Clinical features and biological markers of brain tumors

Manuel Adolfo CASTELLO and Carlo CAPPHELLI

Servizio Speciale di Oncologia Pediatrica, Clinica Pediatrica, Università degli Studi
"La Sapienza", Rome, Italy

Summary. - Brain tumors represent a wide and important field of oncology. Their incidence has increased in the last twenty years but the reason for this, as well as the etiopathogenesis of these tumors, has not been clearly understood yet. In the first part of this paper we have divided brain tumors on a topographic basis in neoplasms which develop in the posterior fossa, in the midbrain and in the hemispheres; the clinical characteristics of the most frequent tumors are also analysed. Particular attention has been given to neoplasms in children. In the second part we deal with the two most useful methods of diagnosis and classification of brain tumors: immunoistochemical markers and biochemical markers.

Key words: brain tumors, clinical features, markers.


Parole chiave: tumori cerebrali, aspetti clinici, markers.

Introduction

Brain tumors represent an important field of oncology, almost the 20% of pediatric solid tumors and they are the fifth most frequent cancer in adulthood [1].

Furthermore, data suggest that their frequency is increasing; the reasons are unknown but are surely correlated to the better diagnostic techniques and probably to the action of environmental agents (see: Fronza et al. in this issue, pp. 159-166).

The diagnosis of “brain tumors” includes a large number of neoplastic diseases if we consider the originary tissue, location, progression time and capacity. We shall try to give a classification in the second part of this paper. The brain tumors hit at every age, as we have seen, and the age is an important factor for the prognosis and for the sequelae of treatment. In fact, at present, therapeutic protocols are prepared on the basis of the age factor, this particularly in pediatrics.

Neurosurgery, radiotherapy and chemotherapy are used for the treatment of brain tumors in combination or separately. Unfortunately, however, the most appropriate therapy of brain tumors has still to be established. New prospective in immunotherapy and gene therapy for the future promise additional beneficial effects. Therefore, it is essential to carry out multicenter cooperative studies in order to achieve in this way an amelioration of both survival and quality of life.

This paper deals, first, with the clinical features of brain tumors, then, with the present state of knowledge and research on the tumoral markers. In both cases, special attention is given to the pediatric aspects of the subject.

Clinical features

A classification of brain tumors is necessary before we proceed to their description. Although in most cases, the etiology of brain tumors is unknown, a correlation with a malformative syndrome has been found in small number of them. The most commonly known is the neurofibromatosis which is frequently associated to low-grade astrocytoma. We can also recall the Tuberous Sclerosis, the Sturge-Weber disease, the Wyburn-Mason syndrome. These and others are dysgenetic syndromes that could constitute the milieu for the development of a brain tumor [1-5]. In some series of adult brain tumors, researchers consider some possible external agents as etiological causes. When discussing brain tumors, it is very difficult to produce a simple classification that is
useful and exhaustive at the same time. It is enough to say that the main division of tumors in benign and malignant causes disputes, as a benign tumor located in the brain can produce more serious damage than a malignant tumor. It is possible to base oneself on histologic or on clinical criteria [6], which are the most frequently used. Considering the aim of our paper, we shall use a topographic criterion to recall the main histologic types arising in that specific location.

After discussing more in detail the most frequent among the tumors of neuroglia, of epithelial cells, the neuronal and glio-neuronal tumors, the embryonal tumors, the tumors of the pineal gland and the germ cell tumors, we shall overlook the tumors of the mesenchymal tissue, and meningothelial cells and of choroid plexus. We shall discuss very briefly the metastatic brain tumors as we believe they interest fields beyond the concern of this study. In fact, the metastatic spreading implies biological features specific to each tumoral histotype and, therefore, belongs to the "history" of the original disease by which it cannot be separated.

Topographically we can divide the brain tumors in tumors arising in the posterior fossa, in the midline and hemispheres. According to this division, we shall analyse the different histotypes most frequently found in the structure we are taking in consideration.

**Posterior fossa**

The first anatomic structure examined is the posterior fossa. The most frequent neoplasms found in this structure are: brainstem tumors, cerebellar tumors and tumors arising from ependymal cells.

**Brainstem tumors**

These tumors appear essentially in childhood and their frequency reaches the 15%. The clinical features appear related to the location and histopathology of the tumor. Mesencephalon,pons and medulla oblongata could be involved. Mainly the glioblastoma multiforme and anaplastic astrocytoma are found, followed by low-grade astrocytoma [7].

The principal signs and symptoms are: cranial nerves disfunction, headaches and vomiting and ataxia. Between the cranial nerves the most frequently compromised are the III, V, VII, IX, X [8].

Different types of mistagmus can be found and they help to localize the tumor [9-11]. The abnormalities of sensitiveness of the face, the asymmetry of the palate, nasal regurgitation are other signs of cranial nerves involvement.

Headaches and vomiting are an effect of the increased intracranial pressure. Frequently a child presents a headache in the morning dismissed by "projectile" vomiting. Often these symptoms are considered as having a psychological cause and, therefore, the diagnosis is retarded, in some cases, even for a long time.

The brainstem tumors cause increased intracranial pressure by occluding the normal CSF flux. Other signs of this are: ventricular dilatation (noted in 60% of cases [12]), papilledema which, if present, is a sign of quick progression. In fact, when we find a ventricular dilatation without papilledema we can suppose that the tumor is slowly occluding the CSF flux.

Ataxia and sensorimotor tract functional deficits are the consequence of the involvement of the pathways passing through the brainstem structures. It is important to know and recognize two other signs of brainstem tumors: personality changes (apathy, psychological lability, loss of acquired school performances) and stiffneck (frequent in cervico-medullar junction tumors). They are relatively rare and the diagnosis is sometimes difficult to make.

While clinical features are more connected to the location, time of progression is tightly related to the histopathology of tumors. In brainstem there are three principal forms: diffuse or infiltrating, focal and exophitic tumors [13]. As previously seen, glioblastoma multiforme is the most frequent histotype; it has a rapid evolution, unlike low-grade astrocytomas which grows slowly. Glioblastoma multiforme appears by CT-scan as an hypodense central area with a ring of contrast enhancement. Anaplastic astrocytoma does not show this ring and the low-grade astrocytoma is a non-enhancing lesion. In spite of the progress achieved in the therapy, at present the prognosis of these tumors remains very serious with a 5-year survival rate of 25% for low-grade astrocytoma and 0% for glioblastoma multiforme [14].

**Cerebellar tumors**

We shall discuss two types of tumors arising in the cerebellum because of their frequency and interest: cerebellar astrocytoma and medulloblastoma.

The former is a tumor that hits children and young adults. It represents 15% of the pediatric tumors [15, 16]. It is usually a pilocytic astrocytoma [17] and presents a large cyst and a solid mural nodule, 80% are cystic [18]. Frequently they are considered as hemispheric tumors but several studies show a prevalence of midline cerebellar location [19-21]. The tumor is diagnosed after an average delay of 15 months from the initial symptoms, which are headaches and vomiting. These symptoms can have long periods of remission and the patient may be visited for gastrointestinal problems, often treated with laxatives. After a long time other signs appear: truncal ataxia in children with midline tumor and dysmetria, well correlated with tumor location by the finger-to-nose and heel-to-shin manoeuvres, in those who have hemispheric neoplasms [18-22]. Stiffneck, papilledema and cerebellar fits (attacks of unconsciousness) are frequent [23].
The prognosis is very good, in fact, with a complete surgical excision, the patients have a disease-free survival rate of 90% at 25 years, without any further treatment [24-26]. If surgical removal results incomplete, a postoperative radiotherapy is indicated.

**Medulloblastoma**

Much has been written about this highly malignant tumor which is more frequent in childhood and has a 2:1 sex ratio. As our aim is the description of the clinical features of brain tumors, we shall not discuss in detail the histological aspects in each chapter, however in this one we shall give at least a general idea of the primitive neuroectodermal tumors (PNET)-medulloblastoma tumors.

All the tumors, arising from primitive indiffereniated cells, have been included till now under the PNET umbrella. Thus, the neoplasms showing small embryonal cells are PNET, but those that have a clearly specific original cell or metabolic pathways, are excluded (neuroblastoma) [27-29].

Medulloblastoma is considered to be a PNET of the posterior fossa. It represents 20% of childhood brain tumors but we can find also in adulthood [17-30]. Symptoms depend on the cerebellar disfunction, IV ventricle obstruction, craniospinal dissemination. The clinical picture at the beginning shows predominantly headaches and vomiting; then truncal ataxia and/or lateralized cerebellar symptoms appear. Frequently head tilt, stiffen in the neck and nistagmus are present in advanced disease. Ataxia could be mild at the beginning but later becomes severe and the patient cannot walk or handle objects. Leptomeningeal metastases are frequent and are revealed by specific signs and symptoms. Extraneural metastases could be present in bone, marrow, bone and other viscera [31, 32]. As far as treatment is concerned, age is one of the most important criteria. Radiotherapy remains the most efficacious treatment but it has too many sequelae in young children. Thus, so far, we have been treating with surgery and chemotherapy (if necessary, also high dose chemotherapy [33]) children under the age of three while the older ones are treated with surgery and radiotherapy with or without chemotherapy. The size of the tumor after surgery and the presence or not of metastases are also fundamental prognostic factors. Generally, localized tumors with a total or subtotal excision tend to have a 60% of disease-free survival rate at 5 years, while metastatic tumors have less than 30% [29, 34, 35].

**Ependymomas**

We include the above pathologic entity under this heading but ependymomas can arise in any part of the ventricular system because of the presence of ependymal cells. Both children and adults can be hit.

The tumor arises from any part of IV ventricle and occludes it. Thus, increased intracranial pressure symptoms are present (hydrocephalus, headache, vomiting, papilledema) and pathognomonic of this tumor is the important pain in the neck because of its growth throughout the foramen magnum. Cranial nerves deficits are seldom observed. Radiographically calcifications are an important factor in the differential diagnosis since other tumors of posterior fossa have no calcifications.

We can divide ependymomas in low- and high-grade tumors in terms of histology. Frequently high-grade tumors are diagnosed more quickly [36] and can spread in CNS. This event is rare in low-grade astrocytomas. An important aspect of treatment depends on this. In fact the craniospinal irradiation is performed only in high-grade tumors. It is necessary to point out that the high-grade ependymoma is totally different from the ependymoblastoma, which is a small cell embryonal neoplasm with ependymal rosettes. It is typical of a child under three and arises in the cerebrum [37].

Several histotypes can be found in most tumors of the posterior fossa which we have already discussed. Within the posterior fossa other neoplasms can develop as which we shall not examine. However we must say that symptoms are generally linked to increased intracranial pressure and to the location of tumor.

**Midbrain**

If we take a look at the midbrain or diencephalon anatomy, we recognize several structures from the back to the front: the pineal region, the third ventricle, the thalamus, the hypothalamus, the pituitary region, the optic chiasm and over these structures the corpus callosum.

**Pineal region tumors**

Starting with the description of the pineal region tumors, we find two kinds of tumors, mainly, the germ cell tumors and the tumors of the pineal gland. The latter can be divided into 'pineocytoma' and 'pineoblastoma'. The first one is a non-infiltrating, non-cystic mass in the posterior third ventricle, almost always found in adults. The second one is an infiltrating and medulloblastoma-like tumor, more frequently discovered in young children (medulloblastoma-like because of its classification among the "small cell embryonal tumors").

The germ cell tumors are present in the pineal region but they could appear in several other sites as gonads, chest and inside the brain (overall suprasellar region). In the brain they could be classified according to Rubinstein [39]: germinomas (pinealomas), atypical pineal teratomas or ectopic pinealomas), teratomas, choriocarcinomas and yolk sac tumors.
All tumors of pineal gland region have, more or less, the same clinical features depending on the location of the tumor: mainly, signs of increased intracranial pressure with Parinaud’s syndrome and lack of convergence. When present, the diabetes insipidus, visual loss and hypopituitarism indicate a germinoma developing in suprasellar region. In the differential diagnosis it must be considered the presence of calcification in germinomas and absence in teratomas and pineal parenchymatous tumors [40, 41]. Moreover the finding of tumor markers, α-feto-protein and β-HCG, in CSF and blood can confirm the diagnosis of a germ cell tumor. Up to now the chemotherapy and surgery with or without radiotherapy help to obtain a 60/70% disease-free survival rate at 5 years, at least in children with non-metastatic tumors.

Tumors arising in third ventricle and thalamus

In the third ventricle ependymomas and choroid plexus tumors are commonly found. The clinical features depend on the increased intracranial pressure.

Thalamic tumors occur in adults and are mainly high-grade astrocytomas. The most frequent signs are headaches, vomiting and mental changes. The latter are represented by apathy, memory loss and rarely psychotic manifestation. Auditory hallucinations and dementia are known. Hemiparesis, dysmetria, visual loss and papilledema are present in the advanced disease. Clinical seizures are unusual.

Hypothalamic tumors

We shall discuss hypothalamic tumors separately from the optic chiasm tumor even if it is often very difficult to distinguish them clinically.

The "juvenile pilocytic astrocytoma" is the histotype more frequently found. The tumors enhance on CT-scan and, on T1-weighted MRI, appear bright. That is an argument for the differential diagnosis. Endocrine dysfunctions and nystagmus without visual loss can indicate an hypothalamic lesion. Frequently we observe the Russell or diencaphalic syndrome characterized by emaciation, pendular searching nystagmus and maintained good activity, almost augmented. This syndrome appears in children under three years of age [42]. The physiologic reason for this is unknown [43]. Another sign of hypothalamic tumor is the precocious puberty and also the accelerated long bone growth. Treatment of these tumors remains surgery followed by radiotherapy. The results are sufficiently satisfactory, unlike those obtained in the treatment of thalamic tumors.

Pituitary tumors

Most pituitary tumors are adenomas. They could be classified in acidophil, basophil and chromophobe subtypes according to their hematoxylin-eosin staining. They appear in adults and very rarely in children, with a distribution of 50% chromophobe, 40% acidophil and 10% basophil.

The symptoms and signs depend on the mechanical action of a space-occupying mass and on related endocrinopathy. Thus, loss of vision from chiasmal invasion, headaches, cranial nerves palsies (III, IV, VI), seizures, papilledema are frequently associated with a pituitary adenoma. Hypopituitarism, isolated hypothanecorticism and hyperpituitarism are the most commonly present endocrinopathies related to these tumors. Another important syndrome must be mentioned: pituitary apoplexy. This syndrome results from a hemorrhage within the pituitary adenoma and causes severe headaches, nausea and vomiting. The patient is confused, with fever and progressive visual loss. The lumbar puncture shows an hemorrhagic CSF. The surgical therapy helps and supplementary hormon therapy is needed.

Another tumor that can be found in this region is the chnaniopharyngioma which could be divided in adamantinomatous and papillary. The former presents in children as a calcified cystic mass associated to hypopituitarism and visual abnormalities. The latter is encountered in adults as a solid mass. The most efficacious therapy is surgery.

Optic pathway tumors

Frequently present in children affected by neurofibromatosis type 1, the optic pathway tumors are astrocytomas and above all "pilocytic astrocytomas". They can be located on one or both optic nerves or they can arise from chiasm and involve optic nerves and/or posterior structures. The most commonly encountered signs and symptoms are: diminished visual acuity, exophthalmos, strabismus, nystagmus, visual field defects, increased intracranial pressure, hydrocephalus. Radiologically, the enlargement of optic foramen and calcifications in the sella turcica region are considered pathognomonic.

The high incidence of these tumors in patients affected by neurofibromatosis might be a reason to perform a control CT-scan in every patient, at least once a year.

In the midbrain other tumors can develop which we shall only mention: the choroid plexus neoplasms, the glanular cell tumors of the infundibulum, the ependymomas.

Hemispheres

Among all the tumors that can be found in the hemispheres we can recognize the glioblastoma multiforme, the anaplastic astrocytoma, the oligodendroglioma and the meningioma. This localization is, surely, more frequent in adults than in children.
Common presenting symptoms are headaches. If they appear with a persistent focality, it is possible to localize the tumor in 93% of the cases [44]. Other frequent symptoms are seizures; their incidence ranges from 30% to 60% [45, 46]. It is interesting to note that seizures are inversely related to the aggressiveness of the tumor and to the prognosis. In fact, slow-growing, low-grade astrocytoma they are very frequent, instead in the glioblastoma multiforme they are quite rare [47].

Clinicians are helped to localize the tumor by some features that are characteristic of a specific region, although not stereotypic.

The frontal lobe tumors present personality changes and contralateral difficulties of movement (up to spastic hemiplegia). The left frontal lobe tumor can cause non-fluent dysphasia with apraxia of tongue.

A tumor situated in one of the temporal lobes frequently reveals homonymous quadrantanopsia auditory hallucinations. A fluent aphasia can be found when the dominant lobe is touched.

Difficulties in reading and problems of awareness as anosognosia, dysgraphia and apraxia can be considered as clinical features of the parietal tumors.

Finally, occipital lobe tumors can cause visual field deficits and visual aberrations.

Some pathologies, as the reader will notice, have not been examined, among which we shall mention some embryonal tumors (as the retinoblastoma and the intracranial neuroblastoma) and the mesenchymal tumors (as hemangiopericytoma, chondroma, chordome).

**Biological markers**

Diagnosis and classification of brain tumors are grounded on some tools, the most important of which are: histology, cytology, immunohistochemistry, molecular and genetics studies, biochemistry, DNA cytofluorometry, neuroimaging. This paper deals with immunohistochemistry, whereas the molecular and genetic aspects will be discussed by Fronza et al. in this issue (pp. 159-166).

**Immunohistochemical markers**

The introduction of immunohistochemistry in neuropathology has given a useful method for analysing brain tumors using the antigen-antibody reaction. The specificity is almost always very high. Thus it was possible to find some immunohistochemical markers which allow a differentiation between the glial cells and the neuronal cells.

The main markers are listed in Table 1.

The glial fibrillary acidic protein (GFAP) is a major marker of glial cytoplasmic filaments. The S-100 protein has a minimal diagnostic utility because it is found in many neoplasms, also outside the CNS.

Neurone-specific enolase (NSE) too is a non-specific marker of neuronal tumors. Synaptophysin is a component of synaptic vesicle membranes. Neoplastic cells, as well as normal cells of meningotheial origin, have a positivity for the epithelial membrane antigen (EMA). Keratin is important in the diagnosis of craniofibrosarcoma. Elevated levels of α-β-cryllin in some are found in more aggressive stage gliomas.

Ki-67 is an antibody directed toward a nuclear antigen: it is a marker of cycling cells.

The Ki-67 with the proliferating cell nuclear antigen (PCNA) are considered proliferation markers. In fact their presence indicates the S-phase of the cell cycle. The GFAP and the S-100 protein decrease along with the increase of gliomas grade. Vimentin increases along with the indifferentiation degree. Thus, these three

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PA: pilocytic astrocytoma; AA: anaplastic astrocytoma; GBLM: glioblastoma multiforme; Medull.: medulloblastoma; Epend.: ependimoma; Pneuoc.: pineocytoma; Germ.: germoma; Menig.: meningioma; Cranio: craniopharyngioma; GFAP: glial fibrillary acidic protein; S-100: S-100 protein; NSE: neurone-specific enolase; EMA: epithelial membrane antigen; CK: cytokeratin; SYN: synaptophysin; α-β-CRY: α-β-cryllin.
markers give a good tool to understand the anaplasia stage of astrocytomas.

Other markers can be mentioned as estrogen receptor-related antigen (ER-DS) in meningioma and hemangio-blastoma. It could have an important role in the growth and angiogenesis of brain tumors [48]; paragloboside that is correlated with the aggressiveness of astrocytomas [49]. Flasminogen activator inhibitor type 1 (PAI-1) is not a marker of tumoral cells but it is positive in glomeruloid-shaped proliferative vessels, which are more frequently present in high-grade tumors than in low-grade ones [50].

**Biochemical markers**

When we refer to biochemical markers, we mean the biochemical properties of a given cell type or tissue, and the presence of several particular products of increased biochemical pathways.

An interesting method of investigation of the biochemical properties of tumors in vivo is the positron emission tomography (PET). Available PET markers are: fluorodeoxyglucose (FDG), 11c-methionine (11c), iododeoxyuridine (IUdR), 11c-pustesocene. The FDG is an interesting marker to study the glucose metabolism [51-53]. Clinical literature shows that although a correlation exists between FDG uptake and histological grading, proliferation of brain tumor is not well investigated by this one.

11c is a useful marker to estimate the aminoacid uptake. Its uptake is increased in low-grade gliomas and can delineate the extent of recurrent brain tumor [54].

The use of IUdR, a halogenated pyrimidine nucleoside, can be a tool to study DNA metabolism and proliferation rate of tumors, but the data of literature are controversial.

The polyanines, such as pustesocene, sphermidine and spermine, are known to be involved in proliferation. Thus, 11c-pustesocene is a good tracer for PET. Furthermore, the polyanines are useful markers for medulloblastoma patients. In fact it is possible to find them in the CSF of these patients as alpha-feto-protein and beta-HCG (two other biochemical markers) are found in CSF and blood of germ cell tumors patients.

We must point out that when a PET is performed, one should consider the role of blood-brain barrier alterations in the tracer uptake in brain tumors.

In this paper we have tried to analyse the principal brain tumors and several of their immunohistochemical and biochemical markers, knowing how difficult it is to make a summary of such a large chapter of oncology, even more so as there are no homogeneous data and opinions in the scientific world on this matter.

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