Review

Neuronal and mixed neuronal glial tumors associated to epilepsy. A heterogeneous and related group of tumours

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Summary. The group of brain tumors with mature components encompasses several pathological entities including: the ganglioneuroma; the gangliocytoma; the ganglioglioma; the desmoplastic ganglioglioma; the neurocitoma and a group of glioneuronal hamartomatous tumorous lesions, such as meningoangiomatosis. The dysembryoplastic neuroepithelial tumor is characterized by the presence of multiple cortical nodules made up of small, oligo-like cells and a myxoid pattern rich in mucopolysaccharides. Mature neuronal cells are frequently detected throughout the tumor. Most of them are associated with microhamartias in the adjacent brain and pharmacoresistant epilepsy. The excellent prognosis of the majority of these tumors and the potential for malignant transformation of the glial component in the ganglioglioma are the two most remarkable findings. Histological signs of anaplasia and greater mitotic and proliferative activities are associated with local recurrences. Atypical neurocytomas occur only exceptionally. Treatment choices are surgical resectioning and, in those cases presenting greater proliferative activity and cytological atypia, postoperative radiotherapy may be recommended.

This paper reviews this heterogeneous group of neoplasms and hamartomatous lesions, pointing out presumable transitions among the different types of mixed neuronal and glial brain tumors. A single term of "mixed neuronal-glial tumors" is defended, distinguishing different subgroups of tumors, depending on the predominant cellular component.

Key words: Hamartias, Gangliogliomas, Glioneuronal, Epilepsy

Introduction

Brain tumors comprised of mature or immature neuronal cells and associated with a mixed neural and glial component are very rare, constituting roughly 1% to 3% of adult brain tumors (Wolf et al., 1993; Hakim et al., 1997), and about 10% of those occurring in children (Chintagumpala et al., 1996). This group encompasses the ganglioneuroma, the gangliocytoma, the ganglioglioma, the desmoplastic ganglioglioma, the ganglioneuroblastoma, the neurocytoma and dysembryoplastic neuroepithelial tumors, in addition to a series of lesions or tumors of a presumably hamartomatous nature. Other tumors that may be histogenetically related are the pleomorphic xanthoastrocytoma, which presents neuronal differentiation, and tumors associated with neurofibromatosis. They are mostly located at the supratentorial level, follow a benign course, and are associated with a long history of drug-resistant epilepsy (Fingarella-Branger et al., 1992; Armstrong, 1993; Daumas-Duport, 1993; Wolf et al., 1993, 1994; Chintangupala et al., 1996; Hakim et al., 1997). These lesions are often detected during the first decades of life, although they have been reported to occur at any age. The mean 5-year survival is over 80% in the majority of the series described in the literature (Schild et al., 1997).

Epilepsy is relatively frequently associated with brain tumors (Ketz, 1974; Morris and Estes, 1993). However, tumors may or may not cause epilepsy, even when they are of the same type and located in the same brain area. Thus, tumors are not intrinsically epileptogenic. Furthermore, seizure activity associated with brain tumors may develop relatively soon or after several years (Ketz, 1974; Spencer et al., 1984; Morrel, 1989; Morris and Estes, 1993). Therefore, it is thought that in the peritumoral cortex occurs a series of changes that eventually may lead to epilepsy occurs.

Detailed microanatomical and neurochemical studies of the peritumoral cortex temporal lobe epileptic patients presenting a variety of tumors have shown a decrease inhibitory GABAergic interneurons (Haglund et al.,

1992; Marco et al., 1996, 1997). Among the inhibitory interneurons that are lost, chandelier cells appear to be one of the most affected neurons (Marco et al., 1996, 1997). Since chandelier cell axons are virtually the only source of inhibitory synapses on pyramidal cell axon initial segments, and this region of the pyramidal cell appears to be strategically important for the control of pyramidal cell excitability, chandelier cells are considered to be the most powerful cortical inhibitory interneuron (De Felipe, 1999). On the other hand, pyramidal cells are the main source of cortical efferent axons and of intracortical collaterals and, consequently, they are responsible for the spread of epileptiform activity. Thus, the loss of chandelier cells has been suggested to play a crucial role in the development of epilepsy (De Felipe, 1999).

General histological features

Although most of these lesions or tumors are located in the temporal lobe, they have been detected throughout the neuroaxis, including the spinal cord. Macroscopically, ganglionic tumors can be solitary or multiple, solid or cystic. They are usuall well circumscribed and the diameter varies. Generally, they present calcifications and may involve the subarachnoid space. The pediatric desmoplastic ganglioglioma is typically identified as a, massive tumor, while the dysembryoplastic tumor is small, barely measuring a few millimeters, and circumscribed, corresponding to multiple superficial cortical nodules of 0.5 to 3 mm in diameter (Ng et al., 1990; Daumas-Duport, 1993). Hamartias are usually microscopic lesions, and hamartomas can measure several mm (Wolf et al., 1994).

At the histological level, this group of tumors is basically made up of: (a) mature gangliocytic neuronal cells with abundant cytoplasm, vesicular nuclei and prominent nucleoli, usually arranged in groups, and scattered binucleated neurons are often present; (b) small, mature neuronal cells, with or without projections, with a small amount of pale or slightly eosinophilic cytoplasm; (c) astrocytic and oligodendroglial glial cells; (d) lymphocytes at the perivascular level; (e) fibrillar stroma, similar to the neuropil, in those lesions presenting a neuronal component; (f) loose, myxoid stroma with occasional cysts, a characteristic of the dysembryoplastic neuroepithelial tumors; (g) cytoarchitectural changes in the adjacent cortex, with neuronal, dysgenetic clusters (abnormal numbers and arrangements of neurons); (h) conspicuous eosinophilic
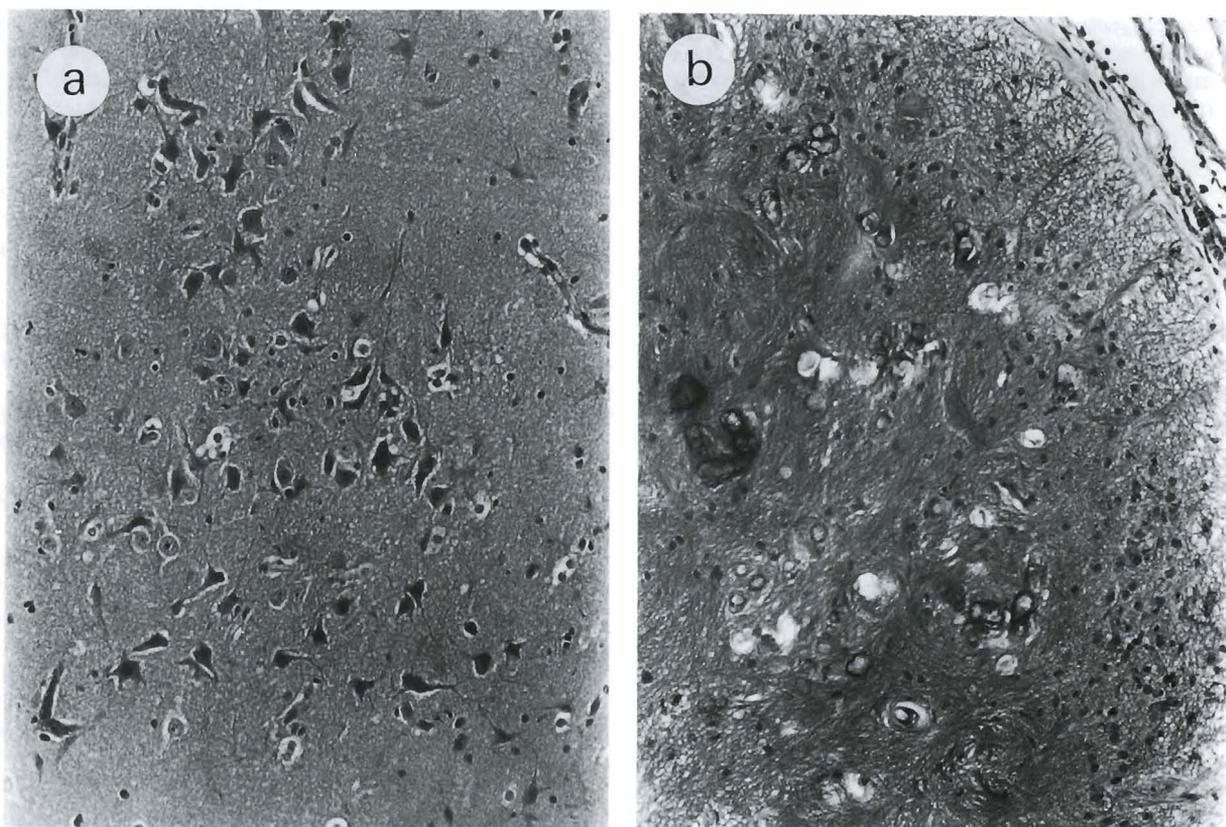

Fig. 1. a. Glioneuronal hamartias. The lesion is composed of circumscribed microscopic aggregates of disorganized mature neuronal and glial elements. **b.** An area of cortex with marked cortical disorganization, gliosis, neuronal loss and microcalcifications. Hematoxylin-eosin, x 250

protein droplets and spherical structures known as granular bodies; and (i) calcifications.

Ultrastructural and immunophenotypic features

Light microscope studies of these tumors must frequently be complemented by ultrastructural and immunohistochemical studies to determine the tumor phenotype. The ultrastructural characteristics of neuronal cells include dense core granules, cell processes with microtubules and synapses associated with clear vesicles. Astrocyte cells contain abundant intermediate filaments.

According to immunophenotypic analysis, the neuronal component expresses markers for a particular cellular strain, as well as neurofilaments (NFP-H/m epitopes), synaptophysin, class III beta-tubulin, MAP 2 and some neuropeptides (neuropeptide Y, met-enkephalin, beta-endorphin, substance P, somatostatin, etc) in almost 100% of cases (chromogranin A in 80% to 90% of tumors); it also expresses the adhesion molecule E-NCAM, an embryonic form of the neuronal cell adhesion molecule, which is positive in many dysplastic neurons, in glioneuronal hamartias and in central neurocytoma. Conversely, the cells in dysembryoplastic neuroepithelial tumors are mostly negative for E-NCAM

(Wolf et al., 1995). Regional neuronal markers, such as calbindin D-28K, expressed in Purkinje cells, can be detected in those tumors arising in the cerebellum.

Description of the different lesions

The hamartoma is defined as a mass of disorganized, but mature, neurons and glial cells; despite its tumor-like gross appearance, it has no histological features of malignancy and no proliferative activity is observed. The glioneuronal hamartias are poorly circumscribed lesions with misplaced neuronal cells (Fig. 1a). They include areas of dysgenesis (focal cortical dysplasia, with groups of large bizarre neurons accompanied by glial cells throughout the cortex) and microdysgenesis in the form of heterotopias, neuronal clustering and rows of perivascular glial cells (Fig. 1b) (Volk and Prayson, 1997).

The ganglioneuroma is composed exclusively of gangliocytic cells with occasional Schwann cells. Most frequently, it arises in association with the autonomous and peripheral nervous systems; the exceptions, reported in the central neuroaxis, are associated with ectopic peripheral neural tissue or peripheral nerve roots (Lantos et al., 1997).

The gangliocytoma represents less than 0.5% of brain tumors (Russell and Rubinstein, 1989). And is
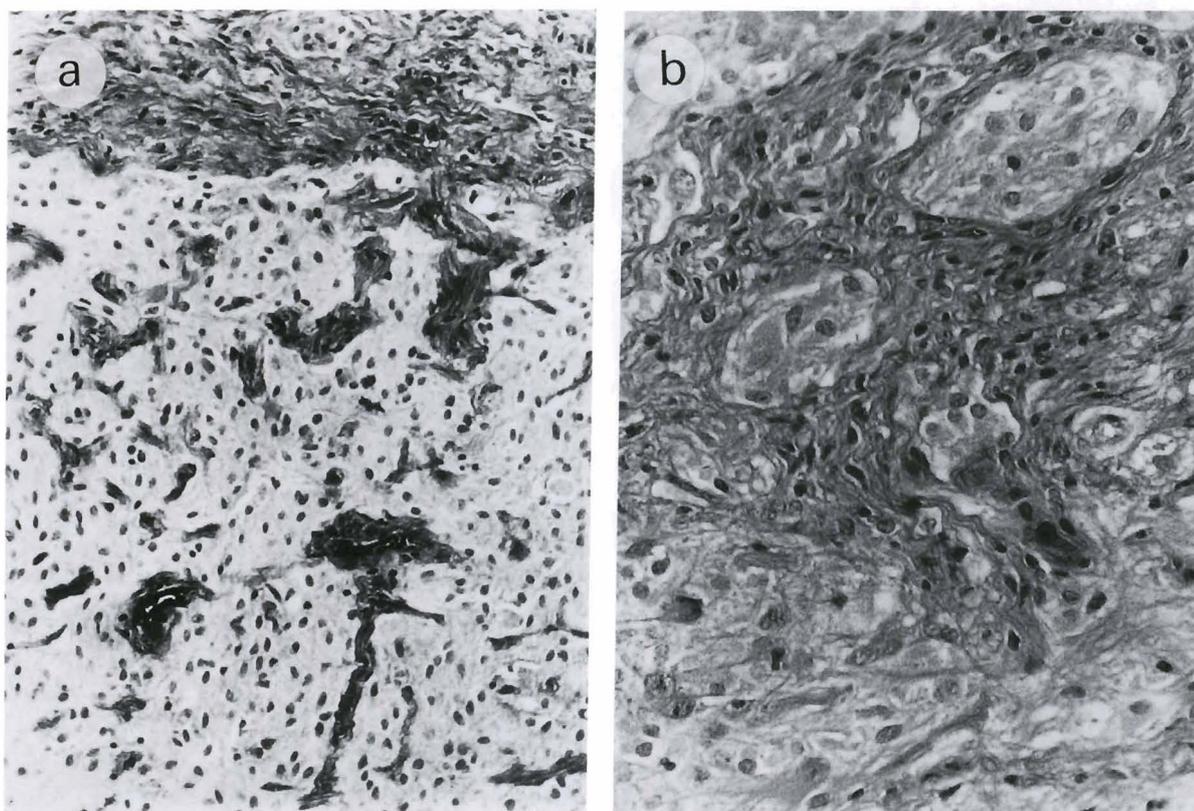

Fig. 2. Gangliogliomas. **a.** An example of ganglioglioma with a diffuse cell growth pattern and the characteristic vascular arborization. **b.** An example of desmoplastic ganglioglioma with neurons enmeshed in a collagenous, reticulin-rich stroma. Hematoxylin-eosin, x 350

composed of neuron-gangliocytic cells and a variable component of non-neoplastic astrocytes. In contrast to the ganglioglioma, it has a less common cystic component. Neurons usually have pleomorphism and bizarre forms. The hamartomatous or neoplastic nature of this lesion has been questioned (Lantos et al., 1997). Tumor recurrence after complete removal has been reported (Felix et al., 1994).

The ganglioglioma is a tumor with a mixed glial and neuronal components (Figs. 2, 3). It is the most common of the glioneuronal neoplasms, with an incidence ranging between 0.4% and 6.25% of primary brain tumors (Russell and Rubistein, 1989; Chintagumpala et al., 1996; Isimbaldi et al., 1996; Hakim et al., 1997; Lantos et al., 1997). It is generally located in the temporal lobe, although it has been observed in frontal lobe and at other sites. The mean patient age at diagnosis is 20 years, ranging from 1 to 80 years. There is a slight male predilection (Ng et al., 1990; Wolf et al., 1994; Chintagumpala et al., 1996; Isimbaldi et al., 1996; Hakim et al., 1997). The macroscopic aspect is generally cystic with a wall nodule. Microscopic study discloses a heterogeneous lesion, with different histological cell-growth patterns. The architectural pattern of this tumor varies from one case to another and even among the different portions of the lesion. It frequently assumes an alveolar arrangement, with a tree of narrow capillary vessels (Fig. 2a), and clustered neuronal cells that tend to present more mature forms in the central area (Figs. 3a,b). Occasionally, there is a prominent desmoplastic reaction with abundant vessels both in the leptomeninges and at the cortical level (Fig. 2b) or tumors with a predominant gangliocytic component (Fig. 4a). The glial component shows a variable cell density with areas similar to the common glial tumor, especially that of the pilocytic astrocytoma. Recently, a distinctive glioneuronal tumor with neuropil-like islands has been described (Fig. 4b). These islands were composed of oligodendrocyte-like elements "neurocytic" and well differentiated neurons (Teo et al., 1999). The ganglioglioma has anaplastic and malignant variants (Sasaki et al., 1996; Hakim et al., 1997). Moreover, composite pleomorphic xanthoastrocitoma (PXA) and ganglioglioma have been described (Perry et al., 1997). These authors describe three forms of association between PXA and GG, with some tumors displaying both neoplastic elements with minimal intermingling, others showing features of typical PXA with dysmorphic ganglion cells which express synaptophisin (SYN) immunoreactivity, and others presenting a composite of
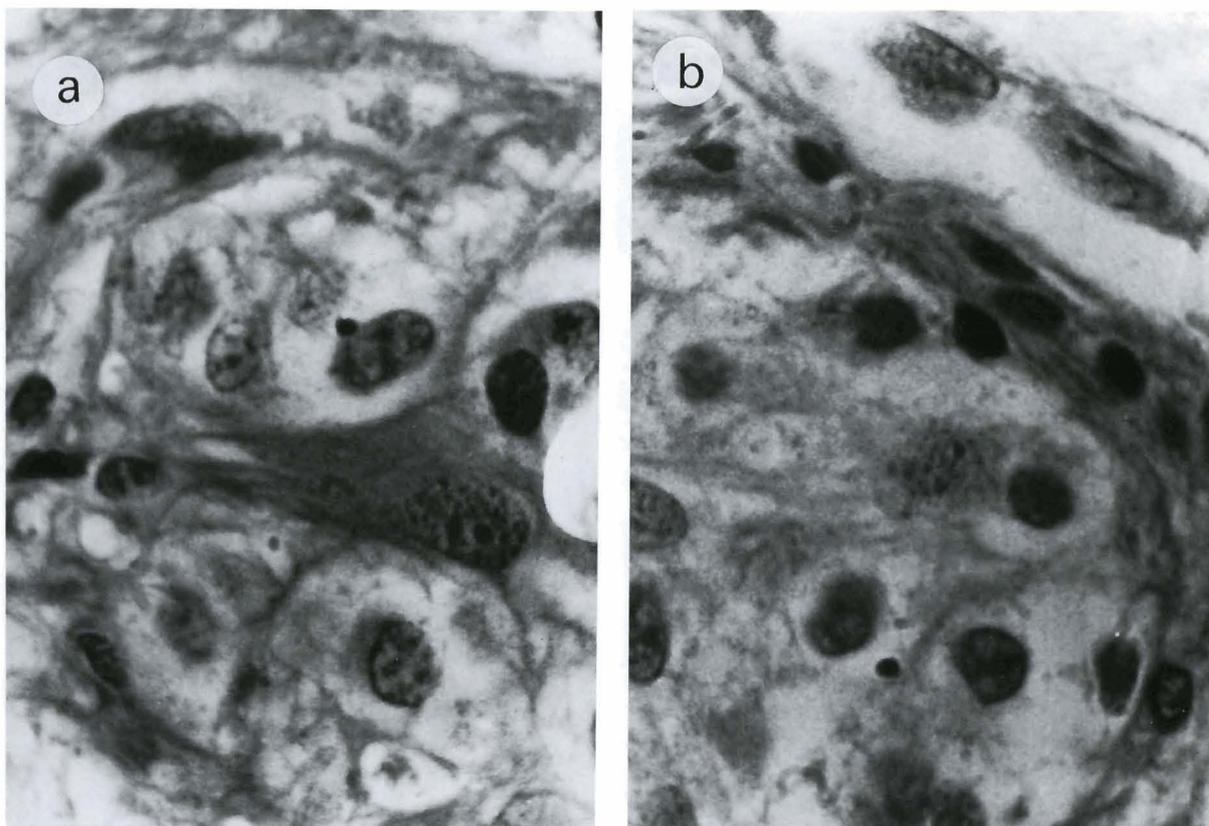

Fig. 3. Gangliogliomas. **a and b.** High magnification of clusters of neuronal cells with a large and mature neuron situated at the center of the lobule (figure a). Hematoxylin-eosin, x 1,000

PXA and GG arranged as in a "collision tumor". We have also observed tumors composed predominantly of typical GG but with abundant multinucleated cells dispersed among the glial and neuronal cells. These cells are immunoreactive for SYN and Glial Fibrilar Acidic Protein (GFAP) and in some areas were associated with a desmoplastic stroma or a pilocitic component of the GG. Those areas could represent incipient PXA (Fig. 5) arising in otherwise typical GG.

The neurocytoma represents approximately 0.5% of intracranial tumors (Kim et al., 1997); the usual location is intraventricular, near the foramen of Monro. Most patients show symptoms of intracranial hypertension and the clinical history is usually short. This lesion is composed of small, mature neurons, fibrillar stroma and frequent calcifications (Fig. 6). It is easily confused with the oligodendroglioma. It presents no cytological atypias or significant mitotic activity (Fingerella-Branger et al., 1992; Nishio et al., 1992; Tsuchida et al., 1996; Lantos et al., 1997). The existence of an extraventricular neoplasm with the features of the neurocytoma has recently been reported (Giangaspero et al., 1997).

The dysembryoplastic neuroepithelial tumor is associated with chronic intractable seizure disorders and may represent up to 25% of all lesions removed to treat chronic drug-resistant epilepsy (Wolf et al., 1993, 1995;

Raymond et al., 1995; Pasquier et al., 1996). It is characterized by the presence of multiple cortical nodules varying in diameter, with a gelatinous consistency and distended cortical ribbon. It is made up of small, oligo-like cells with scarce cytoplasm and a myxoid pattern rich in mucopolysaccharides (Fig. 7). Mature neuronal cells are frequently detected throughout the tumor (Armstrong, 1993; Daumas-Duport, 1993; Hirose et al., 1994). This lesion is also easily confused with the low-grade oligodendroglioma and astrocytoma and frequently there is adjacent cortical migration alterations.

The presence of satellites in the adjacent cortex should be assessed an immunohistochemical study carried out to detect the neuronal component (Daumas-Duport, 1993; Hirose et al., 1994). In contrast to hamartias, the cellular elements do not express E-NCAM immunoreactivity (Wolf et al., 1995).

Another malformative hamartomatous lesion that has a neuronal component is the so-called meningo-angiomatosis, which may present a cytological component comparable to that of the gangliocytoma. It is characterized by its prominent vascular pattern and fibrosis in the leptomeninges, which is extended throughout the Virchow-Robin spaces (Fig. 8) (Goates et al., 1991; Prayson, 1995).
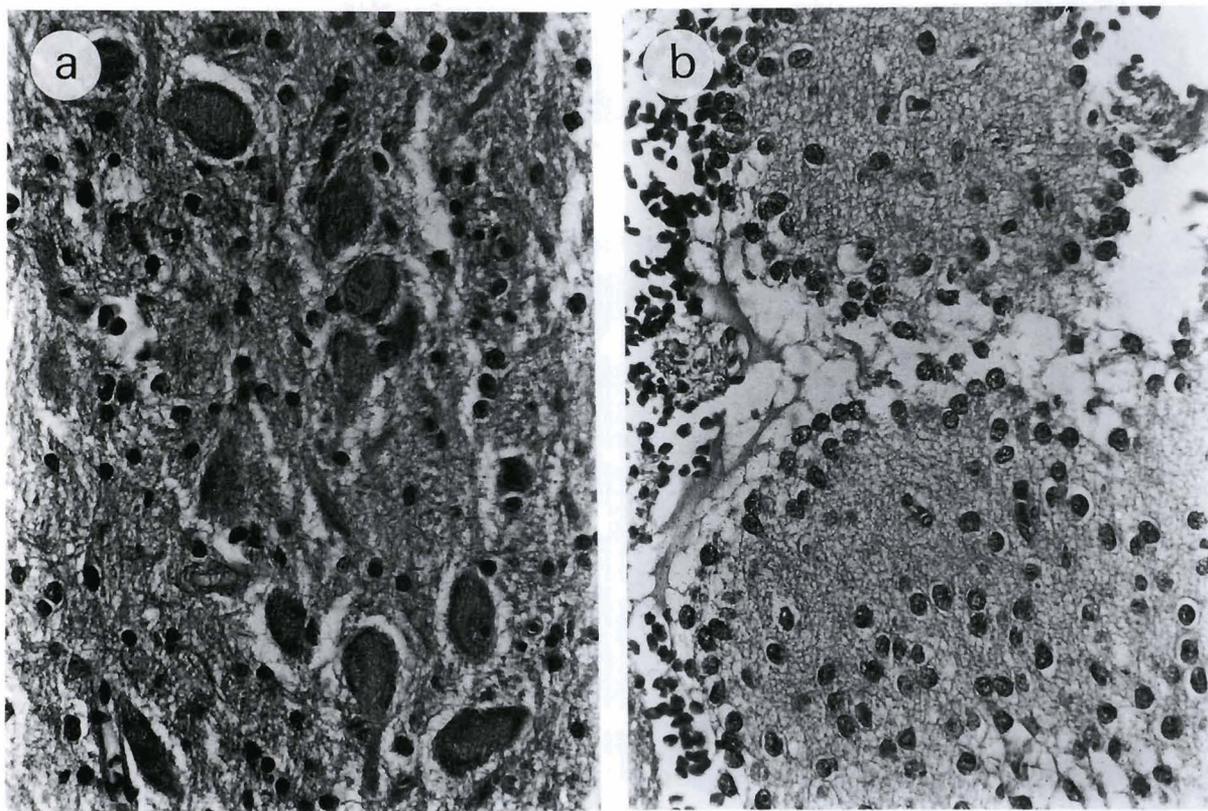

Fig. 4. Examples of glioneuronal tumors with a predominant component of gangliocytic cells **(a)** and a rossetoid growth pattern **(b)**. Hematoxylin-eosin, x 400

Most of these tumors or lesions arise within an underlying hamartomatous condition, including frequent dysplastic pathology in the adjacent cerebral cortex (Wolf et al., 1995; Lantos et al., 1997). Moreover, our findings in over 160 lesions associated with chronic epilepsy coincide with those of other studies involving lesions associated with drug-resistance epilepsy (Wolf et al., 1995; Alvarez et al., 1997) in suggesting presumable
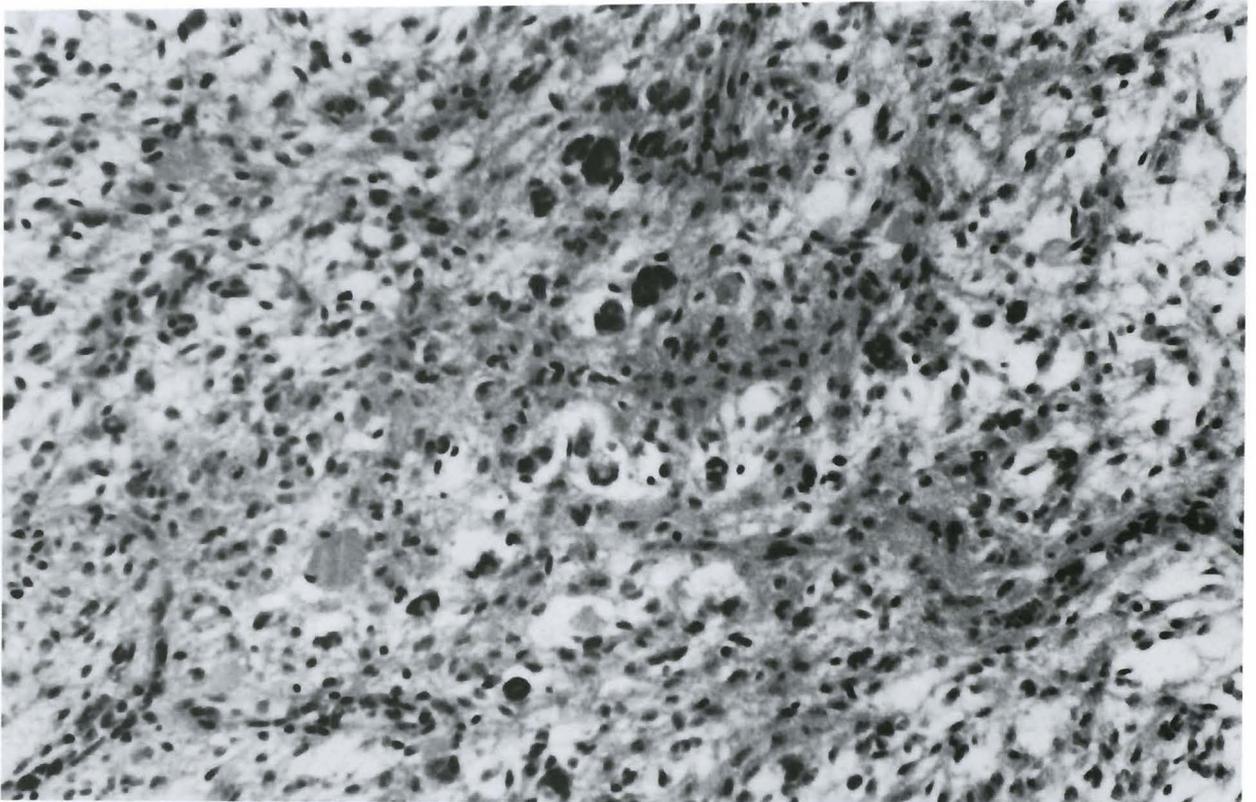

Fig. 5. An example of an xanthoastrocitma pleomorphic showing numerous giant cells and a cellular background of glial cells and very sparse gangliocytic-like cells. Hematoxylin-eosin, x 300
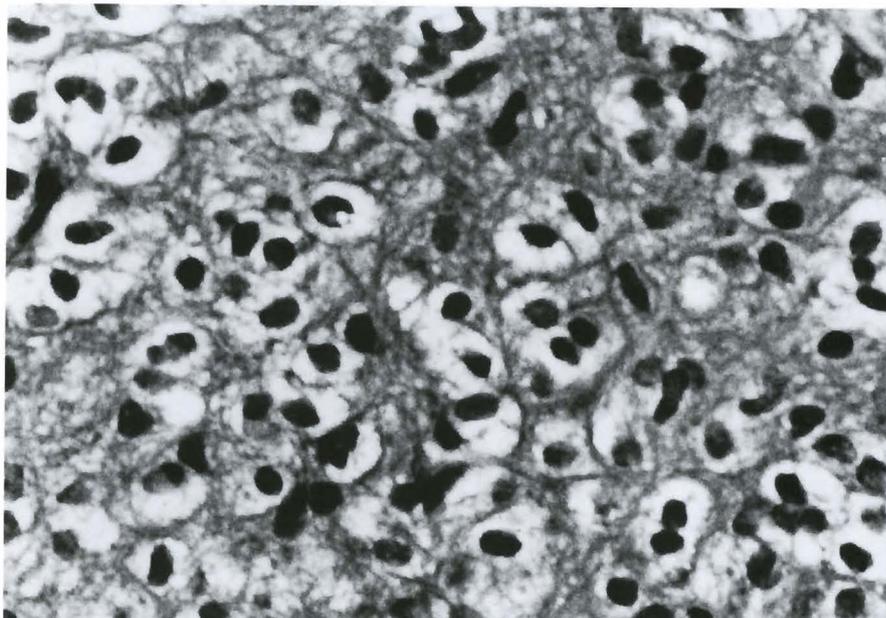

Fig. 6. Neurocytoma. The tumor is composed of small neurocytes in a fine fibrillar background. Hematoxylin-eosin, x400

transitions among the different types of neuronal brain tumors. In fact, we postulate that they may constitute a single tumor group with different subtypes, depending on the predominance of a mature or immature neuronal component, on the glial cellularity or on the accompanying fibrovascular stromal reaction. This unifying concept of glioneuronal tumors of the brain may explain recent reports concerning transitional forms of neuronal brain tumors and the divergent differentiation of these lesions (Powell et al., 1996; Yamamoto et al., 1996; Shimbo et al., 1997). In this context, there are some reports of tumors presenting features of the dysembryoplastic neuroepithelial tumor and the ganglioglioma (Shimbo et al., 1997), as well as of the neurocytoma and the gangliocytoma (Yamamoto et al., 1996) and other combinations.

Prognostic criteria

Most of the tumors or lesions associated to refractary epilepsi and presenting a neuronal component have an excellent prognosis, with a low incidence of recurrence and/or of malignant transformation. Such malignant transformation has been reported in up to 3% of gangliogliomas (Sasaki et al., 1996; Hakim et al., 1997)

and, exceptionally, in the neurocytoma (Mrak, 1994; Yamamoto et al., 1996; Eng et al., 1997). Thus, it is important to identify this group of tumors, differentiating them from others with a more aggressive course that may require chemotherapy and/or radiotherapy. They are frequently confused with astrocytic glial tumors, with oligodendrogliomas and even with primary neuroectodermal tumors. Nevertheless, low-grade astrocytic tumors have been observed in association with chronic epilepsy and, recently, a distinctive group of astrocytic tumors has been reported to be associated with long-term epilepsy, with an excellent prognosis (Bartolomei et al., 1997).

a) Biological criteria

The location of the tumor itself is a prognostic factor related to its suitability for resection, which is the chosen treatment. Even the childhood desmoplastic ganglioglioma, which is detected before the child reaches the age of two and is very large in size, can have a favorable outcome if completely removed (VandenBerg et al., 1987; Ng et al., 1990). The detection of a neurocytoma or ganglioglioma in a patient over 50 years of age is associated with a worse prognosis
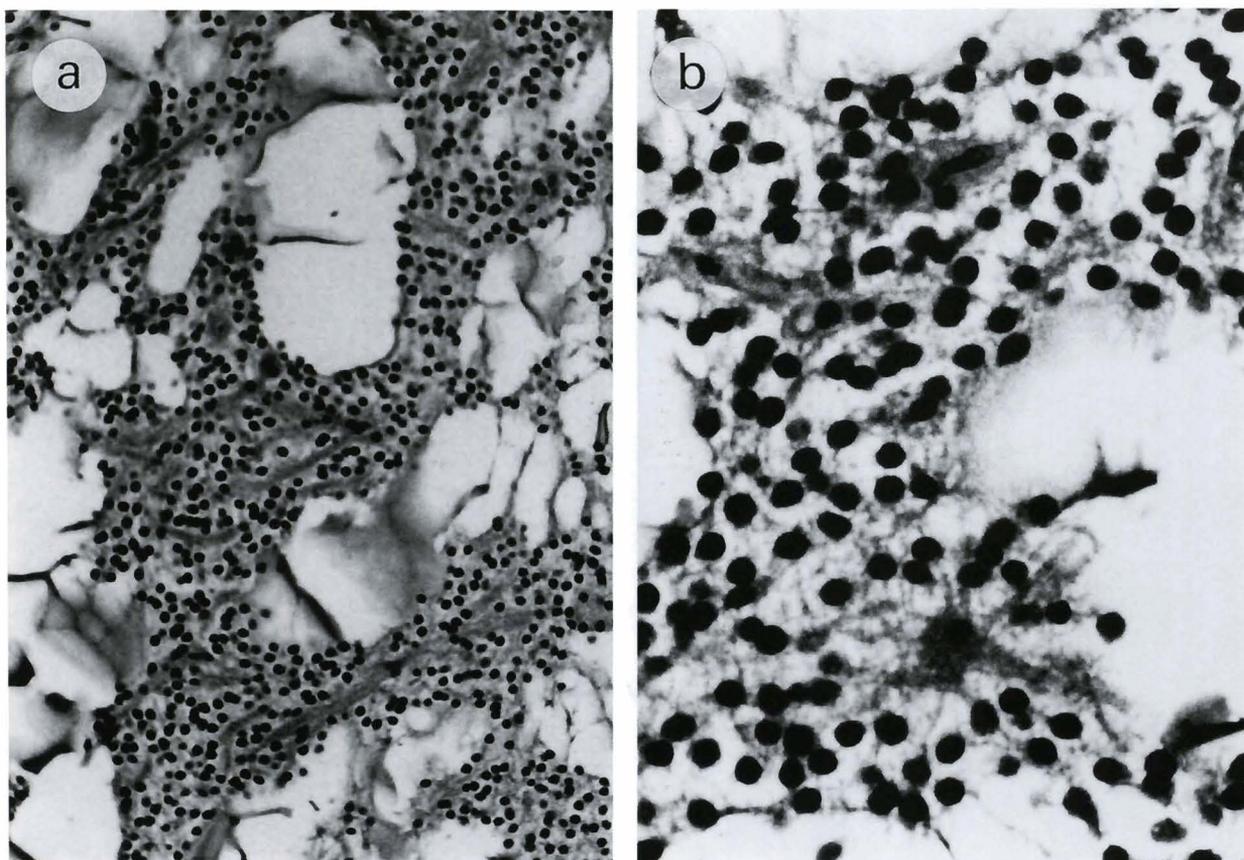

Fig. 7. a and b. Dysembryoplastic neuroepithelial tumor. The intracortical nodules show a mixed population of glial and neuronal cells, with microcysts and a frequent target-like pattern. Hematoxylin-eosin a, x150; b, x 400

(Prayson et al., 1995). Likewise, the ganglioglioma that does not develop within the setting of chronic intractable epilepsy has a short duration and may have a more aggressive clinical behavior (Prayson et al., 1995).

Some tumors may be associated with specific phakomatoses or inheritable diseases (Lantos et al., 1997). The ganglioglioma is not associated with any specific phakomatosis, but it is associated with neuronal migration disorders (in up to 30% of cases) and with Down's syndrome, orofaciodigital synostosis and other congenital disorders (in about 5% of cases). In contrast, the gangliocytoma is associated with Cowden's disease and the ganglioneuroma with the familial tumor syndrome (Lantos et al., 1997).

b) Histological criteria

In this group of tumors having a mixed neuronal and neuronal-glial component, the cytological characteristics of the neurons and of the glia must be assessed separately. The neurons may have dysplastic features, nuclear atypia and abnormal forms, which should not be interpreted as signs of malignancy, but as degenerative changes. The glial component, which sometimes undergoes malignant transformation, must be assessed according to conventional criteria for glial tumors. Among the gangliogliomas, there are recurrent and anaplastic tumors, with nuclear and cytological atypia at the level of the astrocytic component (Kaba et al., 1996; Sasaki et al., 1996; Hakim et al., 1997). Likewise, an increase in the proliferative activity of the glial cells with specific markers, such as Ki67 (MIB1), is detected (Hirose et al., 1997). These histological signs are observed in up to 10% of gangliogliomas, appearing both in the initial biopsy and in the recurrent lesions, and they are associated with a worse prognosis (Hakim et al., 1997). In fact, the 1993 WHO classification identified three grades of ganglioglioma on the basis of cellularity, cytological atypias, the presence of necrosis, and vascular proliferation. Grade I corresponds to the well-differentiated tumor; grade II includes the ganglioglioma having increased cellularity and nuclear pleomorphism; and grade III, those presenting necrosis, numerous mitoses and abundant vascular proliferation. There is a clear correlation between the cytological degree and proliferative activity of a ganglioglioma and the prognosis (Wolf et al., 1994).

Exceptional cases have been reported of atypical neurocytoma, with histological evidence of atypia and necrosis and proliferative indices that also correlated
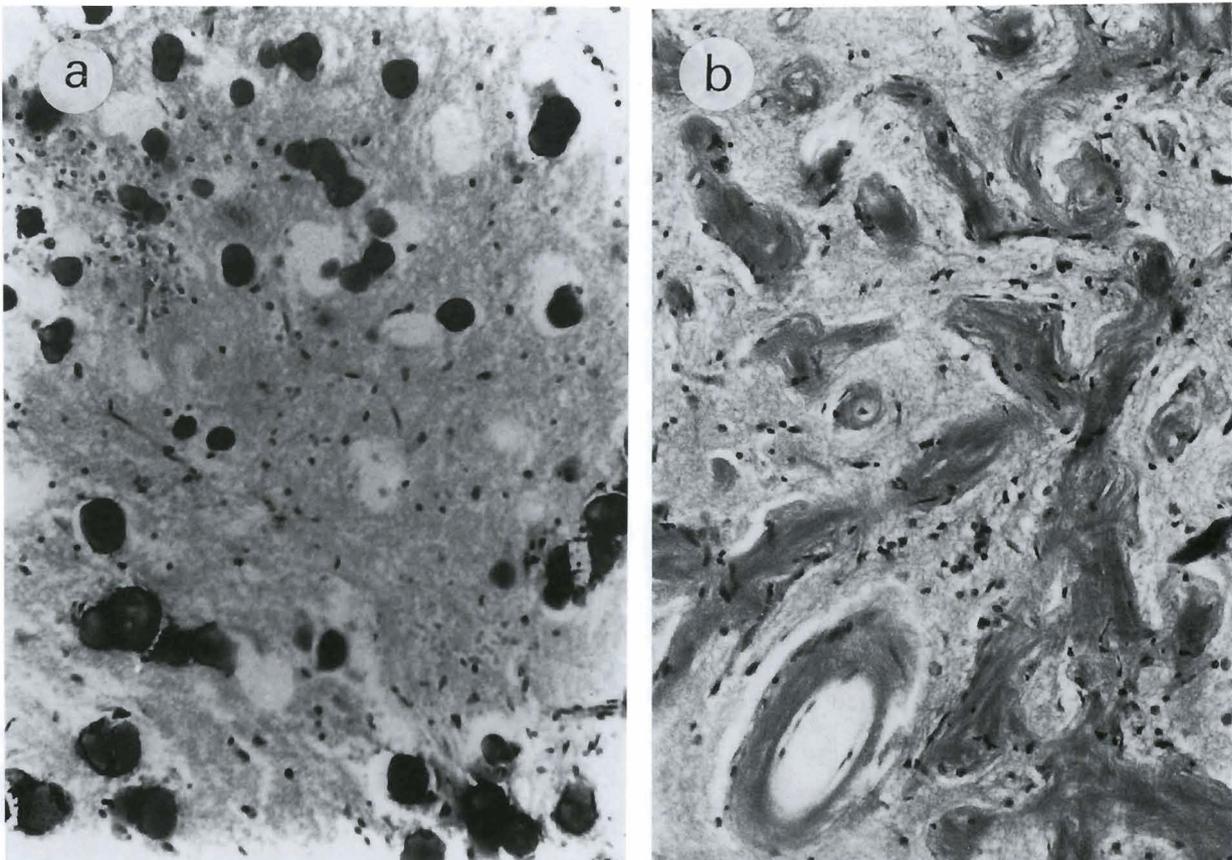
Fig. 8. Meningoangiomatosis. **a.** The lesion shows areas of the cortex with abundant microcalcifications. **b.** A striking fibrosis throughout the Virchow-Robin spaces and a mixed glio-neuronal cell population. Hematoxylin-eosin x 150

with patient survival (Mrark, 1994; Fujimaki et al., 1997). A few cases of craniospinal dissemination of central neurocytoma have been documented (Eng et al., 1997). It is interesting that some series show an incidence of anaplastic transformation in up to 12% of pleomorphic xanthoastrocytomas (Fig. 5) (Perry et al., 1997).

Other classical histological features to be assessed include the interface between the tumor and the adjacent parenchyma, which is usually clear and the extension of the tumor to the leptomeninges and the subarachnoid spaces which, in contrast to other brain tumors, is not always associated with a worse prognosis (VandenBerg et al., 1987; Wolf et al., 1993, 1995; Chintagumpala et al., 1996). Two cases of leptomeningeal dissemination showing no cytological evidence of malignity have recently been reported (Yamamoto et al., 1996; Eng et al., 1997).

c) Immunophenotypic and molecular criteria

For the correct diagnosis of these lesions, the assessment of neuronal and glial differentiation markers is usually necessary. It is essential to reflect the proliferative activity, since it may be of prognostic significance in some types of tumors. In fact, in the ganglioglioma (Hirose et al., 1994; Alvarez et al., 1997). and the central neurocytoma (Yamamoto et al., 1996), the percentage of cells positive for Ki67/MIB1 correlates with the probability of local recurrences. However, it is important to note that other neuronal tumors, such as the dysembryoplastic neuroepithelial tumor, may show a high MIB1 labeling index, but this does not indicate a worse prognosis (Daumas-Duport, 1993).

The expression of oncogenic proteins such as p53 has been detected in some gangliogliomas, and this may be an indicator of a worse prognosis and a tendency to recur (Hirose et al., 1994). Other markers associated with a worse prognosis in primitive neuroectodermal tumors, such as N-myc amplification, are absent or do not indicate a worse prognosis in neuronal tumors.

Immunoreactivity with E-NCAM may be useful in distinguishing hamartias from dysembryoplastic neuroepithelial tumors.

Treatment

The treatment chosen in all these tumors is surgical resection. The 5-year survival rate is over 80%. In the ganglioglioma, surgical excision is curative. Radiotherapy is of questionable utility in grade II lesions and is recommended in those classified as grade III, given the greater probability of recurrence. It is also advisable in those cases in which resection was not complete (Wolf et al., 1994; Hakim et al., 1997). It is interesting to note that remission in a case of grade III ganglioglioma treated with cis-retinoic acid (Perry et al., 1997) has been reported.

In the central neurocytoma, local recurrences are absent in 100% of cases in which the tumor was completely resected and in 50% to 70% of cases of partial resection. In the latter cases, subsequent radiotherapy prevented recurrence in up to 100% of cases, according to some authors (Fujimaki et al., 1997; Perry et al., 1997) with a 5-year survival rate of 88% (Nisio et al., 1992; Isimbaldi et al., 1996).

In dysembryoplastic neuroepithelial tumors, given the excellent clinical prognosis and the fact that recurrence has not been recorded, radiotherapy and chemotherapy are not indicated (Raymond et al., 1995).

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