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Head injury and brain tumours in adults: A case–control study in Rio de Janeiro, Brazil

Gina Torres Rego Monteiro[a,*], *Rosângela Alves Pereira*[b], *Rosalina Jorge Koifman*[a], *Sérgio Koifman*[a]

[a]*Department of Epidemiology, National School of Public Health, FIOCRUZ, Oswaldo Cruz Foundation, Rua Leopoldo Bulhões, 1480 sala 812, Manguinhos, CEP: 21.041-210, Rio de Janeiro, Brazil*
[b]*Institute of Nutrition, Federal University in Rio de Janeiro, Rio de Janeiro, Brazil*

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ABSTRACT

A hospital-based case–control study exploring the association between selected risk factors and head injury in adults, brain trauma included, was carried out in Greater Metropolitan Rio de Janeiro, Brazil. Cases included adults diagnosed with primary brain tumours ($n = 231$). Controls were matched for gender and age among in-patients hospitalized for various conditions unrelated to brain cancer ($n = 261$) identified in the same hospitals where cases were enrolled. Risk of having experienced head injury was more frequent among cases (46%) than controls (36%) ($OR_{adj} = 1.49$; 95% CI = 1.03–2.15). A dose–response effect was observed according to the number of head injuries, and a statistically borderline association was observed for meningioma ($OR_{adj} = 1.63$; 95% CI = 0.96–2.75). Although recall bias cannot be ruled out, our results suggest an association between prior head injury and the development of brain tumours in adults.

1. Introduction

The mortality and incidence rates of central nervous system (CNS) tumours have increased in recent decades in Brazil and worldwide.[1–4] Moreover, brain cancer age-adjusted mortality rates in 1980–1998 showed a 50% increase in Brazil, with an especially marked increment in women and the elderly.[5] Various risk factors have been reported to be possibly associated with this increase, such as exposure to certain chemicals (*N*-nitroso compounds, pesticides, petroleum derivatives, solvents, and vinyl chloride), radiation, anti-convulsive drugs, and prior head injury.[6–8]

The association between head injury and brain tumours has been a matter of controversy for decades, since Cushing and Eisenhardt (1938) reported that one-third of their brain tumour patients presented a history of head injury. Some studies observed that a head injury had occurred years before the tumour diagnosis.[9–11] Preston-Martin and colleagues[9] show case reports with convincing circumstantial evidence of prior head injury (e.g., scar or fracture mark on the tumour site) in 8% of a meningioma case series. Case–control studies have reported excess risk meningioma among individuals with any history of severe head injury, such as boxers.[8–10,12] Epidemiological evidence of the association between head injury and brain tumour is strongest for meningiomas, even considering positive associations reported for gliomas.[10,12–14] However, other studies have failed to show a statistically significant association between prior head injury and brain cancer.[15]

* *Corresponding author:* Tel.: +5521 2598 2617; fax: +5521 2270 6772.
E-mail address: gtorres@cremerj.com.br (G.T.R. Monteiro).
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This paper reports the estimated magnitude of the association between prior head injury and brain cancer in adults in a case–control study in Rio de Janeiro, Brazil.

2. Patients and methods

A hospital-based case–control study assessed the association between specific environmental risk factors and brain cancer in Rio de Janeiro, Brazil. The sample was selected from 30 to 65 year-old patients in Greater Metropolitan Rio de Janeiro who were hospitalized between January 1999 and December 2002 in 10 different hospitals belonging to the National Health System (which covers the general population without admission restrictions). This study presents data on the association between history of head injury and brain cancer.

Cases were defined as individuals with a new diagnosis of primary brain neoplasm (incident cases, 80% of whom with histopathological confirmation and a participation rate of 94%), including cerebral meninges (ICD-10 C70.0; D32.0), brain cancer (C71.0–C71.9), cranial nerve tumours (C72.2–C72.5), and benign and unspecified brain tumours (D33.0–D33.3; D42.0, D43.0–43.3). Extracranial and metastatic tumours were not included in the study.

Gender and age matching was used to select controls among in-patients from the same geographic region as cases and hospitalized in the same 10 hospitals where cases were recruited. Controls were interviewed during the same time period following a case recruitment and were identified among patients diagnosed with various diseases unrelated to brain tumour, such as: trauma (37.4%); gynecological disorders (9.3%); infectious diseases (8.2%); abdominal surgery (7.8%); urinary system disorders (7.8%); rheumatologic diseases (9.0%); cardiovascular diseases (4.5%); and other conditions (16%). The participation rate among controls was 90%.

Head injury was ascertained and classified on the basis of self-report. Individuals were considered exposed if they reported head injury that had occurred at least a year prior to the brain tumour diagnosis (for cases) or hospitalization (for controls), avoiding the inclusion of events which could be a clinical manifestation of an undiagnosed brain tumour. Of the 240 patients recruited as cases and the 268 as controls, some were not included in the current analysis because they reported not remembering the occurrence of previous head trauma episodes. Therefore, this analysis refers to all patients (231 cases and 261 controls) who reported the presence or absence of prior head injury.

A questionnaire developed by IARC/WHO to evaluate brain cancer in adults[9] was adapted with minor changes, and patients were interviewed during hospitalization.

Some trauma severity markers were also explored, particularly hospitalization following these episodes and loss of consciousness and amnesia resulting from the trauma. Patients with hospitalization were defined as reporting at least one head injury followed by hospitalization. They were defined as having experienced loss of consciousness if they reported this after at least one head injury. History of amnesia was defined by a report of at least one head injury followed by loss of memory. The analysis included number of head injuries, time elapsed between injury and brain tumour diagnosis, and severity markers. Potential confounding variables included in the study were age, gender, schooling, epilepsy, and alcohol consumption.

Crude and adjusted odds ratios (OR) for all potential confounding variables and the respective 95% confidence intervals were determined. The study was approved by the Research Ethics Committees at all the participating institutions. All participants signed an informed written consent.

3. Results

Demographic variables showed similar distribution between cases and controls, and women constituted 56.7% of cases and 60.2% of controls. Distributions of cases and controls by age ($P = 0.74$) and schooling ($P = 0.95$) were similar. Both groups showed a high proportion of limited schooling Table 1.

Prior head injury was reported by 107 cases and 95 controls Table 2, and increased risk of brain cancer was detected (OR = 1.51; 95% CI: 1.05–2.16), which did not substantially change when potential confounding factors were introduced in the analysis ($OR_{adj} = 1.49$; 95% CI: 1.03–2.15). However, the positive association disappeared when severity markers were considered Table 3.

The stratified analysis according to number of head injuries Table 2 suggested a dose–response effect ($P = 0.004$), with $OR_{adj} = 3.14$ for two or more injuries.

Patients with head injury 10–19 years prior to brain cancer diagnosis showed a statistically significant risk excess (OR_{adj} 1.31; 95% CI 1.06–1.64) Table 4.

Table 5 shows the association between head injury and histologically specific brain tumours. A borderline significant association was obtained for meningioma ($OR_{adj} = 1.63$; 95% CI: 0.96–2.75). A low and statistically non-significant increased risk was observed for glioma ($OR_{adj} = 1.30$; 95% CI: 0.71–2.35).

Only 10 cases (4.2%) and 13 controls (4.8%) reported a history of boxing, wrestling, or other sports related to head impact; however, eight cases and four controls reported head

Table 1 – Selected demographic variables and history of head injury in brain cancer cases and controls, Rio de Janeiro, 1999–2002

Variable	Strata	Cases no. (%)	Controls no. (%)
Gender	Male	100 (43.3)	104 (39.8)
	Female	131 (56.7)	157 (60.2)
Age (years)	<35	28 (12.1)	34 (13.0)
	35–39	26 (11.3)	34 (13.0)
	40–44	39 (16.9)	38 (14.6)
	45–49	37 (16.0)	55 (21.1)
	50–54	42 (18.2)	39 (14.9)
	55–59	28 (12.1)	28 (10.7)
	60 e+	31 (13.4)	33 (12.6)
Schooling (years)	<5	54 (23.4)	57 (21.8)
	5–7	79 (34.2)	91 (34.9)
	8–12	87 (37.7)	98 (37.5)
	>12	11 (4.8)	15 (5.7)
History of head injury	Yes	107 (46.3)	95 (36.4)
	No	124 (53.7)	166 (63.6)
Total		231 (100.0)	261 (100.0)

Table 2 – Head injury at least 12 months before tumour diagnosis (for cases), brain cancer cases and controls, Rio de Janeiro, 1999–2002

History of head injury	Cases no. (%)	Controls no. (%)	Crude OR (95% IC)	Adjusted OR[a] (95% IC)
Number of head injuries[b]				
None	124 (51.7)	166 (61.9)	1.00	1.00
1	74 (30.8)	78 (29.1)	1.27 (0.86–1.88)	1.29 (0.85–1.96)
2 or more	28 (11.7)	13 (4.9)	2.88 (1.43–5.79)	3.14 (1.50–6.61)
At least 1 injury	107 (44.6)	95 (36.4)	1.51 (1.05–2.16)	1.49 (1.03–2.15)

a Adjusted for age, gender, schooling, epilepsy, and alcohol consumption.
b X^2 trend = 8.320; $P = 0.004$.

Table 5 – Head injury at least 12 months before diagnosis or hospitalization,[a] brain cancer cases and controls, Rio de Janeiro, 1999–2002

History of head injury	No.	Crude OR (95% IC)	Adjusted OR[b] (95% IC)
Controls	261	1.0	1.0
Glioma	31	1.64 (0.95–2.85)	1.30 (0.71–2.35)
Meningioma	38	1.51 (0.91–2.49)	1.63 (0.96–2.75)
Others tumours			
With histopathology	15	1.09 (0.55–2.18)	1.07 (0.52–2.21)
Without histopathology	23	1.75 (0.93–3.28)	1.92 (0.99–3.73)
All	38	1.51 (0.91–2.49)	1.63 (0.96–2.75)

a Tumour diagnosis for cases and hospitalization for controls.
b Adjusted for age, gender, schooling, epilepsy, and alcohol consumption.

injuries resulting from these sports. Meanwhile, 30.0% of cases and 15.4% of controls who reported having practiced these sports also reported having suffered some level of head trauma at least once a week while engaging in them. Additionally, the time during which cases and controls had practiced these sports ranged from 8 months to 57 years. Moreover, 40.0% of cases and 23.1% of controls had practiced such trauma-prone sports for at least 4 years.

4. Discussion

This study detected a statistically significant positive association between head injury and brain tumour ($OR_{adj} = 1.49$; 95% CI: 1.03–2.15). The finding was further substantiated by the risk increment according to reported number of injuries.

According to a case–control study in Los Angeles, men who had suffered severe head injury at least 20 years previously showed a crude odds ratio of 2.3 for meningioma, and the risk increased with the number of events, reaching 6.2 among individuals with three or more severe head injuries.[13]

However, as observed in other studies,[9,12,16,17] the association did not persist after adjusting for severity markers such as hospitalization, loss of consciousness, and amnesia.

An international case–control study estimated glioma and meningioma risk in subjects who had suffered a medically treated head injury at least 5 years before tumour diagnosis[9]. A minor and statistically non-significant excess risk was observed in men for glioma (crude OR = 1.18) and meningioma (crude OR = 1.49). In the subgroup with more than one head

Table 3 – Head injury (once at least) followed by hospitalization, loss of consciousness, or loss of memory, in brain cancer cases and controls, Rio de Janeiro, 1999–2002

Severity markers	Cases no. (%)	Controls no. (%)	Crude OR (95% IC)	Adjusted OR[a] (95% IC)
Hospitalization	15 (12.8)	21 (22.1)	0.80 (0.40–1.59)	0.78 (0.37–1.64)
Loss of consciousness	22 (18.8)	28 (29.5)	0.94 (0.52–1.70)	1.03 (0.55–1.94)
Loss of memory	5 (4.3)	5 (5.3)	1.14 (0.33–4.00)	1.48 (0.38–5.83)
Any severity marker	31 (29.0)	42 (44.2)	0.88 (0.53–1.45)	0.93 (0.54–1.60)

a Adjusted for age, gender, schooling, epilepsy, and alcohol consumption.

Table 4 – Time elapsed between first head injury and diagnosis or hospitalization[a], brain cancer cases and controls, Rio de Janeiro, 1999–2002

Years since first head injury	Cases no. (%)	Controls no. (%)	Crude OR (95% IC)	Adjusted OR[b] (95% IC)
No head injury	124 (53.7)	166 (63.6)	1.00	1.00
1–9	19 (8.2)	22 (8.4)	1.16 (0.60–2.23)	1.18 (0.73–1.89)
10–19	27 (11.7)	18 (6.9)	2.01 (1.06–3.81)	1.31 (1.06–1.64)
20–29	23 (10.0)	23 (8.8)	1.34 (0.72–2.50)	1.07 (0.91–1.27)
30–39	20 (8.7)	16 (6.1)	1.67 (0.83–3.36)	1.09 (0.94–1.26)
40+	18 (7.8)	16 (6.1)	1.51 (0.74–3.07)	1.09 (0.96–1.24)
Total	231 (100.0)	261 (100.0)		

$X^2_{5df} = 1.88$; $P = 0.7587$.
a Tumour diagnosis for cases and hospitalization for controls.
b Adjusted for age, gender, schooling, epilepsy, and alcohol consumption.

injury, the observed risk of glioma was statistically significant (crude OR = 1.52; 95% CI: 1.00–2.32). Meanwhile, categorization by time interval between injury and tumour diagnosis showed a statistically significant excess risk of meningioma among subjects who had suffered head injury 15–24 years prior to tumour diagnosis (crude OR = 5.35; 95% CI: 1.72–16.62). In a case–control population-based study, Phillips et al.[18] also found a higher association when trauma had occurred 10–19 years before tumour diagnosis (crude OR = 4.33; 95% CI: 2.06–9.10).

Furthermore, analysis by histological type showed a positive but statistically non-significant association with meningioma (OR_{adj} = 1.63) and glioma (OR_{adj} = 1.30). This positive association is similar to other studies that analyzed the relationship between prior head injury and risk of glioma and meningioma.[9,10,16,17,19]

Risk of meningioma following head injury appears to depend on the development of chronic inflammation or an invasiveness phenomenon after the initial trauma.[6,10] Hu et al.[16] suggest that development of glioblastoma reflects the reactive proliferation of astroglial cells at the trauma site. Nygren et al. [20] indicate that genetic alterations are involved in such tumour genesis through cell division following tissue repair. Some experimental evidence has suggested that injury could act as a co-carcinogen inducing glioma and meningioma formation.[6,9,20]

Hu et al.[16,19] found a statistically significant risk of glioma (OR_{adj} = 4.09) and meningioma (OR_{adj} = 16.36) after adjusting for several variables among patients in northeast China who reported head injury requiring medical care.

A follow-up study of patients hospitalized for head injury in Denmark showed increased risk of brain tumour (SIR = 1.36), with a weaker association after excluding those diagnosed 12 months after the trauma (SIR = 1.15).[10] However, another study (in Sweden) did not detect a similar risk increase.[20]

So far, it is not clear which mechanisms may be involved in the association between head injury and subsequent brain tumour. It has been suggested that traumatic lesions trigger the effect of other exposures, either by inducing cell proliferation or breaching the blood–brain barrier, resulting in exposure of brain tissue to blood–borne carcinogens. Such hypotheses are reinforced by reports of meningiomas located adjacent to post-traumatic scars.[7,17]

The release of autacoids (such as bradykinin, histamine, and arachidonic acid) in pathological conditions like infection, inflammation, trauma, and hemorrhage is known to modify the blood–brain barrier properties, possibly increasing vascular permeability and allowing diffusion of toxic substances into the brain.[7,15] Thus, cells damaged by initiators of carcinogenesis would proliferate as a natural result of the trauma, leading to tumour development.[9]

Recall bias must be considered in case–control studies, particularly when a risk factor such as trauma is often thought to be related to tumour development. A lower proportion of cases (29.0%) than controls (44.2%) did not report head injury severity markers, suggesting that less severe brain injury was reported differentially.

Even in cohort studies, conflicting results of comparable studies persist. While a Danish cohort of patients hospitalized with head injury and monitored from 1977 to 1992 detected a slight excess risk (SIR = 1.2; 95% CI: 1.0–1.3), a similar study in Sweden (1965–1994) found no association between head injury and brain tumours (SIR = 1.0; 95% CI: 0.9–1.2). Both studies excluded patients with tumour diagnosis within the first 12 months after the injury, thus avoiding inclusion of accidents due to tumour symptoms in the attempt to prevent detection bias. The authors of both studies attributed the case–control findings to recall bias, concluding that if head trauma increases brain tumour risk, the increase is slight and occurs decades later.[10,20] However, to rule out such an association appears unadvisable, since some studies have shown that head injury is a risk factor for meningioma.[8,16,19]

In our study, only head injuries that occurred at least 1 year before tumour diagnosis were included, aiming to control detection bias by avoiding inclusion of episodes possibly caused by brain tumour manifestations. Moreover, favourable methodological aspects included the analysis of incident (rather than prevalent) cases in a defined time interval, reduced lack of response related to target variables, and a high proportion of cases with histological confirmation.

The results suggest a positive dose–response association between prior head injury and the development of brain tumours. Analysis by histological type showed statistically borderline associations with meningioma (OR_{adj} = 1.63) and glioma (OR_{adj} = 1.30). Reproducibility of these results in other epidemiological studies should be investigated to evaluate the causal association between prior head injury and meningioma.

Conflict of interest statement

None declared.

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