ACTA SCIENTIFIC CANCER BIOLOGY

Volume 2 Issue 8 October 2018

Review Article

Chraniopharyngioma and Oil Machinery Fluid

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Received: August 09, 2018; **Published:** October 01, 2018

Abstract

The craniopharyngioma is a solid tumor as cystic, the characteristics of the cystic formations as well as their content that has been called as oil machinery fluid and is little known. We have a theory about this controversial oil machinery fluid, that by different mechanisms epithelial cells are opening favoring the exit of the fluid to the exterior of the tumor, in this process involved various biological mechanisms, chemical, metabolic, inflammatory, cellular adhesion, loss of cilia of the cells etc. What favors cells go to brain tissue causing damage in the cellular microenvironment, thus favoring neoplastic cell dissemination, difficulty for complete resection of the tumor and thus frequent recurrences of this tumor, etc.

Keywords: Craniopharyngioma; Oil Machinery Fluid; Brain Invasion; Recurrence

Abbreviations

CP: Craniopharyngioma; EGFR: Epidermal Growth Factor Receptor; AdaCP: Adamantinomas Craniopharyngioma; PaCP: Papillary Craniopharyngioma; TVF: Third Ventricle Floor; OMF: Oil Machinery Fluid; WHO: World Health Organization; SHh: Sonic Hedgehog

Introduction

Craniopharyngiomas (CPs) are rare and locally aggressive brain tumors, assumed to arise from remnants of the Rathke's pouch, an ectodermal structure which gives rise to the anterior pituitary gland. They represent less than 1% of all primary CNS tumors, but are the most common intracranial non-glial tumor in children [1], with an incidence of 0.5 - 2 cases per million persons per year. A bimodal age distribution has been shown, with peak incidence rates in children aged 5 - 14 years old and adults between the ages of 50 and 74 years [1].

CP is typically located in the seller and suprasellar area. Its progressive growth produces mass-effect to its adjoining critical vascular and neural structures. The onset of symptoms is slow and insidious. At the time of diagnosis, most patients present with neurological (headaches, visual disturbances) and endocrine (growth retardation, delayed puberty) dysfunctions. It can also extend posteriorly and compress the walls of the third ventricle, causing non-communicating hydrocephalus [2,3].

Two major craniopharyngioma phenotypes have been recognized: adamantinomatous craniopharyngioma (adaCP), which occurs both in children and adults; and papillary craniopharyngioma (papCP), which occurs almost exclusively in adults with lower risk of recurrence compared with adaCP [1]. The characteristic location of this tumor in the seller and para-seller region, in addition to its different histological subtypes, altogether have allowed for the proposal of theories that may explain its origin and nature. It is thought that adaCP is similar to enamel forming neoplasms in the oropharynx, while the squamous papillary phenotype is thought to originate from squamous metaplasia [4]. Another theory suggests that the adaPC type arises from epithelial remnants of the craniopharyngeal duct or Rathke's pouch, which is derived from the stomodeum, which, among many other structures, is the embryological origin of teeth primordia [4], and recently published studies have revealed a pituitary stem cells origin [5, 6].

Though CP are classified by the World Health Organization (WHO) as grade 1 tumors, there have been rare reports of malignant transformation [7].

More than 70% of adaCP bear a mutation of the β-catenin gene, which is not detectable in the adult papCP type. While the diagnosis of adaCP may be corroborated with immunohistochemistry for β - catenin, the recent improvement of a specific mutant protein marker for the BRAF V600E provides an additional diagnostic to differentiate it from papCP [5,8,9]. Genetic and molecular pathologic subtypes support a distinct pathogenesis of adaCP and papCP [5,6]. It was reported that papCP expresses BRAF p. V600E mutations in 95% of cases and CTNNB1 mutations are exclusive and specific to adaCPs [10]. It has been proposed that the clusters of cells with upregulated Wnt/β-catenin signalling induce tumor development in a paracrine mechanism [11].

AdaCP is much more frequent than papCP and both are morphologically different from one another [1]. Macroscopically, adaCP is adherent to surrounding structures, commonly invasive to the optic chiasm, vascular stalks and the third ventricle floor (TVF). Histologically, it is characterized by cystic and solid structures, predominantly nodular (80%) or lobular with a sharp, irregular interface. Cyst walls are lined by squamous epithelium (from monocellular, simple epithelium to a more complex stratified epithelium) with focal peripheral palisading. Its wall may show extensive necrotic cell debris, fibrous tissue, chronic inflammation, cholesterol clefts, dystrophic calcifications, wet keratin, ghost cells and focal osteoid metaplasia, as previously reported elsewhere [1]. Stromal cells, also called stellate reticulum, show degenerative changes and word arrays formation [1].

The word arrays considered as a proliferative formation due to β-catenin activation, which increases neoplastic malignancy [5,12]. Furthermore, local invasion of the surrounding healthy brain tissue is observed; as well as reactive gliosis, inflammation, and Rosenthal fibers. There are also anastomosing epithelial islands, nests or clusters of cells. Finally, we can also observe a palisaded layer of cells, as cells with nuclear β-catenin accumulate in finger like protrusions, as well as in an area of keratinization and numerous calcifications [9-11]. There are complex interactions occurring between different cell populations [10]. Necrotic tumor cells are found in clusters with damaged nuclear membranes and irregularly broken and condensed chromatin, forming sparse reticular clots.

On the other hand, papCP tends to present as a unilocular cystic tumor (50%), and as a solid one in the rest of the cases, the cystic contents are clear and homogeneous, it is an encapsulated, discrete tumor, usually non-adhering to surrounding structures, exceptionally gripped to the pituitary stalk through squamous epithelium or stratified epithelium forming papillae and pseudo papillae [1], along with an anastomosing fibro vascular stroma lacking peripheral palisading of cells or stellate reticulum, and ghost cells always lacking nuclear β-catenin accumulation [9-11].

Under electron microscopy, adaCP cells show variable chromatin distribution, abundant ton fibrils in the cytoplasm [12]. Furthermore, abundant microvilli are observed on the cell apical surface, and cells are distributed and conjoined through a vast cell gap in which integrated intercellular desmosomes and multiple connections appeared to have formed [12], as well as presence of abundant mitochondria identified in the CP cells, indicating highly active metabolism, and well-developed rough endoplasmic reticulum and ribosomes are clearly visible, which is typical of fully differentiated and actively functioning cells [12].

AdaCP cyst content is a dark, yellow-brownish fluid with an oily appearance, and has been termed "oil machinery fluid" (OMF), it frequently contains calcifications that are readily identifiable on neuroimaging [2,3]. Little is known about this OMF, it contains cholesterol crystals, several inflammatory proteins (namely, α2-HS-glycoprotein, α1-antichymotrypsin and apolipoproteins), possibly involved in the genesis and growth of the cystic component of adaCP, which have been studied by Massimi., *et al* [13]. Other molecules, such as Apolipoprotein A-I, A-II, C-I and J, hemoglobin fragments, ubiquitin, α-2-HS-glycoprotein or fetuin A, α-1-antichymotrypsin, vitamin D binding protein, and α-1-acid glycoprotein were characterized by Martelli., *et al.* [14] and Desiderio., *et al* [15]. The identification of β-thymosin's in the intracity fluid confirmed the secretion of these proteins in the extracellular environment due to their G-actin-sequestering activity and antiapoptotic and anti-inflammatory properties and concluding that these peptides could be strictly involved in both tumor progression and cyst development and growth. Biochemical quantification has also detected increased concentrations of glucose, triglycerides, cholesterol, and hepatic enzymes [16]. CSF analysis can also show abnormalities in the concentration of lactate dehydrogenase and cholesterol [17]. However, the content of the OMF is yet to be clarified, as well as its secondary effects [18]. The local and systemic consequences of spontaneous rupture of the cystic wall and extravasation of the OMF to the cerebral surrounding tissue are little studied [18,19].

Usually rupture of CP exerts chemical meningitis or an aseptic meningitis, which can be asymptomatic, but its loss of contact and mass-effect to the major neurovascular structures may lead to improvement of neurological symptoms [20]. Sometimes rupture can cause the complete resolution of cyst. Focal rupture into brain parenchyma causes brain oedema or communicating hydrocephalus with aggravation of symptoms. Tumor recurrence and brain invasion and has been correlated to cerebral vasospasm, thrombosis and ischemia [21].

The extravasation of OMF into the cerebral tissue has been represented in experimental animal models, showing that it exerts toxic damage into the CNS [18,19]. We suggest that this rupture may be provoked by a rise of volume or intracystic pressure, or due to post-surgical procedures [22].

Epithelial tumor cell mobility requires detaching from the conjoined cell structure by dissolving cell-cell contacts, such as tight junctions [TJs] formed by cell adhesion molecules like occluding and claudins [10], but also alterations in multiple intercellular connections, tonofilaments and desmosomes, causing loss of interadherence of the epithelial cells and leakage of the OMF into the cerebral parenchyma, causing irritation, oedema, worsening the neurological status [23]. This may also be explained according to the changes in paracrine mechanisms related to cellular senescence [24], and inflammation processes [25]. Induction of an epithelial-mesenchymal transition phenotype, which promotes tumor cell migration, is also involved [26]. It has been reported that multiple cilia suppress tumor formation [27] but loss of primary cilia occurs early in tumor development [28].

Claudins play an important role in cell polarity and cell adhesion, as well as in maintaining paracellular barrier functions [24]. Deregulation, like pathological up- or downregulation, of various members of the claudin family has been previously described for different epithelial neoplasms [24].

The extensive presence of primary cilia in adaCP implicates cilia-dependent sonic hedgehog (SHh) signaling in the pathogenesis of adaCP, and this loss often occurs early in oncogenesis with the activation of Wnt/β-catenin pathway mutations [29,30].

Secreted pro-inflammatory mediators, such as cytokines, may modulate the local immune response and affect tumor cell growth [26]. The participation of complex inflammatory signaling pathways may facilitate the extravasation of tumor cells through the stroma, thereby stimulating tumor progression. Studies performed by Mori., *et al.* [31], strongly implicated IL-6 as the key molecule for adaCP inflammation [24]. Additionally, in some cancer cells, many cytokines, predominantly IL-6, act as an autocrine or paracrine factor that promotes tumor cell proliferation, migration and invasion in vitro [5]. Infiltration of macrophages, neutrophils, lymphocytes and eosinophils has been detected in the tumor mass or the surrounding parenchyma [18,19,32]. The spillage of cyst fluid during surgery can lead to aseptic meningitis. Histologically, finger like protrusions, intense fibrillary gliosis with abundant Rosenthal fibers and infiltration of inflammatory cells are frequently present in the surrounding parenchyma in CPs, particularly adaCP [26,32]. Recently, tumor cell migration in adaCP has been linked to canonical activation of the Wnt signaling pathway characterized by nuclear accumulation of its key player, β-catenin [5]. Furthermore, upregulation of CLDN1 mRNA expression has been linked to tumor cell migration and infiltrative growth pattern [26]. Extension of CP to the posterior cranial fossa occurs in 4 - 5.9% of cases [2]. Posterior fossa CP may occur either as recurrence/extension or primary tumor (*de novo*). The unique anatomical structure of the suprasellar region and the proximity of the tumor to surrounding tissues with critical functions results in difficulties at the time of surgical removal of the tumor. Therefore, total resection of the tumor is complex and can lead to postoperative recurrence, adhesion to adjacent brain structures and a poorer clinical prognosis. Inflammation is a critical component of tumor recurrence even after total tumor removal and rupture of the cystic structures, a certain degree of controversy remains about which the optimal treatment strategy and surgical procedure [3]. Nonetheless, treatment for residual or recurrent tumor includes surgery, radiation therapy or cyst aspiration, cyst instillation with intra-cavitary radioisotopes, bleomycin and more [2].

CPs often pose a substantial challenge to neurosurgeons, due to their location and degree of invasion into surrounding brain tissue, specifically the hypothalamus, pituitary gland, and optic nerve, they make gross total resection a real problem, leading to a high rate of brain invasion and recurrence [3,4], and this can be associated with marked morbidity (hypothalamic dysfunction, altered neuropsychological profile). Endocrine disturbances are normally permanent and need careful hormonal replacement [4]. Obesity, daytime sleepiness, disturbed circadian rhythm, behavioral changes, and imbalances in regulation of thirst, body temperature, heart rate, and/or blood pressure are most of the symptoms related to hypothalamic dysfunction [4]. Its rate dramatically increases following treatment; in some series, up to 65 - 80% [33].

In a yet-to-be published rat experimental model, our team demonstrated that the presence of the OMF in the brain parenchymal tissue, more specifically in the thalamic nuclei, is able to induce obesity. This model was based in findings observed in the obesity experimental model, in which damage to the thalamus provokes weight gaining in rats.

Conclusions

Thus, we must consider the OMF as the primary agent causing secondary toxic and molecular damage to the brain tissue. Certainly, many more studies are necessary to be able to document and prove this wild hypothesis.

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Volume 1 Issue 3 October 2018

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