TRAUMA CRANIOENCEFÁLICO COMO FATOR DE RISCO PARA A OCORRÊNCIA TARDIA DA DOENÇA DE ALZHEIMER: ESTUDO DE META-ANÁLISE

HEAD INJURY AS A RISK FACTOR FOR LATE-ONSET ALZHEIMER'S DISEASE: A META-ANALYSIS STUDY

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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 Mediline 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[1,2,3,4,5]. 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[6,7,8].

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[2,9,10,11]. 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[12,13,14].

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 contingence 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 chance of an exposed group and a non-exposed group. If the chances 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 <0.00000001). 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 unknown[17,18,19,20,21]. 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 process[22,23,24].

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 1 - Odds Ratio for each of the 20 studies

Author	Year	Nº of patients		Total	OR	95%CI	p-value*
		Case	Control				
Broe	1990	8/170	6/170	14/340	1.35	0.41-4.49	0.585
Ferine-Strambi	1990	5/63	10/126	15/189	1.0	0.28-3.38	1.000
Graves	1990	19/130	8/130	27/260	2.61	1.03-6.79	0.025
Li	1992	1/70	2/140	3/210	1.0	0.08-11.21	1.000
Mendez	1992	65/407	9/50	74/457	0.87	0.38-2.02	0.713
Van Duijin	1992	22/198	17/198	39/396	1.33	0.65-2.73	0.399
Fratiglione	1993	4/98	25/266	29/364	0.41	0.12-1.29	0.097
Mayeux	1993	35/138	14/193	49/331	4.34	2.14-8.93	0.0000049
CSHA	1994	13/162	27/420	40/582	1.27	0.60-2.64	0.495
Forster	1995	22/109	16/109	38/218	1.47	0.69-3.16	0.285
Rasmusson	1995	4/68	1/34	5/102	2.06	0.20-50.48	0.518
Mayeux	1995	13/113	10/123	23/236	1.47	0.57-3.80	0.383
Tang	1996	13/113	10/123	23/236	1.47	0.57-3.80	0.383
Schofield	1997	5/39	27/232	32/271	1.12	0.35-3.33	0.832
Salib	1997	53/198	66/340	119/538	1.52	0.98-2.34	0.047
O'Meara	1997	32/349	16/342	349/691	2.06	1.07-4.00	0.020
Tsolaki	1997	14/61	15/69	29/130	1.07	0.43-2.65	0.868
Hall	1998	3/49	13/331	16/380	1.60	0.35-6.32	0.475
Harwood	1999	46/580	17/286	63/866	1.36	0.74-2.53	0.289
Guo	2000	475/3.472	345/13.429	820/16.901	6.01	5.19-6.96	<0.0000001
Combined		852/6.587	654/17.111	1.507/23.698	3.17	3.12-3.92	<0.00000001

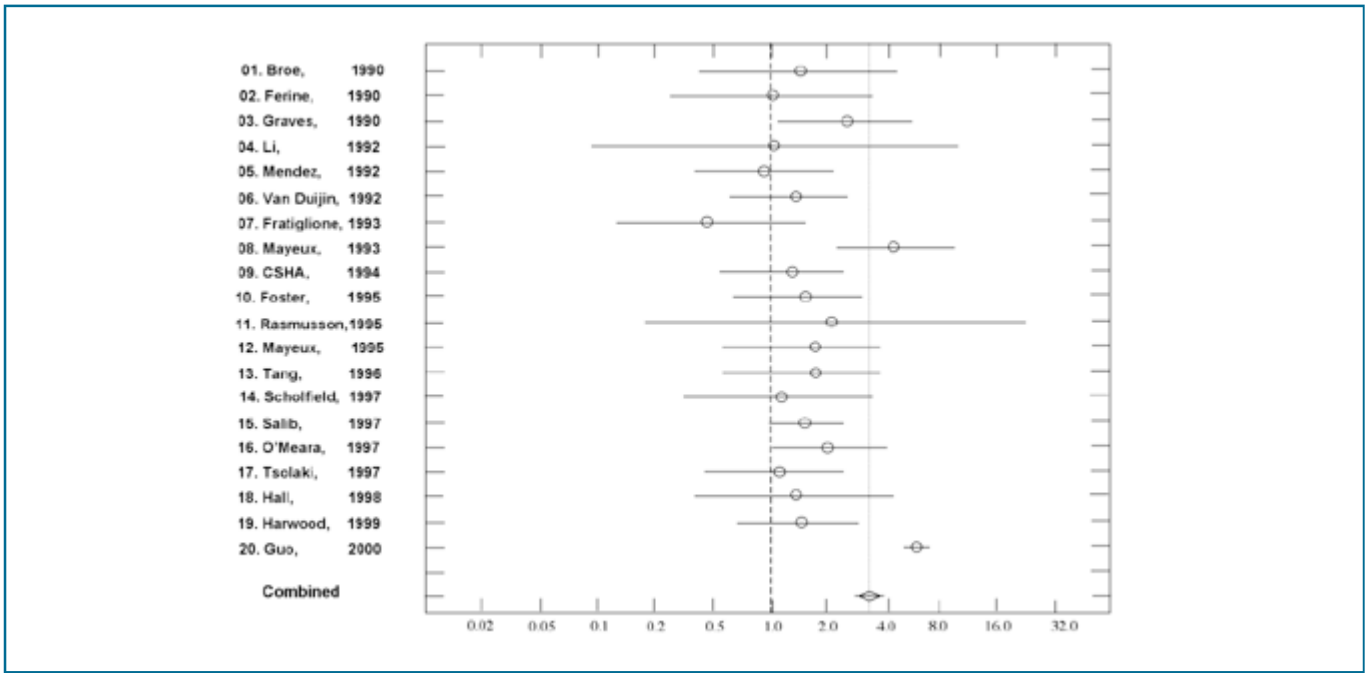

Figure 1 - odds ratio and 95% confidence intervals for each of the 20 studies, and overall estimated odds ratio. Bars indicate 95% confidence in confidence intervals. The dashed line marks an odds ratio of 1.0, or no effect.

the pathogenesis of AD[25,26,27,28]. 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[6,29].

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[1,2]. With severe traumatic brain injury, at least, upregulation of amyloid precursor protein processing may occur, caused by _-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[17,18]. Thus, 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[22], 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. I United States approximately 2 million individuals sustain some head injury degree each year[1,6,10].

In addition, in a retrospective historical cohort design, Plassman et al[10] 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 late in life. Foster et al.[30] 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.[31] found no association between AD and head-injured people. These results were corroborated by Li et al.[32] and Fratiglione et al.[11]. According Guo et al.[9], 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-valor<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 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.

RESUMO

Introdução: A doença de Alzheimer tem sido referida como a causa mais comum de demência em idosos. De etiologia ainda pouco conhecida, seus diversos fatores de risco vêm sendo estudados, entre eles o trauma de crânio, o qual é citado em vários estudos caso-controle. Porém, nestes estudos, os resultados são ainda pouco conclusivos. Objetivo: estudar, em pacientes idosos, o traumatismo cranioencefálico como fator de risco para a ocorrência tardia da doença de Alzheimer. Método: Utilizando-se o modelo estatístico de meta-análise, os autores avaliaram 20 trabalhos científicos, do tipo caso-controle, publicados pela medline no período de 1990 a 2004, os quais investigaram a associação entre o trauma craniano e a doença. A odds ratio (OR) e o intervalo de confiança de 95% foram calculados segundo o método de Mantel-Haenszel. Os valores de p foram obtidos com o programa Epi Info, versão 6.04c. Considerou-se o nível alfa igual a 0,05. Resultados: quando analisados isoladamente, observou-se que, entre os 20 estudos avaliados, 16 deles apresentaram uma associação positiva entre o trauma cranioencefálico e a doença de Alzheimer, com significância estatística presente em cinco estudos, somente. Porém, quando estes estudos foram avaliados conjuntamente, verificou-se a influência significativa deste tipo de trauma como fator de risco para o desenvolvimento tardio da doença de Alzheimer, com OR=3,17; IC95%=3,12-3,92 e p-valor < 0,0001. Conclusão: em pacientes com história pregressa de trauma cranioencefálico, a ocorrência tardia da doença de Alzheimer foi cerca de três vezes maior quando comparada aos pacientes sem história deste tipo de trauma.

Palavras chave: Doença de Alzheimer; Traumatismos Cerebrais.

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