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DEFENSE AND VETERANS BRAIN INJURY CENTER
INFORMATION PAPER ON
AMYOTROPHIC LATERAL SCLEROSIS AND TRAUMATIC BRAIN INJURY

ISSUE

This information paper summarizes the scientific literature about the association of traumatic brain injury (TBI) and amyotrophic lateral sclerosis (ALS).

BLUF

Overall, the evidence supporting a link between TBI and later ALS diagnosis is inconclusive.

BACKGROUND

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), is a progressive neuromuscular disease that leads to muscle weakness and atrophy. ALS affects about five per 100,000 individuals but is the most common motor neuron disease (Sundman, Hall, & Chen, 2014). The cause of ALS is unknown for most cases, though a small number are inherited (Bazarian, Cernak, Noble-Haeusslein, Potolicchio, & Temkin, 2009). Some data suggest that TBI history may be a risk factor for ALS (Chauhan, 2014).

The PubMed database was searched for articles containing TBI-related keywords and ALS-related keywords. The bibliographies of articles of interest were also searched for further information. The searches produced 13 studies and one meta-analysis that provided information on the risk of ALS after TBI as compared to ALS risk in non-TBI groups. Two studies were performed with veteran populations, (Kurtzke & Beebe, 1980; Schmidt, Kwee, Allen, & Oddone, 2010) and the remaining 10 studies with civilian populations. An additional four studies included athlete populations with unspecified TBI history (Belli & Vanacore, 2005; Chio, Benzi, Dossena, Mutani, & Mora, 2005; Lehman, Hein, Baron, & Gersic, 2012; Savica, Parisi, Wold, Josephs, & Ahlskog, 2012). These studies were excluded due to marginal relevance. Two relevant studies that did not include non-ALS controls are also discussed below.

The earlier study of veterans included 36 ALS-related deaths matched with military controls who died from other causes. The authors reported that the ALS cases were exposed to more trauma before and during their service (Kurtzke & Beebe, 1980). A larger, more recent study conducted by Schmidt et al. examined ApoE allele status and self-reported TBI history in 241 ALS cases and 597 non-ALS controls (Schmidt et al., 2010). Those who had sustained a TBI within the last 15 years were twice as likely to receive a diagnosis of ALS as those without a TBI history (7.5 percent of cases versus 3.6 percent of controls). A further analysis of this small group showed that an ApoE allele called ε4 may increase the risk of ALS among those with a TBI history. For those who had sustained a TBI more than 15 years prior, there was no increase in ALS risk.

Eleven studies reported about civilians, and six of those found at least some increase in risk of ALS associated with TBI history (Binazzi et al., 2009; Chen, Richard, Sandler, Umbach, & Kamel, 2007; Peters et al., 2013; Pupillo et al., 2012; Seelen et al., 2014; Turner, Abisgold,

Yeates, Talbot, & Goldacre, 2010). Four found no association (Fournier, Gearing, Upadhyayula, Klein, & Glass, 2015; Murros & Fogelholm, 1983; Qureshi et al., 2006; Williams, Annegers, Kokmen, O'Brien, & Kurland, 1991).

Four of the six studies on civilians that found an association between TBI history and ALS diagnosis did not find an overall increase in risk, but, rather, an association significant only for a portion of ALS cases (Binazzi et al., 2009; Chen et al., 2007; Peters et al., 2013; Turner et al., 2010). In these studies, ALS risk increased only for those with multiple TBIs (Chen et al., 2007) or only those who sustained TBIs within a certain period of time (Binazzi et al., 2009; Chen et al., 2007; Peters et al., 2013; Turner et al., 2010). The study by Peters et al. found a significant association between TBI and subsequent ALS diagnosis only when the TBI was sustained within one year of diagnosis. (Peters et al., 2013) The authors noted that ALS, as a motor neuron disease, increases the risk of fall, and hence TBI risk could be elevated as a consequence of early ALS symptoms. Turner et al. also found an association between TBI and ALS only when the injury was sustained within a year of diagnosis (Turner et al., 2010).

Five separate studies of civilian populations considered patients with multiple TBIs. Two of the studies found an association between multiple TBIs and subsequent ALS diagnosis (Chen et al., 2007; Pupillo et al., 2012). Two studies found no association, (Peters et al., 2013; Williams et al., 1991), and one study had insufficient multiple TBI cases and did not calculate risk (Binazzi et al., 2009).

The meta-analysis by Perry et al. included four studies addressing the association between TBI and ALS (Perry et al., 2016). Three of these studies had no significant association between TBI and ALS. The authors of the fourth and largest study acknowledged that the risk of ALS after TBI only increased among those who might be at risk of a fall associated with motor dysfunction (Turner et al., 2010). The data suggested that TBI does increase the risk of subsequent ALS, but a close examination of the included studies cast doubt on that conclusion.

Two recent studies did not include non-ALS controls but are nonetheless relevant. A recent population-based study by Raj et al. evaluated hospital records in Finland for TBI history and neurodegenerative disease admissions. About 20,000 individuals with moderate/severe TBI history were compared to a similar number of individuals with mild TBI history. The authors found a similar risk of ALS in the two groups, suggesting that moderate/severe TBI does not increase risk of ALS more than mild TBI. (Raj et al., 2017) A recent study found that a history of one or more head/neck injuries was associated with earlier symptom onset in a sample of 92 ALS patients. (Feddermann-Demont et al., 2017)

DISCUSSION

ALS is a relatively rare condition, so analyses of the risk factors contributing to the illness are inherently difficult. Compounding this problem is that the onset of ALS typically occurs many years after the TBI. Prospective studies, which recruit patients before they are diagnosed with the condition of interest (in this case, ALS), are generally considered the strongest evidence regarding causative/prognostic factors in disease (Gronseth, Cox, & Getchius, 2015). But because ALS is so rare and no premorbid signs indicate susceptibility, a prospective study would have to include an extremely large number of subjects and has not been performed.

These factors explain the generally low level of evidence regarding the association between ALS and TBI.

Overall, the evidence supporting a link between TBI and later ALS diagnosis is inconclusive. Some studies only found an association for those with TBI during a certain time period, (Binazzi et al., 2009; Chen et al., 2007; Peters et al., 2013; Turner et al., 2010) or those who sustained multiple TBIs (Chen et al., 2007). The largest study, by Peters et al., found an association between TBI and ALS only for those who sustained the TBI within one year of ALS diagnosis (Peters et al., 2013), but as noted above, TBIs proximal to ALS diagnosis may be attributable to falls due to motor dysfunction.

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