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Narcolepsy, Head Injury, and the Problem of Causality

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Commentary on Ebrahim IO; Peacock KW; Williams AJ. Posttraumatic Narcolepsy-Two Case Reports and a Mini Review. *J Clin Sleep Med* 2005;1(2):153-156

The vast majority of patients with narcolepsy and cataplexy have ultra-low levels of hypocretin-1 in the cerebrospinal fluid, the DQB1*0602 HLA haplotype, and no family history of relatives with the disorder.[1] Their illness commences before the age of 35 years, and no obvious environmental factors are detected at onset. Although as yet unproven, the most likely hypothesis is that the disease arises from an autoimmune attack affecting the hypocretin (orexin)-synthesizing neurons in the posterolateral hypothalamus. However, rare reports of apparently secondary narcolepsy due to other disorders of the brain have appeared since the early years of the 20th century.[2] Most often, focal pathologies in the diencephalon or brainstem have been noted, including neoplasms, sarcoidosis, and arteriovenous malformations,[2-5] but diffuse or multifocal pathologies have also been described. These include multiple sclerosis, hypoxic-ischemic injury, cranial radiation, and, most frequently, head injury.[5-7] In this issue of *SLEEP,* Ebrahim and colleagues describe 2 intriguing cases in which narcolepsy was associated with head trauma,[8] adding to the relatively sparse literature on this topic.

It is hard to prove causative relationships, especially when the association under study is uncommon. For a number of reasons, an etiologic association between head injury and a disorder such as narcolepsy can be especially difficult to demonstrate with a high degree of certainty. First, head injuries are common, with a lifetime prevalence of about 6%.[9] Narcolepsy is not rare, with population studies in the United States demonstrating a prevalence of about 1 in 20,000 persons.[10] The peak incidence of both conditions is in adolescence and young adulthood.[9,10] Thus, coincidence has to be considered in assessing whether association implies causation in case reports linking the 2 conditions. The median age at head injury of the 20 patients reviewed by Ebrahim et al was 34 years, more than a decade older than the median age of onset of narcolepsy in patients with the idiopathic form of the disease.[10] While this is suggestive of a possible secondary cause, alone it is insufficient to establish causality.

Second, patients tend to retrospectively associate the onset of a disorder with serious or memorable life events. The accuracy of such recollections is especially questionable when a long interval has elapsed between the apparent signal event and the onset of symptoms of the secondary disorder. The mean time between the head injury and a firm diagnosis of narcolepsy in the 20 patients reviewed by Ebrahim et al was 25.6 months, with a maximum interval of 8 years. Moreover, the exact date of onset of narcolepsy can be difficult to recall, as most patients first develop sleepiness followed only later by the more novel occurrence of cataplexy.[11] Third, assuming that recollection is accurate, it is reasonable to assume that the closer the onset of narcoleptic symptoms to the head injury, the more likely the 2 are related. The median interval between the trauma and the first symptom of narcolepsy was relatively short (1 month) in the 10 patients with available information in the group reviewed by Ebrahim et al. While 1 patient developed symptoms only 1 day after the event, the onset of symptoms was delayed as long as 11 and 18 months in 2 others, reducing the likelihood of a causative relationship.

Fourth, one might predict that the greater the severity of the head injury, the more likely that narcolepsy might develop. However, many of the patients reported have experienced relatively mild head injuries with normal magnetic resonance imaging scans, including the 2 cases described by Ebrahim et al. While persistent, nonspecific symptoms of headache, dizziness, and concentration difficulties may follow mild closed head injuries,[12] it is hard to imagine such an injury causing highly localized damage to a small group of hypothalamic cells or their axons with no evidence for dysfunction of surrounding areas. Finally, head injuries while driving can be caused by sleepiness, and, thus, narcolepsy in some patients could be the cause of the head trauma rather than vice versa. It is clear that this was not the case in the 2 patients reported by Ebrahim et al.

A few years ago, we attempted to avoid the biases inherent in individual case reports of secondary narcolepsy by identifying from our institutional computerized record system all patients with a diagnosis of both narcolepsy and any other central nervous system disorder.[5] We located 18 such patients seen over a 23-year period. Seven patients (39%) had hypothalamic-pituitary syndromes, including 5 pituitary neoplasms, compared to only 3% of

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the total number of patients with central nervous system disorders. This certainly suggested a true association of narcolepsy with disorders in this region. Narcolepsy commenced less than 12 months after onset of symptoms of the other disorder in 9 of the 18 patients, but our series included only a single patient with a closed head injury who reported developing narcoleptic symptoms 10 days later.

Case-control studies have been used to help resolve similar issues, such as whether the onset of narcolepsy is associated with weight gain.[13] While a similar case-control study could be performed for narcolepsy and head trauma, this would only be helpful if it were hypothesized that head injuries are common precipants of the onset of narcolepsy in genetically predisposed patients. If, on the other hand, it was postulated that very occasional cases of narcolepsy can be caused by direct cerebral trauma, then a negative study would not be definitive. A more promising approach might be to study the rare patient in whom head injury appears to be associated with narcolepsy with advanced imaging and detailed physiologic tests. Hypocretin-1 levels in cerebrospinal fluid could be measured, and positron emission tomographic scans performed. Endocrine testing of the hypothalamic-pituitary axis and assessment of other hypothalamic functions, including markers of circadian rhythm, may be helpful in assessing whether or not there is dysfunction of areas closely adjacent to the hypocretin-synthesizing cells.

In summary, available data do not permit a final answer on whether head injury can cause narcolepsy. However convincing individual case reports might appear to be, care should be taken in reaching a definitive determination of causality.

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