

## Craniopharyngiomas: intratumoral chemotherapy with interferon- $\alpha$ : a multicenter preliminary study with 60 cases

SERGIO CAVALHEIRO, Ph.D.,<sup>1</sup> CONCEZZIO DI ROCCO, Ph.D.,<sup>3</sup> SERGIO VALENZUELA, Ph.D.,<sup>4</sup> PATRICIA A. DASTOLI, M.D.,<sup>1</sup> GIANPIERO TAMBURRINI, M.D.,<sup>3</sup> LUCCA MASSIMI, M.D.,<sup>3</sup> JARDEL M. NICACIO, M.D.,<sup>1</sup> IGOR V. FAQUINI, M.D.,<sup>1</sup> DANIELA F. IERARDI, M.D.,<sup>1</sup> NASJLA S. SILVA, M.D.,<sup>1</sup> BENEDETTA LUDOVICA PETTORINI, M.D.,<sup>5</sup> AND SILVIA R. C. TOLEDO, M.D.<sup>2</sup>

<sup>1</sup>Department of Neurosurgery and <sup>2</sup>Section of Pediatric Neurosurgery, Federal University of São Paulo, Brazil; <sup>3</sup>Department of Neurosurgery, Catholic University of Rome, Italy; <sup>4</sup>Department of Neurosurgery, Neurosurgery Institute of Santiago, Santiago, Chile; and <sup>5</sup>Section of Pediatric Neurosurgery, Department of Neurosurgery, Policlinico Gemelli, Rome, Italy

**Object.** The authors assessed the efficacy of intratumoral interferon- $\alpha$  (IFN $\alpha$ )–based chemotherapy in pediatric patients with cystic craniopharyngiomas.

**Methods.** In a prospective multicenter study of 60 pediatric patients, the authors assessed the efficacy of intratumoral INF $\alpha$ 2A-based chemotherapy. The study was conducted between 2000 and 2009 at 3 locations: the Medical School of the Federal University of São Paulo, Catholic University of Rome, and the Neurosurgery Institute of Santiago, Chile. The assessment included clinical and radiological control examinations, side effects observed, and total dose used.

**Results.** Sixty cases of cystic craniopharyngioma were analyzed. The cohort consisted of 35 male and 25 female children (mean age 11 years). Clinical and radiological improvement was achieved in 76% of the cases. New endocrinological deficits were observed in 13% of the cases. In approximately 30% of the patients, the evolution included some light side effects, the most common being headache (33%) and eyelid edema (28%). The number of cycles varied from 1 to 9 (mean 5 cycles), and the total dose applied per cycle was 36,000,000 IU.

**Conclusions.** This has been the largest documented series of intratumoral chemotherapy using INF $\alpha$  for the control of cystic craniopharyngiomas. The treatment has proved efficacious; there was no mortality, and morbidity rates were low. (DOI: 10.3171/2010.1.FOCUS09310)

**KEY WORDS** • craniopharyngioma • interferon- $\alpha$  •  
hypothalamus • obesity • diabetes insipidus

CRANIOPHARYNGIOMAS are benign slow-growing lesions that challenge every neurosurgeon, even since the advent of major technological developments, with important refinements, such as microscopic techniques, ultrasonic aspirators, neuroendoscopes, and hormone replacement therapy. In major centers of pediatric neurosurgery with excellent endocrinological support, is not uncommon to see patients with CPs suffer deterioration with the onset of obesity, panhypopituitarism, hypercholesterolemia, and psychological disorders.<sup>9</sup> If on the one hand a complete resection of these lesions is tremendously satisfying to neurosurgeons, on the other hand this feeling is temporary because the lesion and the effects of hypothalamic dysfunction will recur. The use of intratumoral chemotherapy with the cytokine INF $\alpha$  is a simple method, with a very low cost, that allows the control of these tumors.

*Abbreviations used in this paper:* CP = craniopharyngioma; IFN $\alpha$  = interferon- $\alpha$ .

### Methods

We prospectively analyzed 60 patients with predominantly cystic CPs (> 60% of the tumor volume). The patients underwent treatment at the Pediatric Oncology Institute of the Federal University of São Paulo (37 cases), Catholic University of Rome (9 cases) and University of Chile (14 cases). Intratumoral chemotherapy involved INF $\alpha$ 2A and the same protocol was used at each institution after the approval of the respective ethics committee. Thirty-five patients were male (58.3%) and 25 female (41.7%). Patients ranged in age from 20 months to 18 years (mean age 11 years). Twenty-five patients (41.7%) presented with initial symptoms such as intracranial hypertension, 6 presented endocrinological disturbances (10%), and only 4 (6.7%) had initial symptoms of isolated visual disturbances. The association of intracranial hypertension with visual impairment was found in 8 cases and with endocrinological disorders in 14 cases; the association of intracranial hypertension with visual impair-

ment and endocrine disorders was observed in 3 cases. Eleven patients presented only with diabetes insipidus and 8 patients with isolated growth hormone dysfunction. Eleven patients had more than 3 hormonal deficits. Of 60 patients, only 39 (65%) were treatment naïve, and the other 21 patients had received other therapies for control of the disease. Eighteen patients had undergone surgery, and 3 patients had undergone intratumoral bleomycin-based chemotherapy.

Nineteen patients had hydrocephalus at presentation and 13 needed shunt implantation.

In 37 patients it was possible to analyze and compare the pre- and posttreatment tumor volume using the modified ellipsoid volume equation:  $A \times B \times C \times 0.52$ , where A, B, and C are the major diameters measured in the 3 special plans.

The treatment protocol begins with the implantation of a catheter into the cystic tumor cavity; the catheter is connected to a subcutaneous Ommaya reservoir. In 40 cases the catheter was implanted via craniotomy, in 13 cases using the neuroendoscope, in 4 guided by neuronavigation, in 2 by free-hand puncture, and in 1 case by neuroendoscopy coupled with neuronavigation (Fig. 1). In 52 cases (86.6%) only 1 catheter was implanted, but 7 patients required 2 catheters, and in 1 case 3 catheters were implanted. Five days after implantation of the catheter, a contrast agent was injected into the cyst to determine if there was any leakage. The presence of leakage was not considered a contraindication for the treatment because the interferon alpha had no related neurotoxicity.

After checking that the catheter was well positioned, we injected, every other day, 3,000,000 IU of INF $\alpha$ 2A. Prior to the injections of INF the liquid of the CP was aspirated.

The amount of fluid removed depended on the symptoms of patients and the size of the cyst. We interrupted suction when more than 20 ml was removed or when the patient complained of headache. Thirty minutes before the puncture of the reservoir, anesthetic ointment was placed over the skin at the puncture site. The volume of injected liquid did not exceed 2 ml, and to avoid a high concentration of INF in the reservoir after the injection, we aspirated more liquid, with the same syringe, and re-injected it another 2–3 times.

Interferon was applied in cycles of 36,000,000 IU, divided into 12 applications of 3,000,000 IU each. The cycles were repeated as often as necessary, according to the reduction in tumor volume or change in the signal on MR imaging. One characteristic is that the often hyperintense cysts on T1-weighted sequences usually become hypointense on T1-weighted images after treatment; whenever control MR imaging revealed that the cyst had become hyperintense again, a new cycle of INF was prescribed.

The number of cycles ranged from 1 to 9 (average 5 cycles) per patient (Figs. 2 and 3). The follow-up duration ranged from 4 to 84 months (average 44 months). All the patients were treated in an ambulatory regimen.

## Results

In 47 patients (78.3%) tumor control was possible.

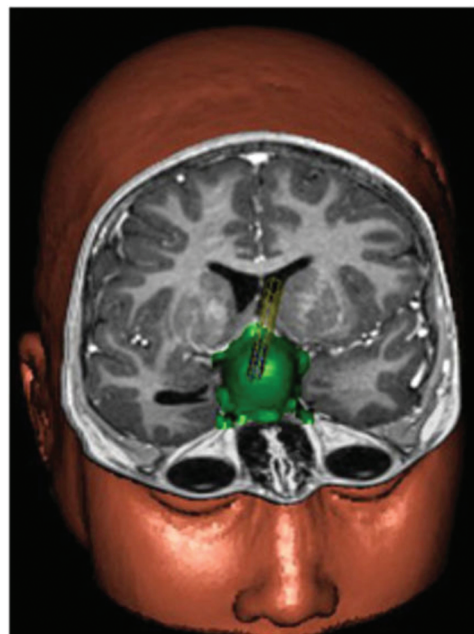


FIG. 1. Neuronavigational image showing the catheter trajectory and the cystic CP.

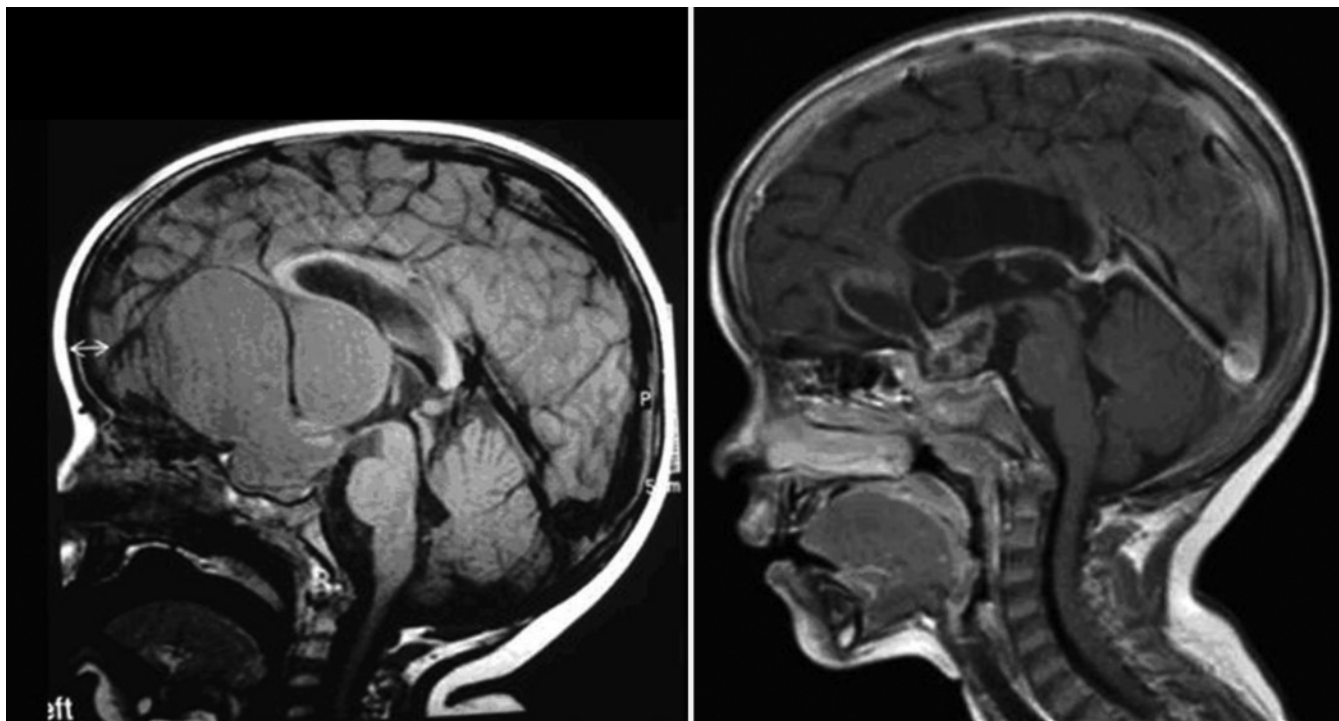
However, in 13 patients the tumor continued to grow and excision was necessary. The pretreatment tumor volume in 37 patients ranged from 3.3 to 134.5 ml (mean 27.7 ml). The posttreatment tumor volume ranged from 0.14 to 70.7 ml (mean 9.6 ml).

We considered disease to be controlled when a tumor decreased more than 50%. In 1 patient, although there was a reduction in the tumor, there was no improvement in visual symptoms, and surgery was required for optic chiasm decompression. Eight patients (13.3%) exhibited new endocrinological dysfunctions after treatment. In 3 patients a thyroidal hormonal deficit developed, in 2 of whom the deficit was associated with corticosteroid deficit and in 1 with testosterone deficit. One patient had only a new testosterone deficit.

Eighteen patients (30%) had some kind of side effect due to INF $\alpha$ 2A therapy, which did not prevent the continuation of treatment. Six patients complained of headache, 5 of palpebral edema, 5 had fever, 1 had chronic fatigue syndrome, and 1 had arthritis. These effects were easily controlled with simple medication and disappeared after treatment. We observed no difference with respect to disease course based on whether the patient had undergone previous treatment or not. Among the 37 cases in which tumor volume measurement was performed, 81.8% of the previously treated patients had a cyst reduction greater than 50%. In 85.5% of the patients who had not undergone a previous treatment, cyst reduction was also greater than 50%. In 3 patients who had been treated with bleomycin, the tumors were controlled with INF.

## Discussion

Interferon-alpha is the first cytokine produced by a DNA recombinant technique that is effective against can-



**Fig. 2. Left and Right:** Sagittal T1-weighted enhanced MR images obtained before treatment of a cystic CP and the 4 years after the IFN $\alpha$ 2A treatment (5 cycles).

cer.<sup>8</sup> It is classified as a helical cytokine and is included in an evolutionary conserved family of secreted proteins. It is used therapeutically for its properties of inducing an “antiviral” state in cells, inhibiting cellular proliferation, and creating immunomodulation.<sup>22</sup> The effects of IFN $\alpha$  are mediated by the interaction with its receptor, which activates the JAK proteins, resulting in the activation by phosphorylation of the STAT proteins, which finally activate the transcription of the *ISGs*.<sup>21</sup> The first use of IFN for control of CP was by Jakacki et al.<sup>16</sup> with good results in 3 of 12 patients treated with subcutaneous injections of interferon in predominantly cystic CP. The first use of intratumoral interferon to control CP was by Cavaleiro et al.<sup>6</sup> Craniopharyngioma is a benign, slow-growing tumor that causes severe disturbances due to involvement of the hypothalamic-pituitary axis and requires a multidisciplinary team for its control. Several therapies have been proposed for patients with CPs, which allows the surgeon to choose the best way to treat each individual patient.<sup>2</sup>

The best treatment for this type of tumor is complete removal with preservation of all endocrine and visual functions, which is achieved in a small number of cases.<sup>11,12</sup>

Curtis et al.<sup>10</sup> reported a low mortality rate after total resection, but almost all patients needed hormone replacement therapy and 50% of the patients were obese, presumably caused by damage to the hypothalamic satiety center. Sanford<sup>18</sup> demonstrated that in 95% of the cases of radical surgery the patients needed hormone replacement.

In 2005 Tomita and McLone<sup>23</sup> report achieving to-

tal resection in 76.7% of 54 children with CPs, 27.3% of whom presented with recurrence in the first 2 years of follow-up. Additionally, in 92.5% of these patients panhypopituitarism developed, and in 9.2% severe obesity developed.<sup>23</sup> The same result was described by Zuccaro,<sup>26</sup> who demonstrated a 77% rate of total resection, with 87% of 153 patients having a hormone deficit. According to the literature, the condition in the vast majority of patients will progress to visual and endocrine dysfunction, hypothalamic dysfunction, disorders of hunger, psychiatric disorders, and a poor quality of life.<sup>14</sup>

Reviewing the data, 50–80% of patients undergoing resection of a CP will present later with hyperphagia and obesity.<sup>3,4,20</sup> All the aforementioned recent results emphasized the thinking of Epstein,<sup>13</sup> who stated, “surgical removal of these tumors is only appropriate for patients living in countries with ready access to appropriate endocrinological follow-up. Those returning to undeveloped countries or even to rural areas in this nation are at great risk of morbidity and even death.”

To begin the treatment of CPs with IFN, we sought to use an easy, inexpensive, nonneurotoxic drug without adverse side effects. We decided to combine 2 previously reported concepts: the treatment of CPs with intratumoral injection of bleomycin (our experience)<sup>7</sup> and the use of subcutaneous injections of IFN for the same purpose (the experience of Jakacki et al.<sup>16</sup>).

We treated 60 patients in a multicenter study, and disease control was achieved in 78% of these patients; only 13% developed a worsening of endocrinological function, and there were few side effects, and the mortality rate was 0%.



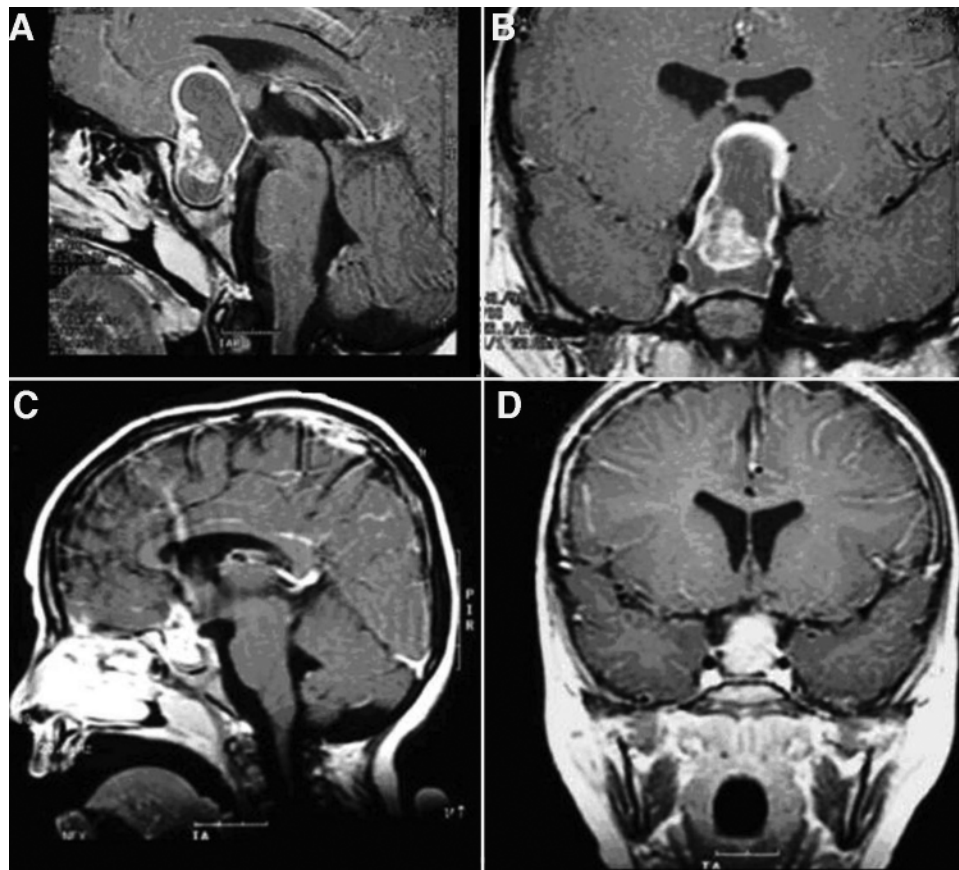


FIG. 3. Magnetic resonance images showing high-volume CPs and posttreatment CPs that have significantly decreased in size after 3 cycles of IFN $\alpha$ 2A and 5 years of follow-up: pretreatment images (A and B), posttreatment image (C), and 5-year follow-up image (D).

In the cases involving a good response to therapy, the reduction in the size of the cystic component was more evident than a reduction in the size of the solid portion of the tumor, as already demonstrated by Jakacki et al.<sup>16</sup>

The main difference between radical surgery and our approach is that no patient in our series developed, during the treatment, hunger disorders, had severe hypothalamic disturbances, or became obese. The results of our therapy proved to be better than those presented in the majority of series that advocate other intratumoral chemotherapy involving radioisotopes or bleomycin.<sup>1,5,19,25</sup>

We emphasized that the medical literature considers a predominantly cystic CP to be one in which greater than 60% of the tumor volume is cystic.<sup>18</sup> It is important keep in mind that 90% of pediatric CPs have this characteristic.<sup>17</sup>

The CP is a slow-growing tumor that demands a chronic management. As we noted in our results, up to 9 cycles of intratumoral IFN $\alpha$ 2A injections are needed to control the disease; in light of this, IFN therapy appears to be a chronic treatment.

During the early stages of this treatment protocol we thought that the decrease in tumor volume might be due to the mechanical action of withdrawing the intratumoral liquid, but Ierardi et al.<sup>15</sup> have shown an increase in the rates of apoptosis when CP fluid was analyzed in different stages of treatment. New research has yet to be carried

out to isolate a “magic” drug, able to control CPs. Perhaps CPs are not tumors themselves, but embryonic immune defects. Indeed, few genetic changes are found in CPs.<sup>24</sup> The balance between the aggressiveness of the tumor and the patient’s immune response will determine the winner of this battle.

There are cases in which even after 9 cycles of treatment there was no tumor control, and there are cases in which a single application could control them. We had more surgical difficulties when we had to surgically treat a patient undergoing bleomycin chemotherapy than when we had to do so after IFN treatment. Perhaps the delivery of intratumoral IFN coated with slow-release capsules may increase the rates of control of CPs, reducing the number of applications per patient.

### Conclusions

Despite tremendous neurosurgical advances and refinements, which make it possible to achieve higher rates of complete CP resection, endocrinological deterioration seems inevitable, especially after invasion of the hypothalamus. In the pursuit of a better quality of life, the quest for other CP-controlling techniques should be encouraged, with the purpose of preserving metabolic functions.

The use of IFN $\alpha$  for the treatment of cystic forms of

## Intratumoral chemotherapy with interferon-alpha

CP has been efficacious, easy to handle, and available at a low cost; it is also associated with a low morbidity rate and few side effects. Further studies are still necessary for better definition of the proper dose, number of cycles, and time of evolution.

### Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: S Cavalheiro, C Di Rocco. Acquisition of data: S Cavalheiro, S Valenzuela, C Di Rocco, PA Dastoli, G Tamburrini, L Massimi, JM Nicacio, IV Faquini, Nasjla Saba da Silva. Analysis and interpretation of data: S Cavalheiro, S Valenzuela, PA Dastoli, G Tamburrini, JM Nicacio, IV Faquini, DF Ierardi. Drafting the article: S Cavalheiro. Critically revising the article: S Cavalheiro, IV Faquini, DF Ierardi. Reviewed final version of the manuscript and approved it for submission: S Cavalheiro, IV Faquini, BL Pettorini, SRC Toledo. Statistical analysis: S Cavalheiro, JM Nicacio, IV Faquini, DF Ierardi. Administrative/technical/material support: S Cavalheiro, JM Nicacio, IV Faquini, DF Ierardi. Study supervision: S Cavalheiro, PA Dastoli, L Massimi, JM Nicacio, IV Faquini.

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Address correspondence to: Sergio Cavalheiro, Ph.D., Rua Botucatu 591/42, São Paulo, Brazil 04023-061. email: iscava@uol.com.br.