ABSTRACT

Introduction: Alzheimer’s disease is referred to as the main cause of dementia in the elderly. Its etiology remains controversial to this day. However, several risk factors have been associated with late-onset disease, such as family history, behavior, and lifestyle.

Among these risk factors, the head trauma injury has been mentioned in a number of case-control studies. Objective: A meta-analysis review was made to determine whether or not remote head trauma injury is a significant risk factor for late-onset Alzheimer’s disease. Methods: An adequate statistical model was applied to review 20 case-control studies published on Medline from 1990 until 2004. The interaction between head trauma and Alzheimer’s disease was evaluated. Mantel-Haenszel adjusted odds ratio (OR) and 95% confidence intervals were calculated in stratified data. Epi Info statistical software was used to determine p-value with significant level at 0.05. Results: An association between head trauma and Alzheimer’s disease was observed in 16 out of 20 evaluated studies but statistical significance was observed only in five studies. However, an overall analysis showed that a prior history of head injury was associated with later-onset of dementia due to Alzheimer’s disease (OR=3.17; 95%CI 3.12 to 3.92, and p=0.00000001). Conclusions: Patients with a history of head trauma injury had a three-fold increased risk of developing Alzheimer’s disease when compared to patients without this kind of trauma.

Keywords: head injury, Alzheimer’s disease

INTRODUCTION

In the literature, Alzheimer’s disease (AD) has been referred to as the main cause of dementia disorder in elderly patients, and its etiology still remains limited, inconsistent, and controversial. On the other hand, there is an increasing interest in identifying the reason for late occurrence of AD. Many studies indicate that several kinds of potential risk factors are involved, such as family history (dementia, mental retardation, Parkinson’s disease), behavior (smoking, alcohol abuse, coffee consumption, dietary habits), medical history (cancer, diabetes, hypertension, heart attack, head injury), life conditions (low level education, starvation/malnutrition) and others.

Although history of closed head injury, with or without loss of consciousness, has been reported as a potential risk factor for AD, the findings from various case-control studies are inconclusive. Some show that this trauma type has a significant or nearly significant effect on AD risk, whereas others have found no association. Besides, the apparent association between remote head injury and dementia may be spurious. In addition, trauma is the most common cause of hospital admission, especially in children, and severe closed head injury is a leading cause of death and disability in the world.

Thus, the purpose of this study was to determine, using a systematic review of meta-analysis studies, whether head injury is a significant risk factor for Alzheimer’s disease.

METHODS

Selection of studies – There are various studies in specialized literature showing the relationship between head trauma injury, as a risk factor, and the later occurrence of AD. Using a meta-analysis statistic model, we investigated the interaction between head trauma and AD. This method of analysis involves three phases: identifying studies in specialized literature that are related to the topic; analyzing the results of the selected studies; integrating the results within a statistical model. The use of meta-analysis in these cases is very efficient, as it not only aggregates the results of selected studies, but also, individually, estimates the effect of each of them and tests the statistical significance of the total result of the studies in association.

Our investigation included 20 case-control studies which had previously been published on Medline from 1990 until 2004. The selection criteria defined as head trauma a broad range of injuries that lead the patient to seek hospitalization or medical care, with or without loss of consciousness; submission at least to a Mini-Mental State Examination (MMSE) to characterize the mental depression.

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Statistical analysis – Analyses of two-by-two contingency table were performed. For each case-control study, the association between prior head trauma injury, with or without loss of consciousness, and AD was estimated in terms of odds ratio and 95% confidence intervals (CI). Mantel-Haenszel adjusted odds ratio (OR) were calculated in stratified data. The Mantel-Haenszel method gives an estimate of the OR for each study when all the studies are jointly considered. Odd ratio calculation, according to the Mantel-Haenszel method, represents the ratio between the change of an exposed group and a non-exposed group. If the changes are the same, the OR will be 1, but if they are not, the OR calculation is a direct way, in relative terms, of showing the different chance (greater or smaller) for the exposed group15,16. This study considered exposure to head trauma injury, which meant that the OR was calculated by finding the ratio of chances of AD occurrence associated to head trauma with the chances of AD occurrence without that kind of trauma. Epi Info statistical software was used to determine p-value with significant level at 5%.

RESULTS

After individually analyzing all the selected studies and reporting the relationship of head trauma injury and AD. In 16 out of the 20 studies evaluated, a direct association between this kind of trauma and occurrence of AD was observed. However, among these 16 studies, there was statistical significance only in five studies. When all the 20 studies were considered jointly the results showed statistical significance. The meta-analyses of all 20 studies showed that a history of head injury was associated with dementia due to AD with OR estimated at 3.17 (95%CI 3.12 to 3.92, and p-value <0.0000001). The results of meta-analysis for all studies are given in table 1. Figure 1 shows the individual and combined OR for all studies.

DISCUSSION

Alzheimer disease is the most common cause of dementia in elderly patients. It is characterized as a heterogeneous disorder that may be caused by genetic or environmental risk factors or by a combination of both. In spite of much research during the last decade, the etiology of AD disease in most cases remains unknown17,18,19,20,21. Pathologically, it is associated with the presence of numerous senile plaques and neurofibrillary tangles throughout the cerebral cortex. New studies have revealed that the altered metabolism of the _amyloid precursor protein, such as aberrant processing or excessive production, is a main event involved in the pathogenesis and maintenance of the disease process22,23,24.

On the other hand, several preexistent conditions have been cited as risk factors for late-onset AD. Based on epidemiological and neuropathological evidence, head injury has been considered a risk factor However, case-control and cohort studies suggest that there has been an over-representation of head injury as the best-established environmental catalyst to trigger or promote an event in

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Case</th>
<th>Control</th>
<th>Total</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value*</th>
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<tr>
<td>Broué</td>
<td>1900</td>
<td>9/170</td>
<td>6/170</td>
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<td>0.41-4.49</td>
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<tr>
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<td>10/126</td>
<td>15/199</td>
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<td>0.29-3.38</td>
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<tr>
<td>Graves</td>
<td>1900</td>
<td>19/130</td>
<td>8/130</td>
<td>27/260</td>
<td>2.61</td>
<td>1.03-6.79</td>
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<tr>
<td>Li</td>
<td>1992</td>
<td>1/70</td>
<td>2/140</td>
<td>3/210</td>
<td>1.0</td>
<td>0.08-11.21</td>
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<td>Mendez</td>
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<td>65/407</td>
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<td>74/457</td>
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<td>17/198</td>
<td>39/396</td>
<td>1.33</td>
<td>0.65-2.73</td>
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<td>25/296</td>
<td>29/342</td>
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<td>0.41-2.51</td>
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<td>14/103</td>
<td>49/331</td>
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<td>16/109</td>
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<td>1/24</td>
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<td>1998</td>
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<td>13/331</td>
<td>16/380</td>
<td>1.60</td>
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<td>Harwood</td>
<td>1999</td>
<td>40/580</td>
<td>17/226</td>
<td>57/806</td>
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<td>0.74-2.53</td>
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<td>Guo</td>
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<td>47/547</td>
<td>345/1249</td>
<td>82/1690</td>
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<td>150/387</td>
<td>654/17,111</td>
<td>1,907/21,698</td>
<td>5.17</td>
<td>3.12-9.05</td>
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the pathogenesis of AD. Consequently, there are several possible mechanisms by which traumatic brain injury might increase the risk for AD. Head injury might cause cerebral damage and lower the reserve against the cognitive consequences of subsequent, entirely unrelated cerebral pathology including AD. As a result neuropsychological abnormalities may persist for weeks or even months after injury.

Even though neurotoxicity of amyloid has not been positively confirmed in experimental animals, recent studies indicate that the relationship between head injury and AD is consistent with a hypothesis that cerebral amyloid deposition may lead to formation of neuritic plaques and neuronal destruction. With severe traumatic brain injury, at least, upregulation of amyloid precursor protein processing may occur, caused by β-amyloid protein accumulation in neurons, presumably as an acute-phase response to injury. This response may result in the destruction of the cell membrane and cytoskeleton with neuronal degeneration and death. Deposited amyloid following severe head injury is thought to be the main environmental risk factor involved as the precursor that contributes to AD onset. Nevertheless, according to Mayeux et al., head injury has been implicated in the causal pathway of other degenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis. This association is questionable or even inconsistent.

Since epidemiological evidence relates traumatic brain injury as an increased risk for subsequent development of molecular alterations involved in neuropathology of earliest stage AD, we expected to observe in the study a stronger association between head injury and this mental affection. In fact, this kind of trauma has significant importance since the most severe traumatic brain injury results in death or long-term disability. In the United States, approximately 2 million individuals sustain some head injury degree each year.

In addition, in a retrospective historical cohort design, Plassman et al. analyzed 548 World War II Navy and Marine male veterans hospitalized during their military service with a diagnosis of either nonpenetrating head injury or another unrelated condition. The authors concluded that moderate and severe head injuries in young men may be associated with increased risk of AD and other dementias in late life. Foster et al. also reported that head injury is associated with younger age of onset of AD. On the other hand, a retrospective cohort study performed by Williams et al. found no association between AD and head-injured people. These results were corroborated by Li et al. and Fratiglione et al. According Guo et al., there is indirect evidence supporting the view that head injury could be a risk factor for AD, such as repeated head injury experienced by boxers, for example.

In this study we investigated, in 20 case-control studies previously published, the risk for subsequent incident of AD associated with a history of head injury. Table 1 demonstrates that most of the studies analyzed presented positive results and a tendency to accept the association...
between head injury and increased risk of AD. In the same way, when all the studies were evaluated as a whole, the result demonstrated that the total odds ratio was highly favorable in relation to AD occurrence following prior head injury (OR=3.17; p-value<0.0000001).

Although, the partial results obtained from previous studies may be inconclusive or even contrary, when taken individually, meta-analysis is an appropriate method to be used, even though those case-control studies are susceptible to recall bias which may explain the different results observed between head injury and this disease. Therefore, the risk factors should be further studied, using meta-analysis with a more consistent and objective approach, so that more information are obtained regarding the true association between traumatic brain injury and Alzheimer's disease.

In summary, our results indicate that trauma head injury may be related with AD, and are consistent with the results of several previous case-control studies. This suggests that a history of head injury, with or without loss of consciousness, is positively associated with AD. Patients with a history of head trauma injury has a three-fold increased risk of developing Alzheimer's disease when compared to patients without this kind of trauma.

**REFERENCES**

NUTRICIONAL ASSESSMENT OF INFANTS ATTENDING A FAMILY HEALTH PROGRAM IN MONTES CLAROS (MG), BRASIL

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RESUMO

Objetivos: Avaliar o estado nutricional e variáveis associadas à desnutrição em menores de dois anos de idade em uma área atendida pelo Programa de Saúde da Família em Montes Claros (MG). Método: Foram avaliadas 138 crianças menores de dois anos de idade, com coleta de dados antropométricos e investigação sobre variáveis demográficas e socioeconômicas. O estado nutricional foi analisado através do programa Epi info. Na análise univariada, o teste do qui-quadrado e o teste exato de Fisher foram utilizados para comparação das proporções, admitindo-se um erro alfa de 5%. A regressão logística foi utilizada para determinação final das variáveis associadas à desnutrição. Resultados: A maioria das crianças avaliadas foi classificada como eutrófica (72.5%). Trinta crianças (21.7%) foram classificadas na faixa de desnutrição leve ou em risco nutricional, e oito crianças (6.8%) foram classificadas como portadoras de desnutrição moderada ou grave através da relação peso/idade. O baixo nível de escolaridade materno e o baixo peso de nascimento foram os fatores associados com a desnutrição (OR=2.97; IC95%=1,04-8.52 e OR=7.25; IC95%=1,75-30.03, respectivamente). Conclusão: O índice de desnutrição geral observado está além do esperado para uma área urbana da Região Sudeste, porém a proporção de formas moderadas e graves é menor do que a observada em outros estudos. Os autores destacam a necessidade de estudos regionais que sirvam de subsídios para efetiva atuação multisectorial no sentido de reverter a situação. Palavras-chave: Estado nutricional; Transtornos da Nutrição Infantil; Antropometria; Programa Saúde da Família.

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