NEURO-ONCOLOGY

NEURO-ONCOLOGY: BLUE BOOKS OF NEUROLOGY SERIES

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SERIES PREFACE

The *Blue Books of Neurology* have a long and distinguished lineage. Life began as the *Modem Trends in Neurology* series and continued with the monographs forming *BIMR Neurology.* The present series was first edited by David Marsden and Arthur Asbury, and saw the publication of 25 volumes over a period of 18 years.

The guiding principle of each volume, the topic of which is selected by the Series Editors, was that each should cover an area where there had been significant advances in research and that such progress had been translated to new or improved patient management.

This has been the guiding spirit behind each volume, and we expect it to continue. In effect, we emphasize basic, translational, and clinical research but principally to the extent that it changes our collective attitudes and practices in caring for those who are neurologically afflicted.

Tony Schapira took over as joint editor in 1999 following David's death, and together with Art oversaw the publication and preparation of a further 8 volumes. In 2005, Art Asbury ended his exceptional co-editorship after 25 years of distinguished contribution and Martin Samuels was asked to continue the co-editorship with Tony.

The current volumes represent the beginning of the next stage in the development of the Blue Books. The editors intend to build upon the excellent reputation established by the Series with a new and attractive visual style incorporating the same level of high-quality review. The ethos of the Series remains the same: up-to-date reviews of topic areas in which there have been important and exciting advances of relevance to the diagnosis and treatment of patients with neurological diseases. The intended audience remains those neurologists in training and those practicing clinicians in search of a contemporary, valuable, and interesting source of information.

ANTHONY H.V. SCHAPIRA
MARTIN A. SAMUELS
Series Editors

PREFACE

This is the first 'Blue Book' in neuro-oncology and now justifies inclusion in this illustrious Neurology series as a sign of the increasing interest and developments in this field. Indeed it is a tribute to the vision of Elsevier that such a book was commissioned, in recognition of the explosive advances in pathology, molecular biology and imaging that have transformed the landscape of neuro-oncology.

These advances, both in the clinical and scientific arena of neuro-oncology, have generated increasing optimism for our patients with these terrible diseases. As a result, a subspecialty that was only of interest to neurosurgeons and neuropathologists has now been adopted by an increasing number of disciplines to the point that clinical care is now delivered by multidisciplinary teams consisting of neurologists, radiation and medical oncologists, clinical nurse specialists, palliative care physicians, neuropsychologists and allied health professionals. It is hoped that this book will appeal to all members of the multidisciplinary team.

The book represents a collaboration between experts on both sides of the Atlantic and aims to provide a comprehensive review of the pathology, genetics, radiological and clinical features of benign and malignant tumors of the nervous system, together with chapters on metastases and the neurological complications of cancer and its treatments. Childhood brain tumors and the neurological complications of bone marrow and organ transplantation are also covered for completeness.

Most chapters have been written by one or two authors from the same institution, who have extensive experience in the management of these tumors. We have tried to recruit specialists from a number of different cancer centers to provide a variety of different viewpoints and we hope that this approach will provide a well-balanced reference for those who work in this field.

We would like to dedicate this work to those patients and their families who live every day with the daunting challenge of these diseases.

JEREMY H. REES, PhD, FRCP
PATRICK Y. WEN, MD

1 Pathology and Molecular Genetics of Common Brain Tumors

V. PETER COLLINS

Introduction

This chapter aims to provide an outline of the surgical pathology and the recognized genetic and molecular changes of common tumors of the nervous system in children and adults. The current World Health Organization (WHO) histological classification for nervous system tumors will be used as its framework.[1] The histological basis for classification and malignancy grading of the tumors is briefly presented and some of the common diagnostic problems outlined. The WHO classification is complex, listing over 120 histological entities. In the case of some of the tumors recognized, there is as yet only a histological description and no genetic information is available. The reader is referred to the fourth edition of the WHO classification of tumors of the nervous system and the specialized literature for the tumor types not addressed here.[1] The genetic and molecular information we have on the common tumors is steadily increasing, but is still rudimentary. While the genetic and molecular findings are not, as yet used, clinically, as soon as molecular targeted therapies become available and are found to be effective, histological investigation will *have* to be supplemented with molecular data.

Most classifications of brain tumors presented during the last 60 years build on the 1926 work of Bailey and Cushing.[2] In their classification, tumors were named after the recognized cell types in the developing embryo/fetus or adult that the tumor cells most resembled histologically. The cell type of origin of the

majority of brain tumors is unknown, as no premalignant states are recognized. In some tumors the cells may be so dysplastic that they show no similarities to any normal cell type—thus the use of terms such as glioblastoma. In the present WHO classification (for an overview, see Table 1-1), tumors are divided up into those of neuroepithelial origin (includes the glial, glioneuronal, neuronal, pineal and embryonal tumors), tumors of cranial and paraspinal nerves, tumors of the meninges, lymphomas and hematopoetic neoplasms, germ cell tumors, tumors of the sellar region and metastases. The tumor types and their possible WHO grades are given in Table 1-1.

It is impossible to cover the histopathology and genetics of all these different tumor types in one chapter, so the focus will be on the common tumors of children (pilocytic astrocytomas, ependymomas, and medulloblastomas), and of adults (the diffuse astrocytic tumors including astrocytomas, anaplastic astrocytomas, and glioblastomas, as well as oligodendrogliomas and meningiomas). In addition, lymphomas and metastases will be very briefly considered.

GENERAL CONSIDERATIONS

Many brain tumors are morphologically heterogeneous, and many brain tumor types are known to become more malignant with time, with their progression initially being focal. Thus, for both reasons, adequate sampling of a tumor is essential to determine the correct tumor classification or type of tumor as well as the WHO grade. Classification of brain tumors is dependent on the recognition of areas with the characteristic histology for a particular tumor type, often assisted by immunocytochemical methods. Immunocytochemistry permits the demonstration of antigens associated with a particular cell type and even their subcellular location. As yet, there are no single antibodies or even panels of antibodies that unequivocally identify any of the brain tumors listed in the 2007 WHO classification.[2] Thus, the presence or absence of an antigen only adds a further piece of information, helping to indicate the tumor type.

Once a tumor has been classified, the histologically most malignant part of the tumor determines the malignancy grade (often referred to as the WHO grade when using the criteria defined by the WHO classification).[1] The histological criteria for malignancy grading are not uniform for all tumor types and thus all tumors must be classified first before a WHO malignancy grade can be determined. The WHO system recognizes four grades of malignancy; these provide an assessment of the biological aggressiveness of the untreated tumor. Grade I tumors are the biologically least aggressive and may be cured by surgery alone (e.g., pilocytic astrocytoma). Grade IV tumors are biologically highly aggressive, with rapid growth and the ability to infiltrate locally and disseminate within the central nervous system. Untreated, they are rapidly fatal (e.g., glioblastoma). General criteria for determining WHO malignancy grade include cellularity, degree of polymorphism and atypia, the incidence of mitoses, the presence of spontaneous necrosis and the degree of angiogenesis induced by the tumor (microvascular proliferation), but, as indicated above, these are not universal. The criteria for determining the WHO grade for each tumor type have been empirically derived by correlating the histology of surgically removed tumor tissue with otherwise untreated patient survival. Extrapolation from such studies provides a basis for

TABLE 1-1 Familial Syndromes Associated with Human Brain Tumors

Disorder	Gene	Location	Protein function	Tumor types associated with disorder	Involved in sporadic CNS tumors	References
Neurofibromatosis type 1	*NF1*	17p11.2	GTPase activating protein homology	Astrocytomas (brain stem, optic nerve) ependymomas, PNETs and meningiomas (pheochromocytoma), etc.	Unknown	246
Neurofibromatosis type 2	*NF2*	22q12.2	Ezrin/moesin/ radixin-like	Vestibular schwannomas, meningiomas, spinal schwannomas	Meningiomas, schwannomas	247
Turcot syndrome A	*APC*	5q21-q22	Regulates β-catenin	Medulloblastoma	Unknown	248
Turcot syndrome B	*MLH1* *MSH2* *MLH3* *PMS1* *PMS2*	3p21.3 2p22-p21 14q24 2q31-q33 7p22	Microsatellite instability (MIN+)	Glioblastoma (unknown if all germline mutations are associated with glioblastoma)	Unknown; astrocytic tumors that are MIN+ occur but are uncommon	249
Basal cell nevus syndrome/ Gorlin syndrome	*PTCH*	9q22.3	Receptor for SHH inhibits SMO	Medulloblastoma	Medulloblastoma	248
Cowden disease (multiple hamartoma syndrome, Lhermitte-Duclos, etc.)	*PTEN*	10q22-q23	Dual specificity phosphatase and tensin homology	Astrocytomas reported but tumors in other organs more common—thyroid, breast, female genitourinary tract	Glioblastoma	250
Tuberous sclerosis	*TSC1*	9q34 (40%)	Binds to pTSC2	Subependymal giant cell astrocytoma as well as various harmartomas	Unknown	251

Table continued on following page

TABLE 1-1 **Familial Syndromes Associated with Human Brain Tumors** (Continued)

Disorder	Gene	Location	Protein function	Tumor types associated with disorder	Involved in sporadic CNS tumors	References
	TSC2	16p13.3	GTPase activating protein homology	Subependymal giant cell astrocytoma as well as various harmartomas	?	251
von Hippel-Lindau	*VHL*	3p26-p25	Part of a transcription elongation factor inhibiting, e.g., VEGF expression	Hemangioblastoma (pheochromocytoma/ RCC, etc.)	Unknown	252
Li Fraumeni	*TP53* (*only 70%*)	17p13.1	Transcription factor, apoptosis induction, etc.	Many including astrocytomas	Mainly astrocytic	253, 254
Melanoma-astrocytoma syndrome	*CDKN2A/ p14ARF*	9p21	Cell cycle control (G1-S)/p53 level control	Astrocytomas	Astrocytic	255

an assessment of prognosis, but the provision of therapy may radically alter this assessment.

Tumor type and grade generally determine the choice of conventional therapy. It is important to remember that radiation therapy or chemotherapy administered prior to histological diagnosis will alter tumor morphology, making classification and grading extremely difficult or impossible. The WHO morphological criteria have been determined for untreated tumors. In addition, WHO grading of a biopsy is always considered a minimum malignancy grading, as more anaplastic regions may be present in unbiopsied areas of the tumor.

The use of objective methods of measuring cell proliferation and cell death (apoptosis) in tumors to determine WHO malignancy grade is conceptually attractive. However, the wide variations in proliferation indices observed in different areas of individual tumors have resulted in difficulties in defining relevant proliferation levels. The same applies to the assessment of the numbers of cells undergoing apoptosis. In the WHO system, mitotic counts (mitoses per ten 0.16 mm^2 high power fields) are currently only used in the grading of meningiomas. The MIB-1 antibody that recognizes the same antigen as the Ki67 antibody and thus cells in the cell cycle can also be used to assess cell cycle activity. Other antibodies that identify antigens associated with proliferation (e.g., Cdc6 and Mcm5) can be applied to formalin-fixed, paraffin-embedded tissues following microwave antigen retrieval.[3,4] However, the WHO system generally only gives information on commonly observed ranges for both the mitotic index and MIB index for most tumor types and WHO malignancy grades.

Today, almost any neoplastic or nonneoplastic lesion in the CNS can be biopsied using widely available neuroradiological and stereotactic techniques. The list of potential diagnoses a neuropathologist may be expected to make, often on the basis of very small and fragmented biopsies, is vast. The importance of clinical information cannot be overemphasized. Information must be provided to the neuropathologist on age, neuroradiological findings including location of the lesion, relevant clinical and family history, and whether the patient has received *any* treatment, including steroids. In the case of stereotactic biopsies, morphology combined with immunocytochemistry may only provide a differential diagnosis with the most likely diagnosis being reached by considering all the information available at a multidisciplinary team meeting.

Most brain tumors are sporadic. However, a number of familial cancer syndromes are associated with an increased risk of brain tumors (see Table 1-1 and the references therein). Even in the case of the commonest syndromes (neurofibromatosis type 1 and neurofibromatosis type 2), the precise relative risk is difficult to define.

In contrast to many epithelial neoplasms, no lesion is recognized as a precursor for any brain tumor type and, as a result, the cell of origin of these monoclonal proliferations is unknown in all cases. Recent work in animal models provides some data supporting the idea that some brain tumors arise from neuroectodermal stem cells. They are present throughout life, have proliferative potential, are migratory and can differentiate along a number of paths—all features they have in common with brain tumor cells. Furthermore, there is some evidence that at least some of the common types of brain tumors may be made up of a smallish population of therapy-resistant tumor-initiating cells (also called tumor stem cells in some texts), with the main bulk of the tumor consisting of a progeny lacking

these tumor-initiating abilities.[5–9] If this tumor-initiating cell population is not eradicated, the tumor will recur–a common experience with current therapies for many of the malignant brain tumors. Thus, much effort is currently being channeled into defining and studying this subpopulation in the hope of finding ways to specifically kill these cells.[10,11] While the genetic status (e.g., gene copy number, mutations, amplifications, etc.) of tumor-initiating cells and their progeny is likely to be identical, the epigenetic status (e.g., methylation) and the expression characteristics may differ considerably.

Childhood Tumors

PILOCYTIC ASTROCYTOMAS

The astrocytomas encompass a number of tumors of differing grade including the pilocytic astrocytomas. The majority of astrocytomas are found in adults (see following discussion). The commonest form of astrocytoma found in children is the pilocytic astrocytoma, WHO malignancy grade I. These tumors may arise anywhere from the optic nerve to the medulla oblongata. They most commonly occur in the cerebellum. They may be solid, mono- or polycystic and are generally well circumscribed. The prognosis for patients with pilocytic astrocytomas that can be excised is relatively good, with over 90% 10-year survival reported.[12] Pilocytic astrocytomas are generally biologically unaggressive, and, in contrast to the adult diffuse astrocytic tumors, maintain their grade I status over years and even decades. Only very occasionally will these tumors progress to malignant astrocytic tumors or seed the neuroaxis.[13] Pilocytic astrocytomas show a wide morphological spectrum, from pilocytic bipolar cellular areas with Rosenthal fibers (Fig. 1-1A) to less cellular protoplasmic astrocytoma-like areas with eosinophilic granular bodies and clear cells. Such clear-cell areas are reminiscent of oligodendrogliomas and, in the posterior fossa, may also be confused with clear cell ependymomas, particularly in biopsies. The presence of features typically associated with a malignant biological behavior (e.g., atypia, microvascular proliferation (Fig. 1-1B), or even mitosis) does not carry the same sinister implications as in the adult diffuse astrocytic tumors. This morphological variability can make histopathological diagnosis extremely difficult. NF1 patients have an increased incidence of pilocytic astrocytomas, particularly involving the optic nerve, and these behave in a particularly benign fashion.[14]

Many cases of pilocytic astrocytomas have been studied cytogenetically and further cases analyzed using conventional comparative genomic hybridization (cCGH). Many show normal cytogenetic and cCGH findings.[15–18] Polysomy has been found, most commonly of chromosomes 5 and 7, and, in addition, of chromosomes 6, 11, 15, and 20 (in decreasing frequency). Polysomy has been reported to be most common in adult patients with pilocytic astrocytoma.[19] Molecular genetic studies have been few; single *TP53* mutations have been reported, and loss of one allele of *NF1* has been found in pilocytic tumors from NF1 patients but not in sporadic cases.[20–24] Studies of promotor methylation of some genes known to be involved in adult diffuse astrocytic gliomas have provided inconsistent data.[25,26] There appears to be no evidence for methylation of the *NF1* gene in sporadic tumors.[27] Recently a number of groups have noted that a small region on 7q34 has