

Medulloblastoma Associated with Brucellosis and its Mortality: What is Known?

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ABSTRACT

Background: Brucellosis is an infectious disease caused by *Brucella* species, being considered a zoonotic disease, with high incidence rates. Medulloblastoma is a brain tumor, having its origin in the fourth ventricle, which is a precursor of granular cells in the outer germ layer.

Methodology: A narrative review was carried out through various databases from January 2011 to May 2021; the search and selection of articles was carried out in journals indexed in English. The following were used as keywords: Medulloblastoma; Brucellosis; Glioblastoma; Mortality; Neurobrucellosis

Results: Medulloblastoma has been widely associated with *Brucella* infection, with possible progression and dissemination associated with the secretion of large amounts of exosomes, which is stimulated by this microorganism, presenting characteristics of drug resistance, metastasis, invasion, angiogenesis and remodeling of the microenvironment. Exosomes being a possible approach in its diagnosis and treatment.

Conclusion: The present review offers a close association between medulloblastoma, glioblastomas, gliomas, metastatic carcinomas, and *Brucella* infection.

KEYWORDS: Medulloblastoma; Brucellosis; Glioblastoma; Mortality; Neurobrucellosis

INTRODUCTION

Remitting fever, undulating fever, Mediterranean fever, Maltese fever, Gibraltar fever, Crimean fever, goat fever and Bang's disease are the names by which brucellosis is known, an infectious disease caused by *Brucella* species, a *coccobacillus*. gram-negative, aerobic and facultative intracellular [1]. It is considered a zoonotic disease, caused by four species: *B. suis*, *B. melitensis*, *B. abortus* and *B. canis* [2]. The consumption of undercooked meat or close contact with livestock and the consumption of milk and dairy products are the mechanisms by which the disease is transmitted from animals to

humans [3,4]. Inhalation of contaminated aerosols, conjunctival inoculation, blood transfusions, transplacentally and in few cases from one person to another are the other mechanisms by which the disease can be transmitted [4]. Studies report a prevalence of *Brucella* spp [5]. 4.4% in humans. While in livestock professionals a prevalence of 15.6% is estimated [6]. Other studies reported high rates in the incidence of the disease caused by *Brucella*, in Kenya there was a figure of 203.07 cases per 100,000 inhabitants, Yemen 89.96, Syria 47.26, Greece 42.96 and in eritrea an incidence of 21.82 [6,7].

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Medulloblastoma, considered an embryonal neuroepithelial tumor of the brain, constitutes 10% of all pediatric brain tumors [8]. Tumor growth begins in the fourth ventricle, being a precursor of granule cells in the outer germ layer of the developing cerebellum. It can present a distant metastatic spread through the subarachnoid system or a local invasion, being considered a highly malignant tumor [9]. The global incidence of medulloblastoma is reported at 1.8 per million person-years [10]. Another study reports a stable incidence from 2001 to 2013 of 2.2%, with a higher incidence in patients aged 10 to 14 years of 3.2%. 70% of cases affect children aged 16 to minors with a maximum incidence at 7 years [11,12]. The infection represents the main cause of human cancer in the world, except for ionizing radiation, sunlight and tobacco, as is the case of cancers of the anogenital tract (Cause: HPV), stomach (Cause: *H. pylori*), Liver (Cause: HBV, HCV), bladder (Cause: hematobio schistosoma), prostate (Cause: XMRV), brain tumors such as glioblastoma multiforme and medulloblastoma (cause: HCMV) among other cancers with possible infectious causes [13].

Currently there is little evidence of a clear etiology of medulloblastoma, presenting a close association with infections [13]. Therefore, this review aims to provide the association between medulloblastoma and brucellosis, which other CNS tumors are associated with brucellosis, and what their current mortality is. Since there are high incidence rates of *Brucella* infections, this association should be made.

MATERIALS AND METHODS

A narrative review was carried out, in which the PubMed, Scielo and ScienceDirect databases, among others, were searched. The collection and selection of articles was carried out in journals indexed in English from the years 2011 to 2021. As keywords, the following terms were used in the databases according to the DeCS and MeSH methodology: Medulloblastoma; brucellosis; glioblastoma; mortality; neurobrucellosis. In this review, 70 original and review publications related to the subject studied were identified, of which 25 articles met the specified inclusion requirements, such as articles that were in a range not less than the year 2011, which were articles of full text and to report on the association between medulloblastoma and brucellosis or neurobrucellosis and its mortality. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of their review.

RESULTS

Association Between Medulloblastoma and Brucellosis

The clinical symptoms of brucellosis are related to inflammatory lesions associated with the bacterial location, since the infection can be distributed to almost any tissue or site *in vitro* [14]. Brain neoplasms in humans have recently been related to *Brucella* infection [15]. It has been identified that in the central nervous system there is evidence of lesions in several places, caused by neurobrucellosis, being a common complication of this infection [16]. Neurobrucellosis has been associated with meningitis, intracranial vasculitis, spinal arachnoiditis, sagittal sinus thrombosis, transverse myelitis, intracranial granuloma, demyelinating syndromes, white matter lesions and cerebral pseudotumor, among other initial clinical manifestations [17]. A study by Binxue et al. [16] demonstrated a correlation between *Brucella* and medulloblastoma. In which, through the set of primers / probes OMP31, DNA of the *Brucella* species was identified in 5 of

20 medulloblastoma tumors from the AFIP tissue depot [16,18]. A possible cause in the progression of Medulloblastoma or in the metastasis of other types of cancers of the Central Nervous System may be due to the secretion of large amounts of exosomes, which is secreted by macrophages and at the same time is stimulated by the M5 strain. *Brucella melitensis* [19].

Through the transmission of heterogeneous charges, exosomes initiate or inhibit different signaling pathways in receptor cells. Drug resistance, metastasis, invasion, angiogenesis, and remodeling of the tumor microenvironment are processes caused by the active participation of exosomes. Therefore, the role of exosomes in different types of cancers could lead us to new methods of diagnosis and treatment [20].

CNS Tumors Associated with Brucellosis

The same study carried out by Binxue et al. [16] identified DNA sequences from *Brucella* sp. From the fragments of the gene for the outer membrane protein -OMP31. It was found in 10 of the 52 patients (19%). Although *B. melitensis*, *B. Suis* and *B. abortus* have not been differentiated by PCR, it is known that *Brucella* is related in 25% of metastatic carcinomas, 60% of glioblastomas and 25% with medulloblastomas [16,21]. Another study reports a case of a brain tumor that mimics a space-occupying lesion of occupational neurobrucellosis [21,22]. Considering that more than a neoplastic process, it was considered an inflammatory process suggested by MRI spectroscopy, with low-grade glioma, lymphoma and neurosarcoidosis the deferent radiological diagnoses [23].

Another study reported a new approach to host (Bovine) - Pathogen (*B. melitensis*) interactome, in which a disturbed host pathway associated with glioma (central nervous system neoplasia originating in glial cells) is evidenced. It was carried out in order to identify bovine protein-protein interactions. In which only bovine protein-protein interactions that were learned by binding of known protein domain or sequence similarity with binding domains were included [23].

Mortality of Medulloblastoma Associated with Brucellosis

Although the mortality of neurobrucellosis is low, from 0% to 5.5%, it can present permanent sequelae after recovery, such as deafness that occurs in 20% to 30% of cases, paraparesis and urinary incontinence in 3.66% of cases, persistent facial paralysis in 3.66% of cases, and hemiparesis in 1.22% of cases [24]. Mortality from medulloblastoma is estimated at 15%. While late mortality is estimated at 23.2% in the 1970s and 12.8% in the 1990s, with 17.7% mortality associated with recurrence. Glioblastoma is the most lethal and common tumor of the central nervous system, with 5-year survival rates of 5% with a median survival of 14 months [24,25]. Mortality associated with brain tumors, notably medulloblastoma or glioblastoma associated with brucellosis infection, does not differ much in their average mortality ranges [20,25].

DISCUSSION

Medulloblastoma and central nervous system tumors have been widely associated with *Brucella* infection, with possible progression and spread associated with the secretion of large amounts of exosomes, with characteristics of drug resistance, metastasis, invasion, angiogenesis, and microenvironment remodeling. This being a possible approach in its diagnosis and

treatment. This issue should be approached with caution, as robust evaluations are required to confirm the findings established in this review. Evaluating a large number of normal and tumor-associated brains, establishing a well-weighted epidemiological case-control study. The study carried out by Binxue et al. [16], as well as the study carried out by Hussein et al. [18]. They are in accordance with our research but present a small sample. A strength of the current study is the methodology implemented, with respect to the literature search, and steps in the selection of relevant articles, quality assessment and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among these are the little evidence from analysis of large-scale clinical trials to accurately determine the relationship between brain or nervous system tumors central and Brucellosis.

CONCLUSION

The idea that brucellosis disease is associated with brain tumors, specifically medulloblastoma or glioblastoma, must be approached with caution, despite the theoretical association between the two. There is a need for a case-control study evaluating large numbers of normal and tumor-associated brains to fully lay the foundation for this hypothesis.

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