identified 34 % of cases with “unstable” diagnoses, identifying non-degenerative psychiatric causes in nearly a third of these cases, 11 % overall (unpublished data). ADHD was not systematically screened for in these cases, but rather the identified causes for decline in these subjects included known ADHD comorbidities of depression, anxiety, and/or substance abuse. These data raise significant concerns about the possible inclusion of ADHD cases in existing cohorts of MCI subjects, as it is a common disorder extending into late life that is not routinely evaluated or screened for in the majority of studies [25].

Clinical Studies of ADHD and MCI or Dementia

Few published studies have investigated the possible connection between ADHD and MCI or dementia. One group of investigators has proposed childhood ADHD to precede dementia

with Lewy bodies (DLB) given the hypodopaminergic role in both diseases [41••]. In this study, subjects were recruited from the Italian Hospital Medical Care Program in Buenos Aires, Argentina between 2000 and 2005. Three groups of subjects meeting inclusion criteria were identified for inclusion in the study including DLB (n= 109), AD (n =251), and cognitively normal controls matched by age, sex, and year of education to the impaired groups (n=149). Retrospective diagnosis of childhood ADHD was performed using adapted DSM-IV criteria, validated by the Spanish version of the Wender Utah Rating Scale. An increased frequency of ADHD (P<0.001, $\chi 2$ test) was seen for DLB (47.8 %), compared with AD (15.2 %), and normal control subjects (15.1 %). The authors speculated that the association between ADHD and DLB seen in this study was mediated by reduced dopaminergic, noradrenergic, and cholinergic activity seen in these disorders. This study did not include evaluation of MCI subjects.

Evaluation of MCI subjects that with pathological confirmation of DLB is limited. Several studies in the literature have attempted to define the prodromal state of MCI due to underlying DLB pathology [42, 43]. These studies have confirmed the role of early attentional deficits in the progression of this disease state. Phonemic (letter) fluency and immediate paragraph recall deficits, attesting to deficits in frontal attentional circuitry, characterize this disease process in the MCI phase [42, 43]. ADHD subjects demonstrate the same pattern of deficits [3•, 25, 44]. While systematic assessment of ADHD was not undertaken in either of these studies, the evidence linking DLB with ADHD, clearly warrants further exploration.

Systematic assessment of ADHD in prevalent MCI cases has only been reported in a single study to date. In this study, 310 subjects spanning the cognitive continuum from normal (n=243) to impaired (n=67) were evaluated with the Wender Utah Rating Scale [25]. The cognitively impaired subjects studied included 42 with MCI (18 non-amnestic and 24 amnestic presentations), 6 who were cognitively impaired but failed to meet current consensus criteria for MCI, and 19 demented subjects. A presumptive diagnosis of ADHD (as assessed by the Wender Utah Rating Scale) was found in 10 cognitively normal and 3 cognitively impaired subjects (4.4 % of the total respondents). Non-linear, quadratic, regression models adjusted for age and education, demonstrated that the Wender Utah Rating Scale score-squared was a significant predictor of performance on attention-dependent tasks including animal naming (P= 0.0299) and WAIS digit span forward (0.0367). However, this study found no correlation between childhood ADHD and mild cognitive impairment (MCI) or dementia [15]. It is possible that the small number (n=67) subjects with cognitive impairment studied, may have precluded the identification of an association between MCI and dementia in this series. Further work examining the association between ADHD and MCI or dementia is clearly needed before strong conclusions can be made regarding a possible association or lack thereof.

Shared Pathogenic Mechanisms?

The exact cause(s) of ADHD are unknown, but available research suggests possible overlap with pathogenic mechanisms responsible for the development of MCI and further progression to a degenerative dementia. ADHD is thought to be caused by a combination of genetics and environmental factors [45, 46] and the same holds true for MCI and degenerative dementia [6, 47]. Identifying areas of overlap between these conditions in regards to genetics, neuroanatomic involvement, and neurochemical pathways is critical in establishing potential overlap or associations between such conditions.

Genetics

The heritability of ADHD is thought to be around 70 % in children and adolescents [48–50], and slightly lower in adults at 30 % [51]. Several genes have been identified as risk alleles for ADHD; specifically, studies have focused on genes involving dopaminergic function including the D4 and D5 receptor genes and the dopamine transporter gene [52–54]. Other genes implicated in ADHD pathology include SNAP-25 (synaptic protein), HTR1B (serotonin receptor), and an as of yet unidentified gene on chromosome 16 [55–58].

None of the genes or chromosomal regions identified to date for ADHD have been directly implicated in any of the degenerative dementias, although the SNAP-25 association in ADHD may suggest common shared pathways involving normal synapse function. Recent genome wide association studies in AD have identified several genes involved in neurotransmitter release at the presynaptic terminal including PICALM, BIN1, and CD2AP [59, 60]. These proteins are involved in clathrin-mediated endocytosis, synaptic vesicle release, and lipid raft formation required for effective maintenance of synaptic structure and function. Further work identifying the interplay between these complex processes in ADHD and degenerative dementia is clearly needed before any relevant associations can be more than speculated.

Structural and Functional Imaging

Recent interest in neuroimaging biomarkers for degenerative dementias and ADHD demonstrate both structural and functional overlap. Imaging abnormalities in ADHD include:

1. ADHD subjects showed subtle global reduction in brain volume, smaller prefrontal volumes, smaller caudate nucleus volumes, and smaller vermis [55, 61]
2. Reduced activation in frontro-striatal networks [55]
3. Reduced frontotemporal activation in ADHD [62]
4. Reduced activation in parietal networks [63]

These very same areas are affected in AD, DLB, FTD, and VaD [6, 64•]. Such structural and/or functional imaging changes could be easily mistaken for a degenerative disease process such as AD, DLB, or FTD in the geriatric population if careful clinical assessment is not performed. Alternatively the overlap in structural and functional imaging correlates of ADHD and degenerative dementia may again suggest intrinsic overlap in the molecular pathogenesis of disease.

Neurotransmitter Systems

Studies of neurotransmitter deficits in ADHD have suggested lowered activity in monoaminergic pathways [65–69]. The most prevalent theory today regarding the pathogenesis of ADHD suggests that dysregulation of mesolimbic dopaminergic pathways projecting from the ventral tegmental area to the nucleus accumbens is causal for the signs and symptoms of this disorder [70]. This pathway is intrinsically involved in motivation and reward/avoidance behaviors. Lower dopamine levels in this area could lead to less motivation to complete tasks that are not perceived as inherently rewarding, resulting in inattention. The hyperactivity seen in ADHD may be the result of promiscuous reward-seeking behaviors.

Noradrenergic pathways originating in the locus coeruleus also play a pivotal role in the maintenance of alertness and attention [65, 67, 69, 71–73]. The current use of stimulant therapy in ADHD is based on proposed deficits in this pathway [66, 67, 73–79]. This

pigmented nucleus has long been recognized for its involvement in the progression of Lewy body pathology throughout the brainstem in PD and DLB [80, 81], however recent work has identified this nucleus as the earliest target of AD pathology [82•]. Immunohistochemical staining of 342 nonselected autopsy brains age 1–100 with an antibody recognizing a pathological phosphorylation of tau (AT8) revealed positive staining in 58 cases in the locus coeruleus for neurofibrillary pathology [82•]. Early neurofibrillary degeneration characteristic of the AD process appears to affect this brain region first in the pathologic sequence of events and can be seen in many as early as young adulthood. It is possible that such pathology could be linked to the early disregulation of noradrenergic function seen in ADHD. These findings have opened the door to investigations of neurotransmitter replacement therapy and modulation in ADHD that will be discussed further below.

Shared Treatment Strategies

Treatment strategies for ADHD have largely focused on stimulant use to date [67, 76, 77], but advances in our understanding of the many discrete, yet interlinked, neuronal pathways involved in arousal and attention have begun to open new doors into treatment strategies that share overlap with therapeutic interventions for degenerative disease states [83–88].

Stimulant treatment for ADHD remains the standard of care today for both children and adults diagnosed with this condition [66, 77]. Stimulants such as methylphenidate work by modulating monoaminergic tone in the frontal and striatal networks via inhibition of monaminergic uptake transporters, disinhibition of dopamine receptor type II (D2) autoregulation, and increased activation of postsynaptic dopamine receptor type I (D1), and stimulation of noradrenergic alpha2 receptors in the cerebral cortex [77]. The efficacy of such agents in ADHD remains undisputed. Side effect profiles and undesired biologic activities limit their use in subjects with late-life dementia [89, 90], and definitive evidence for their utility in treating the cognitive dysfunction seen in these disorders is limited [89, 91–98].

Problematic side effects and potential concerns regarding the use of stimulants in the geriatric population center on the peripheral sympathomimetic actions of such drugs [89, 90]. Reduced appetite and weight loss are often problematic in dementia and can be exacerbated by the use of such agents. Vasoconstriction coupled with increased heart rate can jeopardize the often delicate balance between nutrient and oxygen supply and demand in older persons with pre-existing coronary artery disease and compromised cardiac function. In addition, unwanted central nervous system effects such as hyperactivity/motor restlessness, sleep disturbances, increased anxiety, and paranoia can significantly limit the practical use of such agents in persons with overt dementia who are already predisposed to such conditions.

Despite these concerns, repeated efficacy trials of stimulants have been undertaken for the treatment of the symptoms of late-life dementia since the 1950’s [89, 91, 96, 99]. A recent meta-analysis of stimulant use in dementia suggested that it may reduce apathy, but has little effect on cognition, and the effects on daytime hypersomnolence could not be reliably interpreted [89]. These results appear similar for patients with AD or VaD [92]. One recent study demonstrated the utility of a dextroamphetamine challenge in predicting a response to methylphenidate therapy that could potentially select appropriate patients and lessen the risk of adverse side effects which were greatly increased 3:1 in the study population [94]. Similar to its paradoxical effects in ADHD, another recent study demonstrated that methylphenidate actually reduced risk taking behavior in subjects with FTD [97]. No existing trials of stimulants for the treatment of MCI have been reported.

Borrowing a page from the MCI/dementia literature, several studies have examined the effects of acetylcholinesterase inhibitors in ADHD [83, 84, 88, 100]. The efficacy of such interventions in dementia is well documented. Treatment trials in MCI have not been successful to date, but one such trial suggested a potential temporary benefit in delaying progression to dementia over the first 6 months of use. Efficacy in the management of cognitive symptoms of MCI was marginal at best. Studies in ADHD have followed a similar course. Early case reports described improvements in attention and socialization [84, 88], however controlled clinical trials have failed to show overt efficacy, although a suggestion of a select group of "responders" (22 % of treated subjects) and a potential reduction in motor tics were noted in these studies [84, 88].

It is clear from the variability seen in these studies that effective pharmacotherapy targeting degenerative MCI and late-life ADHD suggest independent mechanisms of disease for these conditions.

Conclusions

While it is interesting to speculate that ADHD could predispose to the development of late-life dementia, the evidence for such an association is less than convincing. Yet, the direct association between MCI and ADHD has only been explored in a single study to date, allowing many opportunities to further explore this possibility. The evidence to date derived from genetic, imaging, and pharmacologic treatment studies does not support a direct link between ADHD and AD, but provides fertile ground for the further exploration of possible linkage to DLB and PD. Given the recent recognition of ADHD as a diagnostic entity that appears to be pervasive throughout life stages, extending into the geriatric years, it is much more likely that the relationship between ADHD and a diagnosis of MCI (designed to predict underlying neurodegenerative disease) is a confound rather than a causal factor. The confound of pervasive ADHD will remain an issue until the prevalence of this disorder in late life is accepted and screening measures for ADHD are adopted into the routine evaluation of MCI presenting initially as an attentional-deficit predominant syndrome.

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