

Modern Approach to Juvenile Nasopharyngeal Angiofibroma: A Literature Review

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Abstract: *Juvenile nasopharyngeal angiofibroma (JNA), also known as juvenile angiofibroma or nasal juvenile angiofibroma, is a benign tumour of vascular origin that occurs predominantly in adolescent males at the average age of 15 (10-25) and is extremely rare in both females and older males. The JNA is considered histopathologically benign, but it behaves as a locally aggressive neoplasm which can destructively erode adjacent soft tissue, cartilage and bone and may provoke complications due to extension to the orbit in approximately 30% and intracranial invasion in 10-20% of all tumours. After years of research, still there is no universal consensus on the most successful surgical method; the therapeutic choice depends on the individual pattern, tumor behaviour and surgeon experience. Regardless of the surgical method chosen for the treatment of nasopharyngeal angiofibroma, no doubt is there that anaesthesia represents an important and unalterable part of its treatment. Good knowledge of such pathology, properly performed preoperative preparation, surgery and anaesthesia give the opportunity angiofibroma to be removed safely.*

Keywords: Juvenile nasopharyngeal angiofibroma, surgery, anaesthesia.

1. Introduction

Juvenile nasopharyngeal angiofibroma (JNA), also known as juvenile angiofibroma or nasal juvenile angiofibroma, is a benign tumour of vascular origin that occurs predominantly in adolescent males at the average age of 15 (10-25) and is extremely rare in both females and older males. Despite its common anatomic localization, age-dependent and gender-specific presentation, it is considered a rare neoplasm accounting for 0.05% to 0.5 % of all head and neck tumours, while also being a diagnostic and surgical challenge in otorhinolaryngology practice. Although uncommon, the JNA is with a very high frequency of 24.6-40.0% among nasopharyngeal benign tumors [1]. Individuals of all races, ethnic groups and geographic regions are almost equally affected, with few reports on higher incidence in the Middle East and India [2].

The JNA is considered histopathologically benign, but it behaves as a locally aggressive neoplasm which can destructively erode adjacent soft tissue, cartilage and bone and may provoke complications due to extension to the orbit in approximately 30% and intracranial invasion in 10-20% of all tumours [3,31]. Malignant transformation of these tumours is very rarely revealed.

The JNAs usually appear as lobulated non/pseudoencapsulated masses slowly filling closer cavities and penetrating through natural foramina and fissures to involve surrounding structures. With enlargement, tumors may provoke facial deformities, pressure atrophy and bone erosion depending on their tridimensional direction of spread [4,5]. Some authors have reported spontaneous regression in untreated patients. Because of the tumour's slow growth and initially nonspecific complains, patients often present with later stage of disease progression and a delay of months or even years after symptom onset. When properly treated, the prognosis of JNA is generally good, but it depends on the stage of severity and often is compromised

by progressive local invasion or recurrence. The tumor has been reported to recur in 46% of patients, with a symptom-free period less than 36 months postoperatively [3]. Moreover, JNA is highly vascular and the surgical approach is associated with serious risks of severe intraoperative bleeding and potentially life-threatening short-term perioperative complications [6,7].

Historically, many theories have been debated regarding the pathogenesis of JNA. First proposed by Ringertz in 1938 to arise from the periosteum of the skull base, the tumor has been later suggested by Brunner (1942) to originate from pharyngobasilar and buccopharyngeal fascia. In 1948, Marten et al. presented a hormonal hypothesis for the angiomatous nature of JNA, followed by Girgis et al. (1973) who suggested the tumor to be a paraganglionoma. Since the completion of Human Genome Project in 2003, researchers have intensively focused on investigating different genes and molecular pathways for association with the development of this type vascular neoplasm. The expression of estrogen-androgen receptors by JNA has been tested, but the hypothesis of hormone-dependent nature of the tumor has not been clearly proven yet. Prooncogene MYC expression and c-MYC protein have also been investigated for contribution to angiogenic transformation in more aggressive phenotypes of JNA. The overexpression of insulin-like growth factor II has been suggested to interplay with the tumor recurrence and prognosis. A 25-time more frequent development of the neoplasm has been reported in patients with familial adenomatous polyposis and a germline mutation in APC gene on chromosome 5q [9]. Alterations in APC gene have been supposed to activate beta-catenin gene which product may act as coactivator of androgen receptors to increase their hormonal sensitivity in adolescent males [2]. The fibro-vascular nature of JNA has also given rise to studies on the role of mesenchymal-endothelial transition, the vascular endothelial growth factor (VEGF) and the basic fibroblast growth factor (bFGF) in angiogenesis and tumorigenesis. [10, 11] Although there have been some positive reports from genomic association studies, there is

Volume 5 Issue 10, October 2016

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still no clear conclusion about the significance of mutations in the tumor suppressor gene p53 and the Her-2/neu oncogene in chromosome 17 for the occurrence of JNA. [2,12]. After decades of extensive studies, now there is much more consistent evidence on the factors involved in the development of this type of tumours, but the molecular findings are still in their early translational phase.

2. Location, histopathology and staging

In most cases, the JNA primary originates from the superior margin of sphenopalatine foramen area and often extends to nasopharynx and nasal cavity, pterygopalatine fossa, infratemporal fossa and paranasal sinuses.

Initially, most tumours grow submucosally to nasopharyngeal area and forward to the maxillary sinus. Laterally, the mass may extend to the pterygomaxillary fossa with later eroding the pterygoid process and filling the infratemporal fossa. The tumour may also expand through the inferior and superior orbital fissures to invade the cavernous sinus and orbita. With further growth through foramen rotundum and pterygoid canal, it may involve the middle fossa and sella turcica with posterior intracranial invasion which is usually extradural; dural penetration is uncommon. The internal maxillary artery plays a key role in supplying blood to the neoplasm and selective embolization prior to surgical excision is currently recommended. [9,13,14] It may also be supplied by the dural, sphenoidal and ophthalmic branches of the internal carotid system and the variability in vascularization should be preemptively considered [15].

Histologically, the tumour has been defined as a haematoma-like angioma with an extended fibrous component progressing from a developmental defect in the embryonic vascular network surrounding the sphenoid bone [16]. This place of origin determines the further prognosis and the specific problems of surgical access [15]. In general, JNA is composed of blood vessels and fibrous stroma with a very little to no amount of smooth muscle and elastic fibres. The later contributes to the risk of massive bleeding with surgical removal of JNA and it is recommended the biopsy specimen to be taken only after the patient is prepared for surgical removal [9,15]. Microscopically, the number and configuration of vascular channels and the amount of stromal collagen vary among tumors. The cells are spindle or stellate-shaped; the fibrous stroma is rich in mast cells and may show hyalinization or myxoid change. Immunohistochemically, endothelial markers (e.g. factor VIII-related antigen, CD31 and CD34) and androgen receptors have been detected in the endothelial and stromal cells. [17].

Although many criteria for classification and staging of JNA on the basis of tumor location and spread have been developed by Sessions et al. (1981), Fish et al. (1983), Chandler et al. (1984), Andrews et al. (1989), Radkowski et al. (1996), Onerci et al. (2006) and Snyderman et al. (2010), authors still have not reached a universal consensus on the ideal algorithm for JNA staging. Table 1 summarizes some of the most popular staging systems reflecting the clinical behavior of JAF and clearly defining its progression. The other classifications are also currently used. The accurate staging helps physicians in selecting the optimal surgical approach to reduce complications and to minimize the risk of recurrence [18,19].

Table 1: Description of the most common staging systems of JAF

Stage	Andrews-Fish et al. 1989 [20]	Radkowski et al. 1996 [21]	Onerci et al. 2006 [22]
I	Limited to nasopharynx and nasal cavity; bone destruction negligible or limited to SPF	(A) Limited to posterior nares and/or nasopharyngeal vault (B) Involving the posterior nares and/or nasopharyngeal vault with involvement of at least one paranasal sinus	Nose, nasopharyngeal vault, ethmoidal-sphenoidal sinuses, or minimal extension to PMF
II	Invading PPF or maxillary, ethmoid or sphenoid sinus with bone destruction	(A) Minimal extension into PPF (B) Occupation of PPF without orbital erosion (C) ITF extension without cheek or pterygoid plate involvement	Maxillary sinus, full occupation of PMF, extension to the anterior cranial fossa, and limited extension to ITF
III	(a) Invading ITF or orbital region without intracranial involvement (b) Invading ITF or orbital region with intracranial extradural (parasellar) involvement	(A) Erosion of the skull base (middle cranial fossa or pterygoids) (B) Erosion of the skull base with intracranial extension with or without cavernous sinus involvement	Deep extension into the cancellous bone at the base of the pterygoid or the body and the greater wing of sphenoid, significant lateral extension to ITF or to the pterygoid plates posteriorly or orbital region, cavernous sinus obliteration
IV	(a) Intracranial intradural without infiltration of the cavernous sinus, pituitary fossa or optic chiasm (b) Intracranial intradural with infiltration of the cavernous sinus, pituitary fossa or optic chiasm	NA	Intracranial extension between the pituitary gland and internal carotid artery, tumor localization lateral to ICA, middle fossa extension, and extensive intracranial extension

Abbreviations: ITF, intratemporal fossa; NA, not applicable; PMF, pterygomaxillary fossa; PPF, pterygopalatine fossa; SPF, sphenopalatine foramen

3. Clinical presentation and diagnostic methods

The diagnosis JNA is suspected in adolescent males with a history of progressive painless nasal obstruction and recurrent epistaxis (mostly unilateral), together with a smooth lobulated nasopharyngeal mass visualized on physical examination [8,23]. In majority of cases, patients generally present with a delay of about 6-7 months from the symptom onset [9]. Epistaxis and nasal stiffness are the most common and occur in approximately 75% of all cases [15]. Glad et al. have reported nasal obstruction in 91% of studied patients, recurrent bleeding in 63% and mucopurulent nasal discharge in 23%, respectively [18]. Depending on the direction of extension and the stage of tumour growth, the classic triade may be accompanied by different other symptoms including trismus, facial pain and swelling, soft palate displacement, secretory otitis media, conductive hearing loss due to Eustachian tube obstruction, rhinolalia and hyposmia/anosmia. With progression, the enlarged mass can provoke proptosis and visual disturbances resulting from involvement of the orbit, also headache (25%) and neurologic alterations due to intracranial extension [2,24]. Advanced lesions may cause massive hemorrhage.

Diagnosis is based on patient demographics and history, precise clinical examination and supportive radiological findings. Biopsy, by reason of uncontrolled bleeding, is not routinely recommended [25]. Plain X-ray of sinuses usually demonstrates a polyp-like mass in the nasopharynx and the method is almost lack of usefulness. On anterior rhinoscopy, the accumulated mucopurulent secretions often mask the tumour from vision, unless it is large and anteriorly prolapsing from the nares [24]. On nasal endoscopy, a hypervascular and soft mass, pink or reddish in color and with a smooth surface is usually visualized behind the middle turbinate. [2].

Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Angiography are the most supportive radiological methods for the diagnosis of JNA. The CT scan is very helpful in evaluation of bone details and destruction due to expansion of lesion growth. On noncontrast head CT (NCCT), the tumour is usually seen as a large, lobular and well-defined soft tissue lesion which shows intense enhancement with hypervascular appearance on contrast-enhanced CT (CECT). Images can reveal anterior bowing of posterior maxillary wall and widen sphenopalatine foramen with a presence of a mass in the pterygomaxillary space, also known as Holman-Miller sign, which may also appear on plain X-ray films. It is considered pathognomic for JNA when the tumour appears at the level of pterygopalatine fossa and an erosion of the pterygoid lamina is also visualized [23, 26]. The CECT gives a high level of certainty in assessing the site of origin and the extension of the tumour when planning its surgical margins [27]. Diagnosis is also confirmed by contrast enhanced MRI which is superior to CT in distinguishing the neoplastic lesion from mucosal oedema with accumulated secretions, better detailing the mass structure as well as more accurately defining the level of intracranial extension [28]. In a review of the evolution of JNA management, Nikolai et al. have recommended the use of contrast-enhanced multislice CT or MRI to assess the vascularization and extension of tumours

and concluded on the similar strength of both techniques in concerning the invasion of the skull base [2,34].

Angiography is used diagnostically to elucidate the vascular structure, blood supply and venous drainage of JNAs. Due to their typical origin, the majority of tumours are found to be initially fed by sphenopalatine artery, a branch of internal maxillary artery. In addition, the more advanced masses can be supplied by other branches of the external carotid artery such as the ascending pharyngeal artery, as well as some branches of the internal carotid artery and the vertebral artery. Bilateral examination of the feeding vessels gives better picture of the local blood supply and can be helpful in planning selective tumour embolization. [28]. When routinely performed 24-72 h before surgery, angiography refines the JAF vascularization and allows to determine more precisely the vessels that should be embolized to reduce bleeding during operation; to assess the outcome of performed embolization, if any; and to consider the way of intraoperative vascular control [29-33]. It has been reported a 30-40% reduction of intraoperative hemorrhage after preoperative selective embolization of involved arteries [18].

4. Treatment modalities, rate of recurrence and long-term prognosis

Surgical removal with preoperative tumour embolization to decrease intraoperative bleeding is the cornerstone of JNA treatment. Additional treatment modalities for residual and recurrent JNA such as radiotherapy, hormone therapy (flutamide), cryotherapy, electrocoagulation and chemotherapy have also been described, but most of them are not routinely used and their importance for the prognosis of JNA still remains discussable [17,34-39].

The most commonly applied surgical techniques are transpalatal, transmaxillar (lateral rhinotomy or midfacial degloving), Le Fort I osteotomy, and infratemporal fossa approaches. Transnasal or intranasal endoscopic surgery has been recommended for low-stage tumors. For large and extensively growing masses, more importance has been given to transmaxillar approaches. Transcranial methods have thought to be suitable for advanced-stage tumours with intracranial extension. Combined intracranial and extracranial approach can be used in complicated cases [17,30]. Stereotactic radiotherapy (ie, Gamma Knife) has been described as reserved radiotherapy for intracranial disease or recurrent cases, because of a lower dose of radiation to surrounding tissues [12].

In recent studies, purely endoscopic, endoscopic-assisted and open surgical approaches to JNA have been shown to be comparable in their effectiveness for tumour removal regardless of stage. The authors of a systematic review of studies on 1042 patients have concluded on the significantly lower rate of recurrence/residual disease with purely endoscopic resection compared to both endoscopic-assisted and open surgical approaches [8]. Although, other studies have reported as crucial for the clinical outcome the appropriate selection of surgical approach, the vascular density of the neoplasm and the age of the patient. In a publication on endoscopic surgery applied to 46 patients with JNA, Nikolai et al. have suggested that the purely

endoscopic method may be useful even in cases of minimal intracranial involvement. However, the open surgery should be reserved for tumors with larger intracranial extension.

After years of research, still there is no universal consensus on the most successful surgical method; the therapeutic choice depends on the individual pattern, tumor behaviour and surgeon experience [36-41]. Recently, researches have focused on the recurrence rate as an important measure of success in JNA treatment. In analysis of 60 recurrences, Mishra et al. have found an overall recurrence rate of 17.59%; the majority of cases have undergone open transpalatal approaches without embolization [42].

Recently, Yi et al (2013) have described a new staging system based on the management of JNA, with recommendations on the choice of surgical methods according to the localization and spread of the tumour [43].

The involvement of pterygoid fossa with intracranial extension, the feeding from the internal carotid artery, the young age of the patient, and a residual tumour have been considered as the major risk factors in long-term prognosis of JNA [30].

5. Anaesthesia

Regardless of the surgical method chosen for the treatment of nasopharyngeal angiofibroma, no doubt is there that anaesthesia represents an important and unalterable part of its treatment. In general, the requirements to the anaesthesiologists are reduced to ensuring of three consecutive stages in curing this type of patients: preoperative, intraoperative and postoperative period [44].

1) Preoperative period

Juvenile nasopharyngeal angiofibroma is a disease that needs a serious preoperative anaesthesiological preparation not only because of the nature of the pathology itself but because of the peculiarities associated with the surgical intervention too. Determination of the anaesthesiological risk and correction of existing preoperatively established anaemic syndrome by means of red cells concentrate or other organic products have an obligatory character.

On the other hand, consultations with professionals and practitioners should not be disregarded at this stage of the treatment of patients. Consultations aim at reducing to minimum of all possible complications, especially if a concomitant pathology is there in such cases.

2) Intraoperative period

This type of operations is associated with significant blood loss which necessitates two intravenous ways to be ensured before any kind of anaesthesia. A placement of central venous catheter is preferred which makes possible the measurement of central venous pressure and mean arterial pressure.

The standard monitoring control should include:

- ECG;
- SpO₂;

- Non-invasive blood pressure;
- ETCO₂;
- Nasopharyngeal temperature control.

According to many authors the frequency of mortality in these cases is in correlation with the blood loss. Therefore, the usage of anaesthetic and surgical techniques is necessary for its decrease [45], [46].

The most commonly used techniques are as follows:

- Artificially induced hypothermia; [44]
- Embolization of tumour; [47], [48]
- The position of the patient on the operating table to be in reverse Trendelenburg posture as venous return reduces in such a way. This in turn reduces preload as well as heart rate and systolic blood pressure;
- Control of fluid therapy

3) Postoperative Period

In surgical operations connected with the removal of the juvenile nasopharyngeal angiofibroma, extubation of patients in the operating room is not preferable. The best thing is these patients to be transferred to ICU where the treatment can continue with appropriate artificial pulmonary ventilation within first 24 hours.

The application of IPPV (Intermittent positive pressure ventilation) is a good decision.

Mechanical ventilation reverses intrathoracic pressure system, modifies venous return and decreases cardiac output.

Ensuring of adequate control over oxygenation of the peripheral tissues is necessary.

Using of CPAP can also decrease the blood loss by affecting cardiac output and systemic vascular resistance [49].

According to Michaelson A., another method is maintaining normothermia during anaesthesia, which contributes to a large extend the operative blood loss to be reduced.

The objective of this article is the most common clinical manifestations to be described as well as diagnostic and therapeutic methods of treatment and anaesthesia used, on the bases of the literature search for juvenile nasopharyngeal angiofibroma.

6. Conclusion

Juvenile nasopharyngeal angiofibroma is a rare disease and given to its location and its ability to spread in adjacent tissues, it has to be removed surgically.

Good knowledge of such pathology, properly performed preoperative preparation, surgery and anaesthesia give the opportunity angiofibroma to be removed safely.

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