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REVIEW ARTICLE

Interferon-alfa in the management of cystic craniopharyngioma in children under 5 years of age

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Abstract

Introduction: the best therapeutic option for the management of craniopharyngioma in younger children remains controversial, ranging from complete surgical resection, partial surgical resection associated with radiotherapy and application of chemotherapeutic agents such as bleomycin and interferon-α.
Objective: to verify the response to treatment with interferon-α via Ommaya reservoir in a group of children under 5 years of age with diagnosis of cystic craniopharyngioma.
Methods: description of a case series through consecutive review of medical records of children under 5 years of age diagnosed with cystic adamantinomatous craniopharyngioma, who had an Ommaya reservoir catheter surgically implanted for intratumoral application of interferon-α. Only children in the high or very high-risk groups were included in the final sample (Liverpool score 2,3 and 4).
Results: seven children aged 18 to 60 months (median 46 months) with the abovementioned diagnosis and treated with interferon-α between 2010 and 2019, according to a pre-established protocol, were identified. A reduction in tumor volume, ranging from 88 to 100%, one year after the end of treatment was observed in the study sample. There were no complications that justified the interruption or modification of the established therapy.
Conclusion: in all the cases evaluated of children less than 5 years of age with predominantly cystic adamantinomatous craniopharyngioma we observed a reduction of tumor volume on magnetic resonance imaging one year after the end of treatment with interferon-α.

Key words: Neurosurgery, Pharmacological treatment, Chemotherapy, Brain tumors.

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Introduction

Craniopharyngiomas are benign neoplasms responsible for approximately 3% of intracranial tumors in children, being the most common tumors of non-glial origin in the pediatric age group [1,2,3]. The incidence rate is increased in 5 to 15 years of age [2,3] and the main clinical manifestations include hydrocephalus and intracranial hypertension, endocrinological disorders and visual impairment [1,2,4]. The best therapeutic option for the management of craniopharyngioma in younger children remains controversial, ranging from complete surgical resection, partial surgical resection associated with radiotherapy depending on the patient's age, in addition to the application of chemotherapeutic agents such as bleomycin and interferon-α (IFN-α) [4-11].

In view of the challenge of establishing the best therapeutic approach to craniopharyngioma in younger children, researches describing the various possibilities along with surgical risk assessment are essential. About twenty years ago (in the early 2000s) results started to be published by Brazilian researchers [12], being corroborated by foreign studies, demonstrating the importance of IFN-α in the management of children with cystic craniopharyngioma [5,7,9,10]. This study aimed to describe a series of children under 5 years of age with adamantinomatous craniopharyngioma with a predominantly cystic component, presenting high or very high surgical risk according to the Liverpool risk grading system [13], submitted to intratumoral application of IFN-α via an Ommaya reservoir catheter.

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Material and Methods

Study design, inclusion and exclusion criteria

The present study was appraised and approved by the research ethics committee and it is the result of a previous investigation (nº 89726318.0.0000.0048). Descriptive retrospective study (2010-2019), case series, through consecutive review of medical records of children under 5 years of age diagnosed with adamantinomatous craniopharyngioma and submitted to intratumoral therapy with IFN-α through a surgically implanted Ommaya reservoir catheter. All included cases were retrospectively reviewed and classified according to the Liverpool risk grading system for surgical risk stratification [13]. Only patients under 5 years of age in the high or very high surgical risk groups were included in the final sample. Patients with craniopharyngioma not submitted to IFN-α as the first option treatment as well as those who did not complete the proposed treatment following a cancer protocol previously established for the abovementioned application, previously operated patients (relapse cases) and those whose surgical indication was radical or partial resection followed by radiotherapy were excluded from the final sample.

Liverpool classification [13]

The Liverpool risk assessment system analyzes four risk factors for the management of craniopharyngiomas:

- Presence of hypothalamic syndrome resulting from injury to the hypothalamic-pituitary axis;
- Hydrocephalus;
- Tumor size (greater than 2 cm);
- Third ventricle floor involvement (considering the radiological Paris grading) [14]:

o Grade 0: no hypothalamic involvement identified on magnetic resonance imaging (MRI) of the sellar region;

o Grade I: displacement of the hypothalamus/floor of the third ventricle by the tumor identified on MRI;

o Grade II: hypothalamic involvement and floor of the third ventricle no longer identifiable on MRI.

Each risk factor in the Liverpool classification system receives one point, and thus the total score varies from 0 to 4 points. Patients are classified as to surgical risk into four subgroups: very high risk (score 4), high risk (scores 2-3), moderate risk (score 1), and low risk (score 0). Only children in the very high or high-risk groups were included in the final sample.

Clinical and radiological profile of the patients

All children included in the study underwent preoperative evaluations by a pediatric neurosurgeon, a pediatric endocrinologist (assessment of the hormonal profile to evaluate the involvement of the hypothalamic-pituitary axis), and an ophthalmologist. In the present study, the presences of the following clinical manifestations at diagnosis, described in the medical records, were evaluated: hydrocephalus, endocrine disorders, and visual impairment (hemianopsia, quadrantopsia or amaurosis). As for the radiological evaluation, MRI findings of the sellar region (tumor volume in cm^3 described in the medical records before starting treatment with IFN-α) and descriptions of hypothalamic and third ventricle floor involvement were analyzed for classification of patients in the Paris [14] and Liverpool [13] grading systems.

Neurosurgical intervention (Ommaya reservoir implantation)

The surgical placement of the Ommaya reservoir catheter was performed according to previously established protocols indicated for patients with predominantly cystic tumors (> 60% of the neoplastic component) [5,12,15]. The device was implanted for intratumoral application of IFN-α following the classic technique: application of general anesthesia, asepsis, antisepsis, and preparation of the surgical field; fronto-temporal incision and craniotomy for fronto-pterional approach; identification and visualization of the tumor and opening of a small entry point in the tumor capsule, just enough to pass the distal end of the catheter, preserving the rest of the capsule to prevent leakage of the chemotherapeutic agent; connection of the proximal end of the catheter to a reservoir (Ommaya reservoir), surgically placed in the subcutaneous (subgaleal or subperiosteal) space; fixation of the reservoir and closing in layers. In all cases, the liquid aspirated through the implantation of the Ommaya reservoir was sent for study of pathological anatomy, which showed a liquid substance with the presence of calcifications in all samples. The application of IFN-α was released approximately 15 days after surgery, after cranial computerized tomography with injection of contrast agent in the reservoir to determine if there was any leakage and confirm the integrity of the tumor capsule, so as to avoid complications described in the literature [16].

Chemotherapy management and radiological monitoring

All applications of IFN-α were performed on an outpatient basis by the pediatric oncology team for an average period of 09 cycles, with 12 applications per cycle (3,000,000 IU on alternate days), with a 1-month interval between cycles, following previous protocols [5,15]. Periodic imaging examinations (MRI of the sellar region) were performed quarterly during treatment to monitor the response. For the purpose of this study, the following parameters were considered to determine volumetric reduction (tumor volume in

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Table 1 - General characteristics and main clinical manifestations of 07 children with adamantinomatous craniopharyngioma with predominant cystic component, treated with intratumoral chemotherapy with interferon-α (Salvador, Bahia, Brazil, 2010-2019).

Patient	Sex	Age	Hydrocephalus	Endocrinological disorder	Visual impairment
1	Female	36 months	Yes	No	No
2	Male	18 months	No	Yes	Yes
3	Female	48 months	Yes	Yes	No
4	Male	41 months	Yes	Yes	Yes
5	Male	60 months	Yes	Yes	Yes
6	Male	46 months	Yes	Yes	Yes
7	Male	60 months	No	Yes	No

Table 2 - Volumetric assessment of the cystic component according to magnetic resonance imaging of the sellar region before the start and 01 year after the end of chemotherapy with interferon-α in 06 children diagnosed with cystic adamantinomatous craniopharyngioma (Salvador, Bahia, Brazil, 2010 -2019).

Patient	Initial volume (cm^3)	Final volume (cm^3)	Volumetric reduction (%)
1	18.6	Undetectable	100%
2	42.6	4.8	88%
3	42.6	4.2	90%
4	18.9	1.1	94%
5	38.2	2.2	94%
6	31.6	Undetectable	100%

cm^3 described in medical records) and response to treatment: description of MRI findings of the sellar region before implantation of the Ommaya reservoir and one year after the end of the treatment with IFN-α. Tumor volume was calculated using the equation: A x B x C x 0.5, where A, B and C corresponded, respectively, to the largest anteroposterior, lateral and craniocaudal dimensions identified in the MRI of the sellar region, using methods previously published in the literature [5].

Results

Twenty children with a diagnosis of adamantinomatous craniopharyngioma with a predominantly cystic component were identified between 2010 and 2019, of which 7 (35%) were under 5 years of age and in the very high (score 4) or high (scores 2-3) surgical risk groups according to the Liverpool classification system, and underwent intratumoral administration of IFN-α. They were 5 boys and 2 girls with ages ranging from 18 to 60 months [median 46 months (3.8 years)]. Clinical manifestations are detailed in Table 1. Table 2 shows tumor volume before Ommaya reservoir placement and one year after completion of treatment according to MRI measurements. With the exception of two patients (patients 1 and 2) who required a second surgery to place a new reservoir due to obstruction of the system before restarting treatment, no child presented complications that justified the interruption or modification of the treatment initially proposed. One child was excluded from the analysis of the therapeutic response (tumor volume after completion of treatment) because of referral to a unit outside our service to complete treatment, and this prevented the follow-up MRI study. We observed a reduction of cystic lesion volume in all patients evaluated one year after the end of treatment with IFN-α (Table 2).

Discussion

Regarding sex, boys predominated, but the sample size and the study design adopted do not allow us to make statistical inferences on this distribution. Previous studies did not show statistically significant differences in the sex distribution of patients with craniopharyngioma [2]. As for the median age found in the present study (46 months), the result is explained by the fact that the sample was composed of children up to 5 years of age, in whom surgical damage to the hypothalamic-pituitary axis resulting from more radical resections can be disastrous [13,14], and radiotherapy should be postponed [2,17].

As for clinical presentation, we observed that all patients included in the sample had manifestations included in the classic triad of cases of craniopharyngiomas, with neurological, endocrinological and/or ophthalmological symptoms. This confirms the importance of a multidisciplinary approach in the management of these patients. In the presence of a combination of clinical manifestations suggestive of intracranial hypertension associated with hormonal disorders and visual impairment in the pediatric population, craniopharyngioma should be considered as a possible diagnosis [2,4,8,14].

Regarding tumor volume at the time of diagnosis, MRI before treatment showed volume values of the cystic portion of the tumor varying between 18.6 and 42.6 cm3, corroborating previous reports with respect to the large dimensions that the cystic component may reach in craniopharyngiomas at the time of diagnosis [4,5,15]. Since surgical risk assessment is fundamental for therapeutic planning in the face of the challenges imposed by this disease, several stratification proposals have been described in the literature. The Liverpool [13] and Paris [14] systems are the most used in our hospital practice. These two scales offer ease of application and calculation,

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facilitating informed decision-making in the management of craniopharyngioma in children.

Regarding the intracranial/intratumoral surgical placement of the catheter reservoir and the treatment with IFN-α, previously described techniques and protocols were adopted [4,5,9,10,11,12,15]. MRI findings of the sellar region one year after the end of treatment with IFN-α showed volumetric reductions of the tumor cyst in all patients ranging from 88 to 100%. Previous studies on the same treatment option described similar outcomes, thus demonstrating the importance of this agent in the management and control of craniopharyngioma evolution in the pediatric age group [5,15]. As for complications related to the surgical implantation of the subcutaneous reservoir and catheter system for intratumoral treatment with IFN-α, there was no surgical-related mortality or serious complications that justified the discontinuation of the treatment initially proposed. Previously published studies have shown neurotoxicity in cases of leakage of IFN-α [16]; due to this risk, we stress the importance of a radiological examination to confirm the integrity of the craniopharyngioma capsule before the application of the drug is started in order to avoid further complications.

Despite the relatively small sample size, this study underscores the importance of investigating alternative therapeutic options for the management of craniopharyngioma in younger children, as indicated in previous researches, especially in those in whom radical surgical resections can severely affect their quality of life (in cases considered of high or very high surgical risk) [13,14], and radiotherapy treatment can also cause neurological damage, and may not prevent recurrence [2,17]. All these difficulties make craniopharyngioma one of the most challenging intracranial tumors in the practice of pediatric neurosurgeons.

Conclusions

We corroborate that treatment with IFN-α can lead to a significant reduction in tumor volume in children less than five years of age classified in the high or very-high risk groups in the Liverpool grading system, diagnosed with predominantly cystic adamantinomatous craniopharyngioma. The reduction of cystic lesion was observed in all children evaluated in the study. Thus, we demonstrate that surgical implantation of a catheter and a subcutaneous reservoir for intratumoral administration of IFN-α can be an excellent therapeutic option in the attempt to delay more aggressive surgical approaches or even radiotherapy in younger children, which can be performed at a later moment, as in the case of tumor recurrence or enlargement.

Disclosure Statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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