MINISTRY OF EDUCATION
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PHD THESIS SUMMARY

THE CLINICAL AND THERAPEUTIC STUDY OF NASOPHARYNGEAL ANGIOFIBROMA

PhD Supervisor,
Prof. Dr. COMȘA Gheorghe Ionel

PhD Candidate,
Dr. IONESCU Paris

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KEY WORDS: angiofibroma, nasopharyngeal, male adolescents, selective embolization, coblation.

INTRODUCTION

The juvenile nasopharyngeal angiofibroma is a benign, puberty tumor, with a high risk of progression and bleeding, that accounts for only 0.05% to 0.5% of all head and neck tumors. However, it is the most common tumor of the nasopharynx, with a clear preference for male subjects, more frequently during adolescence and pre-adolescence, and because this period is one of great hormonal influence, there is a suspicions about the role of the sexual hormones in its pathogenesis.

There are many controversies in the literature about this tumor, involving terminology, etiology and even the different therapeutic approaches.

Etiology is still unknown, but it is known that there is no correlation with heredity, since no case of family illness has been reported.

The benign histological appearance of this tumor is often counterbalanced by a potentially aggressive clinical development due to its local invasion tendency, expressed by severe and recurrent epistaxis, by involving the intracranial structures with possible surgical difficulties and major complications, as well as due to the high incidence of recurrence of the tumor.

Histologically, the tumor is made up of myofibroblasts and numerous vasogenic elements, thus being very well vascularized, most frequently through the internal maxillary artery.

Epistaxis, accompanied by progressive *nasal obstruction*, are the classic symptoms of nasopharyngeal angiofibroma for which these patients present to the physician.

There are a variety of *staging criteria* resulting from the evaluation of this tumor, including those described by Radkowski, Fisch, Chandler, Andrews, Onerci and Sessions.

The diagnosis is based mainly on a careful history, a complete clinical examination, on nasal endoscopy, and on complementary imaging exams using standard *radiography, computed tomography, or magnetic resonance*, the latter being more accurate than CT in intracranial extension assessment.

Biopsy is contraindicated due to the increased risk of bleeding during this procedure, so that the diagnosis of certainty is established by angiography, which also serves as a therapeutic method given that arterial embolization can be performed at the same session.

Although the elective treatment is *surgery*, there are cases where classic radiotherapy, hormone therapy or even stereotactic radiotherapy (Gamma Knife Surgery) are indicated.

Currently, the use of preoperative adjuvant techniques is recommended, namely *superselective embolization or internal jugular artery ligation*, in order to facilitate surgical access and to prevent bleeding complications.

Technological advances and improvements in endonasal techniques allow the use of nasal *endoscopic surgery* to excise certain tumors at the expense of classical surgery.

The first part of the thesis sets out the current stage of knowledge, making in the first two chapters an ample description of the anatomy, histology and physiology of the rhinopharynx, without which it would not be possible to understand the case law at this level, and in the third chapter I focused on the most complete exposure of nasopharyngeal angiofibroma, according to the literature, based on an extensive bibliography.

The second part of the thesis describes the personal scientific research and contains a clinical, statistically and therapeutically, retrospective (2003-2012) study of the nasopharyngeal angiofibroma, totaling a number of 152 patients (the study group), grouped in three study groups (group I of patients diagnosed with nasopharyngeal angiofibroma, group II - patients with nasopharyngeal cancer and group III – the control group), all inhabitants of Constanta County.

PERSONAL SCIENTIFIC RESEARCH

Through this thesis I analyzed the current situation regarding the incidence, the diagnosis, the treatment and the evolution of nasopharyngeal angiofibroma, compared to nasopharyngeal cancer and to epistaxis / nasal obstruction without tumor substrate, over a period of 10 years among patients admitted to The ENT Clinic of the Emergency Clinical Hospital of Constanta County, Medgidia Municipal Hospital and Cernavoda City Hospital (integrated ambulatory).

MEANS AND METHOD

I made a clinical, statistically, therapeutically, prospectively and retrospectively study (2003-2012) of nasopharyngeal angiofibroma, totaling 152 patients (the study group), divided in three groups (the first group of patients diagnosed with nasopharyngeal angiofibroma , group II - patients with nasopharyngeal cancer and group III - the control group), inhabitants of Constanta County.

In the course of the study I had a close connection with the Institute of Phonoaudiology and Functional Surgery "Prof. Dr. Dorin Hociotă ", regarding the diagnostic and therapeutic aspects of this kind of tumor.

The diagnostic algorithm included, along with the careful history and clinical examination, paraclinical investigations - laboratory tests (urinary 17-ketosteroids), imaging investigations (standard face and profile radiographs, computer tomography, selective arteriography) and histopathological examination of he surgical piece.

I systematized data on age, gender, background, debut, conventional or non-conventional exploration, macroscopic aspect of the tumor, disease progression, and prognosis.

The experimental data were processed using the IBM SPSS Statistics 20 statistical processing program. The procedures used were: Descriptive statistics (to characterize discrete and continuously defined variables at the database level), Charts, Parametric Statistical Tests (t-test to compare the average Two independent variables, one-way ANOVA test), non-

parametric statistical tests (the x2 test of the association, the relationship between two categorical variables, with the risk / chance CHR and relative risk Rr in certain situations).

RESULTS AND DISCUSSIONS

A review of the literature reveals controversy in almost every aspect of this tumor. Occasional situations of endocrine dependence, malignant transformation, spontaneous regression, and more cases of nasopharyngeal angiofibroma in women, have increased interest in studying this unusual tumor. There is no clear explanation as how a benign histological tumor can erode skeletal structures and push in and through neighboring tissues.

In this study we analyzed the current situation regarding the incidence, distribution, correlation, treatment and progression of nasopharyngeal angiofibroma, compared to nasopharyngeal cancer, respectively epistaxis / nasal obstruction without tumor substrate over a period of 10 years, starting with 2003 and until 2012, in Constanta County.

We included in the study a group of 38 patients diagnosed with nasopharyngeal angiofibroma, of which 27 male (71%) and 11 female (29%) aged between 15 and 67 years, with an average age of 25.71 years.

By comparing my findings with literature data, we notice a difference in both the age of patients with nasopharyngeal angiofibroma and their gender distribution, including 11 women and 5 patients aged over 30 years.

With regard to the mean age of patients diagnosed with nasopharyngeal angiofibroma included in the study, compared with the mean age of those with nasopharyngeal cancer, we note a statistically significant difference ($p = 0.001$), the mean age of those with nasopharyngeal angiofibroma being only 25.26 years, and patients with nasopharyngeal cancer being 54.10 years.

Choosing the cities (Constanța, Medgidia, Cernavodă) and the neighboring rural area was made according to the pollutant factors existing in this region.

Continuous emissions to air, water and soil from industrial activities (accidental discharges of hazardous substances from industrial installations - including the Cernavodă plant), agricultural (spreading of fertilizers, pesticides, insecticides contaminating soil, water), transport (continuous emissions from transport system operations - including ship-borne pollution) in the area of the Maritime and Terrestrial Area of Constanta County may be important environmental risk factors for the occurrence of nasopharyngeal angiofibroma.

Analyzing the background environment of patients with nasopharyngeal angiofibroma, we found that most of them came from the urban environment (74%).

By analyzing the urinary 17-ketosteroids we note that more than two-thirds of the patients in the nasopharyngeal angiofibroma group had a low value of these urinary metabolites, respectively 26; at the opposite end being the patients in the control group, in which only 3 patients had low levels of this urinary metabolite.

Therefore, the chance of having patients with low urinary 17-ketosteroids in the group of patients diagnosed with nasopharyngeal angiofibroma is by 31.05 times greater than the chance of having patients with low urinary17-ketosteroids in the control group of patients.

A statistically significant relationship was demonstrated between the decrease in urinary 17-ketosteroids among patients with nasopharyngeal angiofibroma, as compared to their decrease in patients diagnosed with nasopharyngeal cancer ($p = 0.001$), and the chance of having patients with low urinary 17-ketosteroids in the group of patients diagnosed with nasopharyngeal angiofibroma is 10.11 times greater than the chance of having patients with low urinary 17-ketosteroids in the group of patients diagnosed with a nasopharyngeal cancer.

In my study, out of a total of 38 patients diagnosed with nasopharyngeal angiofibroma, 18 patients (47.4%) had nasal obstruction as a reason for presenting to a physician, 12 patients (31.6%) had epistaxis and only 8 patients (21.1%) noted the concomitant presence of both symptoms.

From the obtained results, there is a relationship of dependence (connection, association) between the presence / absence of nasal obstruction and diagnosis (nasopharyngeal angiofibroma / control group): $\chi 2calc = 12.038$, $df = 1$, $p < 0.001 < \alpha = 0.05$.

The chance of having patients with nasal obstruction in the group of patients diagnosed with nasopharyngeal angiofibroma is 4.95 times higher than the chance of having patients with nasal obstruction in the control group.

In accordance with the literature, most patients in my study group were diagnosed with nasopharyngeal angiofibroma (47%) and nasopharyngeal cancer (72%) using CT as an imaging method.

According to the results of the present study, 6 patients (16%) required selective arteriography to establish the diagnosis of nasopharyngeal angiofibroma compared to 17 patients (25%) of the cancer group that performed this investigation.

All 38 patients included in the group of nasopharyngeal angiofibroma were surgically treated using one of the two types of approach, either classical or endoscopic one.

In 23 patients (60.5%) diagnosed with nasopharyngeal angiofibroma tumor resection was performed by external approach. Only 15 (39.5%) of patients with nasopharyngeal angiofibroma were treated through intranasal endoscopic surgery. Out of the 23 patients treated by classic surgery, 16 (69.6%) of them were declared healed and only 7 patients (30.4%) relapsed during the study.

Of the 15 patients surgically treated by endoscopic methods, a majority of 12 patients (80%) were cured and only 3 patients (20%) had recurrent tumor until this study was completed.

In 4 cases, superselective embolization was performed during angiography, facilitating surgical intervention. In 8 of the patients, the internal maxillary artery ligation was performed, this being the main artery that serves the tumor, in two of them as a result of the failure of the superselective embolization.

Of the 38 patients included in the group of those with nasopharyngeal angiofibroma, 28 patients (73.7%) had a favorable post-operative progression, having the healed status during the study, only 10 of them (26.3%) had tumor recurrence and no patient died until the end of this study.

The chance to have patients with favorable prognosis in the group of patients diagnosed with nasopharyngeal angiofibroma is 7.22 times higher than the chance of having favorable prognostic patients in the group of patients diagnosed with nasopharyngeal cancer.

The mean age of patients with nasopharyngeal angiofibroma at which the prognosis was a favorable one was 18.89 years, approximately similar to the median age at which relapse occurred, 21 years.

CONCLUSIONS

Nasopharyngeal angiofibroma is a benign, fairly rare tumor, accounting for only 0.05% to 0.5% of the total head and neck tumors. However, it is the most common tumor of the nasopharynx, most often found in male adolescents.

There appears to be an increased incidence of nasopharyngeal angiofibroma in poorly developed or developing countries requiring a better knowledge of this pathology and its prevalence in these areas.

Though histologically it is considered a benign tumor, it often has a compressive and hemorrhagic risk.

By comparing my findings with literature data, we notice a difference in both the age of patients with nasopharyngeal angiofibroma and their gender distribution, including 11 women and 5 patients aged over 30 years.

A statistically significant association can not be achieved between the number of Romanian, Tatar and Turkish patients, the differences being proportional in the three study groups.

Although the cause of the disease remains unknown, it appears that a role is also played by insufficient masculinization, as most of the patients have a low number of urinary 17-ketosteroids, namely those of testicular origin.

In accordance with the literature, most patients in my study group were diagnosed with nasopharyngeal angiofibroma (47%) and nasopharyngeal cancer (72%) using CT as an imaging method.

Biopsy is usually not recommended because of the vascular nature of this tumor and the risk of bleeding, but it can still be done when there is a high suspicion of malignancy.

In general, the diagnostic certainty is established by performing arteriography that serves at the same time as a therapeutic method, so that arterial embolization can be performed during this investigation to reduce the intraoperative bleeding.

Although surgery is the main therapeutic approach to nasopharyngeal angiofibroma, in selected cases correction of endocrine disorders is also necessary. The occurrence of arterial embolization as a preoperative adjuvant, the anti-androgen therapy, the development and improvement of endoscopic resection techniques of the tumor, led to a significant reduction in morbidity and surgical mortality. This facilitates complete tumor resection and reduced hemorrhagic complications.

The mean age of patients with nasopharyngeal angiofibroma at which the prognosis was a favorable one was 18.89 years, approximately similar to the median age at which relapse occurred, 21 years.

Patients were advised for yearly follow-up, until 10 years after surgery, to prevent or correct the relapse, because non-evolutionary, low-volume tumors or peritubular obstructions may remain.

Despite its benign histological features, nasopharyngeal angiofibroma usually acts as an aggressive tumor at local level, causing significant damage both to the structural and functional levels. It is currently being surgically treated, but local recurrence is common and has been reported in 10% of the cases.