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Alpha-Fetoprotein Secretion in a Craniopharyngioma. Are Craniopharyngiomas Part of the Germ Cell Tumor Family?

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Abstract

A 14-months-old girl was admitted to our hospital because of excessive irritability and abnormal eye movements over the last two months. Brain CT and MRI revealed a suprasellar cystic and partially solid mass with calcifications. The laboratory investigation revealed increased serum levels of AFP. These findings were suggestive for a brain germ cell tumor. Therefore, systemic chemotherapy was started. After two courses there was a reduction in the levels of AFP but the tumor size remained unchanged. Subtotal tumor excision was performed that revealed the presence of a craniopharyngioma. One month later there was enlargement of the cystic part of the tumor, while serum AFP was elevated. The child received again systemic chemotherapy and placement of a reservoir into the cystic part of the tumor. Analysis of the intracystic flouid revealed the presence of -HCG and AFP. Following that the patient received brachytherapy with intracavity yttrium placement. Three months later repeated MRI showed a decrease in the size of the cystic part, while the solid part remained unchanged. Thus, the solid part was treated by radiosurgery. One year later the patient was stable but with complete loss of vision. These observations support the theory of a germ cell tumor family, in which craniopharyngioma and germ cell tumor present the two sides of the same entity, while between them a wide variety of tumors, with variable type of secretion of AFP and/or -HCG, may exist.

Key words: craniopharyngioma; -fetoprotein; germ-cell tumor; children.

Introduction

Craniopharyngioma is a benign epithelial tumor of the sellar region that arises from remnants of Rathke's pouch. Craniopharyngioma constitutes the most common non-neuroepithelial intracerebral neoplasm in children and accounts for 5-10 % of all intracranial tumors. The median age at diagnosis is eight years (Janzer *et al.,* 2000). Herewith, we present a case of a 14-month-old girl with a craniopharyngioma and elevated alpha-fetoprotein (AFP) levels.

Case study

A 14-month-old girl was admitted to our hospital because of excessive irritability and abnormal eye movements over the last two months. On clinical examination there were nystagmoid movements of the eyes and inability to follow moving objects. The fundoscopy revealed pallor of the optic nerves without papilloedema. Computed tomography (CT) that ensued revealed a large suprasellar mass with calcifications, expanding to the third ventricle and the optic chiasm and causing enlargement of the sella turcica (Fig. 1A). Magnetic resonance imaging (MRI) delineated the presence of a large suprasellar cystic lesion with a solid part (Fig. 1B). In order to exclude a germ cell tumor, serum AFP and beta-human chorionic gonadotropin (-HCG) were determined. AFP was elevated (30,9 ng/ml, normal values 0-10,9 ng/ml), while - HCG was within normal limits. For further investigation, a chest X-ray and an abdominal ultrasound were performed and excluded the presence of a germ cell tumor in the midline of the body. Endocrinological investigations revealed TSH: 3,4 U/ml (0.5-5 U/ml); 4: 6.2 % (5-13 %); PRL: 17.5 ng/ml (5-20 ng/ml); Cortisol: 9.9 g/dl (4.3-22.4 g/dl); ACTH: 15.9 pg/ml (9-52 vpg/ml).

The differential diagnosis mainly included the presence of a germ cell tumor and a craniopharyn-

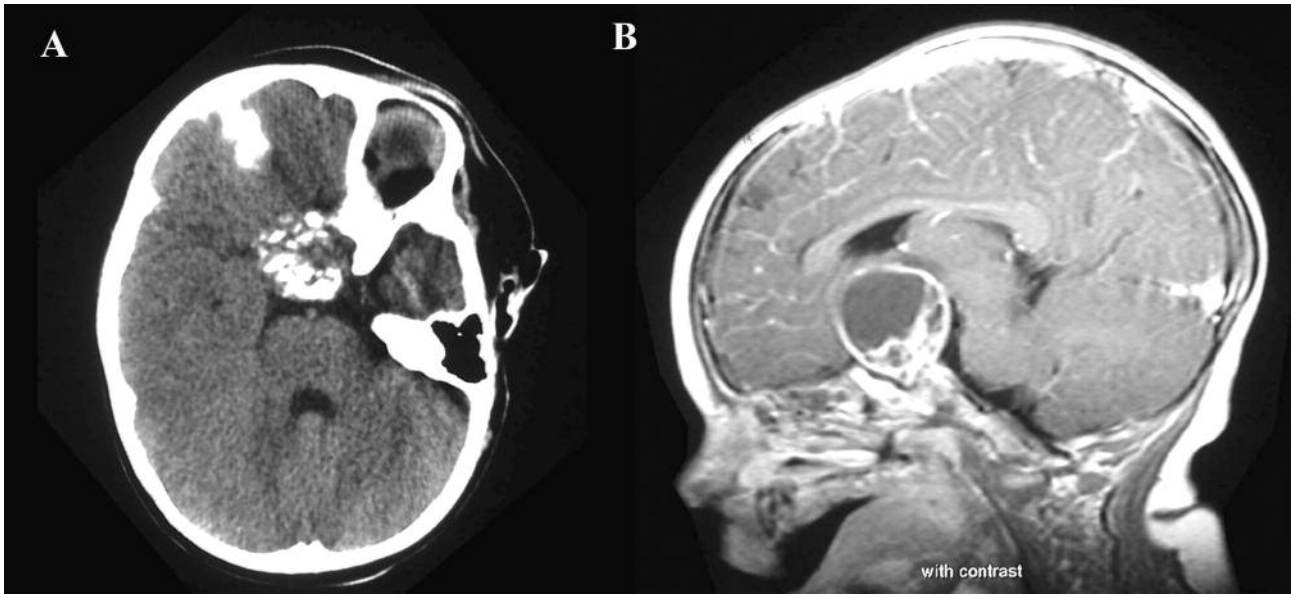

FIG. 1. — A. Brain CT showing a suprasellar mass with calcifications. B. Sagittal MRI after contrast administration revealing a lesion with a cystic and a solid component.

gioma. Because germ cell tumors display a chemotherapeutic response, the patient started systemic chemotherapy with bleomycin, VP16 and platinol. After two courses of chemotherapy, there was reduction of serum AFP (18.9 ng/ml), but the tumor size remained unchanged. Thus, a surgical resection was justified. The lesion was subtotally excised and the histopathological examination revealed the presence of a multistratified squamous epithelium with peripheral palisading of nuclei and calcification. These features were suggestive of an adamantinomatous craniopharyngioma. Immunohistochemistry showed high- and low-weight keratins. The Ki-67 labeling index was 20-30%. In the examined tissue there was no expression of AFP and -HCG. Postoperative, there was a reduction of serum AFP in normal levels (10.4 ng/ml). There were also low levels of T_3, T_4, TSH and cortisol, thus the child received replacement therapy with thyroxin and hydrocortisone. Although radiotherapy was a viable treatment option, because of the patient's age no irradiation was administered.

The child was readmitted one month later because of excessive irritability and abnormal eye movements. MRI confirmed enlargement of the cystic part of the tumor, while serum AFP (22.1 ng/ml) was also elevated. The child received again systemic chemotherapy and a reservoir was implanted into the cystic part, allowing frequent aspirations of the typical 'machine oil' like fluid of craniopharyngiomas. Analysis of the fluid showed elevated levels of -HCG (2,455 ng/ml) with low levels of AFP (9.3 ng/ml). For further treatment, the child received intracavitary brachytherapy with yttrium-90 (Y^{90}). Three months later, repeated MRI demonstrated a decrease in the size of the cystic part, whereas the solid part remained unchanged. Thus, a gamma knife radiosurgery of the tumor's solid part was performed. On follow-up evaluation one year later the child was stable but with complete loss of vision.

Discussion

Craniopharygioma is a benign non-glial tumor, derived from embryonic remnants of Rathke pouch epithelium. There are two clinicopathological variants, the adamantinomatous and the papillary form. The adamantinomatous form preferentially manifest in childhood (Janzer *et al.,* 2000). The histolopathological findings of this sybtype consist of broad strands, cords and bridges of a multistratifind squamous erithelium with peripheral palisading of nuclei. Craniopharyngiomas express high- and low-molecular weight keratins (Janzer *et al.,* 2000). Furthermore, the presence of a neuroendocrine lineage has been suggested to exist, due to the identification of scattered tumor cell groups that may express pituitary hormones and HCG (Hagrave 2006, Harris *et al.,* 1988). Harris *et al* and Tachibana *et al* reported the presence of HCG in the craniopharyngioma's cyst (Tachibana *et al.,* 1994, Harris *et al.,* 1988). Although in our case the serum was positive for AFP and the intracystic fluid for AFP and -HCG, we did not detect AFP or -HCG expression in the tumor histological sample, probably due to inadequate sample size.

Craniopharyngioma usually displays a benign histological character and rarely undergoes malignant transformation (Plowman *et al.,* 2004, Kristopatis *et al.,* 2000, Nelson *et al.,* 1988). Systemic chemotherapy has randomly been reported as a treatment choice in craniopharyngioma's with further untreatable relapses (Hargrave *et al.,* 2006, Lippens *et al.,* 1998, Bremer *et al.,* 1984). In our case, due to AFP secretion the patient received chemotherapy for germ cell tumors. It had a positive effect in AFP production by the tumor cells, while there was a decrease of AFP in serum after systemic chemotherapy. Nevertheless, after the end of chemotherapy there was elevation of AFP with clinical deterioration and tumor enlargement.

Germ cell tumors of the central nervous system are also typically arise within the suprasellar region or pineal region. Germ cell tumors are divided into two main histologic subgroups germinomas and nongerminomatous GCTs. The latter includes the embryonal carcinoma, yolk sac tumors, choriocarcinoma, teratoma (mature, immature or immature with malignant transformation) and mixed GCTs. In NGGCT tumors AFP and -HCG are usually elevated in serum and CSF (Kyritsis AP, 2010) while in germinomas AFP is negative. Consequently, serum and CSF markers can be used to reliably aid in diagnosis and monitor response to a given therapy. In our study the presence of elevated AFP and -HCG suggested the presence of a germ cell tumor and the patient received chemotherapy.

To the best of our knowledge, there are only two other relevant case reports that have been published so far (Table 1) (Plowman *et al.,* 2004, Nada *et al.,* 2000). Nada *et al.,* reported a 15 year old boy presented with visual disturbances, due to a suprasellar mass, that proved to be a craniopharyngioma on the first surgical specimen. The patient did not receive radiotherapy and one month later he was reoperated, due to tumor regrowth. Histology revealed a mixed germ cell tumor. Elevated levels of AFP in serum and CSF were also observed (Nada *et al.,* 2000). Plowman's et al reported the case of a 6.5-year-old girl who presented with headache and papilloedema due to a suprasellar calcified tumor. The patient was treated with radiotherapy. Ten years later the patient presented with symptoms and signs of raised intracranial pressure due to a cystic suprasellar mass. Tumor excision revealed a craniopharyngioma and radiotherapy was administered. During the next 5 years the patient had multiple relapses and a reoperation revealed a malignant craniopharyngioma that responded to systemic chemotherapy (Plowman *et al.,* 2004). Plowman *et al.*, suggested a continuum from craniopharyngioma to germ cell tumor, based on the observations regarding synthesis of -HCG by craniopharyngioma's cells and its chemonsensitivity when undergoes malignant transformation. Similarly, in our patient the positive effect of systemic chemotherapy in the production of AFP by the tumor cells and the detection of AFP and -HCG in the intracystic fluid may denote that craniopharyngioma and germ cell tumors are two faces of the same entity.

These observations support the theory of a germ cell tumor family, in which craniopharyngioma and germ cell tumor present the two sides of the same entity, while between them a wide variety of tumors, with variable type of secretion of AFP and/or HCG, may exist. Further studies will be necessary to clarify this issue which may lead to different treatment approaches for these tumors.

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Table 1.
Literature review of craniopharyngioma with AFP or -HCG secretion.

Author (Ref)	Age at diagnosis	Tumor	Markers in serum	Markers in CSF	Markers in Intracystic fluid
Nada *et al.*, (6)	15 years	Craniorharyngioma Relapse: Mixed germ cell tumor	Elevated AFP Normal -HCG	Elevated AFP Normal -HCG	Not mesured
Plowman *et al.*, (4)	21 years	Craniorharyngioma Relapse: Malignant craniopharyngioma	Not mesured	Not mesured	Not measured
Moschovi *et al.*,	14 months	Craniopharyngioma	Elevated AFP Normal -HCG	Not mesured	Low AFP Elevated -HCG

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