Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: Mechanism for cognitive dysfunction and development of dementia

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Abstract—Sleep apnea is prevalent among patients with traumatic brain injuries (TBIs), and initial studies suggest it is associated with cognitive impairments in these patients. Recent studies found that the apolipoprotein epsilon 4 (APOE epsilon 4) allele increases the risk for sleep disordered breathing, particularly sleep apnea. The APOE epsilon 4 allele is associated with cognitive decline and the development of dementia in the general population as well as in patients with TBI. These findings raise the question of whether patients with TBI who are APOE epsilon 4 allele carriers are more vulnerable to the negative effects of sleep apnea on their cognitive functioning. While few treatments are available for cognitive impairment, highly effective treatments are available for sleep apnea. Here we review these different lines of evidence, making a case that the interactive effects of sleep apnea and the APOE epsilon 4 allele represent an important mechanism by which patients with TBI may develop a range of cognitive and neurobehavioral impairments. Increased understanding of the relationships among sleep apnea, the APOE epsilon 4 allele, and cognition could improve our ability to ameliorate one significant source of cognitive impairment and risk for dementia associated with TBI.

Key words: Alzheimer disease, apolipoprotein epsilon 4, cognition, daytime sleepiness, dementia, mild cognitive impairment, obstructive sleep apnea, sleep apnea, sleep disordered breathing, traumatic brain injury.

INTRODUCTION

In recent years, there has been an increased focus on the prevalence and impact of sleep apnea in traumatic brain injury (TBI). Sleep apnea is well documented to negatively affect neurocognitive and neuropsychiatric functioning, including memory, attention, mood, and anxiety. Sleep apnea has recently been implicated in cognitive decline and risk for developing Alzheimer disease (AD). TBI has long been identified as a risk factor for the development of dementia, with some studies suggesting the risk is greater among those with the vulnerability factor for AD, apolipoprotein epsilon 4 (APOE ε4) allele. Herein we review the literature to date on sleep apnea in TBI and outline the evidence to suggest that these factors in combination with the presence of the APOE ε4 may contribute significantly to cognitive dysfunction and the

Abbreviations: AD = Alzheimer disease, APOE ε4 = apolipoprotein epsilon 4, BiPAP = bilevel positive airway pressure, CI = confidence interval, CPAP = continuous positive airway pressure, CSA = central sleep apnea, MCI = mild cognitive impairment, MinSaO2 = minimum level of arterial oxygen saturation, NFT = neurofibrillary tangle, OR = odds ratio, OSA = obstructive sleep apnea, RDI = Respiratory Disturbance Index, SDB = sleep disordered breathing, SNP = single nucleotide polymorphism, TBI = traumatic brain injury, VA = Department of Veterans Affairs.

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development of dementia in these patients. Because the majority of sleep apnea patients are male and TBI is common among veterans because of combat and other factors, this work has significant importance for the Department of Veterans Affairs (VA).

PREVALENCE OF SLEEP DISORDERED BREATHING IN TBI

Recent evidence suggests an increased incidence of sleep disordered breathing (SDB) in TBI patients, with prevalence ranging from 25 [1] to 35 percent [2] compared with 4 to 9 percent in the general world population [3]. A recent investigation of sleep disorders in patients with TBI suggests as many as 50 to 70 percent of patients with TBI may suffer from some form of SDB [4]. These authors concluded that treatable sleep disorders, such as SDB, may be largely undiagnosed and untreated in the patient population with TBI. One initial investigation also suggests that SDB is associated with cognitive impairment in patients with TBI [3].

One of the most common forms of SDB is sleep apnea, of which obstructive sleep apnea (OSA) is by far the most prevalent. OSA is defined by frequent episodes of obstructed breathing during sleep. Specifically, it is characterized by sleep-related decreases (hypopneas) or pauses (apneas) in respiration with a characteristic association of snoring and excessive daytime sleepiness [5–6]. The diagnosis of OSA is confirmed when the patient presents with excessive daytime sleepiness and a Respiratory Disturbance Index (RDI) of >5 ((apneas + hypopneas) ÷ total sleep time in hours) [7]. However, in general, referral for treatment is not considered for individuals exhibiting an RDI <10 but is routinely considered when an RDI is particularly elevated, even in the absence of daytime sleepiness. An obstructive apnea is defined as interruption of oronasal airflow of at least 10 seconds, corresponding to a complete obstruction of the upper airways (despite continuous chest and abdominal movements) associated with a decrease in oxygen saturation and/or arousals from sleep. An obstructive hypopnea is defined as at least 10 seconds of partial obstruction of the upper airways, resulting in an at least 50 percent decrease in oronasal airflow. These abnormal respiratory events are generally accompanied by heart rate variability and arousals from sleep, with frequent arousals being the most important factor in resultant excessive daytime sleepiness.

The prevalence of OSA is higher in men than in women [8]. OSA is found in all age groups, but despite a lifetime prevalence of between 4 and 9 percent in the general population, its prevalence increases with age [9]. In subjects between the ages of 30 and 65 years, 24 percent of men and 9 percent of women had OSA. Among subjects over 55 years, 30 to 60 percent have an RDI >5 [10]. In a population of community-dwelling older adults, 70 percent of men and 56 percent of women between the ages of 65 and 99 years have evidence of OSA with a criterion of RDI >10 [11].

Effective treatments are available for the alleviation of OSA. Treatment for mild cases includes weight loss, dental devices (which advance the tongue or mandible to increase posterior airway space), or upper airway surgery [12]. Additionally, positional therapies have been employed with success, with patients urged to sleep on their front or sides rather than their backs. The gold standard treatment, however, for moderate to severe cases of OSA is continuous or bilevel positive airway pressure (CPAP/BiPAP) [13]. Other upper airway surgical procedures can be used for particular cases with craniofacial abnormalities [14].

Sleep apnea can be readily characterized with objective measurements of breathing and electroencephalography during an overnight sleep episode. Yet many individuals who, on objective measures, have severely disturbed sleep due to sleep apnea often fail to realize that their sleep is disturbed; more often they describe impaired daytime alertness. This lack of awareness may be exacerbated in patients with severe TBI as these individuals may be unaware of their sleep problems because of cognitive or neurological deficits from their injury or a preoccupation with more immediate medical aspects of their injury. In general, those with severe TBI report fewer posttrauma symptoms than those with lesser injuries [15]. Those with mild trauma may be more aware of their sleep issues because of their capacity to be more acutely aware and sensitive to post-TBI neurological and neuropsychiatric changes. Indeed, disrupted sleep is a common complaint among patients with TBI [16]. Some of the observed sleep disruption in TBI may be due to sleep apnea.
SLEEP APNEA, TBI, COGNITIVE FUNCTIONING, AND DEMENTIA

Sleep apnea is well documented as being associated with cognitive impairment. Impairments in attention memory, psychomotor function, and executive function have all been associated with sleep apnea [17–21]. One of the most consistent findings is that sleep apnea negatively affects delayed recall ability [22].

In a recent investigation of the effect of OSA on the cognitive functioning of patients with TBI, Wilde et al. found not only an increased incidence of OSA in patients with TBI but also a resultant decrease in the domains of delayed recall, attention, vigilance, and retention of both verbal and visual information in patients with both TBI and OSA [3]. Thirty-five patients with TBI were administered a comprehensive neuropsychological battery and assessed for OSA based on standard criteria with nocturnal polysomnography. Nineteen patients with TBI had both OSA and TBI and were compared with sixteen patients who had a TBI and no presence of OSA. Both groups were comparable with respect to age, education, severity of injury, time postinjury, and rating on the Glasgow Coma Scale. While the group with OSA and TBI had more attentional lapses, both groups performed comparably on measures of motor, visual construction, and attentional performance. However, patients with TBI with OSA performed significantly worse than the non-sleep-disordered patients with TBI on measures of both verbal and visual delayed recall.

Impaired delayed recall is a hallmark of typical and pathological cognitive aging and is a key feature of AD. TBI itself is a noted risk factor for dementia. Dementia is an age-related progressive disorder characterized by loss of function in multiple cognitive domains that is severe enough to cause impairment in social and occupational functioning.

AD is the most common form of dementia, accounting for between 50 and 70 percent of all cases. It is a neurodegenerative disorder, characterized neuropathologically by widespread neuronal loss, presence of neurofibrillary tangles (NFTs), and deposits of amyloid beta in cerebral blood vessels and neuritic plaques. The medial-temporal lobes, hippocampus, and association cortex are preferentially affected, leading to a marked decline in cognitive functioning that is the hallmark feature of AD [23]. While individuals with dementia or AD experience cognitive impairment, not all cognitive impairment represents a neurodegenerative disorder. One of the clearest findings to emerge from the field of cognitive aging is that performance on measures of memory and attention worsens with advancing age, which is regarded as part of the normal aging process. However, many older adults find these changes debilitating on a daily basis, interfering with activities ranging from medication compliance to productivity in the workplace. Recognition of age-associated cognitive and memory decline that appeared to go beyond that typically associated with normal aging led to the classification of such problems as cognitive impairment or mild cognitive impairment (MCI), the presence of which can significantly increase the likelihood of developing AD or dementia. Indeed, the types of cognitive and behavioral deficits exhibited appear to be on a continuum of severity from those that hallmark AD and dementia to MCI.

TBI AND RISK FOR DEMENTIA

The suggestion that TBI contributes to the development of AD and dementia has a long past. As early as 1976, Khaime reported on three cases of AD that developed after brain injury [24]. Since then, numerous animal, experimental, and epidemiological studies have supported an association between TBI and dementia.

Animal studies suggest that TBI contributes to the development of core AD pathological features, including increased oxidative stress [25] and increased levels of amyloid beta [26–27]. Human postmortem studies have observed both amyloid beta deposition and tau pathology in patients with TBI [28–29]. Ikonomovic et al. conducted an immunohistochemical study of AD-related changes in temporal cortex resected from 18 patients with TBI (aged 18–64 years) treated surgically for severe TBI [30]. Diffuse cortical amyloid beta deposits were observed in one-third of subjects (aged 35–62 years) as early as 2 hours after injury, with only one individual (35 years of age) exhibiting “mature” dense-cored plaques. Tau-positive, NFT-like changes were detected in only two subjects, both of whom were more advanced in age and had no evidence of amyloid beta deposits. No sex differences were found among the three diagnostic groups. The authors suggested that amyloid beta plaques and early evidence of neuronal degenerative changes may develop rapidly after TBI, while fully developed NFTs may result from more chronic disease- or injury-related processes.
The great majority of epidemiological investigations observe an association between TBI and the development of dementia [31–38], although some negative findings exist [39–41]. In one of the largest studies of veterans with TBI, Plassman et al. examined the association between early adult head injury, as documented by military hospital records, and dementia in late life [42]. Both moderate and severe head injury were associated with increased risk of AD. The results for mild head injury were inconclusive, but overall the findings suggested that moderate and severe head injuries in young men were associated with increased risk of AD and other dementias in later life.

Fleminger et al. [43] undertook a replication and extension of the meta-analysis of Mortimer et al. [44] by conducting a comprehensive and systematic search of electronic databases through August 2001. Fifteen case-control studies were identified that met the inclusion criteria, of which seven postdated Mortimer et al.’s study. Analysis of all 15 case-control studies was significant (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.21–2.06), indicating a history of head injury in those with AD. Also, the authors replicated the finding of Mortimer et al., who found that head injury is a risk factor for AD only in males (males: OR 2.29, 95% CI 1.47–2.06; females: OR 0.91, 95% CI 0.56–1.47) [43].

One proposed explanation for the sex difference in the risk of AD following head injury is the role of the female hormones, such as estrogen and progesterone. Animal models of stroke and TBI suggest that these hormones may confer a neuroprotective effect. Bramlett and Dietrich, for example, employed an animal model of TBI and found contusion volume was significantly smaller in adult female rats than in male and ovariectomized female rats [45]. Estrogen has been implicated as a potential protective factor in the development of AD, although findings are mixed [46]. Whether females may be protected from AD following head injury because of the protective effects of female hormones remains to be more systematically investigated.

TBI AND APOE ε4 ALLELE: INCREASED VULNERABILITY FOR DEMENTIA

Recent evidence points to a potential overlapping pathophysiological mechanism underlying the negative effect of both sleep apnea and TBI on cognitive function-
SLEEP APNEA, TBI, AND APOE ε4 ALLELE

Presence of the APOE ε4 allele has also been found to confer up to a twofold increased risk for OSA [62–63]. In a population-based probability sample of 791 middle-aged adults (mean ± standard deviation age = 49 ± 8 years, range = 32–68 years), the probability of moderate-to-severe SDB was significantly higher in participants with the APOE ε4 allele, independent of age, sex, body mass index, and race/ethnicity [63]. Although negative findings exist, most recently, Gottlieb et al. examined 1,775 subjects and confirmed an age-dependent association between the allele and sleep apnea [62].

Further, O’Hara et al. found that sleep apnea interacted with the APOE ε4 allele to negatively affect memory and suggested that APOE ε4 carriers with sleep apnea may be at increased risk for developing dementia [66]. This finding has recently been independently replicated by two groups: Gozal et al. found that children with OSA and poor cognitive performance were much more likely to be APOE ε4 carriers [65], and similarly, Consentino et al. found that APOE ε4 carriers who had presence of OSA had lower performance on a working memory task than those without apnea [66].

One recent investigation concentrated on several known single nucleotide polymorphisms (SNPs) within the APOE gene and its regulatory region in order to find associations with OSA status among children. They found that SNPs rs157580, rs405509, rs769455, and rs7412 all showed associations with OSA status, with age and body mass index as covariates. They concluded that polymorphisms in more than one locus in the APOE gene and its regulatory region are associated with OSA in children [67]. This finding lends itself to the conclusion that the interaction between TBI, OSA, and APOE genotype may be more complex than originally thought.

Sleep apnea-related cognitive impairment in TBI may reflect the hypoxia that accompanies sleep apnea events, with some additional impairment resulting from sleep fragmentation and daytime sleepiness [68]. Hypoxia is a defining feature of sleep apnea. Investigators have long suggested a model in which the neuronal injury resulting from hypoxia results in sleep apnea-associated cognitive impairment [68]. Hypoxic damage resulting from a broad range of disorders (e.g., brain injury, stroke, cardiac arrest) is well documented to negatively affect function and cognition, although the literature on the relationship between sleep apnea-related measures of hypoxia, such as minimum or average level of oxygen desaturation, and cognitive function is quite limited and the findings mixed [50,69–71]. In our own clinical investigation, we found that although average minimum level of arterial oxygen saturation (MinSaO₂)
displayed a nonsignificant tendency to negatively interact with the APOE ε4 allele to affect memory, the actual number of respiratory events was most strongly associated with impaired cognition [50]. Although most studies of this issue employ a single or average measure of oxygen desaturation, interaction of duration, frequency, and level of hypoxia, rather than MinSaO2 alone, may exert the greatest clinical impact.

An alternate explanation is that apnea/hypopnea-associated sleep fragmentation, rather than hypoxia per se, negatively affects cognition. Individuals with neuronal loss due to a TBI may be particularly vulnerable to the hypoxic events that accompany sleep apnea, as well as to the behavioral outcomes such as cognitive impairment and depression that have been consistently associated with the presence of sleep apnea [57,72]. A recent investigation by Chang et al. found that brain tissue hypoxia is common among patients with TBI; however, no measurement of apnea was included in this finding [73]. Further studies are needed to determine the hypoxic effect of sleep apnea in patients with TBI.

Animal studies suggest that the APOE ε4 allele increases neuronal vulnerability to oxidative stress [74]. The suggestion that APOE ε4 exacerbates sleep apnea-associated cognitive impairment by reducing the brain’s response to the hypoxic events experienced during apnea is consistent with observations that hypoxia and APOE ε4 status impact the hippocampus. Hypoxia has negative effects on neuronal integrity in the hippocampus [75–76]. These same hippocampal regions, which subserve delayed recall, also appear vulnerable to deleterious effects of the APOE ε4 allele [77–79]. Furthermore, our preliminary data found a negative association between even mild levels of sleep apnea and impaired delayed recall only in those with the APOE ε4 allele. Further, the common link between TBI and sleep apnea may be the resultant hypoxic effects exerted on brain tissue by both of these conditions, with presence of the APOE ε4 allele further mitigating against an effective neuronal recovery response to the hypoxia.

Increased understanding of the relationships among sleep apnea, APOE genotype, and hypoxia may provide significant insight into the molecular mechanisms that initiate critical pathological cascades in TBI. Further, the effective treatments available for sleep apnea may go a long way to improving the prognosis for patients with TBI not only in terms of the pathophysiology associated with the disorder but also in terms of improving the negative comorbid cognitive and psychiatric symptoms that are so prevalent in TBI.

**Treatment of Sleep Apnea in TBI**

Sleep hygiene provides subjects with basic education about daily behaviors, environmental conditions, and other sleep-related factors that have the potential to interfere with or support good sleep [80–81]. With respect to sleep apnea, treatment studies indicate that CPAP/BiPAP can be very effective in reducing not only sleep apnea events but also the associated cognitive and affective sequelae [64,72], although compliance can be difficult for all patients. To date, no systematic studies have been conducted on CPAP/BiPAP use in patients with TBI. Given the effectiveness of this treatment approach, it may be particularly valuable for alleviating a range of behavioral and psychiatric symptoms in patients with TBI with comorbid sleep apnea.

**Sleep Apnea in TBI: Vulnerability Factor or Mechanism for Impairment**

Patients who present with OSA may actually be at greater risk for TBI. OSA is well documented to cause sleepiness, which increases the likelihood of having an accident while driving [82]. Motor vehicle accidents may result in TBI or other bodily damage. Sleepiness is a factor in 42 to 54 percent of motor vehicle collisions [2]. Evidence exists that the presence of OSA is associated with increased risk for traffic accidents [83–84]. While there may be some dual causality of TBI and OSA, the direction of the relationship is still not clearly defined. In the United States, 80,000 people become permanently disabled from TBI as a result of motor vehicle crashes, falls, acts of violence, and sports incidents each year [85].

Alternatively, sleep apnea in TBI may occur secondary to the brain injury itself. In contrast to OSA, central sleep apnea (CSA) is defined as a lack of airflow accompanied by a lack of respiratory effort, reflecting impairments in brain areas controlling breathing. The important difference is that while in OSA, there is periodic apnea and asphyxia from upper airway obstruction or collapse in the pharynx, there is continued respiratory effort. CSA, then, may be indicative of more severe TBI or brain malformation [86].

In a recent study, patients who showed progression into white matter disease assessed by longitudinal magnetic resonance imaging scans were significantly more likely to have an increased number of central rather than
obstructive apneas. This result led the investigators to conclude that there is a causal pathway in which CSA contributes to the progression of white matter disease [86]. However, there may be a dual causality, in that it may be the presence of white matter disease that contributes to CSA, which then in turn exacerbates the already present white matter disease.

Webster et al. found that, in a relatively small study, 10 of 28 patients with TBI had sleep apnea and that the majority of these events were central apneas rather than obstructive apneas [87]. Normally, sleep apnea events are about 90 percent obstructive and only 10 percent central in nature [88]. Although the rate of sleep apnea was significantly higher than would be predicted of population norms, there was no correlation between presence of significant sleep apnea and severity of TBI.

**Sleep Apnea in TBI: Relevance to Veterans**

Several investigators have suggested that sleep apnea is highly prevalent in veteran populations, likely reflecting the fact that there is increased prevalence of sleep apnea with age and that this disorder is far more common among men [89–90]. However, in a recent investigation of more than 4,060,504 health records of veterans, Sharafkhaneh et al. found very similar prevalence rates of sleep apnea, namely 2.91 percent, to general population rates [91]. The authors raised the concern that this may reflect the fact that sleep apnea may be underdiagnosed in the veteran population. Indeed, Mustafa et al. used a self-report questionnaire to identify chronic symptoms of sleep disorders among patients in VA medical centers and found that with a mean age of 62.5 years, 47.4 percent met high-risk criteria for sleep apnea [92]. Further, Sharafkhaneh et al. found that those veterans with sleep apnea had far higher rates of psychiatric and medical comorbidity, including posttraumatic stress disorder, anxiety, and dementia, than those without this disorder [91].

Not only is sleep apnea more prevalent in men but the negative relationship of TBI to risk for dementia also seems to be exacerbated in men. Van Duijn et al. conducted a population-based case-control study of the association between head trauma and AD [93]. They compared 198 patients with clinically diagnosed early onset AD and 198 age- and sex-matched population controls. Following adjustment for sex, age, family history of dementia, and education, the OR of a history of head trauma (with loss of consciousness) was 1.6 (95% CI 0.8–3.4). However, the OR for men was 2.5 (95% CI 0.9–7.0), compared with 0.9 (95% CI 0.3–2.8) for women. Thus, male veterans may be at increased risk not only for sleep apnea itself but also for negative neurological and neuropsychiatric consequences of this disorder.

**SUMMARY AND CONCLUSIONS**

Increased understanding of the relationships between sleep apnea, APOE ε4 allele, and cognition could lead to improved therapeutic approaches to the cognitive impairment associated with TBI, as well as increasing our understanding of the pathophysiological mechanisms underlying the negative consequences of TBI.

Recovery from a TBI is often lengthy and difficult, and this recovery process may be hampered by the presence of a comorbid sleep disorder. Disruption of normal sleep by sleep apnea can also exacerbate other neuropsychiatric sequelae of TBI, potentially leading to long-term consequences and a decrement in overall quality of life. Sleep apnea is very prevalent in the veteran population and can be treated with one of the well-established and effective treatment approaches, such as CPAP/BiPAP, positional therapies, surgery, or weight loss. More systematic research is necessary in order to provide a foundation for an evidence-based medical approach to the treatment of sleep in the context of TBI. If, as the literature suggests, the APOE ε4 allele is associated with an increased risk for sleep apnea, then sleep apnea may be responsible for, i.e., mediate, any negative relationship between the APOE ε4 allele and cognitive impairment in TBI (Figure 1). Alternatively, any negative relationship between sleep apnea and cognitive function in TBI may reflect the increased vulnerability of APOE ε4 carriers to the neurological effects of sleep apnea, specifically apnea-associated hypoxia (Figure 2). As such, the APOE ε4 allele would moderate the relationship between sleep apnea and cognition in TBI. In this case, treatments for sleep apnea might target only APOE ε4 carriers. Of course, it is important to note that if there is a negative additive effect of hypoxia and APOE ε4 on the risk for dementia among patients with TBI, sleep apnea is not the only disorder that can result in hypoxia. Conditions such as chronic obstructive pulmonary disorder, pulmonary fibrosis, and asthma, for example, can all result in hypoxia, such that presence of any of these disorders might increase the risk for dementia and cognitive decline in patients with TBI. Another viable possibility is
that apnea/hypopnea-associated sleep fragmentation, rather than hypoxia per se, negatively affects neurological and neuropsychological outcomes. Future studies are required to investigate this possibility.

Larger longitudinal studies are required to clarify these issues—whether the APOE ε4 allele increases vulnerability to the negative effect of SDB on cognition in patients with TBI or whether the relationship between APOE ε4 and cognition is in fact due to the higher prevalence of SDB in these patients. Further, such longitudinal prospective studies, with full polysomnography, are required to address whether the relationship between sleep apnea and risk for dementia and cognitive decline in patients with TBI is mediated by the sleep-apnea associated hypoxia or sleep fragmentation or moderated by characteristics of the TBI itself, such as severity and duration since onset. Such relationships could also be examined within the context of treatment trials of CPAP, for example, for sleep apnea in veterans with TBI.

Overall, however, the evidence suggests that patients with TBI have an increased prevalence of sleep apnea. Considering the high carrier frequency of the APOE ε4 allele in the general population (25%), this polymorphism may account for a very substantial portion of the attributable risk for sleep apnea. Given that the APOE ε4 allele is also associated with increased risk for cognitive impairment and decline, sleep apnea and the APOE ε4 allele may conspire to both exacerbate cognitive impairment and accelerate the cognitive decline in patients with TBI. The risk for sleep apnea is greater in men. Given that the majority of veterans are men who are also at increased risk for TBIs, any relationship between sleep apnea and cognitive dysfunction in this patient group is of particular relevance and importance for the VA. While there are few effective therapeutic approaches for cognitive impairment, effective treatments for sleep apnea are available, including weight loss, dental devices, upper airway surgeries, and CPAP/BiPAP. Increased understanding of the
relationships among sleep apnea, APOE ε4, and cognition could lead to improved therapeutic approaches to the cognitive impairment associated with TBI, as well as increase our understanding of the pathophysiological mechanisms underlying the negative consequences of TBI.

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