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Original article

Medulloblastoma during pregnancy: Hormone-mediated association? Report of 2 cases

Médulloblastome pendant la grossesse: association à médiation hormonale? Rapport de 2 cas

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ABSTRACT

Objective. – To report two rare cases of medulloblastoma in pregnant patients and a review of the literature.
Material and methods. – Report of patients diagnosed with medulloblastoma during their pregnancies, who were treated with surgery and adjuvant therapy. We also reviewed other cases reported in the literature and the association made with hormonal receptors.
Results. – Brain tumors in coincidence with pregnancy are unusual, and the incidence of medulloblastoma in pregnancy is still rarer. We found 8 cases of medulloblastomas diagnosed during pregnancy. Reports suggest that hormonal changes and increases in the levels of growth factors and angiogenic factors during pregnancy influence the rate of growth of brain tumors (not only medulloblastomas but also meningiomas or glial tumors).
Conclusions. – The uniqueness of these cases is their rarity. The symptoms are usually masked by the symptoms of pregnancy. At present, there is still little evidence regarding the pathogenesis and treatment of medulloblastoma in pregnancy.

1. Introduction

Medulloblastoma (MB) is the most common malignant pediatric brain tumor and a leading cause of cancer-related death, accounting for 10-20% of brain tumors in children, but are observed infrequently in adults, accounting for an estimated 1% of primary central nervous system (CNS) tumors in adults [1,2]. Approximately 70% of patients are diagnosed before the age of 20. There is a slight increase in incidence between the ages of 20 to 24 years, and the disease is rare after the fourth decade, consistent with its embryonal origin [3,4]. Medulloblastoma, a primitive neuroectodermal tumor, is now considered to originate from not only cerebellar external granular layer precursors, but also ventricular zone and dorsal brainstem neuronal progenitors. On a molecular level, MB are heterogeneous and can be divided into four distinct subgroups with distinct cellular origins, genetics, clinical behavior, and patient outcomes [5–7]. Patients with MB classically present with clinical signs and symptoms of increased intracranial pressure due to cerebrospinal fluid flow obstruction or cerebellar dysfunction. As the disease progresses and the tumor infiltrates the brainstem, cranial nerves dysfunction becomes more common [8]. It has been described that the cerebellar granule cells can respond to the stimulation of its estrogen receptors, and therefore the association that the high levels of this hormone observed during pregnancy can be a contributing factor for the appearance and growth of MB in predisposed women [9]. In the following article we present 2 cases of medulloblastoma diagnosed in pregnant women, as well as a discussion of the pathogenic mechanisms and management in the context of pregnancy.

Abbreviations: MB, Medulloblastoma; CNS, central nervous system; MRI, Magnetic resonance imaging; ERβ, estrogen receptor β; GCP, granule cell precursors.

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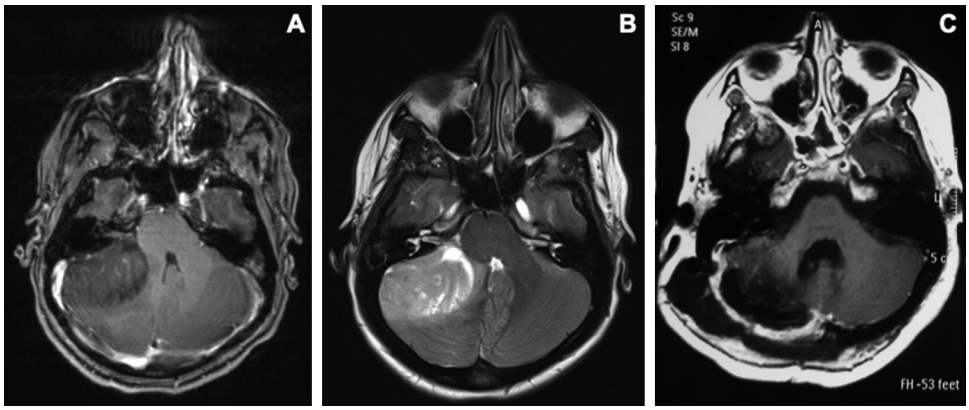

Fig. 1. MRI: (A) T1 W contrast-enhanced axial; (B) T2 axial; (C) Postoperative T1 W gadolinium–enhanced axial.

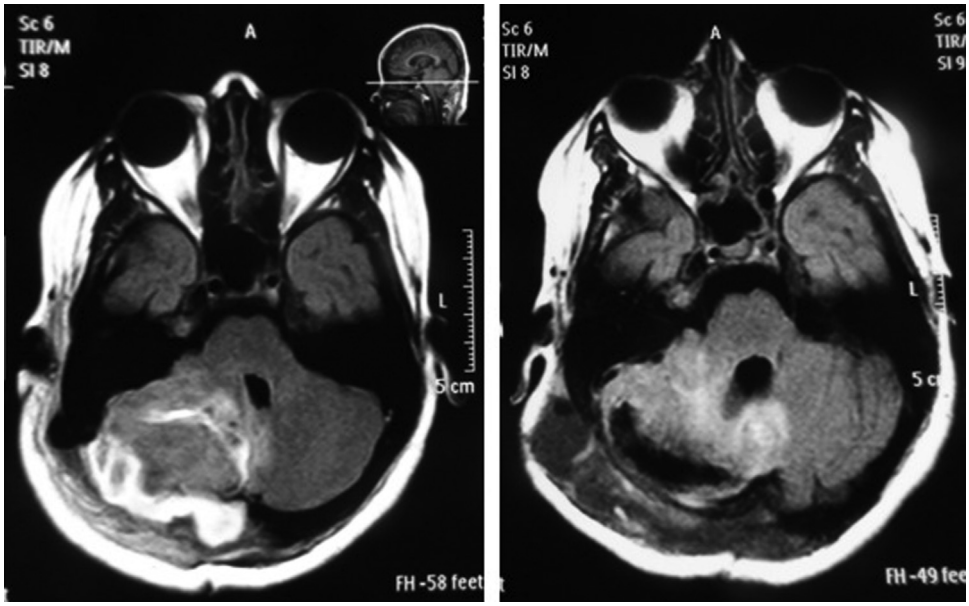

Fig. 2. Left: T1 W contrast-enhanced MRI showing tumor recurrence. Right: Postoperative MRI.

2. Case presentation

2.1.1. Case 1

A 21-year old woman who at 13-week gestation of her first pregnancy was admitted with a 2-month history of gait and balance disturbance, right hemiparesis, dysarthria and holocraneal headache. On physical examination, impaired coordination associated with a cerebellar ataxic gait was observed. Magnetic resonance imaging (MRI) of the brain demonstrated a posterior fossa tumor on the right cerebellar hemisphere producing brainstem compression and partial collapse of the fourth ventricle. The patient was scheduled for surgery with the intention of achieving total macroscopic resection of the tumor (Fig. 1). Pathologic examination revealed malignant cells consistent with desmoplastic medulloblastoma. After six months, there was evidence of tumor recurrence in follow-up MRI, and the patient required new surgical excision of the tumor (Fig. 2). It is noteworthy that the patient continued her pregnancy after surgery, ending at 37-week by caesarean delivery without having received radio- and chemotherapy. One month post-delivery, adjuvant radiation (with a total dose of 36 Gy in daily fractions, followed by a boost to the tumor site) and chemotherapy (lomustine, cisplatin, and vincristine) were initiated. One year after the last surgery, follow-up MRI showed no residual tumor lesion, but subsequent bone marrow biopsy due to pancytopenia showed complete replacement with metastasic MB, with no residual hematopoiesis. The patient coursed with torpid evolution, due to sequelae of adjuvant treatment and bone marrow infiltration, with recurrent respiratory infections that required mechanical ventilation and vasopressor support, dying at the third year after diagnosis.

2.1.2. Case 2

A 20-year-old female patient presented to the emergency department with a 1-month history of intense headache that didn't relieve with analgesics, accompanied by two episodes of generalized tonic-clonic seizures. On her admission, she was in post-ictal period with a Glasgow coma scale of 13/15. She was somnolent, with dysarthria and vomited several times. A brain MRI performed revealed a midline posterior fossa tumor which occupied the vermis and extends laterally in the cerebellar hemispheres, with intratumoral cystic components (Fig. 3). Transvaginal ultrasound was performed on suspicion of pregnancy by the patient, showing a single intrauterine gestational sac of 8.1 weeks. The patient underwent emergency tumor debulking surgery with pathologic examination

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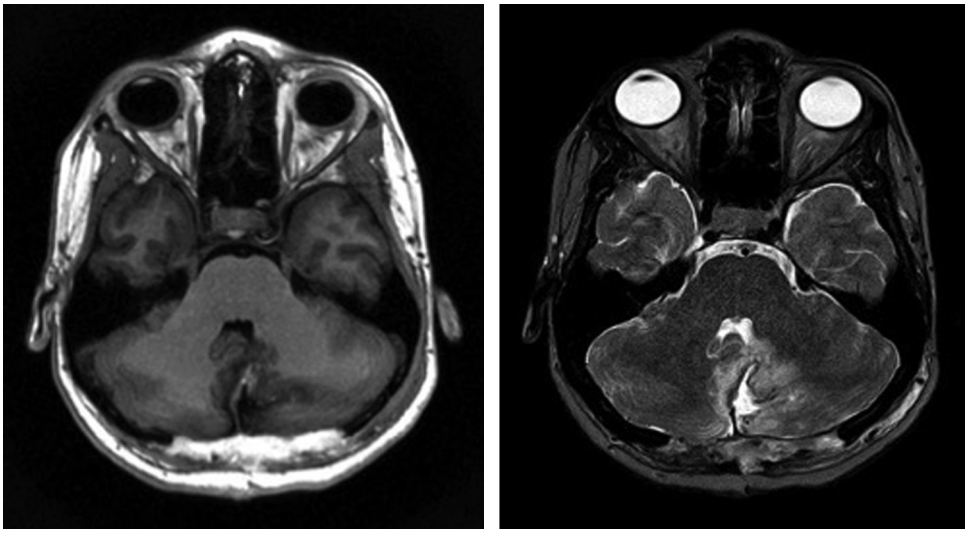

Fig. 3. Left: T1 W contrast-enhanced axial MRI. Right: T2 W MRI.

report consistent with desmoplastic medulloblastoma. At week 12 of gestation, an abortion was presented for unclear reasons, since the patient had not yet received adjuvant treatment until later, under the same scheme mentioned for the patient in the first case, protocolized by our institution. A year later, there is no evidence of recurrence, and the patient is under control after completing the adjuvant scheme.

3. Discussion

Medulloblastoma is a malignant brain tumor (WHO grade IV) that arise from stem cells located in the subependymal matrix or the external granular layer of the cerebellum [10]. The clinical course of this tumor is often rapid, with prominent symptoms of increased intracranial pressure and cerebellar dysfunction. Tumors during pregnancy are not uncommon, but primary brain tumors in coincidence with pregnancy are unusual, and the incidence of medulloblastoma in pregnancy is still rarer [2,11]. In a literature review, we found 8 cases of medulloblastomas diagnosed during pregnancy (Table 1). Reports suggest that hormonal changes and increases in the levels of growth factors and angiogenic factors during pregnancy influence the rate of growth of brain tumors (not only medulloblastomas but also meningiomas or glial tumors) [9,12,13].

Initial indications for a role of estrogen receptors in MB came from studies showing that estrogen receptor β (ERβ) was transiently expressed at high levels in differentiating cerebellar granule cell precursors and that low concentrations of 17β-estradiol (E2) regulated granule cell precursor proliferation and viability [14,15]. Although the role of ERβ in estrogen-responsive cancers or the potential involvement of ERβ in CNS neoplasms is controversial, the role of ERα in the etiology and progression of estrogen dependent breast cancer is well established. In estrogen responsive tissues such as breast, uterus, and prostate, estrogens play a major role in the pathophysiology of hormone-responsive tumors [16]. Chemotherapeutic agents (e.g. tamoxifen) are used as first-line adjuvant therapy to block ER activity and decrease growth of estrogen-responsive tumors. It has been demonstrated that like granule cell precursors (GCPs) and mature granule cells, malignant MB cells express estrogen receptor ERβ, and estrogen can regulate growth rate and migration in normal GCPs and MB cells [14,17]. The growth-promoting effects of estrogen is dependent on changes in gene expression, effects that have been evidenced are blocked by the antiestrogen chemotherapeutic drug fulvestrant [18,19]. Belcher et al. demonstrated that E2 can increase the resistance to chemotherapeutics used to treat MB, and that blockade of ER activity inhibits this effect. This study also revealed that estrogens and the ER activity played an important role in MB and suggest antiestrogen therapy as a potentially adjuvant to current cytotoxic chemotherapy used to treat this condition [19]. In our patients, we only have temporal evidence linking their pregnancies and the appearance of medulloblastoma as the immunohistochemical analysis of the tumor for the estrogen receptor were not performed in our institution. Also, it was not possible to make a molecular determination. However, these cases resemble those reported in literature, enhancing the association already described. The use of aggressive multimodal treatment including tumor resection, followed by radiotherapy and polychemotherapy (a combination of cisplatin, cyclophosphamide, lomustine, and vincristine), has resulted in increased survival for patients with 5-year overall survival rates for MB reaching between 60 and 80%, depending on specific tumor grade or molecular subtype [20,21].

The management of medulloblastoma during pregnancy poses a difficult dilemma, since the well-being of the mother and fetus must be weighed against the risks of treatment. An early delivery should be considered as the outcome of individuals cannot be guaranteed. A tumor causing brainstem compression is an emergency, in which case delay could endanger the life of the mother and fetus. Currently, abortion in Ecuador is illegal except in case of threat to the life or health of women. In the present cases, only one of the gestations could culminate at term without repercussions for the baby.

Hence, surgical treatment implies a challenge to neurosurgeon and anesthesia team. If the team is experienced, surgery in the sitting position is recommended and continuous monitoring of both mother and fetus is essential [22]. Despite the success of the combined treatments, a considerable proportion of patients experience life-long adverse effects such as neurological disabilities, endocrine impairments (primarily associated with the dose of radiation), as well as psychosocial dysfunction which further contribute to diminished quality of life for MB survivors [7,20,23,24]. There is continued need to refine existing therapy and develop new adjuvant therapies that further improve MB outcomes and decrease the adverse side-effects of both the disease and its treatment.

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Table 1
Cases of medulloblastoma in pregnant patients.

Case	Age (yr)	Weeks pregnant at tumor diagnosis	Symptoms	Metastases	Treatment	Recurrence	Survival after diagnosis	TOP	Reference
1	31	32	Headache and vomiting	-	Surgery	-	Not specified	Yes	Roelvink, [25] 1987
2	21	20	Not specified	Bone marrow, placenta	Not specified, history of Intended GTR[a]	Yes	17 months	Yes	Pollack, [2] 1993
3	23	25	Headache, clumsiness of right hand	-	Intended PR[c], radiation	-	6 months	Not specified	Nishio, [26] 1996
4	24	26	Headache, ataxia, double vision, photophobia	-	STR[b], radiation, chemotherapy	Yes	Not specified	Yes	Razak, [11] 2005
5	19	30	Headache and vomiting	-	Intended GTR[a]	-	Not specified	No	Aravind, [22] 2007
6	34	Second trimester - Not specified	Syncopal episode, dizzines, headache, nausea and vomiting	-	Surgery	-	Not specified	Yes	Ishak, [27] 2011
7	32	26	Not specified	Spine	Intended STR[b], radiation, chemotherapy	Yes	Alive	Yes	Kwak, [12] 2011
8	28	30	Headache, visual disturbances, vomiting dizziness	-	Intended STR[b]	-	Not specified	Yes	Sharma, [28] 2013
9	21	13	Headache, gait disturbance, right hemiparesis, dysarthria	Bone marrow	STR[b]	Yes	36 months	No	Valarezo et al.
10	20	8	Headache, tonic-clonic seizures	-	GTR[a]	-	Alive	No	Valarezo et al.

[a] GTR (Gross total removal).
[b] STR (Subtotal removal).
[c] PR (partial removal), TOP (termination of pregnancy).

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4. Conclusion

The uniqueness of these cases is their rarity. The symptoms are usually masked by the symptoms of pregnancy. The radiological report and the general characteristics of the MB may be similar to other CNS tumors. At present, there is still little evidence regarding the pathogenesis and treatment of medulloblastoma in pregnancy.

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Disclosure of interest

The authors declare that they have no competing interest.

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