“FIRST DO NO HARM”: GROWTH HORMONE (hGH) TREATMENT IN A CASE OF RECURRENT CRANIOPHARYNGIOMA.

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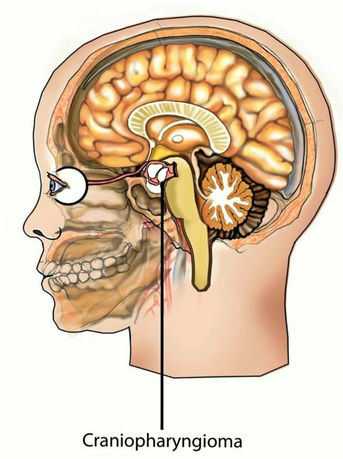
Introduction

❖ Craniopharyngiomas (CP) are benign, dysontogenic supra or intra-sellar tumors. They are locally aggressive with severe endocrine, neurological and ophthalmological implications.[1,2]

❖ Lesions tend to overspread into neighboring structures and relapse after total surgical removal. Bartlett’s argued that complete excision is essentially impossible his idea was supported by his postmortem examinations and high recurrence rate in almost every major surgical series.[2,3,4]

❖ Recurrences occurs at the original site, secondary lesions (ectopic and/or metastatic) are extremely rare yet found after surgery. The possible seeding process is cell dissemination on the surgical path or passage through subarachnoid space or Virchow-Robin spaces.[1,5]

a.)



b.)

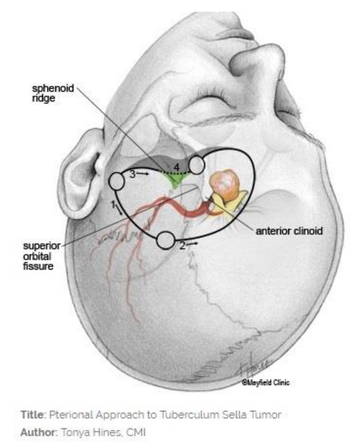


Fig. 1: (a) craniopharyngioma – benign supra/ intra-sellar tumor, (b) Pterional approach to tuberculum sella tumor.

Fig. 1 (a): - <http://www.natural-health-news.com/craniopharyngioma-causes-symptoms-diagnoses-and-treatment>;
Fig. 1 (b): - <http://medillsb.com/ArtistPortfolioLarge.aspx?AID=6703&IID=113829>;

❖Craniopharyngioma represent 1-3% of intracranial tumors and 13% of suprasellar tumors. Craniopharyngioma account for 1,2-4% of all childhood intracranial tumors and 50% of sellar and suprasellar tumors. A modest male predominance exists (55%), and a bimodal age distribution pattern has been reported, with a peak incidence in childhood (5-14 years) and in adult-onset (50-74 years).[2,6]

❖Overall survival rates are high (a mean of 92%), recurrences and progressions are frequent.[2,3]

❖Somatotroph deficiencies rise therapeutic management problems due to increased risk of tumour growth and recurrence, nevertheless the use of hormonal replacement therapy, has a benefic impact on daily activities of patients.[3,7]

Case Report

❖ **Patient** - H.A., male, 18 years

❖ **Medical history**:

- born naturally, late-term (42 weeks, 3200g, Apgar 7, with meconium aspiration syndrome, cared for in incubator for ~2 weeks), third child in a brotherhood of four (apparently healthy parents and brothers), slightly delayed developmental acquisitions (first steps - 1 year, talked - 2 years and 6 months);
- 05.2011- first evaluation in Endocrinology Department (age 13 years 6 months) for growth retardation, investigations pleaded for **pituitary dwarfism** (short stature -2,5 SD, absence of puberty signs, delayed bone age ~10 years, somatotroph axis: low basal GH=0,14ng/ml with no stimulation to arginine 30 min.=0,17ng/ml, 60min.0,29ng/ml, 90min.=0,27ng/ml low IGF-1=40ng/ml) and rhGH therapy was initiated.

❖ **Laboratory and imaging findings :**

- 10.2011- diagnosed with **craniopharyngioma**, admitted to Neurosurgery Department due to severe headache, Jacksonian seizures and optochiasmatic syndrome determined by rapid developing para- and suprasellar compressive craniopharyngioma identified at MRI. Minimally-invasive surgery was performed (partial ablation trough left pterional craniotomy - Fig. 1.b.).

- After surgery further investigations were made:
  - patient developed panhypopituitarism:
  - central hypothyroidism: low TSH levels (0,01uUI/ml N:0,2-4,2), low fT4 levels (6,45pmol/l N:12-22);
  - central adrenal insufficiency: morning cortisol levels (3,4 ug/dl N:5-25), ACTH levels (15,6pg/ml N:<46);
  - growth hormone deficiency: low basal GH levels (0,41ng/ml), low IGF-1 (42,2ng/ml N:220-972), staturo-ponderal delay (height=131cm -3DS, weight=31kg), with delayed bone age~10 years;
  - pituitary-gonadal axis at prepubertary levels (Tanner puberty stage: PI GI, FSH=1,56 mUI/ml, testosteron < 0,028 ng/ml).

Substitutive treatment was initiated (levothyroxine and hydrocortisone with periodic dose adjustments).

EVOULUTION

- two other surgeries were performed for tumor recurrence;
- external radiation (54Gy/30ft/CTV);
- further ophthalmic complications.

-RIGHT EYE OPTIC ATROPHY,
-LEFT EYE CORNEAL ULCERATION

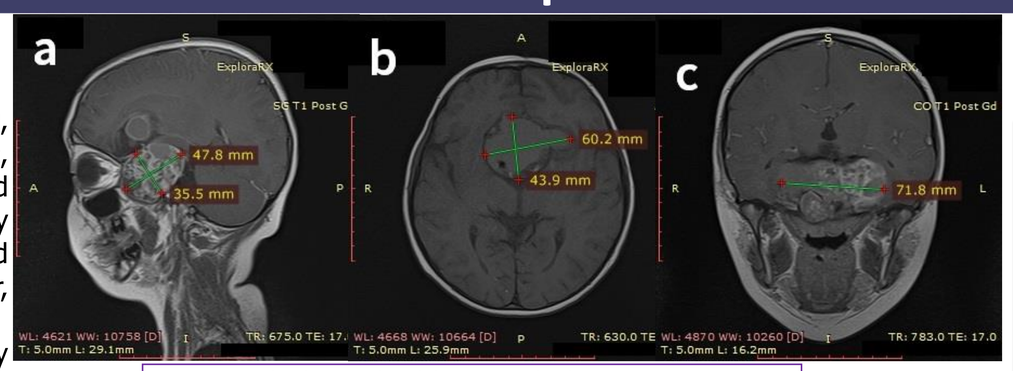


Fig. 2: T1-weighted MRI with gadolinium reveals a large pituitary region mass (mixed but predominantly cystic), craniopharyngioma, in sagittal (a), axial (b), and coronal (c) views. (personal MRI images, used with patient consent)

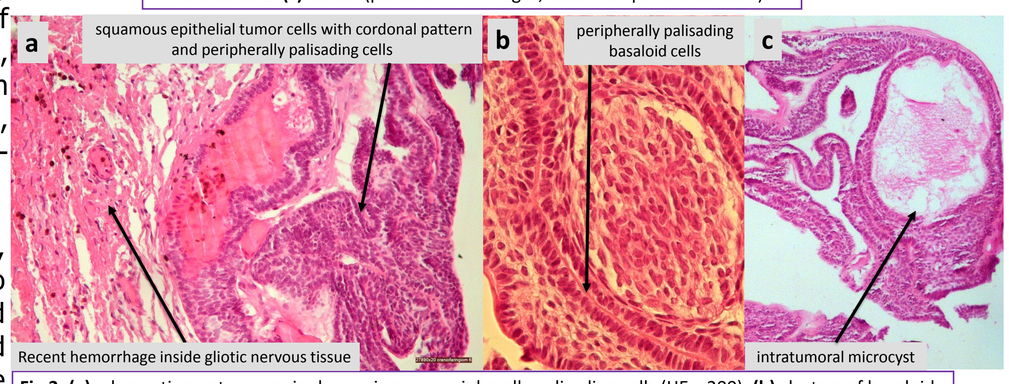


Fig.3: (a) adamantinomatous craniopharyngioma - peripherally palisading cells (HE, x200), **(b)** clusters of basaloid tumor cells with peripheral palisading (HE, x400), **(c)** intratumoral microcystic spaces filled with low eosinophilic, proteic material (HE, x100). (Fig. 3 (a,b,c), Fig. 4: -images form personal collection of Department of Pathology, “Prof. Dr. N. Oblu” Emergency Clinical Hospital, Iaşi, Romania, used with consent from Head Physician Gabriela Dumitrescu)

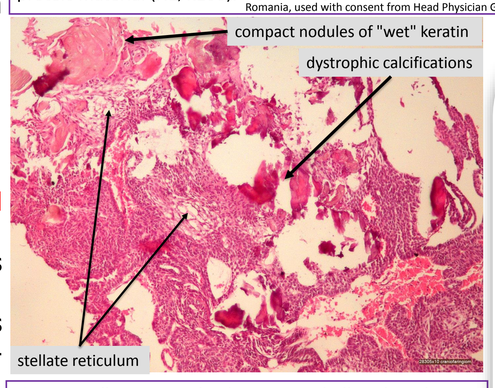


Fig.4: well-recognized diagnostic hallmarks: keratin nodules (wet keratin) and calcifications, squamous epithelium central pattern (stellate reticulum) (HE, x100).

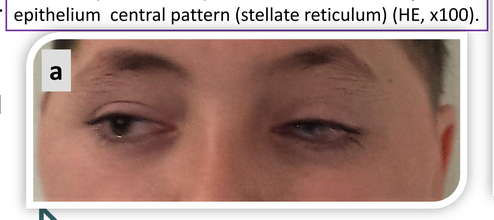


Fig.5: (a) clinical features of ophthalmic complications, **(b)** clinical aspect- severe growth retardation. (photos of patient H.A. used with patient consent)

➢ **03.2012** – patient presented: headache, psychomotor agitation, nausea and vomiting, MRI scan found a recurrent tumoral mass that eroded and spread beyond the confines of the sella turcica, with extension into sphenoidal sinuses, nasal fossae, cavernous sinus bilaterally with elevation of the optic apparatus (polycyclic and cystic in nature, large size 4,6/7,5/7,2 cm).

First surgical reintervention (subtotal resection of the craniopharingyoma) was successfully performed:

- Tumoral components ablation significantly diminished the mass effect upon adjacent brain structures;

➢ **08.2013** – presents with intracranial hypertension syndrome routine MRI on follow-up presented recurrent tumoral mass with mixt structure (cystic and solid components) disposed in selar and supraselar region with further invasion of sphenoidal sinuses, etmoidal cells, nasal fossae, orbital cavities (mostly on right side).

Second surgical reintervention (reopening of old left pterional incision site with subtotal resection of the craniopharingyoma) was successfully performed:

- After surgery the evolution was favorable patient symptomatology was ameliorated;
- Tumor could not be removed completely with surgery alone, and radiotherapy was purposed.

Patient received external fractionated radiotherapy a total curative dose of 54Gy/30ft/CTV which provided long-term tumor control, including stabilization of the present clinical condition.

Anatomopathological exam was performed:

- Macroscopic: 1.) tumor capsule; 2.) tumoral tissue from pituitary region; 3.) liquid from the tumoral cystic component.
- Microscopic: 1.) newly formed fibrovascular tissue with rare mononuclear inflammatory cell infiltrate; 2.) craniopharingyoma with adamantinomatous tisular pattern and numerous intratumoral cysts; 3.) fibrin and nuclear fragments.
- **Immunohystochemistry** revealed: immunostaining positive for cytokeratins (CK) as proof of tumor epithelial origin, low Ki–67 index <2% a common finding in craniopharyngiomas

Post Op

➢ At current evaluation, severe growth retardation (-5.11SD), delayed bone age (11 years 6 months, fertile cartilages) and somatotroph deficiency raised the question of usefulness of rhGH treatment. Given frequent tumor recurrences and the presence of tumor residue, the histological type of CP determination becomes crucial for better adjustment in treatment strategy.

Discussions

➢ **Biological behavior of CPs varies considerably from case to case, some remain constant, while other lesions tend to grow over an random period of time. Subtotal removal without radiotherapy is the strongest factor in predicting CP recurrence. Radical surgical removal and the use of radiation therapy (RT) after a subtotal removal have been recognized as therapeutic practice that notably decrease the rate of CP recurrence. The presence of a thick layer of gliosis at AP exam and high Ki-67 index, should support the need for close follow-up.[2,8,9]**

➢ **CP should be considered a chronic disease, requiring constant monitoring of the cases in order to provide optimal quality of life for patients, and minimize the severe consequences of both the disease and its treatment.[10,11]**

➢ **In addition to surgical management of CPs, substitution of endocrine deficiencies is required. CP and other central nervous system tumors recurrence frequency is identical in hGH treated and untreated patients.[4,12]**

Conclusions

❖ The case illustrates the occurrence of craniopharyngioma (with low-grade histological malignancy), 5 months after hGh therapy for pituitary dwarfism was initiated. Quality of life in children with craniopharyngioma is frequently impaired due to adverse effects caused by the anatomical proximity of the CP to the optic chiasm, the pituitary gland, and the hypothalamus, our patient suffered from panhypopituitarism, sever ophthalmic complications, and also frequent tumor recurrence that imposed surgical reintervention followed by radiotherapy.

❖ Regarding published data on patients treated surgically and with rhGH, CP recurrence is reported at approximatively four years after surgery and two after rhGH therapy. Although GH receptors exist in some craniopharyngiomas, many authors consider rhGH safe. We emphasize the importance of close follow-ups of rhGH treatment, given the rapidly evolving tumour in our patient case.

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