Juvenile nasopharyngeal angiofibroma with intracranial extension—diagnosis and treatment

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B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:
Introduction: This retrospective study analyzes radiological findings, therapeutic management and outcomes of patients with intracranial extension of JNA. The routes of intracranial spread, incidence of intracranial disease and influence on therapeutic approach are discussed.

Material and methods: An evaluation on the records of 62 patients with JNA was performed and 10 patients with intracranial tumors were included in the study. All patients were males aged 10 to 19 years.

Results: According to Andrews’ classification 8 patients presented with stage IIIb, 1 patient stage IVa and another patient stage IVb tumor. Intracranial invasion was extradural in 8 cases and intradural in 2 patient. Surgery was performed in 9 cases and the most common was combined approach: infratemporal fossa and sublabial transantral. One patient was referred for radiotherapy. Follow-up ranged from 8 to 26 years. There was extracranial recurrence in 2 (22%) of 9 operated patients.

Conclusions: The superior orbital fissure is the most frequent route of intracranial spread in patients with extensive involvement of the infratemporal fossa. Due to high risk of recurrence and potential serious complications advanced cases of JNA should be managed by experienced multidisciplinary team, preferably in tertiary referral centers, with an access to modern diagnostic and therapeutic modalities.

KEYWORDS:
computed tomography, intracranial invasion, juvenile nasopharyngeal angiofibroma, magnetic resonance imaging

ABBREVIATIONS
CT – computed tomography
JNA – juvenile nasopharyngeal angiofibroma
MRI – magnetic resonance imaging

INTRODUCTION

JNAs are uncommon, histologically benign tumors occurring predominantly in adolescent males. They account for 0.05% of all head and neck tumors [1]. This highly vascular neoplasm has a propensity to erode bone and invade surrounding anatomical spaces [2]. In the literature, there are few reports of angiofibromas located outside the nasopharynx [3, 4]. The choice of optimal treatment modality and best surgical approach requires precise knowledge of tumor size and extensions, especially intracranial invasion.

The clinical presentation of the patient with JNA includes prolonged nasal obstruction and recurrent epistaxis [5, 6]. Although intracranial involvement may be suspected in patients with ipsilateral facial swelling, proptosis, extracocular muscle paresis, decreased visual acuity, it may be present without any additional clinical symptoms [1, 6]. Therefore, the diagnosis of intracranial disease is based on radiological imaging, and knowledge of routes of intracranial spread is crucial for correct preoperative identification of such extensions.

In this article we present radiological findings in angiofibromas invading the cranial cavity, based on experience in management of this rare tumor over 40-year period. Routes of intracranial spread, the incidence of intracranial disease, evaluation of its stage and influence on therapeutic approach and results of treatment are discussed.

MATERIAL AND METHODS

Retrospective evaluation of clinical data of 62 patients diagnosed at our institution for histopathologically verified JNA during the 43-year period between 1975 and 2018 was performed. Ten patients with intracranially extending tumors, treated 1992–2010 were included in the study. Operative records, imaging results and clinical histories were reviewed and details on the patients’ age, sex, presenting symptoms, tumor extension, preoperative embolization, treatment modality and recurrence rate were collected.
In all patients contrast-enhanced multiplanar MRI and axial CT scans were performed.

All tumors were staged according to Andrews classification [7] (Tab. I.). The study was approved by the institutional ethical committee. One patient with extensive intracranial tumor was referred for external beam radiotherapy. Surgery was performed in 9 patients and several types of approaches were used (Tab. II.). Eight patients had one stage surgery performed by otolaryngologists. In one case neurosurgeon took part during second-stage intracranial dissection. For large middle fossa extensions an infratemporal fossa approach was used combined with a sublabial transantral approach. The main steps of the infratemporal fossa approach were the following:

- inferior displacement of the zygomatic arch and elevation of the temporalis muscle with the coronoid process of the mandible;
- removing the bone of the base of the middle cranial fossa till the intracranial extension;
- elevation of dura over the intracranial part of the tumor.

**RESULTS**

The clinical data of patients included in the study are listed in Tab. II. In all cases middle cranial fossa was involved. In 4 patients large tumor in the infratemporal fossa spread superiorly via superior orbital fissure, which resulted in intracranial extension in proximity of the cavernous sinus (Fig. 1.). In 2 patients with advanced invasion of the sphenoid sinus tumor eroded its lateral wall and spread intracranially medially to the cavernous sinus. In one case deep erosion of the pterygoid base and greater wing of the sphenoid occurred, with tumor invasion laterally to the cavernous sinus (Fig. 2.). In 3 patients extensive erosion of the roof of the infratemporal fossa and sphenoid sinus was observed with main intracranial tumor mass laterally to the cavernous sinus. Additionally, in one case tumor occupied the ethmoid sinus and eroded the base of the anterior cranial fossa, without its invasion. Intracranial invasion was extradural in 8 cases and transdural in 2 patients. In 9 operated patients there was no surgery-related mortality nor serious complications. During surgery in one patient bleeding from the cavernous sinus occurred and was successfully controlled with a Tachocomb sheet. Postoperative complications included temporary (1 week) palsy of the VI cranial nerve in 1 case. Follow-up ranged from 8 to 26 years. Extracranial residual tumors were observed within a year after surgery in 2 (22%) of 9 operated patients and it was easily removed via sublabial approach. One patient after 2 surgical procedures in another institution presented in 1999 with recurrent advanced intracranial extension. He received 3000 Gy external beam radiotherapy, as his parents did not agree for surgery. On subsequent follow-up the tumor in this patient gradually involuted completely and was not visible on follow up MRI 3 years after radiotherapy. No side effects nor symptoms of recurrence were seen during 20 years follow up.

**DISCUSSION**

**Tumor spread**

JNAs develop at the posterolateral wall of the nasal cavity. Anatomically, the site of origin is thought to be the area of the pterygoid canal and the sphenopalatine foramen [6, 8]. From this location tumor grows easily medially to the nasopharynx, forward to the nasal cavity, upward to the sphenoid sinus and laterally to the pterygopalatine fossa. Approximately 20% to 40% of patients have skull base invasion at the time of diagnosis [1, 6, 9]. In our study 10 of all 62 (16%) patients with JNA diagnosed at our institution presented with intracranial extension. According to the literature several routes of intracranial invasion can be identified:

- from the pterygo-palatine fossa via the superior orbital fissure into parasellar compartment of the middle cranial fossa;
- from the sphenoid sinus by direct erosion of its superior wall into pituitary fossa and/or medially to the cavernous sinus;
- from the pterygoid canal deep invasion of the cancellous bone of the pterygoid base and greater wing of the sphenoid may result in involvement of the middle cranial fossa laterally to the cavernous sinus;
from the infratemporal fossa through direct erosion of the floor of the middle cranial fossa and/or natural channels (foramen rotundum, foramen ovale), which perforate the middle fossa; 5) from the ethmoid sinus by erosion of the floor of the anterior cranial fossa [2].

Despite the limited number of patients, all above mentioned routes of spread were observed in our study. Our results indicate, that most frequently the tumor spreads along the first way, via superior orbital fissure, which results in parasellar extension in proximity of the cavernous sinus. This growth pattern is often associated with invasion of the pterygo-palatine and infratemporal fossa. Tumor growth through soft tissue channels is relatively unrestricted in comparison to invasion of anatomical spaces confined within bony walls. It may occur in an early stage of the disease, as natural fissures form a preferable way for tumor spread. Extension to the anterior portion of the cranium is infrequent. It occurs in advanced tumors with massive involvement of the sphenoid and ethmoid sinuses, and was reported by Elsharkawy et al. [10] in 1/23 patients and by Margalit et al. [9] in 3/21 patients. In our study 1 patient had erosion of the floor of the anterior cranial fossa, without significant intracranial extension.

Tumor imaging

Clinical findings typical for JNA is a nasopharyngeal mass in a young male with the history of epistaxis. However, the size of the tumor in the nasopharynx does not always represent the size of the whole tumor, as extensive growth may be clinically silent. CT and MRI studies are essential part of evaluation of the disease and allow precise preoperative staging of the tumor. They are both helpful to confirm the diagnosis and visualize the exact extension of the lesion. CT better delineates bony details of the skull base involved with the tumor, including bony erosion, widening of natural foramina and fissures, invasion into cancellous bone of the greater wing of the sphenoid. MRI has the advantage of showing soft tissue characteristics and is superior in determining intraorbital and intracranial extensions. It is crucial for assessment of tumor relation to important intracranial structures, like the internal carotid artery, cavernous sinus, pituitary gland, as well dural involvement. The extent of cellular invasion of the sphenoid diploe may also be reliably assessed on MR images with use of fat saturation techniques and contrast enhancement.

Intracranial extension of JNA usually displaces the dura or may become to some degree adherent to it. However, it is not always possible to determine radiologically the relationship of the tumor to the dural plane. The radiological criteria of transdural growth, like the lack of interface between the tumor and neurovascular structures or encasement of the internal carotid artery, may lead to misinterpretation and overstaging of tumors [11, 12]. Danesi et al. [13] reported that 50% of patients with preoperative radiological stage IV according to Fisch classification were classified as IIIB on the basis of surgical interpretation. Partial or total encasement of the internal carotid artery on MR images does not determine cavernous sinus involvement and a dural plane is usually present at operation [11]. In our study cavernous sinus involvement occurred in 1 patient. Although in the literature there are a few reports of angiofibromas with intradural extension, in a vast majority of advanced cases tumors remain extradural and brain infiltration has never been observed [2, 6]. Single cases of dural penetration have been reported by Roche et al. [6] and Danesi et al. [11]. Angiography is used to assess tumor vascular composition and blood supply, and enables preoperative embolization. Typically, major arterial supply to this hypervascular tumor is the internal maxillary artery. Branches of the internal carotid artery may be additional feeders in advanced tumors. However, it is not a reliable sign of intracranial invasion. Involvement of the sphenoid sinus may be associated with blood supply from the branches of the cavernous portion of the ICA and invasion of the orbit or ethmoid sinus may result in arterial supply from ethmoid arteries. The presence of cerebral parenchymal vessels with collateral feeding branches to the tumor may be a sign of dural penetration [11].

Tumor staging

Several staging systems relying on CT and MRI findings have been introduced for JNAs (Tab. I.). These classifications depend on tumor involvement of particular anatomical compartments

<table>
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<th>Tab. II. Clinical data of the patients included in the study.</th>
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<td><strong>NUMBER OF PATIENTS</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td><strong>Duration of symptoms (months)</strong></td>
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<tr>
<td><strong>Imaging</strong></td>
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<td><strong>Tumor stage</strong></td>
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<tr>
<td><strong>Radiotherapy</strong></td>
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<td><strong>Surgery – approach</strong></td>
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<td><strong>Follow-up (years)</strong></td>
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<td><strong>Recurrence</strong></td>
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<td><strong>Tumor stage</strong></td>
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<td><strong>Time (months)</strong></td>
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and reflect the risk of postoperative residual/recurrent disease associated with particular locations. Therefore, they are helpful in selection of surgical approach. The most prevalent staging systems seem to be those of Fisch’s, Andrews’ and Radkowski’s. The classification proposed by Fish [15] reflects the growth pattern of JNAs, with intracranial tumors included in stage III and IV. The staging system suggested by Andrews et al. [7] is a modified system introduced by Fish and it more precisely defines intracranial spread, distinguishing extradural parasellar involvement (IIb), intradural (IVA) and intradural with infiltration of the cavernous sinus, pituitary fossa or optic chiasm (IVb). Radkowski et al. [16] proposed a staging system, which highlighted the importance of tumor extension posterior to the pterygoid plates (IIc) and distinction between minimal and extensive intracranial involvement. Another recently proposed staging system by Snyderman et al. [17] is focused on residual vascularity from the intracranial circulation following embolization and routes of intracranial invasion, subdivided into medial or lateral to the cavernous and paracervical segments of the ICA. This endoscopic classification reflects potential morbidity and risk of residual disease associated with these two routes of intracranial growth.

**Treatment strategy**

It is generally accepted that the treatment of choice for extracranial angiofibroma is surgical excision [1, 10, 18, 19]. Endoscopic approaches have been introduced into angiofibroma surgery offering many advantages over traditional approaches, including no external incisions, improved recurrence rates, lower morbidity and lower rate of complications [20, 21]. Exclusively transnasal resection has some limitations in tumors with intracranial and lateral infratemporal fossa extensions [18]. However, accordingly do some authors even advanced intracranial JNAs may be successfully managed using endoscopic techniques, though it sometimes requires several procedures [22]. Among many modalities used for treatment of tumors with intracranial extension surgical extirpation and radiotherapy appear to be effective [1, 5, 10, 23, 24]. Best treatment option for intracranial JNA remains controversial, with proponents of surgery indicating the risk of serious late sequelae of irradiation, and advocates of radiotherapy emphasizing high recurrence rates and postoperative morbidity associated with extensive craniofacial resection.

A tumor with intracranial extension is difficult to remove, especially if the aim of surgery is complete resection [6]. The choice of surgical approach should depend on surgeon’s preference and the route of intracranial spread, including medial or lateral tumor location relative to the cavernous and paracervical segments of the ICA [17]. According to medial or lateral route of spread, anterior or lateral combined external approach should be planned [11, 13]. Anterior approaches, including transmaxillary via midfacial degloving and lateral rhinotomy, allow exposure of tumors invade the pterygopalatine and infratemporal fossa, paranasal sinuses and medial part of the cavernous sinus [24]. The infratemporal approaches offer wide exposure of the infratemporal fossa and are useful in tumors with large lateral extension and/or intracranial invasion laterally to the cavernous sinus [6, 7, 15, 18].

Controversies exist regarding the appropriate management of tumors with extensive involvement of the skull base, abundant blood supply from the ICA, encasement of this artery and/or invasion of the cavernous sinus. Potential complications associated with surgery in proximity of the cavernous sinus include uncontrollable hemorrhage, cranial nerve injury, persistent cerebrospinal fluid leakage, high incidence of residual tumor due to the complex local anatomy [9, 10]. However, invasion of the cavernous sinus is infrequent [11]. It was observed in 4 of 21 cases reported by Margalit et al. [9] and in 3 of 17 cases reported by Tewfik et
al. [21]. In tumors with large intracranial extension some authors advocate one-stage combined intracranial-extracranial approach, which allows good tumor control, but is associated with the risk and morbidity of both methods [6]. Proponents of staged procedure perform incomplete removal of the tumor by extracranial approach, leaving residual intracranial tumor for observation, as tumor remnants may remain stable or spontaneously involute in prolonged follow-up [5, 6, 18]. Some authors remove large residual intracranial lesions (stage IVa tumors) with second-stage neurosurgical operation [18]. Other options proposed in case of residual intracranial tumor is adjunctive radiation therapy or gamma-knife radiosurgery, especially in critical areas like cavernous sinus and optic chiasm, or additional surgery [6, 18, 26]. One patient with tumor invading cavernous sinus in this series was referred for external beam radiotherapy. Due to potential risk of late complications, radiotherapy is mainly reserved for residual/recurrent tumors in anatomically difficult areas or surgically unapproachable lesions [5]. Reported local control rates for radiation therapy as the definitive treatment of Chandler stage III or IV angiofibroma achieved 85% to 91% [23, 27]. However, serious complications of this method have been reported, including secondary head and neck malignancies, cataract, hypophyseal insufficiency, osteoradionecrosis or neuropathy [6, 9]. In our study radiotherapy was effective and no treatment-related complications were observed.

Follow-up and recurrent/residual disease

Despite benign nature of this tumor, recurrence of JNA has been well reported in the literature [11, 20]. However, in case of benign lesion as JNA, tumor recurrence often may represent residual disease following incomplete removal. Residual and recurrence rates of JNA with intracranial extension vary from 18% to 50%, compared to total recurrence rate 15%–28% [7, 11, 13, 15, 21]. Recurrence rate in our study was 22%. Risk factors associated with higher recurrence rate are intracranial extension, invasion of the sphenoid sinus, the base of the sphenoid process, sphenoid sinus invasion and clivus [7, 10, 21]. Rowan et al. [24] highlight the importance of both route of skull base extension and tumor vascularity as two crucial tumor attributes which influence clinical prognosis. Most of recurrent tumors occur within 1 year after surgery [20]. In a recent study of Rowan et al. [25] 12 (32%) patients had postoperative residual disease and all of them had preoperative skull base involvement. Progression of residual disease occurred approximately 7–5 months postoperatively. In our study 2 (22%) patients residual tumor was found 6–12 months after surgery.

MR imaging with fat saturation techniques and tumor post-contrast enhancement is thought to be the first choice modality for radiological follow-up. To visualize bony changes CT scanning may be performed 3 months after surgery [2]. Postoperative radiological surveillance includes first examination 6 months after surgery and annually for 2–3 years [26]. Postoperative imaging at 6-month intervals are recommended in younger patients who may be more likely to need further intervention for residual disease [25].

CONCLUSIONS

The superior orbital fissure is the most frequent route of intracranial spread in patients with extensive involvement of the infratemporal fossa. Due to high risk of recurrence and potential serious complications advanced cases of JNA should be managed by experienced multidisciplinary team, preferably in tertiary referral centers, with an access to modern diagnostic and therapeutic modalities.

REFERENCES

The authors declare that they have no competing interests.

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