ESTHESIONEUROBLASTOMAS WITH INTRACRANIAL EXTENSION

PROLIFERATIVE POTENTIAL AND MANAGEMENT

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SUMMARY - A total of 15 patients with esthesioneuroblastomas were treated between 1978 and 1992 at the Neurosurgery Department, Nordstadt Hospital, Hannover. In 9 cases, the tumors invaded the anterior cranial fossa. One patient died before any surgical intervention. Eight tumors were operated by a combined paranasal and subfrontal approach. Gross total tumor removal was achieved in all cases. Apart from anosmia, the only postoperative complication was transient mental changes in one case. Immunohistochemical analyses with MIB 1 monoclonal antibodies, directed against recombinant parts of Ki-67 antigen, were performed to estimate the proliferative potential of the esthesioneuroblastomas. Most of the tumors showed high proliferating cell indexes, which ranged from 3 to 42% (mean, 16%). The proliferating cell index with MIB 1 showed a correlation with postoperative outcome, although this was not statistically significant. Esthesioneuroblastomas can be totally removed surgically. The proliferating cell index may reflect histologically the biological behavior of tumor. Long-term follow-up is mandatory, and immunohistochemical studies may be of help in predicting outcome.

KEY WORDS: anterior cranial base, MIB 1, neuroblastoma, olfactory nerve, paranasal sinuses, radiotherapy.

Esthesioneuroblastomas com extensão intracraniana: análise do potencial proliferativo e conduta

RESUMO - O índice proliferativo celular tumoral de 8 casos cirúrgicos de estesioneuroblastomas com extensão intracraniana (9 com extensão intracraniana em um total de 15, coletados de 1978 a 1992 no Hospital Nordstadt de Hannover, Alemanha) foi avaliado através do anticorpo monoclonal MIB-1, notando -se uma correlação prognóstica. A maioria dos tumores revelou índice proliferativo alto (3% a 42%, média de 16%) e a classificação histopatológica de Hyam foi utilizada. A ressecção foi radical em 100% dos casos e o acesso cirúrgico combinado (paranasal e subfrontal) o preconizado. Os autores apresentam revisão da literatura discutindo a sua casuística.

PALAVRAS-CHAVE: base craniana anterior, MIB 1, neuroblastoma, nervo olfatório, seios paranasais, radioterapia.

Esthesioneuroblastomas (olfactory neuroblastomas) are uncommon neoplasms probably derived from the neuroepithelial sensory cells of the olfactory mucosa1,2. They arise in the nasal vault, near the ethmoid sinus, usually presenting as masses in the nasal cavity1,3. The most common findings are unilateral nasal obstruction and epistaxis. These tumors frequently invade the paranasal sinuses, the nasopharynx, the palate, the orbit, the base of the cranium, and even the brain4,5. In

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Marcos Tatagiba, MD - Neurochirurgische Klinik, Krankenhaus Nordstadt - Haltenhoffstr. 41 - 30167 Hannover, Germany. Fax 49-511-7638606 // Dr.Paulo Henrique P. Aguiar - Rua Raul Pompéia 1050 apto 111 - 05025-010 São Paulo SP - Brasil.
approximately 20 to 25% of cases they produce neurological symptoms due to intracranial invasion\(^5\). Esthesioneuroblastomas are often slow growing tumors that do demonstrate a response to radiation therapy, but often have a tendency to recur\(^1,6\). Metastases into the regional lymph nodes and to the lung occur in one-fifth of all patients\(^5,7\). The staging system of classification into three groups suggested by Kadish et al. (depending on the location of the tumor) and modified by Morita et al. has been of prognostic value\(^8,10\). Prognosis depends on the histological maturity and the degree of malignancy. However, a systematic evaluation of the proliferation activity of esthesioneuroblastomas using immunohistochemical techniques has not been described so far. The monoclonal antibody MIB 1 has the same sensitivity and specificity of Ki-67 with the major advantage of its utility in paraffin sections preserved for years\(^11\).

We report on our experience in dealing with 8 cases of esthesioneuroblastomas presenting with intracranial extension. The diagnosis of esthesioneuroblastoma was made based on histopathological features and radiological localization of tumor. These cases were operated on via a combined craniofacial approach. The paraffin sections of 7 esthesioneuroblastomas were used for immunohistochemical tests that evaluate the proliferation activity of tumor cells. An attempt has been made to correlate the biological behavior of these tumors with the immunohistochemical studies.

**MATERIAL AND METHODS**

Between 1978 and 1992, 15 patients with olfactory neuroblastomas were treated in the Neurosurgery Department of Nordstadt Hospital. In 9 cases, the tumors invaded the anterior cranial fossa (Fig 1). One patient with a very large intracranial tumor extension died before any surgical intervention was attempted. Eight patients underwent tumor removal by a combined transfacial-subfrontal approach. These 8 cases constitute the object of this study. All patients underwent plain X-rays, nonenhanced and enhanced computed tomography (CT) with soft tissue and bone algorithms (Fig 2). Cerebral angiography was also performed in all cases in order to study the tumor vascularity, and the involvement of the major vessels. Embolization was not carried out in these

![Fig. 1. Preoperative sagittal (left) and coronal (right) Gadolinum-enhanced MRI slices of the esthesioneuroblastoma of Case 8 showing the dorsal part of the tumor involving the ethmoid sinus, sphenoid sinus, and carotid artery. The tumor shows an isointense and a hyperintense portion with suprasellar extension.](image-url)
patients. In 3 most recent cases, magnetic resonance imaging (MRI) was also obtained.

Surgical approach

The surgical procedures usually involved first a paranasal approach and then a intradural subfrontal approach (Fig 3). For the extracranial tumor removal, a paranasal incision was performed extending from the medial third of the eyebrow to the base of the ala nasi. The maxillary process of the frontal bone, and the frontal process of the maxilla were exposed. After removal of bone, the tumor was exposed and was removed in piecemeal. For the intracranial part, the anterior skull base was exposed intradurally through a bifrontal craniotomy and later the tumor was removed with help of microscope and Cavitron Ultrasonic Surgical Aspirator (CUSA). For small tumors, the olfactory nerves were microsurgically dissected and resected. Since the bone resection usually involved the cribiform plate, the ethmoid roofs, and a portion of the planum sphenoidale, the skull base would be reconstructed in two-layers fashion consisting of a dural flap and a galeal pericranial flap. In case of large cranial defect, a methylmethacrylate plate was molded to the shape of the defect and placed between the dural and the galeal flaps.

Histopathological studies

Besides hematoxilin and eosin (H&E), electron microscopy or immunohistochemistry studies (chromogranin, neuron specific enolase, S100, vimentin, and keratin) were performed in all cases. The following histological factors at H&E studies were considered: lobular architecture, mitosis,

Table 1. Hyams' grading system for esthesioneuroblastomas.

<table>
<thead>
<tr>
<th>Histopathological factors</th>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lobular architecture</td>
<td>+</td>
</tr>
<tr>
<td>Mitosis</td>
<td>-</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>-</td>
</tr>
<tr>
<td>Rosettes</td>
<td>HW ±</td>
</tr>
<tr>
<td>Necrosis</td>
<td>-</td>
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HW. Homer-Wright; - absent; +, present; ++, prominent; +++ marked; ±, present or absent
nuclear pleomorphism, necrosis, and rosettes. Based on these factors, a tumor grade from 1 to 4 was established according to the Hyam's Grading System (Table 1).

**Immunohistological studies with MIB 1**

Formalin fixed paraffin sections of 7 consecutive esthesioneuroblastomas were available for immunohistochemical studies. The immunohistochemical staining was performed as described by Cattoretti et al. In summary, the paraffin sections were dewaxed in xylene & acetone and rehydrated. They were then processed in a microwave with 10 mM citric acid buffered with 2M NaOH to pH 6. The sections were treated first with normal serum (rabbit against mouse) in 1:20 dilution, followed by primary antibody MIB 1 (Dianova, Hannover, Germany) in 1:10 dilution. These were stained with APAAP immunostaining technique. The immunostaining was controlled by histologic sections of tonsilla-tissue submitted to the same reactions.

The cell was classified as positive when either the entire nucleus or a portion of the nucleus was stained (Fig 4). The number of positive and negative cells were scored in a total of 500 cells per area (total of 6 areas) or 3000 cells per section. The labelling index (LI) or growth fraction was defined as the proportion of positive cells in relation to the total of 3000 cells evaluated (excluding labelled endothelial cells and lymphocytes). A total of 6 readings were performed. The average LI (LI mean) was obtained by adding all 6 readings and dividing by 6. The maximal LI (LI max) was the highest of the 6 readings.

**Follow-up evaluation**

Postoperatively, besides clinical evaluation all patients underwent endonasal endoscopy and enhanced CT scans at the time of discharge, in order to determine the completeness of the tumor removal. After discharge, clinical, endoscopic, and radiological (CT) follow up was regularly carried out to detect or to exclude tumor recurrence.

Postoperative treatment consisted of radiotherapy, either immediately after the first surgery or later on after detection and removal of tumor recurrence.

**RESULTS**

The esthesioneuroblastomas accounted for 0.3% of all 2800 intracranial tumors, which were operated upon in our Department in the same period. Six patients were women and 2 were men. The average age was 50 years, ranging from 29 to 70 years.

The time interval between beginning of symptoms and diagnosis of the disease varied considerably, ranging from 4 months to 10 years (mean 3 years). Most common symptoms and signs were sensation of nasal obstruction (63%), decrease of smell sensation (50%), epistaxis (38%), and visual loss (13%). One patient with a large intracranial involvement had signs of frontal lobe dysfunction.

In 7 cases, previous transnasal biopsy and extracranial ENT intervention indicated the diagnosis of esthesioneuroblastoma, which led to planning the definitive neurootological procedure. Craniofacial intervention was performed with “total” tumor resection in all cases. Postoperatively, 5 patients received radiotherapy which dosis ranged from 45 to 66 Gy.
Clinical, endoscopic and radiological follow up examinations showed that one patient has been free of disease 5-1/2 years after combined surgery and radiotherapy (Case 5). One patient has been free of tumor 4-1/2 years after surgery (Case 6). One patient presented with lymph node metastasis at the neck 7 years after the surgery, but she had no local recurrence of tumor (Case 1). One patient

Fig 4. Above: MIB 1 immunohistochemical photomicrographs of Hyams grade 3 tumor, displaying strong immunoreactivity for MIB 1 with numerous red-stained nuclei (MIB 1, x 625). Below: MIB 1 immunohistochemical photomicrographs of grade 2 tumor, displaying slight immunoreactivity for MIB 1 with few red-stained nuclei (MIB 1, x 625).
Table 2. Clinical presentation, therapy and follow up in 8 cases of esthesioneuroblastoma with invasion of the anterior cranial fossa.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex &amp; Age</th>
<th>Symptoms duration</th>
<th>Signs &amp; symptoms</th>
<th>Prior treatment</th>
<th>Tumor removal</th>
<th>Radio therapy</th>
<th>Follow up (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 50</td>
<td>5 years</td>
<td>ONR, anosmia</td>
<td>Biopsy</td>
<td>Total</td>
<td>45 Gy</td>
<td>Neck lymph node metastasis but no local recurrence (7 years)</td>
</tr>
<tr>
<td>2</td>
<td>M 70</td>
<td>2 years</td>
<td>Epistaxis, hyposmia</td>
<td>Biopsy</td>
<td>Total</td>
<td>no</td>
<td>Died of cardiovascular disease; autopsy: local recurrence and lymph node metastasis (18 months)</td>
</tr>
<tr>
<td>3</td>
<td>F 29</td>
<td>4 months</td>
<td>ONR epistaxis</td>
<td>Biopsy</td>
<td>Total</td>
<td>no</td>
<td>Recurrence (5 years)</td>
</tr>
<tr>
<td>4</td>
<td>F 47</td>
<td>2 years</td>
<td>Anosmia</td>
<td>ENT surgery</td>
<td>Total</td>
<td>45 Gy</td>
<td>Recurrence (6 months)</td>
</tr>
<tr>
<td>5</td>
<td>F 52</td>
<td>1 year</td>
<td>Epistaxis</td>
<td>Biopsy + radiation</td>
<td>Total</td>
<td>66 Gy</td>
<td>No recurrence (5 1/2 years)</td>
</tr>
<tr>
<td>6</td>
<td>F 54</td>
<td>10 years</td>
<td>ONR anosmia</td>
<td>Biopsy</td>
<td>Total</td>
<td>No</td>
<td>No recurrence (4 1/2 years)</td>
</tr>
<tr>
<td>7</td>
<td>M 55</td>
<td>3 years</td>
<td>ONR visual deficit</td>
<td>Biopsy</td>
<td>Total</td>
<td>45 Gy</td>
<td>Spinal metastasis (18 months)</td>
</tr>
<tr>
<td>8</td>
<td>M 61</td>
<td>4 years</td>
<td>ONR</td>
<td>No</td>
<td>Total</td>
<td>50 Gy</td>
<td>No recurrence (4 1/2 years)</td>
</tr>
</tbody>
</table>

ONR, obstruction of nasal respiration; ENT surgery transethmoidal approach by ear, nose and throat surgeon

Table 3. Histopathological studies in 8 cases of esthesioneuroblastomas

<table>
<thead>
<tr>
<th>Case No</th>
<th>Electron microscopy</th>
<th>Immunohistochemistry</th>
<th>Hyams'grade</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>NSE</td>
<td>Chromogranin</td>
</tr>
<tr>
<td>1</td>
<td>yes</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>yes</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>yes</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>yes</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>n.d.</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7</td>
<td>n.d.</td>
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<tr>
<td>8</td>
<td>n.d.</td>
<td>+</td>
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</table>

NSE, neuron specific enolase; n.d., not done; +, positive; -, negative.
developed paraplegia due to spinal metastasis of the esthesioneuroblastoma at 1st thoracic vertebral
level 18 months after surgery (Case 7) without local recurrence of tumor. One patient had local
recurrence 6 months after tumor removal & radiotherapy (Case 4). One patient died of cardiovascular
disease 18 months after tumor removal; autopsy demonstrated local tumor recurrence and lymph
node metastasis (Case 2). One patient had local recurrence 5 years after surgery (Case 3) (Table 2).

Histopathological findings

The histopathological findings are summarized at Table 3. The proliferation activity of tumor
cells at MIB 1 was considered high, ranging from 3% to 42% (average, 16%). Seven of the 8 tumors
had Hyams' Grade 2; the only Grade 3 tumor had the highest proliferation activity of 42% (Fig 4).

COMMENTS

Esthesioneuroblastoma, which is also called by various names, namely olfactory neuroblastoma,
olfactory neural neoplasm, olfactory esthesioneuroblastoma, olfactory esthesioneuroma, olfactory
esthesioneuroepithelioma, esthesioneurocytoma, and neuroendocrine carcinoma, was first described
by Berger and Luc in 1924 in French literature and in 1951 by Schall and Linback in American
literature. These tumors are rare and the incidence has been estimated to be between 2-3% of all
malignant intranasal neoplasm from olfactory mucosa in close proximity to the cribiform plate.

Clinical aspects

Esthesioneuroblastomas is a disease of young adults or middle-aged people with two peaks,
one at 10-20 years and another at 50-60 years. In our series, the youngest was 29 and oldest was 70
years with female predominance (M:F, 3:5). Some authors have noted male predominance, but
thorough review of literature did not reveal any difference. Reported duration of symptoms ranged
from 1 month to 10 years. The patients frequently present with nasal obstruction, epistaxis, and
lacrimation. Intracranial symptoms include anosmia, increased intracranial pressure, frontal
syndrome, diplopia, sudden blindness, psychomotor seizures, optic atrophy, proptosis, retroorbital
pain, and decreased sensation on the face.

Radiological investigations

Radiological investigations in the past have included plain X-rays, tomography and
angiography. Currently, high resolution CT scan with bone windows and MRI are the investigation
of choice. These have revolutionized the surgical management of the disease. Plain X-rays reveal
soft tissue masses in the nasal and paranasal areas, mucosal thickening, opacification of sinuses
along with bone destruction. Occasionally calcification or hyperostosis may be seen. Angiography
is not mandatory but if performed it delineates a high vascularized mass in 59% of cases.

Thorough literature search revealed that CT scan with bone windows in 78% of patients
showed bony changes representing either erosion or molding with occasional tumor calcification.
Typically these tumors are isodense in nonenhanced CT scan.

MRI is the investigation of choice for demonstration of tumor and the involvement of
surrounding soft tissue. In T1 weighted images, the tumor is seen as hypointense becoming
hyperintense after intravenous Gadolinium administration. The ability to produce sagittal images
and the ability to see the submucosal spread of the tumor, vascularity and displacement of vessels
and visualization of dural involvement have made this investigation indispensable.

Spread of tumor

Esthesioneuroblastomas are locally invasive and have the tendency to spread submucosally
in the nose and paranasal sinuses, and with time they may invade the skull base, may become
intracranial, and by violating the meninges produce cerebral edema and increased intracranial pressure.
Involvement of the CNS in 20-30% of cases, orbital extrusion in 17%, distant metastases in 30%,
and lymph node involvement in 8 to 17% have been noted in literature. Distant metastases mainly invade bone, lungs, liver, mediastinum, spleen, adrenal glands.

Though these tumors histologically resemble lymphoma, undifferentiated carcinoma, plasmocytoma, Ewing's sarcoma, embryonal rhabdomyosarcoma, oat cell carcinoma, and melanomas, special staining methods, electron microscopy and immunohistochemistry usually distinguish these tumors from one another.

Biological behavior of these tumors is often difficult to predict due to the fact that there are no definite pathological features that would help prognosticate these tumors. Depending on the cell of origin, either sensory nerve cells or epithelial cells, these tumors are called olfactory neuroblastomas or olfactory neuroepitheliomas, respectively. There appears to be no exact correlation between histological variant and prognosis. Based on mitotic activity, lobular architecture, nuclear pleomorphism, rosettes and necrosis, Hyams et al. suggested four grades of malignancy. This grading system was found to be a significant prognostic factor in 49 cases studied retrospectively by Morita et al. Patients with grade 4 tumors had poorer prognosis than those with low grade tumors (grade 1-2). However, no significant difference in survival rate was found among patients with grade 1, 2, or 3 tumors. In our series, 7 tumors were classified as Hyams' grade 2, and one tumor as grade 3. This particular patient with grade 3 tumor had local recurrence 5 years after surgery.

In our study, cell proliferation with MIB 1 has been carefully evaluated from a prognosis point of view. This showed great differences among the cases, with the highest proliferation index (42%) in the grade 3 tumor. In our series, the MIB 1 ranged from 3% to 42%. The patient who had Hyams' grade 3 tumor had MIB 1 of 42% and this patient had tumor recurrence in 5 years. Another patient (Case 5) had Hyams' grade 2 tumor and MIB 1 of 3%; this particular patient had been tumor free for 5-1/2 years. Other patients, though had low levels of MIB 1 (Case 1 and 7) eventually developed distant metastases in the absence of local recurrence. Though no conclusion could be drawn from these observations because of the small number of patients, it is likely that a higher level of MIB 1 seems to correlate with higher grade of malignancy.

Immunohistochemical tests that determine the proliferation of cell index appear to be more sensitive to differentiate the esthesioneuroblastomas than a simple histological classification based on only hematoxylin and eosin studies as used in the Hyams' Classification System. Further MIB 1 studies with a larger number of cases are thus necessary to support this observation.

**Treatment**

There is a continuous debate on various modes of management of the esthesioneuroblastomas: primary radiotherapy, primary surgical therapy, or a combination of these two or chemotherapy. Since these tumors are slow growing with local invasion and high local recurrence rate, it is conceivable that the course of the disease can be changed by performing radical surgery. Review of literature suggests that combination of therapy is superior to single mode of treatment.

Currently the approach is multidisciplinary. In stage A and B, when the tumor is confined to nasal cavity and paranasal sinuses, surgical involvement is mandatory. Till recently, there seems to be little controversy as to the mode of management of stage A and B where surgery, radiotherapy and combined therapy have been met with good results, though Newbill et al. and Kadish et al. favoured primarily radiation as the mainstay of treatment. Incomplete tumor resection by extracranial surgery alone is directly related to high rate of recurrence which is not altered even when the patient received preoperatively radiotherapy. Biller et al. found that radiotherapy is not necessarily advantageous if adequate excision of tumor can be performed. Since the incidence of metastasis may be related to radiation, these authors reserve radiation for patients with incomplete tumor resection, postoperative recurrence, or nonsurgical cases.
Most of the authors agree that stage C needs to have craniofacial tumor resection. Doyle in 1971 was the first to perform craniofacial resection even in cases where there was no involvement of the anterior cranial fossa. Fahlbusch et al. preferred the transfronto-transbasal approach without transfacial operation in stage C tumors, achieving total resection of tumors.

Harrison and Biller et al. have advocated craniofacial resection even in stage A and B. Their results stated that radiotherapy followed by extracranial surgery alone had a local recurrence rate of 60% compared to craniofacial resection with 12% recurrence in stage A and B patients. Cantrell had better results with preoperative radiotherapy followed by craniofacial resections but Mack et al., and our previous experience indicate that craniofacial resection with or without radiotherapy made no difference in outcome.

We strongly believe adequate bifrontal craniotomy and resection of both olfactory bulbs along with dura covering the anterior skull base, ethmoidal roof and anterior part of planum sphenoidale, crista galli and repairing the cranial fossa floor in 3 layers, in association with lateral rhinotomy and en bloc resection of nasal tumor would give good surgical results.

Five year survival rate with esthesioneuroblastomas ranges from 18-71%. Survival of these patients depends on the size of the tumor, intracranial extension and lymphonode involvement. In patients with stage C disease, 5 years survival was 60%, and with stage A 100%.

Postoperatively, these patients need to be followed up by frequent CT scan or MRI, and if necessary, endonasal endoscopy. Any recurrence needs to be intervened surgically. Long term survival is likely if radical surgical resection is combined with the postoperative radiation. The role of chemotherapy seems promising, particularly in those cases with distant metastases.

CONCLUSIONS

It is difficult to prognosticate the esthesioneuroblastomas by the tumor location or histological grading alone. Immunohistochemistry, especially MIB 1 antibody studies may in future help or at least complement the existing factors to prognosticate these tumors. Radical surgical resection with postoperative radiation and in cases of distant metastases (stage C) adjuvant chemotherapy would give optimal results and a longer survival.

REFERENCES