M.A. Hayat
Editor

Tumors of the Central Nervous System

Volume 9

Lymphoma, Supratentorial Tumors, Glioneuronal Tumors, Gangliogliomas, Neuroblastoma in Adults, Astrocytomas, Ependymomas, Hemangiomas, and Craniopharyngiomas

Springer

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Springer

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ISBN 978-94-007-5487-4 ISBN 978-94-007-5488-1 (eBook)
DOI 10.1007/978-94-007-5488-1
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2012954561

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

"Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena."

Richard J. Reed, MD

One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test, may revert to normal cells. Tumor shrinkage, regression, dormancy, senescence, reversal, or stabilization is not impossible. Can prosenescence therapy be an efficient alternative strategy to standard therapies for cancer prevention and treatment?

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guin et al. 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al. 2008). These and other studies justify the "wait and see" strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless *MYCN* gene is amplified. Infants with nonamplified *MYCN* and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without *MYCN* have excellent survival with minimal or no treatment. Another example of spontaneous shrinkage and loss of tumors without any treatment is an intradural lipoma (Endoh et al. 1998).

Although cancers grow progressively, various lesions such as cysts and thyroid adenomas show self-limiting growth. Probably, cellular senescence occurs in many organ types following initial mutations. Cellular senescence, the growth arrest seen in normal mammalian cells after a limited number of divisions, is controlled by tumor suppressors, including p53 and p16, and so this phenomenon is believed to be a crucial barrier to tumor development. It is well-established that cell proliferation and transformation induced by oncogene activation are restrained by cellular senescence.

Metastasis is the main cause of death from cancer. Fortunately, metastasis is an inefficient process. Only a few of the many cancer cells detached from the primary tumor succeed in forming secondary tumors. Metastatic inefficiency varies depending on the location within an organ, but the malignancy may continue to grow preferentially in a specific tissue environment. Some of the cancer cells shed from the primary tumor are lost in the circulation due to hemodynamic forces or the immune system, macrophages, and natural killer cells.

Periodic rejection of a drug by FDA, which was previously approved by the FDA, is not uncommon. Most recently, the FDA ruled that Avastin should not be used to treat advanced breast cancer, although it remains on the market to treat other cancers, including colon and lung malignancies. Side-effects of Avastin include high blood pressure, massive bleeding, heart attack, and damage to the stomach and intestines.

Unwanted side effects of some drug excipients (e.g., propylene glycol, menthol) may also pose safety concerns in some patients. Excipients are defined as the constituents of the pharmaceutical formulation used to guarantee stability, and physicochemical, organoleptic and biopharmaceutical properties. Excipients frequently make up the majority of the volume of oral and parenteral drugs. Not all excipients are inert from the biological point of view. Although adverse drug reactions caused by the excipients are a minority of all adverse effects of medicinal products, the lack of awareness of the possible risk from excipients should be a concern for regulatory agencies, physicians, and patients (Ursino et al. 2011). Knowledge of the potential side effects of excipients is important in clinical practice.

It is known that chemotherapy can cause very serious side-effects. One most recent example of such side-effects was reported by Rubsam et al. (2011). Advanced hepatocellular carcinoma (HCC) induced by hepatitis C virus was treated with Sorafenib. It is an oral multikinase inhibitor that interferes with the serine/threonine kinases RAF-1 and B-Raf and the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the platelet-derived growth factor receptor-beta. Although sorafenib is effective in regressing HCC, it shows serious side-effects including increasingly pruritic and painful skin changes (cutaneous eruption).

An example of unnecessary surgery is the removal of all the armpit lymph nodes after a biopsy when a sentinel node shows early stage breast cancer; removal of only the sentinel node may be needed. Limiting the surgery to the sentinel node avoids painful surgery of the armpit lymph nodes, which can have complications such as swelling and infection (such limited surgery is already being practiced at the Memorial Sloan-Kettering Cancer Research Center). Radiation-induced second cerebral tumors constitute a significant risk for persons undergoing radiotherapy for the management of cerebral neoplasms. High-grade gliomas are the most common radiation-induced tumors in children (Pettorini et al. 2008). The actual incidence of this complication is not known, although it is thought to be generally low.

Medical Radiation

Chromosome aberrations induced by ionizing radiation are well-known. Medical radiation-induced tumors are well-documented. For example, several types of tumors (sarcomas, meningiomas) can develop in the CNS after irradiation of the head and neck region (Parent 1990). Tumorigenic mechanisms underlying the radiation therapy of the CNS are discussed by Amirjamshidi and Abbassioun (2000) (see below).

Radiation therapy is commonly used to treat, for example, patients with primary and secondary brain tumors. Unfortunately, ionizing radiation has limited tissue specificity, and tends to damage both neoplastic and normal brain tissues. Radiation-induced brain injury, in fact, is a potential, insidious later cerebral side-effect of radiotherapy. Most commonly it consists of damage in small arteries and capillaries, resulting in secondary processes of ischemia.

After radiation therapy, imaging techniques (CT, MRI, SPECT) can be used to assess treatment response and detect radiation-induced lesions and recurrent tumors. Optical spectroscopy has also been used for detecting radiation damage (Lin et al. 2005). The F_{500} nm spectral peak allows accurate selection of tissues for biopsy in evaluating patients with new, contrast enhancing lesions in the setting of previous irradiation. This peak is highly correlated with a histological pattern of radiation injury. Deep lesions require a stereotactic biopsy to be conclusive. Also, much of the radiation effect is mediated by acute and chronic inflammatory cellular reactions. Biopsy samples supplement pathological differentiation of radiation effect from tumor progression. It should be noted that most of the biopsies show radionecrosis as well as scattered tumor cells.

Women treated with therapeutic chest radiation may develop cancer. This possibility becomes exceedingly serious considering that 50,000–55,000 women in the United States have been treated with moderate to high-dose chest radiation (~20 Gy). This possibility is much more serious for pediatric or young adult cancer patients, because these women are at a significantly increased risk of breast cancer and breast cancer mortality following cure of their primary malignancy (Mertens et al. 2008). A recent study also indicates that such young women develop breast cancer at a young age, which does not appear to plateau (Henderson et al. 2010). In this high-risk population, ironically there is a benefit associated with early detection. In other words, young women with early stage breast cancer following chest radiation have a high likelihood for favorable outcome, although life-long surveillance is needed.

Presently, although approximately 80% of the children with cancer are cured, the curative therapy could damage a child's developing organ system; for example, cognitive deficits following cranial radiotherapy are well known. Childhood survivors of malignant diseases are also at an increased risk of primary thyroid cancer (Sigurdson et al. 2005). The risk of this cancer increases with radiation doses up to 20–29 Gy. In fact, exposure to radiation therapy is the most important risk factor for the development of a new CNS tumor in survivors of childhood cancer, including leukemia and brain tumors. The higher risk of subsequent glioma in children subjected to medical radiation at a very young age reflects greater susceptibility of the developing brain to

radiation. The details of the dose–response relationships, the expression of excess risk over time, and the modifying effects of other host and treatment factors have not been well defined (Neglia et al. 2006).

A recent study indicates that childhood brain tumor survivors are at an increased risk of late endocrine effects, particularly the patients treated with cranial radiation and diagnosed at a younger age (Shalitin et al. 2011). Among children with cancer, the application of radiotherapy, therefore, should not be taken lightly, and it should be administered only when absolutely necessary to successfully treat the primary tumor. When radiotherapy is administered, use of the minimum effective dose tends to minimize the risk of second CNS neoplasms (late effect). Prolonged follow-up of childhood cancer survivors (particularly those treated with radiation) is necessary because of the long period between treatment and the development of malignancy. This practice should be a part of the effective therapy of the primary disease.

It is well established that radiation doses are related to risk for subsequent malignant neoplasms in children with Hodgkin's disease. It has been reported that increasing radiation dose was associated with increasing standardized incidence ratio ($p=0.0085$) in survivors of childhood Hodgkin's disease (Constine et al. 2008). Approximately, 75% of subsequent malignancies occurred within the radiation field. Although subsequent malignancies occur, for example, in breast cancer survivors in the absence of radiotherapy, the rise increases with radiation dose.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, chemotherapy or hormonal therapy or a combination of these therapies? Although the conventional belief is that cancer represents an "arrow that advances unidirectionally", it is becoming clear that for cancer to progress, it requires cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression, and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Prostate Cancer

There were an estimated 217,730 new cases of prostate cancer in the United States in 2010 with 32,050 deaths, making it the second leading cause of cancer deaths in men. Currently, there are more than 2,000,000 men in the United States who have had radical or partial prostate surgery performed. Considering this huge number of prostate surgeries and the absence of a cumulative outcome data, it seems appropriate to carefully examine the benefits of radical surgery, especially in younger men.

Clinical prostate cancer is very rare in men of the ages younger than 40 years. In this age group the frequency of prostate malignancy is 1 in 10,000 individuals. Unfortunately, the incidence of malignancy increases over the ensuing decades, that is, the chance of prostate malignancy may reach to 1 in 7 in men between the ages of 60 and 79 years. Reactive or aging-related alterations in the tumor microenvironment provide sufficient influence,

promoting tumor cell invasion and metastasis. It has been shown that nontumorigenic prostate epithelial cells can become tumorigenic when cocultured with fibroblasts obtained from regions near tumors (Olumi et al. 1999).

Prostate cancer treatment is one of the worst examples of overtreatment. Serum prostate specific antigen (PSA) testing for the early detection of prostate cancer is in wide use. However, the benefit of this testing has become controversial. The normal cut-off for serum levels of PSA is 4 ng/ml, so a man presenting with a PSA above this level is likely to require a rectal biopsy, but only 25% of men with serum levels of PSA between 4 ng and 10 ng/ml have cancer (Masters 2007). The PSA threshold currently being used for biopsy ranges between 2.5 and 3.4 ng/ml. Up to 50% of men presenting with prostate cancer have PSA levels within the normal range. It is apparent that screening of prostate cancer using PSA has a low specificity, resulting in many unnecessary biopsies, particularly for gray zone values (4 ng–10 ng/ml). According to one point of view, the risks of prostate cancer overdetection are substantial. In this context, overdetection means treating a cancer that otherwise would not progress to clinically significant disease during the lifetime of the individual. Overdetection results in overtreatment. The advantages and limitations of PSA test in diagnosing prostate cancer were reviewed by Hayat (2005, 2008).

Androgen deprivation therapy (ADT) is an important treatment for patients with advanced stage prostate cancer. This therapy is carried out by blocking androgen receptor or medical or surgical castration. Although ADT is initially very effective, treated tumors inevitably progress to androgen-independent prostate cancer (AIPC), which is incurable. One possible mechanism responsible for the development of AIPC is modulation of the tissue microenvironment by neuroendocrine-like cancer cells, which emerge after ADT (Nelson et al. 2007).

Recently, Pernicova et al. (2011) have further clarified the role of androgen deprivation in promoting the clonal expansion of androgen-independent prostate cancer. They reported a novel linkage between the inhibition of the androgen receptor activity, down-regulation of S-phase kinase-associated protein 2, and the formation of secretory, senescent cells in prostate tumor cells. It is known that several components of the SASP secretome, such as IL-6, IL-8, KGH, and epidermal growth factor, are capable of transactivating androgen receptor under androgen-depleted conditions (Seaton et al. 2008). It needs to be pointed out that androgen deprivation therapy, used in high-risk patients with prostate cancer, may cause reduced libido, erectile dysfunction, fatigue, and muscle loss; osteoporosis is also a late complication. Therefore, periodic bone density scanning needs to be considered.

Recently, the FDA cleared the use of NADiA (nucleic acid detection immunoassay) ProsVue prognostic cancer test. This proprietary nucleic acid detection immunoassay technology identifies extremely low concentrations of proteins that have not been routinely used as a diagnostic or prognostic aid. It is an in vitro diagnostic assay for determining the rate of change of serum total PSA over a period of time. The assay can quantitate PSA at levels <1 ng/ml. This technique can be used as a prognostic marker, in conjunction with clinical evaluation, to help identify patients at reduced risk for recurrence of prostate

cancer for years following prostatectomy. It targets the early detection of proteins associated with cancer and infectious diseases. This technique combines immunoassay and real-time PCR methodologies with the potential to detect proteins with femtogram/ml sensitivity (10–15 g/ml). Additional clinical information is needed regarding its usefulness in predicting the recurrence.

A significant decrease in the risk of prostate cancer-specific mortality is observed in men with few or no comorbidities. Indeed, active surveillance in lieu of immediate treatment (surgery or radiation, or both) is gaining acceptance. Most men with prostate cancer, even those with high-risk disease, ultimately die as a result of other causes (Lu-Yao et al. 2009). Debate on this controversy is welcome, but narrow opinions and facile guidelines will not lead to facts and new information; men worldwide deserve it (Carroll et al. 2011). Automatic linking positive diagnosis with treatment, unfortunately, is a common clinical practice. Unfortunately, even men who are excellent candidates for active surveillance in the United States often undergo some treatment. Deferment of treatment is advised in men with low-risk disease, especially of a younger age.

Active surveillance is proposed for patients with low-risk prostate cancer in order to reduce the undesirable effects of overdiagnosis. Prostate specific antigen serum level lower than 10 ng/L and Gleason score lower than 7 are the main criteria to select patients for active surveillance. The correct use of these two criteria is essential to differentiate between aggressive and nonaggressive prostate cancer. Autopsy studies indicate that approximately one out of three men older than 50 years show histological evidence of prostate cancer (Klotz, 2008). Thus, a large proportion of prostate cancers are latent, never destined to progress, or affect the life of the patient. It is estimated that the percentage of low-risk prostate cancer is between 50 and 60% of newly diagnosed cases. A large number of patients die having prostate cancer, but not because of this cancer (Filella et al. 2011).

First whole genome sequences of prostate tumors were recently published online in *Nature* journal (vol. 470: 214–220, 2011). This study revealed that rather than single spelling errors, the tumor has long "paragraphs" of DNA that seem to have broken off and moved to another part of the genome (rearrangement of genes), where they are most active. These portions of DNA contain genes that help drive cancer progression. The mutated genes involved include PTEN, CADM2, MAG12, SPOP, and SPTA1. This information may lead to the development of more efficient, less invasive ways to diagnose and treat this cancer. Such information, in addition, should lead to personalized therapeutics according to sequencing results of different gene mutations or chromosomal rearrangements. The urgent need of such studies becomes apparent considering the huge number of new cases of prostate problems reported every year.

In contrast to prostate cancer, cardiovascular disorders take the heavier toll of life. In other words, the risk of death for men in the United States between the ages of 55 and 74 years due to cardiovascular disease surpasses that of prostate cancer. Cardiovascular disease is the most common of the chronic non-communicable diseases that impact global mortality. Approximately,

30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by cardiovascular disease alone.

In conclusion, initial treatment with standard surgery, irradiation, chemotherapy, or hormonal therapy, or combination of these protocols can result in both local and systemic sequelae. Therefore, surveillance for late recurrence and secondary primary malignancies is recommended for most cancer patients. Patients with breast, lung, prostate, colorectal, and head and neck cancers constitute the largest groups requiring long-term monitoring and follow-up care.

Eric Hayat

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Preface

It is recognized that scientific journals and books not only provide current information but also facilitate exchange of information, resulting in rapid progress in the medical field. In this endeavor, the main role of scientific books is to present current information in more details after careful additional evaluation of the investigational results, especially those of new or relatively new therapeutic methods and their potential toxic side-effects.

Although subjects of diagnosis, drug development, therapy and its assessment, and prognosis of tumors of the central nervous system, cancer recurrence, and resistance to chemotherapy are scattered in a vast number of journals and books, there is need of combining these subjects in single volumes. An attempt will be made to accomplish this goal in the projected ten-volume series of handbooks.

In the era of cost-effectiveness, my opinion may be minority perspective, but it needs to be recognized that the potential for false-positive or false-negative interpretation on the basis of a single laboratory test in clinical pathology does exist. Interobserver or intraobserver variability in the interpretation of results in pathology is not uncommon. Interpretative differences often are related to the relative importance of the criteria being used.

Generally, no test always performs perfectly. Although there is no perfect remedy to this problem, standardized classifications with written definitions and guidelines will help. Standardization of methods to achieve objectivity is imperative in this effort. The validity of a test should be based on the careful, objective interpretation of the tomographic images, photo-micrographs, and other tests. The interpretation of the results should be explicit rather than implicit. To achieve accurate diagnosis and correct prognosis, the use of molecular criteria and targeted medicine is important. Equally important are the translation of molecular genetics into clinical practice and evidence-based therapy. Translation of medicine from the laboratory to clinical application needs to be carefully expedited. Indeed, molecular medicine has arrived.

This is the ninth volume in the series, *Tumors of the Central Nervous System*. As in the case of the seven previously published volumes, this volume mainly contains information on the diagnosis, therapy, and prognosis of brain tumors. Various aspects of nine types of brain tumors (Astrocytoma, Lymphoma, Supratentorial Tumors, Glioneuronal Tumors, Gangliogliomas, Neuroblastoma in Adults, Hemangioma, and Ependymoma) are discussed.

Introduction to new technologies and their applications to tumor diagnosis, treatment, and therapy assessment are explained. Molecular profiling of brain

tumors to select therapy in clinical trials of brain tumors is included. Several surgical treatments, including resection and radiosurgery, are discussed. The remaining volumes in this series will provide additional recent information on this and other aspects of CNS malignancies.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against this terrible disease. It would be difficult for a single author to discuss effectively the complexity of diagnosis, therapy, and prognosis of any type of tumor in one volume. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of the CNS cancer. I hope these goals will be fulfilled in this and other volumes of this series. This volume was written by 68 contributors representing 17 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the reader in this important area of disease. I respect and appreciate the hard work and exceptional insight into the nature of cancer provided by these contributors. The contents of the volume are divided into nine parts: Lymphoma, Supratentorial Tumors, Glioneuronal Tumors, Gangliogliomas, Neuroblastoma in Adults, Astrocytoma and Ependymoma, Hemangiomas, Craniopharyngiomas, and Neurogenesis for the convenience of the reader.

It is my hope that the current volume will join the preceding volumes of the series for assisting in the more complete understanding of globally relevant cancer syndromes. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure, and hopefully prevention. In the light of existing cancer calamity, financial funding by governments must give priority to eradicating this deadly malignancy over military superiority.

I am thankful to Dr. Dawood Farahi and Dr. Kristie Reilly for recognizing the importance of medical research and publishing through an institution of higher education. I am thankful to my students for their contribution to the prepartion of this volume.

May, 2012 M.A. Hayat

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Part I

Lymphoma

Neurolymphomatosis: Diagnosis, Treatment, and Outcome

1

Tali Siegal

Contents

Abstract

The term neurolymphomatosis (NL) encompasses nerve infiltration by neurotropic neoplastic cells in the setting of an unknown or a known hematologic malignancy. It is a rare neurologic manifestation of non-Hodgkin lymphoma (NHL) and leukemia with a poorly defined incidence. The typical manifestations of NL are of a neuropathy that may affect peripheral nerves, nerve roots, plexus, or cranial nerves. The most common presentations include painful peripheral neuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy and peripheral mononeuropathy or a mononeuropathy multiplex. Successful therapy is contingent upon the recognition of this unique neurological complication, yet the diagnosis is difficult and often elusive. Of all diagnostic tools, imaging studies are of greatest clinical utility. MRI yields abnormal findings in ~80% of affected patients and FDG-PET appears to be a highly sensitive diagnostic method facilitating identification of NL. There is no known standard treatment for NL and therefore, optimal management is ill-defined. Treatment of NL consists of either chemotherapy alone or combined with radiotherapy. An aggressive multimodality therapy can prevent neurological deterioration and is associated with a prolonged survival in a subset of patients.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_1,

Introduction

The term neurolymphomatosis (NL) encompasses nerve infiltration by neurotropic neoplastic cells in the setting of an unknown or a known hematologic malignancy. It is a rare neurologic manifestation of non-Hodgkin lymphoma (NHL) and leukemia with a poorly defined incidence. The most comprehensive reviews identified 166 cases of NL reported during a 36 year period (Baehring et al. 2003; Grisariu et al. 2010).

The typical manifestations of NL are of a neuropathy that may affect peripheral nerves, nerve roots, plexus, or cranial nerves. The most common presentations include painful peripheral neuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy and peripheral mononeuropathy or a mononeuropathy multiplex. NL is usually identified when the clinical neuropathy affects nerve structures outside the thecal sac, in contrast to the infiltration of nerve roots from leptomeningeal seeding or neural compression by epidural lymphoma. The malignant lymphocytes of NL distinguish it from the benign infiltrates observed in paraneoplastic or inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) or paraproteinemias, and from the acellular neuropathic complications of chemotherapeutic agents such as vinca alkaloids or bortezomib. Successful therapy is contingent upon the recognition of this unique neurological complication, yet the diagnosis is difficult. A high index of suspicion is essential in order to prove the diagnosis but even with a careful search definitive findings may sometimes be obtained only at autopsy (Baehring et al. 2003; Grisariu et al. 2010).

Epidemiology and Pathogenesis

Neurolymphomatosis is a rare manifestation of NHL and leukemias. Its true incidence is unknown but the rate of diagnosis is probably increasing with the use of contemporary imaging techniques (Grisariu et al. 2010). More than half of the 50 patients recently reported (Grisariu et al. 2010) on behalf of the International Primary CNS Lymphoma Collaborative Group (IPCG) were diagnosed in the last 5 years. Still, this rate of diagnosis most likely represents an underestimation as the majority of cases probably remain undiagnosed.

Pathogenesis

Most NL is due to diffuse large B-cell lymphoma (Baehring et al. 2003; Grisariu et al. 2010) and the causative cells stain for B-cell-associated surface antigens. NL in T-cell lymphoma accounts for ~10–20% of all cases, and there are anecdotal reports of NK-cell types or an association with Sezary syndrome (Odabasi et al. 2001; Bezier et al. 2009). It is possible that on a molecular level NL bears a resemblance to CNS lymphoma with cells similar to germinal center or post-germinal center B-cells, corroborating the theory that it is a systemic disease with unique proclivity to affect neural structures (Larocca et al. 1998; Julien et al. 1999; Montesinos-Rongen et al. 1999; McCann et al. 2009).

It has been claimed (Baehring et al. 2003) that NL patients have a higher than expected frequency of autoimmune disorders such as recurrent chorioretinitis, hypothyroidism, Sjögren's syndrome, and lupus erythematosus. Yet, the precise figures were not given and population-based data to support this contention are lacking. Clinical similarities to Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculopathy (CIDP) are obvious and a pathogenetic link might be supported by anecdotal reports (Borit and Altrocchi 1971; Baehring et al. 2003; Pages et al. 2004; Tajima et al. 2007). In these cases years of exacerbations of painless polyradiculoneuropathy were observed. In one patient (Tajima et al. 2007) a dramatic response to intravenous immunoglobulin therapy was documented years prior to the final episode of unremitting neurological worsening that led to the diagnosis of NL. Other descriptions (Kuntzer et al. 2000) include long-standing vasculitic neuropathy that preceded NL. It is conceivable that lymphoma arises by malignant transformation of an autoreactive B-cell clone targeting peripheral neural structures

in patients with long-standing peripheral nervous system disorders.

Different trafficking pathways apply to lymphoid neoplasms of T- and B-cell lineage. T-lymphocytes accessing nonlymphoid tissues are equipped with a very different set of addressins and chemokine receptors than B-cells, which can act at a distance through secretion of antibodies. It has been suggested that B-cell migration to extralymphoid sites occurs almost exclusively in the context of chronic inflammation driven by various antigens. The reacting lymphoid tissue contains a specific expression pattern of vascular addressins and chemokine receptors (Pals et al. 1997). Ectopic chemokine expression at sites of chronic inflammation is presumably responsible for selective homing of B cells to these sites.

Site-specificity in NL is presumed to be analogous to other antigen-driven extranodal NHLs such as mucosa-associated lymphoid tissue (MALT) lymphomas and intravascular subtypes, and may share with these other lymphoid neoplasms target-organ selection derived from tissue expression of a stimulating antigen. Putative antigens include autoantigens, bacterial or viral antigens. As in normal lymphoid cells, adhesion receptors seem to determine the tissue-specific dissemination patterns of certain lymphoma subtypes (Pals et al. 1997; Drillenburg and Pals 2000). The final distribution of neoplastic lymphocytes, like their physiologic counterparts, depends on the balance of entry, proliferation, and retention (Pals et al. 1997). Specific adhesion molecules as the basis for organ selectivity of NL remain to be identified, if they exist.

Neurolymphomatosis has to be distinguished from other peripheral neuropathies occurring in the setting of hematologic malignancy (e.g., autoimmune, paraneoplastic, vasculitis, paraproteinemia, or chemotherapy-induced neuropathy). How difficult this distinction can be is exemplified by Marek's disease, a T-cell lymphoma in chicken induced by infection with oncogenic alphaherpes virus (Osterrieder et al. 2006). Marek's disease is characterized by four different forms: cutaneous, neural (nerve form), ocular, and visceral. When the disease was initially described, it was referred to as 'neurolymphomatosis gallinarum' due to the associated rapidly progressive polyneuropathy. Histologic examination revealed thickened peripheral nerves infiltrated with mononuclear cells. The infiltrates affected both the sciatic nerves and areas of the spinal cord. Although the polyneuropathy is often neuritic and not neoplastic, some phenotypic studies demonstrated that nerve fibers were infiltrated by malignant T-cells (Okada et al. 1997).

Clinical Features

Symptoms and signs of NL may appear either in the setting of a known systemic lymphoproliferative malignancy or in a patient harboring the diagnosis of primary CNS lymphoma (PCNSL). In these settings NL is a site of relapse or progression of a previously diagnosed lymphoma or leukemia. It may, however, occur as the first relapse site of a previously treated lymphoma or as the first manifestation of the neoplastic disorder (primary NL). The latter is particularly challenging diagnostically as it is the first sign of the hematologic malignancy. Primary NL accounted for 26% of the cases collected retrospectively by the IPCG (Grisariu et al. 2010). In this series NL was due to lymphoma in 90% of patients and leukemia in 10% of cases and PCNSL accounted for ~20% of all IPCG NL cases.

The most common clinical presentations of NL are a painful peripheral neuropathy or radiculopathy, followed by cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy (Baehring et al. 2003; Grisariu et al. 2010). The pain is usually severe, relentless, and dysesthetic. The neuropathy is most often characterized as a sensorimotor type but pure motor neuropathy has been described in ~20% of patients while pure sensory neuropathy is less frequent. Weakness often progresses, eventually resulting in symmetric paraparesis or quadriparesis with evolving muscle atrophy. In some patients the asymmetry of symptoms is similar to mononeuropathy multiplex. Plexopathies are frequent (30–40%) (Figs. 1.1a, b, e and 1.2a, b) but an isolated plexopathy is less common. The syndromes progress

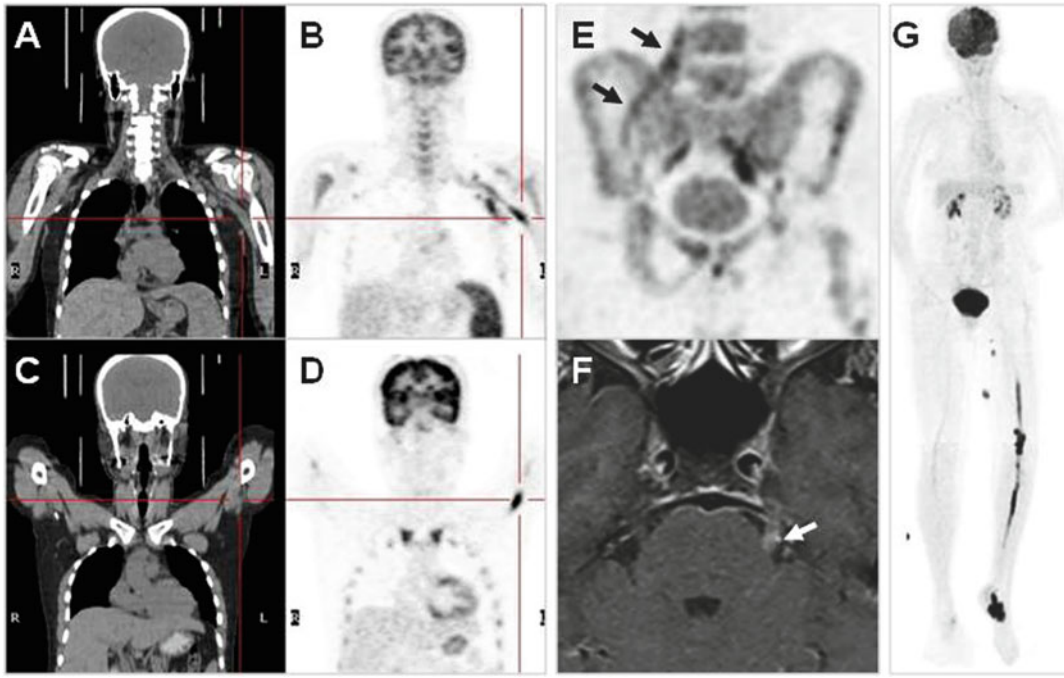

Fig. 1.1 Imaging in neurolymphomatosis (**a** and **b**) Increased uptake of the FDG tracer is demonstrated on the left brachial plexus (**b**) with localization co registered on the CT (**a**). The abnormal tracer uptake indicates that the neural structure is infiltrated by a previously diagnosed and treated lymphoma. (**c** and **d**) Left radial nerve involvement demonstrated by FDG-PET (**b**) with localization co registered on the CT (**c**) in a patient with a previous diagnosis of non-Hodgkin lymphoma. (**e**) FGD-PET imaging of the same patient as in **c** and **d** demonstrating an increased tracer uptake in the region of the right lumbosacral plexus. Multifocal infiltration of neural structures is sometimes demonstrated and accounts for the asymmetric neuropathy. (**f**) MRI imaging (Gadolinium enhanced T_1-weighted image) demonstrating an abnormal enhancement of a thickened left fifth cranial nerve (*arrow*). The patient presented with a painful trigeminal neuropathy that was later proved to be the initial manifestation of NL. (**g**) FDG-PET imaging of the same patient as in **f** demonstrating massive involvement of the left sciatic nerve. The PET study was obtained when the patient developed a painful left leg weakness. The diagnosis of primary NL was obtained by sural nerve biopsy of the affected leg

over weeks to months. Hyperacute variants reminiscent of Guillain-Barre syndrome are rare.

Mononeuropathies secondary to malignant lymphocytic infiltration of nerves occur in the sciatic, median, radial, ulnar, and intercostal nerves or may manifest as cranial mononeuropathy (Karadag et al. 2002; Dakwar et al. 2004; Bulsara et al. 2005; Iplikcioglu et al. 2006; Strobel et al. 2007; Czepczynski et al. 2008; Kitzmann et al. 2008). Motor and sensory deficits are more common than pain syndromes and may precede diagnosis of NL by months to years.

A painless neuropathy occurs in 25–30% of cases (Grisariu et al. 2010). Paresthesias, numbness, and loss of deep tendon reflexes precede weakness. Examples of painless asymmetric or patchy numbness as well as early painless proximal limb weakness reflecting plexus invasion are rare.

Involvement of cranial nerves has been detected in ~50% of patients with NL during the course of the disease (Baehring et al. 2003), but a single cranial neuropathy may herald diagnosis in ~20%. The cranial neuropathies are usually painless but painful trigeminal neuropathies have been reported (Kinoshita et al. 2003; Bulsara et al. 2005; Iplikcioglu et al. 2006; Czepczynski et al. 2008).

The majority of the patients are known to have a history of systemic or CNS lymphoma at the

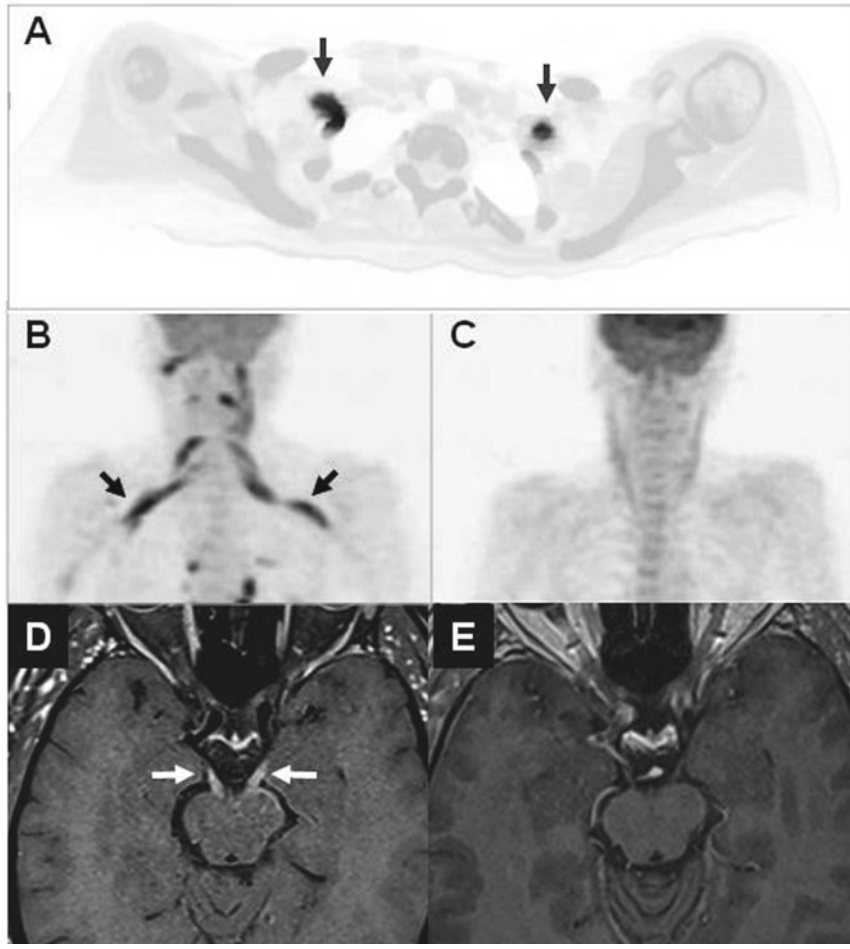

Fig. 1.2 Imaging demonstration of response to treatment in neurolymphomatosis. (**a** and **b**) FDG-PET scan (**a** is an axial view with CT co registration) of a patient with a history of non-Hodgkin lymphoma who presented with asymmetric upper extremity weakness and muscle wasting associated with mild proximal pain. The PET demonstrated abnormal uptake of the tracer in cervical spinal nerve roots (**b**) and along both brachial plexi (**a** and **b**) suggesting infiltration of the neural structures by the lymphoma. (**c**) FDG-PET scan of the same patient as in **a** and **b** after treatment with high-dose methotrexate and procarbazine. The *scan* shows no abnormal uptake. The objective response was associated with marked clinical improvement. (**d**) Bilateral symmetric thickening and enhancement of the third cranial nerves (*arrows*) demonstrated by MRI (Gadolinium enhanced T_1-weighted image) in a patient with neurolymphomatosis presenting as the first relapse site of systemic non-Hodgkin lymphoma. (**e**) Imaging of the same patients as in (**d**) following 2 months of treatment with high-dose methotrexate and intra-CSF cytarabine. The post-contrast MRI reveals normal third cranial nerve without enhancement

time of presentation with a clinical syndrome compatible with NL. In ~25–30% of cases, NL is the first manifestation of the malignancy (primary NL) but it is likely that systemic involvement will also be discovered after diagnostic evaluation at NL presentation. However, in some patients no dissemination either systemically or in the CNS is recognized and this rare variant of isolated NL may be diagnosed only at the time of autopsy if the involved neural structure cannot be considered for a diagnostic biopsy (Kuroda et al. 1989; Grisold et al. 1990; Diaz-Arrastia et al. 1992; Baehring and Cooper 2004; Grisariu et al. 2010).

Diagnosis

Diagnosis of NL requires integration of information from the clinical presentation (symptoms/signs), imaging findings, and morphological data obtained from neural or nonneural tissue and the CSF. A high index of suspicion and familiarity with the clinical manifestations of NL is necessary. As it is a rare expression of hematologic malignancies, diagnosis is often delayed. Clinically, NL mimics nonneoplastic or paraneoplastic neuropathies. Clinical findings that suggest NL, as opposed to a remote effect of cancer or an inflammatory process, include severe pain, asymmetric distribution, and rapid evolution. Still, the diagnosis is often elusive and 46% of patients identified up to the year 2000 were diagnosed only at autopsy (Baehring et al. 2003). With increasing awareness of this entity, NL is identified ante mortem more frequently, and diagnosis at autopsy was reported in only 8% of the 50 patients in the most recent IPCG series (Grisariu et al. 2010). These four patients that were diagnosed post mortem had an extensive evaluation prior to death for suspected NL but no definite diagnosis could be established.

The inclusion criteria used for the IPCG study (Grisariu et al. 2010) should be followed for identifying NL. In principle, NL is defined as neuropathy which is characterized by infiltration of malignant cells. Yet, manifestation of either cranial neuropathy or cauda equina involvement in the presence of positive cytology is not considered as NL unless evidence exists for intradural as well as extradural infiltration of the affected nerves or alternatively, additional data indicate that malignant infiltration of either peripheral nerves and/or neural plexi has also developed. Malignant infiltration of nerve structures that occurs in the set-up of a bulky disease that entraps and infiltrates the neural elements is not compatible with the definition of NL. In primary NL, infiltration of the affected neural structure has to be proved by a biopsy or at autopsy. In secondary NL, the diagnosis required exclusion of other causes of neuropathy, presence of positive imaging findings that detects specific neural involvement and evidences for disease progression. If diagnosis remains in doubt, a biopsy of the affected structure is required or otherwise autopsy findings eventually indicate the final diagnosis.

Imaging studies are of greatest utility (Figs. 1.1 and 1.2). Magnetic resonance imaging (MRI) reveals nerve or nerve root enlargement or enhancement and sometimes involvement of a neural plexus which is more difficult to detect (Moore et al. 2001; Baehring et al. 2003; Baehring and Cooper 2004; Iplikcioglu et al. 2006; Kim et al. 2006; Matano et al. 2006; Dong et al. 2008; Khong et al. 2008; Levin et al. 2008). MRI findings are not specific for NL and might sometimes be seen in acute or chronic inflammatory radiculoneuropathies, neurofibromatosis, inflammatory pseudotumor, and malignant tumors of the peripheral nerve sheath. Interpretation of imaging studies in the context of the clinical manifestations and laboratory tests is necessary. MRI yields abnormal findings in ~80% of patients (Grisariu et al. 2010) and it facilitates the diagnosis particularly when there is a history of hematologic malignancy.

In lymphomas, fusion ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET-CT is a standard diagnostic tool which is used for staging and monitoring of therapeutic response. It seems to be a highly sensitive test in NL and although the total number of reported cases is still small, it may indicate the diagnosis and suggest which nerve is the best target for biopsy (Fig. 1.1a–g). Recent data suggest that FDG-PET yielded positive findings in up to 90% of patients studied by this modality (Grisariu et al. 2010). Yet, FDG-PET is not specific for NL and it may be positive when other malignancies affect peripheral or cranial nerves. However, in the setting of known lymphoma with clinical findings compatible with NL it may be diagnostic.

Identification of malignant cells in the CSF is a confirmatory diagnostic test for NL. However, both cytologic evaluation and flow cytometry have modest sensitivity and positive findings are reported in only ~40% of patients (Baehring et al. 2003; Grisariu et al. 2010). Tests that suggest monoclonality of cells within the CSF (e.g., flow cytometry and PCR-based gene rearrangement of either the immunoglobulin heavy-chain in B-cells

or of the T-cell receptor) have been applied sporadically. These tests may confirm that malignant cells entered the CSF when the morphology is in doubt.

Although most of the reported cases were evaluated by multiple diagnostic modalities, a biopsy of an affected nerve was still indicated and has been performed in >40% of NL patients. The diagnostic yield of the biopsy is high and infiltration of a peripheral or cranial nerve by malignant cells is demonstrated histopathologically in 80–90% of biopsy samples (Baehring et al. 2003; Grisariu et al. 2010). The majority of cases are classified by immunohistochemistry as B-cell malignancy. Therefore, if imaging and CSF findings are non-conclusive, a nerve biopsy presents a reasonable approach if the risk does not outweigh the expected benefit.

Treatment and Outcome

There is no known standard treatment for NL and therefore, optimal management is ill defined. Treatment of NL consists of either chemotherapy alone or combined with radiotherapy. In order to select the appropriate therapy knowledge of the extent of systemic and nervous system involvement is essential. Staging with FDG-PET is effective for delineation of systemic disease as well as the involved nerves (Figs. 1.1 and 1.2a, b). Contrast-enhanced MR images of brain and the complete spine should also be obtained. NL involves roots within, as well as beyond, the borders of the subarachnoid space and thus intra-CSF chemotherapy and standard craniospinal radiation fields will not treat all of the involved areas. Systemic chemotherapy is critical to address the multiple sites of involvement.

In the recent series of the IPCG, 90% of the patients were treated for NL, a rate that appears higher than that reported previously (Baehring et al. 2003; Grisariu et al. 2010). This is probably related to the fact that in the IPCG retrospective chart review specific attention was requested for information related to therapeutic management. In contrast, the information collected from the literature contains inadequate information on clinical management as some of the case reports addressed only the unusual neuroimaging findings (Moore et al. 2001; Odabasi et al. 2001; Dakwar et al. 2004; Kim et al. 2006; Ozturk et al. 2006; Strobel et al. 2007; Yazawa et al. 2007; Dong et al. 2008; Shima et al. 2008; Kosa et al. 2009).

In the IPCG series (Grisariu et al. 2010), the majority of patients (70%) were managed by systemic chemotherapy. The most effective regimen is unknown and the selection is often based on protocols used to treat CNS involvement by malignant lymphoma. Many centers employed intravenous high-dose methotrexate, either alone or in combination with other drugs and particularly with high-dose cytarabine. Methotrexate is effective against lymphoma affecting the nervous system and when given in high doses can penetrate the blood–brain and blood-nerve barrier. Any other choice of chemotherapy must also meet those criteria. However, in the IPCG series ~30% of treated patients did not receive systemic chemotherapy due to the fact that NL represented relapse of a chemoresistant disease.

Radiotherapy has a limited role in the treatment of NL due to involvement of multiple sites, affecting both the CNS and the peripheral nervous system. Extensive radiation fields are poorly tolerated in most patients but limited-field radiotherapy can be very effective in relieving unremitting neuropathic pain attributed to a particular nerve, plexus, or nerve root.

Clinical improvement (functional recovery, reduction of pain), as well as radiographic resolution (improvement of nerve root enlargement, reduction or normalization of abnormal enhancement or fading of FDG-PET uptake) have been observed in 50–70% of treated patients (Grisariu et al. 2010) (Fig. 1.2a–e). Standardized criteria to measure response are not available and, therefore, no recommendations can be made regarding treatment response.

Regarding the fact that most literature related to NL consists of case reports and descriptions of imaging findings no information on overall survival of patients with NL was available prior to the publication of the IPCG series (Grisariu et al. 2010). The median overall median survival

from diagnosis of NL in this series was 10 months with 36-month survival proportion of 24%. These data indicate that an aggressive multimodality therapeutic approach can achieve long term survival in some patients. When survival of patients with primary NL was compared to survival of secondary NL, no statistically significant difference was observed although the median survival of the 13 patients with primary NL was 20 months and that of secondary NL was 8 months. The trend toward longer median survival observed in primary NL likely reflects the fact that NL was the presenting manifestation of the malignant disease unlike in secondary NL where it is an extranodal relapse. Nonetheless, long term survival was observed in secondary NL with one in four of all patients alive at 3 years.

In conclusion, it appears that NL is more frequently diagnosed in recent years. It is likely related to increased awareness of the disease and an enhanced rate of diagnosis due to the extensive use of contemporary imaging techniques that accurately localize abnormal process affecting neural structures. Early recognition and treatment of this rare neurological manifestation of lymphoma and leukemia may improve outcome.

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Primary Central Nervous System Lymphoma: Systemic Relapse

2

Hervé Ghesquières

Contents

Abstract

Primary CNS lymphoma (PCNSL) is characterized by the presence of lymphoma cells limited to the CNS, with possible involvement of the eyes or the cerebrospinal fluid. A majority of PCNSL are diffuse large B-cell lymphomas with an aggressive course. Retrospective series show that about 4% of patients (range, 0–24%) may experience a systemic relapse, mainly with unusual extranodal involvement. Systemic relapse can occur very early after initial diagnosis of PCNSL, raising the question of the existence of a systemic lymphoma going undetected at the time of conventional PCNSL staging. Late relapse can occur more than 5 years after the diagnosis, suggesting the development of a second lymphoma or the emergence of a systemic lymphoma arising from circulating clones. Globally, the prognosis is poor but seems slightly more favorable than for patients with intra-cerebral relapse. The present chapter reviews the biological implications of systemic relapse in the pathogenesis of PCNSL.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare disease accounting for 1–3% of all central nervous system (CNS) malignancies and for less than 5% of non-Hodgkin's

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_2,

lymphomas. More than 90% of PCNSL are Diffuse Large B-cell Lymphomas (DLBCL). The disease is usually confined to the CNS at the time of diagnosis and relapse occurs mainly within the CNS. Patient management has been the subject of intense investigation and of numerous phase II trials. The outcome of PCNSL had dramatically changed with the use of chemotherapy drugs that cross the blood–brain barrier, such as high-dose methotrexate and cytarabine which are generally used in polychemotherapy regimens (Blay et al. 1998; Ferreri et al. 2009). With high-dose methotrexate-based chemotherapy followed by radiotherapy, complete response is in the range of 56–87% and 5-year overall survival (OS) rates are between 32 and 50% (Abrey et al. 2000; DeAngelis et al. 2002; Ferreri et al. 2006; Gavrilovic et al. 2006; Ghesquieres et al. 2010; O'Brien et al. 2000; Omuro et al. 2005). The use of radiation therapy after chemotherapy remains a subject of debate given its toxicity to the neurological system, in particular in elderly patients. A recent large randomized trial has shown no difference in OS between patients treated with consolidation radiotherapy or not after high-dose methotrexate chemotherapy (Thiel et al. 2010). After relapse, the prognosis is poor with a short survival. Patients who achieve a new complete response after salvage therapy followed by a consolidation treatment with high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) seem to have a better outcome. A small proportion of patients may experience a systemic relapse without CNS progression. A review of data from 15 recently published studies in which the site of relapse was analyzed has identified a median rate of isolated systemic relapse of 4% (range, 0–24%) but only four retrospective series provide details on this type of relapse (Abrey et al. 2000; Angelov et al. 2009; DeAngelis et al. 2002; Ferreri et al. 2006; Gavrilovic et al. 2006; Ghesquieres et al. 2010; O'Brien et al. 2000; Omuro et al. 2005, 2007; Ferreri et al. 2009; Gerstner et al. 2008; Herrlinger et al. 2005; McAllister et al. 2000; Pels et al. 2003; Provencher et al. 2011)

Systemic Staging at Diagnosis of Primary Central Nervous System Lymphoma

Current work-up recommendations (once a pathological diagnosis has been made) include brain MRI, total spine MRI (if clinically indicated), lumbar puncture for cerebrospinal fluid (CSF) cytology, ophthalmology examination with slit-lamp biomicroscopy, computed tomography (CT)-scan of the chest/abdomen/pelvis, bone marrow biopsy, testicular ultrasound for older men, HIV testing and analysis of serum LDH level (Abrey et al. 2005). After this staging procedure, a systemic dissemination can be detected. In a series of 16 PCNSL, Ferreri et al. (1996) have found two patients with systemic dissemination, and another series of patients with PCNSL criteria has shown occult systemic NHL in 5/128 cases (O'Neill et al. 1995). In the series reported by Provencher et al. (2011), two patients who presented with an isolated systemic relapse had some pathological lymphoid cells in the bone marrow at diagnosis of PCNSL, but no flow cytometry or PCR detection was performed on these samples to confirm their monoclonality. 18-FDG PET-CT imaging has improved initial staging and response assessment after first-line therapy for systemic DLBCL but is not currently recommended for the initial work-up of PCNSL. Mohile et al. (2008) have addressed this question in a study of forty-two 18-FDG PET-CT tests performed for the purpose of initial staging. They have identified eight abnormal findings. Three biopsies (7%) were positive for lymphoma (left tibia, mediastinal nodes, liver), one for adrenal adenoma and one for metastatic duodenal carcinoma. This tool needs to be evaluated prospectively to determine whether it should be performed systematically at diagnosis of a cerebral lymphoma mass and whether the findings can change the prognosis of patients. In case of PET-CT positivity, the data reported by Mohile et al. (2008) were in favor of a documented biopsy of the lesion with abnormal PET-CT findings: among

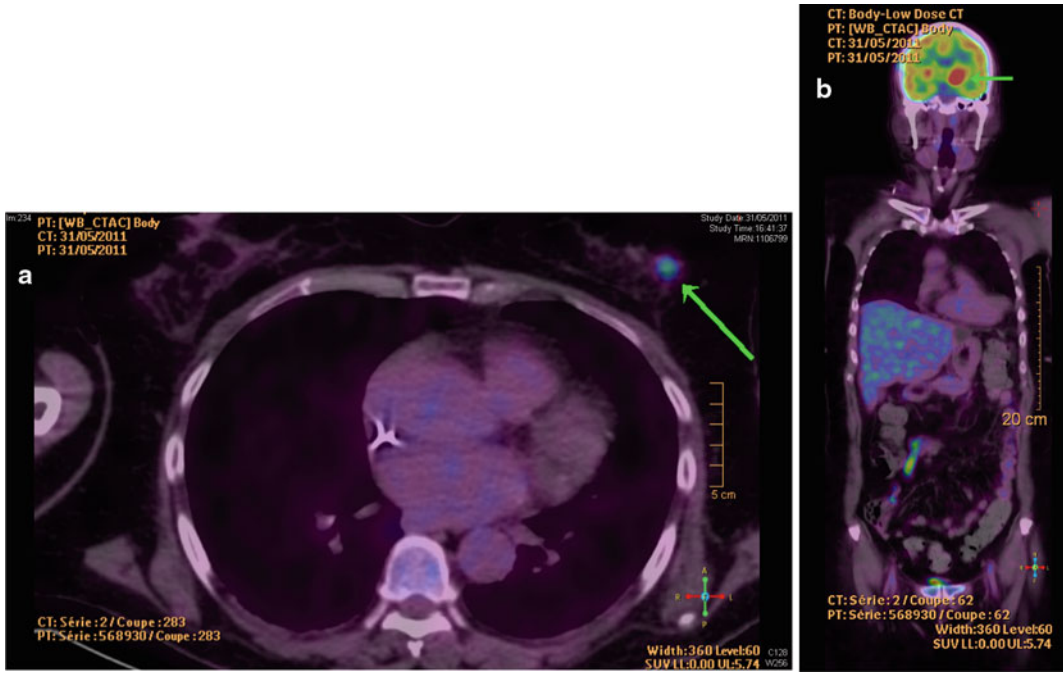

Fig. 2.1 PET-CT at staging of a diffuse large B-Cell lymphoma revealed by a brain tumor. A 64-year-old woman presented with confusion, aphasia and a right hemiplegia. Brain CT-scan and MRI showed a left paraventricular lesion. Stereotactic biopsy proved the presence of a Diffuse Large B-Cell Lymphoma (DLBCL). PET-CT revealed a breast lesion (**a**) and confirmed 18-FDG uptake in the brain tumor (**b**). The biopsy of the breast mass confirmed the presence of DLBCL. The patient was treated by two courses of high-dose methotrexate and the R-CHOP regimen. Two intensive care hospitalizations were needed for septic shock and Pneumocystis pneumonia. Evaluation showed that complete response was obtained after the two chemotherapy courses. Less intensive chemotherapy with rituximab, high-dose methotrexate and cytarabine was continued

the eight lesions with positive PET-CT, three were in relation with lymphoma, but three were actually false positives and two corresponded to other malignancies. If lymphoma is confirmed by pathology after biopsy, a modification of treatment for patients with systemic DLBCL with brain involvement should be discussed. In fact, in case of PCNSL, patients are treated with high-dose methotrexate and cytarabine based chemotherapy (frequently with alkylating agents), but in the presence of systemic DLBCL, standard treatment must also include anthracyclin-based chemotherapy (CHOP regimen) and rituximab. Combination of a CHOP-like regimen with high-dose methotrexate and cytarabine is effective but induces major toxicity in elderly patients (Ghesquieres et al. 2010). An illustrative case is reported in Fig. 2.1.

Characteristics of Systemic Relapse of Primary CNS Lymphoma

Only four series have studied the characteristics of systemic relapse in PCNSL (Provencher et al. 2011; O'Brien et al. 2000; Jahnke et al. 2006b; DeAngelis et al. 2002). In the series by De Angelis et al., 5 of 102 patients (5%) developed extra CNS disease in the breast (n = 1), the orbit (n = 1), the muscle/subcutaneous tissue (n = 2), or the lymph nodes (n = 1). In the series by O'Brien et al., 3 of 46 patients (6.5%) developed extranodal relapses in the muscles (n = 2) or in the skin (n = 1). Jahnke et al. have reported 6 patients with isolated systemic relapses out of 143 (4.2%). The sites of relapse were principally the lymph nodes (n = 4), the musculoskeletal system (n = 3), the testis (n = 3), the bone marrow (n = 2), renal

and adrenal structures (n = 1) and the liver (n = 1); some patients had more than one site involved. Consistent with previous findings, Provencher et al. have confirmed that most relapses (10/209 patients, 4.8%) were extra-nodal and occurred in unusual locations: soft tissue (n = 3), small intestine (n = 1), liver (n = 1), adrenal gland (n = 1), testis (n = 1), bone marrow (n = 2), lymph nodes (n = 3). The four reports confirmed this tendency for PCNSL to relapse in uncommon extra-nodal sites, suggesting the existence of specific biological dissemination properties of PCNSL cells. The case reported in Fig. 2.2 illustrates a testicular relapse after initial diagnosis of PCNSL.

Treatment of Systemic Relapse of Primary CNS Lymphoma

Only two reports provide some information on the treatment of systemic relapses of PCNSL (Jahnke et al. 2006b; Provencher et al. 2011). In the series by Provencher et al., seven patients were treated by salvage chemotherapy, two received radiation therapy or surgery for a localized relapse in the soft tissue of the left arm and in the abdominal wall, respectively. The remaining patient had no specific treatment because of a poor performance status. In this series, only two patients were in continuous complete response, one after the resection of a local lesion and one after salvage chemotherapy followed by HDT and ASCT. In the study by Jahnke et al. (2006a) the six patients with a systemic relapse were treated by chemotherapy (2 patients), surgery and radiotherapy (2 patients), radiotherapy (1 patient) surgery alone (1 patient). Five patients could obtain a complete response and one had progressive disease. The optimal treatment for systemic relapse is not known. Patients younger than 65 years with relapse of systemic DLBCL should receive salvage chemotherapy followed by HDT and ASCT (Gisselbrecht et al. 2010). The salvage

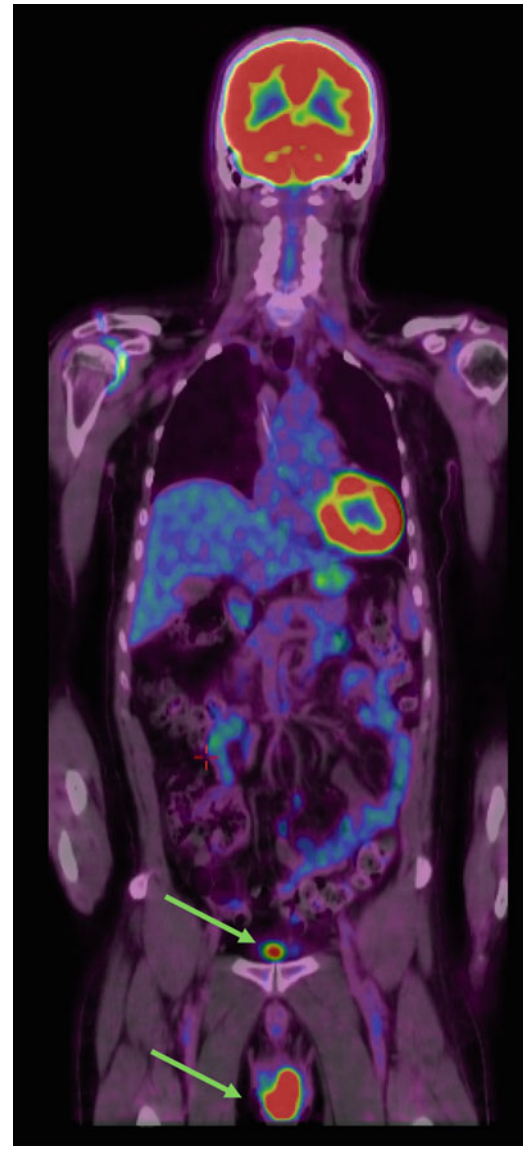

Fig. 2.2 TEP-CT at staging in a man treated for a primary CNS lymphoma, presenting with a testicular relapse 5 months after initial treatment. A 58-year-old man with DLBCL involving the left thalamic region was treated by high-dose methotrexate and cytarabine chemotherapy followed by brain radiotherapy. A complete response was obtained after chemotherapy and radiotherapy. The initial staging was normal. Five months after the end of the treatment, a left testicular mass was discovered by the patient. Orchidectomy revealed a DLBCL. A new staging was performed: PET-CT showed testicular and lombo-aortic lymph node involvement. Brain MRI and bone marrow biopsy were normal. The patient was treated with three courses of the rituximab, carboplatin, ifosfamide, etoposide (R-ICE) regimen followed by high-dose chemotherapy and autologous stem cell transplantation. One year after this treatment, the patient remained in complete response.

The question regarding this early relapse is whether the patient had occult testicular involvement at initial presentation. Initial clinical examination was normal and the first PET-CT did not reveal any systemic abnormalities, but no testicular ultrasound was performed

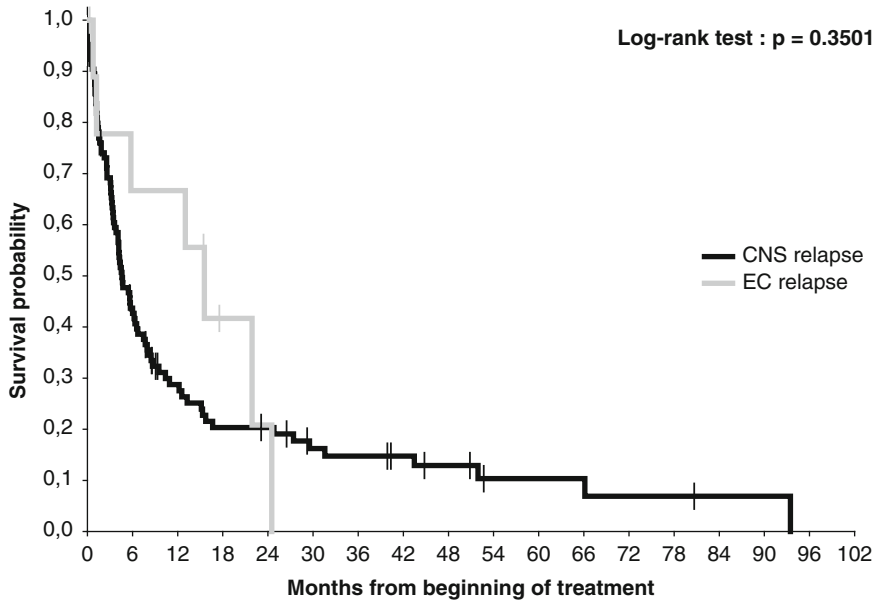

Fig. 2.3 Overall survival after CNS progression (105 patients) and extra-cerebral progression (10 patients). Series from the LNHCP93 Groupe d'Etude des Lymphomes de l'Adulte (GELA) (92 patients) and the Centre Léon Bérard, Lyon France series (117 patients)

treatment for systemic relapse of PCNSL could include a combination of rituximab with the CHOP regimen (R-CHOP). PCNSL patients do not usually receive first-line therapy with anthracyclins. R-CHOP is the standard of care in first line for patients with systemic DLBCL. For patients treated with anthracyclin-based chemotherapy in first line, salvage treatment could include platinum-based chemotherapy with high-dose cytarabine (DHAP regimen) in combination with rituximab. PCNSL patients who have already received high-dose cytarabine as first-line therapy could be treated with rituximab, carboplatin, etoposide and ifosfamide (R-ICE regimen) (Gisselbrecht et al. 2010). Consolidation treatment with HDT followed by ASCT should be discussed for responders to salvage treatment. In spite of this treatment modality, one of the patients reported by Provencher et al. relapsed 13 months after HDT and ASCT. Another important therapeutic problem is that PCNSL patients can present, at time of systemic relapse, with an altered PS and a neurological deterioration preventing the use of intensive treatment. This situation probably accounts, in the two series, for the choice of local treatment with radiotherapy and surgery without chemotherapy, or of no active treatment for 4 of the 16 described patients. Of note, one patient reported by Provencher et al. had a second relapse in the brain without evolution of systemic sites, showing that these patients remain at risk of CNS relapse. In the series by Jahnke et al. (2006a) one patient already had CNS evolution at the time of systemic relapse, as also observed in another series (McAllister et al. 2000): two of six patients with systemic relapses also had a CNS relapse, which likely reflects the importance of performing a brain MRI at the time of systemic relapse.

Prognostic of Systemic Relapse of Primary CNS Lymphoma

Only two series have explored median OS after extra-cerebral relapse (Jahnke et al. 2006b; Provencher et al. 2011). In the series reported by Jahnke et al., the median OS after isolated systemic relapse was 13.5 months. Patients with systemic relapse and no CNS progression seemed to

have a better post-relapse survival than patients with CNS relapse (13.5 vs. 4.5 months) in univariate analysis. This hypothesis was confirmed by Provencher et al. with a median OS after isolated systemic relapse of 15.5 months, but this result was not significantly different from the median OS after CNS relapse (4.6 months, $p=0.35$) and was obtained in a low number of patients (Fig. 2.3). In a third study, three of six patients with extra-cerebral relapse succumbed after salvage treatment (Gerstner et al. 2008). In conclusion, the prognosis of these patients remains poor due to the aggressiveness of the disease, the difficulties to obtain a new response after salvage treatment and usually the presence of co-morbidities with altered PS and poor neurological status.

Late Extra-Cerebral Relapse of Primary CNS Lymphoma

Several series have highlighted the fact that some systemic relapses can occur very late after initial diagnosis. For instance, Gavrilovic et al. (2006) have reported the case of a patient with a PCNSL who relapsed 7.4 years after primary diagnosis, and Nayak et al. (2011) have observed a patient who relapsed with a renal mass, 7.3 years after PCNSL presentation. In a series of 209 PCNSL, Provencher et al. (2011) have observed 10 systemic relapses, of which 5 occurred more than 41, 56, 69, 71, and 94 months after initial diagnosis of PCNSL. The five remaining patients experienced an early relapse between 3 and 25 months after diagnosis. The authors suggest the existence of two different patterns, early and late systemic relapse. When relapse occurs early after the beginning of treatment, this raises the question of the possible presence of an occult systemic disease not detected by conventional staging at the time of PCNSL diagnosis. Of note, in two patients who relapsed after 3 and 8 months, respectively, small pathological lymphoid cells were observed (25 and 6% of bone marrow cellularity, respectively). None of the five patients who experienced early relapses had undergone PET-CT at diagnosis. Late recurrences from PCNSL raise the question of whether the second tumor is a clonally related disease or a second malignancy. To test this hypothesis, clonality analyses on cells from the initial tumor and from the relapse should be performed.

What Does Systemic Relapse Tell About the Pathogenesis of Primary CNS Lymphoma?

PCNSL arise in an organ that has no lymphoid structure, and the number of B-cells capable to migrate to the brain is very low. Report cases of late systemic relapses after PCNSL have raised the question of a circulating peripheral clone of B-cells. Chuang et al. (2009) have reported on a patient treated for a PCNSL who presented with a skin relapse; they have been able to prove that the two localizations had similar clonal origin and Nayak et al. (2011) observed similar result for a patient who presented a brain relapse 13.8 years after diagnosis, the lymphoma at diagnosis and at relapse provided from a similar clone. In systemic DLBCL, de Jong et al. (2003) have shown that a majority of very late relapses are clonally related with the initial tumor. To address the question of a possible common origin, Jahnke et al. (2006a) have analyzed bone marrow and peripheral blood specimens from 24 PCNSL patients using polymerase chain reaction (PCR) for identifying clonally rearranged immunoglobulin heavy-chain (*IgH*) genes. Identical dominant PCR products have been found in the bone marrow, blood and tumor samples from two patients, indicating occult systemic disease gone undetected with conventional methods. McCann et al. (2009) have analyzed the clonal evolution of tumor cells in the brain, blood and bone marrow of 12 PCNSL patients. In three patients, clonal tumor cells were found in the bone marrow and/or blood, and the analysis of V-gene mutations has shown that additional variants existed in extra-cerebral sites. The authors suggest that a tumor clone can evolve into an aggressive lymphoma in the context of brain environment associated with the presence of an indolent clone in peripheral sites. Subclones

identified in peripheral sites do not seem to reenter the CNS. Whether these clones could favor later CNS relapse or loose their ability to cross the blood–brain barrier remains questionable. It also seems that these peripheral clones have no clinical consequence as no patient in Jahnke et al. series has developed a systemic relapse after a follow-up of 24 months. Of note, only few patients in these two series had peripheral clones. Whether these are virtually present in all PCNSL patients and were not found because of a technical failure or were destroyed by the glucocorticoids used for the treatment of the brain tumor is questionable. More biological studies are needed to decipher the role of circulating peripheral clones in PCNSL and their clinical and therapeutic implications.

In conclusion, systemic relapse after PCNSL is rare and arises in about 4% of patients. However when only PCNSL patients in complete response after initial treatment are considered, the rates of isolated systemic relapse increase to 15% as reported by Provencher et al. (2011). Similarly, the rate of systemic relapse could also be underestimated, in particular at time of CNS relapse, for patients not undergoing systematic chest/abdominal/pelvis CT-scan and bone marrow evaluation. Patients developing systemic relapse after PCNSL should undergo a new biopsy to confirm the lymphoid nature of the tumor. A new global staging should be performed, including a brain MRI to exclude a concomitant brain evolution. For research purposes, it would be interesting to compare the clonality of the initial brain tumor and of the systemic tumor. Treatment after systemic relapse is very similar to the first-line treatment of systemic DLBCL with the R-CHOP regimen; the majority of patients do not receive anthracyclin-based chemotherapy and rituximab at the time of PCNSL diagnosis. Other alternative regimens, such as R-DHAP or R-ICE, can also be proposed. A consolidation treatment with HDT followed by ASCT, which is the standard of care for relapses of systemic DLBCL, can also be proposed for fit younger patients in response after salvage therapy. However, the level of proof of this strategy for systemic relapse after PCNSL is low. Globally, prognosis remains poor, patients are generally old (the median age at diagnosis of PCNSL is 60 years) and can have altered performance and neurological status incompatible with intensive treatment. Whether, the relapsed tumor outside the brain has acquired some specificity in term of aggressiveness needs to be biologically assessed by testing, for instance, the specific dissemination pattern in other extranodal sites. All these unresolved questions require extensive cooperative research based on a large number of colligated cases and large tumor samples for biological investigations.

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Central Nervous System Recurrence in the Primary Mediastinal Large B-Cell Lymphoma: Treatment

3

Makoto Sasaki and Koichi Sugimoto

Contents

Abstract

Primary mediastinal large B-cell lymphoma (PMLBL) is a rare subtype of diffuse large B-cell lymphoma (DLBL), and it is recently recognized as a clinicopathological entity. Treatment of PMLBL with combination chemotherapy and radiotherapy has shown good outcome. Central nervous system (CNS) relapse of aggressive lymphoma is rare but has poor prognosis. A strategy for CNS prophylaxis and treatment in DLBL remains to be clarified because most of studies performed till date have been small scale and retrospective and have variable outcomes. Involvement of specific sites such as the testis, breast, nasal/paranasal sinuses and bone marrow is associated with a high rate of CNS relapse, which may require CNS prophylaxis. Further, CNS recurrence has been reported in 2–11% of PMLBL patients, and measures for the CNS prophylaxis have not been discussed for this new disease entity. Therefore, in this manuscript, we have reviewed CNS relapse and prophylaxis in PMLBL.

Introduction

Primary mediastinal large B-cell lymphoma (PMLBL) accounts for 6–13% of diffuse large B-cell lymphoma (DLBL) and 2–4% of non-Hodgkin's lymphoma (NHL). Patients are usually young to middle age and show female

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_3,

predominance. At the initial presentation, patients with involvement of the tumor to the lung, pleura, thoracic wall, and pericardium show clinical manifestations such as cough, dyspnea, and thoracic pain. Superior vena cava syndrome and thrombosis caused by vessel involvement are also commonly observed. Because these symptoms often appear at an early stage, a large number of cases are estimated as Stage I or II at diagnosis. Although extra thoracic involvement is rare at first, relapse occurs in unusual sites such as the kidney, adrenal gland, and brain. Histological features of PMLBL include diffuse proliferation of large B-cells with clear cytoplasm and the presence of a variable degree of sclerosis. The tumor cells express B-cell antigens such as CD19, CD20, CD22, and CD79a, but they lack immunoglobulin (Swerdlow et al. 2008).

Although no randomized studies are available, some large-scale retrospective comparisons suggested that third-generation regimens, especially methotrexate (MTX), doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin (MACOP-B), have a superior outcome compared to the conventional cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen (Zinzani et al. 2008). MACOP-B with or without involved-field radiation therapy (IF-RT) has been reported to show excellent complete response (CR) rate (60–90%), 5 years overall survival (OS) (70–95%) and progression-free survival (PFS) (60–95%) in most of the previous studies. Owing to a high proportion of fibrotic tissue in PMLBL, a residual mediastinal mass is often observed after the chemotherapy. However, active tumor in a residual mediastinal mass cannot be easily distinguished from post-chemotherapeutic inflammatory changes like fibrosis and necrosis by computed tomography (CT) scanning and magnetic resonance (MR) imaging. ^{67}Gallium-citrate single photon emission tomography (^{67}Ga-SPECT), which is used to determine the nature (fibrosis/necrosis vs. residual disease) of a lesion, has been used to identify patients who are likely to show relapse of PMLBL. Moreover, several reports have showed that the disappearance of accumulation in ^{67}Ga-SPECT is a good prognostic factor for restaging patients treated for PMLBL. ^{18}Fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) has shown to be superior to ^{67}Ga-SPECT in detecting residual disease. On the basis of these results, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation presented a guideline for the management of primary mediastinal lymphomas and recommended anthracyline-based chemotherapy, such as MACOP-B and CHOP, with or without IF-RT following accurate restaging with ^{67}Ga-SPECT/^{18}FDG-PET (Zinzani et al. 2008).

Diffuse Large B-Cell Lymphoma: Central Nervous System Recurrence

CNS recurrence of systemic NHL is a well-recognized and highly fatal complication that tends to recur within 12 months of initial treatment. CNS infiltration has a poor prognosis, with median survival of up to 6 months. In the majority of cases, CNS recurrence is accompanied or followed by systemic relapse of NHL.

Several risk factors for CNS relapse have been identified in aggressive lymphoma. These risk factors include advanced clinical stage, high international prognostic index (IPI), elevated lactic dehydrogenase (LDH) levels, involvement of more than 1 extranodal site, young age, low albumin levels, B-symptoms, and retroperitoneal disease. Many studies have also identified the involvement of specific sites, including bone marrow, breast, testis, orbit, nasal/paranasal sinuses, and mediastinum as a risk factor for CNS relapse. Hollender et al. identified the following five significant risk factors for aggressive lymphoma on the basis of multivariate analysis: elevated LDH levels, serum albumin <35 g/L, age <60 years, retroperitoneal disease, and more than 1 extranodal site (Hollender et al. 2002). In this risk model, if three or less of these risk factors were present, the probability of CNS relapse within 5 years would be maximum 6%. However, if four of these risk factors were present, this rate increased up to 25%.

Diffuse Large B-Cell Lymphoma: Prophylaxis for Central Nervous System Involvement

DLBL is an aggressive subtype of NHL. About 5–10% of aggressive NHL patients who were treated with CHOP or rituximab (R)-CHOP and no CNS prophylaxis, show CNS relapse. Prophylactic intrathecal MTX and hydrocortisone injection remarkably reduces the incidence of CNS recurrence following CR in aggressive NHL patients treated with MACOP-B modified regimen (0% vs. 15%) (Tomita et al. 2002). Although intrathecal MTX and high-dose MTX (HD-MTX) reduced CNS relapse in patients to 2 and 3% (Haioun et al. 2000; Tilly et al. 2003), other retrospective studies have not shown benefit in favor of CNS prophylaxis. Therefore, studies on the efficacy of CNS prophylaxis in DLBL have generally been small, retrospective, and have variable outcome. Due to the low probability of CNS recurrence (around 5%), CNS prophylaxis cannot be recommended for all patients except for patients with Burkitt and lymphoblastic lymphoma who may require CNS prophylaxis. The role of CNS prophylaxis in the treatment of aggressive NHL, including DLBL, is unclear, and its use varies between institutions.

Hollender et al. recommended the use of CNS prophylaxis, if four or more of these above-mentioned risk factors (elevated LDH levels, serum albumin levels <35 g/L, age <60 years, retroperitoneal disease, and more than 1 extranodal site) were present in aggressive lymphoma (Hollender et al. 2002). An improved risk model that includes more accurate predictors of CNS relapse is required so that prophylactic treatment can be targeted to high-risk patients.

Primary Mediastinal Large B-Cell Lymphoma: Central Nervous System Recurrence

Only about 20 cases of CNS recurrence have been reported in PMLBL (Todeschini et al. 1990; Kirn et al. 1993; Lazzarino et al. 1993; Abou-Elella et al. 1999; Bishop et al. 1999; Etienne et al. 1999; Stefoni et al. 2009; Sasaki et al. 2010). Most of these patients were treated with chemotherapy with or without IF-RT and no CNS prophylaxis. Bishop et al. reviewed 23 cases of PMLBL and showed that CNS infiltration occurs in 9% of newly diagnosed PMLBL cases and in 27% of relapsed ones (Bishop et al. 1999). In addition, CNS recurrence has been reported in 2–10% of PMLBL patients (Todeschini et al. 1990; Kirn et al. 1993; Lazzarino et al. 1993). Two cases of CNS parenchymal relapse of PMLBL have been reported after 3 and 4 months of R-MACOP-B plus radiotherapy recommended by the above-mentioned Italian groups (Stefoni et al. 2009; Sasaki et al. 2010). These results may suggest an advantage and necessity of additional CNS prophylaxis with (R-)MACOP-B with or without IF-RT in PMLBL.

Treatment of Central Nervous System Recurrence

Although a variety of regimens have been used to treat patients with CNS relapse, they show poor prognosis. Almost studies report a median survival of 2–6 months, with a 1-year survival rate of 2–25% after conventional treatment (van Besien et al. 1998; Hollender et al. 2002; Colocci et al. 2004).

High-Dose Methotrexate

Because MTX has a low capability to cross the blood-brain barrier (BBB), remarkably high doses of MTX are administered to obtain therapeutic concentrations in the CNS tumor tissue. For CNS lymphoid diseases, the problem of low penetration has been overcome by the use of so-called "HD-MTX" in doses ranging from 1 to 8 g/m^2. Intravenous HD-MTX was introduced as a part of treatment regimen for acute lymphoblastic leukemia (ALL) to prevent CNS relapse. Because of its ability to cross the BBB, the HD-MTX-based regimen has been used effectively in the management of both primary and secondary CNS lymphomas. Trials using 8 g/m^2 of HD-MTX against primary central nervous

system lymphoma (PCNSL) resulted in overall response rates of 35–100% and median overall survival of 22.8–30.4 months (Guha-Thakurta et al. 1999; Batchelor et al. 2003; Herrlinger et al. 2005). A retrospective multicenter analysis showed that treatment with HD-MTX improved the survival of PCNSL patients (Ferreri et al. 2002). Doolittle et al. revealed two risk factors (age less than 60 years at relapse and MTX as a frontline agent for brain relapse) that were significantly associated with longer survival in systemic NHL with CNS relapse (Doolittle et al. 2008). Therefore, HD-MTX seems to be a key regimen for the treatment of not only primary but also secondary CNS lymphoma.

Intrathecal Methotrexate

In the more recent setting of HD-MTX-based regimens, the use of intrathecal treatment for PCNSL is controversial. Patients who receive at least 3 g/m^2 of MTX acquire adequate concentrations in the cerebrospinal fluid. Therefore, patients who receive this dose and who do not have evidence of positive cerebrospinal fluid cytology may safely omit intrathecal treatment (Morris and Abrey 2009).

Combination Chemotherapy Including High-Dose Methotrexate

Some lipophilic chemotherapeutic agents easily cross the BBB, and their concentration reaches the therapeutic range in the tumor bed. Several drugs, such as cytarabine, liposomal cytarabine, thiotepa, ifosfamide, temozolomide, procarbazine, and nitrosoureas, have been combined with HD-MTX to improve outcome. Some of these drugs have been recently used in induction combination chemotherapy with HD-MTX or in high-dose chemotherapy before autologous stem-cell transplantation.

The combination regimens, e.g., MTX, vincristine, and procarbazine (MVP); MTX, carmustine, teniposide, and methylprednisolone (MBVP); and MTX, cytarabine, thiotepa, and idarubicin (MATILDA) are associated with a high response rate. A retrospective study of PCNSL revealed that the use of HD-MTX improved survival and that the addition of HD-cytarabine was associated with a better outcome in this group (Ferreri et al. 2002). Furthermore, a phase II prospective randomized study showed the benefits of HD-MTX plus HD-cytarabine over HD-MTX monotherapy in PCNSL (ORR: 69% vs. 40%; 3y-OS: 46% vs. 32%) (Ferreri et al. 2009).

Disruption of the Blood-Brain Barrier

An alternative strategy for the delivery of chemotherapeutic drugs into the CNS is the disruption of the BBB. This approach involves cannulation of the carotid or vertebral arteries, osmotic disruption of the BBB with mannitol infusion, and intra-arterial chemotherapy. This strategy seems to be less effective than the standard chemotherapies and whole brain radiotherapy.

Whole Brain Irradiation

In the era of recent MTX-based chemotherapy, the role of whole brain radiotherapy has been increasingly questioned. It has become clear that the addition of MTX-based chemotherapy to whole brain radiotherapy commonly results in an improvement in disease control and overall survival (Colombat et al. 2006; Illerhaus et al. 2006; Shah et al. 2007). However, follow-up studies on long-term survivors have clarified the neurotoxic effects of whole brain radiotherapy. These adverse effects, so-called "leukoencephalopathy," include treatment-related dementia, gait disturbance, and urinary incontinence. Patients older than 60 years and combination therapy with HD-MTX are particularly the specific high risk factors in the use of whole brain radiotherapy. Importantly, neurotolerability has been evaluated only retrospectively in small groups of highly-selected patients. On-going prospective studies will help define a cohort of patients who can be safely treated with whole brain radiotherapy as part of their initial treatment.

High-Dose Chemotherapy with Autologous Stem-Cell Transplantation

For patients with relapsed/refractory or high-risk systemic NHL, high-dose chemotherapy with autologous stem-cell transplantation (AST) is an effective treatment option. In PCNSL, this approach has been used as salvage therapy for refractory/relapsed patients or as consolidation therapy after primary HD-MTX-based chemotherapy, either replacing or preceding whole brain irradiation. In several phase II studies, AST is feasible and is associated with a reasonable response in PCNSL as front-line therapy (Abrey et al. 2003; Colombat et al. 2006; Illerhaus et al. 2006). These studies used either carmustine, etoposide, cytarabine, and melphalan (BEAM) or thiotepa-based conditioning regimes before AST and showed high treatment-related mortality and significant morbidity. Therefore, this approach should be considered only in patients with good general and organ status, younger age, and chemo-sensitive disease.

Rituximab

Because CD20 is a cell-surface protein that exists almost exclusively on mature B-cells, the anti-CD20 antibody rituximab drastically changes the treatment strategy and outcome in systemic B-cell NHL. Although rituximab might not cross the BBB, a rituximab-combined MVP regimen showed good outcome of 2 years OS (67%) and PFS (57%) (Shah et al. 2007). The addition of intravenous rituximab therapy may improve the outcome in PCNSL therapy. As an alternative strategy, some studies have used intraventricular rituximab injection against primary or relapsed CNS lymphoma (Schulz et al. 2004; Rubenstein et al. 2007). According to these reports, intrathecal or intraventricular rituximab administration was effective not only for lymphomatous meningitis but also for parenchymal and intraocular lymphoma. Further studies are required to verify whether intravenous or intraventricular rituximab administration results in more significant improvement in patient outcome than standard therapy.

In conclusion, the best modality of CNS treatment in aggressive NHL is still unclear. The strategy for CNS relapse in PMLBL, a rare subtype of aggressive NHL, is also unknown. A high incidence of CNS relapse has been observed in testicular, nasal/paranasal sinuses, breast, orbital, and bone marrow lymphomas. CNS prophylaxis is recommended in some of them, and actually, clinicians in the UK used CNS prophylaxis in 65–88% of such patients (Cheung et al. 2005). In contrast, although the prevalence of CNS relapses in PMLBL has been 2–10%, the strategy for CNS prophylaxis and treatment has not yet been discussed. Further investigation is required to evaluate the risk of CNS relapse and its prophylaxis in PMLBL.

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Primary Central Nervous System Lymphoma Resulting in Stroke and Leukoencephalopathy

4

Stefan Kiechl, Benjamin Matosevic, and Johann Willeit

Contents

Abstract

In rare instances primary CNS lymphoma (PCNSL) manifests as an intravascular tumour or shows a diffuse infiltrating phenotype known as "lymphomatosis cerebri". Intravascular PCNSL presents with multiple cerebral infarcts caused by the occlusion of small- to medium-sized vessels while diffuse infiltrating PCNSL is characterized by progressive white matter lesions translating into behavioural changes and cognitive decline. We describe the clinical and histological peculiarities, key imaging findings, diagnostic challenges and differential diagnoses of these special types of PCNSL, and provide a review of literature cases. Prognosis is generally worse than that of classic PCNSL and critically depends on an early diagnosis.

Introductory Remarks

Epidemiology

Primary central nervous system lymphoma (PCNSL) accounts for 3–5% of all primary brain tumours. Patients with HIV face a particularly high risk of PCNSL with a life-time prevalence of 2–10% even though recent advances in anti-viral therapy strategies resulted in a drop of disease rates. For renal, cardiac and liver allotransplant patients risk estimates for PCNSL range from 1 to 7% (Sierra del Rio et al. 2009).

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_4,

Histology

Up to 90% of PCNSL are diffuse large B-Cell lymphoma. The remaining 10% are composed of low-grade B-cell lymphoma, Burkitt lymphoma and T-cell lymphoma. The neurotropism of B-cell lymphoma is not fully understood but expression of specific extracellular matrix-related genes and interaction between homing receptors and ligands exposed on the endothelium of cerebral vessels may contribute to this phenomenon (Gerstner and Batchelor 2007, 2010). Owing to the fact that the CNS lacks resident lymphatic tissue, PCNSL cells may derive from monoclonal proliferation of lymphocytes in the context of an inflammatory process. An alternative hypothesis considers PCNSL to emerge from metastatic spread of an occult systemic lymphoma that is subsequently eradicated by systemic immune defence and exclusively proliferates in the immunologically privileged CNS (Sierra del Rio et al. 2009).

Phenotypes

In more than 95% of cases, PNCSL presents with solid tumour masses showing archetypical solitary or multifocal (especially in immunocompromised patients) contrast-enhancing lesions at typical locations like cerebral hemispheres, corpus callosum, basal ganglia, and exceptionally with a leptomenigeal tumour spread (Kuker et al. 2005). Of note, up to 10% of lesions do not or only marginally enhance contrast agent on CT or MR (Batchelor and Loeffler 2006; Soussain and Hoang-Xuan 2009). In 2–3% of PCNSL cases lymphoma manifests as an exclusively intravascular tumour (Glass et al. 1993) and in rare instances (<1%) PCSNL diffusely infiltrates the brain causing progressive white matter disease (Raz et al. 2011). The latter phenotype is also known as "lymphomatosis cerebri".

Clinical Presentation

Patients are usually in their 50s and men are more often affected than women (sex ratio 1.2–1.7 to 1). B-symptoms like prominent weight loss, nigth sweat and unexplained fever are commonly absent in the early phase of disease. Clinical presentation of classic PCNSL is variable and includes focal neurological deficits (~70%), neuropsychiatric symptoms (~40%), signs of increased intracranial pressure (~10%), seizures (~33%) and visual symptoms like blurred vision, floaters or painful red eyes, and diminished visual acuity on one or both eyes (~4%) (Batchelor and Loeffler 2006; Gerstner and Batchelor 2010). The following part of the chapter is dedicated to the two rare subtypes of PCSNL – the diffuse infiltrating and primary intravascular PCNSL. These phenotypes are hallmarked by recurrent strokes and progressive leukoencephalopathy clinically presenting with behavioural changes and dementia.

Diffuse Infiltrating and Intravascular Lymphoma

Pathophysiology and Peculiarities

Diffuse infiltrating PCNSL like the majority of PCNSLs exhibit a B-cell phenotype. Only 1 out of 19 cases so far described in the literature was classified as a T-cell lymphoma (Weaver et al. 2007). Remarkably, there is not a single patient with diffuse infiltrating PCNSL positive for Epstein-Barr virus. Severe and rapidly progressive white matter lesions derive from microvessel occlusion and direct inflammatory damage elicited by invasion and activation of reactive T-cells. Low expression of the CD-11 surface antigen on lymphoma cells renders them incapable of forming solid tumour masses and thus may give rise to this particular phenotype (Rollins et al. 2005).

Unlike diffuse infiltrating PCNSL, intravascular PCNSL in most instances is not *a priorily* confined to the CNS. As a matter of fact intravascular lymphoma usually constitutes a systemic illness that preferentially affects the CNS (~30%). Other sites of predilection are the skin (~40%), liver and spleen (~20%) and less frequently all other organs (Shimada et al. 2010; Glass et al. 1993).

Lymphoma growth is restricted to the intravascular space. Immunohistochemically, intravascular lymphoma cells lack surface markers like CD-11a, CD-18, CD-28 or CD-54 and matrix degrading enzymes. Expression of these adhesion molecules and matrix metalloproteinases 8 and 9 is considered essential for the extravasation of malignant B-cells (Kinoshita et al. 2008; Nakamichi et al. 2008). In close agreement with classic PCNSL the intravascular phenotype typically has a B-cell origin (diffuse large B-cell lymphoma) (Mihaljevic et al. 2010). However, T-cell and natural killer cell lymphoma occur as well (Nakamichi et al. 2008).

In one intriguing case of PCNSL, large B-cell lymphoma both infiltrated the white matter and accumulated within the lumen of medium-sized vessels. There may be an overlap between intravascular and diffuse infiltrating types of PCNSL suggesting a fluent transition from one phenotype to the other in the same patient (Matosevic et al. 2010) (Fig. 4.1).

Clinical Presentation

A total of 15 papers on diffuse infiltrating PNCSL were published in literature (1995–2010) describing 19 individual cases. In all but one case lymphomatosis cerebri evolved in the absence of a compromised immune system contrary to the assumption that PCNSL typically presents as a solitary lesion in immunocompetent patients and as multifocal or widespread disease in immunocompromised. Overall, 8 patients were male and 11 female (sex ratio 0.7 to 1). Mean age at diagnosis was 58 years and ranged from 28 to 80 years. The most frequent symptoms are behavioural changes, disorders of gait and progressive cognitive decline all the way to dementia. Neuropsychological deficits like aphasia, apraxia, anomia and visuo-spatial problems are common as well. During the course of disease but rarely in an early stage patients complain of headache or develop motor deficits. A history of weight loss may be a clue to the diagnosis of malignant disease but more commonly complicates advanced illness when dysphagia manifests. Characteristics and peculiarities of all 19 literature cases are depicted in Table 4.1 (Bakshi et al. 1999; Brecher et al. 1998; Carlson 1996; de et al. 2008; Furusawa et al. 1998; Kanai et al. 2008; Lewerenz et al. 2007; Matosevic et al. 2010; Matsumoto et al. 1995; Raz et al. 2011; Rollins et al. 2005; Terae and Ogata 1996; Thurnher et al. 2001; Vital and Sibon 2007; Weaver et al. 2007; Ayuso-Peralta et al. 2001).

Intravascular CNS lymphoma usually is a neurological manifestation of a systemic disease (Rahman and Pittaluga 2009; Glass et al. 1993). As to CNS involvement, multiple cerebral infarcts with both a temporal and spatial dispersion due to occlusion of small- to medium-sized vessels result in focal neurological deficits like hemiparesis, hemihypaesthesia, hemianopia, aphasia and dysarthria, and in seizures (Bergmann et al. 1994; Mihaljevic et al. 2010). In contrast to diffuse infiltrating PCNSL gait disorders, psychomotor slowing, dementia and personality changes occur later in the disease – then indicating multi-infarct syndrome. In the rare case of an involvement of the spinal cord and radices patients suffer flaccid or spastic paraparesis and complain of a sensory level, radicular pain and/or urinary retention. In addition, muscular atrophy and fasciculations emerge. Mononeuritis multiplex, mono- and polyneuropathy all are rare (5%) and indicative of lymphoma manifestation in the vasa nervorum. Apart from the CNS and skin, bone marrow, liver, spleen and adrenal glands may be affected (Ferreri et al. 2004b; Glass et al. 1993; Shimada et al. 2010). Main characteristics, elaborated in five independent case-series of intravascular lymphoma patients with CNS-involvement, are summarized in Table 4.2.

Diagnostic Work-Up

Lymphomatosis cerebri and intravascular PCNSL can be suspected based on the clinical presentation and imaging peculiarities.

On MRI, diffuse infiltrating lymphoma presents as confluent and rapidly progressing hyperintensities on T2-weighted and FLAIR images involving the subcortical and periventricular white

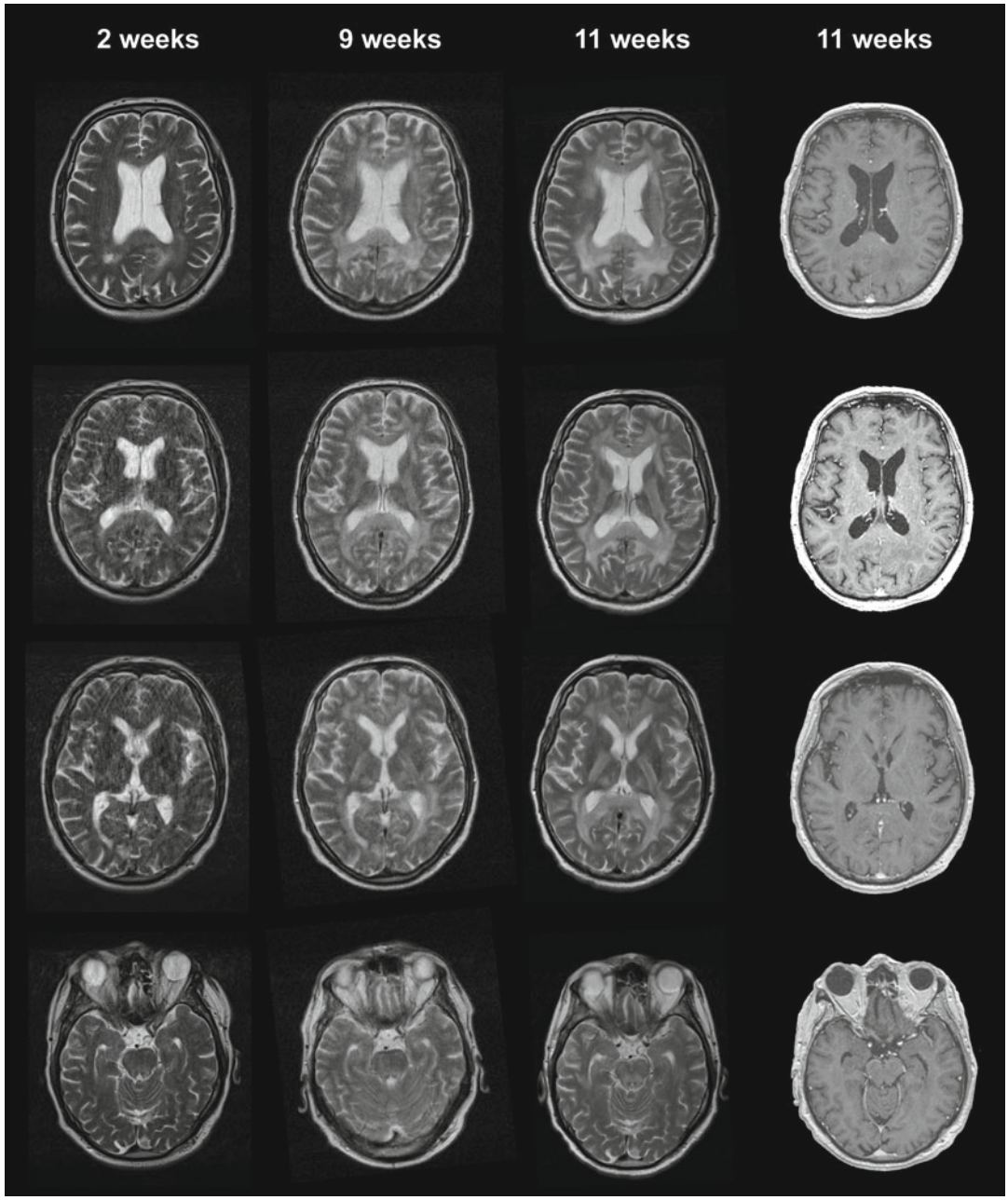

Fig. 4.1 *Upper rows*: T2-weighted MR images (2 mm slice thickness) in corresponding levels showing progressive and confluent white matter hyperintensities involving the corpus callosum and both thalami. No contrast enhancement was seen on T1-weighted images in serial exams (1.3 mm slice thickness, *right image row*) (Reproduced with permission from *J Clin Pathol* (Matosevic et al. 2010))

matter, the corpus callosum as well as the basal ganglia and in some cases the brainstem (Anda et al. 2008; Anghel et al. 2003; Matosevic et al. 2010; Raz et al. 2011) (Fig. 4.2). In patients with intravascular lymphoma MRI is characterized by cortical and sub-cortical ischemic and less frequently hemorrhagic infarcts in various vascular territories. Corresponding to their stages the

Table 4.1 Summary of cases with diffuse infiltrating primary central nervous system lymphoma (PCNSL)

Author (year)	Sex/age (years)	Clinical presentation	Immune status IC/ICM	CSF examination	Type/diagnosis	MR imaging (T2-hyperintensities)	Treatment	Outcome
Ayuso-Peralta et al. (2001)	Female/58	Gait ataxia, dysarthria, diplopia, positive pyramidal signs, after 2 months: dysphagia, tetraparesis	IC	Cell count, 8/mm^3 protein, 52 mg/dL	B-Cell/brain biopsy	Both hemispheres, splenium, cerebellum and corpus callosum	Cytarabine	Died 9 months after disease onset
Bakshi et al. (1999)	Male/41	Cognitive decline (forgetfulness, disorganization, disorientation), gait ataxia, positive frontal signs	IC	Cell count, 18/mm^3	B-Cell/autopsy	Patchy T2 lesions in the frontal WM, pons, cerebellum and corpus callosum	Steroids	Died within 6 months
	Female/75	Rapid progressive dementia, paranoia, hallucinations, gait ataxia, positive pyramidal signs	IC	Protein, 94 mg/dL	B-Cell/brain biopsy	Scattered T2 lesions in the supratentorial WM	n.r.	n.r.
Brecher et al. (1998)	Female/35	Blurred vision at disease onset, after 12 months: fatigue, numbness, dizziness, myalgias, headache	IC	Cell count, 6/mm^3	B-Cell/brain biopsy	Initially focal, then confluent T2 lesions in the frontal lobe and corpus callosum	MTX, cyclophosphamid, vincristine, adriamycin, steroids, whole brain radiation	Died 45 months after disease onset, 14 after diagnosis
Carlson (1996)	Female/76	Lethargy, confusion, disorientation, dysphasia	IC	Elevated cell count and protein	B-Cell/brain biopsy	T2 lesions in the deep subcortical WM and thalami	Steroids	Died 1 month after dismissal
Furusawa et al. (1998)	Female/55	Disease onset: lower extremity weakness, headache, unstable gait 4 months later: tetraparesis, pseudobulbar palsy, akinetic mutism	IC	n.r.	n.r.	Bilateral hemispherical T2 lesions	n.r.	Died

(continued)

Table 4.1 (continued)

Author (year)	Sex/age (years)	Clinical presentation	Immune status IC/ICM	CSF examination	Type/diagnosis	MR imaging (T2-hyperintensities)	Treatment	Outcome
De Toledo et al. (2008)	Female/56	Sub-acute onset of dementia, rapid disorientation	IC	n.r.	B-Cell/brain biopsy	Diffuse T2 lesions in the deep WM, basal ganglia, brainstem, patchy enhancement during disease	–	Died
Kanai et al. (2008)	Male/58	Fatigue, dizziness, clumsiness, 4 months later: gait ataxia and hemiparesis	IC	Cell count, 9/mm^3 protein, 52 mg/dl	B-Cell/brain biopsy	Supratentorial asymmetric WML	Whole brain radiation, steroids	Alive 11 months after disease onset
Lewerenz et al. (2007)	Female/65	Dementia, double vision, sixth nerve palsy	IC	Cell count, 18/mm^3 IgM synthesis and oligoclonal bands	B-Cell/brain biopsy	T2 lesions in the putamen, caudate nuclei, thalami, mesencephalon, frontal WM	High-dose MTX	Died 7 months after disease onset
Matosevic et al. (2010)	Male/65	Disease onset: weight loss, gait ataxia, facial palsy 2 months later: dysarthria, aphasia, anomia, dysphagia, apraxia, urinary incontinence, brisk reflexes, positive pyramidal signs	IC	Protein, 69 mg/dl weak 14-3-3 band	B-Cell/brain biopsy	Symmetrical WML in both hemispheres, corpus callosum and thalamus	High-dose MTX	Died 3 months after disease onset
Matsumoto et al. (1995)	Female/42	Headache, general fatigue and disorientation, had a history of a solid PCNSL	IC	Cell count, 133/mm^3 atypical lymphocytes	B-Cell/CSF and autopsy	Bilateral frontal, temporal and parietal WM, midbrain basal ganglia	Adriamycin, vincristine, cyclophosphamid, steroids	Died 6 months after diagnosis
Raz et al. (2011)	Male/72	Weight loss, gait ataxia, cognitive impairment	IC	Cell count, 7/mm^3 protein, 93 mg/dl	B-Cell/brain biopsy	Both hemispheres, cerebellum, brainstem	n.r.	n.r.
Rollins et al. (2005)	Male/65	Memory loss, unstable gait, dysarthria, spasticity, hyperreflexia	IC	n.r.	B-Cell/brain biopsy	Both hemispheres, corpus callosum	High-dose MTX	Died 14 months after disease onset

	Female/80	Flat affect, facial palsy, apathy, lethargy, dysarthria, hallucinations	IC	Atypical lymphocytes	B-Cell/CSF	Deep WM of both hemispheres, hypothalamus, brainstem	None	Died 7 months after disease onset
	Male/62	Flaccid hemiparesis, grasp reflexes	IC	n.r.	B-Cell/brain biopsy	Predominantly in the left deep WM, thalamus, corpus callosum	High-dose steroids	n.r.
Terae and Ogata (1996)	Male/34	Diminished work performance	IC	n.r.	n.r.	Frontal WM, corpus callosum, basal ganglia, hypothalamus	n.r.	Died
Thurnher et al. (2001)	Female/28	Depressive mood, slow thoughts	ICM HIV positive	n.r.	B-Cell/brain biopsy	Bilateral hemispheric WM	n.r.	Died
Vital and Sibon (2007)	Female/64	Cognitive decline, gait ataxia	IC	Weak band for 14-3-3 protein	B-Cell/autopsy	Periventricular WM	n.r.	Died 3 months after disease onset
Weaver et al. (2007)	Male/72	Rapidly progressive dementia, reduced speech, positive primitive reflexes	IC	Cell count, 46/mm^3 weak band for 14-3-3 protein	T-Cell/brain biopsy	Right temporal WM, left insular WM, centrum semiovale	n.r.	Died 2 months after disease onset

WM white matter, *WML* white matter lesions

Table 4.2 Summary of independent case series of patients with primary intravascular lymphoma involving the central nervous system

Author (year)	Number of patients	Male sex/mean age (years)	Clinical presentation	Phenotype	Treatment	Prognosis
Bergmann et al. (1994)	5	80%/52	Psychomotor slowing, strokes or TIA	All B-Cell	Corticosteroids	Mean survival after symptom onset, 4 months
Beristain and Azzarelli (2002)	8	50%/63	Focal neurological deficits, encephalopathy, seizures, dementia, myopathy	Predominantly B-Cell	n.r.	Mean survival after symptom onset, 8 months
Ferreri et al. (2004b)	38	47%/70	Patients with cutaneous manifestations, 34% (n = 13) with neurological symptoms at diagnosis: sensorimotor deficits, aphasia, seizures, myoclonus, neuropathy	Predominantly B-Cell	Antracycline-based chemotherapy, surgery, whole brain radiation, AST	24 month survival, 25%
Glass et al. (1993)	7	66%/65	Multifocal infarcts and sensorimotor deficits, sub-acute encephalopathy, peripheral and cranial neuropathies, skin lesions	All but one B-Cell	CHOP, MTX, whole brain radiation, cyclophosphamide	Mean survival after symptom onset, 11 months
Shimada et al. (2010)	25 with CNS involvement 109 overall	64%/64	Sensorimotor deficits, altered consciousness, seizures	All B-Cell	CHOP, CHOP like, R-CHOP, AST	All patients died within 1–62 months

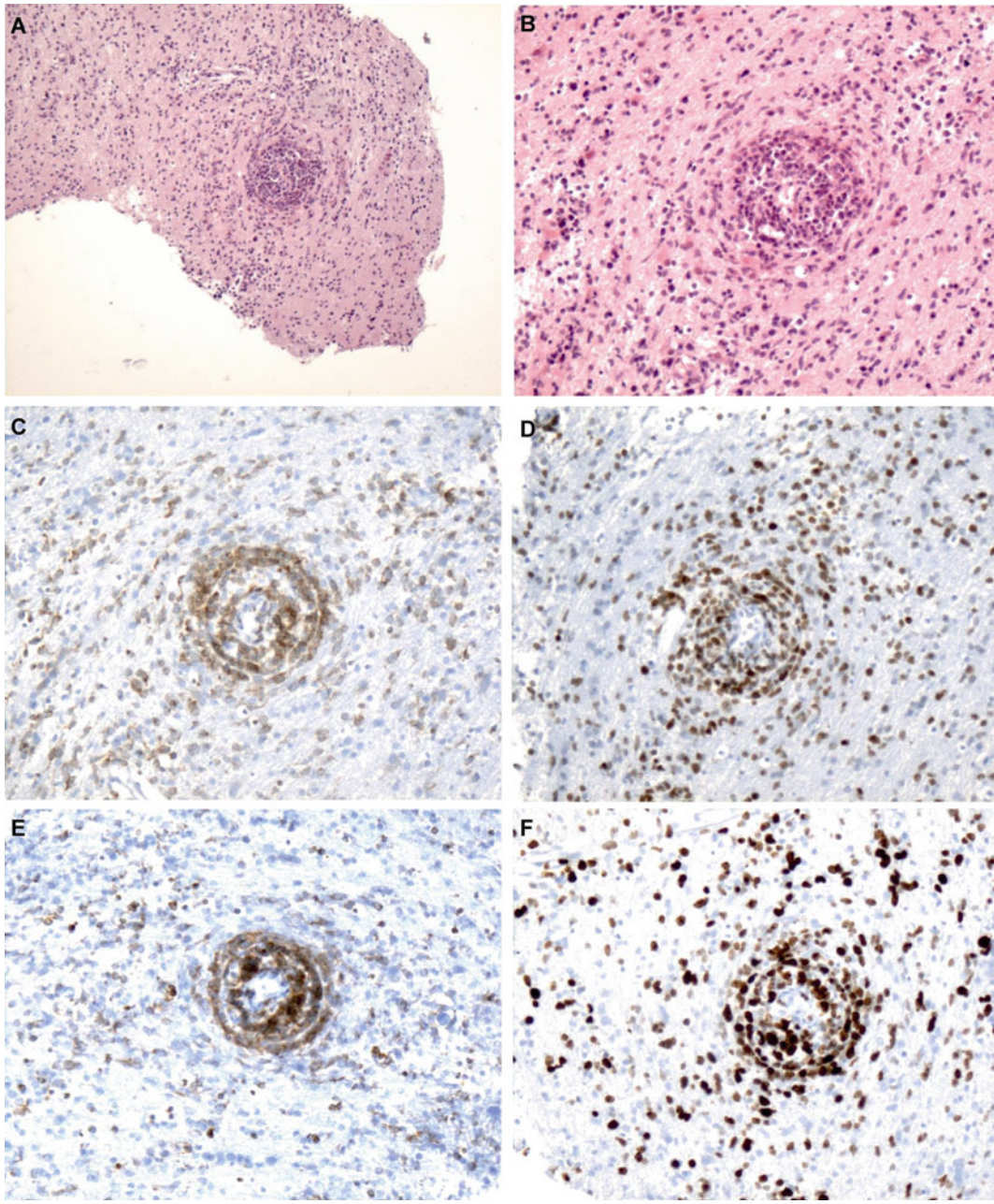

Fig. 4.2 White matter biopsies (**a**, **b**) showing prominent diffuse, perivascular and intravascular infiltrates of atypical large B-cells and blasts and strong staining for CD 79a (**c**), bcl-2 (**d**) bcl-6 (**e**) and for ki-67 indicative of highly proliferating cells (**f**). **a**, H&E, ×100; **b**, H&E, ×200; **c**, anti-CD79a, ×200; **d**, anti-bcl2, ×200; **e**, anti-bcl6, ×200; **f**, anti-MIB1, ×200 (Reproduced with permission from *J Clin Pathol* (Matosevic et al. 2010))

strokes show variable signal abnormalities on DWI, T1- and T2-weighted imaging modalities and may or may not enhance gadolinium. Angiography (MRA, CTA or DSA) sometimes unravels vasculitis-like abnormalities including high-grade vessel stenosis or occlusion of peripheral branches (Anda et al. 2008; Anghel et al. 2003; Glass et al. 1993).

CSF examination in patients with diffuse infiltrating PCNSL shows protein elevation and occasionally pleocytosis and atypical lymphocytes (see Table 4.1). Repeated lumbar punctures have been recommended to enhance diagnostic sensitivity to around 15–20%. Bone marrow aspiration was negative in all cases of lymphomatosis cerebri and in two third of patients with primary intravascular lymphoma involving the CNS. Frequent laboratory abnormalities seen in patient with intravascular lymphoma are anaemia, high erythrocyte sedimentation rate and elevated lactate dehydrogenase level. Owing to the lack of specific non-invasive diagnostic markers, stereotactic brain biopsy is usually required in order to settle the correct diagnosis.

Differential Diagnosis

A number of diseases other than PCNSL can cause diffuse white matter lesions and multiple strokes. Disorders like Binswanger's disease, acute and tumefactive forms of multiple sclerosis, Balo's disease, acute disseminated encephalomyelitis (ADEM), progressive multifocal leukoencephalopathy (PML), limbic encephalitis, vitamin B12 deficiency, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS), Fabry's disease, and cerebral autosomal recessive or dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL and CADASIL) can easily be distinguished on clinical grounds and based on MRI findings, course of disease and ancillary tests (blood and CSF). Other differential diagnoses like cerebral vasculitis, extrapontine myelinolysis, reversible posterior leukoencephalopathy syndrome (RPLS), reversible cerebral vasoconstriction syndrome (RCVS) and inflammatory cerebral amyloid angiopathy (CAA) (Greenberg et al. 2010) are more demanding – especially in young individuals.

A weak protein 14-3-3 band is occasionally found in the CSF of lymphomatosis cerebri patients and indicates neuronal loss like in Alzheimer's disease. In the absence of other specific diagnostic criteria (periodic sharp-wave complexes on EEG) 14-3-3 protein is not significant for Creutzfeld-Jakob disease.

Treatment and Prognosis

As depicted in Tables 4.1 and 4.2, prognosis in both diffuse infiltrating and intravascular PCNSL is poor with a lethality of more than 90% (16 of 17 patients with adequate follow-up and information provided) and 70–100%, respectively. Regarding intravascular lymphoma, CNS involvement at the time of diagnosis is a predictor for short survival (Bergmann et al. 1994; Beristain and Azzarelli 2002; Ferreri et al. 2004b). Mainstays of therapy in diffuse infiltrating lymphoma are high-dose methotrexate alone or in combination with whole brain radiation. For treatment of intravascular lymphoma antracycline-based regimens (MACOP, CHOP, R-CHOP) are used (Ferreri et al. 2004a; Mihaljevic et al. 2010).

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5 Primary CNS Lymphoma: Immunohistochemistry of BCL-6 and Treatment with High-Dose Methotrexate

Hiroyuki Momota

Contents

Abstract

Several biomarkers have been identified as prognostic factors in primary central nervous system lymphoma (PCNSL). As a part of biomarkers, immunostaining for CD10, BCL-6, and MUM-1 has been widely investigated to determine the histogenetic origin of diffuse large B-cell lymphoma of PCNSL. B-cell lymphomas are able to be categorized into three known subtypes: germinal center B-cell (GCB), activated-GCB, and post-GCB subtypes according to immunostaining for these three markers. However, the correlation between immunophenotypic profile of PCNSL and the response to therapy is still unclear. The response to induction high-dose methotrexate therapy has been also identified as a prognostic factor of PCNSL. This review focuses on the immunohistochemistry for BCL-6 and the response to induction high-dose methotrexate therapy as prognostic factors of PCNSL.

Introduction

Primary central nervous system lymphoma (PCNSL) is one of the most aggressive primary brain tumors. PCNSL is a relatively rare neoplasm representing less than 1% of all non-Hodgkin lymphoma and approximately 3% of primary brain tumors, but the incidence of PCNSL has markedly increased (Coté et al. 1996; Olson et al.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_5,

2002). More than 95% of PCNSLs are diffuse large B-cell lymphoma (DLBCL), which consist of blastic cells with large pleomorphic nuclei and distinct nucleoli, and they express pan B-cell markers such as CD19, CD20, and CD79a. In addition, the cellular origin of DLBCL can be speculated by immunohistochemistry for CD10, BCL-6, and MUM-1. The expression patterns of these antigens have been currently studied to predict patients' prognosis.

Several factors including treatment modality affect on the survival in patients with PCNSL. High-dose methotrexate (HD-MTX) therapy is now recognized as the most effective chemotherapy for PCNSL and combined chemotherapy and radiotherapy has improved median survival times up to 60 months (Abrey et al. 2000; DeAngelis et al. 2002). However, the effect of HD-MTX varies among patients with PCNSL. Several reports have demonstrated that the response to HD-MTX therapy is a strong predictor for survival in patients with PCNSL. This review summarizes the value of immunohistochemical profile of DLBCL and the response to HD-MTX therapy as predictors of prognosis.

B-Cell Differentiation and Its Markers

B-cell lymphomas tend to reflect normal B-cell differentiation and the classification of B-cell lymphoma corresponds to stages of B-cell maturation (Jaffe et al. 2008). Normal B-cell differentiation begins with precursor B-cells that mature in the bone marrow. Precursor B-cells undergo immunoglobulin *VDJ* gene rearrangement and develop into mature naïve B-cells. Naïve B-cells circulate in the peripheral blood, undergoing exposure to antigen and blast transformation, and enter the germinal center (GC) where somatic hyper mutation and heavy chain class switching occur. The transformed cells of the GC are called centroblasts and develop into centrocytes. Centrocytes then migrate out of the GC, circulate in the peripheral blood again, and develop into either plasma cells or memory/marginal zone B-cells. Through this B-cell differentiation, CD5 is expressed on the surface of naïve B-cells in the peripheral blood or primary lymphoid follicles and follicle mantle zones. BCL-6 is not expressed in naïve B-cells, while CD10 and BCL-6 are both expressed in centroblasts. MUM-1 expression is seen in late centrocyte and plasma cells. As MUM-1 plays a critical role in down-regulating BCL-6 expression, BCL-6 and MUM-1 are reciprocally expressed.

Most DLBCLs are composed of cells resembles centroblasts or centrocytes in the GC and already have somatic hypermutation of immunoglobulin genes. Therefore, the cellular origin of DLBCLs is considered to be in the stage of germinal center B-cells (GCBs) or early post-GCBs. According to the normal B-cell differentiation, CD10 and BCL-6 are used as markers for GCBs (Dogan et al. 2000; Dent et al. 1997). MUM-1 is used as a marker for late GCBs or early post-GCBs, and its expression represents activated (antigen stimulated)-GCBs that have the capacity to differentiate toward CD138-expressing plasma cells (Falini et al. 2000; Natkunam et al. 2001). Using these markers, DLBCLs have been classified into two (GCB and non-GCB) or three (GCB, activated-GCB, and post-GCB) subgroups (Hans et al. 2004; Chang et al. 2004). In the later classification, GCB subgroup includes at least one positive GCB marker (CD10 or BCL-6) and negative MUM-1 tumors. Activated-GCB subgroup was defined as those with at least one positive GCB marker and MUM-1-positive immunophenotype. Post-GCB subgroup consists of no positive GCB marker and MUM-1-positive tumors. Several studies have shown that GCB subtype or BCL-6 expression is a better prognostic factor both in systemic and primary CNS DLBCLs (Braaten et al. 2003; Camilleri-Broët et al. 2006; Lin et al. 2006; Levy et al. 2008). However, other groups observed no difference or even worse survival between patients based on BCL-6 expression (Chang et al. 2004; Sugita et al. 2004; Momota et al. 2010). In one study, BCL-6 expression was associated with older age and worse performance status (Sugita et al. 2004). Another study showed that BCL-6 expression might represent non-GCB subtype that is associated with poor prognosis (Momota et al. 2010). CD5 is expressed in about 10% of systemic

DLBCLs, and has been suggested to be a poor prognostic marker (Yamaguchi et al. 2002), but the role in PCNSL remains unsolved.

High-Dose Methotrexate Therapy and the Response

HD-MTX therapy is the primary chemotherapy for PCNSL. Recent randomized phase II trial suggests that the combination of HD-MTX and high dose cytarabine (HD-AraC) followed by whole brain radiotherapy (WBRT) is superior to HD-MTX alone in overall survival in patients with PCNSL (Ferreri et al. 2009). However, there are many therapeutic options for the combined chemotherapies with HD-MTX. HD-MTX is used with other chemotherapeutic drugs such as vincristine and procarbazine other than AraC, and these combined chemotherapies appear to have the same therapeutic potential with good median survival time as the combination of HD-MTX and HD-AraC (Abrey et al. 2000; DeAngelis et al. 2002; Silvani et al. 2007; Ferreri et al. 2009). Although the scientific evidence is still insufficient, conventional therapy for PCNSL is therefore considered as HD-MTX-based chemotherapy, either as a single agent or in combination.

The effect of HD-MTX yet varies among patients with PCNSL. The mechanism for this variety is still unclear, but the responses to induction methotrexate therapy are found to be strong predictors for prognosis (McAllister et al. 2000; Momota et al. 2010; Pels et al. 2010). These findings imply that the prognosis of the patients with PCNSL has been determined before radiation therapy. Interestingly, both BCL-6 expression and post-GCB subtype appear to have no effect on the response to HD-MTX therapy (Momota et al. 2010). Good responders to HD-MTX possibly reflect benign characteristics of the tumor regardless of the known prognostic factors.

In conclusion, prognostic values of several biomarkers and the response to methotrexate therapy have been identified in patients with PCNSL. Although the correlation between BCL-6 expression and survival remains still uncertain, differentiation status of B-cell seems to affect prognosis in this disease. More studies are needed to confirm the true value of these prognostic factors. Exploration of the correlation between new biomarkers and treatment response will provide us novel molecular therapies based on the distinct subgroups of PCNSL.

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Thiamine Deficiency Complicating the Treatment of Primary CNS Lymphoma

6

Simon E. Richardson and Christopher McNamara

Contents

Abstract

Patients undergoing high-dose chemotherapy for CNS lymphomas are predisposed to thiamine deficiency. With the presence of pre-existing neurological deficits and the lack of a definitive diagnostic test the complications of Wernicke's encephalopathy and Korsakoff's dementia are easily missed. Clinicians should be aware of thiamine deficiency as a differential diagnosis for neurological or cardiovascular deterioration is PCNSL patients. We propose that prophylactic, parenteral thiamine should be administered to all patients receiving second-line anti-emetic therapy during high-dose chemotherapy for CNS malignancy.

Introduction

Supportive care of patients undergoing treatment of primary CNS lymphoma (PCNSL) is a particular challenge. This group of patients often present with significant morbidity from their disease that can mask symptoms from the intensive treatments used to achieve a cure. Evidence is growing that thiamine deficiency is a frequently overlooked cause of morbidity and mortality in such patients in both the paediatric (Vasconcelos et al. 1999) and adult (Richardson et al. 2010) setting.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_6,

Pathology

Vitamin B1 (thiamine) is an essential co-enzyme with roles in carbohydrate, lipid (including myelin) and amino acid metabolism, as well as the production of neurotransmitters. Thiamine stores are sufficient for 18 days, beyond which enzymes requiring thiamine pyrophosphate as a co-factor are impaired.

A number of genetic and environmental factors affect thiamine metabolism. A number of genetic mutations associated with the Wernicke-Korsakoff syndrome have been demonstrated; examples of these affect the affinity of transketolase for thiamine, as well as changes in the high affinity thiamine transporter protein SLC19A2 and the $GABA_A$ receptor subunit genes. It is likely that such genetic subtypes are only clinically important on occasions where thiamine availability is reduced, either by reduced intake or increased metabolism.

Alcohol excess and hyperemesis are established as the classical causes of thiamine deficiency in adults. In children, however, cancer and its treatment is the primary cause of thiamine deficiency syndromes and this is becoming increasingly recognised in the adult population. Factors that predispose cancer patients to thiamine deficiency include thiamine use by cancer cells, malnutrition, hyperemesis, diarrhoea, intermittent carbohydrate loading, chemotherapeutic drugs including ifosfamide (Buesa et al. 2003), erbulozole (Van Belle et al. 1993), and 5-fluorouracil (Cho et al. 2009), other drugs such as tetracycline antibiotics, gastrointestinal surgery and hypomagnesaemia.

Clinical Manifestations

Wernicke's encephalopathy (WE) is an acute, neuropsychiatric syndrome first described in 1881 by Carl Wernicke in two alcoholic males and a woman who developed severe vomiting due to pyloric stenosis following sulphuric acid ingestion. In acute WE, a sudden fall in CNS thiamine causes oedema and haemorrhage particularly affecting the peri-aqueductal gray matter, mamillary bodies and medial thalamus. It is characterised by the classical triad of confusion (82%), gait disturbance (23%) and ocular signs (29%) such as opthalmoplegia and nystagmus. Neuropathological studies by Harper et al. (1986), however, demonstrated that this triad is present in only 16% of cases and that the condition was significantly under-diagnosed with 80% of cases diagnosed at post-mortem.

Uncommon manifestations at presentation include autonomic dysfunction such as hypotension, tachycardia and hypothermia, visual disturbance due to retinal haemorrhages and papilloedema, hearing loss, seizures, hallucinations and behavioural changes. As the syndrome progresses motor symptoms become more prominent including paralysis and dyskinesia. Hyperthermia and coma can also occur. Chronic thiamine deficiency can present as a peripheral neuropathy (dry beri beri), although high or low output cardiac failure (wet beri beri) is more commonly seen in Asians.

If treated promptly the clinical manifestations of acute WE are reversible. The outcome from untreated acute WE is poor, however, with an estimated mortality of 17%. 80% of such patients develop Korsakoff's dementia defined as disproportionate memory impairment relative to other cognitive functions secondary to thiamine deficiency.

Diagnosis and Treatment

Importantly, the neurological manifestations of thiamine deficiency in PCNSL may be ascribed to the underlying lymphoma, delaying replacement therapy. There is no specific diagnostic test and it remains a clinical diagnosis based on a high index of suspicion. Blood tests such as blood thiamine concentrations and red blood cell transketolase activity are technically difficult, lack specificity and are rarely available on a timescale that would change management. High signal in the peri-aqueductal gray matter, mamillary bodies and medial thalamus on T2-weighted

MRI images has a sensitivity of 53% and specificity of 93% for WE making MRI scanning the most useful diagnostic modality (Antunez et al. 1998).

Optimal therapy for WE is controversial; consensus opinion recommends treatment with a minimum of 500 mg parenteral thiamine per day, continued until there is no further neurological recovery. Thiamine is inexpensive, safe and easy to administer. Concerns about growth-promoting effects on paediatric tumours are not supported by available evidence (Lee et al. 2005).

In conclusion, patients undergoing high-dose chemotherapy for CNS lymphomas are predisposed to thiamine deficiency. With the presence of pre-existing neurological deficits and the lack of a definitive diagnostic test the complications of Wernicke's encephalopathy and Korsakoff's dementia are easily missed. Clinicians should be aware of thiamine deficiency as a differential diagnosis for neurological or cardiovascular deterioration is PCNSL patients. We propose that prophylactic, parenteral thiamine should be administered to all patients receiving second-line anti-emetic therapy during high-dose chemotherapy for CNS malignancy.

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Metastatic Brain Irradiation-Induced Lymphocytosis Predicts Efficacy of Radiotherapy

7

Paolo Lissoni

Contents

Abstract

The prognosis of cancer depends on both tumor and patient biological characteristics. Within host biological variables, lymphocytopenia is associated with a poor prognosis in advanced cancer patients. Moreover, lymphocyte number has been proven to be influenced by both tumor growth and antitumor therapies, among them radiotherapy (RT) would represent the most lymphocytopenic treatment, particularly the pelvic irradiation. The present investigation was performed to evaluate the effects of brain irradiation on lymphocyte count in relation to the efficacy of treatment, and those induced by the pineal hormone melatonin (MLT) on the radiosensitivity of brain metastases due to radioresistant neoplasms. In a first study, we evaluated 70 solid tumor patients with brain metastases, who were treated by brain RT. In a second study, we evaluated the influence of a concomitant MLT administration (20 mg/day orally in the evening) in 14 patients treated by RT for brain metastases due to lung adenocarcinoma or large cell carcinoma, by comparing the results to those obtained in a control-group of 28 comparable patients treated by RT alone. In both studies, the dose of brain RT was 30 Gy. Patients who achieved an objective regression of brain metastases showed a statistically significant increase in lymphocyte mean number with respect to those found in patients who had no benefit. On the same way, the

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_7, © Springer Science+Business Media Dordrecht 2012

concomitant administration of MLT significantly increased the percent of partial or complete brain metastasis regression with respect to the results observed in patients treated by the only RT. The results of this preliminary study seem to suggest that brain irradiation-induced increase in lymphocyte amount may predict the efficacy of the treatment in patients with brain metastases due to solid neoplasms, and that the concomitant administration of neuroactive substances capable of modulating immune system and tissue radiosensitivity, such as the pineal indole MLT, may modulate the biological effects and the efficacy of brain irradiation.

Introduction

It is known for more than 30 years that the evidence of lymphocytopenia is associated with a poor prognosis in advanced cancer patients irrespective of tumor histotype and disease extension (Riesco 1970). Therefore, lymphocytopenia represents a tumor histology-independent negative prognostic variable in advanced cancer patients. However, despite the well known prognostic significance of at least lymphocyte number in the clinical course of the neoplastic disease, lymphocyte count is not generally taken into consideration by the oncologists during the clinical management of cancer patients. On the contrary, preliminary clinical studies would suggest that lymphocyte variations occurring during cancer chemotherapy may predict the clinical response and the efficacy of treatment (Ehrke et al. 1989). In more detail, lymphocyte number has been proven to either increase or decrease under cancer chemotherapy, and the occurrence of chemotherapy-induced lymphocytosis has appeared to predict an objective tumor regression or at least a disease stabilization (Lissoni et al. 1999, 2009). On the other hand, radiotherapy has been proven to constantly induce a severe lymphocytopenia, which may persist for several months (Louagie et al. 1999), and at present radiotherapy would represent the most lymphocytopenic antitumor conventional therapy. Because the antitumor immune response mainly depends on lymphocyte number and functionless (Atzpodien and Kirchner 1990), radiotherapy would clearly suppress the anticancer immunity. Then, radiotherapy-induced lymphocytopenia would negatively influence the prognosis of the neoplastic disease and its efficacy itself. The evidence of lymphocytopenia has been described for pelvic, mediastinic, and head and neck irradiation (Louagie et al. 1999; Lissoni et al. 2005), whereas only few data are available about the effect of brain irradiation on lymphocyte count. From a theoretical point of view, brain being a fundamental area involved in the psychoneuroendocrine modulation of the immune response (Rubinow 1990), we could expect that brain irradiation may represent the most detrimental condition in terms of suppression of lymphocyte functions, with the following induction of a severe immunosuppressive status. Moreover, recent experimental studies have suggested that radiotherapy-induced inhibitory effect on lymphocyte proliferation and function may be modulated by acting on the psychoneuroimmune interactions. In particular, it has been shown that both interleukin-2 (IL-2), which is the major T lymphocyte growth factor (Grimm et al. 1982), and the pineal hormones may prevent at least in part radiotherapy-induced lymphocytopenia (Lissoni et al. 2008), suggesting the existence of a psychoneuroimmune regulation of lymphocyte sensitivity to the irradiation, which could influence lymphocyte response to radiotherapy. The possible importance of the neuroimmune modulation of lymphocyte radio sensitivity could be particularly relevant in the case of brain irradiation. Brain is the main body area containing the major neuroendocrine structures that are involved in the neuroimmunomodulation, with potential stimulatory and inhibitory effects on the immune responses, including the anticancer immunity. On these bases, two different studies have been performed in an attempt to evaluate the influence of brain irradiation on lymphocyte count in patients with brain metastases due to solid neoplasms. Also, a study has been carried out to investigate the possible immunomodulatory effect of a concomitant administration of the pineal hormone melatonin (MLT) on brain irradiation-induced changes in lymphocyte count

and on the efficacy of radiotherapy itself. These studies were done with cancer patients with brain metastases due to radio-resistant solid neoplasms, such as lung adenocarcinoma and large cell carcinoma.

Materials and Methods

In a first study, we evaluated changes in lymphocyte count in 70 solid tumor patients with single or multiple brain metastases treated by palliative brain irradiation, by comparing the results in relation to the efficacy of radiotherapy itself. Tumor histotypes were as follows: non-small cell lung cancer (NSCLC): 32; small cell lung cancer (SCLC): 12; breast cancer: 17; colorectal cancer: 5; malignant melanoma: 4. Multiple brain metastases were present in 44 patients, whereas the remaining 26 patients had single brain metastasis.

In a second study we have evaluated changes in lymphocyte count and the clinical response in 14 NSCLC patients with brain metastases treated by brain irradiation in association with MLT therapy. The results were compared with those observed in a historical control group of 28 patients with comparable tumor histotypes. Tumor histotypes were lung adenocarcinoma in ten patients and lung large cell carcinoma in the remaining four patients. In the same way, within the historical control group, tumor histotypes were lung adenocarcinoma in 21 and lung large cell carcinoma in the last 7 patients. MLT was given orally at a pharmacological daily dose of 20 mg during the dark period of the day, every day starting 7 days prior to the onset of radiotherapy.

In both studies, brain radiotherapy consisted of a total dose of 30 Gy at daily fractions of 3 Gy for 5 days a week during two consecutive weeks. Patients were concomitantly treated by a supportive care consisting of dexamethasone at a daily dose of 12 mg intramuscularly plus phenobarbital at a daily dose of 100 mg in the evening during the whole period of brain irradiation. Moreover, in both studies eligibility criteria were as follows: histologically proven metastatic solid neoplasms, presence of single or multiple brain metastases, measurable lesions, no previous brain irradiation and no concomitant chemotherapy. To evaluate change in lymphocyte count, venous blood samples were collected in the morning before the onset of radiotherapy and at weekly intervals during radiotherapy and for the next month after brain irradiation. Data were reported as mean +/− SE and statistically analyzed by the chi-square test, the Student's t test, and the analysis of variance, as appropriate.

Results

The results of the first study documented a complete response (CR) in 8/70 (11%) patients NSCLC: 2/32 (6%); SCLC: 4/12 (33%); breast cancer: 2/17 (12%). Moreover, a partial response (PR) was achieved in other 13/70 (19%) patients (NSCLC: 4/32 (12%), SCLC: 5/12 (42%); breast cancer: 3/17 (18%); colorectal cancer: 1/5 (20%)). Therefore, an objective tumor regression (CR + PR) was obtained in 21/70 (30%). Finally, a stable disease (SC) was observed in 24/70 (35%) patients, whereas the other 25/70 (36%) patients had a progressive disease (PD). Changes in lymphocyte count occurring on radiotherapy in relation to the clinical response are illustrated in Fig. 7.1. As shown, no significant difference in lymphocyte mean number was seen prior to radiotherapy between patients with objective tumor regression and those with SD or PD. On the other hand, lymphocyte mean number increased in the only responder patients, and lymphocyte mean count observed in responder patients at the end of radiotherapy. During the successive month, was significantly higher than that found in patients with SD or PD. Lymphocyte mean number observed after radiotherapy was higher in patients with SD than in those with PD, without however, statistically significant differences.

The results of the second study showed an objective tumor regression in 6/14 (43%) lung cancer patients treated by radiotherapy plus MLT, consisting of a CR in 2 (14%) and a PR in the other 4/14 (28%). A SD occurred in

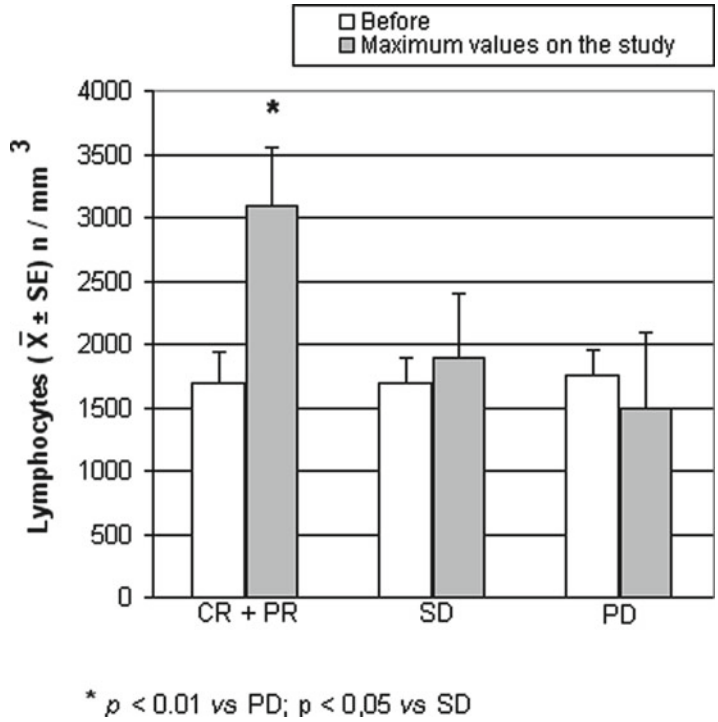

Fig. 7.1 Lymphocyte mean number before and after brain radiotherapy in solid tumor patients with brain metastases, in relation to tumor response. (*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease)

other three patients, then a disease-control (DC) (CR + PR + SD) was obtained in 9/14 (64%), whereas the remaining 5/14 (36%) patients had a PD. On the other hand, within the group of patients treated by brain radiotherapy alone, a CR and a PR were achieved in 1/28 (4%) and in 3/28 (11%), respectively with a tumor regression rate of 15%, corresponding to 4/28 patients. Then, tumor regression rate achieved in patients concomitantly treated with radiotherapy plus MLT was significantly higher with respect to that observed in patients treated by the radiotherapy only (6/14 vs 5/28, $P < 0.05$). In the same way, the percentage of DC obtained in patients concomitantly treated with MLT was significantly higher than in those treated with the brain irradiation only (9/14 vs 12/28, $P < 0.05$). Finally, as shown in Fig. 7.2, lymphocyte mean count significantly increased on radiotherapy in patients concomitantly treated by MLT with respect to the values achieved in those who received the radiotherapy only ($P < 0.01$), whereas no significant difference was observed in the pretreatment values of lymphocytes.

In conclusion, the results of these studies show that brain irradiation may induce either a decline or an increase in circulating lymphocyte number. This finding is surprising if we compare the effects on lymphocyte count exerted by brain irradiation with those observed during radiotherapy of body regions other than brain, which constantly induces lymphocytopenia (Louagie et al. 1999). Moreover, the results of these studies demonstrate that lymphocyte variations may have prognostic significance in terms of prediction of the clinical response. In fact, the evidence of an increase in lymphocyte count under brain irradiation has been proven to be associated with an objective tumor regression of brain metastases. Therefore, brain radiotherapy-induced lymphocytosis may predict the efficacy of irradiation itself in terms of regression of brain metastases due to solid neoplasms. These findings would confirm the importance of brain areas in the modulation of the immune system, including lymphocyte proliferation and activity. The inhibitory or the stimulatory effect of brain irradiation on lymphocyte count would depend on the type

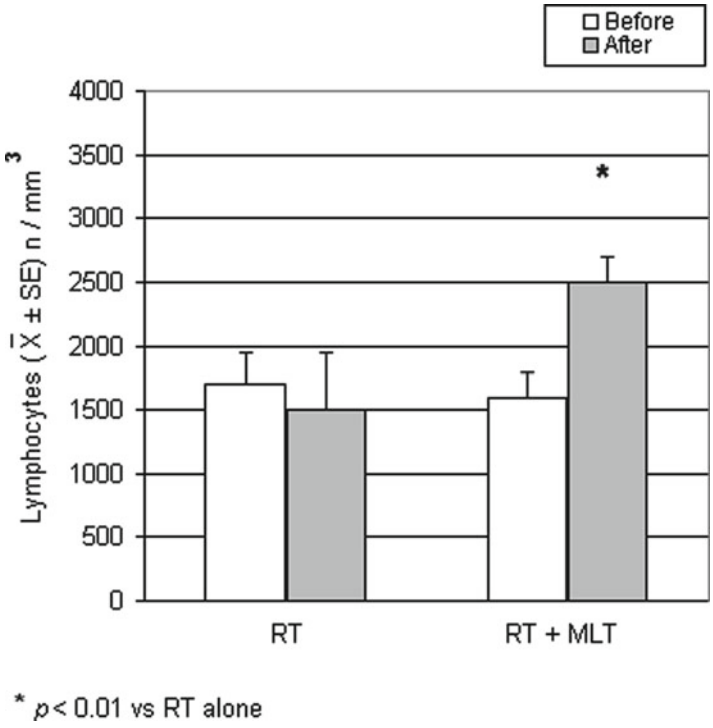

Fig. 7.2 Lymphocyte mean number before and after brain radiotherapy alone or radiotherapy plus melatonin (MLT) in non-small cell lung cancer patients with brain metastases

of nervous damage of the various brain areas, which exert different effects on the immune system through complex immunoneuroendocrine interactions (Rubinow 1990). Nevertheless, the relatively low number of patients and the different histotypes do not allow us to establish a well defined relation with the different tumor histotypes.

Within the brain structures, the pineal gland has been proven to play a fundamental immunoneuroendocrine role (Maestroni 1993). In agreement with previous experimental investigations (Lissoni et al. 2008), the present study suggests that the pineal hormone MLT may have a radioprotective action on lymphocytes, as confirmed by the higher lymphocyte number in patients concomitantly treated by MLT with respect to the results observed in patients treated by brain radiotherapy alone. Moreover, the present results show that the concomitant administration of MLT may enhance the efficacy of brain radiotherapy in terms of tumor regression in less radiosensitive neoplasms, such as lung adenocarcinoma and large cell carcinoma. MLT-induced amplification of the efficacy of brain radiotherapy may be due to either the prevention of irradiation-induced decline in lymphocyte number, or the enhancement of tumor radiosensitivity described with MLT under experimental conditions (Reiter et al. 2002). Therefore, these preliminary results would justify further randomized clinical studies with radiotherapy alone versus radiotherapy plus MLT in the treatment of brain metastases due to solid neoplasms.

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Primary Central Nervous System Lymphoma: Treatment with High-Dose Methotrexate

8

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Contents

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Abstract

Methotrexate at doses ≥1 g/m^2 remains the most efficient anticancer drug against primary central nervous system lymphoma, and is the most widely used drug in prospective clinical trials. Methotrexate is a folate analogue that inhibits dihydrofolate reductase, thereby blocking de novo purine synthesis. After intracellular uptake by the reduced folate carrier and the folate receptor-α, methotrexate undergoes intracellular polyglutamation by folypolyglutamate synthase on the γ-position of the parent glutamate moiety, resulting in the active polyglutamate moieties. Methotrexate as well as 7-hydroxy-methotrexate, its main metabolite in serum, are both eliminated by the kidneys. Accordingly, the elimination of methotrexate is prolonged in patients with renal impairment or third space fluid collections, due to a slow redistribution of methotrexate from this extravascular compartment. Main unwanted adverse events with high-dose methotrexate include severe myelosuppression, renal dysfunction and mucositis with diarrhea or stomatitis. Therefore, supportive measures such as rigorous hydration, urine alkalinization and careful drug monitoring with supplemental leucovorin rescue are used to avoid significant drug-related adverse events. A recent randomized clinical study has established a new treatment standard by showing an improved clinical outcome with

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_8,

the addition of high-dose cytarabine 2 g/m^2 twice daily on days 2 and 3 to high-dose methotrexate 3.5 g/m^2 on day 1, repeated every 3 weeks, and followed by consolidating radiotherapy if necessary.

Introduction

Primary CNS non-Hodgkin lymphoma (PCNSL) is increasing in incidence. This appears to be a consequence of the increasing population of those older than 65 years, in whom PCNSL occurs most often. PCNSL often has a favorable response to treatment and aggressive management may result in extended survival and also cure in a proportion of patients less than 65 years of age. Historically, radiotherapy has been used upfront, achieving complete response and a significant clinical improvement in the majority of patients, but also relapse within a few months in most cases. The addition of chemotherapy has consistently improved survival rates, and there is prospective evidence supporting the superiority of sequential chemoradiotherapy (DeAngelis et al. 1992). Methotrexate at doses ≥1 g/m^2 (high-dose methotrexate, HDMTX) seems to be the most efficient anticancer drug against PCNLS, and is the most widely used drug in prospective clinical trials.

The majority of neuro-oncologist advocate to utilize HDMTX as the backbone for upfront treatment of these neoplasms. Single-agent MTX at a dose of 8 g/m^2 has been studied in phase II trials (Herrlinger et al. 2005), resulting in a median progression-free survival of about 1 year. Second agents including procarbazine, temozolomide, vincristine high-dose cytarabine, ifosfamide, cyclophosphamide and rituximab have all been combined with HDMTX. Despite methodological concerns about comparing small phase II studies, data strongly suggest multiagent regimens that include alkylating agents to produce higher response rates and progression-free survival as compared to HDMTX alone (Pels et al. 2003; Shah et al. 2007). However, the only randomized data in PCNSL came from the International Extranodal Lymphoma Study Group (IELSG), showing improved clinical outcome in patients receiving combined HD-MTX and high-dose cytarabine as compared to patients receiving HDMTX monotherapy, both combined with consolidating local radiotherapy (Ferreri et al. 2009). The latter study showed an advantage for the addition of high-dose cytarabine both in terms of response rate before the use of radiation, and in terms of progression-free and overall survival. Finally, predictive markers such as MTX area under the curve (AUC_{MTX}) has been shown to have a strong and independent impact on clinical outcome (Ferreri et al. 2004; Joerger et al. 2010), and might be used in the future to individualize PCNSL treatment.

Methotrexate Mechanism of Action

Methotrexate is one of the earliest cancer chemotherapy agents, and continues to be used extensively in the treatment of mainly lymphomas, acute lymphatic leukemia and osteosarcoma. Methotrexate is a folate analogue that was originally designed to inhibit dihydrofolate reductase (DHFR), that naturally reduces tetrahydrofolate (THF). Reduced folate or THF is the proximal single carbon donor in several reactions involved in the de novo synthetic pathway for purines and pyrimidines, formation of polyamines, and transmethylation of phospholipids and proteins. In the treatment of cancer, the rationale for the use of methotrexate is that after treatment with methotrexate the malignant cells become starved for the purine and pyrimidine precursors of DNA and RNA required for proliferation. As a result of their inability to synthesize DNA and RNA, the malignant cells are unable to proliferate and cause further damage resulting in cell apoptosis.

The efficacy of MTX results from its extensive uptake by cells, rapid intracellular polyglutamylation and virtually stoichiometric inhibition of DHFR, a key enzyme in cell replication. Besides DHFR, MTX also inhibits thymidylate synthase (TYMS) and *de novo* purine synthesis. There is ample data on the mode of action of MTX and the mechanisms by which tumors exhibit inherent or acquired resistance to the drug. The uptake of

methotrexate into the cell is primarily mediated by a low affinity-high capacity reduced folate carrier (RFC), and in a lesser amount by a high affinity-low capacity transporter, the folate receptor-α. The principal endogenous substrate of this carrier-mediated active cellular transport system is 5-methyltetrahydrofolate (MTHF). Intracellularly, MTX is extensively polyglutamated by folypolyglutamate synthase (FPGS) on the γ-position of the parent glutamate moiety. The polyglutamated form is retained in the cell due to its negative charge, and represents the active moiety of the drug. Gamma-glutamyl hydrolase (GGH, also known as folypolyglutamase hydrolase or FPGH) converts long-chain MTX polyglutamates into short-chain polyglutamates, and ultimately reverts them back MTX, and may result in higher efflux and diminished efficacy of methotrexate. Finally, there is an intracellular equilibrium between methotrexate polyglutamation and hydrolation of polyglutamates back to the MTX parent compound. The MTX pentaglutamate moiety is most active, in that it tightly binds to DHFR as defined from X-ray crystallographic studies of the enzyme-drug complex. Inhibitory metabolic rate constants (K_i) of the polyglutamate compounds are roughly 100 times below the K_i values of the nonglutamated compound.

Resistance to MTX, encountered in cell culture model systems or in cancer patients, can result from an increased levels of the DHFR enzyme due to gene amplification, or to mutant DHFR with reduced affinity for MTX. Alternative mechanisms for drug resistance include decreased uptake or polyglutamation of methotrexate. Although DHFR is an extremely well-studied enzyme, there is still some uncertainty about its kinetics, mechanism for reduction of folate, multiple forms, and activation by a diverse group of agents. Prodrug forms of MTX, e.g., MTX α-phenylalanine, which can be activated by carboxypeptidase, might be a strategy to improve the efficacy of the drug by selective targeting to tumors. Additionally, the multitargeted antifolate pemetrexed has successfully entered the clinic. Pemetrexed inhibits at least three key enzymes in the folate metabolism, i.e. thymidilate synthase (TS), DHFR and glycinamide ribonucleotide formyltransferase (GARFT), in contrast to MTX that primarily inhibits DHFR.

Folate supplements are commonly administered to patients with rheumatoid arthritis taking long-term, low-dose oral methotrexate to avoid MTX-induced toxicity. Such folate supplementation does not diminish the therapeutic efficacy of MTX. Additionally, MTX-related myelosuppression and stomatitis are most likely caused by inhibition of cellular proliferation, but do not necessarily correlate with the therapeutic effects of the drug. Accordingly, avoiding folate deficiency is important with long-term, low-dose administration of MTX, while leucovorin rescue is an important therapeutic intervention for avoiding severe toxicity when administering MTX at high doses.

Methotrexate Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics

Methotrexate is a widely used antifolate drug. Antiproliferative activity is achieved by blocking thymidylate synthase, dihydrofolate reductase and *de novo* purine synthesis. Seven-hydroxy-methotrexate (7-OH-MTX) is the main metabolite in serum following HDMTX infusion (Jolivet et al. 1983), and it contributes to the activity and toxicity of the drug. The concentrations of 7-OH-MTX exceed those of the parent compound in plasma shortly after MTX infusion (Erttmann et al. 1985). Both MTX and 7-OH-MTX exhibit first-order pharmacokinetics (Jolivet et al. 1983). MTX enters the cell through the reduced folate carrier system, and by additional diffusion at higher plasma concentrations (>20 μmol/L). Finally, MTX undergoes intracellular activation by polyglutamation (Jolivet et al. 1983), which is increased at higher MTX doses and results in enhanced drug activity. MTX is eliminated by renal excretion involving passive glomerular filtration and active tubular reabsorption and secretion. The metabolite 7-OH-MTX is also renally cleared but more slowly than MTX

(Jolivet et al. 1983). The elimination of MTX is prolonged in patients with renal impairment or third space fluid collections, due to a slow redistribution of MTX from these extravascular compartment (Jolivet et al. 1983). HD-MTX induced acute renal dysfunction, mediated by the precipitation of MTX and 7-OH-MTX in the kidney tubules, is a potentially life-threatening complication and occurs in 1.8% of patients. The introduction of aggressive hydration, urine alkalinization and leucovorin rescue has been shown to decrease the morbidity rate in patients receiving HD-MTX, but severe morbidity and mortality secondary to HDMTX induced renal dysfunction are still major concerns. Methotrexate is particularly prone to drug–drug interactions, especially non-steroidal antirheumatics (NSAR) (Joerger et al. 2006), and this subject is further outlined below.

The systemic toxicity has been shown to be partly related to MTX plasma concentrations in patients receiving HDMTX, and important predictors for MTX plasma concentration include individual renal function and interacting drugs such as NSAR, benzimidazoles, penicillins and sulfonamides among others (Joerger et al. 2006). Because of considerable inter-patient variability, it is difficult for clinicians to choose appropriate dosage regimens for individual patients. Evaluation and management of such variability are the basis for individualized pharmacotherapy. Therefore, therapeutic drug monitoring (TDM) is essential to identify patients at high risk for developing significant toxicity, especially those with renal dysfunction, and reduces the occurrence of severe or even life-threatening toxicity. The measured concentration would indicate if there is a need for increased hydration, increase of calcium folinate (leucovorin) rescue, or when the rescue can be discontinued safely. Patients with high MTX concentrations are at risk of toxicity and should receive increased doses of leucovorin. Generally, blood samples should be collected and MTX serum concentration measured until it reaches the threshold of 0.05 μmol/L, as outlined below. Once MTX elimination is found to be delayed, leucovorin rescue is intensified according to certain thresholds. More recent studies suggest individual exposure to MTX to be an important predictor of a favourable treatment response in patients with PCNSL (Ferreri et al. 2004; Joerger et al. 2010). Because of the obvious association between MTX serum concentrations to both clinical toxicity and treatment response in patients with PCNSL, bayesian estimation of individual pharmacokinetic parameters from routine MTX monitoring might be a useful tool to individualize high doses of MTX in this group of patients.

Unwanted Adverse Events

Before pre-emptive measures such as MTX therapeutic drug monitoring (TDM) with supplemental leucovorin rescue were incorporated into HDMTX regimens, considerable MTX-associated toxicity was frequently seen. Von Hoff et al. (1977), reviewing the records of 498 patients treated with HDMTX before 1977, noted a 6% incidence of drug-related deaths. Of these deaths, 80% were attributed to severe myelosuppression, which resulted in either sepsis or hemorrhage; the remaining 20% were attributed to renal failure. More contemporary series, incorporating rigorous hydration, urine alkalinization, and careful drug monitoring with supplemental leucovorin rescue, have shown a considerable variation in toxicity, apparently depending largely on patient age. Younger patients usually had mild, tolerable toxicities when treated with HDMTX, whereas older patients exhibited significant toxicities, including drug-related death. In the HDMTX monotherapy arm of the recent International Extranodal Lymphoma Study Group (IELSG) trial no. 20, toxic death rate was 4 out of 79 patients (5%) (Ferreri et al. 2009). Severe hematological toxicity was described in 8% (thrombocytopenia), 10% (anemia) and 15% (neutropenia), respectively. Severe non-hematological toxicity included hepatotoxicity in 3%, nephrotoxicity and mucositis in 5% each, cardiotoxicity in 3% and coagulopathy with venous thrombosis in 10% of the patients (Ferreri et al. 2009). Renal toxicity is caused by saturated solubility of MTX in the urine and subsequent intratubular precipitation (crystal nephropathy).

Importantly, while PCNSL patients might not be generally more prone to HDMTX associated as compared to younger patients such as those with osteosarcoma, they are more susceptible to HDMTX-associated nephrotoxicity. In osteosarcoma patients with a median age of 16 years receiving preoperative HDMTX at a dose of 8–12 g/m^2, mild gastrointestinal complaints (nausea, oral mucositis, diarrhea) were the most common adverse effects of HDMTX, and no deaths occurred (Saeter et al. 1991). Severe bone marrow toxicity (WHO grade 3 or 4) complicated only 0.5% of treatment courses and was not accompanied by life-threatening infections. Renal toxicity, was seen in no more than 1.4% of all treatment courses (Saeter et al. 1991). Delayed renal dysfunction following HDMTX is of special concern, as it might result in late increases of serum MTX concentration after standard drug monitoring has been discontinued. Accordingly, impending severe toxicity might not be recognized early enough to start efficient supportive measures. To assess the prevalence of delayed renal dysfunction following HDMTX, Pauley and colleagues searched the computer records of St Jude Children's Research Hospital from 1992 to 2001 for all HDMTX courses with episodes of elevated serum creatinine values occurring within 30 days of the HDMTX treatment (Pauley et al. 2004). Among 6,861 courses, 33 courses were associated with delayed renal dysfunction within 4 weeks of the administration of HDMTX. Of those 33 courses, eight patients had MTX serum concentrations >1 umol/L 44 h after MTX infusion, and thus were closely monitored until MTX serum concentrations were below toxic thresholds. Therefore, the occurrence of renal dysfunction without delayed MTX excretion was estimated to be 0.36% (25 out of 6,861 course). Although it appears to be a very rare occurrence, the onset of renal dysfunction in the weeks following HDMTX, even in a patient who initially has normal clearance, may be an indication for continued and aggressive therapeutic drug monitoring, as outlined below.

Conventional treatment for HDMTX-induced renal dysfunction includes a prompt increase in the leucovorin dose based on plasma MTX concentrations and the continuation of hydration and urine alkalinization, provided adequate urine output can be maintained. Hemodialysis-based methods of MTX removal are a potential treatment option in otherwise refractory cases. Finally, carboxypeptidase-G2 (CPDG2), a recombinant bacterial enzyme that hydrolyzes MTX to the inactive metabolite 2, 4-diamino-N10-methylpteroic acid (DAMPA), is another treatment option for treatment-refractory HDMTX-associated renal dysfunction. When administered to patients with MTX-induced renal dysfunction, CPDG2 lowers plasma MTX concentrations within 15 min of administration by roughly 99%.

Supporting Measures to Avoid Severe Toxicity

Careful patient selection, adequate hydration and urinary alkalinization, avoidance of drug interactions, drainage of third-space fluids (when present), and pharmacokinetic monitoring with appropriate adjustment of LV doses have succeeded in making HDMTX, in general, a well-tolerated chemotherapy.

Assessing Renal Function

Determination of a normal renal function is a prerequisite for the administration of HDMTX. Glomerular filtration, tubular secretion and tubular reabsorption are all involved in MTX renal excretion. Transient decreases in creatinine clearance after HDMTX are often seen in adult patients, and usually are not associated with clinical toxicity. A normal serum creatinine concentration and a minimum GFR of 60 mL/min have generally been adopted as reasonable criteria for adequate renal function to ensure sufficient clearance of HDMTX. However, the association between pretreatment GFR, MTX clearance (CL_{MTX}) and clinical toxicity is controversial. On the one hand, pretreatment GFR was not associated with CL_{MTX} and subsequent toxicity in a study by Kerr et al. (1983). On the other hand, GFR was significantly associated with CL_{MTX} in two

population pharmacokinetic analyses (Joerger et al. 2006, 2010), and a lower CL_{MTX} was also independently associated with improved overall survival in 45 patients with PCNSL (Ferreri et al. 2004). Definitely, GFR only explains part of the interindividual variability in CL_{MTX}, that has been estimated to roughly 20% (Joerger et al. 2006, 2010), supporting the need for careful monitoring of MTX plasma concentrations.

Maintaining Adequate Hydration

Aggressive hydration is necessary along with urine alkalinization to promote adequate diuresis and prevent intratubular precipitation of MTX (crystal nephropathy), MTX-related renal failure, and subsequent toxicity due to increased MTX-exposure. This is further emphasized by the fact that 7-OH-MTX is only produced at relevant amounts in HDMTX-schedules, but plays a significant role for nephrotoxicity because of its limited aqueous solubility and risk of intratubular precipitation (Jacobs et al. 1977). One possible standard scheme for hydration reads as follows: 1,500 mL of 0.9 g/L saline solution, 1,500 mL of 5% glucose solution, 20 mEq KCl and 100 mEq HCO_3^- given over 24 h before MTX administration. In diabetic or recently operated patients, hydration should be modified according to clinical requirements. The optimal diuresis for administering HD-MTX should be >100 mL/h. A considerably higher urine flow is needed in case the urine pH is <8, because of the marked decrease in drug solubility at more acidic pH. Post MTX hydration should reach a total volume of ≥2,000 mL.

Maintaining Alkaline Urine

MTX and its metabolite 7-OH-MTX, which is formed predominantly with HDMTX therapy, show a 20- and 12-fold increase in solubility when pH increases from 5.0 to 7.0, respectively (Jacobs et al. 1977). Renal tubular precipitation of MTX and 7-OH-MTX occurs in an acidic urine environment (pH < 5.7), and this is likely to contribute to renal failure and delayed MTX clearance (Jacobs et al. 1977). Pitman et al. showed that urinary alkalinization achieved with oral sodium bicarbonate resulted in substantially less nephrotoxicity and myelotoxicity when historically compared with patients without urinary alkalization (Pitman and Frei 1977). In the latter study, a urine pH of >7.0 was maintained in addition to rigorous hydration (≥3 L/day). One possible standard scheme for urine alkalinization reads as follows: Urinary pH is determined every 8 h after MTX infusion, and values must be >8 at any time. In the case of urine pH < 8.0, 100 mEq HCO_3^- is administered as necessary, and parenteral hydration is accelerated.

Avoiding Drug Interactions

There is a multitude of drugs potentially interacting with MTX, including concurrently administered anticancer drugs, antibiotics and other supportive drugs. Accordingly, comedication should carefully be reviewed in patients considered to receive HDMTX. The following section gives an overview over the most important drug interactions to be considered when using MTX. There is strong evidence for nonsteroidal antirheumatics (NSAR) and salicylic acid to impair the tubular secretion of MTX, thereby increasing MTX exposure (Joerger et al. 2006; Thyss et al. 1986). Similarly, probenecid is impairing the tubular transport of MTX and can result in higher plasma concentrations of MTX. Penicilline derivatives and sulfonamides also result in decreased renal excretion of MTX (Ferrazzini et al. 1990), and have been shown to increase the hematological and gastrointestinal toxicity of MTX. Fluorochinolones should not be given concurrently with MTX due to a potential increase in cutaneous, renal, hepatic and hematological toxicity.

Concurrent use of trimethoprim/sulfamethoxazole infrequently has been associated with severe myelosuppression, potentially as a consequence of additive antifolate activity (Ferrazzini

et al. 1990). Additive or synergistic renal toxicity should be considered in the case nephrotoxic drugs are intended to be given concurrently with MTX. Cisplatin is an example of an anticancer drug that should not be used concurrently with HDMTX due to additive renal toxicity. Additive hepatotoxicity might also be an issue for concurrent drugs such as leflunomide, azathioprim, sulfasalacin among others. In such a case, regular monitoring of transaminases and cholestase parameters is recommended. By increasing intracellular concentrations of dihydrofolate reductase, the potassium-sparing diuretic triamteren might result in impaired activity of MTX. Similarly, allopurinol can impair the clinical activity of MTX due to its intracellular, purine-lowering effects (Masson et al. 1996). Vitamin supplements containing folic acid or its derivatives should not be used concurrently with MTX, as this might antagonize the antifolate effects of MTX.

As a special note, addition of folic acid and vitamin B12 to the other important antifolate – pemetrexed – does not impair clinical activity, but reduces myelosuppression. High doses of leucovorin should only be used if indicated for prolonged elimination of MTX. Vinca alkaloids, etoposide and probenecid increase the intracellular retention of MTX-polyglutamates, thereby increasing MTX activity and toxicity. On the contrary, corticosteroids, L-asparaginase, bleomycin and penicillines potentially block the cellular uptake of MTX. Finally, benzimidazoles reduce the clearance of MTX, potentially via the drug transporter breast cancer resistance protein (BCRP), thereby increasing the risk for severe toxicity (Joerger et al. 2006).

Interactions by Displacement of Methotrexate from Albumin Binding Sites

Usually, about 50% of MTX is bound to serum proteins, a fairly constant proportion irrespective of serum MTX concentration. There are multiple highly protein-bound drugs that potentially interfere with MTX by competition via albumin binding sites, including the anticancer drugs doxorubicin, bleomycin, cyclophosphamide, the antiepileptics phenytoin and barbiturates, the antibiotics sulfonamides, tetracyclines and chloramphenicol, NSAR, salicylic acid and sulfonylurea. As a consequence of displacement of MTX from albumin binding sites, serum concentrations of the unbound (active) fraction of MTX increases temporarily, until a new equilibrium is built up. Usually, a temporary increase of the free active fraction of a drug that is continuously given over longer periods of time is not considered of high clinical relevancy, but this might be different with the use of HDMTX, where even small changes of available albumin binding sites might have some effects on drug toxicity and activity.

Drainage of Third-Space Effusions

The presence of third-space effusions (e.g., ascites, pleural or pericardial effusions) is a contraindication for the administration of HDMTX. Prolonged back-diffusion from any third-space to the intravascular compartment results in prolonged MTX exposure and potentially severe toxicity. Accordingly, drainage of third-space fluids before HDMTX administration is strongly recommended to avoid severe toxicity.

In advanced cancer, third-space effusions might result from various issues, the most obvious being malignant effusions, but also concurrent cardiac or renal insufficiency, obstructed lymph drainage due to nodal metastases among others. The normal volume of fluid in the pleural, peritoneal and pericardial spaces is several milliliters. Once malignant effusions are established, these cavities may contain several liters. This may be due to the increased vascular permeability characteristics of the malignant tissue in the cavity, obstruction of normal drainage mechanisms such as lymph vessels, or changes in the osmotic pressure of the fluid due to high protein content. As a consequence, body cavities can become regions for sequestering

chemotherapeutic agents, thereby influencing plasma drug pharmacokinetics with markedly prolonged terminal half life.

Malignant effusions are usually detected in individuals with advanced metastatic disease, with malignant pleural effusions being the most prevalent. Although not as prevalent, pericardial and peritoneal effusions are also seen in patients with advanced cancer. Malignant effusions are often late complications of progressive cancer, and typically associated with a poor prognosis. Mechanistically, the dilution of MTX into a larger than normal volume of distribution in those patients with third-space effusions results in a prolonged terminal plasma half-live, and is associated with increased hematological or non-hematological toxicity from MTX. Importantly, malignant effusions can influence the pharmacokinetics of MTX to the extent that even the administration of moderate doses of MTX can result in life-threatening toxicity. So far, there has not been a systematic study of the effect of malignant effusions on the pharmacokinetics of MTX, but a detailed mechanistically-based pharmacokinetic and model on the quantitative influence of third-space effusions on MTX has been reported (Li and Gwilt 2002). The results of this simulation study provides a pharmacokinetic basis for the clinical observations that patients with malignant effusions being treated with MTX are at particular risk of toxicity following high-dose chemotherapy due to an increased terminal half-life of MTX.

In conclusion, every patient with even small amounts of third-space effusions considered for the administration of MTX at any dose should be considered high-risk, because of a considerable risk of prolonged elimination of MTX. Complicating matters further, redistribution of MTX from the third-space to the central compartment frequently results in secondary or late increases of serum MTX concentration, after standard drug monitoring is already discontinued. This compromises early detection of prolonged MTX exposure and delays the initiation of adequate supportive measures such as hydration and intensified leucovorin rescue.

Monitoring Serum Methotrexate Concentrations

Therapeutic drug monitoring (TDM) is essential when administering MTX at high doses. So far, TDM has exclusively been used to identify patients at the highest risk for HDMTX-related toxicity. In doing so, prompt action can be taken to minimize subsequent severe toxicity. With the usual 3-h HDMTX infusion, TDM starts 24 h after the end of MTX infusion, and is repeated every 24 h until MTX serum concentrations reach a threshold that is seen as "save". Various thresholds for stopping routine TMD after high doses of MTX have been reported, ranging between 0.05 μmol/L at any time (Ferreri et al. 2009), and 0.5 μmol/L 42–48 h after the infusion without concurrent risk factors (poor renal function, third-space effusions or gastrointestinal obstruction), or 0.1 μmol/L with concurrent risk factors (Pauley et al. 2004). The lower limit of quantification (LLQ) of standard TDM assays for MTX is ~0.1–0.2 μmol/L. Several nomograms based on the elimination kinetics of MTX have empirically been used to identify those patients at highest risk for toxicity. The threshold values for intensifying LV rescue or initiating other rescue measures are somewhat dependent on the MTX-schedule used. Furthermore, a threshold MTX serum concentration of ≥0.5 μmol/L at 48 h post infusion is usually considered for intensifying LV rescue. Stoller et al. (1977) measured MTX plasma clearance in 78 patients (395 treatment courses) who received HDMTX in a 6-h infusion. By 48 h post infusion, a MTX serum concentration of 0.9 μmol/L was associated with a significant increase in severe myelosuppression (Stoller et al. 1977). Previously, various cutoff points have been used to identify patients at increased risk for MTX-associated toxicity, but the threshold of 0.05 μmol/L at 48 h has widely been used with the shorter HDMTX infusion of 3 h. Although it appears to be a very rare occurrence, the onset of renal dysfunction in the weeks following HDMTX might be an indication for continued and aggressive therapeutic drug monitoring. If the MTX plasma concentration is elevated, a search for a third space should be made and leucovorin rescue reinstituted.

Leucovorin Rescue

Methotrexate at high dose would be lethal without the ensuing administration of reduced folates – such as leucovorin (LV) – to circumvent the metabolic block imposed by MTX. Most importantly, LV when given concurrently with MTX can abrogate the therapeutic effects of the latter, and therapeutic administration of LV is not given before 12 h post infusion for this reason. Overall, the timing of LV rescue has a marked impact on clinical outcome by improving the index of normal versus malignant cell rescue. In humans, LV administration can be delayed up to 24–36 h post MTX infusion and still maintain fairly tolerable toxicity. Usually, LV rescue starts 24 h after the start of MTX infusion at a dose of 15 mg/m^2 intravenous push every 6 h for 3 days (or 12 times).

In vivo, LV is converted to methylene-tetrahydro-folate (MTHF), which serves as the major circulating reduced folate, and which acts to replete the reduced intracellular folate pool required for the production of thymidylate and the purines. In addition to repleting reduced intracellular folate pools, excess extracellular concentrations of LV may promote "rescue" by competing with MTX for active transport into the cells. Duration of the LV rescue is also important and should be continued until serum MTX concentrations are <0.05 μmol/L, at which point circulating natural folates are believed to be sufficient to prevent cytotoxicity. In the case of persisting high MTX serum concentrations 48 h after the end of infusion, LV rescue should be modified according to the actual pharmacokinetic data. The following is a possible standard scheme: If MTX is between 0.05 and 0.5 μmol/L, LV should be kept at 15 mg/m^2 every 6 h; if MTX is between 0.5 and 1 μmol/L, LV should be increased to 50 mg/m^2 every 6 h; if MTX is >1 μmol/L, LV should be increased to 100 mg/m^2 every 6 h. Delayed elimination of MTX is the most important factor for causing severe toxicity, and every patient with suspected dysfunctional elimination of the drug should be presented to an oncologist experienced in the use of HDMTX, or a clinical pharmacologist.

Upfront Methotrexate as Monotherapy

Methotrexate with or Without Radiotherapy

Systemic HDMTX at doses ≥1 g/m^2 is seen as the most effective drug in PCNSL (Blay et al. 1998; Reni et al. 1997), and chemotherapy with HDMTX followed by whole-brain radiotherapy is the most commonly used approach for patients with newly diagnosed PCNSL, resulting in a 5-year survival of 20–35%. Single-agent MTX at a dose of 8 g/m^2 has been studied in phase II trials (Batchelor et al. 2003; Herrlinger et al. 2005), resulting in a median progression-free survival of ~1 year. The best dose of MTX for the use in PCNSL patients however remains undefined. Doses above 3 g/m^2 appear to obviate the need for additional intrathecal prophylaxis, although this is less clear for patients who have overt cerebrospinal fluid involvement at presentation.

The addition of chemotherapy to radiotherapy has been recommended to improve the overall survival of PCNSL patients (Blay et al. 1998; Reni et al. 1997), although the older data remained somewhat controversial. For example, a large series treated with modern radiotherapy obtained similar 3 and 5-year survival rates to those reported with the combined strategy of chemotherapy followed by radiotherapy (Laperriere et al. 1997). The superiority of the combined strategy was later confirmed by three large retrospective multicentre surveys reporting therapeutic results in over 1,000 patients treated in Europe and Japan (Bataille et al. 2000; Ferreri et al. 2002; Hayabuchi et al. 1999). These studies uniformly showed that HDMTX ≥1 g/m^2 is the most active cytostatic drug, while any regimen without HDMTX is associated with outcomes no better than with radiotherapy alone (Bataille et al. 2000; Blay et al. 1998; Ferreri et al. 2002; Reni et al. 1997). Although a survival advantage for HDMTX-based chemotherapy followed by radiotherapy has not been proven by a randomized study, a trial comparing this strategy to radiotherapy alone would likely be unacceptable to the majority of

clinicians, and the combined approach should be retained as the first-choice strategy. However, given the increased risk of treatment-related neurotoxicity, especially among elderly patients (Blay et al. 1998; Glass et al. 1994), some authorities recommend deferral of radiotherapy until relapse in this most vulnerable patient population.

Methotrexate in Combination with Other Anticancer Drugs

Multiple potential partner agents such as procarbazine, temozolomide, vincristine, ifosfamide, cyclophosphamide and rituximab have all been combined with HDMTX in nonrandomized studies. It is not possible to directly compare the results of multiple relatively small phase II studies with varying patient populations. Nonetheless, certain features may be distinguishable. Multiagent regimens that include alkylating agents appear to produce higher response rates and progression-free survival than HDMTX alone. Illustrative of this are the Memorial Sloan Kettering multiagent regimens (Shah et al. 2007).

Of special interest is also the possibility of using the monoclonal anti-CD20 antibody rituximab for PCNSL, in view of the improvement in long-term cure rate seen in systemic large B-cell lymphoma with the addition of rituximab to chemotherapy. Although such a large molecule should not cross the blood-brain barrier, this barrier is clearly disrupted in areas of contrast-enhancing tumor, and a number of anecdotal reports of activity in relapsed disease exist. A phase II trial studying the effect of adding rituximab to HDMTX, procarbazine, vincristine, and high-dose cytarabine showed an overall response rate of 93% with a 78% complete response rate. Median progression-free survival and overall survival had not been reached at 3 years, representing a major improvement over historical data for a similar regimen without rituximab (Shah et al. 2007). Of note, more severe neutropenia was seen, in keeping with the results of systemic lymphoma studies, in which the addition of rituximab has consistently increased the severity of hematologic toxicity. A number of studies are exploring the addition of rituximab to chemotherapy regimens for PCNSL. The Eastern Cooperative Oncology Group (ECOG)/North Central Cancer Treatment Group (NCCTG) phase II protocol introduces rituximab at the outset of therapy, before enhancing tumor disappears, and applies three times per week rituximab dosing to maximize blood levels at an early time point.

Obviously, several drugs have been combined with HDMTX on the basis of their capability to penetrate the blood–brain barrier and on their efficacy against systemic lymphomas rather than against MTX-refractory PCNSL. One exception is the antimetabolite cytarabine, that was found to provide a survival benefit in patients with PCNSL when added to HDMTX in a meta-analysis of 19 prospective trials (Reni et al. 2001) of PCNSL and an international retrospective study of 378 patients (Ferreri et al. 2002). The rationale for the administration of high-dose cytarabine after HDMTX is the continued exposure of proliferating cells to S-phase-specific cytostatics and the increased formation of pharmacologically active cytarabine triphosphates, resulting in synergistic cytotoxicity. A subsequent open, randomized phase II study was performed by the International Extranodal Lymphoma Study Group (IELSG) in 79 patients with PCNSL exclusively localised into the CNS, cranial nerves, or eyes, an ECOG performance status of ≤3 and measurable disease. Patients were randomly assigned to receive four courses of either HDMTX 3.5 g/m^2 on day 1 (n = 40) or HDMTX 3.5 g/m^2 on day 1 plus cytarabine 2 g/m^2 twice daily on days 2–3 (n = 39), repeated every 3 weeks. Overall response rate (69 vs. 40%, $p = 0.009$), 3-year failure-free survival (38 vs. 21%, $p = 0.01$) and 3-year overall survival (46 vs. 32%, $p = 0.07$) were all superior in the combination chemotherapy group as compared to the HDMTX monotherapy group. Grade 3–4 haematological toxicity was more common in the methotrexate plus cytarabine group than in the methotrexate group (92 vs 15%, $p < 0.001$). This study defines combined HDMTX and high-dose cytarabine as a new standard for patients ≤75 years of age and an ECOG performance score ≤3, as it improves clinical outcome with acceptable toxicity.

Predictors of Upfront Methotrexate Clinical Activity

After the identification of HDMTX as the most effective drug against PCNSL, a further approach for improving and individualizing patient treatment could be the identification of predictors for clinical outcome in patients receiving HDMTX. In 2004, Ferreri et al. studied the impact of MTX area under the curve (MTX_{AUC}), dose intensity, infusion rate and creatinine clearance (CL_{crea}) on clinical outcome and toxicity in 45 PCNSL patients receiving three different HDMTX-based combination regimens (Ferreri et al. 2004). Both a low CL_{crea} and AUC_{MTX} >1,100 μmol/L were independently associated with an improved overall survival, while a low CL_{crea} was associated with increased overall toxicity. These data are supported by a subanalysis of the IELSG study no. 20, including 55 patients with available pharmacokinetic data from the original study to define the predictive value of AUC_{MTX} and to identify clinical and therapeutic variables that could be manipulated to improve MTX efficacy in patients with PCNSL (Joerger et al. 2010). For this purpose, individual AUC_{MTX} estimates were derived from population analysis, and subsequently tested on drug toxicity and clinical outcome using multivariate logistic regression analysis and Cox hazards modelling. AUC_{MTX}, the IELSG score and treatment group (HDMTX versus combined HDMTX and high-dose cytarabine) were significant predictors for objective treatment response in the adjusted model. AUC_{MTX} did not predict toxicity with the exception of liver toxicity and neutropenia. Most importantly, a high AUC_{MTX} was associated with a significantly higher 3-year event-free and overall survival. Both the AUC_{MTX} and the IELSG score were significant predictors of the 3-year event-free and overall survival in the adjusted model (Joerger et al. 2010). Therefore, achieving a minimum AUC_{MTX} is suggested to be of unique significance to achieve a favourable clinical outcome in patients with PCNSL, and the cutoff is estimated to be between 1,000 (Joerger et al. 2010) and 1,100 μmol*h/L (Ferreri et al. 2004).

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Paraneoplastic Syndromes in Primary CNS Lymphoma

9

Zaher K. Otrock and Ali Bazarbachi

Contents

Abstract

Lymphomas are a heterogeneous group of malignancies with diverse biological behavior and prognosis. They are divided into two large groups which encompass non-Hodgkin and Hodgkin lymphoma. They are at times associated with paraneoplastic manifestations that vary in terms of their frequency, but are often clinically significant. These manifestations are almost always autoimmune in nature. Paraneoplastic syndromes are rarely described in primary central nervous system lymphoma (PCNSL). A few isolated case reports in the medical literature have described the coexistence of PCNSL with myasthenia gravis, cerebral salt wasting syndrome, peripheral neuropathy, and leukoencephalopathy as paraneoplastic phenomena. The majority of these cases reveal a poorer prognosis of PCNSL when associated with paraneoplastic syndromes. This chapter reviews what has been described in the medical literature of these occurrences.

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Paraneoplastic Syndromes in Lymphoma

Paraneoplastic syndromes are a constellation of signs and symptoms that are occasionally seen in patients with an underlying malignancy. These atypical cells have adverse effects distant from

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_9,

the primary tumor or metastases, typically through ectopic hormone production or autoimmune phenomena. In some instances, paraneoplastic syndromes may be the presenting symptom of an underlying malignancy, and they have been described in many tumors such as lung, breast, gastric and hematologic malignancies.

Paraneoplastic syndromes in association with lymphoproliferative disorders vary in terms of their frequency, but are often clinically significant, causing morbidity and even mortality. In the case of lymphomas, the most common presentation of paraneoplasia is in the form of autoimmune phenomena. The association of lymphomas is strongest with rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus (SLE) and autoimmune thyroid disease (Varoczy et al. 2002).

Paraneoplastic syndromes in association with lymphoproliferative disorders can affect any organ, including the central nervous system (CNS), skin, blood vessels, kidneys, heart, and even the gastrointestinal tract. The neurologic paraneoplastic syndromes are typically the most devastating, and these include paraneoplastic cerebellar degeneration, paraneoplastic limbic encephalitis and peripheral neuropathies in the form of Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP). Paraneoplastic pemphigus is the most clinically significant cutaneous syndrome associated with lymphomas, as it portrays a poor prognosis with mortality rates greater than 90% (Nousari et al. 1999). Other less grave but equally important paraneoplastic manifestations of lymphomas include autoimmune hemolytic anemias, idiopathic thrombocytopenic purpura, and vasculitis of the cutaneous, ophthalmic, and central nervous systems (Hagler and Lynch 2004).

Primary CNS Lymphoma

Primary central nervous system lymphoma (PCNSL) is an uncommon subset of extranodal high-grade non Hodgkin lymphoma (NHL) that can affect any part of the CNS, including the brain, eyes, leptomeninges or spinal cord. PCNSL represents 1–2% of all brain tumors and almost 1% of all NHLs (Villegas et al. 1997). However, these percentages have increased threefold over the past decades, owing to the increasing population of congenital or acquired immunodeficiency (Eby et al. 1988). Individuals with human immunodeficiency virus (HIV) infection are at greater risk for developing this tumor. PCNSL has been reported in up to 6% of HIV-infected patients, and the incidence is expected to escalate as patients with low CD4+ counts are surviving longer (Garcia-Rayo et al. 1998). However, the increase in incidence is beyond what can be explained by HIV alone. Epstein-Barr virus (EBV) infection has been implicated to increase the risk of CNS lymphoma in the immunosuppressed population (Cingolani et al. 2000). PCNSL has also been described following solid organ transplantation as part of post-transplant lymphoproliferative disease (PTLD) (Phan et al. 2000).

From the histopathological point of view, the lymphoma cells of PCNSL are predominantly of the activated B-cell-like type (Camilleri-Broet et al. 2006), and are likely to originate from the late germinal center (Montesinos-Rongen et al. 2008). Ninety percent of PCNSLs are diffuse large B-cell lymphoma, whereas the remaining 10% are poorly characterized low-grade lymphomas, Burkitt lymphomas, and T-cell lymphomas (Miller et al. 1994).

The typical presentation of PCNSL in immunocompetent patients is usually during the sixth and seventh decades of life (DeAngelis et al. 1992), and it clinically presents with a focal mass lesion in more than 50% of cases. A study conducted on 248 immunocompetent patients by Bataille et al. (2000), demonstrated that 43% of patients presented with neuropsychiatric signs, 33% had increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms. Seizures in this population are less frequent than with other types of brain tumors since PCNSL primarily affects the subcortical white matter rather than the epileptogenic gray matter. In contrast to other forms of NHL, patients with PCNSL rarely present with B symptoms such as fever, weight loss, or night sweats.

PCNSL typically carries a poor prognosis with a 5-year survival of 4%, and without treatment,

patients rapidly deteriorate with a mean survival of 3 months (Henry et al. 1974). Factors that predict decreased survival include age greater than 60 years, impaired performance status, elevated serum lactate dehydrogenase (LDH), increased cerebrospinal fluid (CSF) protein, and involvement of deep brain structures. Many authors have shown that B-cell lymphoma-6 (BCL6) is expressed in most PCNSL cases, but its prognostic value is still controversial. Earlier studies demonstrated that BCL6 is associated with a favorable prognosis; however recently, Raoux et al. (2010) established that BCL6 is correlated with a poorer prognosis.

Contrast-enhanced brain magnetic resonance imaging (MRI) is the imaging modality of choice in patients with suspected PCNSL. The lymphoma tends to enhance homogeneously on both MRI and computed tomography (CT) scan, whereas in HIV-associated PCNSL, the lesions are often ring-enhancing due to the presence of necrosis. They are solitary in 65% of cases and are commonly located supratentorially; 38% in a cerebral hemisphere, 16% in the thalamus/basal ganglia, 14% in the corpus callosum, 12% in the periventricular region, and only 9% in the cerebellum and 1% in the spinal cord (Kuker et al. 2005).

Paraneoplastic Syndromes in PCNSL

Paraneoplastic syndromes, although very common in systemic lymphomas, are rarely described in PCNSL. A few isolated case reports in the medical literature have described the coexistence of PCNSL with myasthenia gravis, cerebral salt wasting syndrome, peripheral neuropathy, and leukoencephalopathy as paraneoplastic phenomena. The majority of these cases reveal a poorer prognosis of PCNSL when associated with paraneoplastic syndromes.

Myasthenia Gravis

The most credible evidence for a paraneoplastic phenomenon occurring with PCNSL is that of myasthenia gravis. Myasthenia gravis is a well known autoimmune disease characterized by the production of autoantibodies against the acetylcholine receptor in the neuromuscular junction, causing muscle weakness and fatigability (Vincent et al. 2001). It is a well known paraneoplastic sign of thymomas; however, it is rarely described with other tumors. Only two reports in the literature depict myasthenia gravis occurring as a paraneoplastic incident with PCNSL.

In the first report by Shams et al. (2002), the authors described a 54-year-old man who presented with signs of ocular myasthenia gravis, with normal findings on contrast enhanced CT of the brain, negative antiacetylcholine receptor antibodies, and an abrupt response to cholinesterase inhibitors. However, clinical relapse a few months later lead to administration of systemic steroids, which caused initial improvement, but then a rebound neurological deterioration. This time, MRI of the brain revealed a high signal lesion involving the brain stem, right thalamus, and basal ganglia with a mild mass effect. A brain stem biopsy performed 8 months after the initial presentation confirmed the diagnosis of B-cell lymphoma, and this was soon followed by the patient's death (Shams et al. 2002). This case illustrated an example of PCNSL simulating myasthenia with ocular findings and negative antiacetylcholine receptor antibodies.

The second case of myasthenia gravis occurring as a paraneoplastic manifestation of PCNSL was reported by Masroujeh et al. (2010). Contrary to the earlier case, the authors described a patient who was already diagnosed with PCNSL and then later developed myasthenia gravis. After histopathologic diagnosis of a diffuse large B cell lymphoma, the 68-year-old patient was treated with intravenous methotrexate, whole brain irradiation and high dose corticosteroids. Three months following end of radiation therapy, the patient developed proximal muscle weakness, dysphagia and dysarthria. This time, his brain MRI was unremarkable, however, his electromyography (EMG) with repetitive stimulation of left axillary nerve showed decrement in action potential amplitude up to 60%, which are changes

compatible with myasthenia gravis. In addition, the acetylcholine receptor antibodies were found to be elevated. The patient improved on oral pyridostigmine, and the corticosteroids were tapered followed by treatment of residual brain lymphoma (Masroujeh et al. 2010). This is the only case that describes myasthenia gravis developing in the course of a previously diagnosed PCNSL, and not otherwise. This strengthens the argument that myasthenia gravis is a paraneoplastic event that should be considered in patients with PCNSL who develop muscle weakness and speech problems.

Cerebral Salt Wasting Syndrome

Another paraneoplastic syndrome seen in patients with PCNSL is cerebral salt wasting syndrome (CSW), as described by Prochazka et al. (2009). A previously healthy 48-year-old male patient was admitted to a psychiatric department for a recent history of a behavior disorder. A CT scan of the brain verified a tumor affecting the area of the basal ganglia and the right part of the thalamus and oppressing the third brain ventricle. Histologic examination of a brain tissue biopsy confirmed the diagnosis of diffuse large B-cell lymphoma. Clinically, the patient was soporous, and his laboratory tests revealed severe serum hyponatremia, hypochloremia, hypoosmolality and polyuria with normal serum levels or urea, creatinine, glucose and calcium. These findings, along with high specific gravity of the urine, and elevated brain natriuretic peptide, are diagnostic of severe salt wasting syndrome (Prochazka et al. 2009). The patient was intensively hydrated and chemotherapy was initiated. After the first chemotherapy cycle, the CT scan showed regression in the tumor size accompanied by patient's improved cognition as well as decreased polyuria and urine electrolyte excretion. Although this syndrome is very common in patients with brain pathology, this was the first case that described CSW after the diagnosis of PCNSL, and this entity should be included in the differential of any patient with CNS lymphoma presenting with hyponatremia.

Paraneoplastic Autonomic Neuropathy

Paraneoplastic autonomic neuropathy has been noted with various neoplasms including small cell carcinoma of the lung (Martin et al. 2007), pancreatic adenocarcinoma (Ashraf and Farrow 1992), and Hodgkin's lymphoma (van Lieshout et al. 1986). However, only one case reported in 2009 described autonomic dysfunction occurring in the setting of PCNSL. A 68-year-old male patient presented for progressive impotence and postural lightheadedness of 6-month duration; workup at the time was negative for any infection, metabolic abnormality or malignancy. The patient worsened clinically and was readmitted several months later, only this time to discover multiple enhancing lesions seen in the brainstem. He underwent craniotomy with biopsy of the medullar lesion which was histologically consistent with large B cell CNS lymphoma. The etiology of this patient's autonomic dysfunction could be explained by the lymphomatous involvement of the medulla; however, quantitative sudomotor axon reflex tests (QSART) illustrated a peripheral autonomic neuropathy rather than a central cause for the autonomic dysfunction (Ficker and Hammack 1995). This implies that the patient's autonomic dysfunction was a paraneoplastic manifestation, rather than a contiguous effect of the malignant cells.

Leukoencephalopathy

A less straightforward paraneoplastic syndrome associated with PCNSL is leukoencephalopathy. Several case reports in the literature describe the co-existence of leukoencephalopathy with PCNSL. Brecher et al. (1998) were the first to describe the case of a 35-year-old woman who presented with a picture identical to that of multiple sclerosis, and was treated as such for several months. Her MRI demonstrated multiple non-enhancing white matter lesions; these radiological findings were very unusual for CNS lymphoma, which classically enhances after contrast administration. Thirty months after her initial presentation, she was diagnosed with PCNSL by

confirming new enhancing brain lesions on MRI, and by histopathology which additionally showed severe demyelination (Brecher et al. 1998). The patient was treated with chemotherapy and brain irradiation, but she died 14 months after the diagnosis of lymphoma.

A similar presentation was documented few years later in Spain, where a 58-year-old woman was treated as multiple sclerosis for 6 months after she presented with focal neurological signs and a brain MRI showing scattered and confluent white matter lesions without contrast enhancement (Ayuso-Peralta et al. 2001). Six months after initial presentation, the patient's neurologic situation worsened and a new cranial MRI showed worsening of the previous white matter lesions with no enhancement. An open brain biopsy revealed diffuse demyelination together with malignant cells of diffuse large B cell lymphoma type. Treatment with cytarabine was started, but the patient died shortly after.

Finally, the third case of leukoencephalopathy was reported by Kuhlmann et al. (2001), where they described the case of a 65-year-old man who presented with focal neurological complaints, and MRI findings in the left cerebellar hemisphere consistent with multiple sclerosis. Several months of corticosteroids lead to a short-lived improvement followed by clinical deterioration and the appearance of new contrast enhancing lesions that were diagnosed histologically as B cell lymphoma. Serum analysis at the time revealed the presence of autoantibodies directed against myelin oligodendrocyte glycoprotein (MOG), which may be implicated in promoting autoimmune demyelination (Kuhlmann et al. 2001). The patient was treated with prednisolone, methotrexate, and radiation; however, his clinical situation deteriorated and he died 2 months after the diagnosis of lymphoma.

In the three cases described above, the patients died within a short period of diagnosis, signifying a poorer prognosis associated with this clinical picture, along with the delay in diagnosis and initiation of appropriate treatment. The controversy remains with calling demyelination in these cases a paraneoplastic phenomenon or a consequence of the same etiologic process. Alderson et al. (1996) raised the possibility that lymphocytic infiltrates which accompany leukoencephalopathy may undergo transformation into malignant B cell populations. Epstein-Barr virus has been implicated as a transformative agent in this progress, and the association of PCNSL with immunodeficiency and EBV positivity could be the missing link. However, the three case reports previously described document negative EBV testing by PCR, excluding this possibility, and raising the likelihood of demyelination as a paraneoplastic process. In addition, the report by Kuhlmann et al. (2001) demonstrated the presence of serum antibodies against myelin oligodendrocyte glycoprotein, which further authenticates the paraneoplastic etiology. Two other reports in the literature have described biopsy confirmation of large focal demyelinating lesions in the brain associated with seminoma (Jaster et al. 1996; Wong et al. 1998). This further reinforces the fact that demyelination could be secondary to a paraneoplastic process, especially since these cases had remarkable temporal association and spatial distance. Thus, one could state that demyelination may be secondary to factors or autoantibodies released by the tumor rather than a direct effect. Many questions concerning the etiology of demyelination in these cases are unanswered; however the information available raises the suspicion of a paraneoplastic mechanism.

In conclusion, despite the fact that PCNSL is more commonly seen in patients with HIV/AIDS, none of the reported cases of paraneoplasia associated with PCNSL were HIV positive. This interesting finding could be merely due to the small number of reported cases, yet one may like to question this relationship. Could the state of T-cell immunodeficiency inhibit the production of factors involved in paraneoplasia? Is it possible that treatment of HIV/AIDS also restrains the tumor cells from generating disorders elsewhere? Is the state of immunocompetence a risk factor to develop paraneoplastic phenomenon in patients with PCNSL? All these questions are emerging, yet more time and additional studies are needed to answer them.

Although paraneoplastic manifestations are rare in PCNSL, they signify a more serious course and

outcome of this aggressive form of lymphoma. This poor prognosis could be secondary to the release of tumor factors that stimulate the manifestations expressed in distant organs. The so far reported paraneoplastic syndromes in PCNSL are myasthenia gravis, cerebral salt wasting syndrome, peripheral neuropathy, and leukoencephalopathy. These syndromes should alert physicians to their presence in patients with PCNSL. We encourage reporting such clinical cases to better understand the pathogenesis and outcome of paraneoplastic syndromes in these patients.

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Part II

Supratentorial Tumors

Supratentorial Primitive Neuroectodermal Tumor: Biology

10

James Hayden and Barry Pizer

Contents

Abstract

Supratentorial primitive neuroectodermal tumours (StPNETs) share similar histopathological features to medulloblastomas, and have accordingly been treated alongside their infratentorial counterparts but have a significantly inferior prognosis. The biological study of these tumours has been limited, but a number of crucial insights have recently been identified. The cytogenetic features of pineal and non-pineal StPNETs differ, and chromosome 17p loss, which characterises up to 40% of medulloblastomas is not a feature of StPNET disease. Disruption of developmental pathways including Wnt signalling, Notch and Sonic hedgehog pathways occur in a small subset of StPNET tumours. p53 pathway disruption in contrast, and in distinction from medulloblastoma, is a frequent feature of StPNET. Genetic features including mutations in *IDH1* and carrying a discrete amplification on chromosome 19 (19q13.41) are associated with StPNET clinical characteristics. Further studies are required to facilitate the exploitation of these genetic features to update and enhance the current classification, treatment and outcome in this disease.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_10,

Introduction

Intracranial primitive neuroectodermal tumours (PNETs) may arise in the supratentorial and infratentorial compartments. Supratentorial PNETs (StPNETS) and infratentorial PNETs (medulloblastomas), respectively share similar histopathological features and have accordingly been treated using unified approaches. The outcome for children with intracranial PNETs at different sites however differs markedly, which in part reflects diversity at the molecular genetics level. The current understanding of the biological basis of StPNET tumourigenesis is however limited. Studies that specifically characterise StPNET and discover disease distinct events have rarely been undertaken. Insights into the development of these tumours have been derived predominantly either from tumours developed in children with genetic predisposition syndromes or from larger intracranial PNET studies which have included a limited number of StPNETs. Taken together, these studies have shown that StPNETs are a diverse group of tumours with a variety of genetic and epigenetic mechanisms implicated in their tumorigenesis.

Genetic Predisposition

A number of different familial conditions are associated with the development of brain tumours. Li Fraumeni syndrome (LFS) and Turcot syndrome have both been shown to be associated with the development of StPNET. In LFS, an autosomal dominantly inherited disorder characterised by the development of multiple tumours in childhood and in adult life, brain tumours occur in 10–15% of patients before the age of 45. The majority of these tumours are gliomas, but in up to a third are medulloblastomas and StPNETs. LFS results from mutation in the *TP53* gene, commonly involving the mutation "hot-spot" codons 175, 213, 245, 248, 273, and 282. Patients with Turcot syndrome, an autosomal dominantly inherited condition characterised by adenomatous colorectal polyps or colonic carcinomas in addition to brain tumour, have an increased risk of developing a brain tumours including glioblastomas (Type 1 Turcot syndrome) and medulloblastomas (Type 2 Turcot syndrome). Turcot syndrome has however also been described in children who develop StPNETs with mutations in germline *PMS2* and *MSH2* (De Vos et al. 2006; Jeans et al. 2009). Finally, in trilateral retinoblastoma, pineal-StPNETs may arise in patients who have germline mutations of the RB gene.

Cytogenetic Abnormalities

A series of studies have characterised the karyotype of StPNETs (reviewed in Li et al. 2005). The most common abnormalities in non-pineal StPNETs were found with chromosome 11 in 10/23 (43%) cases and included gains (1/23, 4%), losses (3/23, 13%), translocations (4/23, 17%) and other abnormalities (duplications, deletions and gain of additional material) in 4/23 (17%). A gain of chromosome 7 was observed in 4/23 (17%) and loss of chromosome 13 also in 4/23 (17%). The most common cytogenetic abnormality seen in medulloblastoma is loss of the p-arm of chromosome 17 occurring in up to 40% of tumours that may occur in association with a gain of 17q and the formation of an isochromosome (i17q) or may arise as an isolated defect. 17p loss or i17q formation was not found in any of the StPNET cases described. However loss of chromosome 17 and a deletion of 17q21.3 have both been observed in isolated cases. In a third of cases (8/23) a normal karyotype was found. In contrast the most frequent abnormalities in pineal StPNETs are gains in chromosome 1 (4/12, 33%) and chromosome 19 (3/12, 25%) and loss of chromosome 20 (3/12, 25%). A translocation between chromosomes 16 and 22, deletion at 11q13 and monosomy 22 were observed in isolated cases.

Cytogenetic alterations have also been identified using comparative genomic hybridization (CGH) undertaken in a small number of cases. Three recent studies have interrogated StPNETs by array-CGH, which has provided an enhanced resolution of genetic abnormalities observed in these tumours (Kagawa et al. 2006; McCabe et al. 2006;

Pfister et al. 2007). Even with the superior resolution that array CGH provides, in keeping with the previous karyotyping studies, in three cases (3/20, 15%) no abnormality was observed. In total, genetic gains were observed in 35% (7/20) involving chromosome 12, 30% (6/20) with chromosome 7q, and 20% (4/20) for both chromosomes 17q and 2p. Interestingly, in the Pfister series, loss of 17p was seen in two cases (2/10, 20%), and the region of loss (17p11.2-pter) occurred at the breakpoint similar to that which has been observed in medulloblastomas.

Finally, using a high resolution SNP array on 39 StPNETs, Li et al., in common with the previous array CGH studies, identified recurrent gains (8/39, 21%) on chromosome 2 incorporating the *MYCN* locus and also a novel amplicon on chromosome 19 (19q13.41) incorporating a micro RNA cluster (8/39, 21%) (Li et al. 2009). Amplification at this locus was shown to confer an adverse prognosis (survival 4 ± 1.3 months in amplified cases versus 44 ± 12.8 months in non-amplified cases; $p < 0.0001$). This genetic defect has also been shown to be associated with specific histopathological features including ependymoblastic rosettes and neuronal differentiation referred to as embryonal tumours with abundant neuropil and true rosettes, (ETANTR) occurring in young children in particular (Li et al. 2009; Korshunov et al. 2010).

Developmental Pathway Disruption

The development of StPNETs in those with cancer predisposition syndromes has suggested a role of a number of cell signalling pathways, including Wnt/wingless, p53, sonic hedgehog and Notch, in StPNET tumourigenesis. Aberrations of components of these pathways have subsequently been shown to be implicated in this disease. P53 pathway involvement in the development of StPNETs was first observed in Li Fraumeni syndrome. Subsequently mice models have provided further evidence for the importance of p53 in StPNET tumourigenesis with the development of StPNETs as well as medulloblastomas in $p53^{-/-}$ mice (Tong et al. 2003). StPNETs have also been shown to develop in p53 deficient murine models with *c-myc* and/or *β-catenin* (Momota et al. 2008).

Evidence of p53 pathway dysregulation appears to be a common event in StPNET and occurs significantly more frequently than in medulloblastomas (Eberhart et al. 2005). In the Eberhart et al. study, p53 pathway dysregulation, was observed immunohistochemically with the accumulation of p53 in 88% (7/8) StPNETs but in only 18% (8/44) of classic medulloblastomas ($p < 0.001$). Mutations in *TP53* occur rarely, and it has been suggested more frequently in StPNETs arising in adults (Li et al. 2005), but do not account for the observed frequency of p53 pathway dysregulation. Array CGH studies have also identified that loss of *CDKN2A* at 9p21.3, a regulator within the p53 pathway occurs in a subset of StPNETs (McCabe et al. 2006; Pfister et al. 2007). Using fluorescence *in situ* hybridisation (FISH) in a second cohort Pfister et al., showed loss of *CDKN2A* in a total of 7/21 (33%) of StPNETs, and reported a trend towards an association with metastatic disease ($p = 0.07$).

Aberrant Wnt signalling resulting from germ line defects in the Wnt signalling pathway may give rise to medulloblastoma or StPNET development, has been described in the context of Turcot syndrome. In clinical trials, aberrant Wnt signalling, identified by β-catenin accumulation and mutations of *CTNNB1* has been shown to occur in 16% of patients with medulloblastomas (Ellison et al. 2010). Wnt pathway disruption has also been shown to occur in StPNET (Koch et al. 2001; Rogers et al. 2009), but unlike in medulloblastoma, where Wnt pathway disruption characterization defines a favourable prognostic group (Ellison et al. 2010), the effect of *CTNNB1* mutations and β-catenin accumulation in StPNET has not yet been determined.

Sonic hedgehog (Shh) pathway signalling is required in normal cerebellar development. In Gorlin syndrome mutation in the patched gene (PTCH1), which codes for a component of the Shh pathway results in the development of medulloblastomas. In murine models, downstream effectors of Shh signalling (Gli 1–3) have been identified in the cerebral cortex and midbrain in addition to

the cerebellum, suggesting that Shh signalling may also be implicated in brain development outside of the infratentorial compartment (Dahmane et al. 2001). The role of the Shh pathway in StPNET pathogenesis has not been extensively investigated but there is some evidence that aberrant Shh signalling may be a feature in a small subset of StPNETs. Firstly, in a study of three StPNET tumours, all expressed the downstream target of the Shh-Gli pathway, MYCN (Moriuchi et al. 1996), and in a second study three out of eight StPNETs harboured mutations at 9q22.3, the *PTCH* gene locus (Vorechovsky et al. 1997).

To date there has been limited research on the NOTCH signalling pathway in intracranial PNET development but activation of this pathway has been shown in two studies suggesting that it may play a role in StPNET development (Rostomily et al. 1997; Fan et al. 2004). Rostomily et al. (1997) demonstrated differential expression of hASH1, a basic helix-loop-helix protein inhibited by NOTCH signalling, in StPNETs. In the subsequent Fan et al. (2004) study, differential expression of NOTCH 1 and 2 was shown in StPNET and medulloblastoma, with high levels of NOTCH 2 detectable in StPNETs. In addition, inactivation and associated cell growth retardation in the StPNET cell line PFSK has provided further support for the role of *NOTCH2* in StPNET tumourigenesis.

Gene Defects

MYCC or *MYCN* amplification occurs in 10% of medulloblastomas and is associated with the large cell and anaplastic subtypes and an unfavourable outcome (Pfister et al. 2009a; Ellison et al. 2010). Few studies however have investigated the *MYC* family of oncogenes and *MYC* amplification in StPNETs. In murine models, StPNETs have been shown to develop with increased *c-myc* expression. In a study involving p53 deficient mice, StPNETs developed in 35% (15/43) of cases, located in the periventricular region in 53% (Momota et al. 2008). In human studies, 54 StPNET tumour samples analysed across three clinical cohorts revealed *MYCC* and *MYCN* amplification in 5% cases (Fruhwald et al. 2000; Pfister et al. 2007; Behdad and Perry 2010). In StPNETs unlike in medulloblastomas however, no clinicopathological correlation with MYC expression has been derived.

A genome wide screen in glioblastoma multiforme (GBM) identified recurrent mutations in *IDH1*, a gene not previously known to be associated with GBM tumorigenesis (Parsons et al. 2008). Located on chromosome 2q33.3, *IDH1* encodes isocitrate dehydrogenase-1, an enzyme that catalyses the rate-limiting step in the citric acid (Kreb's) cycle converting isocitrate to α-ketoglutarate (α-KG). In two subsequent studies, embryonal tumours were screened for *IDH1* mutations and found to occur in StPNETs but not in medulloblastomas (3/9 StPNET vs 0/113 medulloblastomas; $p=0.0003$) (Balss et al. 2008; Yan et al. 2009). In a further large study, *IDH1* mutations were shown to occur solely in adult cases (combined data: 5/12 adults (>16 years) v 0/21 childhood (<16 years) tumours ($p=0.003$)) (Hayden et al. 2009) and represents the only biological aberration to date to be associated specifically with the adult StPNET phenotype. This in turn suggests for the first time that tumorigenesis mechanisms within the spectrum of StPNET disease may be different at different ages.

Epigenetic Events

The role of epigenetic modification in StPNET is currently emerging. A number of recent studies investigating micro RNAs in StPNET have provided significant insights into StPNET tumourigenesis and have supported the hypothesis that this disease may in fact consist of a number of entities. In a case report in 2009, Pfister et al. (2009b) reported the molecular features of a 2 year old girl with the ETANTR StPNET subtype. Molecular analysis revealed a 19q13.42 amplicon containing C19MC, a known microRNA cluster. In a subsequent study by Li et al., 45 CNS-PNET tumours were investigated and a similar amplification of C19MC within the 19q13.41 amplicon was identified in 24% (11/45) (Li et al. 2009). Expression of miR-520g and

miR-517c from within this cluster were found to be significantly elevated in the amplified cases, and in both *in vivo* and *in vitro* models associated with oncogenic effects including promoting cell survival.

Changes in DNA methylation patterns appear also to be a significant feature of intracranial PNETs, and studies have estimated that aberrant hypermethylation occurs in up to 1% of CpG islands in primary PNET tumours (Fruhwald et al. 2001). Reported DNA methylation events in StPNET, in common with genetic aberrations, have been identified as a part of wider brain tumour or intracranial PNET cohorts, rather than specific StPNET studies. In common with other intracranial PNETs, the most commonly methylated gene identified in StPNET to date is *RASSF1A*. *RASSF1A* promoter hypermethylation has been shown to occur in 77% (30/39) of cases (Chang et al. 2005; Muhlisch et al. 2006; Inda and Castresana 2007). Methylation of the *RASSF1A* promoter has not been shown however to be associated with any survival or disease clinicopathological feature. A series of additional genes have also been shown to exhibit aberrant methylation in StPNET, the most common of which include *CDH1* and *CASP8*. *CDH1* was found to be frequently methylated in 60% (3/5) whilst hypermethylation of the *CASP8* promoter has been observed in a third (8/24) of StPNETs (Muhlisch et al. 2006, 2007).

In conclusion, based on their similar histopathological features, StPNETs have been considered to be a part of the "PNET" family of tumours and have consequently been managed using a unified multi-modal therapy approach. Despite this uniform approach however, the outcome for children with StPNETs compared with medulloblastomas remains consistently and significantly inferior. Research to date into the genetic characterisation of StPNET has been limited, occurring predominantly in small studies and typically affording only partial insights into their tumourigenesis. In studies investigating the aberrant signalling of pathways associated with medulloblastoma development, a role for p53, Wnt/wingless, sonic hedgehog and Notch pathways has been identified in StPNET subpopulations. Further detailed studies are required to fully elucidate their role in StPNET tumorigenesis.

Cytogenetic studies have shown that pineal and non-pineal StPNET differ not only in their site of origin but in their genetic identities. Cytogenetic and molecular studies have also shown different features in StPNET compared with medulloblastomas, including infrequent abnormalities of chromosome 17p, loss of *CDKN2A* and the presence of *IDH1* mutations only in StPNET. Taken together these findings suggest that, in contrast to the unifying PNET concept, pineal StPNETs, non-pineal StPNETs and medulloblastomas differ at the molecular level, and that this may account for the observed variance in their biological behaviours. Furthermore, classification and treatments based on the assumption that these are similar tumours does not now appear to be valid.

The recent identification of a novel amplicon on chromosome 19 in a subset of StPNETs has demonstrated the importance of studying these tumours as an entity distinct from medulloblastoma. The chromosome 19 amplicon is the only molecular feature identified to date in this disease to be associated with distinctive histopathological characteristics. Importantly, the discovery in addition that this defect may also confer an adverse outcome could finally facilitate a clinical sub-classification of this traditionally considered heterogenous group of tumours.

Further investigation of genetic events in well-characterised StPNET cohorts is now required to resolve the molecular features of this disease. An enhanced understanding may then be exploited in disease classification and the development of targeted therapeutic approaches which are urgently needed to improve the poor outcome associated with this tumour.

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Outpatient Brain Biopsy and Craniotomy for Supratentorial Tumor

11

Teresa Purzner, Jamie Purzner, and Mark Bernstein

Contents

Abstract

There exists a growing body of evidence that outpatient brain biopsy and craniotomy for supratentorial tumour is both safe and effective. Furthermore, qualitative studies support high patient satisfaction and preliminary findings suggest a theoretical benefit in decreased post-operative nosocomial complications, health-care spending and patient flow. However, to be properly instituted a day surgery unit (DSU) requires rigorous adherence to well-established protocols, thorough patient education and a knowledgeable team of anesthetists, surgeons and nurses.

Introduction

High resolution and functional imaging, intra-operative navigation, improved neuroleptic anesthesia as well as minimally invasive, endoscopic and endovascular approaches have allowed patients to undergo neurosurgical procedures with lower morbidity and mortality than previously possible. With an ever growing body of clinical data describing the timing and characteristics of post-operative complications, post-operative stay times have shortened with many procedures now being performed with a single overnight stay. Recently, the possibility of out-patient neurosurgery has arisen.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_11,

Brain biopsy and craniotomy for intra-axial tumours were some of the first procedures attempted on an out-patient basis. They are frequently performed operations, have an excellent safety profile and the timing and frequency of their post-operative complications have been well characterized (Barnett et al. 1999; Bednar 1999; Bernstein and Parrent 1994; Cabantog and Bernstein 1994; Kulkarni et al. 1998; Liu et al. 2009; Sawaya et al. 1998). With this in mind, the first pilot studies were undertaken in 2001. These suggested both excellent safety and high rates of successful discharge from the DSU (Bernstein 2001; Bhardwaj and Bernstein 2002). There have since been several large scale studies again reflecting excellent safety and efficiency (Purzner et al. 2011) and qualitative studies on patients' perception reflected a high level of patient satisfaction (Khu et al. 2009).

Despite these promising studies, out-patient neurosurgery is still only performed in select centers. In a large, multi-center survey of practicing neurosurgeons in North America the majority of physicians considered outpatient image-guided biopsy to be safe and reasonable, however only 6% were actually performing cases on an outpatient basis (Warnick et al. 2003). This likely suggests a continued perception that delayed neurological deterioration occurs with high enough frequency that close observation overnight is warranted. Certainly, delayed recognition and management of post-operative complications such as perilesional edema, seizures and intracranial hemorrhage (ICH) can result in devastating outcomes. Fortunately, the timing and frequency of post-operative complications in craniotomy and brain biopsy has been extensively studied. As such, the duration of post-operative observation can be tailored to ensure outpatient surgery is equally safe to inpatient procedures.

Safety of Outpatient Craniotomy and Brain Biopsy

Image-guided brain biopsy and craniotomy for resection of supratentorial tumour is associated with a morbidity and mortality of 1.2–6.3% (Bernstein and Parrent 1994; Barnett et al. 1999; Bhardwaj and Bernstein 2002; Field et al. 2001; Kulkarni et al. 1998; Sawin et al. 1998) and 2.9–19.7% respectively (Cabantog and Bernstein 1994; Fadul et al. 1988). One of the most worrisome and best characterized post-operative complications requiring timely intervention is post-op ICH. The largest study performed investigating the timing of post-op ICH included 2,305 elective craniotomies or biopsies, 50 of which developed post-operative ICH. Of these, 44 developed ICH within 6 h and the remaining 6 patients developed a delayed ICH occurring after 24 h (Patchell et al. 1990). Similarly, a study of 269 patients undergoing elective biopsies, 8 patients developed post-operative ICH all of which occurred within 6 h. Importantly, any patient who experienced a sustained deficit demonstrated a clot on postoperative CT scans (Kaakaji et al. 2001). These studies have helped tailor the criteria for discharge from day surgery units where patients are observed for a minimum of 6 h and must demonstrate a non-worrisome CT scan before leaving.

The first pilot study for outpatient craniotomy (Bernstein 2001) included 47 patients, all of whom underwent elective craniotomy for supratentorial tumors. Again, all patients received a post-operative CT scan and were then discharged following a minimum of 6 h of observation in a day surgery unit (DSU) if they remained neurologically intact. In this study, 89% of patients were successfully discharged from the DSU and no patients experienced an adverse outcome as a result of early discharge. Complication and readmission rates were comparable to those patients who had the normal extended post-operative stay. A similar study was performed in 2002, this time including 102 patients undergoing stereotactic biopsy. There was a success rate of 98% and again, readmission rates were comparable to those with the extended stay and no patients who were clinically well and had a normal CT developed delayed deterioration. A small UK study on outpatient craniotomy and biopsy was reported in 2008, again supporting the safety of outpatient surgery with no patients suffering an adverse event as a result of outpatient surgery (Grundy et al. 2008). The largest study to date was published in 2011 involving 1,003 prospectively selected patients undergoing outpatient biopsy,

craniotomy and spine surgery (Purzner et al. 2011). The safety of outpatient craniotomy and biopsy was again supported with success rates of 93–94% in both outpatient craniotomy and biopsy and 1.5% readmission rate. No patient suffered a negative outcome as a result of early discharge. Overall, early studies are highly supportive of the safety of outpatient neurosurgery.

Patient Perspective and Health-Care Benefits

Qualitative studies on patients' perceptions of outpatient craniotomy have shown high patient satisfaction. In fact, the possibility of being discharged the same day as their operation made the disease and its management seem less serious (Khu et al. 2009). The privacy of home on the first post-operative day allows for overnight observation and assistance by family members and friends without the disturbances of other in-patients. Indeed, approximately half of patients believed they would recover quicker and more comfortably at home (Khu et al. 2009). Overall, patients were more concerned about the disease than their operative intervention. Particularly in the case of patients with high grade gliomas or brain metastases, helping to alleviate the psychological impact of their diagnosis and management while minimizing the total hospital stay associated with each intervention was important for overall quality of life.

There is also a theoretical benefit in decreased case cancellation given that there is no longer need for a high observation bed for overnight care. A decrease in case cancellation benefits the flow of the healthcare system as a whole but more importantly the patient themselves. Operations require a great deal of forethought and planning and occupational as well as logistical arrangements must be made in advance by both themselves and their family members who will assist with post-operative recovery. Therefore case cancellation results in significant emotional and financial consequence to the patient and their loved ones.

While there is an intuitive advantage of outpatient neurosurgery and decreased hospital stay in terms of patient flow and nosocomial complications, this remains an area to be studied. Large-scale studies suggest a decrease in post-operative thromboembolic events, urinary tract infections, pneumonia, adverse events and wound infection in comparison to previously published rates (Purzner et al. 2011). However, these subgroups were not analysed independently or directly compared to an inpatient cohort.

It is estimated that the cost of a high observation neurosurgical bed is approximately $1,200. Given that readmission rates are similar to the traditional inpatient stays, it was estimated that in the 1,003 patients undergoing outpatient neurosurgery in the Purzner et al. 2011 study, there was a financial savings of $3,437,160.00 by decreased days in hospital.

Instituting a Successful Outpatient Practice

One of the most important aspects of a successful outpatient practice is patient selection, pre-operative patient education, multi-disciplinary collaboration and rigorous adherence to a pre-set protocol. A summary of the protocols used in the day surgery program can be seen in Fig. 11.1. In general, patients must be free of significant medical comorbidities (cardiovascular, respiratory, severe obesity or difficult airways), and they should not suffer from uncontrolled epilepsy or have a poor preoperative neurological status. Importantly, they must have available a responsible care-giver for overnight observation in relative proximity to the hospital. The inclusion and exclusion criteria for the day surgery unit are listed in Table 11.1. Once selected, all patients have a pre-operative assessment by the anesthesia team and undergo extensive patient education by the surgical team. Procedures are generally performed without airway manipulation or invasive monitoring. Generous local anesthesia is used to allow for judicious use of sedation. A minimal, lesion targeted and image guided flap is followed by brain mapping and tumour resection. Patients all receive a post-operative CT scan and are observed for a minimum of 6 h. If they neurologically well, have a non-worrisome CT and are able to ambulate, void and demonstrate adequate pain

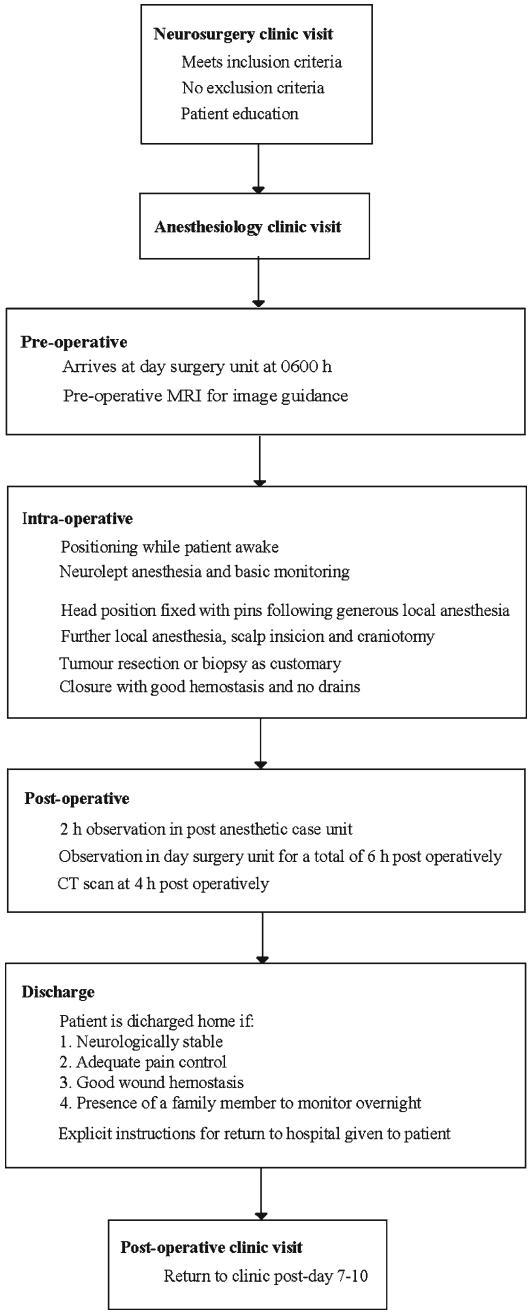

Fig. 11.1 Summary of the steps involved in day surgery program

control, then the patient is discharged with written instructions on expected and worrisome signs and symptoms.

With rigorous adherence to patient safety, outpatient craniotomy and biopsy presents a safe, cost-efficient well-tolerated alternative pathway in patient care. To be properly implemented it requires well-established protocols, thorough patient education and a well-versed team of anesthetists, surgeons and nurses. Prior to discharge, the healthcare team must be cognoscente of the early signs and symptoms of rare but serious complications and the patient and family member should be leave well educated on expected and unexpected post-operative symptoms. A low threshold to return to the emergency room should be encouraged as delay in recognizing clinical deterioration can result in negative outcomes. As minimally invasive and targeted therapy improves and the clinical evidence of outpatient neurosurgery grows, same-day procedures may continue to expand as a viable option in surgical care.

Table 11.1 Inclusion and exclusion criteria for day neurosurgery (Carrabba et al. 2008)

Inclusion criteria for day surgery
Intra-axial supra-tentorial tumor
Patient staying in relative proximity of the hospital
Care-giver availability overnight
Exclusion criteria for day surgery awake craniotomy
Neuropsychological unsuitability
Significant co-morbidities (e.g., cardiovascular/ respiratory insufficiencies)
Severe obesity
Anticipated difficult airways
Expected long surgery
Uncontrolled epilepsy
Poor neurological status
Patient's preference for inpatient stay
Already inpatient for other reasons
Procedure ending later then allowed by day surgery unit

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Wrong-Site Craniotomy Prevention

12

Daniel Mendelsohn and Mark Bernstein

Contents

Abstract

Wrong-site surgery (WSS) is a devastating error that has gained increasing attention in the medical community and the general public. Wrong-site craniotomy (WSC) in particular, is an uncommon event but carries the potential of serious neurologic harm. Here we describe the clinical and legal outcomes of known WSC cases, the factors contributing to the errors, systems for prevention, the evidence for preventative systems, and future directions. Ultimately, the elimination of this lamentable error will require improving communication in the OR, embracing systematic verification procedures, incorporating novel verification technologies, and the open reporting of cases to facilitate thorough error analyses and the development of effective preventative strategies.

Introduction

Errors in medicine have gained increasing attention among medical practitioners and the general public in the past two decades. The Institute of Medicine's 1999 report, *To Err is Human* (Corrigan et al. 2000), demonstrated a sobering picture of patient safety and quality assurance issues affecting America's health care system. Large-scale studies in Utah, Colorado, and Massachusetts suggested that medical errors

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_12,

translate into nearly 100,000 deaths in America per year (Brennan et al. 2004; Thomas et al. 2000). The majority of the patient safety literature to date has focused on medication-related errors with errors in surgery receiving less attention. Patient safety in surgery is a difficult topic to approach for several reasons; the complexity of operations introduces many opportunities for mistakes to occur and studying these errors is inherently challenging (Etchells et al. 2003). Additionally, in an environment where errors can lead to devastating consequences, obvious barriers exist to the open reporting of errors which prevents quality assurance practices and the development and implementation of systems for prevention (Bernstein et al. 2003).

In this chapter we focus on one of the most regrettable errors in neurosurgery: wrong-site craniotomy (WSC). Unlike other complications in surgery, wrong-site surgery (WSS) is considered a "never event"; an error that should always be preventable (Michaels et al. 2007). The scope of the problem including the range of clinical and legal outcomes, reasons why these errors occur, systems for prevention and future directions are discussed.

Scope of the Problem

Defined as a surgery performed on the incorrect side, incorrect site, or incorrect patient (Kwaan et al. 2006), wrong-site surgery (WSS) is the third most common reported sentinel event to the Joint Commission (The Joint Commission 2011), an organization that accredits health care organizations. Neurosurgery is the third most vulnerable specialty to WSS behind orthopaedic and general surgery (The Joint Commission 2001). These specialties are predisposed to WSS because their operations involve multiple surgeons and frequently occur under emergent conditions where time pressures may cause verification steps to be rushed or skipped (Cohen et al. 2010; The Joint Commission 1998). In neurosurgery in particular, the contralaterality between clinical presentation and pathology introduces additional sources of confusion (Mitchell et al. 2006).

Estimating the incidence of WSS in general is challenged by various barriers to reporting. Reporting sentinel events to the Joint Commission is voluntary and it is estimated that only 2% of WSS are reported (Croteau 2007; Seiden and Barach 2006). One Canadian survey study estimated the incidence of WSC among Canadian neurosurgeons to be 2.2 per 10,000 (Jhawar et al. 2007). Using this estimated incidence with surgical data from the Congress of Neurological Surgeons and the US Census Bureau, of the 145,000 craniotomies performed in America in 2002, 32 were performed on the wrong side (Cohen et al. 2010).

In neurosurgery, performing a WSC may lead to a wide range of clinical outcomes. A review of 35 cases of WSC identified through medical, legal and media databases found that the majority of cases had minor effects on neurological outcomes (Cohen et al. 2010). A similar review of eight cases found no impact on neurological outcomes (Mitchell et al. 2006). However, in some cases involving particularly invasive operations, patients were left with anosmia, seizures, personality changes and cognitive deficits including memory impairment and difficulties concentrating leading to occupational limitations. In one case where the incorrect patient received an operation they did not need, the other patient deteriorated neurologically and eventually passed. Irrespective of whether a WSC leads to neurologic deficits, in all cases of WSC, the error leads to delays in surgery, unnecessary pain and disfigurement from superfluous incisions (Cohen et al. 2010).

Wrong-site craniotomies can also lead to broad range of legal and disciplinary outcomes. After a WSC has occurred, some hospitals launch investigations and modify preoperative procedures to prevent recurrences. Disciplinary actions from state licensing boards vary considerably. Following a WSC, state boards will typically issue a letter of concern, impose fines and occasionally will require mandatory continuing medical education (Cohen et al. 2010; The Joint Commission 2001). Most commonly, licensure revocation does not occur after an isolated incident. With respect to litigation, approximately

half of publicized cases have led to civil lawsuits which have involved the surgeons, hospitals and even radiologists or circulating OR nurses as defendants. In general, state medical licensing boards have no standard disciplinary protocols for WSS and cases are managed on an individual basis (Cohen et al. 2010).

Why Do These Errors Occur?

A number of groups have investigated why WSS occurs using various analytical systems. Ultimately, a WSS is the consequence of one or more human errors translating into a preventable medical complication because systems for prevention failed. The major factors contributing to the errors can be classified into: inherent risk factors, communication breakdown, inadequate preoperative checks, and technical factors/imaging (Table 12.1).

Inherent risk factors are typically non-modifiable variables that increase the likelihood of performing a WSS. Several studies have demonstrated that operations performed under time pressures or late at night are at increased risk of being on the wrong side (Cohen et al. 2010; The Joint Commission 2001). When multiple surgeons are involved in a single case, or multiple procedures are performed on the same patient, the likelihood of communication breakdown within the team increases which predisposes to WSS (Cohen et al. 2010; The Joint Commission 2001).

Communication failure is a commonly cited contributing to factor to WSS (Devine et al. 2010; Seiden and Barach 2006; Stahel et al. 2010; The Joint Commission 2001). Errors in communication can occur within the surgical team or between departments. As neurosurgical operations are complex frequently involving multiple surgeons, communication within the surgical team is crucial. Several WSC occurred when a different physician prepped and draped the patient and the primary surgeon falsely assumed the correct side was prepped. Other WSC cases could have been prevented if members of the OR team felt comfortable voicing concerns, or if the primary surgeon listened to concerns that were raised (Cohen et al. 2010). These cases illustrate the importance of maintaining a proper OR environment where members of the surgical team can question surgical practices when appropriate. Ensuring the correct patient and correct site has been prepped is the responsibility of the entire surgical team including anaesthesia and OR nurses and thus the importance of communication in preventing WSC cannot be overstated.

Communication failure can also occur between the surgical team and other medical departments. Miscommunications with diagnostic imaging have led to several WSC cases. These cases

Table 12.1 Factors contributing to wrong-site craniotomy

Inherent risk factors	Communication breakdown	Inadequate pre-operative checks	Technical factors/imaging
Multiple surgeons involved in the case	Miscommunication between surgical team and the patient/family	Failure to review the medical records and imaging pre-operatively	Incorrectly labeled images
			Wrong patient on image
			Laterality reversed
			Scan hung backwards on viewing box
Emergency operations and time pressures	Miscommunication between surgical team and radiology	Failure to verify correct patient in pre-operative area	Equipment issues or unusual room setup
Surgeries performed afterhours	Miscommunication within the surgical team	Failure to verify and mark correct site in pre-operative area	
Multiple procedures performed on the same patient	Failure of all members to verify correct site and patient	Absence of medical record or imaging in the OR	
	Failure to voice concerns if present	Failure to perform a surgical time-out	
	Falsely assuming correct site/patient has been prepped		

typically involved mislabeled radiology reports or scans, unconventional scanning practices leading to reversed laterality labeling, or use acquisition of new equipment that reversed laterality conventions (Cohen et al. 2010). Several of these cases led to civil lawsuits involving the diagnostic imaging department, further illustrating the scope of responsibility for preventing WSC errors.

Preoperative checklists are practices based on error prevention systems developed by the aviation industry and have recently become the standard of practice. The most commonly used verification procedures involve several preoperative checks, marking the incision, and a preincision surgical timeout. These steps are outlined in the Joint Commissions Universal Protocol (The Joint Commission 2009) and the recently developed WHO safe surgery checklist (Haynes et al. 2009) and are endorsed the American College of Surgeons (American College of Surgeons 2002). Failure to perform these basic preoperative verification procedures has led to dozens of WSC cases in the past. Steps that are commonly overlooked include verifying the medical record, marking the incision, ensuring the correct identity of the patient, and ensuring that the correct imaging is visible in the OR (Cohen et al. 2010; Mitchell et al. 2006). A systematic checklist can help ensure that these steps are carried out efficiently prior to making the incision.

Several technical factors have been credited for WSC cases in the past. In particular, incorrectly labeled images of the wrong patient or images with laterality labeling reversed have led to WSC. These errors illustrate the importance of quality control checks within diagnostic imaging departments and interdepartmental communication. Before the digital imaging era, CT scans hung backwards on the OR viewing box led to several WSC. Additionally, in some cases, surgeons suggested that the absence of necessary equipment or last minute changes in OR table positioning generated confusion leading to WSC (Cohen et al. 2010). Other unexpected events can distract and confuse the surgical team during prepping and draping; however, appropriate verification procedures should prevent these unexpected events from precipitating a WSC error.

The factors described above were identified from research on specifically WSC. Far more studies have investigated factors leading to WSS in general. Similar to the WSC literature, communication failure and inadequate preoperative checks are the most commonly cited root causes (Devine et al. 2010; Seiden and Barach 2006; Stahel et al. 2010; The Joint Commission 2001). However, additional causes of WSS include diagnostic errors, incorrect indications for operating, scheduling errors, change of personnel, high surgeon workload, inexperience, incompetence or inadequate training, patients with common names or shared names between patients, inability to engage the patient or patient confusion, patients or families providing inaccurate information during verification procedures, larger body habitus or unusual patient anatomy (Devine et al. 2010; Seiden and Barach 2006; Stahel et al. 2010; The Joint Commission 2001). Although these factors have not been identified as contributors to known cases of WSC, they have been implicated in WSS and should be acknowledged.

Systems for Prevention

Human error is inevitable and will always occur. Systems for prevention are designed to create barriers preventing a human error from translating into adverse events. Prevention systems for WSC can be classified into systemic and process approaches. Systemic approaches involve general organizational environmental considerations and process factors constitute checks and verification procedures.

The OR environment is traditionally governed by a hierarchical structure lead by the primary surgeon. Medical care is evolving towards more team-based approaches with defined roles for the various members of the operating team. All members of the OR team should be aware of patient identity and the intended side and site of the operation. When issues arise, members of the operative team must feel comfortable raising concerns (Watson 2006). Given that communication is pivotal in preventing WSC, an open and safe OR environment where all members of the

team are able to communication concerns is paramount in preventing these errors. The OR environment should also be optimized to minimize distractions such as conversations unrelated to the operation or preventable equipment issues. From a broader perspective, hospital organizations should ensure that all members of the OR team are adequately trained, and they should adopt accepted pre-operative verification procedures and encourage a culture where error reporting is viewed as a constructive practice rather than a counter-productive blaming exercise (Bernstein et al. 2003).

The preoperative verification procedures should begin prior to entering the OR and should take place up until immediately before the incision is made. Prior to entering the OR, the following steps are recommended: (1) review of the medical record and consent form, (2) examination of the patient, (3) confirming the patient's identity, the side and site of the operation with the patient (and their family if possible) at the bedside, and (4) marking the surgical site at the time of confirmation. The site and side of the operation should be properly indicated on the consent form. Once the patient's identity and the site and side of the operation is confirmed, the surgical site should be marked using accepted marking procedures with the patient awake, aware and involved if possible. Some surgical marking practices can be ambiguous and difficult to interpret such as using "NO" or an "X" to mark the non-operative side. "NO" can be read upside down as "ON" and an "X" can indicate the operative or non-operative side. Often a surgeon will mark the site with their initials which can be vague in cases where the initials spell words like "NO". The Joint Commission recommends only marking the operative site with a "YES" or a line representing the incision by the surgeon performing the operation. The Joint Commission also recommends positioning the mark in a manner that will be visible after prepping and draping. Marking procedures should be consistent within an organization (The Joint Commission 2009). Some have recommended the patients mark the site themselves; however, one study has demonstrated that only 60% of patients correctly mark the operative site when asked to and the remainder fail to mark or mark incorrectly (DiGiovanni et al. 2003).

Table 12.2 Recommended preoperative verification procedures

Prior to entering the OR
1. Review of the medical record and consent form
2. Examination of the patient
3. Confirm the patient's identity, the side and site of the operation with the patient (and their family if possible)
4. Marking the surgical site at the time of confirmation with a "YES" or a line representing the incision site
In the OR
1. Ensure the medical record is present with a signed consent form indicating the site and side of the surgery
2. Display the imaging and verify the imaging belongs to the patient and is correctly displayed
Surgical time-out
1. Verify the patient's identity
2. Verify the procedure to be performed with the consent form
3. Verify the site and side of the operation with the consent form and imaging

Marking the correct side may be a complicated practice for certain neurosurgical approaches. For instance, transphenoidal surgeries are midline approaches but the pathology may be lateralized to one side. Bifrontal craniotomies for unilateral pathology pose a similar dilemma (Mitchell et al. 2006). For these approaches, common sense must be used. Once the initial approach has achieved adequate exposure, surgeons should confirm the side of the pathology with the imaging at that time.

In the OR, the surgical team must ensure that the medical record is present, the appropriate imaging is displayed and a surgical time-out should be carried out prior to making the incision. The medical record must be present to confirm the side of the operation with the consent form. The individual responsible for displaying the imaging should ensure that the correct patient's image is displayed and that the laterality of the pathology matches the side written on the consent form. Finally, a surgical time-out verifies the patient's identity, the procedure to be performed, and the side of the operation (The Joint Commission 2009) (Table 12.2). With respect to timing, British guidelines recommend performing the time-out prior to final positioning, insertion of head pins, or making the incision (National Patient Safety Agency 2008).

Adhering to these pre-operative verification steps is crucial as omitting single verification steps are frequent root causes of WSC (Cohen et al. 2010; Mitchell et al. 2006).

Errors in diagnostic imaging procedures are an important contributing factor because pre-operative verification steps depend heavily on the use of the correctly labeled imaging. Several WSC have resulted from images or imaging reports being mislabeled with the incorrect patients' name or the incorrect laterality. Diagnostic imaging departments must adhere to internal checks to ensure that images are acquired correctly and labeled correctly. From the surgeon's perspective, OR teams must recognize that images are occasionally incorrectly labeled and that if any discrepancy between the medical record, the physical exam and the patient's imaging is present, that the operation be delayed to clarify the discrepancy. In terms of laterality labeling, an automated system for verifying the laterality labeling exists which can determine the laterality of brain images with 100% sensitivity and 98% specificity (Christensen et al. 2006). Technological solutions such as these will vastly aid in the prevention of imaging errors in the future. However, not all neuropathologies are visible on imaging studies, such as trigeminal neuralgia or focal epilepsy. For surgeries performed on patients with no visible anatomical abnormalities on imaging studies, we recommend placing a vitamin E tablet or a fiducial on the pathologic side to mark the side on the MRI (Cohen et al. 2010). Image-guided technologies, such surgical navigation system or frameless stereotaxy, are becoming increasingly common practice at many neurosurgical centers. When used at the appropriate time, this technology serves as an adjuvant method for preventing WSC (Bernstein 2003).

Evidence for Prevention and Future Directions

Studying the efficacy of systems for prevention is complicated by inadequate reporting and the relative infrequency of these events limits the prospective assessment of preventative strategies (Devine et al. 2010; Michaels et al. 2007). The most comprehensive analysis on the efficacy of the Universal Protocol and other checklists used hospital records and a malpractice insurance claim database to identify cases and qualitatively assessed whether a preoperative checklist would have prevented the WSS (Kwaan et al. 2006). The study concluded that site-verification protocols could have prevented 62% (8 of 13) of cases analyzed, but that 38% (5 of 13) were not preventable. One "non-preventable" case involved the use of incorrect imaging, reinforcing the importance of internal checks among diagnostic imaging departments. Some industry experts have criticized the present protocol's emphasis on redundant checks which can lead to provider's "going through the motions" and omitting and skipping steps rather than meaningfully communicating (Kwaan et al. 2006). Mandatory reporting introduced in some states has permitted the prospective analysis of the incidence of WSS after introducing the Universal Protocol. In New York state, 1 year following the implementation of site verification procedures, the number of WSS decreased from 25 cases in 2002 to 17 cases in 2003 (Flink et al. 2005). In another study assessing the impact of preoperative safety briefings on patient safety, the incidence of WSS declined from three to zero (DeFrontes and Surbida 2004). The Joint Commission's preliminary analysis of the impact of the Universal Protocol were less encouraging; the number of reported sentinel events increased in the first year after implementing the protocol (Wong and Watters 2007). It is unclear whether these represent an actual increase in the incidence of WSS cases or increased reporting and awareness. Another study investigating the impact of operating room briefings on perceived risk for wrong-site surgery concluded that these briefings improved communication and collaboration among members of the OR team and increased awareness about the site of the operation (Makary et al. 2007). Similarly, preoperative safety briefings improve the OR teams' perception of patient safety as a priority and communication and morale among personnel (DeFrontes and Surbida 2004). At the present

time, the level of evidence supporting the effectiveness of preoperative checks is weak, but it is likely that an insufficient amount of time has passed since the implementation of the Universal Protocol to allow for a robust efficacy analysis (Gibbs 2005).

The development of preventative systems depends heavily on the reporting of WSC cases so that root causes can be determined and prevented in the future. At the present time, only some states have imposed mandatory reporting of adverse events including WSS (Seiden and Barach 2006). Of note, no health care systems require the mandatory reporting of 'near-misses', which are ideal opportunities to learn from events that are close calls but have no impact on patient care (Etchells et al. 2003; Rothman 2006). Mandatory reporting is a concept initially adopted by the aviation industry which has achieved in 40% decrease in pilot error over two decades credited to mandatory reporting, thorough error analyses and error-prevention systems (Baker et al. 2008). In medicine, the risk of death post-blood transfusion has seen a 2,000 fold reduction since 1942 through similar practices adopted by the aviation industry (Dzik et al. 2003). Surgery can become safer using these proven practices from other industries and specialties in medicine. As mandatory reporting increases, studying WSS cases retrospectively, and ideally prospectively, will be more feasible enabling the evaluation of the existing preventative systems and the development of novel strategies.

In conclusion, the Joint Commission's Universal Protocol and the WHO's surgical checklist were major accomplishments. These efforts have raised awareness about WSS and provided a practical method for preventing these lamentable errors. Wrong-site craniotomies continue to occur despite these checklists most commonly due to omission of verification procedures and breakdowns in communication. Future initiatives should aim at encouraging adherence to preoperative verification steps, embracing a collaborative culture in the operating room, and improving communication among surgical teams.

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Part III

Glioneuronal Tumors

Diffuse Leptomeningeal Glioneuronal Tumors: Histology. Is It a New Entity?

13

Marina P. Gardiman and Matteo Fassan

Contents

Abstract

The updated World Health Organization (WHO) Classification of Tumors of the Central Nervous Systems has recently expanded the category of mixed glioneuronal tumors with three new entities (i.e. papillary glioneuronal tumor, rosetted glioneuronal tumor with neuropil-like islands, and rosette-forming glioneuronal tumor of the fourth ventricle). This classificatory extension is in part the consequence of the constantly increasing availability of novel immunostains, which have enabled the pathologists' community to more readily identify neuronal differentiation in tumors morphologically resembling glial neoplasms. However, despite this growing list of new entities, in the routine diagnostic practice it is still possible to encounter glioneuronal tumors that cannot be placed into any of the well-defined WHO categories. We have recently reported the unusual radiologic and pathologic findings of four analogous paediatric cases in which both the morphological and the immunohistochemical findings strongly supported a glioneuronal commitment of the tumors. Because of the unique overlapping clinical and neuroradiological characteristics, we propose to consider this group of neoplasms as a new possible distinct pathological and clinical entity in the group of glioneuronal tumors.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_13,

Introduction

Glioneuronal tumors are a group of primary brain neoplasms of relatively recent acquisition in the World Health Organization (WHO) Classification of the Central Nervous System (CNS) tumors. This classification has recently been expanded with new recognized entities such as rosette-forming tumor of the fourth ventricle, papillary glioneuronal tumor and rosetted glioneuronal tumor/glioneuronal tumor with neuropil-like islands (Louis et al. 2007). Glioneuronal tumors are characterized by a biphasic neurocytic and glial population. The neuronal component consists of synaptophysin-positive neurocytes with round nuclei and clear cytoplasm occasionally intermingled with neurons and intermediate-sized "ganglioid" cells, whereas the glial component exhibits features of glial fibrillary acidic protein (GFAP) positive astrocytes. The histogenesis of these tumors is unclear, but an origin from multipotent precursors capable of divergent differentiation has been suggested (Allende and Prayson 2009). Leptomeningeal dissemination in glioneuronal tumors is very rare, but the incidence in low grade gliomas (a name for a wide variety of neoplasms of glial or mixed glial-neuronal origin) is estimated at 5% at diagnosis and 7–10% at subsequent tumor progression (Perilongo et al. 2003). Among neoplasms of astrocytic origin, it is well known that pilocytic astrocitomas can disseminate (Civitello et al. 1988; Hukin et al. 2002; Mamelak et al. 1994; Pollack et al. 1994). Also a new codified glial neoplasm in the 2007 WHO Classification of tumors of the CNS, such as pilomyxoid astrocitoma, shows a characteristic high tendency to disseminate (Louis et al. 2007). In the last few years, the spreading of glioneuronal neoplasms along the subarachnoidal spaces of cerebrospinal fluid (CSF) has been reported more frequently than in the past, probably because of the more diffused use of magnetic resonance imaging (MRI) in tumor staging and follow-up. Well-established examples of glioneuronal tumors with leptomeningeal dissemination include gangliоglioma and pleomorphic xanthoastrocytoma (Passone et al. 2006). However, despite this growing list of new nosological entities, in the diagnostic practice it is still possible to encounter glioneuronal tumors that cannot be placed into any of the well-defined WHO categories. We recently published four pediatric cases of diffuse leptomeningeal tumors which, although having the histological and immunohistochemical criteria necessary in order to be considered as glioneuronal tumors, cannot easily be classified in the currently used CNS WHO classification. The tumors were characterized by a similar histological appearance and a peculiar mixed immunohistochemical profile combining neuronal/glial markers and widespread tumor cell invasion of the leptomeninges without evidence of a primary intraparenchymal mass. We believe that similar cases have already been published in the literature under the name of diffuse leptomeningeal oligodendrogliomas (Armao et al. 2000; Bae et al. 2000; Bourne et al. 2006; Chen et al. 1995; Gilmer-Hill et al. 2000; Ho-Keung and Wai-Sang 1999; Huang et al. 2001; Stödberg et al. 2002) or neurocytomas/gangliocytomas (Yamamoto et al. 1996). Because of the unique overlapping clinical and neuroradiological characteristics, we propose to consider this group of neoplasms as a new distinct pathological and clinical entity in the group of glioneuronal tumors.

Clinical and Neuroradiological Findings

Three children were admitted to the Padua University Hospital between 1990 and 2007 with a brief history of progressively worsening neurological signs due to endocranial hypertension, such as ataxia, morning headache, nausea and vomiting. One case had previously been reported as spinal low-grade neoplasm with diffuse leptomeningeal dissemination (Perilongo et al. 2002). The fourth patient, after a first biopsy in a peripheral Hospital, was referred to the Department of Paediatric Oncology of the University of Padua for clinical and interventional follow-up. We reviewed the original slides and performed additional immunohistochemical and FISH analyses on the first and a second biopsy. The patients

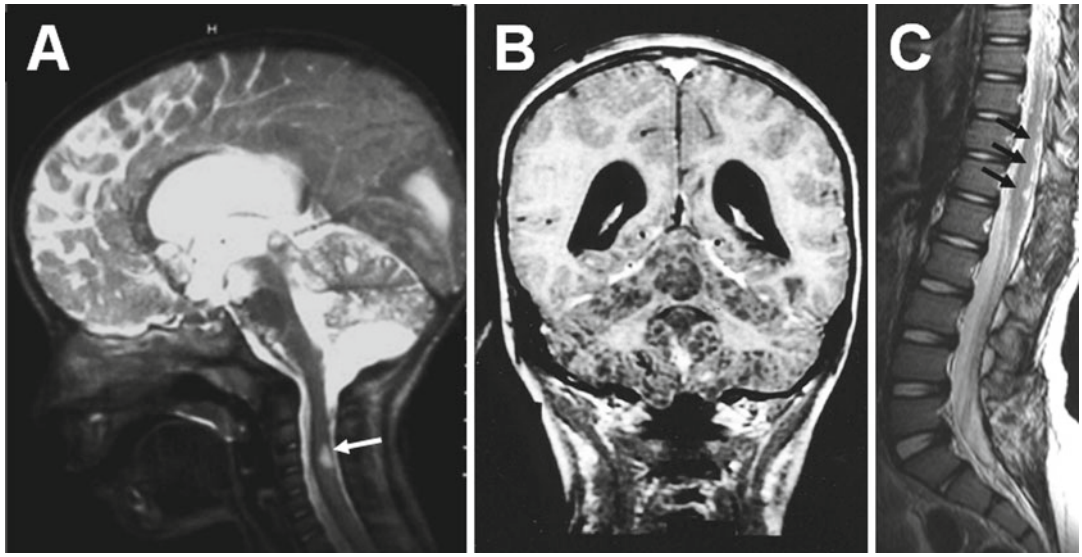

Fig. 13.1 Representative neuroradiological features of the described tumors at initial presentation. (**a**) Sagittal contrast-enhanced T2 images depict a small intramedullary lesion posterior to C3–C4 (*white arrow*) and a marked cerebral and spinal leptomeningeal enhancement coexisting with a tetraventricular communicating hydrocephalus and an empty sella. (**b**) Coronal contrast-enhanced T1 images demonstrates small non-enhancing cysts scattered throughout the cerebellar pontine surface. (**c**) Spinal sagittal T2 image reveals a marked nodular and linear leptomeningeal enhancement (*black arrows*) involving the spinal cord and small cystic lesions involving the posterior surface of the conus medullaris (Kind gift of Dr. M. Calderone)

underwent contrast enhanced head and spinal MRI which revealed similar radiological appearances (Fig. 13.1): a tetraventricular communicating hydrocephalus and thickened and abnormally enhanced subarachnoid spaces, particularly at the level of basal cisterns and interhemispheric fissures. Furthermore numerous small, non-enhancing cysts were scattered throughout the spinal cord and brain (mainly in the cerebellum). In all these patients a well defined intraparenchymal mass was missing. However, during follow-up a small intramedullary lesion appeared within the cervical spine of two of our patients of whom one subsequently developed a brain parenchymal intraventricular lesion.

Pathological Findings

In all cases a dural biopsy was performed. Minute samples characterized by a pearly opacified surface and an increased consistence were obtained. The histological samples showed thickened desmoplastic leptomeninges with sclerohyaline bands and enlarged capillary-sized blood vessels diffusely infiltrated by a monotonous population of cells arranged in straight lines or in small lobules within a compact to loose fibrillary stroma (Fig. 13.2). Cells were characterized by round to oval nuclei with finely granular dispersed chromatin, inconspicuous nucleoli with clear oligodendrocyte-like features and perinuclear haloes. No mitosis, necrosis, calcifications, lymphoid infiltrations, myxoid changes or endothelial vascular proliferations were observed. No Rosenthal fibers, nor rosettes or pseudorosettes were detected. Immunohistochemical analysis was performed using the standard avidin-biotin-peroxidase method (Vecchione et al. 2004) (Table 13.1). Tumor cells showed diffuse immunoreactivity for synaptophysin and S100, patchy reactivity for GFAP and were negative for neurofilaments or epithelial membrane antigen (EMA). Proliferation index, as percentage of MIB1-positive cells [MIB1 labeling index (MIB1 L.I.)], was constantly less than 1%. Only in case

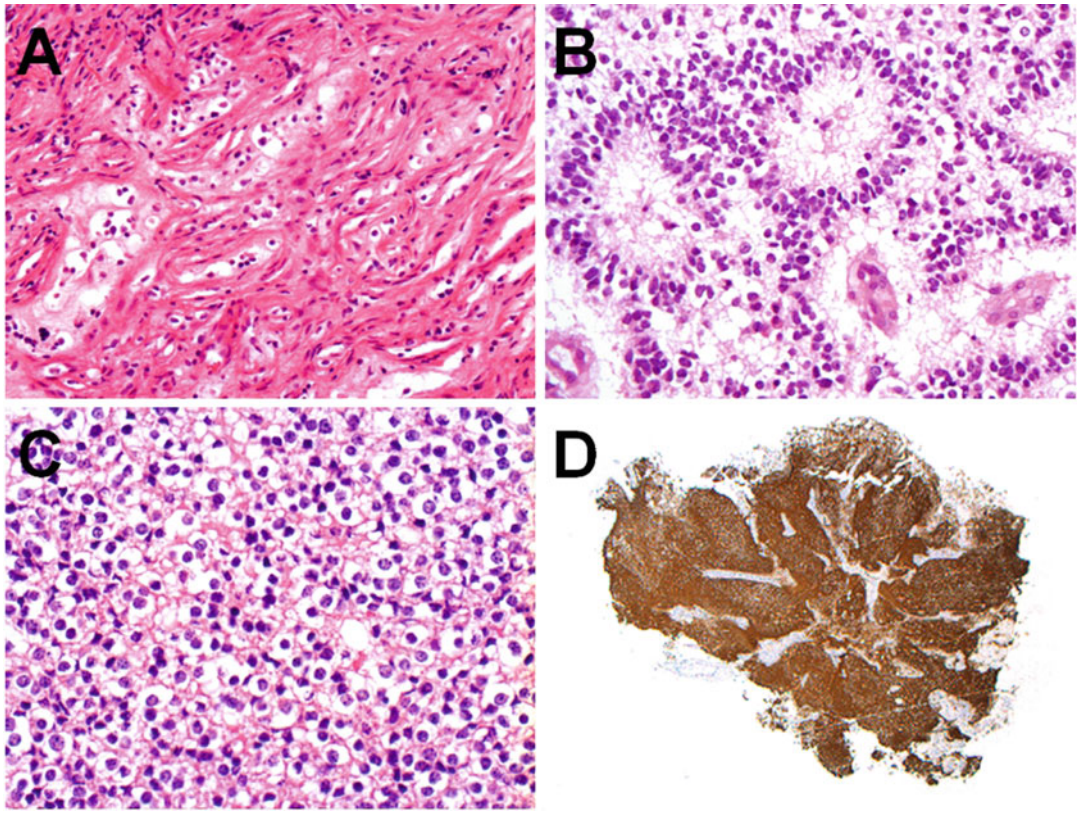

Fig. 13.2 Representative histopathological features of the described tumors. (**a**) Thickened leptomeninges diffusely infiltrated by monotonous population of tumor cells characterized by round nuclei with inconspicuous nucleoli and perinuclear haloes. (**b**) Neoplastic cells are occasionally arranged in perivascular pseudorosettes. (**c**) Perinuclear haloes with honeycomb appearance: this is a potentially misleading feature because it is a characteristic, but not limited, of oligodendroglioma. (**d**) Strongly cytoplasmatic synaptophysin-immunoreactive tumor cells in a pseudopapillary intraventricular portion of the tumor. Original magnifications 20× and 40×

Table 13.1 Primary antibodies and results of immunohistochemical stains

Antibody	Dilution	Source	#1	#2	#3	#4
Synaptophysin	1:400	Dako, Glostrup, Denmark	+	+	+	+
GFAP	1:2,500	Dako, Glostrup, Denmark	+/–	+/–	+/–	+/–
Neurofilaments	1:6	Dako, Glostrup, Denmark	–	–	–	–
Neu-N	1:100	Chemicon Int., Temecula, California	NA	NA	+	NA
S100	1:1,500	Immunotech, Marseille, France	+	+	+	+
EMA	1:500	Dako, Glostrup, Denmark	–	–	–	–
MIB1	1:100	Dako, Glostrup, Denmark	<1%	0%	<1%	<1%

#3, after a first dural biopsy (performed in 2002), we obtained a significative sample of tissue from the lesion which developed on the inner surface of the frontal horn of the lateral ventricle (2007). The analyzed sample was composed of a biphasic architecture. The more differentiated part of the tumor, abutting in the ventricle lumen, was composed of uniform and small cuboidal cells with round nuclei and scant clear cytoplasm intermingled with "ganglioid" cells which occasionally

arranged in perivascular pseudorosettes or pseudopapillary structures. We want to stress that synaptophysin and Neu-N immunohistochemical reactions were strongly positive in this pseudopapillary intraventricular portion of the tumor, without intermingled normal brain tissue. Moreover, the Neu-N positive cells did not represent entrapped pre-existing neurons. Additional features included fibrillary areas mimicking neuropil and rare foci of microvascular proliferation of capillary-sized blood vessels. Conversely, the inner part of the tumor showed anaplastic histological features with increased cellularity and a diffuse honeycomb growth-pattern. The neoplastic oligodendrocyte-like cells, diffusely infiltrating the brain parenchyma, showed mild polymorphism with hyperchromatic nuclei. Endothelial proliferation in the branching capillaries was evident. No tumoral necrosis was observed. An increased mitotic activity (three mitotic figures ×10 high-power fields) with a MIB1 L.I. higher than 5% was detected. Fluorescence in situ hybridization (FISH) was performed on formalin-fixed, paraffin-embedded tissues of one of the considered cases and revealed a deletion of the short arm of chromosome 1, whereas there were no cytogenetically detectable alterations concerning 19q.

Discussion

In the neuropathologists' community, unusual diffuse leptomeningeal tumors are an emergent field of discussion (Gardiman et al. 2010). In our opinion, the peculiar clinical, neuroradiological and histological similarities of the tumors affecting these four pediatric patients deserve special considerations. In all the cases, the neuroradiological appearance was characteristic (Fig. 13.1): a thick and diffuse leptomeningeal enhancement designing the surface of the brain and the basal cisterns (similar to that described in tuberculous meningitis) was supported on T1 post-gadolinium sequences. The spinal cord was always involved disclosing a diffuse linear or nodular leptomeningeal enhancement. The most peculiar and specific neuroradiological finding was the presence of multiple small cysts scattered over the surface of the cerebellum, brainstem, spinal cord, medial temporal lobes and inferior frontal lobes. The cystic lesions were numerous and pronounced; nevertheless, in one case, they were small and had to be sought carefully. On MRI analysis, these cystic lesions were hyperintense on T2 images and iso-hypo-intense on T1 and FLAIR images. These neuroradiological findings could be related to both a serous or mixoid content of the cysts, but solid evidence is missing; indeed, it remains unclear what these cysts may represent. A variable neuroradiological progression of the lesions was observed. Moreover, an adequate chemio-radiological treatment was difficult to explore because of the small number of cases. Of interest, some of these cysts showed a progressive enlargement and extension from the brain surface into the cerebral parenchyma with an inhomogeneous central contrast enhancement. A small solid enhancing lesion, extending from the surface to the internal part of the spinal cord, appeared during follow-up in two of our cases; this supports the hypothesis of neoplastic dissemination via the Virchow–Robin perivascular spaces. Armao and colleagues have previously described the subsequent development of a discrete C6–C7 spinal lesion, 5 years after the presentation of the initial symptoms, in an 8-year-old boy who at onset presented with nothing but a diffuse leptomeningeal enhancement (Armao et al. 2000). In this case, the post-mortem examination revealed that the lesion was caused by tumor cell infiltration and expansion into the perivascular spaces (Armao et al. 2000). Repeated CSF examinations in all patients did not show any malignant cells, although CSF protein was elevated. It has to be underlined that in none of the resembling cases described in the literature, a cytological diagnosis of the tumor cells in CSF was performed (Armao et al. 2000; Bae et al. 2000; Bourne et al. 2006; Chen et al. 1995; Ho-Keung and Wai-Sang 1999; Stödberg et al. 2002; Yamamoto et al. 1996). The elevated CSF protein in the absence of any malignant cells could result from of the entrapment of tumor cells by the dense desmoplastic reactive fibrous tissue. From the histological point of view, these tumors

were composed of cells characterized by round to oval nuclei with finely granular dispersed chromatin and inconspicuous nucleoli with clear oligodendrocyte-like cytoplasm. In some of the similar previously described cases, these histological findings might have favoured the diagnosis of oligodendrogliomas and oligodendrogliomatosis (Armao et al. 2000; Bae et al. 2000; Bourne et al. 2006; Chen et al. 1995; Gilmer-Hill et al. 2000; Ho-Keung and Wai-Sang 1999; Huang et al. 2001; Stödberg et al. 2002). Moreover, in this cases the diagnosis of oligodendrogliomas was achieved only by cytologic criteria, that is, clear cytoplasm and round nuclei caused by the lack of specific markers for oligodendrogliomas. Of interest, as previously described in a case of diffuse leptomeningeal oligodendroglioma (Bourne et al. 2006), FISH analysis revealed a deletion in 1p. This deletion is neither pathognomonic of oligodendrogliomas (Brandes et al. 2006; Smith et al. 2000) nor particularly frequent in pediatric cases that usually do not show 1p/19q co-deletions (Kreiger et al. 2005; Pollack et al. 2003; Raghavan et al. 2003). In oligodendrogliomas, synaptophysin immunoreactivity is usually caused by residual parenchyma and is frequently seen at the infiltrating tumor borders. In our cases, the constantly observed immunohistochemical profiles (i.e. the positive reactivity for synaptophysin and Neu-N) strongly suggest a glioneuronal commitment of the neoplasms. Neurocytomas and dysembrioplastic neuroepithelial tumors (DNT) show similar histological/immunophenotypical profiles (Yamamoto et al. 1996). In contrast with the other described glioneuronal tumors (i.e. DNT, extraventricular neurocytoma, papillary glioneuronal tumor and rosette-forming glioneuronal tumor) (Louis et al. 2007), in our cases a common characteristic was the absence of a primary neoplastic mass. The existence of isolated groups of glioneuronal progenitor cells entrapped in the context of the leptomeninges during the primitive migration could be a possible explanation for the origin of these diffuse leptomeningeal tumors. Theoretically, these embryonic cells could be capable of divergent differentiation with neuronal, oligodendroglial and astrocytic features (Perry et al. 2002; Rowitch et al. 2002; Williams et al. 1991). In the available literature cases of morphologically classic oligodendroglioma with neurocytic rosettes or neurocytomas harbouring 1p/19q deletions have been described (Perry et al. 2002, 2003). This suggests a histogenetic overlap between oligodendrogliomas and extraventricular neurocytomas (Perry et al. 2002), and further supports the existence of a new "superfamily" of tumors with oligodendroglial and neurocytic potential in which our series of diffuse leptomeningeal glioneuronal tumors could be included. Interestingly, in the other similar cases presented in literature, considered as diffuse leptomeningeal oligodendrogliomas, the immunohistochemical profiles are quite variable and sometimes inconsistent. This could be related to the glioneuronal nature of the described neoplasms and further underlines the difficulty in classifying these tumors. Three of our four patients are still alive at 2 years follow-up, after minimal to no clinical intervention, and these data indicates these tumors as neoplasms with a slow progression and quite indolent course. However, in case #3, the subsequent appearance of a bulking neoplastic intraventricular lesion with anaplasia, high mitotic index and focal vascular endothelial proliferation points to the possibility of a potentially aggressive biological transformation.

Conclusions

In conclusion, we presented a series of glioneuronal tumors that could be proposed as new nosological entity characterized by: (a) intense enhancement of subarachnoidal spaces with cystic lesions; (b) diffuse leptomeningeal infiltration by glioneuronal cells without a primary mass; and (c) relatively indolent course. On these bases, we would like to propose for this group of neoplasms the descriptively name of "diffuse leptomeningeal glioneuronal tumors". Further clinico-pathological studies and validation in larger patients' series are needed to test our hypothesis in order to eventually confirm "leptomeningeal glioneuronal tumors" as a distinct nosological entity in the CNS tumor classification.

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Temporomesial Glioneuronal Tumors: Epilepsy Surgery

14

Marco Giulioni, Guido Rubboli, Gianluca Marucci, Matteo Martinoni, Fiorina Bartiromo, Anna Federica Marliani, and Fabio Calbucci

Contents

Abstract

Glioneuronal tumors (GNTs) are an increasingly recognized cause of focal epilepsies, particularly in children and young adults. These tumors consist of a mixture of glial and neuronal elements and most commonly arise in the temporal lobe, particularly in the temporo-anterio- basal mesial site and are often associated with cortical dysplasia or other neuronal migration abnormalities. Typically, epilepsy associated with GNT is insufficiently controlled by antiepileptic drugs. On the other hand, epilepsies associated with GNTs are extremely responsive to surgical treatment. However the best management strategy of tumor related focal epilepsy syndrome remains controversial and is one of the contemporary issues in epilepsy surgery. Temporo-mesial GNT

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_14,

are associated with a widespread epileptic network, defining therefore a distinct anatomo-clinico-pathological group with complex epileptogenic mechanisms. The best seizure outcome results are obtained with resection of the tumor and the adjacent epileptogenic zone as identified by non invasive presurgical neurophysiological study. By using an epilepsy surgery oriented strategy to treat temporomesial GNT associated with focal epilepsies an excellent seizure outcome can be achieved, and therefore surgical treatment can be offered early to avoid both the consequences of uncontrolled seizures as well as the side effects of prolonged pharmacological therapy and the rare risk of tumor grow or malignant transformation.

Introduction

The pathologic substrates underlying medically intractable mesial temporal lobe epilepsy (MTLE) are well established and most commonly include hippocampal sclerosis, malformations of cortical development cortical dysplasia (CO), and low-grade tumors, especially glioneuronal tumor (Schramm and Aliashkevich 2008; Luyken et al. 2003; Prayson et al. 2010). Glioneuronal tumors (GNTs), are an increasingly recognized cause of focal epilepsies, particularly in children and young adults. GNTs consist of a mixture of glial and neuronal elements and most commonly arise in the temporal lobe, particularly in the temporo- anterior-basal -mesial site. GNTs are frequently associated with cortical dysplasias (40–80% of cases) and rarely with hippocampal sclerosis (2–25% of cases) (Aronica et al. 2001; Blumcke and Wiestler 2002; Cataltepe et al. 2005; Minkin et al. 2008).

It is still unknown whether these lesions merely coexist, whether they are different phenotypic manifestations of disrupted or abnormal development, whether they represent the opposite ends of the same spectrum, or finally whether GNT arise out of the malformation of cortical development. Recently, GNTs have been considered by some authors as the extreme neoplastic end of the histopathological spectrum of CD (Becker et al. 2006).

Epidemiological Aspects and Tumors Type

Several reports examined the incidence of various tumor types associated with medically intractable epilepsy (Cataltepe et al. 2005; Luyken et al. 2003). The prevalence of tumors in this setting ranged from 12.6 to 56.3% (Prayson et al. 2010). Occurrence of seizures is reported in up to 100% of dysembryoblastic neuroepithelial tumours, 80–90% of gangliogliomas and of 60–85% of low-grade astrocytomas and oligodendrogliomas.

GNTs account for 0.4–1.3% of all brain tumors and are more common in infancy with an incidence of 7.6%.

Gangliogliomas

Gangliogliomas (GGs) are the most common neoplasm causing chronic focal epileptic disorders (Blumcke and Wiestler 2002; Morris et al. 1998) (accounting for about 40% of all epileptogenic tumors). GGs can occur in any part of the central nervous system, although the temporal lobe, particularly the anterior -basal-mesial site, is the most common location (Adachi and Yagishita 2008; Giulioni et al. 2006; Luyken et al. 2003) followed by the frontal lobe, the optic pathway, the spinal cord, the brainstem, the cerebellum and the pineal gland.

Dysembryoplastic Neuroepithelial Tumors

Dysembryoplastic Neuroepithelial Tumors (DNETs) are benign, solid tumors with cystic/microcystic components, that were first described by Daumas-Duport et al. (1988) as a typically cortical tumor affecting children and young adults with long-standing, drug-resistant epilepsy. Usually DNETs are located in the cerebral cortex, most frequently in the temporal lobe at the temporo-mesial site (Giulioni et al. 2005; Minkin et al. 2008). Only a minority of the reported DNETs occur outside the cerebral cortex, and the most frequent ectopic locations include the

septum pellucidum and the caudate nucleus. Furthermore, DNETs have been reported in the pons, thalamus, basal ganglia, cerebellum, third ventricle, and brainstem. Familial occurrence of these neoplasms have been described.

Pleomorphic Xantoastrocitoma

Recently also Pleomorphic Xantoastrocitoma (PXA) has been considered part of this group of tumors. In fact, in addition to the astrocytic nature, there is growing evidence that PXA exhibits some histological, immunophenotypic and ultrastructural neuronal features occasionally cortical dysplasia can be associated with PXA (Prayson et al. 2010).

GNTs are usually benign, indolent tumors whose main or only symptom is epilepsy; however even if rare, the possibility of malignant evolution and growth has been reported (Hammond et al. 2000; Luyken et al. 2003). In fact a malignant transformation has been reported in 6% of gangliogliomas, 10–15% of Pleomorfic Xantoastrocitoma, and only sporadically in DNETs.

Extraventricular Neurocytoma

Furthermore the rare entity of extraventricular neurocytoma, may be considered in the spectrum of low-grade neuronal, glio-neuronal neoplasms associated with focal epilepsy (Giulioni et al. 2010). Finally, transitional forms between GGs and DNETs, disclosing histological features of both tumor types, have been described (Prayson et al. 2010).

Pathophysiological Mechanisms Leading to GNTs Epilepsy

Epileptogenesis of brain tumors depends on the tumor type and anatomical location, but the heterogeneity of structural and molecular changes among tumoral pathologies implies that the pathophysiology is multifactorial. Several mechanisms, such as metabolic imbalance, ph abnormalities, aminoacid and neuroreceptor disturbances, local changes in the levels of gamma-aminobutyric acid, somatostatin, glutamate, extracellular potassium and cytokines mass effect, ischemia, hypoxia, or membrane distortion leading to abnormal ion channel permeability and immune-mediated responses have been proposed. Pathogenetic mechanisms underlying focal cortical hyperexcitability in patients with GNTs have not been fully elucidated yet; however, it can be hypothesized that GGs and DNETs might be particularly prone to develop specific epileptogenic activities due to their neuronal and glial components (Aronica et al. 2001; Becker et al. 2006; Blumcke and Wiestler 2002). In fact, neurochemical profiles of GNTs show some similarities in expression of various enzymes and receptors to neocortical neurons. The relatively low incidence of Hippocampal sclerosis associated with epileptogenic temporal tumors also suggests that these latter may be the primary source of the epilectic disorder (Blumcke and Wiestler 2002). On the other hand, identification of a coexistent dysplastic pathology adjacent to the tumor may be epileptologically relevant (Becker et al. 2006; Cataltepe et al. 2005; Prayson et al. 2010). The epileptological implication is that excising the tumor and leaving in place the nearby abnormal epileptogenic dysplastic tissue, may give unsatisfactory results on the seizure outcome. Finally, in about a third of patients, the epileptogenic focus does not correspond to tumour location, suggesting a secondary epileptogenesis process in which an actively discharging epileptogenic focus induces similar paroxysmal activity in regions that are distant to the original site. This secondary focus is seen more frequently with temporal tumours. Young age and long duration of illness are associated with an increased risk of secondary epileptogenesis.

Clinical and EEG Features of Focal Epilepsy Associated with GNTs

Clinical Features

Focal epilepsy is the most common and often the only symptom of GNTs. In fact, neurological deficits are relatively uncommon, varying from 0 to

15% according to different series : the neurological sparing might depend on the indolent and slow course of GNTs that might allow compensation of possible brain impairment by slowly developing plastic processes, particularly in the young age (Ozlen et al. 2010). Epilepsy can appear at any age: however, the majority of cases present with an epilepsy onset in adolescence and young adulthood. Seizure semiology is related to the site of tumor. In general, complex partial seizures with aura are more common in GNTs located in the temporal lobe, whereas secondary generalization is more common in epilepsies associated with extratemporal GNTs (Morris et al. 1998). However, the extension of the tumor-related epileptogenic area may vary according to the anatomical location of the neoplasm: in fact, several data suggest that epileptogenic zone may be more widespread and complex in focal epilepsies associated to GNTs in the mesial temporal lobe in comparison to neocortical temporal lateral locations (Clusmann et al. 2002; Giulioni et al. 2006, 2009). Occurrence of status epilepticus has been reported to be rare. Clinical parameters that differentiated patients operated on in childhood from patients operated on in adulthood were: (a) aura that was reported more often in the adult group, but it should be noted that this finding might at least partially depend on the fact that, in general, children are less able to refer their auras; (b). mean age at seizure onset that was lower in children; this might be due to the fact that a developing brain has a low seizure threshold which leads to early and frequent seizures and early diagnosis of the disease(Ozlen et al. 2010). Moreover, in pediatric age, lesional epilepsy is more frequently associated with a malformation of cortical development often characterized by a high seizure frequency that can facilitate an early diagnosis and that can lead to early evaluation for a surgical approach. No differences between the clinical features of epilepsy associated with DNETs and with GGs have been reported, suggesting that the clinical variables are not tumor-specific. More importantly, among the clinical characteristics, short duration of epilepsy, only partial seizure and the lack of secondary generalization showed a strong association with favorable seizure outcome. Response of GNTs-associated epilepsy to antiepileptic treatment is variable, but drug-resistance is quite common (Cataltepe et al. 2005; Luyken et al. 2003; Morris et al. 1998).

EEG Features

Usually interictal EEG shows spikes and/or, sharp waves, sometimes intermixed with slow activities; in some instances normal EEG have been reported. These abnormalities, in preoperative EEG are commonly lateralized to the tumor side, less often to the correct lobe. However, Morris et al. (1998) reported that the occurrence of interictal EEG abnormalities and ictal EEG onset in correspondence of the site of the tumor may not be predictive of seizure outcome; indeed, in some cases a post-operative poor seizure outcome has been reported in patients with EEG interictal and ictal findings perfectly concordant with tumor location. On the other hand, also patients with EEG slow or epileptiform abnormalities distant from the tumor site or with ictal EEG onset non-localized or widespread to a whole hemisphere improved regarding seizure outcome after tumor resection (Morris et al. 1998). In temporal lobe GNTs, long-term video-EEG monitoring may allow recording of seizures and identification of the epileptogenic zone; indeed, several data suggest that in mesial temporal lobe GNTs a tailored resection that include, besides the tumor, the epileptogenic area (as defined by the anatomo-electro-clinical correlations performed on the ictal video-EEG data), provides better post-operative seizure outcome compared to simple lesionectomy (Clusmann et al. 2002; Giulioni et al. 2006, 2009; Luyken et al. 2003). In cases of undetermined lateralization of seizure focus, invasive EEG investigations may provide useful information, although in GNT-associated focal epilepsy the main goal of intracerebral recordings is usually to map eloquent cortex in proximity of the neoplasm. While there are several reports on ECoG spike discharge patterns in FCD, with persistence of seizure patterns or ictal-like and/or continuous epileptiform discharges in post-resection ECoG recordings

being predictive of poor surgical outcome (Ferrier et al. 2006), less is known about the ECoG spike discharge patterns in patients with GNTs, often because only small patient samples have been investigated (Ferrier et al. 2006; Gelinas et al. 2011; Ozlen et al. 2010). Because of the common neurodevelopmental origin and features of GNTs and FCDs, patients with these disorders may have similar electrocorticographic abnormalities. Continuous spiking, bursts, and recruiting discharges have been indeed observed in patients with FCDs and GNTs, although continuous spiking was reported significantly more often in patients with FCD. When continuous spiking is found in GNTs, it is likely to be due to associated dysplastic regions with a high neuronal density. Controversial data on the usefulness of electrocorticographic mappings have been reported, some suggesting that post-operative seizure outcome was not affected by having performed or not electrocortical mapping, others showing that intraoperative electrocorticography identified extralesional interictal activity, which led to extended lesionectomy or lobectomy, leading to better seizure outcome (Gelinas et al. 2011).

Imaging

Gangliogliomas

GGs share many imaging features with other low-grade neoplasms. Imaging studies reveal a solid or cystic mass, or more frequently a solid-cystic combination that is typically located in the periphery of a cerebral hemisphere. Calcification is a common finding (Adachi and Yagishita 2008; Ozlen et al. 2010) (Fig. 14.1). The tumor size is variable (2–3 cm), tipically larger in children: some authors suggest that GGs that occur in children tend to have greater overall tumor volume (average: eight times larger) than those arising in adults. Reflecting a generally benign biologic nature, there is usually little associated mass effect or evidence of surrounding vasogenic edema. GGs have variable manifestations at nonenhanced CT. Calcification is less commonly seen in association with solid-appearing lesions. Superficial lesions may expand cortex and remodel bone. Occasionally, the neoplasm may be completely undetectable at CT. The MR imaging appearance of GGs is also variable and nonspecific. In general, the lesions are hypointense to isointense relative to gray matter on short TR images and hyperintense relative to gray matter on long TR images. The solid-appearing components have an even more variable presentation at imaging. Some tumors may manifest as a hyperintense mass on T1-weighted images for calcium presence, that can mimics in T2* GRE area of "blooming" They commonly have at least some regions of high signal intensity on T2-weighted images. Not all GGs are truly cystic despite a cyst-like appearance. Enhancement following intravenous administration of gadolinium contrast material is highly variable, usually moderate but heterogeneous but also nonenhancing, "ringlike" or at least intense homogeneity. GGs may show

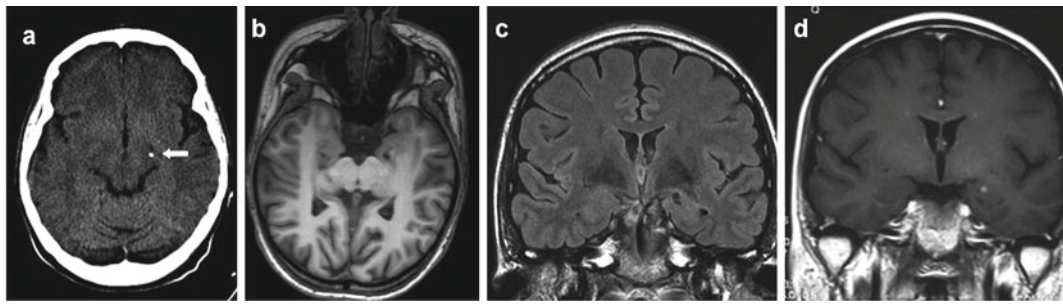

Fig. 14.1 (**a**) Axial CT image shows a calcified GG (*arrow*) of the mesial left temporal lobe. (**b**) Axial 3D SPGR T1-W MR image better shows the true size and morphology of the lesion; it is heterogeneously hypointense. (**c**) Coronal FLAIR T2-W and (**d**) After gadolinium injection coronal T1-WI shows a little enhancement of the mass

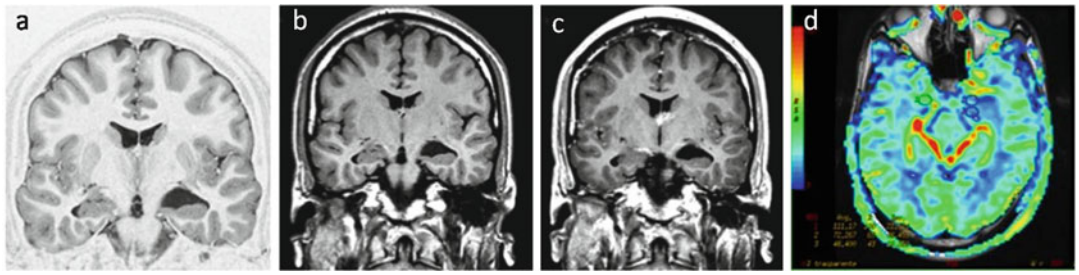

Fig. 14.2 (**a**) Coronal IR T1 WI, (**b**) Coronal FLAIR T1WI before and (**c**) after contrast medium administration releave an Hypo-isointense DNET that doesn't enhance (**d**) Perfusion study shows rCBV value lower than the controlateral side due to the lack of neoangiogenesis

focal leptomeningeal involvement, although predominant leptomeningeal involvement is extremely rare.

Dysembryoplastic Neuroepithelial Tumor

DNETs are well-demarcated, wedge shaped, multinodular, "bubbly" intracortical tumors.

The appearance on neuroimaging of DNETs is similar to those of other low-grade glial tumors, and in some cases it may be impossible to distinguish this tumor from diffuse astrocytoma, GG, oligodendroglioma, or other low-grade neoplasms. DNETs on CT scan appear as a cortical-subcortical hypoattenuating mass that may occasionally have areas of calcifications. Scalloping of the adjacent inner table of the skull may also be present. In some instances, DNETs may mimic a stroke. At MR imaging, DNETs most commonly manifest as pseudocistic, multinodular cortical masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images with minimal or without mass effect and surrounding vasogenic edema (Ozlen et al. 2010) (Fig. 14.2). Some lesions may expand involving cortical gyri and, producing a soap bubble appearance at the cortical margin ("megagyrus" appearance). According to some authors DNETs may show a multicystic morphology more frequently than GGs. About one-third of DNETs enhance following intravenous administration of contrast medium. Absent or very slow increase in size over time is typical of DNETs, and recurrence is also extremely rare (Hammond et al. 2000).

Pleomorphic Xanthoastrocytoma

PXA classically, although not specifically, appear as a cystic supratentorial mass containing a mural nodule that is adjacent to the peripheral leptomeninges (Louis et al. 2007). PXA are usually located in supratentorial regions involving cortex and meninges. The size and morphology are variable; PXA are formed by a cystic component and mural nodule (usually solid) that abuts meninges, but they can appear also as a round/oval mass, or as infiltrative lesions, through VRSs (perivascular spaces of Virchow-Robin), CT scans of PXA show a hypo- or isoattenuating mass at nonenhanced CT. Calcifications are rare. Lesions may be well-circumscribed or ill defined. Evidence of skull erosion or lytic change is uncommon. Strong, sometimes heterogenous enhancement of tumoral nodule is a common finding. At MR imaging, PXA are usually hypo- to isointense relative to gray matter on T1- weighted images and hyperntense or mixed signal intensity relative to gray matter on T2-weighted images (Fig. 14.3). Involvement of the leptomeninges is highly characteristic and it is reported in 71% of cases in one series, whereas peritumoral edema is relatively uncommon. The solid portions of the tumor enhance intensely following intravenous administration of contrast material. Despite variability in the imaging appearance reported in the literature, the peripheral location of these tumors

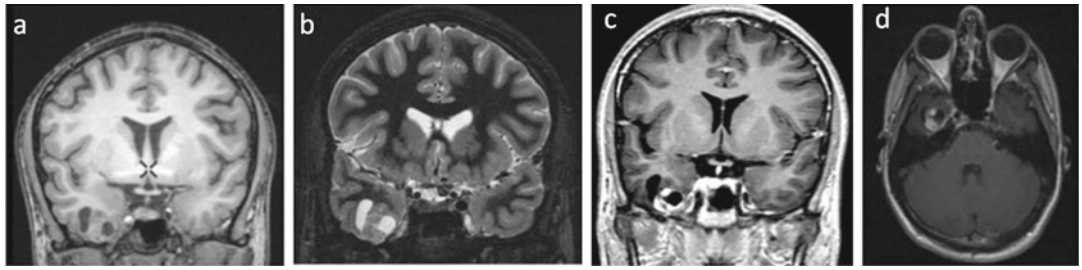

Fig. 14.3 (**a**) Coronal SPGR T1-WI, (**b**) Coronal T2-WI and (**c** and **d**) Coronal SPGR T1-W and axial T1 after gadolinium injection reveal a temporo mesial PXA that tipically shows strong and inhomogeneus enhancement. On coronal views it is also visible the bony scalloping

is the single most consistent imaging feature. PXA is usually circumscribed, slow growing tumor that recurs rarely.

Extraventricular Neurocytoma

Extraventricular neurocytoma (EVN) may be difficult to differentiate from other types of low-grade tumor, such as GGs or DNET. Generally these lesions are circumscribed, sometimes large, complex, and variably enhancing masses. These tumors can have a solid portion and a variable appearance on CT and MR imaging depending on the cellularity and degree of calcification. They are often cystic, frequently calcified (>10%), and may or may not be associated with peritumoral edema. Hemorrhage has been reported sporadically

Histopathology

GGs (Grade I WHO, Louis et al. 2007) consists of a combination of dysmorphic and haphazardly arranged neurons and neoplastic glial cells (Fig. 14.4a), surrounded by a reticulin network. Neoplastic nature of neuronal cells is demonstrated by binucleation and aggregates of Nissl substance. The astrocytic component may resemble a fibrillary or a pilocytic astrocytoma. Calcifications, perivascular inflammatory infiltrates and eosinophilic granular bodies are common. Evident mitotic activity and necrosis are generally absent. Microvascular proliferation may be appreciated, without altering the grade of the tumor. Ki-67 labelling index is generally very low and in practice it is negative in neuronal cells.

In contrast to WHO grade II diffuse glioma, GGs are usually characterized by an excellent prognosis. A series of morphological features can be useful in differential diagnosis: perivascular chronic inflammation, neoplastic neurons and eosinophilic granular bodies are more typical of ganglioglioma. Furthermore the presence of focal cortical dysplasia in adjacent brain tissue is frequently observed in GGs, while it is really uncommon in diffuse gliomas (Blumcke and Wiestler 2002; Blumcke et al. 2011).

DNETs (Grade I WHO, Louis et al. 2007) are intracortical tumors with a multinodular architecture. Microscopic examination (Fig. 14.4b) shows nodules composed by parallel strands of axons, immunopositive for synaptophisin and neurofilaments, ensheated in oligodendrocyte-like cells, and microcystic mucopolysaccharide-rich areas, containing large floating ganglion cells, immunopositive for Neu-N. These features constitute the so called specific glioneuronal element. Mitoses are rare and Ki67 label index is extremely low. Neither atypia nor necrosis are usually observed. Frequently adjacent brain tissue shows areas of FCDs (Blumcke et al. 2011) Even though the biological behavior of DNETs is usually benign and indolent, unusual cases of tumor progression or malignant transformation have been reported (Hammond et al. 2000). DNETs may mimic the appearance of oligodendroglioma and this can be a challenging differential histopathological diagnosis.

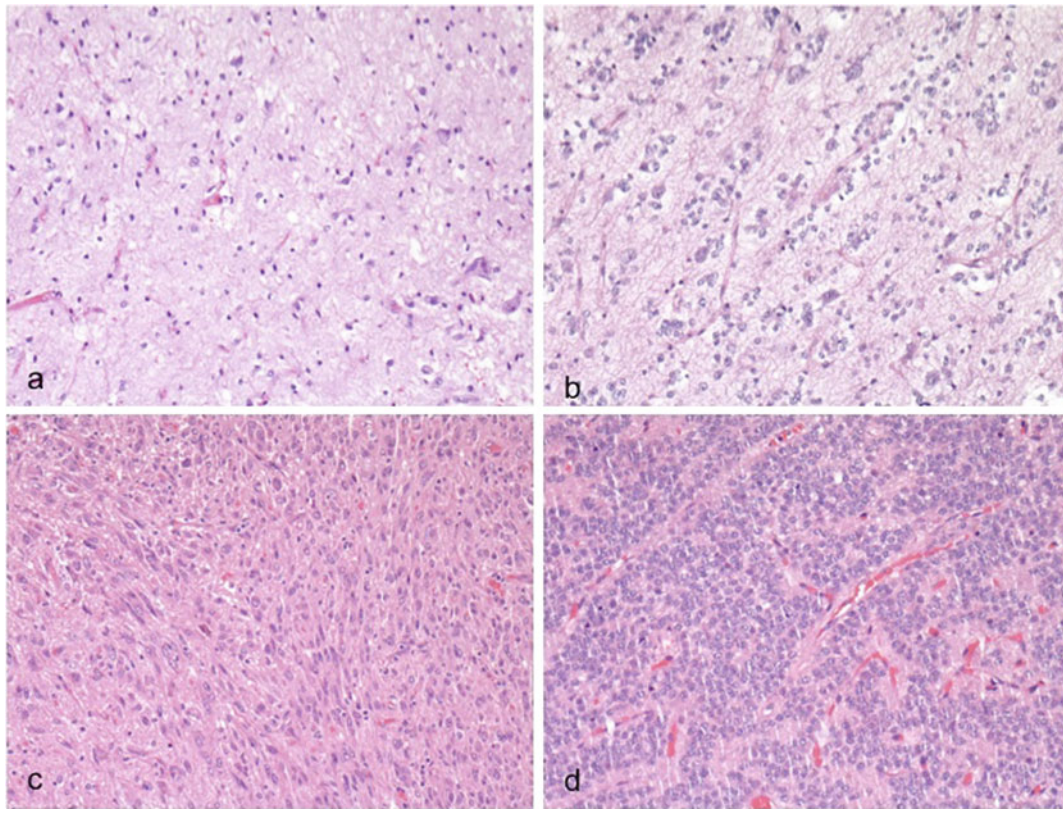

Fig. 14.4 (**a**) An histological picture of ganglioglioma. It can be observed some dysmorphic and occasionally binucleated neurons in a context of neoplastic glial cells (H&E, 200× magnification). (**b**) Dysembrioplastic neuroepithelial tumor. Microscopic examination shows parallel strands of axons ensheated in oligodendrocyte-like cells, and microcystic mucopolysaccharide-rich areas, containing large floating ganglion cells (H&E, 200× magnification). (**c**) On histological examination pleomorphic xanthoastrocytoma is composed of giant neoplastic cells showing nuclear pleomorphism and xanthomatous changes. Nuclei have large nucleoli in clear chromatin and resemble neuronal nuclei. Occasional eosinophilic granular bodies are also present (H&E, 200× magnification). (**d**) Extraventricular neurocytoma. Microscopically the tumor is largely composed by oligodendrocyte-like cells, characterized by central round nuclei and perinuclear halos. The *background* shows a granular neuropil appearance (H&E, 200× magnification)

PXA (Grade II WHO, Louis et al. 2007,) is a brain tumor superficially located in the cortex, leptomeninges and superficial white matter, preferentially of the temporal lobe. This tumor is more sharply circumscribed than a classic glioma and is composed of giant neoplastic cells (Fig. 14.4c) showing nuclear pleomorphism and xanthomatous changes, surrounded by a reticulin network. Despite of a huge cytological pleomorphism, the tumor lacks microvascular proliferation and necrosis; mitotic figures are not common. Ki67 label index is usually less than 5%. Following reports in the literature of composite GGs/PXA and the immunohistochemical evidence of expression of neuronal markers PXA is considered related to GNTs (Powell et al. 1996).

EVN (Grade II WHO, Louis et al. 2007) is a cellular tumor (Fig. 14.4d) that closely resembles oligodendroglioma, largely composed by oligodendrocyte-like cells, characterized by central round nuclei and perinuclear halos. The background shows a granular neuropil appearance with synaptophysin immunopositivity. Mitotic activity, cytological atypia, vascular proliferation and necrosis are usually absent. The neoplastic cells are stained by neuronal markers, particularly NeuN: this feature is helpful in differential diagnosis with oligodendroglioma.

These tumours, particularly GGs and DNETs, may be frequently associated with FCD. The classification of FCD, recently proposed by ILAE Commission (Blumcke et al. 2011) distinguishes FCD Type I, II and III. The first type, characterized by abnormal cortical lamination, is further subdivided in Ia, Ib and Ic. In FCD Type IIa dysmorphic neurons are present, while in type IIb balloon cells are observed. Finally FCD III is constituted by cortical lamination abnormalities associated to other lesions; FCD associated with one of the tumors previously listed, are diagnosed as FCD type IIIb.

Epilepsy Surgery

GNTs related epilepsies are usually unsatisfactorily controlled by antiepileptic drugs, whereas they can be extremely responsive to surgical treatment (80–90% of these patients are seizure-free after surgery in most series) (Aronica et al. 2001; Cataltepe et al. 2005; Clusmann et al. 2002; Luyken et al. 2003).

There are several features that make the temporal lobe unique. In fact, histologically, the temporal lobe presents areas of different cortical organization, such as the three-layered allocortex, that includes the prepiriform area, the semilunar gyrus of the uncus, and the hippocampus; the six-layered mesocortex, that includes the parahippocampal gyrus and the six-layered isocortex which is the superior, middle, inferior, and transverse temporal gyri and the fusiform gyrus. There is thus a gradual transition from a more primitive allocortex in the mesial temporal area to the more recent isocortex located mainly in the lateral temporal area, with a transitional area, the basal temporal area. This differentiation in cortical organization plays an important role in making the temporal lobe the preferred site for certain tumors and epilepsy (Wen et al. 1999).

The role played by the temporal amygdala, entorhinal area, allocortex, mesocortex, and hippocampus in the genesis and circuitry of mesial temporal lobe epilepsy have been demonstrated as is the importance of removal of these structures in seizure control of intractable temporal epilepsy.

Surgical Approaches

Various surgical approaches have been adopted for the radical resection of these tumors. The choice of surgical approach is also related to the goal of surgical strategy.

The surgical strategy may be directed only to oncological issues and/or to solve epilepsy.

In this last condition we must have an epilepsy surgery oriented approach. This means a presurgical study to determine if whether treating seizures it is sufficient only a tumor resection (lesionectomy) or it is necessary to remove the lesion and the epileptogenic zone (tailored resection).

Anterior temporal lobectomy is the most common procedure, followed by tailored resection, transsylvian approach (Yasargil et al. 2010), transsuperior temporal gyrus approach, transcortical approach, sub-temporal approach and recently a limited inferior temporal gyrus approach to mesial basal temporal lobe tumors was described (Uribe and Vale 2009). Our approach initially was a transsylvian approach for lesionectomy; in the last years we perform a tailored antero-mesial temporal resection (Fig. 14.5).

Surgical Anatomy

The mesial temporal structures are hidden deep within the remainder of the temporal lobe and the ventricular system, and are surrounded by vascular and neural elements that, must be preserved during surgery. During the surgical procedure it must be reminded that only a thin arachnoidal layer separates the lesion from the important vascular and neural structures that, if damaged, can lead to severe neurological deficits. It's mandatory to know the complex anatomy of uncus-amygdala region, the hippocampus, the paraippocampus and the anatomy of the mesial cisterns (in particular crural and ambient) with their vascular and neural contents (the third cranial nerve, internal carotid artery, the anterior choroidal artery, posterior cerebral artery, the basal vein of Rosenthal and moreover the cerebral peduncle).

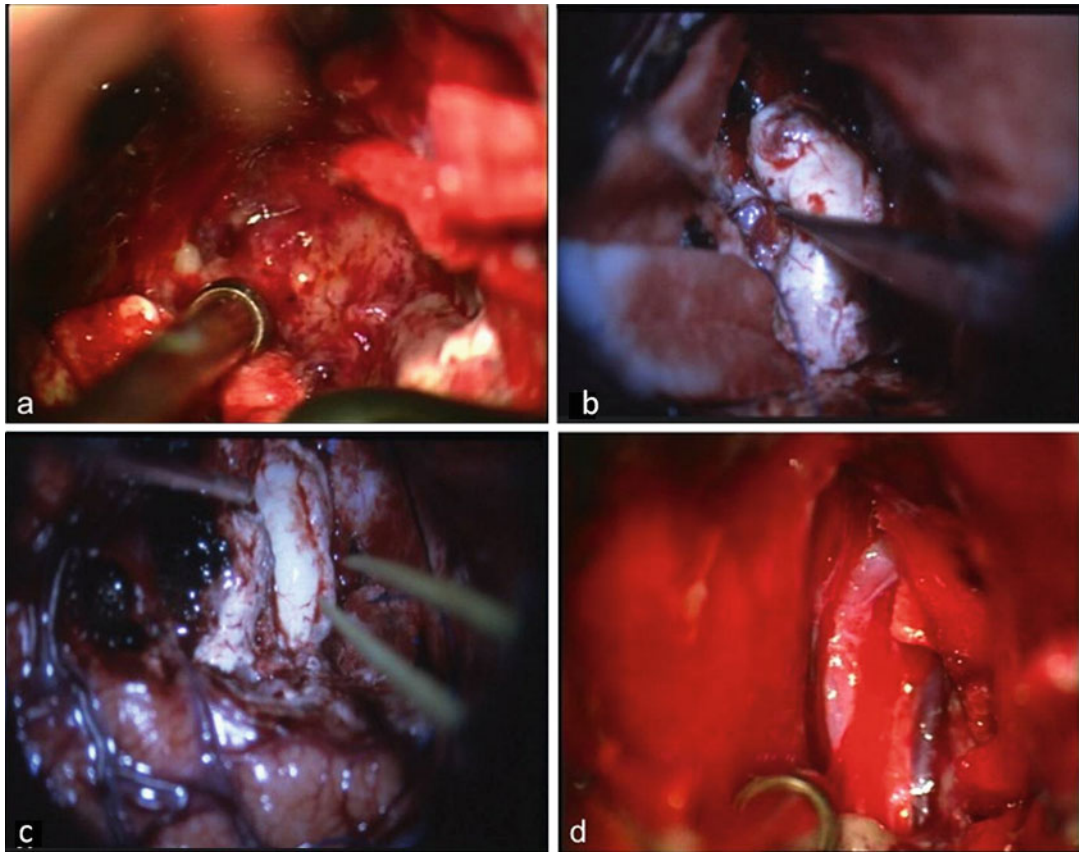

Fig. 14.5 After tailored removing the anterior part of the temporal lobe we identify and remove the tumor that usually involves the uncus, amygdala and the anterior part of hippocampus. (**a**) Tumors, in this case a GG, are tipically characterized by discromic-brownish color compared than surrounding parenchyma. (**b** and **c**) Once identified the hippocampus it is isolated first by detaching it from collateral sulcus, choroidal fissure and sectioning the tail; then hippocampus and parahippocampal gyrus are excised en bloc trying to keep intact the arachnoidal layer of crural and ambiens cistern. (**d**) Through this arachnoidal film it is possible to identify the III cranial nerve, the posterior cerebral artery the vein of Rosenthal

The essential anatomical landmarks for such type of surgery are the vascular and neural structures displayed through the aracnoidal mesial layer, the choroid plexus, the temporal horn and the choroidal fissure (Campero et al. 2006; Wen et al. 1999).

Surgical Strategies

Several studies have analyzed the surgical treatment and epileptological outcome of patients with tumor-related chronic epilepsy. Most of these studies have included a variety of neoplasms involving different brain regions, whereas others have focused on different surgical strategy, such as lesionectomy, anterior temporal lobectomy and tailored resection (Cataltepe et al. 2005; Giulioni et al. 2005, 2006; Lombardi et al. 1997;). Some investigators consider resection of the tumor alone sufficient for good seizure control while others advocate additional resection of epileptogenic zones adjacent to the tumor in order to optimize seizure outcome. Epileptogenic mechanisms may be also related to the anatomical brain site of GNTs location. There are only a few studies that discus the influence of the anatomical location in the decision-making process regarding the best surgical strategy to obtain a good seizure outcome (Cataltepe et al. 2005; Giulioni et al. 2009; Luyken et al. 2003).

There are some shared opinions and consensus that lesionectomy alone provides the best seizure outcome results in GNTs located in the extratemporal and temporo-lateral site. Conversely, in the temporomesial site, the results of lesionectomy alone appear disappointing (Giulioni et al. 2006, 2009; Luyken et al. 2003). Particularly, there are some suggestions that the anatomical location of these tumors (i.e. extratemporal versus temporal and temporo-mesial versus temporo- lateral) may influence the extension and complexity of the epileptogenic zone, thus affecting the choice of the more effective surgical approach. Temporo mesio-basal GNTs tipically involve the uncus-amygdala-entorhinal zone, sometimes involving the hippocampal head (corresponding to Class A of Schramm temporomesio-basal tumor classification) (Adachi and Yagishita 2008; Giulioni et al. 2009; Schramm and Aliashkevich 2008)

From a surgical point of view, another controversial issue is the resection of temporomesial structures, (particularly the hippocampal-parahippocampal complex) in addition to the tumor, when the hippocampus is not involved the lesion and it appears normal on MR imaging. However, it is well known that the medial temporal lobe, specifically the hippocampus and the entorhinal cortex, have a greater epileptogenicity (Wen et al. 1999) and that the amount of tissue resected in temporomesial operations is considered crucial for surgical success in mesial TLE.

Surgical Challenges

To perform a safer tailored antero-mesial temporal resection we have to carry out some precautions and to respect the following suggestions:

The tailored anterior-mesial temporal lobe resection must be performed without the use of any fixed retractors

The vascular anatomy of the cortex has to be taken into account before finally determining the extent of the lateral resection.

A microsurgical subpial techniques dissection and the use of blunt instruments (such as curettes) are of great importance.

In the mesial site using the vacuum cleaner and ultrasonic aspirator (CUSA) at a very low power so that the aspirator cannot breech the arachnoid and using as little as possible bipolar coagulation.

Extreme caution and patience should be applied during the potential bleeding from mesial aracnoidal layer thus to avoid as much as possible that the bipolar coagulation with the related adverse effect on the important vessels (i.e. anterior choroideal artery, posterior cerebral artery as the proximal collateral arterial feeders that supply the internal capsule, caudate nucleus and optic tract). In most cases it is safer waiting for a spontaneous healing without further intervention directly.

Disconnection and removal of the hippocampus should be done with extreme caution. In particular, it is necessary to identify the arachnoid sleeve that contains the arteries that go deep to the hilum of the hippocampus and to disassociate these small vessels following them in their own arachnoidal layer. These hippocampal vessels must be isolated and disassociated as much as possible far away until the limit of the hilum hippocampi. At this point the lumen of the vessel should collapse spontaneously.

In some patients the tumor may have destroyed the mesial arachnoid layer growing into the perimesencephalic cistern and protruding between blood vessels and the cranial nerves. In these cases extreme caution needs to be taken as one of the principal surgical anatomical landmarks no longer exists.

To prevent remote hemorrhages, particular attention should be paid to all the factors related to an increase in transmural venous pressure such as head position, cerebrospinal fluid withdrawal, and drugs that reduce intracranial pressure.

Complications

Although cranial neurosurgery has become safer in the last years, performing surgery on the mesial -temporal lobe poses a risk of complications. Most of these are transient and both morbidity

and mortality are low with approximately 1–2% permanent morbidity. A complication can be defined as major if causes significant neurological deficit or affects activities of daily living. The risk of postoperative major complications in temporal lobe antero-mesial resections range between 1 and 4% and that of minor complication ranges from 5 to 10% (Behrens et al. 1997; Clusmann et al. 2002). Usually, minor complications resolve within 3 months Mortality is inferior to 1%. Typical major neurological complications after surgery for TLE include temporary dysphasia or hemiparesis and hemianopia. Schramm, in his temporo-basal tumor series (Schramm and Aliashkevich 2008) reported 1.7% of major neurological complication. Typically, visual field defect (VFDs) occur in the superior homonymous field contralateral to the resection and are due to a damage to the most anterior portion of the optic radiation (Meyer's loop). Disorders of the visual field related to surgery on the anterior mesial temporal region may also occur for damage to the optic tract, or lateral geniculate body. Anyway, a certain amount of visual field defects should be considered an event included in the intervention rather than a true complication, and that therefore the patient should be well informed in the preoperative counselling. The most recent development in the study of the optic radiation has been the application of diffusion tensor tractography (Yogarajah et al. 2009) (DTI) which can reliably depict the optic radiation, including Meyer's loop..The definitive goal of tractography of the optic radiation is its integration into stereo-navigational systems together with T1-weighted anatomical images; it could reduce post-operative VFD.

Hemorrhage can be a possible complication after surgery for TLE; a particular kind of hemorrhages may occur distant from the site of surgery, such as in the upper cerebellar vermis and foliae (Zebra sign) (Friedman et al. 2001; Giulioni et al. 2006). Cerebellar haemorrhages after supratentorial craniotomy have been reported in 0.6% of all supratentorial craniotomies, and particularly after surgery for unruptured aneurysms and epilepsy. Although its venous origin has been recognised, the pathogenesis of cerebellar haemorrhage is unclear. We suggested that the increase in transmural venous pressure (intravascular venous pressure minus extravascular pressure; that is intracranial pressure) associated with normal intracranial pressure is the critical factor. In our opinion, cerebellar haemorrhage might be caused by an increase in transmural venous pressure related either to venous pressure increase favoured by head position, or to intracranial pressure decrease determined by cerebrospinal fluid withdrawal, or to a combination of both factors. In order to avoid cerebellar haemorrhage, attention should be paid to the factors related to an increase in transmural venous pressure such as head position, cerebrospinal fluid withdrawal, and drugs that reduce intracranial pressure (Giulioni et al. 2006).

Seizure Outcome

Epilepsy associated with GGs and DNT shows the best seizure outcome(Clusmann et al. 2002; Giulioni et al. 2005, 2006, 2009; Luyken et al. 2003). Some authors observed improvement of seizure outcome in young patients whereas others found no correlation with age at the time of surgery (Aronica et al. 2001).

However, a short duration of epilepsy prior to surgery appears associated with a better seizure outcome (Yang et al. 2011).

Only few studies correlated seizures outcome with the lesion site in temporal low-grade tumors, including GNT, (i.e. temporal mesial versus temporal lateral and extratemporal), using, as surgical strategy, the removal of the epileptogenic focus, including the lesion (i.e. tailored surgery) (Clusmann et al. 2002; Giulioni et al. 2009; Luyken et al. 2003). We evaluated the effects on epilepsy outcome of only pure GNT lesionectomy (Giulioni et al. 2005, 2006), and we observed that patients with extra-temporal and neocortical lateral temporal GNT did benefit from lesionectomy more than those with temporo-mesial GNT. This finding suggests that, to further improve seizure outcome, presurgical neurophysiological assessment may be useful in patients with temporo-mesial GNT to define the epileptogenic area and its relationship with the

lesion, in order to evaluate the possibility of a tailored surgery. Indeed, in a retrospective study comparing the seizure outcome in two homogeneous series of temporo-mesial GNTs causing epilepsy, one treated with simple lesionectomy and the other with lesionectomy and tailored resection of the epileptogenic zone, we observed that only 42.8% of those treated by lesionectomy alone (Group A) were seizure-free (Engel et al. 1993)compared with 93% of those who underwent a tailored resection (Group B); this difference was statistically significant (Giulioni et al. 2009). Therefore, we believe that in temporomesial glioneuronal tumors lesionectomy associated with temporal tailored resection of the epileptogenic zone appears to offer the best results for seizure outcome. Furthermore, GNT are frequently embedded in and/or associated with dysplastic, possibly epileptogenic, cortex (Blumcke et al. 2011), which is more likely to be removed when performing a tailored resection.

The good seizure outcome in temporo-mesial GNTs submitted to tailored resection suggests that the epileptogenic focus is often larger than the extrahippocampal lesion, supporting the concept that in the mesial temporal lobe both the lesion, the hippocampus and the temporal pole are often epileptogenic even if MR imaging does not show hippocampal abnormalities and histological examination shows normal features in the majority of cases. In conclusion, using an epilepsy surgery oriented strategy, the presence of temporomesial GNT constitutes a predictive factor of excellent seizure outcome, and therefore surgical treatment can be offered early to avoid both the consequences of uncontrolled seizures as well as the side effects of pharmacological therapy, and the risk, although infrequent, of malignant transformation.

Further studies are necessary to clarify either the epileptological mechanisms of these lesions, and the predisposition of these tumors to the temporomesial region.

The existence in subgranular zone (SGZ) of the Dentate Gyrus of the hippocampus of neural cell precursors and the occurrence of postnatal life neurogenesis may contribute to either a more complex epileptogenesis or to the development of these glioneuronal lesions (tumors and other developmental dysplastic abnormalities) (Becker et al. 2006; Blumcke and Wiestler 2002; Gonzalez-Martinez et al. 2007; Paradisi et al. 2010).

Furthermore, the strong association with cortical dysplasia also suggests a tumor origin from precursor cells either during embryological cortical development, either during post-natal life.

It remains a controversial issue, whether epileptic seizures have an effect on or even increase hippocampal neurogenesis in humans. Recent data support the notion that seizures induce neurogenesis in young patients, whereas the capacity of neuronal recruitment and proliferation decreases with age.

The possibility of isolation and in vitro expansion of human hippocampal precursor cells, as well as their differentiation into neurons may help in the future to elucidate the relationships between neurogenesis, glioneuronal and dysplastic lesion and epileptogenesis (Blumcke et al. 2011; Gonzalez-Martinez et al. 2007; Paradisi et al. 2010).

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Rosette-Forming Glioneuronal Tumor: Conservative Management Strategy

15

Caroline C. Tan

Contents

Abstract

The rosette-forming glioneuronal tumor was first included in the World Health Organisation Classification of Tumors of the Central Nervous System under the category of "neuronal and mixed glioneuronal tumors" in 2007. It is an uncommon to rare entity that classically occurs in a midline posterior fossa location and often involves the fourth ventricle but there has been growing recognition of considerable variations in its location within the brain. Herein is presented a review of published cases of this tumor in the English medical literature, focusing on the relative clinical outcomes of various treatment approaches. The results suggest that, one may defend a conservative treatment approach in which the primary aim of surgery is the procurement of tissue for confirmation of the histological diagnosis and the relief of any accompanying threat of obstructive hydrocephalus rather than the attempted extirpation of tumor.

Keywords

Rosette-forming glioneuronal tumor • Conservative management • Surgery

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_15,

Introduction

The rosette-forming glioneuronal tumor (RGNT) is a rare and fairly recently recognized neoplasm. It has been included in the World Health Organisation Classification of Tumors of the Central Nervous System under the category of "neuronal and mixed glioneuronal tumors" since 2007 (Louis et al. 2007). Classically, it has a unique biphasic cellular architecture consisting of (1) a neurocytic component of Homer-Wright type rosettes with eosinophilic, synaptophysin-positive cores and/or pericapillary pseudorosettes and (2) a proliferating pilocytic astrocyte component (Louis et al. 2007). It is not to be confused with the similarly named rosetted glioneuronal tumor, otherwise known as the glioneuronal tumor with rosetted neuropil islands, in which there are large and often irregular neuropil-containing macrorosettes, most unlike those in RGNT (Rickert et al. 2006). In fact, the RGNT has probably often been misdiagnosed in the past due to superficial histological resemblance to a variety of other tumors, especially dysembryoplastic neuroepithelial tumor (Komori et al. 2002; Shah et al. 2010). The RGNT came to be established as a novel clinico-pathological entity through the assembly and description by Komori et al. (2002) of 11 cases, which remains to this day the largest case series ever published. As of mid 2011, the English medical literature contained 48 cerebral cases, with more than half of these published in the last 3 years (Table 15.1). An analysis of these cases reveals a mean age of 29 years (ranging from 6 to 59 years) and a female to male preponderence of 2:1. There have been no known hereditary cases and no established association with familial tumor syndromes. As there has only been one known case in the spinal cord, the following discussion is confined to cerebral RGNT (Anan et al. 2009).

Although originally regarded as an exclusively midline infratentorial lesion, the growing body of literature on the RGNT has dispelled this notion. This tumor classically occupies the fourth ventricle, and hence its previous designation of rosette-forming glioneuronal tumor of the fourth ventricle. While there have been cases of RGNT that have been confined to the ventricular system, the most common pattern is varying degrees of simultaneous involvement of the fourth ventricle and adjacent structures, particularly the vermis, and, less often, the medial cerebellar hemispheres, brainstem, thalamus, pineal gland and tectum (Komori et al. 2002). However, involvement of the fourth ventricle is certainly not invariable and there have been a number of cases of RGNT within midline infratentorial structures that are adjacent to but not encroaching on the fourth ventricle, such as the cerebral aqueduct, vermis and, most of all, the pineal region (Tan et al. 2008; Pimentel et al. 2008; Ghosal et al. 2010; Frydenburg et al. 2010; Solis et al. 2011; Sharma et al. 2011). Marhold et al. (2008) even encountered a laterally situated RGNT that arose from the left cerebellar flocculus and was therefore remote from the fourth ventricle. More unexpected still has been the diagnosis of RGNT in supratentorial sites, such as the lateral ventricles (Wang et al. 2009), midbrain (Sharma et al. 2011), hypothalamus (Sharma et al. 2011) and the left optic chiasm and proximal optic nerve (Scheithauer et al. 2009).

Biological Activity of Rosette-Forming Glioneuronal Tumor

Multiple lines of evidence indicate that the RGNT is a benign tumor and corresponds to grade 1 on the World Health Organisation "malignancy scale". The histology of the glial component is typified by piloid astrocytes, oftentimes with Rosenthal fibres and eosinophilic granules, which correlate with indolent biological behaviour in other glial neoplasms. Also reassuring, is a paucity of mitoses, absence of cellular atypia and the measurement of very low cellular proliferation indices. In terms of presenting symptoms, it is noteworthy that even in patients with sizeable posterior fossa tumors or dilatation of the ventricles secondary to obstruction by tumor, any headaches are often described as being of a non-specific type and are usually unaccompanied by signs of raised intracranial pressure: observations that can

Table 15.1 Summary of English literature on cerebral rosette-forming glioneuronal tumors

Reference	Case No.	Age/Sex	Neurological examination	Treatment	Complications	Oncological outcome	Follow-up
Komori et al. (2002)	1	25 M	CN4 palsy	B	None	NI	–
	2	59 M	Ataxia	STR + RT	Ataxia, CN6 & CN7 palsies	Died	3 years 9 months
	3	24 F	Ataxia, dysarthria	STR	None	NRP	2 years
	4	18 M	Normal	GTR	None	NRP	2 years
	5	40 F	Normal	GTR	Ataxia, CN6 & CN7 palsies	NRP	6 months
	6	38 F	Normal	GTR	None	NRP	1 year 4 months
	7	39 F	Normal	GTR	CN6 & CN7 palsies	NRP	2 years
	8	27 M	Ataxia	STR	Ataxia, dysphasia, CN6 & CN7 palsies	NRP	13 years 6 months
	9	18 F	Ataxia	STR	Ataxia	NRP	1 year
	10	46 M	Ataxia	STR	CN6 & CN7 palsies	NRP	1 year
Kuchelmeister et al. (1995)	12	28 F	Normal	GTR	NI	NI	–
Albanese et al. (2005)	13	32 F	Dysmetria	GTR	More dysmetria, CN6 & CN7 palsies	NRP	9 months
Adachi et al. (2005)	14	18 F	Ataxia	STR	Mutism, ataxia	NRP	4 years
Jacques et al. (2006)	15	33 F	Nystagmus	"Resected"	None	NRP	20 months
	16	33 F	Ataxia	"Resected"	NI	Recurrence	10 years
	17	42 M	Very mild papilledema	"Resected"	NI	NI	–
Johnson et al. (2006)	18	29 F	Normal	STR	NI	NI	–
Vajtai et al. (2007)	19	16 F	Ataxia	GTR	yes	NI	–
	20	30 F	Normal	GTR	None	NI	–
Pimentel et al. (2008)	21	38 F	Normal	STR	Ataxia	NRP	18 months
	22	51 F	Normal	GTR	None	NI	8 months
Tan et al. (2008)	23	42 M	Normal	B	Diplopia	NRP	2 years
	24	39 F	Normal	STR	None	NRP	6 years 8 months (20 months post-op)
Marhold et al. (2008)	25	20 M	Somnolence, ataxia, dysarthria	STR	Increased ataxia	NRP	30 months
	26	47 F	Hemiparasthesia	GTR	Ataxia	??	23 months
	27	39 F	Normal	STR	None	NI	2 months
	28	35 M	Normal	STR	None	NRP	18 months
Joseph et al. (2009)	29	38 F	Normal	GTR	None	NRP	3 years
	30	24 M	Anisocoria	STR	None	NRP	6 months

(continued)

Table 15.1 (continued)

Reference	Case No.	Age/Sex	Neurological examination	Treatment	Complications	Oncological outcome	Follow-up
Scheithauer et al. (2009)	31	23 M	Visual field defect	B	None	CS	5 years
Kinno et al. (2010)	32	18 M	Ataxia	STR	NI	NI	–
	33	18 F	Ataxia	STR	NI	NI	–
Wang et al. (2009)	34	16 F	NI	B, RT	None	NRP	7 months
Li et al. (2009)	35	27 M	Ataxia	GTR	NI	NI	–
Ghosal et al. (2010)	36	22 M	Partial CN3 palsy	B	NI	NI	–
Shah et al. (2010)	37	10 F	Normal	GTR	Mild nystagmus, diplopia, ataxia	NRP	7 years
	38	41 F	Normal	GTR	None	NRP	6 years
	39	59 F	Normal	STR	NI	NI	–
	40	16 F	Normal	GTR	None	NRP	3 months
	41	17 F	Normal	GTR	None	NRP	18 months
	42	6 F	Hypoacusis	GTR	NI	NI	–
Luan et al. (2010)	43	30 F	Normal	GTR	NI	NI	–
Arai et al. (2010)	44	15 F	Normal	GTR	Dysarthria, ataxia, CN6 & CN7 palsies	NRP	3 years
Frydenburg et al. (2010)	45	29 M	Drowsiness, vomiting	GTR	NI	NI	NI
Sharma et al. (2011)	46	16 F	Normal	B	NI	CS	6 months
	47	17 M	Low conscious state	B	NI	CS	NI
Solis et al. (2011)	48	16 F	Papilledema	STR	None	CS	2 months

NI No information, *NRP* No radiological recurrence or progression, *CS* clinically stable, *B* Biopsy, *STR* sub-total resection, *GTR* gross total resection

be explained only if the growth of the tumor has been so gradual that physiological compensation has been able to occur. Indeed, only two out of the 45 cases in the English literature presented emergently with symptoms and signs of raised intracranial pressure. In the first case, the patient had previously been asymptomatic and was found to have obstructive hydrocephalus from a 9.6 by 4.6 by 6.4 cm tumor containing some fresh blood, suggesting that this patient's presentation had been precipitated by intratumoral hemorrhage rather than by the growth of the tumor (Marhold et al. 2008). In the second case, no prior history of illness is mentioned but there was an acute presentation with obstructive hydrocephalus from a 1.8 by 2.3 by 2.0 cm pineal tumor with extension into the cerebral aqueduct.

Furthermore, follow-up data indicates that the RGNT is probably associated with a good oncological prognosis, even without complete resection. Only three cases of pre-operative tumor progression and one case of post-operative recurrence have been documented in the literature to date and none of these resulted in death (Komori et al. 2002; Jacques et al. 2006; Pimentel et al. 2008). Two of the three examples of progression were included in the series published by Komori et al. (2002): one patient experienced a late but "significant increase" in tumor size over an unknown interval after at least 6 prior years of radiological quiescence and another patient experienced a 50% increase in tumor size over 6 months. In the third case of documented progression, surgery was prompted by the enlargement of a 5 mm tumor by 50% over the course of 1 year (Pimentel et al. 2008). Yet the limitation of the extent of tumor resection by tumor location, multicentricity or brainstem infiltration does not appear to be incompatible with prolonged progression free survival (Komori et al. 2002). Of all reported cases of RGNT, no more than half underwent gross total resection and three merely underwent a biopsy (Table 15.1), yet there has only been one case with a known post-operative recurrence (Jacques et al. 2006). Furthermore, this recurrence was local and came to notice late in the follow-up period, 10 years after surgical resection. The only death that has been reported in the literature on RGNT occurred 4 years after subtotal resection, in the context of post-operative adjuvant radiotherapy and the development of a new ring-enhancing mass, that Komori et al. (2002) hypothesized represented radionecrosis rather than tumor recurrence. As the deceased did not undergo an autopsy, the true cause of death will never be established (Komori et al. 2002). Of note, no case of true RGNT has ever been shown to be capable of dissemination in the cerebrospinal fluid or malignant transformation.

Conservative Strategy: Rationale

The principal arguments in support of conservative treatment for RGNT are the tumor's apparently benign natural history and the risk of neurological complications from surgery. As Table 15.1 shows, there has been a high incidence of significant neurological complications following the subtotal or total resection of RGNT, chief among these being 6th and 7th cranial nerve palsies, gait ataxia, dysmetria and dysarthria. Such morbidity is not unique to the surgery of RGNT. The 6th and 7th cranial nerve nuclei are situated in the brainstem just under the floor of the fourth ventricle and are susceptible to damage during the resection of any fourth ventricular tumor, which then manifests as diplopia and facial paralysis respectively. Gait ataxia, dysmetria and dysarthria represent impairment of the well-recognized role of the cerebellum in the coordination of motor functions of balance, gait, limb movements and speech and are well-recognized sequelae of cerebellar injury. Less easily explained is the report by Adachi et al. (2005) of post-operative mutism following the subtotal resection of a RGNT. "Cerebellar mutism" is a phenomenon that has been reported in upwards of 15% of children following the resection of midline cerebellar tumors and it is generally accompanied by abnormal behaviours and emotional lability (Sherman et al. 2005). Although the pathophysiology is unclear, it has been postulated that trauma to the cerebellar vermis, even if it is only to create a surgical corridor for access to the fourth ventricle, is the anatomical substrate

for cerebellar mutism (Tanriover et al. 2004). Interestingly, careful neurological study over the past decade has revealed that the cerebellum is involved in areas of neurological processing other than pure motor control. It is now apparent that cerebellar injury of various etiologies, including posterior fossa surgery, has the capacity to cause multiple complex cognitive and affective defects: the cerebellar cognitive-affective syndrome (Zuzak et al. 2008). This syndrome, which was originally characterised in adults (Schmahmann and Sherman 1998), has also been extensively documented in long-term survivors of childhood surgery for a variety of posterior fossa tumors (Zuzak et al. 2008) and includes deficits in the core areas of executive function, language and visuo-spatial cognition, as well as affective and personality change ranging from emotional blunting to disinhibition and psychosis. Cerebellar mutism can be seen as an extreme manifestation of the language deficits seen in the cerebellar cognitive-affective syndrome. Clearly, it is possible for a patient who has undergone resection of a classically situated RGNT to be left with iatrogenic functional deficits that can have a major impact on his or her quality of life, employment and interpersonal relationships. As the literature on RGNT is universally lacking in evidence of detailed post-operative neurological and psychological testing, it is conceivable that the incidence of post-operative complications has been considerably under-reported. Many of the symptoms of cerebellar cognitive-affective syndrome may also have been missed in post-operative patients by their misinterpretation as signs of reactive depression.

Conservative Strategy: Recommendations

The minimum elements of any conservative management strategy are tumor biopsy and long-term radiological surveillance. MRI is undoubtedly the superior imaging modality, but while the MRI appearances of RGNT are fairly uniform, there are no pathognomonic or sufficiently distinctive imaging features to permit a confident radiological diagnosis. Hence, there can be no equivalent substitute for surgical biopsy of the tumor and histological confirmation of the diagnosis. If the biopsy succeeds in adequately sampling both pilocytic astrocytoma and neurocytic rosette components, a diagnosis of RGNT may be possible on an intraoperative smear preparation (Ghosal et al. 2010; Kinno et al. 2010), which would have value in lending confidence to a decision made at the time of biopsy as to whether or not to proceed with tumor resection at the same sitting. Regardless of the nature of surgery, regular radiological surveillance with MRI as part of the post-operative follow-up will ensure the early detection and treatment of progressive or recurrent disease in every case. As discussed above, in only four reported cases have RGNT been observed to progress or recur, half of which were preceded by many years of apparent quiescence. There does not seem to have been any clinical, radiological or histological feature to distinguish these four tumors that progressed or recurred from the majority that did not. Therefore all RGNT have to be regarded as capable of unpredictable growth, and it would be prudent to continue regular MRI surveillance for a minimum of 10 years even if the tumor appears to be static.

Once a confirmatory biopsy has been obtained on a RGNT, the need for and extent of any further surgery needs to be considered on an individual basis but a macroscopically complete resection should not be pursued for its own sake. The main risk to the patient of a conservative treatment strategy is the development or progression of obstructive hydrocephalus from unchecked tumor growth. Yet the neurological risks from the attempted extirpation of a RGNT are considerable. A biopsy without any other surgery can be appropriate if the tumor is small, particularly if the ventricular system is uninvolved. On the other hand, it is indisputable that a patient presenting with symptoms and signs of raised intracranial pressure due to RGNT requires emergent surgery. If the resection of a RGNT is considered to be desirable, whether to relieve mass effect from the tumor or to reopen obstructed cerebrospinal fluid pathways, then it is preferable to preserve as much of the cerebellar vermis as possible and to

leave undisturbed any tumor at the interface with the floor of the fourth ventricle in order to minimize the risk of post-operative neurological deficits. As an alternative to tumor resection, it should be borne in mind that the threat of obstructive hydrocephalus may also be effectively relieved by a third ventriculostomy or ventriculoperitoneal shunt, both of which have a lower overall risk of neurological morbidity than a craniotomy for the resection of tumor in and around the fourth ventricle. Indeed, in the series reported by Komori et al. (2002), one of the patients remained asymptomatic for nearly 13 years after undergoing nothing more than a tumor biopsy and insertion of a ventriculoperitoneal shunt. Tan et al. (2008) previously reported on a patient who underwent a biopsy and third ventriculostomy for a RGNT situated in the cerebral aqueduct and subsequent (unpublished) follow-up of this case has revealed ongoing excellent functional status and no evidence of radiological progression out to 5 years after surgery. Of course, the initial election of a conservative treatment strategy does not obviate the possibility of attempting total resection at a later stage, should there be the justification of unexpected and excessive tumor growth.

Due to a lack of data on the efficacy or otherwise of radiotherapy and chemotherapy, these cannot be recommended as standard treatment. There is no information on the use of chemotherapy for the RGNT. Being to all appearances a slow-growing tumor, it is difficult to see any beneficial effect of radiotherapy on the RGNT. In fact, radiotherapy might cause major and potentially life-threatening complications of radionecrosis or malignancy. Admittedly, the former would be an unlikely event if radiotherapy is carefully planned and the latter is so far only a theoretical risk that is suggested by the rare but significant incidence of either malignant transformation to, or the induction of, malignant astrocytoma following the irradiation of other low-grade glial or mixed glioneuronal tumors such as the dysembroplastic neuroepithelial tumor and pilocytic astrocytoma (Ray et al. 2009). So far, there are only two reported cases of RGNTs that have been treated with radiotherapy. The first of these cases died 4 years after subtotal resection and radiotherapy, following the development of a ring-enhancing mass at the original site of disease, which could have represented recurrence, malignant transformation or radionecrosis (Komori et al. 2002). In the second case, there is only very minimal follow-up information available, so the results of the radiotherapy are unknown (Wang et al. 2009).

Conservative Strategy: Caveats

Our recommendations with respect to conservative treatment strategy are based on a modest although steadily growing body of literature, which is limited by a lack of quality long-term follow-up data in the vast majority of cases. The RGNT is currently perceived to be an indolent tumor, with no confirmed reports of malignant behaviour and the majority of cases exhibiting no clinical or radiological progression regardless of their treatment over follow-up periods ranging from 2 months to 13.5 years (Table 15.1). There remains a small possibility that as the recognition and reporting of this relatively novel tumor increases, new information will be revealed that might challenge this perception. Aside from this lingering uncertainty about the natural history of RGNT, the experience of Marhold et al. (2008) raises the concern that the occurrence of spontaneous hemorrhage within large tumors may precipitate acute symptoms of obstructive hydrocephalus and necessitate urgent medical attention. Therefore, factors such as the exact size and location of the tumor, the reliability of the patient's participation in long-term follow-up, and the patient's ease of access to MRI facilities and emergency neurosurgical care must enter into deliberations about the best management of each individual with a diagnosis of RGNT.

In conclusion, the RGNT is a fairly recent addition to the mixed glioneuronal category of the WHO classification of central nervous system tumors. It classically occurs in a midline posterior fossa location and often involves the fourth ventricle, and may thereby either directly or indirectly cause obstructive hydrocephalus. A lack of quality long-term follow-up data precludes any

firm recommendations regarding the optimal treatment of this rare, and probably benign tumour. Based on the information that is currently available in the English medical literature, the neurological risks of gross total surgical resection greatly exceed the risks of tumor progression from subtotal resection. Therefore, in all new cases of RGNT, cautious consideration should be given to the initial adoption of a conservative management strategy, in which the primary aim of surgery is the procurement of tissue for confirmation of the histological diagnosis and the relief of any accompanying threat of obstructive hydrocephalus, rather than the attempted extirpation of tumor. Regardless of the extent of tumor resection, regular radiological follow-up should be conducted for at least a 10-year term to ensure the early detection and treatment of any unexpected tumor growth.

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Part IV

Gangliogliomas

Ganglioneuroma: An Overview

16

Cihangir Erem

Contents

Abstract

Ganglioneuromas (GNs) are rare, benign, well-differentiated, slow-growing tumors that arise from neural crest tissue of the sympathetic nervous system. The effective diagnosis and management of the patient with GN involves the close collaboration of endocrinologists, endocrine surgeons, radiologists, and pathologists. GNs occur most commonly in children and young adults, rarely in adults. They most commonly occur within the posterior mediastinum and retroperitoneum and less commonly in the adrenal medulla. Most GNs are asymptomatic and are discovered incidentally through imaging studies such as ultrasonograpy, computed tomography, and magnetic resonance imaging. Some patients may experience compressive symptoms such as abdominal distention, nonspecific epigastric distress, ptosis, gait disturbance and chest pain. Although GNs are generally considered to be nonsecretory (hormonally inactive), some GNs are endocrinologically active. These tumors may cause some symptoms such as diarrhea, flushing, diaphoresis, cough, abdominal pain, dyspnea, headache, palpitations, tremor, anxiety, hypertension, or virilisation related to secreting hormones. It is difficult to diagnose these tumors precisely by radiologic examination. Radiographically, GNs are relatively homogeneus, encapsulated tumors well-marginated borders. Tumor generally do

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_16, © Springer Science+Business Media Dordrecht 2012

not invade adjacent structures. However, very rarely, malignant GN has been defined in the literature. Preoperative diagnosis of GNs is often difficult and the diagnosis is usually based on histopathological findings after surgical excision of the tumor. In some cases, fine-needle aspiration biopsy has been reported to be useful in the preoperative diagnosis of GNs. Cytologic diagnosis of GNs requires the experienced cytopathologist to be aware of the cytologic features of these tumors. The definitive treatment of choice for GN is usually completed surgical resection. Most tumors can be excised totally. If the tumor is catecholamine secreting, the acute and chronic effects of increased plasma catecholamines should be reversed prior to the surgical excision of the tumor. Combined α-and β-adrenergic blockades are required preoperatively to control high blood pressure and to prevent intraoperative hypertensive crises. Laparoscopic surgery for abdominal GNs may be a better substitute for traditional open surgery due to it is minimal invasive procedure, especially in tumors with a smaller than 6 cm in diameter. On pathologic examination, grossly, GNs are large, well-circumcribed, solid, encapsulated masses of firm consistence with a homogeneous grayish-white cut surface. Microscopically, tumor composed of mature ganglion cells and Schwann's cells in a fibrous stroma. Immature elements (such as neuroblasts), intermediate cells, cellular atypia, mitotic figures, and necrosis are not features of GN. Overall, patients with GN have a favourable prognosis. The recurrence rate is near zero, and postoperative complications are rare. However, life-long clinical and biochemical follow-up patients with hormone-secreting GNs, adrenal composite pheochromocytoma-GN and metastatic disease is essential.

Introduction

Neuroblastomas (NBs), ganglioneuroblastomas (GNBs), and ganglioneuromas (GNs) are tumors of the sympathetic nervous system that arise from embryonal sympathogonia (primordial neural crest cells) (Lonergan et al. 2002). GNs are rare, benign, well-differentiated, slow-growing neoplasms arising from neural crest tissue (Duffy et al. 2005; Erem et al. 2008, 2009). They occur most commonly in children and young adults (Erem et al. 2009; Lonergan et al. 2002) and are discovered in approximately 1 in 100,000 children, with an approximate incidence of 1 case/million/year in the United States for children under the age of 15 year, with the median age at diagnosis being approximately 7 year (Lonergan et al. 2002; Lora et al. 2005). Conversely, GNs rarely occurs in adults. However, they can be found at any age (some cases are of congenital presentation and others are diagnosed in adults).

It is not surprising that GNs may arise anywhere along the paravertebral sympathetic plexus (Chen et al. 2000; Erem et al. 2009). They most commonly occur within the posterior mediastinum (60–80%) and retroperitoneum (32–37.5%) and less commonly in the adrenal medulla (10–15%), the organ of Zuckerkandl, parapharyngeal region, visceral ganglia, or cranial nerve ganglia (Duffy et al. 2005; Erem et al. 2008, 2009; Kamoun et al. 2010). They have been reported very rarely in the orbital space, tongue, mandible, middle ear, heart, urine bladder, uterus, ovary, spermatic cord, prostate, testes, scrotum, gastrointestinal tract, and skin and bone (Al-Daraji and Al-Dawoud 2005; Geoerger et al. 2001; Gültekin et al. 2005; Kamoun et al. 2010; Thway and Fisher 2009). Ganglioneuromatosis affecting any part of gastrointestinal tract has also been described (Nguyen et al. 2006; Thway and Fisher 2009). In a case series of 49 patients with primary GN, Geoerger et al. (2001) reported that of the 49 tumors, 18 were thoracic in the dorsal mediastinum (37.5%), 2 thoracic/abdominal (4%), 18 abdominal, nonadrenal (37.5%), and adrenal tumors (21%). For gender distribution between males and females, the data in the literature vary from a preference of the female gender to no gender difference (Caballero et al. 1986; Geoerger et al. 2001).

Pathology

Grossly, GNs are large, well-circumcribed, solid, encapsulated masses of firm consistence with a homogeneous whitish grey and gelatinous

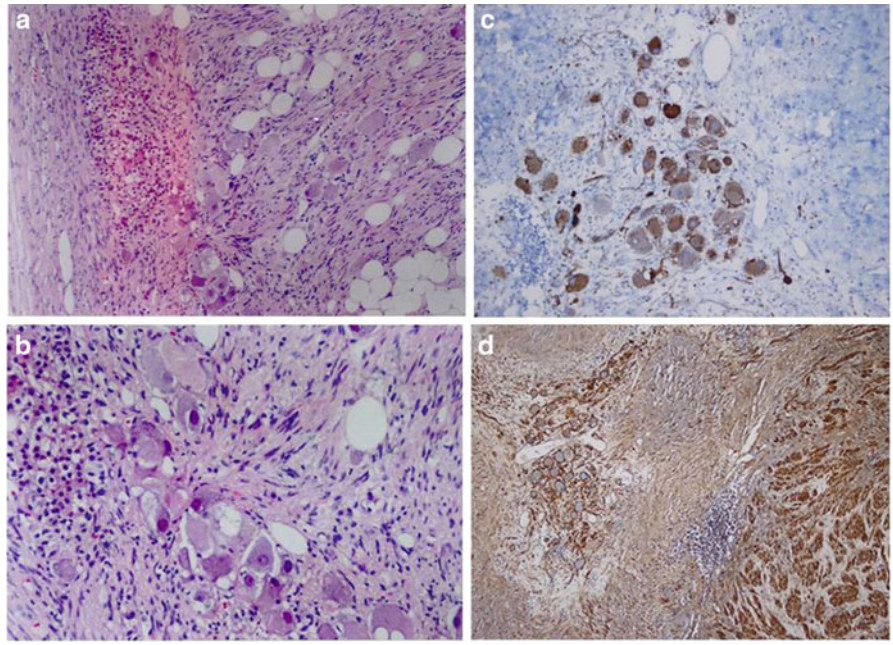

Fig. 16.1 (**a**) Microscopic findings show ganglioneuronal tumor (adrenal ganglioneuroma) neigboring atrophic adrenal cortex. (hematoxylin and eosin staining, original magnification × 100), (**b**) Microscopic findings show scattered mature ganglionic cells in background of spindle shaped cells (Schwann cells), (hematoxylin and eosin staining, original magnification × 400), (**c**) Neoplastic ganglionic cells were positive for synaptophysin (immunoperoxidase staining, × 200), (**d**) Spindle-shaped sustentacular cells (Schwann cells) stained brown for S-100 protein (immunoperoxidase staining, × 100) (Erem 2008, 2009)

appearance in the cut surface without evidence of hemorrhage or necrosis (Duffy et al. 2005; Erem et al. 2008, 2009). They may demonstrate calcifications or a whorled pattern on cut section (Duffy et al. 2005). Microscopically, they are of two subtypes (Fig. 16.1). The mature subtype consists of a spindle cell tumor resembling a neuroblastoma but has fascicles composed of neuritic processes, Schwann cells and perineural cells and show numerous ganglion cells (Erem et al. 2009; Gültekin et al. 2005). Ganglion cells are fully mature cells with abundant cytoplasm, rounded contour, and large nuclei with distinc and prominent nucleoli (Lonergan et al. 2002). The maturing subtype has a similar stroma but with ganglion cells of differing maturation, from fully mature ones to neuroblasts (Erem et al. 2009; Geoerger et al. 2001). Immature elements (such as neuroblasts), intermediate cells, cellular atypia, mitotic figures, and necrosis are not features of GN (Geoerger et al. 2001). On immunohistochemical analysis, they are characterized by reactivity with S-100 and neuronal markers such as NSE and synaptophysin (Erem et al. 2009). In differential diagnosis between adrenal pheochromocytoma (PHEO) and adrenal GN: adrenal PHEO varies in shape and content ranging from solid to cystic and cystosolid and is often accompanied by hemorrhage and necrosis, while adrenal GN is, in most cases, nodular or sublobar in shape with gray or greyish yellow sections and intact capsules (Bing-bing et al. 2009).

Most of the GNs are sporadic but a few are familial (Koch et al. 2002; Tosaka et al. 1999; Leavitt et al. 2000). The molecular pathogenesis of GNs is unknown. Koch et al. (2003) did not detect allelic losses at chromosomal loci 1p34-36 and 17p13 (the p53 gene locus) in a patients with adrenal GN presenting with severe hypertension and diarrhea. In contrast, there are genetic abnormalities in NB and GNB (Lonergan et al. 2002). However, Nguyen et al. (2006) firstly described a

case of isolated intestinal ganglioneuromatosis with a new RET mutation (Gly691Ser) without any other characteristics of multiple endocrine neoplasia 2B.

Diagnosis

Clinical Presentation

The clinical presentation of the most patients with GN is asymptomatic until they reach large size in which case they cause symptoms due to local expansion and pressure on adjacent structures (Gültekin et al. 2005). Clinical signs and symptoms of GNs are nonspecific and related to location site (Erem et al. 2009; Koch et al. 2003). Despite their generally benign nature, GNs may come attention by compressing neighboring structures (Koch et al. 2003). Some patients with GN experience abdominal distention, nonspecific epigastric distress, ptosis, gait disturbance and chest pain.

Although GNs are generally considered to be nonsecretory (hormonally inactive), some GNs are endocrinologically active (Çelik et al. 1996; Erem et al. 2008; Geoerger et al. 2001; Gültekin et al. 2005; Lucas et al. 1994; Tosaka et al. 1999). These tumors may cause some symptoms such as diarrhea, flushing, diaphoresis, cough, abdominal pain, dyspnea, headache, palpitations, tremor, anxiety, hypertension, or virilisation related to secreting hormones (Erem et al. 2008; Geoerger et al. 2001; Gültekin et al. 2005; Lucas et al. 1994). Since GNs may release catecholamines, surgeons should be aware of the possibility of hypertensive crisis during the surgery (Gültekin et al. 2005; Moriwaki et al. 1992). Lucas et al. (1994) reported the increased levels of catecholamines in 4 of 20 patients with GN. Geoerger et al. also (2001) reported increased levels of catecholamines in 39% of patients with GN. Koch et al. (2003) reported the adrenal GN in a patient presenting with severe hypertension and diarrhea. In the case, immunohistochemical investigation of the tumor was positive for vasoactive intestinal peptide, a hormone commonly expressed in ganglion cells. Also we firstly reported a case of dopamine-secreting adrenal GN associated with paroxismal hypertension attacks (Erem et al. 2008). In the present case, we observed a small increase in the urinary levels of both dopamine and its urinary metabolite, homovanillic acid (HVA). This could be explained by the aforementioned mechanism, consisting of a relative insufficiency of dopamine-beta-oxidase, resulting in accumulation of dopamine and a small increase of its metabolites like HVA. Interestingly, the urinary levels of metanephrine and normetanephrine were suppressed. The urinary excretory pattern of dihydroxyphenylalanine (DOPA) metabolites in ganglioneuroma and neuroblastoma varies widely. There is the possibility of a normal excretion of norepinephrine (NE) and its metabolites, including vanillylmandelic acid (VMA), with an elevated excretion of DOPA, dopamine, and their metabolites, including HVA. This can be explained by the high production of DOPA and dopamine from the tumor, with a relative insufficiency of dopamine-beta-hydroxylase, or by abnormal tumor enzymatic systems and altered regulatory mechanisms (Leavitt et al. 2000). Chen et al. (2007) firstly reported a case of malign GN arising from mediastinal mixed germ cell tumor presenting with dry cough, infertility. Moreover, the cases of composite adrenal PHEO and GN (Khan et al. 2010), adrenal GN in a patient with Turner syndrome (Kamoun et al. 2010), diffuse ganglioneuromatosis in small intestine associated with neurofibromatosis type 1 (Thway and Fisher 2009), and composite paraganglioma-GN of the urinary bladder presenting with painless hematuria (Chen et al. 2009) have been reported. Reddy et al. (2007) reported a case of ectopic ACTH-producing paraaortic GN presenting as Cushing's syndrome. Very recently, Dai et al. (2009) reported a case of multiple GNs in the maxillary sinus, liver, adrenal and mediastinum of a 30-years-old female patient. In differential diagnosis between adrenal PHEO and adrenal GN, paroxysmal hypertension attacks is the main symptom of PHEO, while adrenal GN usually are asymptomatic, (Bing-bing et al. 2009; Erem et al. 2008;) An increased catecholamines and their metabolites in 24-h urine is a positive indication in PHEO, while the same tests may be

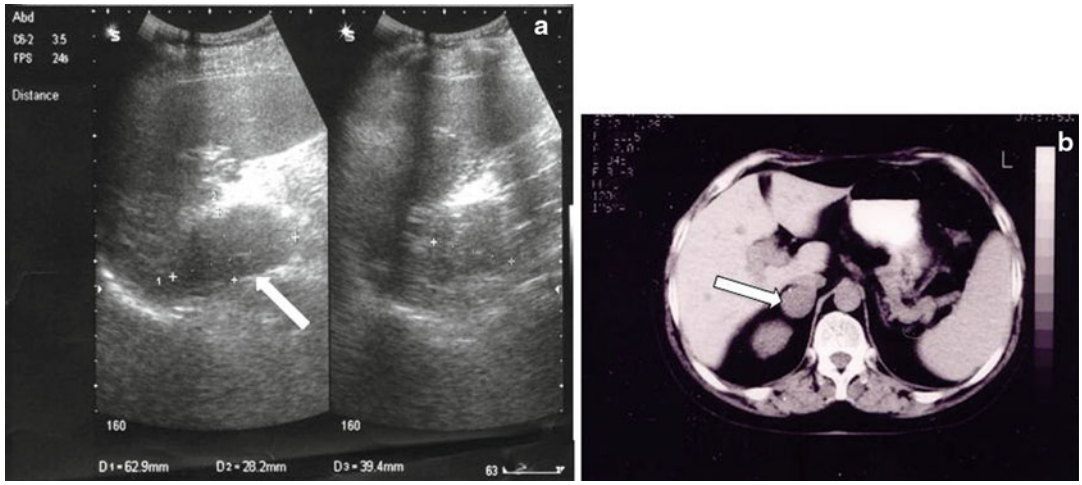

Fig. 16.2 (**a**) Abdominal US shows a heterogeneous hypoechogenic left adrenal ganglioneuroma measuring 63×40×28 mm (*arrow*), (**b**) CT scan shows 30×35 mm right adrenal ganglioneuroma as homogeneous (*arrow*) (Erem 2008, 2009)

negative in GN patients since the tumor cells do not secrete any steroid hormone such as catecholamine (Bing-bing et al. 2009).

Localization Studies

Radiologic examination has no diagnostic value in most cases (Gültekin et al. 2005). As imaging procedures such as ultrasonography (US) and computed tomography (CT) have become more widely performed, the number of GNs found incidentally has increased (Chen et al. 2000; Yamaguchi et al. 2006). However, it is difficult to diagnose these tumors precisely as GN preoperatively. Radiographically, GNs are relatively homogeneus, encapsulated tumors with well-marginated borders (Lora et al. 2005). Tumor generally do not invade adjacent structures (Geoerger et al. 2001; Lora et al. 2005). However, very rarely, malignant GN was defined by Chen et al. (2007). Corcerning the imaging characteristics of adrenal GN, US shows a homogeneous, hypoechogenic solid mass with well-defined borders (Fig. 16.2a). However, US is not useful for determining the quality of the adrenal mass (Lonergan et al. 2002; Lucas et al. 1994).

On CT imaging, GNs appear as well-circumscribed homogeneous masses with low attenuation (hypodense) than that of muscle (Duffy et al. 2005; Erem et al. 2009; Lora et al. 2005) (Fig. 16.2b). In some cases, the tumor may be heterogeneous. At CT, calcification has been reported in approximately 20–60% of GN cases (Duffy et al. 2005; Ichikawa et al. 1996; Lonergan et al. 2002) and is typically punctate, fine and speckled as opposed to the coarse pattern seen with NBs and GNBs (Duffy et al. 2005; Ichikawa et al. 1996). In differential diagnosis between adrenal PHEO and adrenal GN: a significant enhancement of CT scan is frequently seen in adrenal PHEO, while the most significant imaging feature adrenal GN is a less than 40 HU on CT (Bing-bing et al. 2009).

On magnetic resonance imaging (MRI), GNs appear as homogeneous masses with low and, less commonly intermediate signal intensity on T1-weighted images (Duffy et al. 2005; Erem et al. 2009; Ichikawa et al. 1996; Zhang et al. 2001) (Fig. 16.3a). In contrast, on T2-weighted images, the signal intensity is usually heterogeneous and either intermediate to high or markedly high than that of liver (Fig. 16.3b, d) (Duffy et al. 2005; Ichikawa et al. 1996; Zhang et al. 2001). Several reports indicate that relatively high signal

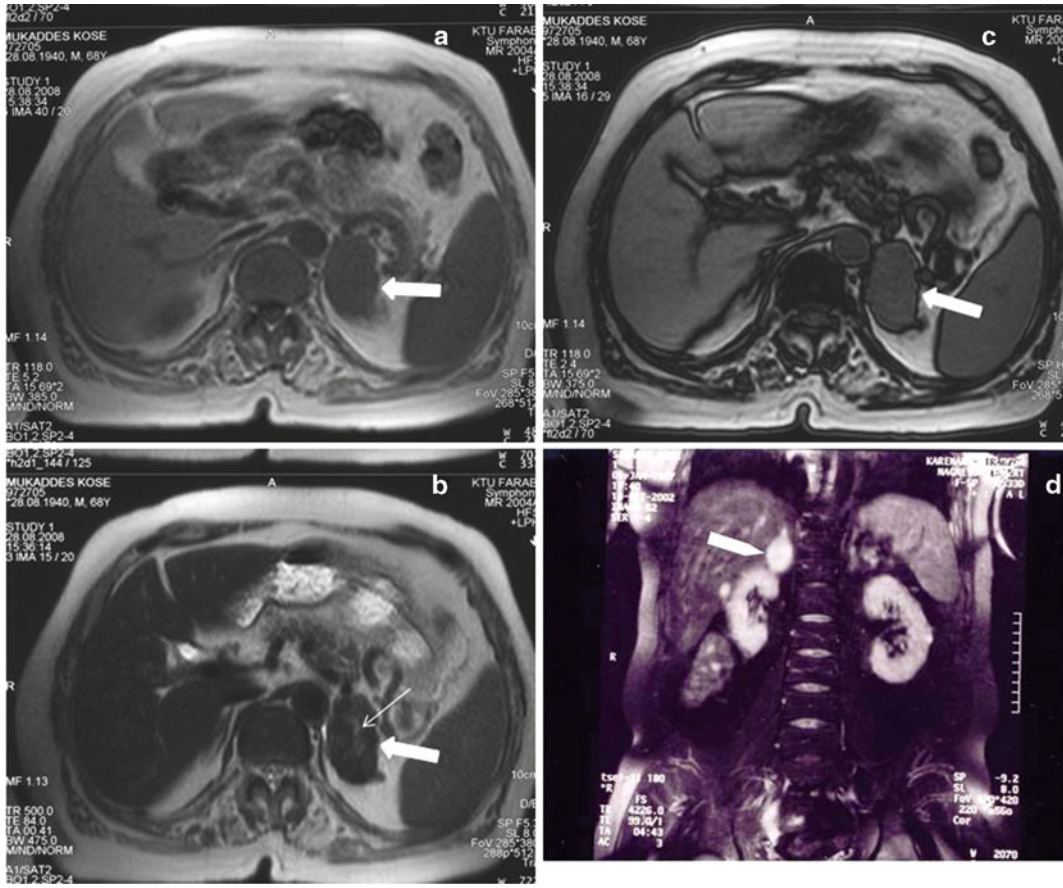

Fig. 16.3 (**a**) Transverse T1-weighted MRI shows a oval, slightly lobulated left adrenal ganglioneuroma that measures 60×45 mm (*arrow*). The mass is homogeneous, with signal intensity less than that of liver (hypointense), (**b**) Transverse T_2-weighted MRI scan demonstrating oval heterogeneous mass (*thick arrow*) with slightly high signal intensity greater than that of liver and with central crescent-shaped calcifications in left adrenal ganglioneuroma (slightly hyperintensity) (*thin arrow*), (**c**) Out-of-phase MRI no showing significant signal loss in the lesion when compared with in-phase MRI (*arrow*), (**d**) Coronal T_2-weighted magnetic resonance image of adrenal mass demonstrated on CT scan in Fig. 16.2, round homogeneous tumor with hyperintensity signal (high signal intensity) on the pole of the right kidney (*right* adrenal ganglioneuroma) (*arrow*) (Erem 2008, 2009)

intensity on T2-weighted images correlates with GN (Fig. 16.3d); the apperance is presumed to be caused by a combination of abundant myxoid stroma and relatively low amounts of ganglion cells (Duffy et al. 2005; Lonergan et al. 2002; Zhang et al. 2001). MRI enhancement varies from mild to marked (Duffy et al. 2005; Ichikawa et al. 1996; Lonergan et al. 2002; Zhang et al. 2001). Early enhancement at dynamic MRI is not typically seen in GN. GN does appear to accumulate contrast material over time. However, so delayed images may reveal increasing enhancement (Duffy et al. 2005; Lonergan et al. 2002). Ring enhancement may correspond to the capsule of the tumor (Duffy et al. 2005; Zhang et al. 2001). GNs reveal no absolute change in signal intensity on chemical shift imaging (out-of-phase MRI) (Fig. 16.3c) (Erem et al. 2009). For the pure GNs, heterogeneous high signal intensity on T2-weighted MR images may be helpful in the differential diagnosis of other masses that have high signal intensity on T2-weighted images

(Erem et al. 2009). However, more studies are needed especially for the mixed pathologies such as the GN-PHEO combination (Gültekin et al. 2005).

Metaiodobenzylguanidine (MIBG) is a guanidine derivate that resembles NE and is selectively accumulated in neurosecretory granules. In general, MIBG positivity is mainly determined by an active sodium-and chloride-dependent process performed in the cell membrane NE transporter, called uptake 1 (Koch et al. 2003). Although GNs do not concentrate the radionucleotide MIBG ([^{131}I])-or ([^{131}IMIBG]) as well as neuroblastomas or PHEOs, approximately 60% of GN cases may show some uptake with MIBG (Lora et al. 2005). As previously noted, most controversial in the literature are the data on metabolic activity (Geoerger et al. 2001). The uptake in GN was indistinguishable from those of other neural crest-associated tumors. Geoerger et al. reported that 57% of all primary GNs demonstrated detectable MIBG uptake, even in very small tumors (Geoerger et al. 2001). In this study, levels of catecholamines in plasma and/or urine were increased in 39%. Although metabolically active tumors were described as immature GNs in their grade of differentiation, and both mature GNs were metabolically inactive, increased levels of catecholamines and MIBG uptake do not exclude the diagnosis of GN and vice versa (Geoerger et al. 2001). In addition, the lower rate of MIBG uptake in GNs may be due to their histological composition (Koch et al. 2003). In differential diagnosis between adrenal PHEO and adrenal GN: ^{131}IMIBG imaging is highly sensitive (100%) and specific (95%) for PHEO, but not for GN (Bing-bing et al. 2009).

GNs are composed of ganglion cells, neurites, Schwann cells, and fibrous tissue. Immature elements, such as neuroblasts, which can easily take up MIBG, are not part of a mature GN (Koch et al. 2003). Therefore, although some clinical characteristics may suggest the diagnosis of GN, there is no single relible imaging modality or biochemical test that will accurately differentiate GN from NB or PHEO (Koch et al. 2003; Lora et al. 2005). Moreover, GNs have been shown to have high concentrations of somatostatin (higher than those in NBs or PHEO) (Kogner et al. 1997), whether this feature can assist in somatostatin receptor scintigraphy remains to be assessed (Ilias et al. 2005). In conclusion, radiological studies are no diagnostic value in most cases with GN. Unless typical CT and/or MRI findings are present, diagnosis of GNs is difficult radiologically (Gültekin et al. 2005). Although GN tends to be a more homogeneous tumor than NB or GNB, it is not possible at imaging evaluation to discriminate among these 3 tumors (Lonergan et al. 2002).

Fine-Needle Aspiration Biopsy (FNAB)

Preoperative diagnosis of GNs is often difficult and the diagnosis is usually based on histopathological findings after surgical excision of the tumor (Domanski 2005; Erem et al. 2008, 2009; Gültekin et al. 2005). In some cases, FNAB has been reported to be useful in the preoperative diagnosis of GNs. Because of the rarity of GNs, few reports describing FNAB features of this rare tumor exist in English literature (Domanski 2005). In these reports, the cytologic features of GN have been described as rather characteristic, provided that a smear contains both large, differentiated ganglion cells and spindle shaped cells (Schwann cells) on a background of loose fibrous tissue (Domanski 2005; Jain et al. 1999; Yen and Cobb 1998). FNAB smears of GNs must be differentiated from other lesions (NB, GNB, and malign neuroectodermal tumor) that yield aspirates with spindle cells. FNAB smears of GNB show both elements resembling benign GN (e.g. mature ganglion cells, Schwann cells) and immature cells, small blue round neuroblasts frequently forming scattered Homer-Wright rosettes on a background at loose connective tissue (Domanski 2005). Domanski (2005) pointed out that the morphology of FNAB smears from benign nerve sheath tumors neurilemmomas and neurofibromas may be very similar to that of GNs in cases of suboptimal sampling and in absence of differentiated ganglion cells. Most neurofibromas are widely distributed superficial or subcutaneous tumor, neurilemmomas are intramuscular or

deeply subcutaneous in the extremities or the head and neck areas (Domanski 2005). Also, neurofibromas are distinguished by the presence of scattered most cells (Yen and Cobb 1998). Finally, cytologic diagnosis of GNs requires the experienced cytopathologist to be aware of the cytologic features of these tumors. A correct diagnosis by FNAB smears is required clinical data and use of ancillary methods (Domanski 2005). FNAB of a catecholamine-secreting adrenal GN may precipitate a hypertensive crisis, retroperitoneal hemorrhage, and death. Therefore, all patients with incidental adrenal mass should undergo hormonal evaluation for catecholamine-secreting adrenal GN before proceeding to FNAB of the adrenal mass.

Treatment and Prognosis

To our knowledge, no medical treatment for GN has been described. The definitive treatment of choice for GN is usually completed surgical resection for localized, nonsecretory, or nonmetastatic tumors when possible (Lonergan et al. 2002; Gültekin et al. 2005; Reddy et al. 2007). Complet resection ensures thorough sampling of the tumor, such that a confident diagnosis of GN can be made (Lonergan et al. 2002). Preoperative or postoperative chemotherapy or radiotherapy have no value in the treatment (Gültekin et al. 2005) and such modalities used unnecessarily for these patients not only cause side effects but also may be associated with secondary malignancies at the tumor localization after radiotherapy (Gültekin et al. 2005). If the tumor is catecholamine secreting, the acute and chronic effects of increased plasma catecholamines should be reversed prior to the surgical excision of the tumor. Combined α-and β-adrenergic blockades are required preoperatively to control high blood pressure and to prevent intraoperative hypertensive crises. An α-adrenergic blockade (e.g., phenoxybenzamine or doxazosin) should be started at least 7 days preoperatively to allow for expansion of the contracted blood volume. A liberal salt diet is advised during the preoperative period. Once adequate α-adrenergic blockade is achieved, β-adrenergic blockade (e.g., propranolol or labetalol) is initiated (e.g., at least 3 days preoperatively).

Laparoscopic surgery for abdominal GNs may be a better substitute for traditional open surgery due to it is minimal invasive procedure. Laparoscopy may be perform through a transperitoneal or retroperitoneal approach (Bing-bing et al. 2009). For example, Bing-bing et al. (2009) have reported that since most adrenal GNs are benign tumors and surrounded by many great vessels, a better choice for them is a transperitoneal laparoscopic surgery with clearer anatomical landmarks and much less injury of the great vessels. But, with a shorter convalescent period of gastrointestinal function and much less injury to abdominal organs, laparoscopic neoplasmotomy through a retroperitoneal rather than transperitoneal approach may be the first choice for smaller adrenal GNs with a smooth periphery and completely intact envelope. However, the indication of laparoscopic surgery for adrenal mass is somewhat doubtful. Because the likelihood of adrenal cancer has been revealed to increase in adrenal lesions with a diameter greater than 6 cm, a recent National Institutes at Health State-of-the-Science Statement recommended that nonsecretory adrenal incidentalomas larger than 6 cm or with suspicious features of malignancy on imaging procedures should be treated using adrenalectomy with open surgery because of the increased prevalence of malignancy (Yamaguchi et al. 2006).

Overall, patients with GN have a favourable prognosis (Reddy et al. 2007). The recurrence rate for GN is near zero, and postoperative complications are rare. However, malignant transformation of GN into malignant peripheral nerve sheath tumors (Ghali et al. 1992) or NBs (Kulkarni et al. 1998) have been reported. Therefore, GNs should be surgically excised completely and should be followed for a long period after the operation (Tosaka et al. 1999). In addition, lifelong clinical and biochemical follow-up patients with hormone-secreting GNs and adrenal composite PHEO-GN is essential.

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Ganglioglioma, mTOR Activation, and Epileptogenesis

17

Jelte Helferrich and Peter B. Crino

Contents

Abstract

Gangliogliomas are rare brain tumors but represent the most common neoplasm associated with medically intractable epilepsy. These tumors, which are more often seen in younger patients, are composed of a neuronal and a glial component. Although relatively benign, malignant transformation is sometimes seen in the glial component. The molecular mechanisms behind this transformation as well as those involved in epileptogenesis in gangliogliomas remain unclear. In the past years the mTOR pathway has gained more interest as an important molecular pathway in different forms of cancer. Recently a role for mTOR in the development of epilepsy has been proposed. Because mTOR also seems to be activated in gangliogliomas, it may be important for tumorigenesis and epileptogenesis in these tumors. We will summarize the current knowledge about gangliogliomas, with a focus on mTOR activation and epileptogenesis.

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Introduction

The first description of a ganglioglioma dates back to 1930, when Courville described this brain tumor with mixed neuronal and glial elements (Courville 1930). Since then there have been a significant advances in knowledge regarding

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_17,

the molecular mechanisms in tumorigenesis and epileptogenesis in these rare neoplasms. Gangliogliomas are usually relatively benign tumors, with a WHO grade I. They only represent 1.3% of all brain tumors, but are more common in children, representing 5% of the brain tumors in this age group. The average age of diagnosis varies between 10 and 22 in different study populations. A slightly higher prevalence in males compared to females is found in most studies. Most gangliogliomas are located in the temporal lobe, representing 71.3% of the tumors in a study group of 195 patients with gangliogliomas. Other tumor locations include the frontal lobe, occipital lobe, parietal lobe, cerebellum and spinal cord or, in rarer cases, the pituitary gland, pineal gland, hypothalamus and brainstem (Morris et al. 1998).

The most common presenting symptom of gangliogliomas is medically intractable epilepsy. A long seizure history of up to 25 years prior to diagnosis is often seen. A focal seizure onset is almost always present and can be observed through electroencephalography. Complex partial seizures are commonly seen in patients with temporal lobe gangliogliomas as compared to patients with extratemporal lobe gangliogliomas, while secondary generalized seizures are more common in the latter group. While other tumor-related symptoms like dysphasia, visual field defects, dysarthria, ataxia and facial weakness are occasionally seen in gangliogliomas, focal seizures remain the most important presenting feature of these brain tumors (Blumke and Wiestler 2002).

Neuroimaging studies such as MRI and CT are used to localize ganglioglioma. MRI is more effective than CT in tumor detection and may show contrast enhancement in the tumor area. Other MRI findings may include cystic change and cerebral edema. While the main purpose of MRI is to detect the tumor and determine its location, a useful diagnostic imaging technique may be ^{11}C-methinine PET, showing an increased C-methinine uptake in gangliogliomas as compared to cortical dysplasia (Phi et al. 2010). The final diagnosis of gangliogliomas, however, is be made after histological analysis.

Histology

Gangliogliomas are composed of a combination of neuronal and glial elements, with a histopathological spectrum varying from tumors with a predominant neuronal phenotype to those with a prominent glial element (Fig. 17.1; Blumcke and Wiestler 2002; Wolf et al. 1994). The neuronal component consists of large, occasionally multinucleated or so called "atypical" ganglion cells (Fig.17.1a–e). These ganglion cells not only have an abnormal size and shape, but are also characterized by a loss of cytoarchitectural organization, abnormal location and a clustered appearance. Furthermore, the neuronal component can be identified by the demonstration of perimembranous aggregated Nissl substance, as well as through immunohistochemical staining for neuronal markers such as synaptophysin, neurofilament, and NeuN. The glial component consists of a spectrum of glial cells showing great variability. This component can be distinguished from the neuronal cells by staining for glial markers like glial fibrillary acid protein (GFAP) and S-100 (Blumcke and Wiestler 2002; Wolf et al. 1994).

The glial component is considered the cellular origin and determinant of neoplastic activity. Neoplastic transformation of a ganglioglioma is detected by positive immunostaining for the mitotic and cell proliferative markers Ki67, PNCA and survivin (Rousseau et al. 2006). The percentage of Ki67 and survivin positive cells, however, usually remains low (~1%), reflecting the relatively benign course of gangliogliomas. This is further reflected by the low WHO grade (grade I) observed in the vast majority of gangliogliomas. Transformation to an anaplastic ganglioglioma (WHO grade III) is occasionally seen and is associated with increased proliferation and cellularity, as well as higher percentages of Ki67 and survivin-positive cells and loss of CD34-staining. Furthermore, necrosis and microvascular proliferates may be seen in anaplastic gangliogliomas. Malignant transformation and tumor recurrence more often occur in older ganglioglioma patients (Blumcke and Wiestler 2002).

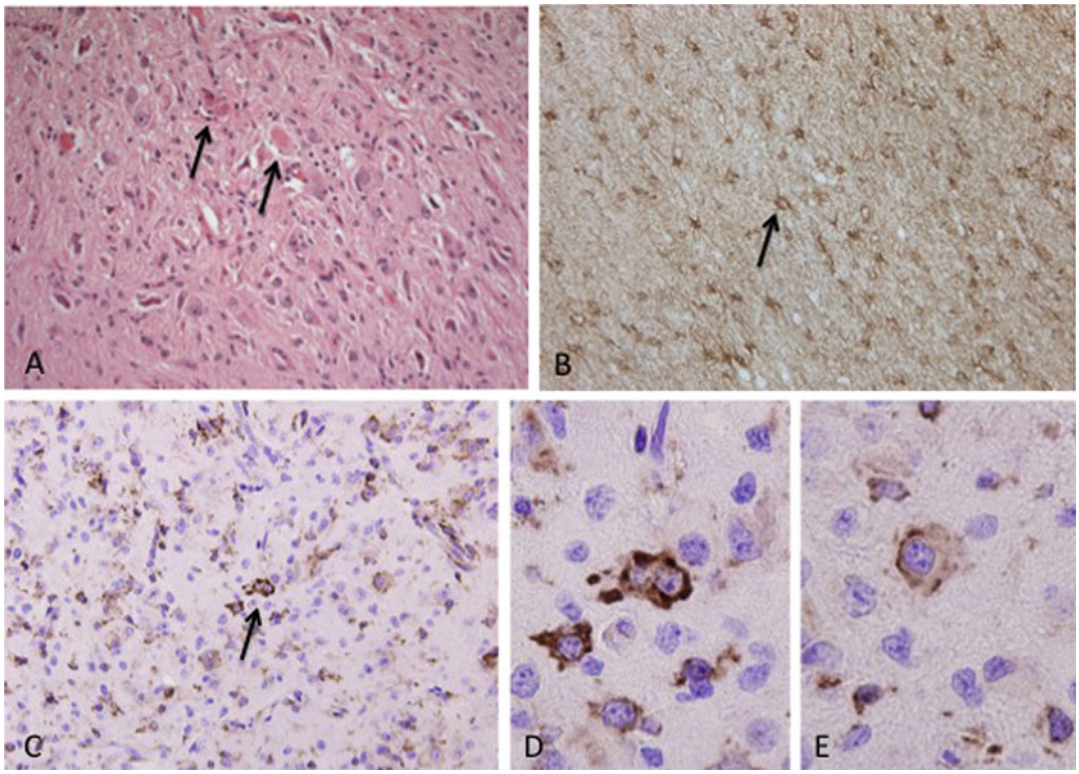

Fig. 17.1 (**a**) Hematoxylin and eosin stain demonstrating the cellular elements of ganglioglioma including eosinophilic atypical gangion cells (*arrows*). (**b**) glial fibrillary acidic protein (GFAP) staining of astrocytes (*arrow*) in ganglioglioma. (**c**–**e**), low and higher magnification photographs of phosphorylated S6 protein, a downstream mTORc1 substrate, in ganglioglioma (*arrow*) (Panels (**c**–**e**) courtesy of E. Aronica, Acedemic Medical Center, The Netherlands)

The underlying mechanism of malignant transformation remains unknown. The $BRAF^{V600E}$ mutation, characterized by an exchange of valine by glutamate at a mutational hotspot at amino acid 600, activates the RAS/RAF/MEK/ERK pathway (Schindler et al. 2011). This mutation is frequently found in gangliogliomas and may be associated with malignant transformation. Mutations in Isocitrate Dehydrogenase 1 are also related to a higher grade of malignancy and may distinguish gangliogliomas from higher grade gliomas (Horbinski et al. 2011).

The variability in histopathological phenotype and the heterogeneity of the two components of gangliogliomas can make ganglioglioma a diagnostic challenge. The differential diagnosis includes pilocytic astrocytomas, astrocytomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumors, pleiomorphic xanthoastrocytomas, cortical dysplasia and gangliocytomas. The expression of CD34 in the neuronal component of gangliogliomas distinguishes it from most of these tumors. Other distinguishing features include the coexistence of neuronal and glial cells, the low proliferation grade and low MAP2 staining in the glial component. Differentiating gangliogliomas from cortical dysplasia remains difficult and is further complicated by the sometimes observed coexistence of cortical dysplasia with gangliogliomas.

Molecular Pathogenesis

Although the cause of gangliogliomas remains unknown, an origin of a dysplastic precursor malformation has been proposed. This theory is supported by its relatively benign behaviour and

the glioneuronal phenotype as well as the expression of the stem cell markers CD34 and nestin (Samadani et al. 2007; Duggal and Hammond 2002). Therefore, ganglioglioma is sometimes considered a malformation of cortical development, along with disorders like focal cortical dysplasia type II (FCDII) and tubers in Tuberous Sclerosis Complex (TSC). However, the potential for malignant transformation is clearly a distinguishing feature of ganglioglioma.

A gene expression array analysis, comparing ganglioglioma tissue with the adjacent cortex, revealed an altered expression of 94 genes. The LIM-domain-binding 2 (LDB2) transcript, critical for brain development during embryogenesis, was one of the genes with a great reduction in expression (Aronica et al. 2008). This finding agrees with the proposed origin from an aberrant glioneural precursor. Another gene expression profile analysis comparing ganglioglioma tissue to epileptic control brains revealed an increased expression of genes important for inflammation along with a reduced expression of genes key to synaptic transmission (Fassunke et al. 2008). Different pathways may be associated with the development of gangliogliomas and the epileptogenesis in gangliogliomas. Although no mutations in p53, EGFR or PTEN have been found in gangliogliomas (Becker et al. 2006), activation of the PI3K-Akt-mTOR pathway has been shown in these tumors. Interestingly, there is a single case report of a ganglioglioma seen in association with Peutz-Jeghers syndrome, in association with a LKB1 mutation (De Tommasi et al. 2008). LKB is an important upstream marker of mTOR activation (Fig. 17.2). We will focus here on the mTOR pathway and its role in the tumorigenesis and epileptogenesis of gangliogliomas.

mTOR Pathway Activation and a Role in Gangliogliomas

The mammalian target of rapamycin (mTOR) ser-threonine kinase is a subunit of two complexes, mTOR complex 1 (mTORc1) and mTORc2 (Zoncu et al. 2011; LaPlante and Sabatini 2009). mTORc1 is regulated by the availability of nutrients and growth factors as well as energy and stress levels in the cell. An important mechanism by which this regulation is facilitated includes activation of mTORc1 by the PI3K-Akt pathway and LKB1-AMPK-pathway. mTORc1 promotes cell growth and proliferation and inhibits autophagy by different mechanisms. These include the phosphorylation of S6kinase (S6K) and 4-elongation factor binding protein-1 (4EBP1). S6K phosphorylates and activates S6, while the phosphorylation of 4EBP1 causes a release of inhibition of eIF4e. Less is known about mTORc2, but this complex seems to be important for cell survival through activation of Akt. Furthermore, mTORc2 has a role in metabolism, proliferation and cytoskeletal organization Although knowledge in the field of mTORc2 signalling and its importance in different cellular processes is growing, we will focus on mTORc1 signaling, because the studies that have been done with gangliogliomas focussed on this pathway.

Considering its important role in proliferation and cell growth, it is no surprise that hyperactivation of the mTOR pathway is associated with different forms of cancer, including malignant gliomas. Other syndromes associated with mTOR activation include various malformations of cortical development, such as FCDII, TSC (Baybis et al 2004), and gangliogliomas (Samadani et al. 2007; Boer et al. 2010). In TSC, hyperactivation of the mTOR pathway is caused by a mutation in one of the two TSC genes, while the mechanism underlying mTOR activation in FCDII is unknown. The histological similarities between atypical ganglion cells in ganglioglioma and giant cells observed in tubers suggests a common mechanism for mTOR activation in these entities. Although polymorphisms in the *TSC2* gene have been shown in gangliogliomas, no functional mutations in this gene have been found, so the cause of mTOR activation in gangliogliomas is yet to be determined (Becker et al. 2001).

mTOR activation in gangliogliomas has been shown by the increased expression of different phosphorylated components of the mTOR

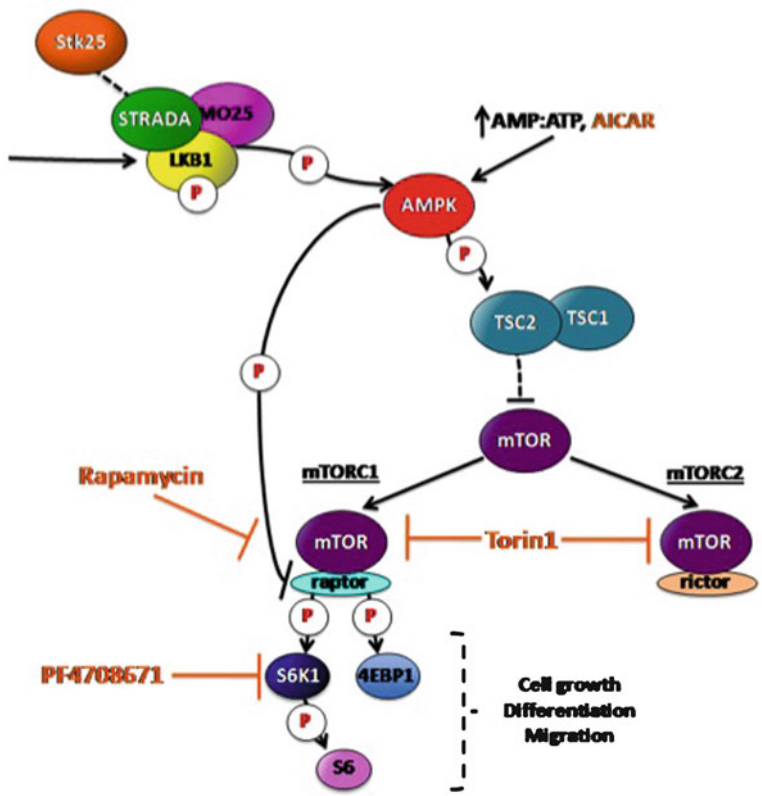

Fig. 17.2 Schematic of the mTOR pathway. Note upstream reguators LKB1, AMPK, TSC1, and TSC2. Not shown are inputs from the cell surface via PI3K and Akt

pathway, including the above mentioned 4EBP1, eIF4e, S6K and ribosomal protein S6 (Fig. 17.1; Samadani et al. 2007; Boer et al. 2010). Furthermore a high expression of ezrin, radixin, and moezin is seen in gangliogliomas. These proteins have been implicated in cell migration in TSC and have an important role in cytoskeletal organization (Lamb et al. 2000). Interestingly all of these markers of mTOR activation were only observed in the neuronal component. This is in line with the almost exclusive staining for mTOR markers in giant cells in TSC and balloon cells in FCDII, which suggests common molecular mechanisms underlying tumorigenesis in ganglioglioma. The malignant transformation that distinguishes ganglioglioma from TSC and FCDII, however, remains unexplained by mTOR signalling.

mTOR Pathway and Epileptogenesis in Ganglioglioma

Gangliogliomas, TSC, and FCDII are all associated with mTOR activation and medically intractable epilepsy, which raises the possibility for a role for mTOR signalling in epileptogenesis. Involvement of mTOR signalling in epileptogenesis was implicated in a rat model of temporal lobe epilepsy. A biphasic mTOR activation was seen after a kainate-induced status epilepticus and this activation was blocked by rapamycin treatment, correlating with decreased mossy fiber sprouting and a lower chance of development of spontaneous epilepsy (Zeng et al. 2010).

TSC is often seen as a model system for other diseases, because of its association with epilepsy and the fact that the mechanism of

mTOR activation is known. In mouse models of TSC, early rapamycin treatment prevented the development of epilepsy, while rapamycin treatment after seizure onset reduced seizure frequency. Considering these studies and the histological similarities between tubers and gangliogliomas, mTOR signalling may contribute to epileptogenesis in gangliogliomas. Furthermore mTOR inhibition may provide a possible treatment of both epilepsy and the tumor itself. However, mTOR signalling in epilepsy is still a developing research field and more needs to be investigated before the clinical appliance of mTOR inhibitors for epilepsy can be initiated (Wong 2008).

Although mTOR activation could provide a possible mechanism of epileptogenesis in gangliogliomas, other mechanisms may cooperate with or cause the medically intractable epilepsy commonly associated with gangliogliomas. Developmental alterations in the balance between excitation and inhibition were suggested by several studies, while an inflammatory response may also have a role in epileptogenesis. Another possibility is that the disturbance of the brain circuitry has a role in the development of epilepsy, as is seen in cortical dysplasia. It is likely that a combination of this network disturbance with different molecular mechanisms lies at the basis of epileptogenesis in gangliogliomas. Another question remains the actual focus of epilepsy in gangliogliomas. There is evidence suggesting that the perilesional region may contribute to epiletogenesis or may in fact serve as the actual epileptic focus. Indeed, in glioma, the regions surrounding the tumor has the highest epileptogenic potential. It may be important to determine what the actual focus of epilepsy in gangliogliomas is, for the extent of surgical removal (Yang et al. 2011).

Treatment Options

Although seizures are typically intractable to anti-epileptic drugs, tumor resection is associated with good clinical and seizure outcome. Tumor resection is curative for both tumor progression and epilepsy in most patients. Even the group that is not completely cured by surgery still has a noticeable reduction in seizure frequency. An early resection is preferable, because an improved clinical seizure control after surgery and reduced risk of malignant progression are achieved. Furthermore there is a shorter period of adverse medical and psychosocial impact associated with medically intractable seizures (Yang et al. 2011; Mehta 2010). A gross total resection is associated with higher rates of local control and survival, but can be a surgical challenge, due to an unclear boundary between the tumor and the functional brain surrounding it. If subtotal resection is achieved, adjuvant radiotherapy has a significant positive effect Because of the possible role of mTOR in tumorigenesis and epileptogenesis in gangliogliomas, mTOR inhibition may be a promising treatment. Adjuvant treatment with mTOR inhibitors could especially be helpful in the treatment of patients, in whom tumor resection is not curative.

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18 Gangliogliomas and Other Low Grade Neuronal Neoplasms of the Central Nervous System: Diagnosis, Treatment, and Prognosis

Douglas C. Miller and Wayne C. Paullus

Contents

Abstract

Glioneuronal tumors of the brain and spinal cord are relatively uncommon but highly interesting neoplasms, whose very existence provides support for current stem cell theories regarding the origins of central nervous system tumors. This chapter describes the clinical presentations, neuroradiological features, and diagnostic pathological characteristics of gangliogliomas, parenchymal neurocytic tumors, and other intra-parenchymal (not intraventricular) neuronal neoplasms of the CNS, together with summaries of current treatment options. Gangliogliomas are tumors composed of mixtures of glial cells, usually astrocytoma cells, with large neoplastic neurons (ganglion cells); the majority are slow-growing, indolent neoplasms which respond best to neurosurgical extirpation. Pleiomorphic Xanthoastrocytomas, subependymal giant cell tumors, and some anaplastic large cell gliomas all may exhibit co-expression of glial and neuronal antigens in the same cells. Parenchymal neurocytic tumors mostly resemble oligodendrogliomas, but like their intraventricular counterparts have immunoreactivity for synaptophysin, neurofilament protein, and other neuronal antigens. These are more controversial entities, with a range of appearances (some have ganglion cells, some lack astrocytic elements whereas in others they are

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_18,

present, and many have anaplastic changes such as vascular hyperplasia, necrosis, and high mitotic rates).

Introduction

The majority of intrinsic, neuroepithelial tumors of the brain and spinal cord are classified as gliomas, including astrocytomas, oligodendrogliomas, and ependymomas, and their variants, and are conventionally regarded as arising from glial cells in the relevant lineages. Tumors of neuronal origin or differentiation, or which have mixed glial and neuronal elements, provoke interest because mature neuronal cells are post-mitotic and so it is conceptually difficult to have neoplastic cells with the characteristics of mature neurons. (This necessarily excludes primitive or embryonal tumors with neuroblastic elements, which do not produce such conceptual problems). Nevertheless, it has long been well-recognized that some tumors of the brain and spinal cord consist of, or contain, neoplastic cells with relatively mature neuronal characteristics. These tumors, the best known of which are gangliogliomas and gangliocytomas, but which also include tumors of smaller neuronal cells which generally fit in the broad category of neurocytomatous cells, are usually low grade malignancies which are more common in younger patients and are often associated clinically with epilepsy. Their existence has helped to promote areas of research suggesting that neuroepithelial CNS tumors in fact arise from tumor stem cells or progenitor cells which retain considerable developmental plasticity and can give rise to neoplastic cells with the characteristics of neurons, particular classes of glia, or both. This chapter will review the clinical and pathological diagnostic features of these tumors, particularly but not exclusively gangliogliomas, the current state of treatment for them, and the prognosis of the patients who have them. An accompanying chapter (in volume 6 of this series) has described the special features of neuropathological diagnosis of gangliogliomas, particularly in the spinal cord where there are, perhaps, special difficulties in such diagnosis.

Brain Gangliogliomas

Clinical Presentation

Gangliogliomas are (almost always) slow-growing, low grade tumors which are best known to arise in the temporal lobes, where they frequently present clinically as a cause of complex partial seizures. Those examples which occur in other cerebral lobes, or deeper in cerebral tissues, in the brainstem, or cerebellum and spinal cord, present clinically by virtue of their mass effect and by the focal neurological deficits they produce. In this they are not different from any other CNS neoplasms, except for the usual insidious onset and slow progression of symptoms other than epilepsy.

Gangliogliomas lack distinctive features by computed tomography (CT) although they may, like other low grade neuroepithelial tumors, contain calcium deposits which are easily seen when present on CT. In MRI images they may be solid or cystic, the latter examples often having a solid mural nodule at one border of the cyst (Castillo et al. 1990; Adachi and Yagishita 2008; Im et al. 2002) (Fig. 18.1a–b). They often do not enhance with intravenous gadolinium administration, but some do have some mild enhancement in a diffuse or patchy fashion without any ring appearance (Fig. 18.1b). Conventionally they are said to be sharply circumscribed or bordered against adjacent normal brain tissues by MRI, but some are more infiltrative and are indistinguishable by MRI from diffuse gliomas (astrocytomas, oligodendrogliomas, and mixed gliomas, and other diffuse glioneuronal tumors). In general, the diagnosis may be suggested by clinical features and MRI characteristics, but can only be established by histopathological examination.

Histopathological Diagnosis

The characteristic feature of gangliogliomas is that they contain substantial numbers of large neuron-like cells with large pale nuclei with prominent nucleoli, set in large cell bodies which

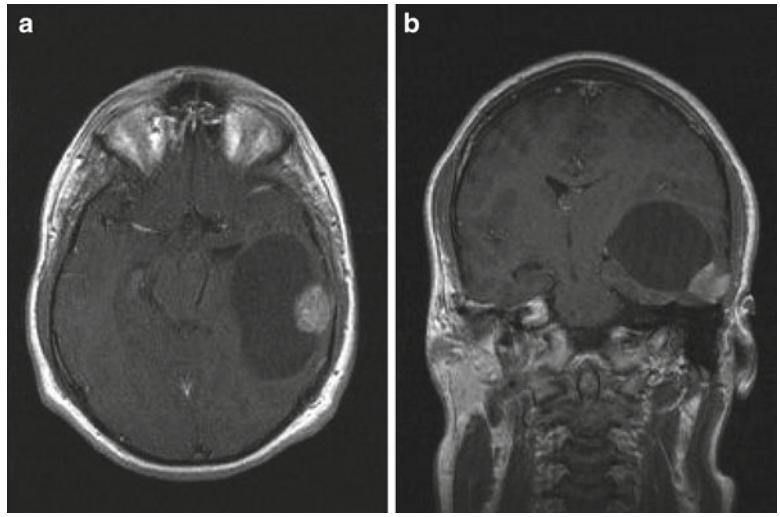

Fig. 18.1 Magnetic Resonance Imaging of gangliogliomas. Large cystic ganglioglioma in the left temporal lobe. (**a**) Axial T1-weighted image after administration of intravenous gadolinium shows the large cystic tumor with an enhancing mural nodule. There is no enhancement around the wall of the cyst separate from the nodule. (**b**) Coronal T1-weighted image of the same tumor

may contain basophilic granules histologically similar to or identical with the Nissl granules of normal neurons (Fig. 18.2a) (Becker et al. 2007; Miller et al. 1993; Miller 2009). If a neoplasm is composed essentially solely of such cells without distinctive neoplastic glial elements, it is termed a gangliocytoma. Gangliocytomas are most uncommon, and the majority of CNS tumors with ganglion cells are gangliogliomas. The glial elements are usually morphologically and immunohistochemically consistent with astrocytes, and resemble the cells of low grade diffuse astrocytomas (Fig. 18.2a), or, in some cases, pilocytic astrocytomas (Fig. 18.2b), complete with Rosenthal fibers or eosinophilic granular bodies; the presence of an apparently neoplastic oligodendroglioma-like population with admixed tumor ganglion cells should suggest that the oligodendroglioma-like cells are more likely neurocytoma cells, which can be demonstrated with appropriate immunostains (Giangasapero et al. 1997; Miller et al. 1993; Brat et al. 2001; Figarella-Branger et al. 2007).

In some cases the ganglion cells are so obvious, and their neuronal character is so unambiguous, that the diagnosis of ganglioglioma can be made solely on the basis of the tumor's appearance in conventional hematoxylin and eosin (H&E) stains (Fig. 18.2a). These classical examples have neurons in a range of sizes, which has been well-described long ago by Russell and Rubinstein (1989) for example, admixed with small bland tumor astrocytes. There is usually little or no discernible mitotic activity, and there is neither necrosis nor vascular hyperplasia such as characterizes high grade gliomas. Many examples have prominent lymphohistiocytic infiltrates around vessels in the tumor, although the absence of such inflammatory reactions do not argue against the diagnosis; and many examples have at least some desmoplasia, that is the deposition of collagen, in the neuropil (Miller et al. 1993; Jaffey et al. 1996).

For the pathologist, gangliogliomas present two potential diagnostic problems. First, a neoplasm may contain large cells that are obviously neurons, but it is unclear whether these are normal neurons entrapped in an infiltrating astrocytoma, or that they are in fact part of the neoplasm. Second, a tumor may contain some large clearly neoplastic cells with large nuclei, prominent nucleoli, but mostly eosinophilic cytoplasm, and these cells might be large tumor astrocytes or

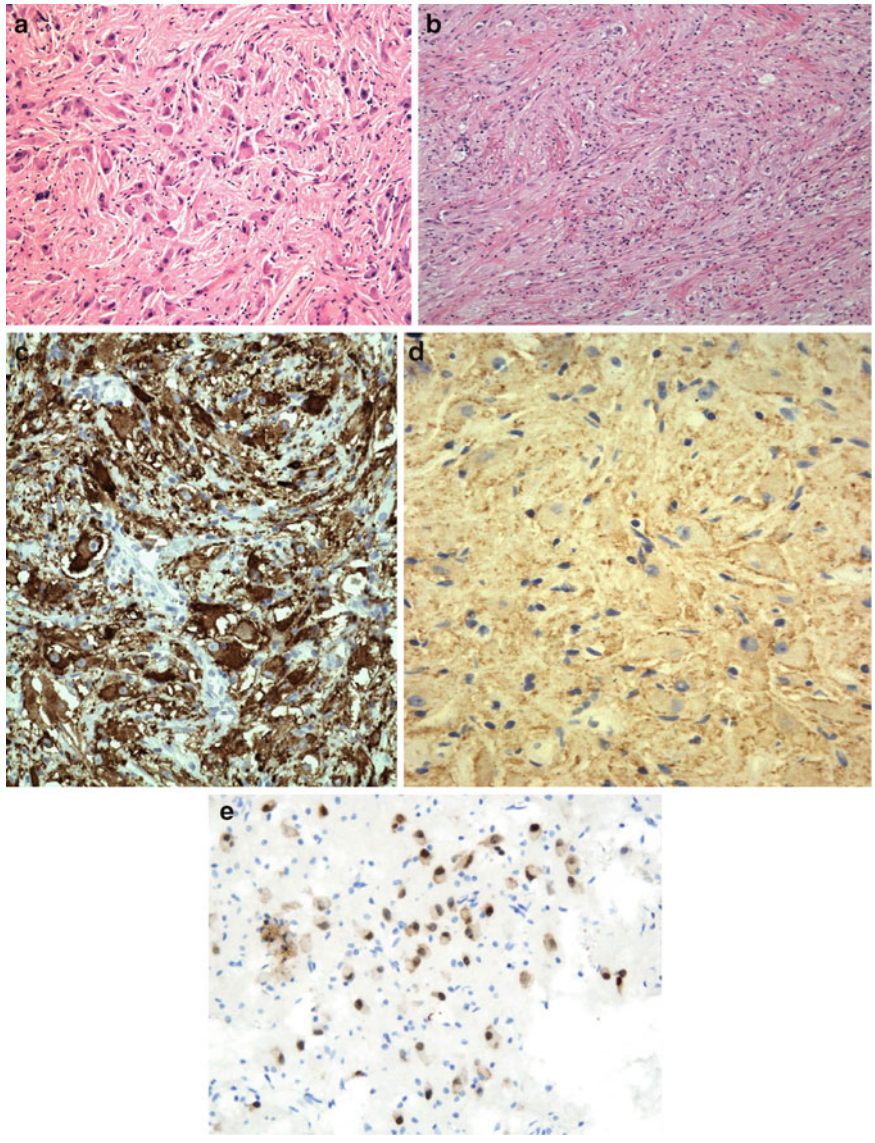

Fig. 18.2 Histopathology and immunohistochemical stains of gangliogliomas. (**a**) This typical ganglioglioma has an abundant population of large ganglion cells with polygonal cell bodies and large pale nuclei with prominent nucleoli; the background has numerous smaller astrocytic cells. H&E, 400× original magnification. (**b**) Another ganglioglioma has a prominent piloid astrocytic background with scattered ganglion cells. H&E, 400× original magnification. (**c**) Synaptophysin immunostain of a ganglioglioma. In this example some of the large neurons have cytoplasmic immunopositivity, suggesting delayed axonal transport, but there is also the characteristic perikaryal granular surface immunopositivity which identifies these as abnormal, *ie* neoplastic neurons. 400× original magnification. (**d**) Another synaptophysin immunostain from a different ganglioglioma has a much less dense and somewhat discontinuous but still identifiable perikaryal surface immunoreactivity around neoplastic neurons. 400× original magnification. (**e**) A Neu-N immunostain of a ganglioglioma variably marks the nuclei (and sometimes less densely the cytoplasm) of some tumor cells, with other obvious ganglion cells not immunopositive or with much less intense nuclear immunoreactivity. Here the variability of immunopositivity, including some wholly immunonegative cells, in cells clearly neuronal by other criteria helps identify these as abnormal neurons as well. 400× original magnification

they might be tumor neurons. For each of these problems, the correct diagnosis can only be determined using immunohistochemistry. The second problem is less difficult, as a variety of neuron-specific markers are now available to characterize tumor cells as neuronal. These include antibodies recognizing neurofilament protein (NFP), particularly the low (NF-L) and intermediate (NF-M) molecular weight types, since the high molecular weight NFP (NF-H) is less commonly recognized in neuronal cell bodies in general and in neoplastic neuronal cell bodies in particular; antibodies to neuronal forms of tubulin, particularly ß-III tubulin, which is relatively neuron-specific in the CNS; antibodies to the neuronal nuclear antigen (Neu-N); and antibodies to synaptic vesicle components, including chromogranin, synapsin-I, and synaptophysin. In the neuropathology practice of the first author, a combination of antibodies to NF-M, Neu-N, and especially synaptophysin have been especially helpful in the diagnosis of gangliogliomas (Miller 2009). If a clearly neoplastic population of large cells marks with one or more of these neuronal markers (Fig. 18.2c–e), then the cells are identified as neoplastic ganglion cells, and the tumor is a ganglioglioma unless it fits certain other special categories (see below). Most commonly, neoplastic ganglion cells will mark in their cytoplasm for NF-M, and will have a distinctive perikaryal surface immunopositivity for synaptophysin (Miller et al. 1990, 1993) (Fig. 18.2c, d); Neu-N immunopositivity is less common (Fig. 18.2e). Other immunostains have been suggested as helpful adjuncts to the diagnosis of ganglioglioma, such as anti-CD34 (Blümcke and Wiestler 2002; Luyken et al. 2004; Miller 2009). When suspect large tumor cells are positive in the right setting, CD34 immunopositivity can be helpful, but the absence of CD34 immunostaining ought not to preclude the diagnosis of ganglioglioma when neuron-specific markers are positive.

Determining whether neuronal cells within a tumor are part of the neoplasm or part of the nervous system infiltrated by a "pure" glioma is a more difficult process. This is not a problem when the tumor is in neocortex or hippocampus as the ordered nature of the neuronal arrangements in those structures makes it easier to recognize normal neurons in such laminar structure; for this purpose a Neu-N immunostain is often most valuable in discerning such structure when it might be obscured in an H&E stained section of tumor. Other brain tissues, such as particularly the amygdala, can be more problematic, however. It is helpful to identify the location of the tumor as in gray matter or white matter with stains for myelin such as Luxol Fast Blue, or for axons (silver stains or NFP immunostains), as a tumor in white matter with a large number of neurons is likely a ganglioglioma. In gray matter, the most useful tool is the pattern of synaptophysin immunopositivity, as the perikaryal surface immunopositivity is not characteristic of normal neurons of cortex, basal ganglia, thalamus, hypothalamus, amygdala, or hippocampus (Miller et al. 1990). There are some difficulties with this in the spinal cord, and perhaps in the lower brainstem, which are better discussed in the companion chapter to this one focused on these issues in the spinal cord.

The indolent character of most gangliogliomas is also reflected in the absence of mitotic figures in most examples, and by a low level of immunopositivity for the Ki67 nuclear cell-cycle associated antigen (usually detected with the antibody MIB1). Typically results of such immunostains are reported as a labeling index (LI), representing the proportion of tumor cell nuclei labeled by the antibody stain (the number of immunopositive from the total number of tumor cell nuclei in a sample of about 1,000 cells). The WHO classifies gangliogliomas as Grade I (although they should probably be Grade II), and the Ki67 LI for most examples is up to 5% but not more. Labeling indices of greater than 10% suggest an anaplastic transformation and mandate diagnosis as a higher grade ganglioglioma (Anaplastic Ganglioglioma, WHO Grade III).

Treatment

Cerebral gangliogliomas are mostly low grade indolent tumors. They respond relatively poorly to radiation and chemotherapy, and these therapies,

particularly radiation, carry risks of inducing transformation to higher grade neoplasia. Treatment in almost all cases, then, is focused on gross total neurosurgical excision of the tumor. Those cases that are apparently circumscribed by MRI lend themselves well to this approach using modern image-guided stereotactic neurosurgical techniques. More infiltrative examples may have to be subtotally resected, and as these tumors are never encapsulated and always have some degree of microscopic infiltration pathologically even gross total excisions will leave behind some cells. In unusual locations, particularly some brainstem sites, gross total excision may not be an option, so if there is substantial residual tumor, radiation may be considered on a case-by-case basis. Several authors have reported on their experience with gangliogliomas in the brainstem, and most feel that a resection of any exophytic portion followed by radiation therapy is the best treatment approach. There have been a few reports on the use of radiation therapy after subtotal resection. Rades et al. (2010) demonstrated that after subtotal resection of a ganglioglioma, whole brain radiation therapy conferred improved local control, but did not improve overall survival. In a smaller study, Liauw et al. (2007) showed that adjuvant radiation therapy for subtotally resected low grade gangliogliomas resulted in a 75% local control rate.

Prognosis

Gangliogliomas may be cured by gross total excision (Lang et al. 1993; Zentner et al. 1994). For those patients in whom seizures were a presenting symptom, excision of the tumor is also the best therapy for the epilepsy. Ogiwara et al. (2010) reported on 30 patients who underwent resection of gangliglioma with a history of medically intractable epilepsy. At 3.5 years, it was shown that 90% of the patients were found to be seizure free and off all seizure medications. Guilioni et al. (2006) analyzed seizure outcomes in 21 patients and showed that 66% were seizure free and 33% showed marked reduction in seizure frequency, with a mean follow up of 5.4 years. A follow-up study, however (Guilioni et al. 2009) suggested yet further improvement in seizure treatment with surgery tailored to resect the tumor and surrounding epileptogenic tissue.

In some patients, presumably due to microscopic residual tumor, a recurrent mass will emerge years after initial treatment; similarly in patients with subtotally resected gangliogliomas recurrent or progressive growth can be seen months to years after excision. Second surgical excision is usually still the best option for patients with progressive/recurrent gangliogliomas, for all the reasons surgery is the best approach for initial therapy of these tumors (Lang et al. 1993).

A small minority of patients with gangliogliomas will have recurrent tumors that have more rapid growth and, when excised, are clearly no longer low grade. The histological appearance may vary, in that the tumor may retain characteristics of a ganglioglioma but will have a detectable mitotic rate, a higher Ki67 labeling index (10% or more, usually), and, often, vascular hyperplasia or necrosis. (One must be careful in interpretation of necrosis if the patient has undergone other treatment, such as radiation). Other examples of high grade tumor following a diagnosis of low grade ganglioglioma lose their neuroglial mixed character, and resemble or constitute high grade "pure" gliomas, including examples resembling or constituting glioblastoma, with necrosis, vascular hyperplasia, increased nuclear pleiomorphism, and high mitotic rates. This may in unusual situations follow excision of a low grade ganglioglioma by as little as a few months. (For this reason, we resist the tendency to characterize ordinary gangliogliomas as "benign"; they behave more like low grade gliomas which have the potential for transformation to higher grade. This is exactly why they are better regarded as WHO Grade II tumors). These high grade histologic appearances have the usual correlation with more aggressive clinical behavior and a poor prognosis. Majores et al. (2008) reviewed their experience with subtotally resected gangliogliomas, and ones with both atypical and/or anaplastic features. They found the 5 year survival rate for "atypical gangliogliomas", which they termed grade II tumors to be 79%,

with survival of only 53% for anaplastic gangliogliomas (grade III).

Contrariwise, El Khashab et al. (2009) found that the achievement of gross total resection, seizures as presenting symptom and hemispheric location all portended good outcome. Similarly, Majores et al. (2008) showed that patients presenting with drug resistant epilepsy had improved outcome. They also showed that the pathological features of a gemistocytic cell component, lack of protein droplets, and positive CD-34 immunolabeling were predictors of an adverse clinical course.

Other CNS Tumors with Ganglion Cell-Like Components

There is a subtype of gangliogliomas which is both clinically and pathologically distinctive, namely the desmoplastic ganglioglioma (often termed "superficial desmoplastic ganglioglioma of infancy", although not all cases occur in infants or even children). These are typically massive cystic and solid tumors with an alarming MRI appearance, which histologically are at least in part densely fibrotic. Ganglion cells are often inconspicuous until immunostains, particularly synaptophysin stains, reveal them hidden in the dense fibrosis and spindle cell astrocytic background. Histologically these are otherwise typical of gangliogliomas and need no extra illustration here. Despite their alarming large MRI presentation patients with these tumors mostly do very well with gross total surgical excision alone (Miller 2009).

Another brain tumor with a histologic mixture of cell types including large neuron-like cells is the pleiomorphic xanthoastrocytoma (PXA) (Kepes et al. 1979; Giannini et al. 2007; Miller 2009). PXAs, like gangliogliomas, often involve the cortex, are often found in the temporal lobes of younger patients, and are often associated with seizures. Most examples, if examined with antibodies to neuronal antigens, have cells which are labeled with these immunostains, so that PXAs are actually glioneuronal tumors (Powell et al. 1996; Im et al. 2004). Also similar to gangliogliomas, PXAs are low grade neoplasms, usually sharply circumscribed but with some infiltrative borders histologically, and some have recurred after gross total excision as higher grade tumors, including some with all the characteristics of glioblastomas. As with gangliogliomas, then, gross total excision may be curative of low grade PXAs, but some will recur or progress and may require second surgery, and some may transform to higher grade tumors with a worse prognosis.

Some high grade gliomas, tumors with the characteristics of glioblastomas but with large pleiomorphic cells as a major component of the cellular populations, include cells which have immunopositivity for neuronal markers, often co-existing in the same cell as immunoreactivity for GFAP, S100 protein, or vimentin, typically markers of glial differentiation. These tumors ought not to be classified as gangliogliomas despite having these large, provably neuronal cells, and they behave as aggressive glioblastoma-like neoplasms (Miller 2009; Varlet et al. 2004; Rodriguez et al. 2005). These tumors, too, support the hypothesis that gliomas arise from multipotential progenitor cells ("tumor stem cells") and that in some cases they retain mixed glial and neuronal characteristics in the same cells.

A tumor with considerable similarity to PXA in regard to co-expression of glial and neuronal phenotypes is the subependymal giant cell astrocytoma, now being suggested to be termed "subependymal giant cell tumor" in view of its mixed glial and neuronal nature. Some but not all of these tumors are associated with Tuberous Sclerosis Complex. All consist of uniformly large cells with large cell bodies which in H&E stains are usually brightly eosinophilic and resemble those of large gemistocytic astrocytes, while the nuclei are also large and have pale chromatin with prominent nucleoli and resemble neuronal nuclei (Miller 2009). These cells regularly co-express GFAP, Vimentin, Synaptophysin, and Neurofilament Protein, and thus are neither astrocytes nor neurons, but hybrids or bipotential cells. Almost all of them occur at the foramen of Monro, and present with obstruction of the foramen and resulting hydrocephalus, often with headache as the presenting symptom.

Their location and uniform MRI appearance is strongly suggestive of the correct diagnosis. Recommended therapy is gross total excision, and recurrences either do not occur in such cases or are very rare; however TSC patients may develop other primary SEGTs after resection of one.

Neurocytomas and Variants

Prior to 1982 there was little use of the term "neurocytoma", and it was not a standard description of any kind of CNS neoplasm. In that year Hassoun et al. (1982) described ultrastructural evidence that oligodendroglioma-like tumors in young adults located in the lateral ventricles attached to the septum pellucidum were in fact tumors of small mature neurons, hence "neurocytoma". Eventually the WHO classification incorporated these lesions as "central neurocytomas". However from the early 1990s the neuropathologist author of this chapter, and several other neuropathologists in other centers, began to describe neuronal differentiation in tumors with oligodendrogliomatous elements (either "pure" oligodendroglioma or mixed gliomas dominated by oligodendroglioma-like cells) in the brain parenchyma, not in the ventricles (Nishio et al. 1990; Miller et al. 1993; Ng et al. 1994; Giangasapero et al. 1997; Brat et al. 2001) (Fig. 18.3a–h). There was no accepted classification for these until recently, and the WHO classification while recognizing their existence still has very little on them (Figarella-Branger et al. 2007). They have been termed "extraventricular neurocytomas", "parenchymal neurocytomas", or, based on their apparent differentiation, "glioneurocytomas", "gangli-oneurocytomas", or "ganglioglioneurocytomas" (Sharma et al. 2006; Miller 2009), the last term reflecting a component with neoplastic ganglion cells in addition to astrocytic, possible oligodendrogliomatous, and neurocytic elements.

These tumors tend to fall into two groups by histological appearance: those that are otherwise ordinary infiltrative gliomas, particularly oligodendrogliomas (Fig. 18.3a, b), and those with special histological features, such as adipose cell differentiation, papillary patterns of growth around blood vessels or the formation of distinctive rosette-like structures (Miller 2009; Kleihues et al. 2007; Nakazato et al. 2007; Hainfellner et al. 2007). They have been described more often in younger patients but are not restricted to any age group, and they have been found in all sites of the neuraxis. Most have the character of low grade (WHO Grade II) tumors, but appropriate investigations of anaplastic oligodendroglioma-like lesions with vascular hyperplasia, high Ki67 LI, or even necrosis have shown that some such tumors are predominately neurocytic. Neuropathological diagnosis depends on appropriate immunostains, as with gangliogliomas, but usually ganglion cell elements are absent or sparse and one must depend on neuronal marker immunopositivity of the smaller neurocytic cells to make the diagnosis (Fig. 18.3d, e, h). Of note here is that, as with "central" (intraventricular) neurocytomas, synaptophysin immunopositivity is rare in the cell bodies of the tumor cells, but is dense, granular, and intense in the neuropil-like tissues between the cells (Fig. 18.3d, h). As this appearance is also seen in normal gray matter, identifying the location of any given tumor sample as within gray matter or white matter is essential to proper interpretation of the synaptophysin immunoreactivity in such tumors (Miller 2009). The diagnosis of neurocytoma instead of oligodendroglioma may be suggested by the presence of rosette-like arrangements around fibrillary neuropil zones resembling Homer-Wright rosettes but larger (Fig. 18.3a, g, h) but still generally requires immunohistochemical confirmation. Of note also is that these parenchymal neurocytic tumors frequently have some cells with either astrocytic appearances or cells otherwise typical of some variants of oligodendroglioma, such that there may be GFAP immunopositivity in some cells (Fig. 18.3c) and there may be "mini-gemistocytes" as described in oligodendroglioma (Fig. 18.3f).

The nosology of and diagnostic criteria for all of these tumors with neurocytic elements is still being developed, hence prognostic statements can at best be tentative. Some suggested entities are so rare that only small numbers have been

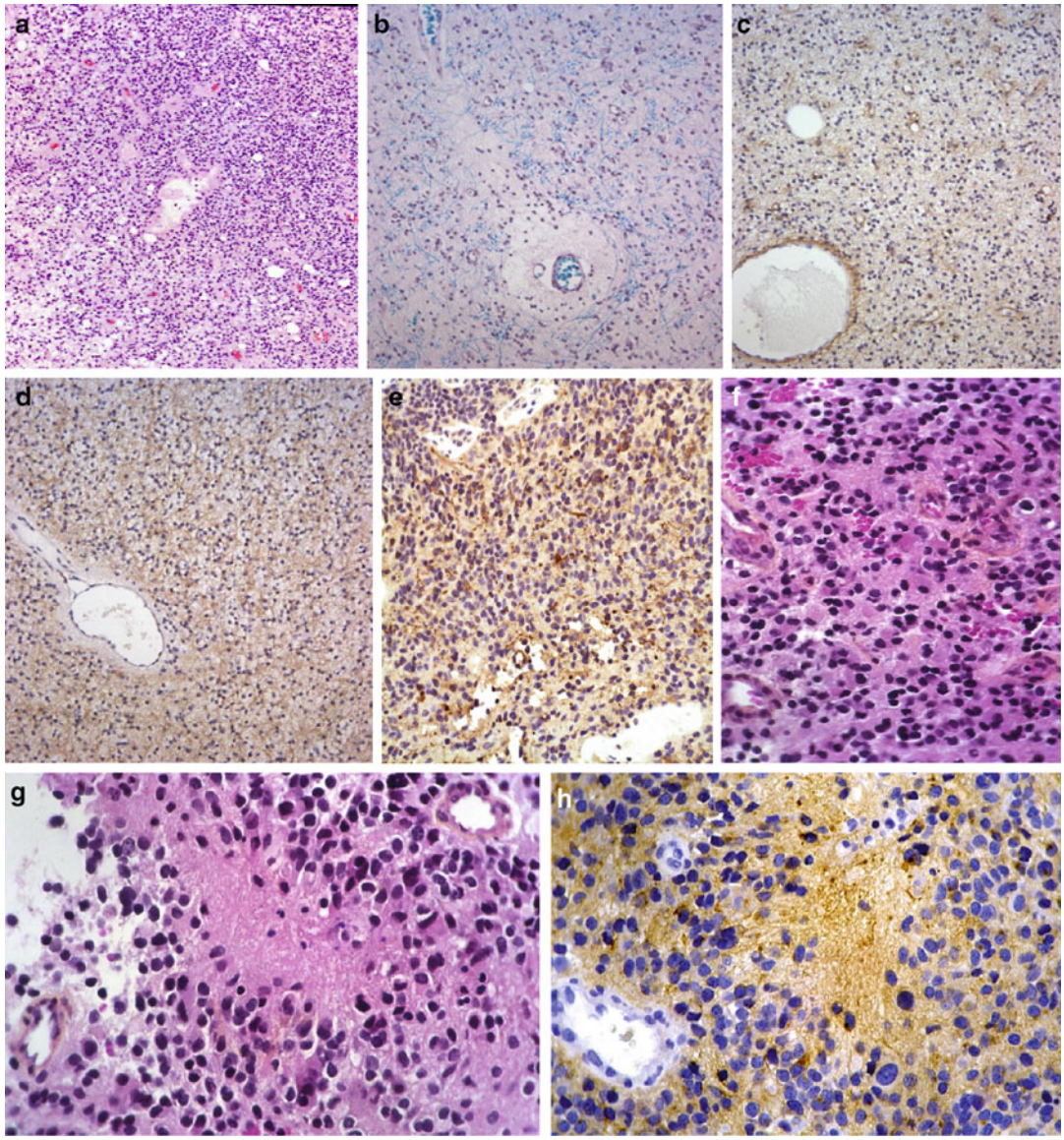

Fig. 18.3 Histopathology and immunohistochemical stains of parenchymal neurocytic tumors. (**a**) Cellular neurocytic tumor composed of small to medium size cells with monotonous bland round nuclei centrally located in the cell bodies, resembling oligodendroglioma. The tumor cells make vague perivascular pseudorosette-like arrangements and some rosette-like arrangements around anucleate neuropil, suggesting the neurocytic rather than oligodendrogliomatous nature of the tumor. H&E, 100× original magnification. (**b**) Infiltrating neurocytic tumor in white matter among myelinated axons, which are *blue* in this myelin stain. Luxol Fast Blue/H&E combination stain, 200× original magnification. (**c**) Sparse astrocytic cells in a parenchymal neurocytoma are highlighted this GFAP immunostain. 200× original magnification. (**d**) The neuropil-like synaptophysin immunopositivity between these tumor cells demonstrates the neurocytic nature of the neoplasm. 200× original magnification. (**e**) Strong cytoplasmic neurofilament protein immunopositivity (antibody RMDO20, to intermediate molecular weight NFP) similarly shows that the oligodendroglioma-like tumor cells are in fact neuronal. 400× original magnification. (**f**) Some neurocytomas have cells with a minigemistocytic appearance just like their oligodendrogliomatous counterparts. Such cells have round nuclei at one side of a small eosinophilic "bag" of cytoplasm. Hematoxylin-Phloxine-Saffranin (HPS), 400× original magnification. (**g**) Neurocytic ("giant Homer Wright") rosette. The tumor cells surround an anuclear fibrillary zone, and send processes into it. This appearance must not be confused with pseudopalisades of tumor cells around necrosis such as is seen in glioblastoma and other high grade gliomas. HPS, 400× original magnification. (**h**) A neurocytic rosette has strong granular immunopositivity for synaptophysin. 400× original magnification

reported, making prognostication statistically impossible. As many examples of oligodendroglioma or mixed glioma are not conventionally investigated for neuronal differentiation, the true incidence of parenchymal neurocytic tumors and any possible prognostic differences between those tumors which have neuronal marker positivity and those oligodendroglioma-like tumors which do not remains unknown. Some authors have suggested that there are distinctions between parenchymal neurocytic tumors ("extraventricular neurocytomas") and oligodendrogliomas with neuronal differentiation, although the diagnostic criteria and means to divide these as two entities are hardly described, much less agreed-upon (Perry et al. 2002). Similarly as noted some gangliogliomas have oligodendroglioma-like elements which by immunohistochemistry are neurocytic (Miller et al. 1993; Chou et al. 2010); now there is a proposal to separate oligodendrogliomas with ganglion cell elements from these ganglioneurocytomas (Perry et al. 2010). This remains an area within neuropathology and neuro-oncology which is unsettled and controversial, and only after additional data are accumulated and at least an international consensus is built will new classification schemes be built. Until such time it seems unreasonable to separate these various "entities", and we prefer to group them as parenchymal neurocytic tumors and specify the identifiable other differentiation (ganglion cells, astrocytes) as necessary.

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Part V

Neuroblastoma in Adults

Adult Neuroblastoma Diagnosis

19

Meeta Singh, Swapnil Agarwal, Nita Khurana, and Rishi Kumar

Contents

Abstract

Neuroblastoma is the most common extracranial solid tumor in children. Adult onset neuroblastoma (ANB) is an extremely rare entity with an incidence of 0.2–0.3 cases per million years. Sites of presentation in adults are similar to children with abdomen and pelvis being the most common; however, some rare sites like thorax and extremities have also been reported in the literature. Unlike the pediatric counterpart it rarely secretes chatecholamines and very few expresses n-myc amplification. Thus the diagnosis relies solely on strong clinicoradiological suspicion along with histopathological and immunohistochemical correlation. The diagnosis of ANB implies an overall poor patient outcome in-spite of indolent course of illness. Unfortunately most of these patients suffer from multiple recurrences even with intensive chemotherapy and myeloablation.

Introduction

Neuroblastoma is the tumor of neural crest cells arising in sympathetic nervous system. It is the most common extracranial solid tumor in children accounting for upto 600 new cases per year in United States. It is typically a malignancy of childhood with 36% of patients diagnosed before 1 year, 75% before 5 years and more than 90%

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_19,

cases diagnosed before 10 years of age (Matthay and Schwartz 1991; Matthay 1994; Brodeur et al. 1993).

Adult onset neuroblastoma (ANB) is an extremely rare entity with an incidence of 0.2–0.3 cases per million years between age group of 30–40 years (Davis et al. 1987; Esiashvili et al. 2007). The literature regarding ANB is scanty and only few scattered case reports, small groups of series and reviews exist. Less than 300 odd cases of ANB exist in the literature so far, however the ones diagnosed before the advent of modern diagnostic tools should be cautiously interpreted. In view of unusual occurrence of ANB, it is seldom suspected creating a delay in the diagnosis and further management. The present manuscript thus reviews the existing literature on ANB and focuses on clinico-radiological and pathological differential diagnosis of this rare entity.

Clinical Presentation

Most common age of presentation of ANB is the third decade. According to study by Esiashvili et al. (2007) the largest series published so far which included 144 cases of both ANB and ganglioneuroblastomas over a period of 30 years, almost 50% cases diagnosed were between 20 and 39 years. A very small subset of cases with ANB beyond 50 years of age were observed in this study. In another study by Kushner et al. (2003) which included 30 cases of adolescents and adults the median age at presentation was 19 years. In an earlier study by Franks et al. (1997) comprising of 16 adults/adolescent cases of neuroblastoma, the median age of diagnosis was 22 years with age range of 13–33 years. Hasegawa et al. (2001) reported 8 cases of pure neuroblastomas in adults (excluding adolescents and ganglioneuroblastomas) with mean age of presentation being 38 years.

No gender bias has been observed in ANB cases with overall male to female ratio being almost same. In the above mentioned study by Esiashvili et al. (2007) out of 144 patients 70 were male and 74 were females. In series by Hasegawa et al. (2001), out of 8 patients 4 were men. In another series by Kushner et al. (2003) of 30 patients 16 (53%) were men. In a series by Franks et al. (1997) out of 16 cases 9 were males. Pertinent literature review of 57 cases published before this series showed male to female ratio of 27:30 (total 57). Most of these cases occurred in whites as compared to other races, however this data should be interpreted in view of the fact that in most of the studies whites were the predominant population (Esiashvili et al. 2007).

Most common site of presentation of ANB is abdomen similar to its pediatric counterpart, out of which retroperitoneum is the most frequent followed by adrenal gland. Rare intra-abdominal sites like mesentry have also been reported. On excluding the study by Esiashvili et al. (2007) (where exact site has not been indicated), out of 117 cases (Kushner et al. 2003; Hasegawa et al. 2001; Franks et al. 1997; Tateishi et al. 2003); 63 (54%) cases were abdominal, 17 (14.5%) occurred in thorax including maximum cases in mediastinum followed by thoracic spine, 13 (11%) were pelvic, 7 (6%) were cervical in location, with single case each in extremity and epidural space (<1%) and 5 (4.2%) involved both thorax and abdomen. In 10 (7.6%) cases primary site could was not identified due to presence of tumor at multiple locations (Tateishi et al. 2003). A rare and interesting case of ANB presenting as bilateral ovarian masses has been reported by the authors (Singh et al. 2010) Rare thymic and primarily renal origin of ANB is also known (Argani et al. 1997; Kawakami et al. 2001).

Clinically, patients with ANB may be totally asymptomatic. The disease being indolent in its course, the clinical presentation may be so protean as to mimic chronic inflammatory conditions like sarcoidosis, tuberculosis or rheumatoid arthritis. Symptomatic patients may present with local or systemic symptoms including mass, local or systemic pain, generalized fatigue, fever, constipation, loss of weight and appetite. Initial presentation as mass at the metastatic site is not uncommon. Rare presentations like ascites, obstructive jaundice, pancytopenia and inferior vena-caval thrombosis, syndrome of inappropriate secretion of anti diuretic hormone have also been reported (Argani et al. 1997).

Though ANB is a slowly progressive disease most of the patients have metastasis at diagnosis, present with metastasis. Out of 144 patients, 43 (~30%) presented with metastatic disease while 26 (18%) presented with regional spread and only 21 (14.6%) had localized disease; rest 54 cases were unstaged (Esiashvili et al. 2007) The picture was worse in the study by Kushner et al. (2003) where 27 out of 30 (90%) patients presented with a stage 4 disease comprising of 3 cases of soft tissue metastasis and 24 cases of bone/ bone marrow metastasis. Franks et al. (1997) used Evans system of staging and found 9 out of 16 patients (56%) patients in stage IV, 2 patients each in stage I and III and 3 in stage II (Evans et al. 1971). 4 out of 8 cases (50%) reported by Hasegawa et al. (2001) were in Evans stage IV while 3 in stage I and single in stage III. Bone/ bone-marrow involvement happens to be the commonest site of metastasis in adults similar to pediatric population. Other sites of metastasis include lymphnodes, brain, breast, pleura, peritoneum liver, skin and rarely small intestinal wall (Franks et al. 1997; Hasegawa et al. 2001).

Laboratory Findings

It is an established fact that about 90–95% of the pediatric neuroblastomas have elevated levels of catecholamines and their metabolites vanillylmandelic acid (VMA), 3-methoxy-4-hydroxyphenylglycol (MHPG), homovanillic acid (HVA) and dopamine are excreted in the urine. These are considered reliable marker of the disease at diagnosis and assume greater significance (with a great significance) in post therapy follow-up. However, results on urinary catecholamine excretion in ANB are variable in different studies. The overall incidence is 40–57% in ANB which is much lower than the pediatric population (Matthay 1997). This may reflect reduced production or increased storage of these metabolites by the tumor cells and thus underlies biological dissimilarity between adult and pediatric neuroblastomas. Exceptional is a study in which 18 out of 20 (90%) newly diagnosed ANB and 8 out of 10 (80%) cases on treatment tested positive for urinary chatecholamine levels (Kushner et al. 2003). Elevated serum levels of nonadrenaline and VMA have also been observed although rare (Hasegawa et al. 2001). Studies regarding, which have a role in prognosis of pediatric cases, are absent in ANB. No studies are available in the literature regarding urinary HVA/VMA ratios in ANB. These have proved to be valuable in prognosticating pediatric cases.

Ferritin, an iron binding protein presumably synthesized by the neuroblastoma cells is an important poor prognostic indicator in pediatric patients. The prognostic significance is not quite known in ANB and has rarely been described in the existing studies. In a study it was noted that approximately 73% of the patients (11 out of 15 cases) had serum ferritin >142 ng/ml (Kushner et al. 2003). Since overall prognosis in ANB is poor, high rate of increased serum ferritin values could act as a diagnostic as well as prognostic tool in these cases.

Elevated levels of serum Neuron-specific enolase have also been noted in some patients of ANB (Hasegawa et al. 2001). Other laboratory markers of disease activity include elevated C- reactive protein and erythrocyte sedimentation rate which have no diagnostic role. Serum LDH levels are a reliable indicator of progressive and metastatic disease. In a study 50% of the patients showed elevated LDH while in another study only 1 out of 17 patients (6%) had elevated LDH levels (Hasegawa et al. 2001; Kushner et al. 2003). In view of such variable results LDH should not be labeled as a reliable prognostic marker.

Neuropeptide Y, a biologically active polypeptide that co-localizes with catecholamines is found in high levels in the serum of pediatric patients with neuroblastoma. Even though the studies on levels of this protein are absent, it is a possibility that its reliability will parallel the serum and urinary catecholamine levels in adult patients.

Radiological Features

CT and MR findings have been rarely described in ANB cases and only few case reports/small series exist (Tateishi et al. 2003; Feinstein et al. 1984;

Custodio et al. 1999; Kawakami et al. 2001). The overall radiological findings are very nonspecific and therefore should not be used to differentiate ANB from other malignancies more common in this age group.

Calcification within the tumor identified by CT scans is a reliable diagnostic clue, as it occurs in 50–80% of pediatric neuroblastoma cases (Stark et al. 1983; Boechat et al. 1985; Cremin and Mervis 1983; Berdon et al. 1999; David et al. 1989). Calcification exists primarily in areas of necrosis present within both primary and metastatic foci. Unlike pediatric cases calcification is not a very reliable feature in ANB cases. In a series of 6 cases, calcification was not found in any of ANB cases on CT scan either in primary or metastatic foci (Tateishi et al. 2003). Another study showed that only 4 out of 31(13%) Japanese subjects with ANB had calcification on CT scan (Kawakami et al. 2001).

The encasement and displacement of the surrounding structures is commonly observed phenomenon in locally spreading neuroblastomas of both children and adults. However a characteristic feature of crossing over the midline exhibited by pediatric adrenal counterpart is not a reliable suggestive feature of ANB. As noted in two separate studies none of the adrenal ANB crossed the midline (Tateishi et al. 2003; Custodio et al. 1999). Inspite of having smooth capsule, ANB have infiltrative patterns of spread and most of them are higher stage or metastatic at presentation which is unlike the pediatric counterparts which even though are huge masses rarely have metastasis. Many high grade malignancies like lymphomas and disseminated carcinomas more likely in adult age group share this feature of ANB again creating a diagnostic dilemma.

Enhancement patterns of ANB highlight the hypervascular nature of these tumors. In atrerial phase of contrast enhanced CT scan diffuse or punctate enhancement may be noted which indicate diffuse vascular proliferation or stromal dilated vessels in pathological specimens respectively. On contrast MR, the ANB has low intensity on T1-weighted and a high intensity on T2-weighted imaging. On T2-weighted imaging heterogenous architecture with or without septations of low signal intensity may also be noted. This appearance suggests compartmentalization, fibrous solid portions and hemorrhagic nature within the tumor mass. Peripheral nodular enhancement can also be seen in some cases (Custodio et al. 1999).

Radiological findings as described above are very nonspecific for ANB and thus do not help in distinguishing other malignancies with similar clinical picture in this group. Radiologically high grade lymphomas, metastatic carcinoma, pleomorphic sarcomas, EWS/PNET (Ewings Sarcoma/ Primitive Neuroectodermal Tumor) and site specific malignancies like adrenal cortical carcinomas, paragangliomas, neuroendocrine carcinomas and adenocarcinomas, at times can be totally indistinguishable from ANB.

Histopathological Features

Gross

Grossly ANB can be of variable sizes with mean diameter of 7.3–8.7 cm. Ranging from 5.5–15 to 4.5–10 cm in various studies (Hasegawa et al. 2001; Tateishi et al. 2003). The masses are usually soft to ruberry with smooth outline (pseudocapsule) and white to grey–pink in appearance. At times nodular or lobulated appearance may also be noted. On cut section it is usually variegated in appearance with small to large areas of hemorrhage and necrosis with minimal to marked cystic degeneration. Areas of calcification are uncommon. Generally the compressed normal appearing organ is rarely seen with complete effacement of the same.

Microscopy

Microscopically the tumor like the pediatric ones is classically composed of small round cells with hyperchromatic nuclei and high nucleo–cytoplasmic ratio arranged in sheets and divided by delicate fibrovascular septa into small lobules. A promiment backgound of neuropill is observed with some of the cells organised in form of

abortive rosettes or rarely typical Homer-Wright rosettes. The chromatin pattern is characteristic salt and pepper with indistinct to prominent one to two nucleoli . Anaplastic forms, large cell forms, and largely necrotic tumors may also be present. According to Shimada et al. (1999) neuroblastomas have been classically divided into undifferentiated, poorly-differentiated and differentiating subtypes depending upon the presence and extent of shwannian stroma and ganglioneuromatous differentiation. Whole range of Shimada histology including the anaplastic forms have been observed in ANB cases with no predominance of any specific type (Hasegawa et al. 2001; Cowan et al. 1997).

In undifferentiated subtype the background neuropill is not usually prominent, thus these tumors can be confused with other more common malignancies of adulthood. The closest differential diagnosis is EWS/PNET with can be totally indistinguishable clinicoradiologically and even on morphology. However some differences like greater degree of nuclear irregularity and hyperchromasia is usually present in ANB as compared to EWS/PNET. Typical well defined Homer-Wright rosettes are more prominent in PNET as compared to ANB in which few abortve rosettes may only be noted. Mats of neuropill, nuclear enlargement, vesicular nucleus having coarsely clumped chromatin and conspicuous nucleoli is a prominent feature in poorly-differentiated variants, thus help in differentiating PNET from ANB cases (Hasegawa et al. 2001). Some ANB presenting primarily as bony metastastsis can be confused with EWS or small cell variant of osteo/chondrosarcoma.

Other malignancies apart from PNET having a "small-round cell" morphology can be confused with ANB. Considering its usual site of occurrence lymphomas, undifferentiated small cell carcinomas, round cell variants of sarcomas particularly rhabdomyosarcoma, rarely neuroendocrine carcinomas, paragangliomas and soft tissue deposits of acute leukemias need to be ruled out before signing out the final diagnosis. Thus in difficult situations where serological and urinary findings are noncontributory and even otherwise, immunohistochemistry plays a major role and is absolutely imperitive for a conclusive opinion.

Immunohistochemistry

Positive markers used for neuroblastomas includes neuron specific enolase (NSE), chromogranin A (CHR), synaptophysin (SYN), tyrosine hydroxylase (TH), CD-56, neurofilament (NF) and S-100. All are variably positive in neuroblastomas with later two strongly positive in poorly differentiated subtypes. All of them have been studied in ANB cases (Hasegawa et al. 2001; Cowan et al. 1997; Franks et al. 1997). Some others such as protein gene product 9.5, GD2 (disialoganglioside, a ganglioside on human neuroblastoma cell membrane), and NB84, are also positive in a variable proportion of pediatric cases; though their expression and diagnostic utility has not much studied in terms of ANB. In anaplstic variants vimentin (Vim) may be weakly positive.

Negative markers are often of greater value in making the diagnosis by excluding the close histologic differential diagnosis. These include CD-99 (MIC2 gene) or membranous staining for a cell surface glycoprotein, p30/32 (a product of the *MIC*2 gene), commonly seen in PNET/Ewing's sarcoma thus ruling out the same.

Other negative markers like leukocyte common antigen (CD45) rules out lymphoma or leukemia, desmin, myoglobin and MyoD1 ruling out rhabdomyosarcoma, low molecular-weight cytokeratin and epithelial membrane antigen ruling out small cell or neuroendocrine carcinomas. Small cell histologic variants of Paragangliomas can be ruled out by staining pattern of S-100 (positive in sustentacular cells).

Cytogenetics

MYCN amplification imparts a dismal prognosis to pediatric neuroblastoma patients and the overall prevalence rate is 20–25% approximately. The great biological dissimilarity between pediatric and ANB is highlighted by the fact that MYCN amplification is extremely rare in ANB patients even in advanced stages of disease. The overall prevalence of MYCN amplification is 0–3% in ANB patients. In a study none out of 6 patients and only one out of 32 adolescent patients tested

positive (Franks et al. 1997). In another series of 22 patients tested, all were negative for MYCN amplification (Kushner et al. 2003). A single case reported of anaplastic ANB was also negative for MYCN amplification (Cowan et al. 1997).

Rearrangement of chromosome17q, which has been correlated with poor outcome and expression of TrkA protooncogene which denotes a favourable prognosis, both have been found in a single case of anaplastic ANB. However studies regarding cytogenetics and karyotypic analysis of ANB are extremely deficient and thus should not be used to extrapolate prognostic significance. Molecular evaluation of EWS-FLI1 transcript is of particular significance in the diagnosis of ANB cases as EWS/PNET pose a major diagnostic difficulty on histopathology and sometimes even on immunohistochemistry. In a study, both the cases of ANB evaluated for EWS-FLI1 transcript were negative for the same as compared to EWS/PNET cases included in the study (Hasegawa et al. 2001).

Ultrastructural Features

The overall electron microscopic findings in ANB cases are similar to pediatric tumors. Ultrastructurally, the cells show scant rim of cytoplasm, scattered ribosomes, few mitochondrias and small golgi regions. Most characteristic finding is presence of many cytoplasmic dendritic processes which contain microtubules and variable number of small, dense core neurosecretory granules (Mackay et al. 1976; Hasegawa et al. 2001).

Though in the modern era of cytogenetics and immunohitochemistry, electron-microscopy is seldom approached for the diagnosis, it is still of a major help in difficult and rare cases like ANB.

Prognosis

ANB though follows an indolent and protracted course; it has a significantly dismal outcome as compared to pediatric counterparts. As mentioned, most of these cases are in advanced stage with locoregional stage being relatively rare at presentation. Observations from most series suggest that even locoregional neuroblastomas which are highly curable in children with minimal therapy, had poor overall survival in adults. In a study overall survival was 75% at 2 years, 44% at 5 years, 37% at 10 years and fell to less than 10% at 20 years from diagnosis (Esiashvili et al. 2007). The survival was better in subset of patients between 20 and 39 years of age as compared to ones beyond 50 years of age, even though age did not influence the stage much. This underlines the fact that age at diagnosis is the most important prognostic factor in neuroblastomas in general. As expected, advanced cancers fare poorly in term of prognosis even after extensive treatment. The gender and race did not influence the overall survival.

Histological subtype of the tumor strongly influences the survival in pediatric cases, however studies have not described prognosis of ANB in this reference. Absence of MYCN amplification signifies a favorable prognostic sign in pediatric age group. Inspite of poor prognosis of ANBs MYCN amplification is extremely rare, thus cannot be used as reliable prognostic marker. Raised serum ferritin value (>142 ng/ml) which implies a poor prognosis in pediatric cases have also been observed in ANB, thus may act as reliable prognostic marker.

Since urinary catecholamine levels are usually not upto the detection limit in ANB cases urinary VMA/HVA levels hold no prognostic significance. Literature regarding Trk A expression, serum NSE levels, karyotypic characteristics is very scanty in ANB; therefore it is too early to draw conclusion on prognostic implication of these factors. And because increased serum levels of LDH are an indicator of any metastatic disease, it may be used to judge the course of ANB with this marker.

Treatment

Standard recommendations and treatment protocols of ANB are absent due to paucity of cases, thus they are often treated according to pediatric guidelines. Surgical resection, radiotherapy and

standard chemotherapy underlie the treatment protocols. The most active chemotherapeutic agents include cyclophosphamide, cisplatin, doxorubicin, carboplatin and ifosfamide used in standard doses either in combination or alone. However it has been noticed that in ANB cases chemotherapeutic agents in standard doses had only palliative effect and a more aggressive approach with high dose chemotherapy combined with surgery and immunotherapy yield a higher response rate. The classical approach of wait and watch post resection in localized disease yield a high rate of recurrence. However an important point to be noted is that high dose myeloablative chemotherapy regimen are better tolerable in adults but may still be less effective in them as compared to pediatric counterparts.

In conclusion, diagnosis of tumors with unusual presentation is still a major disappointment in field of medical oncology even with the advent of modern techniques. Adult onset neuroblastoma is just one of such tumors which is seldom kept as a differential in patients with small-round cell tumors in this age group. Clinico-radiological suspicion and histopathological suggestion in addition to immunohistochemical confirmation is the only way of diagnosing this rare malignancy which may be aided by ultrastructural evaluation. There is a huge lacuna in existing literature regarding the treatment and prognostic guidelines of ANB and thus there is a need for larger studies and clinical trials for a tailored therapy of these patients.

But no matter how much we work, patients with rare malignancies presenting at advanced clinical stage are and will remain unfortunate in medical world.

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Proliferation of Neuroblasts in the Adult Brain: Role of Diversin

20

Yuki Hirota and Kazunobu Sawamoto

Contents

Abstract

The subventricular zone (SVZ) is the largest neurogenic region in the adult rodent brain. In this region, new neurons that originate from neural stem cells (NSCs) migrate to the olfactory bulb, where they mature into interneurons. During neurogenesis, the proliferation of NSCs and neuronal progenitor cells are precisely regulated by multiple signaling pathways to maintain homeostasis. Wnt signaling is one mechanism that controls the proliferation of SVZ cells. In addition to NSCs and progenitor cells, the migration of new neurons (neuroblasts) also maintains the proliferative capacity. Recently, Diversin, which is a component of the Wnt signaling pathway, has been shown to promote the proliferation of neuroblasts in the SVZ. Neuroblast proliferation may be an important step in regenerative responses to brain injury and in normal physiological neurogenesis.

Introduction

In the adult brains of mammals, neurogenesis continuously occurs and supplies new neurons in the two germinal regions: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus, where neural stem cells (NSCs) exist throughout life of the organisms. Adult neurogenesis has crucial roles in physiological processes, including cell replacement and adult tissue homeostasis. In addition, recent studies indicate ischemic stimuli induce

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_20,

neurogenesis in the SVZ, and new neurons that are generated in the SVZ migrate toward areas of brain injury to repair tissue. Neurogenesis is regulated at multiple steps, including the self-renewal and proliferation of NSCs and progenitor cells, in addition to the migration, differentiation, survival, and maturation of new neurons. Understanding these processes in detail will facilitate the development of strategies for therapies in the treatment of neurodegenerative diseases and brain injury by amplifying endogenous neurogenesis. Proliferation is particularly important to the expansion of neuronal cell populations that integrate into neural circuits. In addition to the proliferation of NSCs and progenitor cells, the proliferation of migrating young neurons (neuroblasts) is shown to contribute to neurogenesis. This review will focus on the regulation of neuroblast proliferation in the adult brain.

The Proliferation of Subventrivular Zone Cells

The SVZ is the largest neurogenic region in the adult rodent brain and consists of a thin cell layer that is located on the lateral wall of the lateral ventricles, which contain cerebrospinal fluid (CSF) (Fig. 20.1). The SVZ consists of four cell types: SVZ astrocytes (type B cells), rapidly dividing transit-amplifying precursor cells (type C cells), migrating neuroblasts (type A cells), and multiciliated ependymal cells (type E cells) (Doetsch et al. 1997) (Fig. 20.1). Ependymal cells are postmitotic in the adult brain under physiological conditions, but brain injury stimulates these cells to generate neuronal cells. SVZ astrocytes function as NSCs and generate the transit-amplifying precursor cells. Transit-amplifying precursor cells proliferate and then differentiate into type A cells (neuroblasts) (Doetsch et al. 1999). Neuroblasts form cell aggregates called chains and migrate long distances inside of the astrocytic tunnels via the rostral migratory stream (RMS) toward the olfactory bulb (OB) (Sawada et al. 2011). In the OB, neuroblasts mature into two kinds of interneurons, granule neurons and periglomerular neurons. Each of the three proliferating cell types in the SVZ (NSCs, transit-amplifying precursor cells, and neuroblasts) regulates its cell cycle by a different mechanism.

NSCs in the adult SVZ originate from radial glial cells, which are neural stem cells in the embryonic brain, are quiescent under normal conditions and are considered to be "slowly dividing"

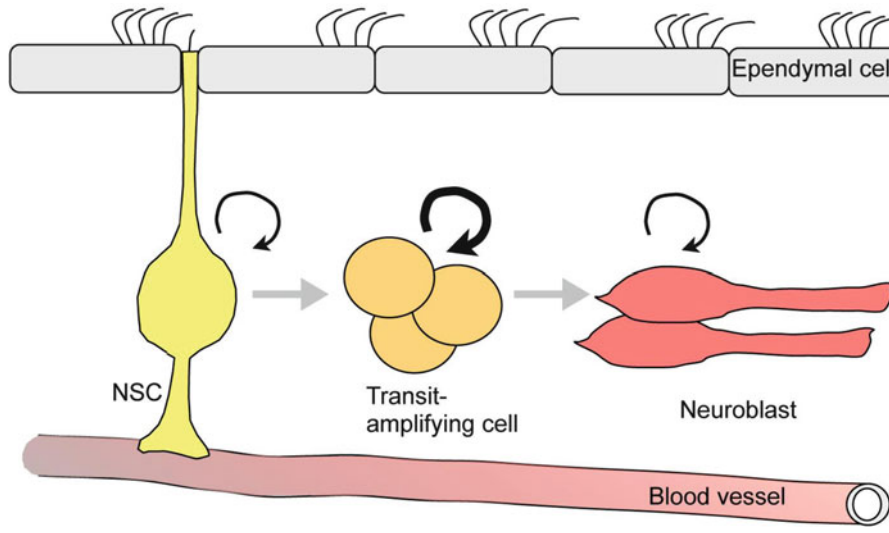

Fig. 20.1 Cell lineage and SVZ cell proliferation. NSCs (*yellow*) extend an apical projection to contact the ventricle and a long basal process to contact blood vessels. They slowly divide and generate transit-amplifying cells (*orange*), which in turn then rapidly divide to expand neuronal progenitor populations and differentiate into migrating neuroblasts (*red*). Ependymal cells (*grey*), which line the walls of the lateral ventricles, do not divide under normal conditions

cells that self-renew and generate neurons throughout life. NSCs extend an apical protrusion to contact the ventricle and a long basal process that contacts blood vessels, suggesting that they receive signals from both the ventricle and vasculature (Mirzadeh et al. 2008). The identity of NSCs is believed to depend on the specialized local microenvironment, which contains unique cytoarchitecture and cell-cell contacts and is called the "stem cell niche." In the niche, several diffusible and membrane-bound factors that regulate stem cell numbers have been identified. For example, Galectin-1, which is a soluble carbohydrate-binding protein, is secreted from the NSCs and promotes the proliferation of NSCs (Sakaguchi et al. 2006). Several cytokines and growth factors are also involved in the proliferation of NSCs. Interleukin-15 is expressed in the NSCs of the SVZ and regulates both the proliferation and differentiation of NSCs via activation of the JAK/STAT and ERK pathways (Gomez-Nicola et al. 2011). Fibroblast growth factor (FGF) 2 is released from astrocytes in the adult SVZ and enhances the proliferation of FGF receptor (FGFR) 1-expressing NSCs (Frinchi et al. 2008). Vascular endothelial growth factor-C (VEGF-C) promotes the proliferation of NSCs that express their receptor (VEGFR-3) (Calvo et al. 2011). Intracellular regulators also contribute to the proliferation of NSCs. Tailless (Tlx), which is a member of the nuclear receptor superfamily, is expressed in NSCs in the adult SVZ and SGZ and functions as a key regulator to maintain the proliferative state of NSCs (Liu et al. 2008). Epigenetic regulation is also important. $GABA_AR$ signaling regulates the proliferation of NSCs via the activation of PI3 kinase-related kinases ATM/ATR and the phosphorylation of histone H2AX in the SVZ (Fernando et al. 2011). Cross talk between miRNA and epigenetic regulation also contributes to the control of NSCs. MeCP2, which is a DNA methyl-CpG-binding protein, epigenetically regulates miR-137, which is one of miRNAs that is expressed in NSCs to promote the proliferation of NSCs in the SVZ (Szulwach et al. 2010). Thus, the proliferation of NSCs seems to depend on both niche signals and intracellular signaling.

In contrast to NSCs, transit-amplifying cells are highly proliferative and rapidly divide to expand cell populations. Several signaling pathways have been shown to be involved in the proliferation of transit-amplifying cells. Epidermal growth factor (EGF) and transforming growth factor-α activate EGF receptor (EGFR) and stimulate precursor proliferation in the adult SVZ (Kuhn et al. 1997). Nitric oxide (NO) inhibits EGFR tyrosine kinase and its downstream signaling pathway, PI3K-Akt, under physiological conditions and functions as a negative regulator of SVZ neurogenesis (Torroglosa et al. 2007). $p27^{KIP1}$, which is a member of the cyclin-dependent kinase inhibitory protein family, is also a negative regulator of the cell division of transit amplifying progenitors (Doetsch et al. 2002). The interactions between transit-amplifying cells and NSCs are also important for maintaining a balance between the number of cells of each type in the population. Activated EGFR signaling in transit-amplifying cells reduces Notch signal activation in NSCs through Numb-dependent Notch1 ubiquitination and controls the balance between NSCs and transit-amplifying cells (Aguirre et al. 2010).

Several reports have demonstrated that neuroblasts, which originate in the SVZ and commit to a neuronal fate, retain their proliferative capacity while migrating in the SVZ and RMS toward the OB. In contrast, in the embryonic brain, most migrating neuronal progenitors are postmitotic. Thus, the neuroblasts that are generated in the SVZ are inhibited from exiting the cell cycle, and this proliferative capacity of migrating neuroblasts is a unique feature of adult neurogenesis. The exit of the cell cycle by neuroblasts is likely to be regulated by precise mechanisms. $p27^{KIP1}$ is expressed in neuroblasts that migrate in the RMS and promotes cell cycle exit in neuroblasts in the postnatal brain (Li et al. 2009).

Wnt Signaling in Embryonic and Adult Neurogenesis

Wnt signal transduction is known to be important in the development, tissue homeostasis and disease processes of various organs, including the brain, via the regulation of cell fate determination, differentiation, and proliferation (Ciani and Salinas 2005). The Wnt signaling pathway

has two main branches of downstream cascades. One is the canonical β-catenin-dependent pathway (Wnt/β-catenin pathway), which regulates embryonic patterning, tumorigenesis, cell proliferation and the self-renewal of stem cells. The other is the non-canonical β-catenin-independent Wnt signaling pathway, which controls cytoskeletal rearrangements and the planar cell polarity (PCP) of various tissues (Wnt/PCP pathway). The latter pathway leads to cytoskeletal changes by signalling via core PCP proteins, including the transmembrane proteins Frizzled, Strabismus/Vang-like 2 (Stbm/Vangl2) and Flamingo and the intracellular proteins Dishevelled, Prickle (Pk), c-Jun N-terminal kinase (JNK) and Rho GTPase.

Numerous studies have demonstrated that the canonical Wnt/β-catenin pathway regulates the proliferation and differentiation of neural progenitor cells in the embryonic brain. In the adult SVZ, the Wnt/β-catenin pathway is activated by Tlx to stimulate the proliferation and self-renewal of NSCs (Qu et al. 2010). The Wnt/β-catenin pathway also promotes the proliferation of neural progenitors to expand them in the adult SVZ (Adachi et al. 2007). In addition, recent studies show that Wnt/PCP signaling is also involved in neurogenesis in the embryonic brain. During cortical development, Vangl2 functions to maintain neuronal progenitors via regulation of the spindle orientation (Lake and Sokol 2009).

Diversin in Wnt Signaling

Given that Wnt/β-catenin and Wnt/PCP pathways share signaling components, such as Frizzled and Dishevelled, the balance between the two pathways is likely to be precisely controlled. For example, pathway specificity is likely determined by the utilization of distinct combinations of Frizzled receptors, low-density lipoprotein, receptor-related proteins (LRP-5 and LRP-6) or tyrosine-kinase receptors Ror and Ryk (Gordon and Nusse 2006). Intracellular mediators are likely to be involved in the control of signaling specificity. One such intracellular protein that regulates distinct signaling branches is Diversin. Diversin, which is an ankyrin-repeat protein, was identified in a yeast two-hybrid screen as the binding partner of conductin/axin2, which is a negative regulator of β-catenin (Schwarz-Romond et al. 2002). Biochemical experiments have shown that Diversin recruits casein kinase Iε (CKIε) to the β-catenin degradation complex, which consists of conductin/axin2 and GSK3β, and leads to the efficient phosphorylation of β-catenin, thereby inhibiting Wnt/β-catenin signals. The inhibition of Wnt/β-catenin signals by Diversin results in axis formation defects in the early embryogenesis of frog and zebrafish (Schwarz-Romond et al. 2002). Diversin was also shown to be involved in the Wnt/PCP pathway, where it directly interacts with Dishevelled and promotes heart formation and gastrulation during zebrafish embryogenesis through the activation of Rho and JNK (Schwarz-Romond et al. 2002; Moeller et al. 2006). Thus, Diversin is characterized as a molecular switch that blocks the Wnt/β-catenin pathway and promotes the Wnt/PCP pathway.

The Role of Diversin in Neuroblast Proliferation

As mentioned above, in the adult SVZ-RMS-OB migratory path, neuroblasts maintain their proliferative capacity. Little is known about the molecular mechanisms that underlie this unique feature. Diversin is expressed in the periventricular tissue of both embryonic and adult brains (Schwarz-Romond et al. 2002; Ikeda et al. 2010). In the adult SVZ-RMS-OB path, Diversin is expressed in almost all migrating neuroblasts. The overexpression of Diversin in mitotic SVZ cells through retroviral vector-mediated gene expression has been observed to induce an increased proliferation of neuroblasts (Fig. 20.2) (Ikeda et al. 2010), whereas the differentiation of SVZ cells was not affected. In contrast, the knockdown of Diversin resulted in a decreased proliferation of neuroblasts (Fig. 20.2) (Ikeda et al. 2010). These results indicate that Diversin is required for the proliferation of neuroblasts during migration. The proliferation-promoting activity of

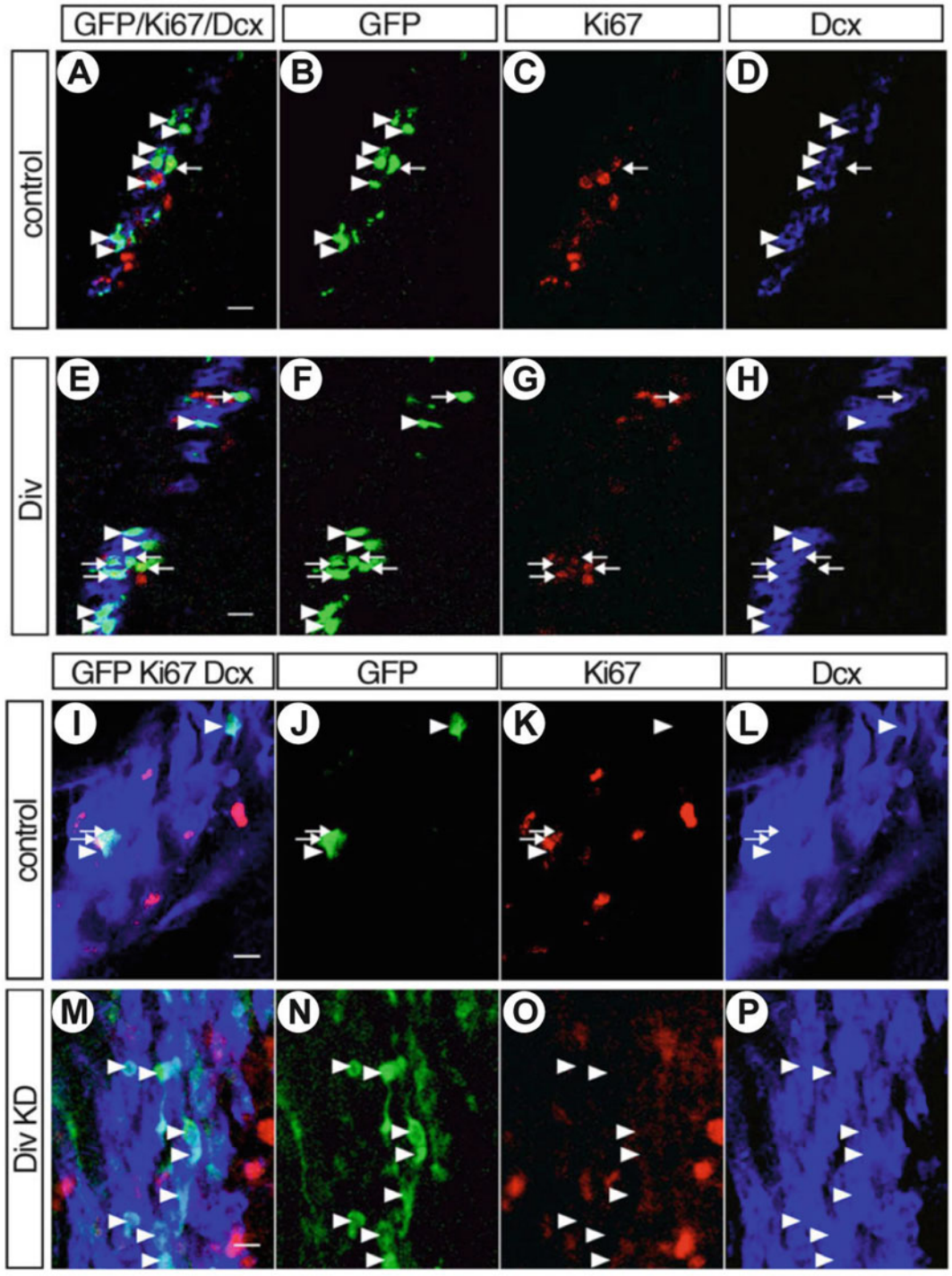

Fig. 20.2 The proliferation-promoting role of Diversin in neuroblasts in the adult SVZ. Retrovirus-mediated overexpression and knockdown of Diversin affect the number of dividing neuroblasts that migrate into the OB. Sections of the SVZ that were harvested 48 h after the injection of virus were stained for GFP (*green*), Ki67 (*red*, proliferation marker) and Doublecortin (*blue*, neuroblast marker). GFP^+Ki67^+ (dividing) cells and GFP^+Ki67^- (non-dividing) cells are *indicated by arrows and arrowheads*, respectively. (**a–h**) The overexpression of Diversin (**e–h**) induced the increased proliferation of neuroblasts in comparison to the controls (**a–d**). (**i–p**) In contrast, the knockdown of Diversin (**m–p**) resulted in a decreased proliferation of neuroblasts in comparison to the controls (**i–l**)

Diversin depends on its ankyrin repeats, which are required for the interaction with Dishevelled and activation of Wnt/PCP signaling (Moeller et al. 2006). In addition, JNK activation, which is an indicator of Wnt/PCP signaling, is detectable in proliferating neuroblasts (Ikeda et al. 2010). Thus, Diversin likely promotes the proliferation of neuroblasts via activation of the Wnt/PCP pathway. Given that the Wnt/β-catenin pathway promotes the proliferation of type C cells (Adachi et al. 2007), switching from the Wnt/β-catenin pathway to the Wnt/PCP pathway might be an important process that is required to change the proliferation rate in different cell types in the adult SVZ.

Neuroblast Proliferation in the Damaged Brain

Analyses using several animal models of brain injury have revealed that brain damage promotes the proliferation of NSCs and progenitor cells and the production of neuroblasts in the SVZ (Jin et al. 2001). Neuroblasts that are generated in the SVZ migrate toward the damaged area in close association with blood vessels (Ohab et al. 2006; Yamashita et al. 2006) and differentiate into mature neurons that potentially contribute to functional recovery. In addition to migration, the proliferative capacity of neuroblasts is also altered by brain injury. After ischemic stroke, the proliferation of neuroblasts in the SVZ is increased through a shortening of the cell cycle and an increase in cell-cycle re-entry (Zhang et al. 2007), possibly contributing to the expansion of the population of neuroblasts that arrive to the damaged area. Several studies have shown that Wnt signaling is involved in injury-induced neurogenesis. Inhibition of β-catenin resulted in a decreased stroke-induced SVZ neurogenesis (Lei et al. 2008). In addition, Wnt signaling regulates the symmetric divisions of NSCs in the SVZ after stroke (Piccin and Morshead 2011). Thus, it is possible that the proliferation of neuroblasts that migrate towards the injured tissues is also controlled by a mechanism that involves the Diversin and Wnt pathways. Understanding the cellular and molecular mechanisms that underlie the regulation of SVZ cell proliferation in pathological conditions is important for development of neuronal regeneration therapies for the damaged human central nervous system.

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Part VI

Astrocytomas and Ependymomas

Subependymal Giant Cell Astrocytoma: Treatment

21

Cynthia J. Campen

Contents

Abstract

Tuberous sclerosis complex (TSC), a relatively common genetic disorder, is associated with inactivation of tumor suppressor genes. Hence, tumors of many organ systems are seen in patients with TSC, and with subependymal giant cell astrocytomas (SEGA) seen in 5–20%. SEGAs are low-grade mixed glial/neuronal intracranial tumors arising from the subependymal lining of the ventricles. The primary complication from SEGAs is obstructive hydrocephalus, with sequelae including headache, vision impairment, diplopia, and brainstem herniation. Because of their progressive course, and potentially fatal complications, SEGAs usually require treatment. Standard of care has been surgical resection, with low rates of regrowth; making surgical resection a successful and permanent therapeutic strategy. In addition to surgical resection of SEGAs there are now other treatment options including pharmacotherapy and radiotherapy. In case series, sirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR), suppressed the growth, and in some cases shrank the size of SEGAs.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_21,

Introduction

Inactivation of the tumor suppressor genes hamartin (TSC1) or tuberin (TSC2) is associated with tuberous sclerosis complex (TSC), a relatively common autosomal dominant genetic disorder affecting up to 1 in 6,000 people (Osborne et al. 1991). The TSC1 and TSC2 proteins act as a heterodimer to suppress mammalian targets of rapamycin (mTOR) a serine/threonine protein kinase important in regulating cell growth and division. Multiple organs are at risk for tumor formation, including the heart, lungs, skin and kidneys. The most common findings in the brain of TSC patients include tubers in the cortical parenchyma that are relatively static. Cortical tubers are thought to contribute to the high rate of epilepsy in TSC, but do not have a high rate of oncologic growth potential. MRI, in the majority of patients with TSC, reveals subependymal nodules lining the ventricles with a subset being calcified or showing contrast enhancement (Nabbout et al. 1999; Goh et al. 2004). To date, no radiographic features have been identified that accurately predict those subependymal nodules that will grow, thereby requiring treatment. Reportedly, 5–20% (Goh et al. 2004; Cuccia et al. 2003) of TSC patients develop low-grade CNS lesions known as subependymal giant cell astrocytoma (SEGA) (World Health Organization grade I) which appear to arise from subependymal nodules based on neuroimaging findings.

Histopathology

Histopathologically, SEGAs are indistinguishable from subependymal nodules with loosely cohesive clusters of large cells with round to oval nuclei and no, or minimal, atypia; fine, evenly distributed chromatin; and abundant eosinophilic cytoplasm embedded in abundant thin, hairlike processes (Takei et al. 2008). Formed by three types of cells, fibrillated spindle cells, swollen gemistocytic-like cells and giant pyramidal cells with a ganglioid appearance, SEGAs show both glial and neuronal features. Some authors have demonstrated that all subependymal nodules are clonal and have the capacity to proliferate (Fujiwara et al. 1989; Jozwiak et al. 2005).

Natural History

SEGAs arise from subependymal nodules in the area of the foramen of Monro, and can be unilateral or bilateral. These are slow growing tumors and typically have no symptoms until obstructive hydrocephalus develops (Nabbout et al. 1999; Goh et al. 2004). They are distinguished from subependymal nodules by increasing size on serial neuroimaging, or by signs and symptoms of obstructive hydrocephalus. Without intervention, SEGAs continue to slowly grow over weeks to months, with only sparse evidence of regression or growth stabilization. Rarely, SEGAs exhibit more aggressive behavior, associated with parenchymal invasion, extensive peri-tumoral edema, or occur in an atypical location, such as the pineal or hypothalamic regions. They typically project into the ventricle and can produce acute or chronic hydrocephalus.

Serial neuroimaging every 1–3 years is recommended in pediatric patients with TSC, even in the absence of symptoms (Roach et al. 1998). If a subependymal nodule grows over the interval of routine imaging, more frequent follow-up imaging is appropriate. Early in presentation, SEGA symptoms can be subtle, but complaints in patients with TSC warranting urgent imaging include: positional headache (worse in a dependent position), sudden worsening of seizures, and headache progressing to include nausea, vomiting, diplopia, and lethargy.

Clinical series suggest a male predominance for SEGA, with a mean age at surgery of 11 years (Goh et al. 2004; Cuccia et al. 2003). In a series of 14 surgical subjects, SEGA was identified at a mean of 90 months of age, and surgical intervention occurred at a mean of 38 months after identification. Surgery was performed for evidence of hydrocephalus in 9/12, and evidence of tumor growth 5/12 (Clarke et al. 2006). In one series, reported by Braffman et al. (1992), 10 of 21 patients with SEGA died, six as a direct result

of tumor growth (acute obstructive hydrocephalus in five, and intratumoral hemorrhage in one). In this series, death from SEGA was most common in the 10–19 year-old age group. In patients followed by a neurologist experienced in caring for patients with TSC, death from SEGAs is rare, though morbidity, including vision loss, chronic ventriculo-peritoneal shunting, and headache remains.

Treatment

Surgery

Standard therapy for SEGAs has been operative resection, which is curative in the setting of a gross total resection (Cuccia et al. 2003; Frerebeau et al. 1985; Jiang et al. 2011). If tumor remains, it frequently will continue to grow. Historically, surgery was performed for one of three indications, acute hydrocephalus, worsened seizure burden, or significant interval growth on serial neuroimaging. More recently, some authors have argued for earlier surgical intervention to avoid the sequelae of hydrocephalus (Goh et al. 2004; de Ribaupierre et al. 2007).

Complications of intraventricular surgery are numerous including, transient memory impairment, hemiparesis, infection and shunting. Permanent sequelae include rare cases of stroke with resultant hemiparesis, chronic ventriculo-peritoneal shunt placement, and death (Cuccia et al. 2003; Jiang et al. 2011).

Pharmacotherapy

Avoiding the morbidities associated with surgery while insuring shrinkage or stabilization of the SEGA is the goal of pharmacologic therapy. Rapamycin (sirolimus, Rapamune) and more recently, everolimus (Afinitor- approved for treatment of SEGA by FDA- October 2010) have been shown to have efficacy in the stabilization of, and in some cases may shrink SEGAs (Krueger et al. 2010; Franz et al. 2006). Rapamycin and everolimus are very similar in their chemical composition (in everolimus, a 2-hydroxyethyl group has been introduced in position 40 of rapamycin). This change results in a slight increase in bioavailability and shorter half-life. The side effect profiles are similar between the two drugs.

Rapamycin initially showed efficacy against renal angiomyolipomas, and subsequent investigations into its efficacy for SEGA demonstrated similar efficacy (Bissler et al. 2008). In a report by Franz et al. (2006) of five cases of patients with SEGA and TSC treated with rapamycin, all tumors reduced significantly in size. An average of 65% reduction in volume was observed. Surgery was avoided in all five, and only mild adverse effects were observed. However, clinical response may not be durable; in most cases, when rapamycin was stopped, the SEGA regrew. Krueger et al. (2010) reported a study of 28 patients, 3 years of age and older treated with everolimus, and noted a significant reduction in SEGA size in 75% of patients. The patients also had a mild improvement in seizure burden. Whether this seizure reduction was due to decreased intracranial pressure or a direct effect of mTOR inhibition on the seizure focus was not clear. Longer term follow-up of this patient population will help determine the duration of therapy needed to prevent re-growth of SEGAs in this high-risk population.

Rapamycin (sirolimus) and everolimus should not be used in SEGAs causing significant hydrocephalus and impending herniation. These patients should undergo surgical resection for acute management. Furthermore, severe infections are a contraindication for rapamycin and sirolimus therapy, because they decrease immune function. Sirolimus and everolimus are known to be substrates for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus and everolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase concentrations. Because epilepsy is a common problem in patients with TSC and some anti-epilepsy drugs utilize CYP3A4 and the P-gp transporter, these

drugs may have complex interactions with anti-seizure medications. Known inducers of the CYP3A4 include phenytoin, carbamazepine, phenobarbital, oxcarbazepine, and rufinamide. The main side effects of treatment with sirolimus or everolimus include: aphthous ulcers, hypercholesterolemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing.

Radiosurgery

A sustained reduction in SEGA size and no regrowth over at least a 2-year follow-up period have been reported in small case series of 2–6 patients treated with radiosurgery (Frerebeau et al. 1985; Park et al. 2011). Park et al. (2011), investigating stereotactic radiosurgery in SEGA, reported a total of six patients, three with TSC. Of these, all had radiosurgery as the primary treatment for the SEGA. The pre-radiosurgery tumor volumes were 5.9, 3.4, 2.1 cm^3, they received 13, 15, 11 Gy, with progression in one patient, progression free interval of 2 and 4¾ years in the remaining two, and mean follow up of 5.8 years. For radiosurgery therapy to become standard of care, prospective studies investigating short and long term outcomes are needed to assess efficacy and safety.

Of special concern in TSC patients, who lack one copy of a tumor suppressor gene, is the potential increased risk of a radiation induced secondary malignancy. Matsumura et al. (1998) reported development of a glioblastoma multiforme in a patient 8 years after radiation. As surgical resection and mTOR inhibitors do not pose this theoretical risk, it seems prudent to reserve this treatment for patients who failed or have contraindications to the more standard treatment regimens. Importantly, the reduction in SEGA size following radiotherapy is not immediate, thus this modality should be reserved for relatively small tumors with minimal symptoms of hydrocephalus.

Conclusions

While relatively rare, SEGAs represent a significant cause of morbidity and are the main cause of mortality in TSC patients. Historically, treatment consisted only of surgery. However, recent insights into the cell signaling abnormalities of TSC offer hope for a durable medical treatment in the future. Medical versus surgical management of SEGAs is a difficult treatment decision. SEGAs have been reported to re-grow if mTOR inhibitor therapy is stopped; raising the possibility that long-term medication may be required to prevent tumor growth and subsequent hydrocephalus. The question of regrowth following medication withdrawal will need to be addressed in large, randomized, prospective studies, to establish the optimal duration of therapy. The risks of surgery including acute morbidity, and the permanent need for ventriculo- peritoneal shunting should be balanced against medication side effects. mTOR inhibitors have multiple possible risks including: immunosuppression and resultant infections, mouth sores, hypercholesterolemia, and the need for chronic drug monitoring. There are however, some potentially additional benefits to mTOR inhibition in patients with tuberous sclerosis complex (TSC) including shrinkage of angiofibromas, angiomyolipomas, and possible decrease in seizure burden. Recent reports of successful non-surgical treatment of SEGAs are promising and specifics on dosing, duration, and long-term outcome should be forthcoming, allowing patients and physicians to make informed therapeutic choices.

Presently, treatment recommendations for SEGAs remain routine surveillance neuroimaging with close clinical follow-up, paying particular attention to signs and symptoms of acute hydrocephalus. If symptoms arise, or if serial neuroimaging demonstrates tumor growth, neurosurgical intervention is recommended. When gross total resection is impossible, rapamycin and everolimus may be considered when tumor regrowth occurs, but may not offer a durable response.

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Acquired Retinal Astrocytoma

22

Daniel Vilaplana

Contents

Abstract

Acquired retinal astrocytoma is a rare intraretinal tumor, appearing as a yellow-white nodular mass of the retina. This tumor resembles retinal astrocytic hamartoma, and it is rarely associated with tuberous sclerosis. Acquired retinal astrocytoma is a benign tumor in which no systemic metastasis has been described. In its evolution, it can cause exudative retinal detachment, and it is difficult to differentiate it from choroidal melanoma and retinoblastoma. All previously reported cases until 2006 have been managed with enucleation because of incorrect diagnoses as well as intraocular complications derived from the tumor itself. The first case described in literature approached with conservative treatment was performed by our team in 2003 and published in 2006. In this Chapter we describe the etiopathogeny, the clinical course, the exploratory techniques, the pathological anatomy, the differential diagnosis and the treatment. We compare tumoral endoresection with PTD as a conservatives therapies in the management of this tumor. The advantage of the surgical technique is that it is able to remove completely the tumor and PDT option causes minimal secondary effects and it is easy to perform, compared to the first technique that needs a high experienced surgeon.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_22,

Introduction

Acquired retinal astrocytoma is a very rare intraretinal tumor. It has received several names such as astrocytic hamartoma of the retina not associated with tuberous sclerosis (Reeser et al. 1978), giant cell astrocytoma of the retina (Jakobiec et al. 1983), astrocytic tumor of the retina (Ulbright et al. 1984), solitary retinal astrocytoma (Arnold et al. 1985), atypical retinal astrocytic hamartoma (Shields et al. 1996), retinal massive gliosis (Yanoff et al. 1971), solitary evolutionary astrocytoma (Zoógrafos 2002), and acquired retinal astrocytoma (Shields et al. 2004a) being this last name the most widely accepted nowadays.

This tumor is benign, locally aggressive, white-yellowish, intraretinal and can produce exudation as a lipid deposition surrounding the lesion in a circinate fashion with an associated exudative retinal detachment. The magnitude of this exudation depends on the individual evolution of each case (Fig. 22.1). It usually affects the juxtapapillary region (Shields et al. 2004b) and can cause vision loss in cases that are close to the macula.

Etiopathogeny

It is an astrocytic benign tumor of the retina that appears sporadically in patients without tuberous sclerosis (Bourneville disease) or Neurofibromatosis (von Reclinghausen disease). Its cause is not known and it can appear at any age. As opposed to retinal astrocytic hamartomas associated to diseases mentioned above, acquired retinal astrocytomas are progressive. Exceptionally, there are some progressive tumors associated to tuberous sclerosis called *aggressive retinal astrocitomas* (Gunduz et al. 1999; Shields et al. 2004a, 2005; Mennel et al. 2006) but this is not the rule. Despite they cellularity is benign in origin and without metastatic ability, they don't have a good prognosis due to their ability to locally destruct the organ they have invaded leading sometimes to a massive exudative retinal detachment, neovascular glaucoma, ptisis bulbi and enucleation (Shields et al. 2004a).

Clinical Course

Symptoms

Symptoms can be very variable. While tumor is not active and exudation does not affect macula they can be inadvertent. Early in the disease, some patients describe nonspecific symptoms like floaters. Visual field disturbances usually are not remarkable either and tend to be asymptomatic. As the process advances and macula begins to be altered, patients explain metamorphopsia and vision

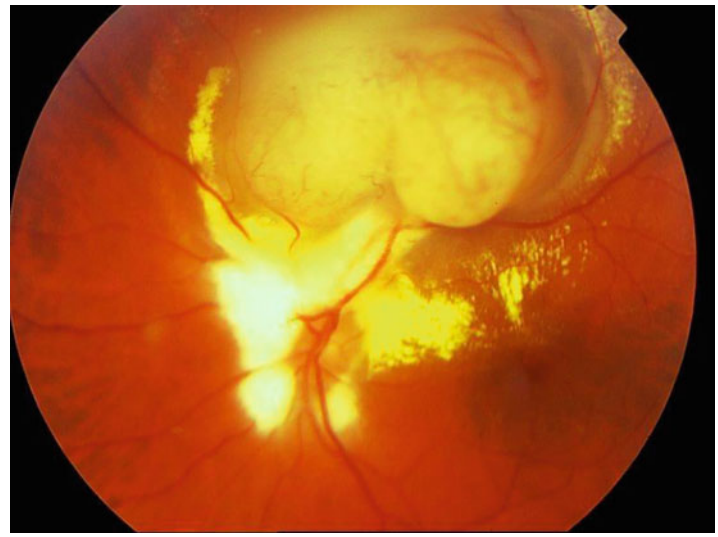

Fig. 22.1 Acquired retinal Astrocytoma. White-yellow tumor, endophytic, with lipid deposits surrounding it in a circinate fashion. Associated papillary myelin fibers

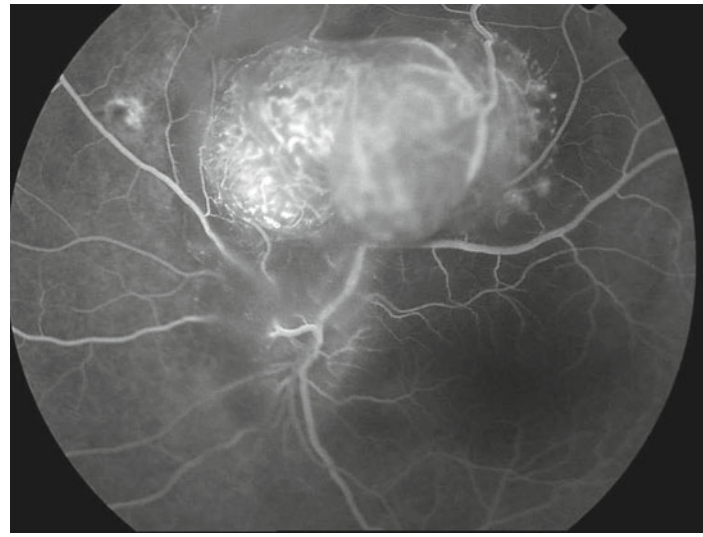

Fig. 22.2 Fluorescein angiography. Venous times: parietal contrast impregnation in the tumoral circulation

loss in more or less magnitude depending on posterior pole affectation.

Signs

Fundus examination highlights a white-yellow mass located at the juxtapapillary area. Typically, perilesional lipid deposits are observed and in some patients, peritumoral hemorrhages have been described depending on the evolution grade of the tumor. Leukocoria caused by the tumor can be assessed using color photography with a conventional retinograph.

Exploratory Techniques

Ultrasound

In the very few cases described calcifications are absent (Zoógrafos 2002; Shields and Shields 1992, 1999), but they can be present although be inadvertent due to their small size. In ultrasound, a nodular homogeneous echogenic mass with medium to high intern reflectivity can be detected (Zoógrafos 2002; Shields and Shields 1999; Shields et al. 2004a).

Fluorescein Angiography

Fluorescein angiography shows the rich vascularization of this tumor (Fig. 22.2). In this territory, retinal capillaries altered by tumor expansion and compression is seen. Tumor feeding vasculature can also be visualized as a fine net of vessels that grows from own retinal vessels. Consequently, retinal vessels morphology is modified and this, together with the tumor vessels, causes a loss of contrast that is the origin of the surrounding lipid deposits.

Indocyanine Green Angiography

This exam has not been described previously in literature. We have observed that with Indocyanine Green (ICG) we are able to see a dilated retinal circulation on the tumor surface and an extensive tumoral vascularization above. Patiently and in early phases we can find an afferent vessel feeding the tumor (Fig. 22.3). In early and late times we cannot see colorant diffusion because of indocyanine green characteristics. Diffusion will happen in very late times, about 30–45 min and in a very discreet fashion.

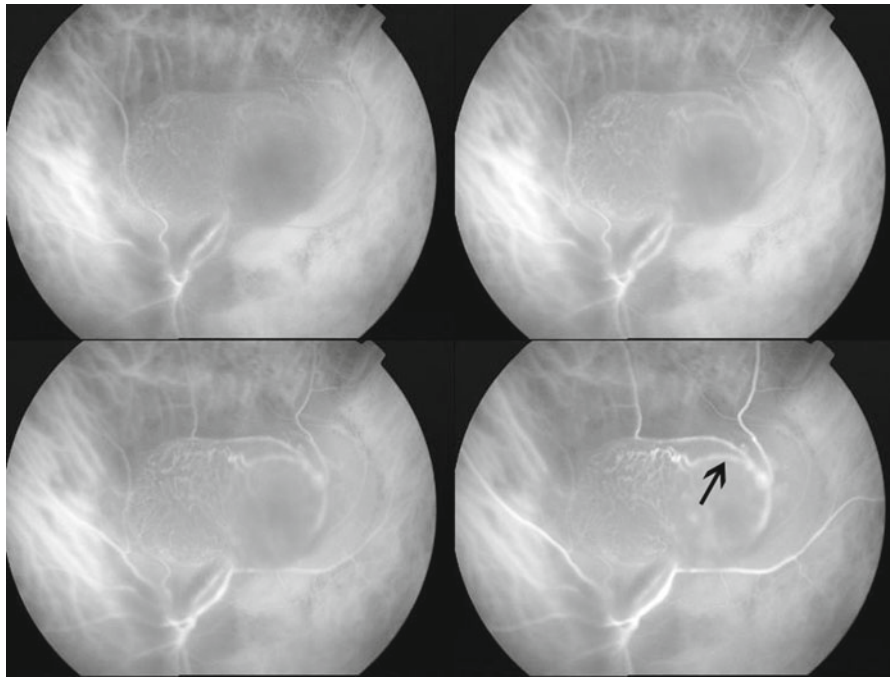

Fig. 22.3 Indocianine green angiography. Early times. *Arrow* indicates tumor feeding afferent vessel

Magnetic Resonance Imaging

Orbital axial T1 Magnetic Resonance Imaging does not allow visualization of the tumor that, however, can be seen using axial T2 mode.

Pathological Anatomy

After enucleation this tumor appears as an eosinophilic mass in the neurosensorial retina adjacent to the optic nerve (Shields and Shields 1999). With hematoxylin-eosin well-differentiated astrocytes are observed. The histopathological exam shows a cytological heterogeneity very similar to that of the giant cell subependimary astrocytomas of the central nervous system. They can be made of glial cells, fusiform astrocytes, gemistocyes, giant cells or a mixture of all of the above. There is no evidence of mitotic activity or it is minimal (Fig. 22.4a–d). (With authorization of Retina. Ophthalmic Communications Society)

Differential Diagnosis

Differential diagnosis includes intraocular tumors, especially choroidhemangiomas and amelanotic melanomas in adults and retinoblastomas in children. In a review of all worldwide cases described until 2004 published by Shields et al. (2004a) of a total of 15 cases, preoperative suspected clinical diagnosis before pathology was as follows: Three cases unknown, one case of tuberculoma, two cases of retinal hemangioma, two cases of choroid melanoma, five cases of retinoblastoma and only one case (by the same author Shields) with a pre-surgical correct diagnosis of astrocytoma. Being such a rare entity makes it difficult to diagnose.

Ophthalmoscopic appearance is very suggestive but if needed fine needle aspiration biopsy can be performed. This technique sometimes can't obtain useful information since it is a very compact solid tumor. During the puncture procedureand due to the hardness of the tumor, a very characteristic fact can happen: A small movement

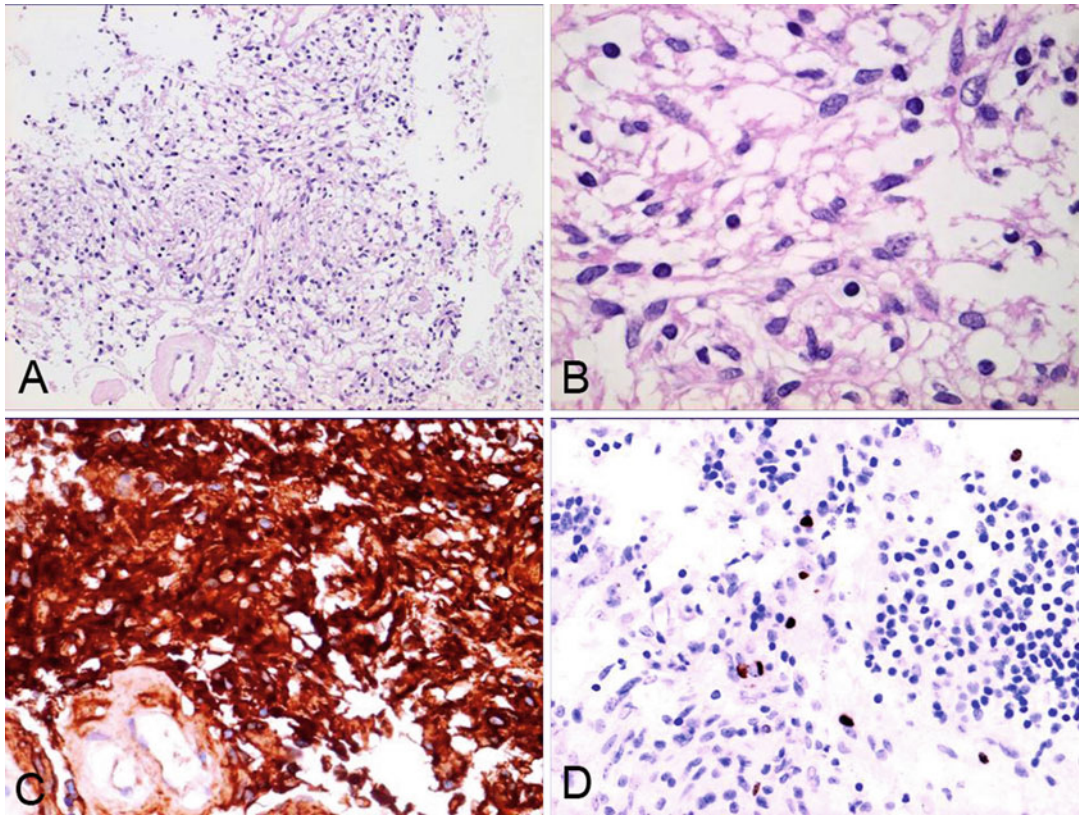

Fig. 22.4 Histopathology. (**a**) General view: Elongated cells (bipolars) disposed in bundles. There are not malignant criteria (hematoxylin-eosin). (With authorization of Retina. Ophthalmic Communications Society) (**b**) Detail: Bipolar cells with fair to moderate pleomorphism. (**c**) Immunohistochemical stain of glial protein showing high immunoreactivity, meaning these cells are astrocytes. (**d**) General view: Tumor and accompanying lymphoid infiltration

of the needle swaying the tumor within the retina can be felt, since typically the tumor is attached to the intraretinal space onto the surface of the adjacent pigmented epithelium but it does not invade it nor affects choroid. We have called this maneuver "tumoral slipping" (Vilaplana et al. 2006).

When retinoblastoma is suspected as differential diagnosis, fine-needle aspiration is not widely indicated because of the risk of extraocular extension (Shields et al. 1996; Shields and Shields 1999; Robertson 1997). In this case, other diagnostic methods and consulting to an ophthalmology oncologist should be the options chosen first to avoid unnecessary iatrogenesis.

In this regard and in order to differentiate both entities, it is important to remember that in contrast to retinoblastomas, astrocytomas can show peritumoral retinal tractions, atrophic areas of the pigmented epithelium that surrounds the tumoral mass and exudative areas next to the lesion. Similarly, retinoblastomas appear in childhood whereas acquired astrocytomas are typically diagnosed in young adults.

Vitreous seeds are very rare in astrocytic hamartomas but are not uncommon in retinoblastomas. However, de Juan et al. (1984) described a patient with astrocytic hamartoma in both eyes associated to tuberous sclerosis and vitreous seeds. Before this Van der Hoeve (1921) already described a cystic degeneration of an astrocytic hamartoma in small pieces that released the tumor and floated in the vitreous cavity. Vitreous hemorrhage does not help as a

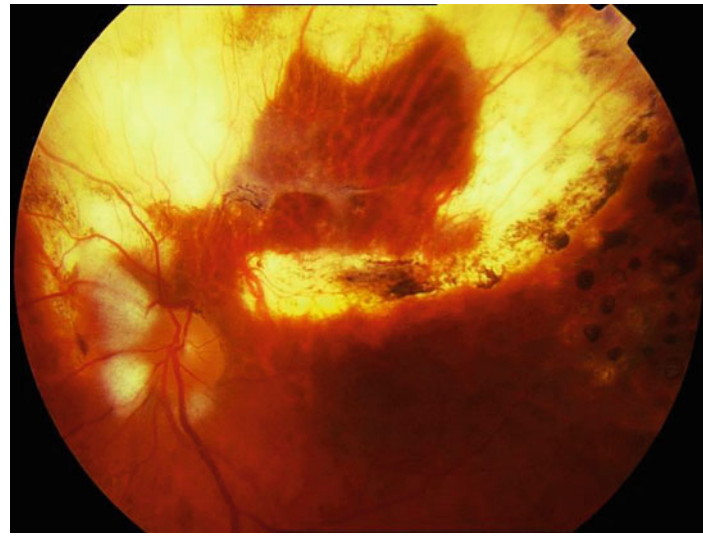

Fig. 22.5 Late post-surgical retinography. Choroid-retinal laser photocoagulation scars surrounding the retinal tumorectomy. Lipid deposits have completely disappeared. Note the sharp peripapillary myelination without exudation. Temporally to posterior pole post-laser scars are visible. During surgery section of the superior temporal vessels induced ischemia in that area that required photocoagulation

differential sign since it can happen in most of the intraocular tumors processes (Atkinson et al. 1973; Kroll et al. 1981).

Treatment

In contrast to the stationary, non-aggressive astrocytic retinal hamartomas (Zimmer-Galler and Robertson 1995) associated to tuberous sclerosis that do not cause ocular complications, acquired retinal astrocytomas need treatment due to their locally destructive behavior. All previously reported cases until 2006 have been managed with enucleation because of incorrect diagnoses as well as intraocular complications derived from the tumor itself (Zoógrafos 2002; Shields et al. 2004a; Shields and Shields 1999).

Radiotherapy is not effective in this pathology. Similarly to low-grade intracerebral astrocytomas, they are progressive and relapses after resection are frequent (Scanlon and Taylor 1979; Fazekas 1977) Laser photocoagulation (Bloom and Mahl 1991; Eskelin et al. 2008) and transpupillary thermotherapy have not been proved effective in retinal astrocytomas (Vilaplana et al. 2006).

The first case described in literature approached with conservative treatment was performed by our team in 2003 (Vilaplana et al. 2006) and published in 2006. We reported the case of a 49-year-old man with progressive vision loss for 5 months unsuccessfully treated with transpupillary thermotherapy (two sessions). Preoperative visual acuity was 20/200. Surgical technique consisted of vitrectomy, endodiathermy of the feeding retinal vessels, peritumoral retinotomy, use of perfluorocarbon liquid to position the retina, endophotocoagulation around the retinotomy, tumorectomy with the vitrectomy instrument and, at the end of the surgery, reconstitution of the ocular cavity with 5,000 Cs silicone oil. Six months later we performed silicone removal and phacoemulsification with intraocular lens implantation. Final visual acuity (Fig. 22.5) 8 years after surgery is 20/30 for distance and precision tasks for proximity without relapse signs of the disease. The advantage of retinal surgeons avoiding tumoral recurrence compared to brain surgery is that retinal resection can be performed with wide tumor-free security margins since the "only" consequence would be an increase of the visual field defect which is not a very worrisome fact considering the severity of the disease.

In April of the same year Mennel et al. (2006) reported for the first time photodynamic therapy with verteporfin (PDT) to treat a young man with vision loss secondary to an exudative hamartoma associated to tuberous sclerosis, which nowadays

is known as *aggressive retinal astrocytomas*. His visual acuity went down from 20/80 to 20/200 in 5 weeks of observation. Once it was treated with one PTD session with double amount of conventional exposition time (166 s) patient did not show recurrent vascularization of the tumor in 4 years of follow up with a final VA of 20/32.

Eskelin et al. (2008) treated two patients with retinal hamartomas with PTD using usual parameters for age related macular degeneration (689 nm, 600 mW/cm^2, 83 s. 50 J/cm^2). The first case was a juxtapapillary retinal astrocytoma secondary to tuberous sclerosis (*aggressive retinal astrocytoma)* that progressed affecting fovea in the last 7 months. The second one was a patient suffering from an acquired retinal astrocytoma that was growing despite of laser photocoagulation. Both cases experienced a reduction of the vascularized retinal portion of the tumor, with minimal changes in the congenital portion of the tumor. VA improved in the first case, from hands movements to 20/800, but did not change in the second cases being stable at 20/200. None of the two cases relapsed in the two next years. Exudative retinal detachment resolved completely. Tumor size decreased in a 30 %. Tumor regression was attributed to the tumoral vessels and the peritumoral capillary obliteration. Analyzing the three cases published of retinal hamartomas treated with PTD, only one of them turned to be an acquired retinal astrocytoma that did not show VA improvement (20/200). On the other hand, our case treated with endoresection had a final VA of 20/30.

Although conservative therapy in the management of acquired retinal astrocytomas is very limited, we could indicate PTD as a first treatment option since it causes minimal secondary effects and it is easy to perform compared to tumoral endoresection that needs a high experienced surgeon. The advantage of the surgical technique is that it is able to remove completely the tumor and when it is not invading fovea can provide VA improvement even in cases with exudative retinal detachment affecting macula. In contrast, PTD cannot eliminate the tumor and it maintains it in a remission state, being the 2 years the longest follow-up reported in the literature.

Acknowledgement Acknowledgments to Marta Pazos, for her contribution to the chapter translation.

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Presence of Both Ependymoma and Astrocytoma in the Same Patient: Diagnosis

23

Gordan Grahovac

Contents

Abstract

Multiple primary tumors in the central nervous system of different histological cell types are uncommon. Only case reports of concomitant central nervous system tumors have been reported, and only one case report of concomitant ependymoma and astrocytoma in one patient has been published. Multiplicity of primary CNS tumors should be considered in certain occasions, when clinical symptoms and signs are pointing in that direction. The entire spinal cord and brain should be imaged.

Introduction

Multiple metastatic brain tumors and multifocal primary brain tumors of a single histological type have been published in the adult and pediatric neurosurgical literature. However, the simultaneous occurrence of multiple primary brain tumors with different cell types is rare. Russell and Rubinstein classified multiple intracranial tumors into two categories that are still used today: multiple tumors and multicentric tumors. Multiple tumors were interpreted to result from dissemination by an "established" route such as via the commissural pathways, blood, CSF channels or through local extension. Multicentric tumors are widely separated lesions in different locations that do not easily fit into one of the pathways of dissemination (Russell and Rubinstein 1977).

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_23,

Multiple or multicentric central nervous system neoplasm can occur in patients who have been treated with chemotherapy or radiotherapy, patients with know genetic mutations, or those with multiple tumors occurring at different times (Butti et al. 1982; Schoenberg 1977). It has been shown that the patients with neurofibromatosis and tuberous sclerosis have increased incidence of multiple tumors (Lothe et al. 1993). Several genes mutations including *TP53, hSNF5/INI-1,* as well as other chromosomal abnormalities showed that multiple tumors occur in syndromes such as Li-Fraumeni, Aicardi X, and Turcot Syndromes (Pollack et al. 2002; Sévenet et al. 1999). The true incidence of two simultaneously occurring tumors of different histology cannot be calculated due to extreme rarity of such central nervous system neoplasm. Search of the literature revealed only one case of co-occurrence of cerebellar pilocytic astrocytoma and ependymoma of cauda equina (Marinovic et al. 2009).

Case Presentation

In our case a 26-year-old previously healthy woman presented with 10-year history of progressive low back pain, which had become worse in the last few months. She also presented with sensation of numbness and pain that radiated down the left foot and noticed increased weakness of the left leg. There was no bowel or bladder dysfunction. Spinal magnetic resonance imaging (MRI) scans demonstrated a well demarcated highly enhanced round mass at L1 to L5 level (Fig. 23.1). To exclude possible ependymoma drop metastasis an additional MRI scans of the neuroaxis was performed. Brain MRI revealed small cystic mass in the right cerebellar hemisphere (Fig. 23.2). Histologically, the conus medullaris tumor was diagnosed as myxopapillary ependymoma (WHO Grade I), and the cerebellar tumor was diagnosed as pilocytic astrocytoma.

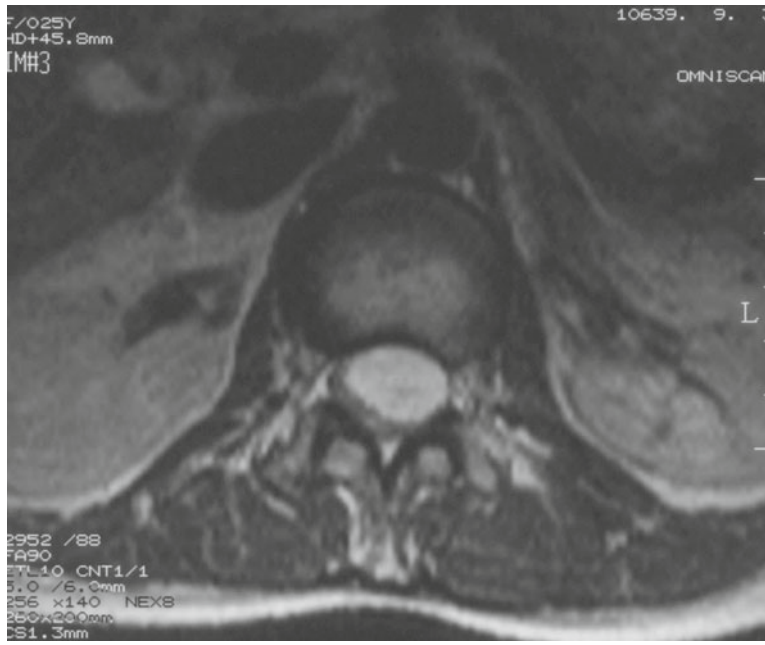

Fig. 23.1 Contrast-enhanced axial T2-weighted image of the lumbar spine showing intradural extramedullary lesion in 26-year-old woman with myxopapillary ependymoma

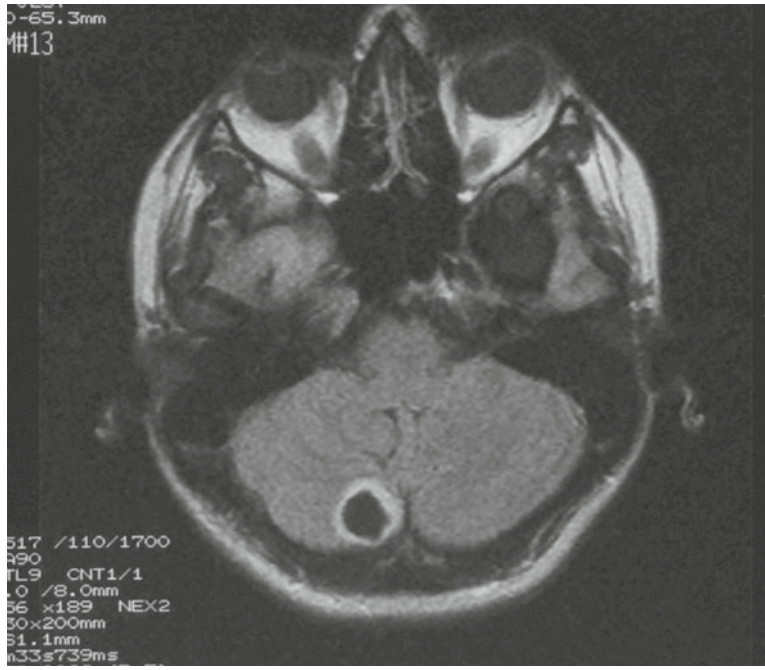

Fig. 23.2 Contrast enhanced axial FLAIR-weighted MRI scan of the head showing cystic tumor of the right cerebellar hemisphere

Pilocytic Astrocytoma Imaging Features

Pilocytic astrocytomas (WHO grade I) are well-circumscribed tumors that predominantly reside within the cerebellum, brainstem, optic nerve and third ventricle in children and young adults. They are macroscopically well delineated from the normal brain tissue, and they tend to grow very slowly. Sometimes they may have a significant cystic portion. Computed tomography (CT) might be the first-line diagnostic imaging. The lesion usually appears hypodense, and contrast enhancement is usually low or absent. MRI is the "gold standard" imaging study for showing the tumor's exact location, size, extent, vascularity, and relationship to adjacent structures. On MRI, pilocytic astrocytoma appears as hypointense structures on T1-weighted images and as hyperintense lesions on T2-weighted images. Contrast enhancement is almost absent. If they show significant contrast enhancement they may cause confusion with high-grade glioma.

Myxopapilary Ependymoma Imaging Features

Imaging of the spine and spinal cord has traditionally been accomplished with plain radiography, myelography, and CT. MRI imaging has become the technique of choice in the assessment of lesions of the spine and spinal cord. Myxopapillary ependymomas are highly vascular tumors that arise almost exclusively in the thoracolumbar region and produce symptoms that may mimic discogenic pathology. The MRI findings in myxopapillary ependymoma are nonspecific. Lesions are occurring most often at the level of the L2 vertebral body, and seldom tumor extends over five or more vertebral segments. Tumor might extend also into neural

foramina. The T1-weighted signal of the tumor mass is usually isointense, but it can be also hypointense and less commonly hyperintense. The T2-weighted signal of the tumor mass is always hyperintense. Enhancement degree and pattern is variable in spinal cord ependymomas (Wippold et al. 1995).

In conclusion, only one case of simultaneous myxopapilary ependymoma of the conus medullaris and pilocytic astrocytoma of the cerebellum has been reported in the literature. The final diagnosis can be reached only after histopathologic examination. The co-occurrence of two different neuroepithelial tumors raises interesting question of possible associative mechanism between this two different histologic pathologies.

The suggested mechanism of this association is that primitive multipotent cells might have been displaced in the different CNS areas and developed in different tumor cells.

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Part VII

Hemangiomas

Total Removal of Cavernous Hemangioma Using the Tonsillouveal Transaqueductal Approach (Method)

24

Ruben Dammers, Ernst J. Delwel, and Ali F. Krisht

Contents

Abstract

Recent advances in microsurgical techniques facilitate surgical resection of brainstem lesions that were previously considered inoperable. Cavernous hemangiomas with repeated hemorrhage that reach the pial surface or display progressive neurological deficits can be resected safely with acceptable morbidity. Various approaches to the mesencephalon or midbrain, tailored to the exact location of the lesion, have been described. In this chapter we describe a novel approach to the mesencephalic tegmentum via the aqueduct, adding to contemporary microneurosurgery, respecting functional anatomy and minimizing neurological deficits.

Introduction

Dorsal Mesencephalon Anatomy

The mesencephalon or midbrain connects the rhombencephalon (pons, cerebellum, and medulla oblongata) with the thalamencephalon and cerebral hemispheres. Traditionally, it is divided into three regions, from dorsal to ventral surface: the tectum, tegmentum, and basis pedunculi or crus cerebri. The posterior midbrain or tectum contains the inferior and superior colliculi, together termed the corpora quadrigemina. The tectum and the more ventral tegmentum are separated by

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_24,

the narrow, about 15 mm long, cerebral or Sylvian aqueduct, connecting the third and fourth ventricle. The aqueduct is surrounded by a nuclear region, the periaqueductal gray. The tegmentum extents from the substantia nigra ventrally to the periaqueductal gray dorsally. It also contains, amongst others, the red nucleus, medial lemniscus, spinothalamic tract, medial longitudinal fasciculus, decussation of cerebellar peduncle, oculomotor and trochlear nucleus, and Edinger-Westphal nucleus.

Midbrain Cavernous Hemangioma

Cavernous hemangiomas or cavernomas are well-defined, lobulated low-flow vascular lesions, varying in size from approximately 1 mm to 4 cm (Jellinger 1986; Lekovic et al. 2011). Their lumpy appearance has often been compared to a mulberry, a comparison that is emphasized by its dark reddish color. The mass is a honeycomb of unequal spaces filled with blood and separated by fine fibrous strands. The blood spaces are lined with a monolayer of endothelial cells and lack normal vessel wall elements such as smooth muscle cells. The neighboring tissues are usually toughened by gliosis and stained yellowish brown by hemosiderin, suggestive of recurrent hemorrhages.

Both sporadic and familial forms of cavernous hemangiomas exist. The familial form is usually manifested as multiple supra- and infratentorial lesions (Hayman et al. 1982; Brunereau et al. 2000). Three genetic loci have been mapped thus far: CCM1 (CCM = cerebral cavernous malformation) on chromosome 7q, CCM2 on7p, and CCM3 on 3q (Dashti et al. 2006; Mindea et al. 2006). The sporadic form occurs as an isolated event, most commonly with a single de novo lesion. (Hayman et al. 1982; Mindea et al. 2006) The true prevalence of cerebral cavernomas in the general population is unknown. Data from post-mortem studies suggest that cavernous malformations affect up to 0.7% of the population (Voigt and Yaşargil 1976; Otten et al. 1989; Kim et al. 1997). This corresponds well with the results of large MRI-studies, calculating an incidence rate of 0.4–0.5% (Del Curling et al. 1991; Robinson et al. 1991). Cerebral cavernomas can be found in every region of the central nervous system, with the supratentorial location represented in almost 70–80% of intracranial cases. In the infratentorial compartment, approximately 20% of cavernous hemangiomas are located in the mesencephalon (Fritschi et al. 1994; Abla et al. 2010).

Clinical Correlates

The annual rates of hemorrhage estimated from surgical series are in the range of 2.5–6.8% per year (Del Curling et al. 1991; Robinson et al. 1991; Fritschi et al. 1994; Kim et al. 1997; Porter et al. 1999; Lekovic et al. 2011). For patients with a history of prior symptomatic hemorrhage, the risk of rehemorrhage ranged from 5.1 to 60% annually (Porter et al. 1999; Wang et al. 2003). In the midbrain, because of the eloquence of surrounding structures, even relatively small hemorrhages are likely to be symptomatic.

Generally, the clinical course shows a stuttering pattern with improvement in between episodes of hemorrhage. The development of symptoms in patients experiencing a hemorrhage from a cavernous hemangioma is characteristically acute and maximal at onset (Porter et al. 1999; Abla et al. 2010; Lekovic et al. 2011). The neurological deficits from this first episode tend to resolve nearly completely as the hemorrhage is organized and absorbed. When, however, rebleeding occurs, there is an increased risk for more severe and permanent deficits.

For the mesencephalon, the clinical presentation of a symptomatic hemorrhage obviously depends on the nuclei and tracts that are displaced or affected. We focus on lesions in the tectum and tegmentum in this chapter. Frequently encountered symptoms include impaired consciousness (29%), signs of increased intracranial pressure (38%), cranial nerve deficits (37%) (amongst which Parinaud's syndrome (3%), diplopia with and without internuclear ophthalmoplegia (26–69%), and pupillary abnormalities), sensory disturbances (3–20%), vertigo (23%),

hemiataxia (31–38%), intention tremor (10%), hemichorea, hemiathetosis, and/or hemiplegia (51%) (Fritschi et al. 1994; Porter et al. 1999; Sindou et al. 2000; Wang et al. 2003; Abla et al. 2010; Giliberto et al. 2010).

Approaches to the Dorsal Midbrain

Surgery is warranted in appropriately selected patients given that surgical outcome is favorable compared to natural history. Indications for surgery are appropriate if the cavernoma or hematoma reaches the pial surface, if progressive neurological deficits (due to mass effect or repeated hemorrhages) are observed, or if overt (sub)acute hemorrhage results in significant mass effect. Hemorrhages extending beyond the lesion capsule are experienced to have a greater risk of rebleeding and are therefore treated surgically at first presentation (Sindou et al. 2000; Abla et al. 2010; Lekovic et al. 2011). Asymptomatic patients or those with a considerable rim of brainstem tissue that would need to be transgressed to resect a brainstem cavernoma should be observed. Future hemorrhagic events in observed patients may provide a more accessible corridor to the cavernoma for resection. An associated venous anomaly should always be salvaged as damaging it might result in venous infarction or congestion (Porter et al. 1999; Perrini and Lanzino 2006).

In general and regardless of location, cavernous hemangiomas are accessed through minimal cortical openings. This can be achieved by applying the so-called two-point method as proposed by Brown et al. (1996). One point is placed at the center of the lesion, and a second point is placed either where the lesion comes closest to a pial surface or at the safest entry point into the brainstem. Connecting these two points, a line is drawn and extended to the skull, guiding the selection of the most appropriate craniotomy. Several "safe entry zones" have been described, that can be used as relatively safe but narrow surgical corridors into the brainstem where critical neural structures are sparse and no perforating arteries are encountered (Giliberto et al. 2010). Neuronavigation can be of great help to localize the lesion or "safe entry zone", but should never replace a neurosurgeon's experience and neuroanatomical knowledge. Intraoperative monitoring, such as somatosensory evoked potentials, electroencephalography, motor evoked potentials, and brainstem auditory evoked potentials, is a valuable adjunct to minimize complications (Morota et al. 2010). Although these techniques provide continual feedback, neurological deficits are not always preceded by changes in the waveforms. Again, a meticulous microneurosurgical technique and profound knowledge of neuroanatomy are extremely important for avoiding postoperative deficits.

Lesions in the posterior midbrain are approached by the infratentorial supracerebellar route, with several modifications described (Yaşargil 1984–1996; Kaku et al. 1999; Porter et al. 1999; Sindou et al. 2000; Steinberg et al. 2000; Ammirati et al. 2002; Abla et al. 2010; de Oliveira et al. 2010; Giliberto et al. 2010; Lekovic et al. 2011). In a cadaveric study, Ammirati et al. (2002) have shown that the median, paramedian, and extreme-lateral variants provide sufficient access to different parts of the posterior midbrain. Kaku et al. (1999) add that the paramedian infratentorial supracerebellar approach, extended through a transcollicular approach, permits safe removal of intrinsic tectal lesions, without causing any apparent neurological deficit. The occipital transtentorial approach is an alternative for patients with a steep tentorial slope (Sindou et al. 2000; Steinberg et al. 2000; Wang et al. 2003). Furthermore, there has been one recording of a combined infratentorial supracerebellar and transaqueductal approach for resection of a periaqueductal glioma (Koziarski et al. 2004).

Tonsillouveal Transaqueductal Approach

To begin with, again the risk-benefit ratio of surgical intervention for mesencephalic cavernous hemangiomas is ambiguous and poses a complex decision-making process. Therefore, the tonsillouveal transaqueductal approach as presented here should not be considered the approach of

Fig. 24.1 Artist impression of the tonsillouveal transaqueductal approach

choice for every cavernoma in the tegmentum. The tonsillouveal part of the approach and its relevant surgical anatomy have been described extensively in the past (Lister et al. 1982; Matsushima et al. 1982; Mussi and Rhoton 2000; Tanriover et al. 2004; Deshmukh et al. 2006; Yasargil and Abdulrauf 2008), and corresponds to the originally coined telovelar approach in a series of papers in the early 1980s (Lister et al. 1982; Matsushima et al. 1982). We postulated the term tonsillouveal in 2009 (Dammers et al. 2009), in concordance with Shigeno et al. (2002) and the description of a median inferior suboccipital approach along the tonsillouveal sulcus by Yaşargil (1984–1996). It is considered the optimal route for approaching lesions of the fourth ventricle. Patients are either positioned in semi-sitting position or prone with the head flexed, depending on the surgeon's preference. A craniocaudal midline incision is extended from the inion to approximately the C2-3 spinous processes. A suboccipital craniotomy, from just below the torcula to the foramen magnum, with or without C1 laminectomy is performed. The cisterna magna is then opened through a midline dural incision below the circumflex sinus and opened in a Y-shaped manner over the cerebellar hemispheres to release cerebrospinal fluid. Using the operating microscope, the cerebellomedullary fissure is identified between the cerebellar tonsils and medulla. Microsurgical opening of the arachnoidal layers allows the separation of the two tonsils and provides access to the tonsillouveal sulcus, located between the uvula and the nodulus. This allows visualization of the foramen of Magendie, the tela choroidea, and the inferior medullary velum. The tela and velum arachnoid layers are opened up to the level of the choroidal point of the posterior inferior cerebellar artery. The choroid plexus is then split in the midline, providing a wide access to the entire floor of the fourth ventricle and exposure of the ipsilateral superolateral recess and foramen of Luschka. By removal of the C1 arch the craniocaudal exposure of the rostral aspect of the fourth ventricle is improved (Tanriover et al. 2004). The inferior outlet of the cerebral aqueduct is thus exposed. Figure 24.1 gives an artist expression of this

approach by the senior author (AFK). The operative angle of the approach is limited by the superior medullary velum.

When the aqueduct is reached, the part of the cavernoma that grows exophytically into the aqueductal lumen or where it reaches the surface on the aqueductal anterior surface is identified. By evacuating the intralesional hematoma, gently dissection, and circumferentially coagulating at low intensity the cavernoma is shrunk in a concentric manner. This minimizes the need to enlarge the window through the floor of the aqueduct. A piecemeal resection of the cavernoma is thus performed. At the end of the resection, the lesion cavity is precisely examined to ascertain the complete removal and to obtain meticulous hemostasis. In some cases the caverns of the cavernoma may lack a surrounding gliosis, and the caverns may be hidden within the parenchyma. These parts deserve particular attention in order to ensure complete resection. This surgical finding of a multi-lobulated cavernoma with a thin wall and satellite nodules separated by a thin layer of intact white matter, as opposed to the more frequent finding of a discrete lesion with a thick capsule, carries a higher risk of residual cavernoma. Any associated venous anomaly should be salvaged as stated earlier (Porter et al. 1999; Perrini and Lanzino 2006).

Illustrative Case

This case was reported previously (Dammers et al. 2009). A 52-year old, right-handed woman presented with an 8-year history of slowly progressive hemiparesis and ataxia involving the right side of her body. During the last 6 months she developed dysarthria and dysphagia. There were no signs of increased intracranial pressure. Otherwise, the patient had normal cognition, was well oriented, and her cranial nerve examination did not show any significant deficits. Her motor examination revealed right-sided spastic hemiparesis (MRC 4). Cerebellar examination was abnormal with bilateral ataxia and dysdiadochokinesias. Her deep-tendon reflexes were increased bilaterally in all extremities and she had positive Babinski signs as well. She had an abnormal gait with an element of ataxia with circumduction of the right leg. The patient's magnetic resonance imaging revealed a relatively large, rounded lesion involving the tegmentum of the mesencephalon (Fig. 24.2). On T1- and T2-weighted images, as well as on the fluid attenuated inversion recovery (FLAIR) images, the lesion had the characteristics and intensity features of a cavernous hemangioma.

The operative approach is described above. Looking through the aqueduct and at a point 5 mm superior to its inferior inlet, there was a small cherrylike blister protruding into the aqueductal anterior surface. This was consequently used as the entry point to access the cavernoma. The total removal of the lesion was achieved with preservation of a venous channel, noted within the bed of the cavernoma cavity. Histopathology was consistent with a cavernous hemangioma.

Immediately postoperatively, the patient was noticed to be lethargic. It appeared that there was a non-communicating hydrocephalus secondary to obstruction within the aqueduct. An external ventricular shunt was inserted, after which the patient immediately improved and became awake and alert, following commands and moving all extremities. Eventually, the patient needed a ventriculoperitoneal shunt. At the time of discharge, cranial nerve examination revealed a right-sided internuclear ophthalmoplegia and worsened dysarthria. Otherwise, the neurological examination was consistent with preoperative findings. The 1-year postoperative neurological examination was consistent with preoperative findings, although some diplopia persisted. Figure 24.2 shows the preoperative and postoperative MRI scans after 1 year.

Hazards and Complications

In general, for brainstem cavernomas surgical resection is deemed appropriate if they reach the pial surface, show progressive neurological deficits, or cause significant mass effect due to large intra- or extralesional hemorrhage. When indicated, brain stem cavernoma surgery is

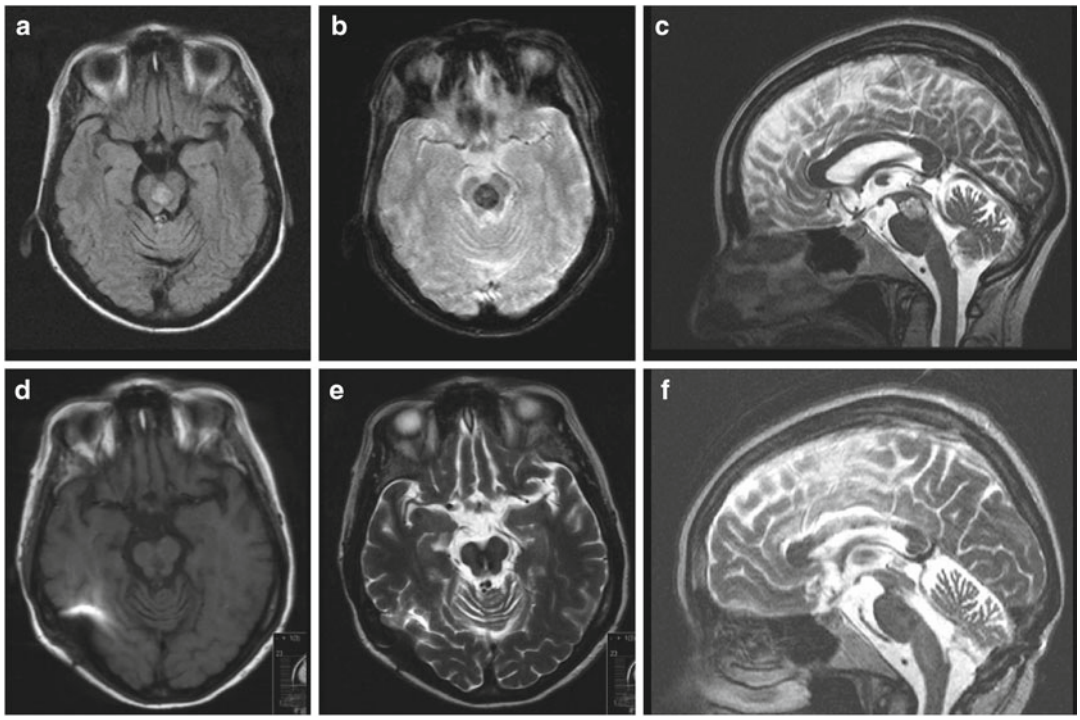

Fig. 24.2 Pre- (a–c) and postoperative (d–f) magnetic resonance imaging scans of a patient with mesencephalic cavernous hemangioma. (**a**) T1-weighted axial image of the cavernoma. (**b**) gradient spin echo axial image showing the hemosiderin deposit. (**c**) T2-weighted sagittal image of the cavernoma. (**d**) T1-weighted axial image 1-year postoperatively. (**e**) T2-weighted axial image 1-year postoperatively. (**f**) T2-weighted midline sagittal image showing the resection bed. The cavernoma has been resected completely

challenging and demanding and is to be performed by neurosurgeons who are well-trained in microneurosurgical techniques and have proficient neuroanatomical knowledge of the brainstem region and posterior fossa. Complications may be related to either the surgical approach, positioning of the patient, anesthesia, injury to surrounding vessels or brain parenchyma, or inadequate microsurgical techniques. It is therefore important to select the optimal surgical approach and anticipate the surgical window and trajectory carefully, preferably using the two-point method. One needs to bear in mind that transgression of eloquent brainstem areas should always be avoided and safe entry zones can be assessed by the use of neuroanatomical landmarks, neuronavigation, and electrophysiological monitoring. Again, the tonsillouveal transaqueductal approach as described in this chapter is not to be regarded a standard approach to lesions within the brainstem tegmentum. It is, however, an approach that may also be considered when planning for surgery in individual patients.

Mortality for brainstem cavernoma surgery is low (0–4%), and severe morbidity is experienced in 10–15% of patients (Fritschi et al. 1994; Porter et al. 1999; Sindou et al. 2000; Steinberg et al. 2000; Wang et al. 2003; Lekovic et al. 2011). An early intra-axial rebleed is rare, but can have devastating results. Patients with new deficits experience symptoms similar to those that appeared with prior hemorrhages, and often make a significant recovery over time. The neurological symptoms correspond to nuclei and structures located at the site of the lesion and the approach used. Also, hydrocephalus and cerebrospinal fluid leakage might occur in about 15% of cases. Residual cavernoma might be found on postoperative MRI and should be closely monitored. It poses a future risk of rebleeding. In cases with suspected residual lesion, patients

might be returned to (second look) surgery to remove additional cavernoma to maximize protection from future events or cavernoma growth.

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Cavernous Sinus Hemangiomas Treated with Gamma Knife Surgery

25

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Contents

Abstract

Cavernous hemangiomas within the cavernous sinus (CS) are a rare group of extra-axial vascular tumors. They share a similar histology with the more common intra-axial cerebral cavernous malformations. However, these two lesions are different in clinical behavior and treatment response. CS hemangiomas are true vascular neoplasms that produce symptoms and signs as a result of progressive tumor growth and mass effects. Microsurgical resection of the tumor may be associated with high risks of excessive hemorrhage and damage to cranial nerves during surgery. Incomplete surgical removal necessitates additional fractionated radiotherapy or stereotactic radiosurgery.

Although the use of stereotactic radiosurgery for the management of cerebral cavernous malformations is controversial, it is generally agreed that radiosurgery is very effective in treating CS hemangiomas. Cumulative data from the most recent decade have demonstrated that radiosurgery can significantly reduce the tumor size and improve patients' clinical symptoms/signs within several months after treatment. Complications related to radiosurgery are rare. Long-term follow-up after treatment reveals a high tumor control rate without recurrence of the tumor. In this report, we review the literature, and include our experience in the radiosurgical management of CS hemangiomas. Characteristic

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_25,

neuroradiological imaging findings of the tumor, radiosurgical methods, and treatment results for this unique group of tumors are described.

Introduction

Cavernous hemangioma arising from the cavernous sinus (CS) is a rare extra-axial vascular neoplasm that accounts for 2–3% of all CS tumors (Linskey and Sekhar 1992), and occurs predominantly in middle-aged female patients (Gonzalez et al. 2006). Both the extra-axial CS hemangioma and intra-axial cavernous malformation share a similar histological feature, that is, they are composed of multiple vascular sinusoids lined by a single-layer endothelium, and separated by fibroconnective tissue stroma without intervening of the brain tissue. Differing from the more common intra-axial or parenchymal cavernous malformation, CS hemangioma grows and enlarges over time, and distorts and compresses adjacent structures, but rarely bleeds spontaneously. CS hemangioma is a true benign neoplasm with a well-demarcated margin, and produces symptoms and signs as a result of the progressive tumor growth and mass effect. In contrast, cavernous malformation is a vascular hamartoma or malformation, and usually induces seizures or focal deficits as sequelae after a hemorrhagic event. CS hemangioma is now considered as an entity apart from the cavernous malformation, because they both differ in clinical manifestations and natural courses of the disease (Gonzalez et al. 2006).

The typical MR imaging appearance of a CS hemangioma includes a low-to-iso-dense mass lesion on the T1-weighted image, extremely high intensity on the T2-weighted image (as bright as the signal of cerebrospinal fluid), and strong homogeneous or heterogeneous enhancement after a Gd-DTPA injection (Katayama et al. 1991; Sohn et al. 2003; Yao et al. 2006; Jinhu et al. 2008). As the CS hemangioma grows, the internal carotid artery is usually encased by the tumor, but without narrowing. This MR appearance can be differentiated from that of the more common CS meningioma, in which the carotid artery is usually compressed and narrowed (Chou et al. 2010). Because of accumulated experience and improved knowledge in the neuroimaging diagnosis, most CS hemangiomas can now be identified and differentiated from other tumors on MR images, based on their characteristic radiological findings.

The optimal treatment strategy for CS hemangioma is still controversial. Microsurgery with piecemeal dissection of the tumor may result in severe intraoperative bleeding and cranial neuropathy, due to the hypervascularity of the tumor and the CS opening. The post-operative mortality rate was high in the past as a result of the uncontrollable bleeding, with a death rate of 36% before 1983 (Linskey and Sekhar 1992) and 12.5% in 65 reported cases before 1999 (Ohata et al. 1999). Over the years, neurosurgeons have regarded the resection of CS hemangiomas to be a great challenge, thus several surgical techniques have been recommended. These techniques include a combined intradural and extradural approach with proximal vascular control (Linskey and Sekhar 1992), an extradural approach (Goel et al. 2003; Suri et al. 2007), induced systemic hypotension (Ohata et al. 1999), pre-operative embolization (Namba 1983), and intratumoral injection of the plastic adhesive material (Hashimoto et al. 2000). In the recent literature, the documented rate of complete excision of the tumor has ranged from 40.0 to 92.3%, and the neurological complications rate has ranged from 45 to 80% in several larger series of more than ten treated cases (Zhang et al. 2005; Zhou et al. 2003; Goel et al. 2003; Shi et al. 1999). For patients with incomplete tumor excision, fractionated radiotherapy has been recommended as an adjuvant treatment. Although only ten patients were reported in the literature between 1987 and 2006, most of these patients demonstrated tumor shrinkage with favorable responses after the radiation treatment (Shibata and Mori 1987; Yamamoto et al. 1992; Maruishi et al. 1994; Jamjoom 1996; Miserocchi et al. 1997; Tsao et al. 2003; Grosu and Nieder 2006).

Although fractionated radiotherapy has shown its efficacy in treating CS hemangiomas, stereotactic radiosurgery using the Gamma

Knife for a single-session conformal treatment is seemingly more beneficial. Iwai et al. (1999) reported a single case of CS hemangioma successfully treated with Gamma Knife radiosurgery (GKS) after a partial tumor removal. Because of the dramatic response in tumor shrinkage and favorable outcome in patients after GKS, nine more reports related to GKS for CS hemangiomas have since been published. In the earlier publications, the case number in each report was small (1–5 patients), with a shorter follow-up time, ranging from 6 months to 3 years (Thompson et al. 2000; Seo et al. 2000; Kida et al. 2001; Nakamura et al. 2002; Peker et al. 2004; Ivanov et al. 2008). Recently, several reports with a larger number of patients and a longer follow-up period have been published (Khan et al. 2009; Yamamoto et al. 2010; Chou et al. 2010). These recent reports confirmed the efficacy of radiosurgery for long-term tumor control. In most of the patients, marked tumor shrinkage, with 50–90% volume reduction, and symptomatic improvement were observed as early as several months post-treatment, and there was no evidence of tumor recurrence during up to 13 years of follow-up. Based on the promising results obtained with GKS, the authors recommended that stereotactic radiosurgery can serve as a primary treatment for patients who have demonstrated clear neuroimaging characteristics of CS hemangiomas.

Clinical Presentation

Women have an overwhelming predilection for CS hemangiomas. In Linskey and Sekhar's (1992) review of 53 patients with CS hemangiomas reported between 1943 and 1992, 94% were female patients. In a recent series report by Chou et al. (2010), 71% (5 of 7) of patients were women, with a median age of 47 years at the time of diagnosis. In 30 cases in a recently reported Japanese combined study, the female/male ratio was 19/11 (Yamamoto et al. 2010). It is generally agreed that CS hemangiomas are more commonly found in middle-aged patients of 40–50 years old, although a wide range of age may be seen.

The clinical manifestations and clinical tumor course do not differentiate CS hemangiomas from other benign CS neoplasms. The development of symptoms and signs of a CS hemangioma is mainly related to the expanding mass effect of the tumor, which may result in compressive damage to the 3rd–6th cranial nerves within the CS. Patients with CS hemangiomas most often have cranial neuropathies with diplopia, ptosis, progressive visual impairment and headaches. Less frequent clinical manifestations include endocrinopathy, exophthalmos, trigeminal neuralgia and hemi- or monoparesis. Rarely, CS hemangiomas may be associated with cutaneous hemangiomas on the face or scalp (Thompson et al. 2000; Chou et al. 2010).

Radiological Characteristics

With its ability to demonstrate versatile tissue contrast, anatomic details and major vasculatures, MRI has become the primary diagnostic tool for detecting cavernous sinus tumors. CS hemangiomas usually appear on MRI as a well circumscribed, lobulated mass with hypointense or isointense signals on T1-weighted images, markedly hyperintense signals on T2-weighted images, and strongly homogeneous enhancement on delayed contrasted images. These characteristic MR features are due to the abundant blood filling the sinusoid spaces, soft tissue contents and presence of a fibrous pseudo-capsule (Linskey and Sekhar 1992; Sohn et al. 2003). The high T2-weighted signal intensity of the CS hemangioma can be as bright as the surrounding cerebrospinal fluid, and readily differentiated from the iso- or low-signal intensity caused by soft tissue components in other CS tumors (Fig. 25.1). When the CS hemangioma enlarges, it will encase the cavernous segment of the internal carotid artery. However, the caliber of the artery usually remains normal due to the soft and vascular consistency of the tumor (Fig. 25.1a, b). Similar to cavernous hemangiomas in other extracranial organs, CS hemangiomas may demonstrate a characteristic MR enhancing pattern of progressive "filling in" of the contrast material on

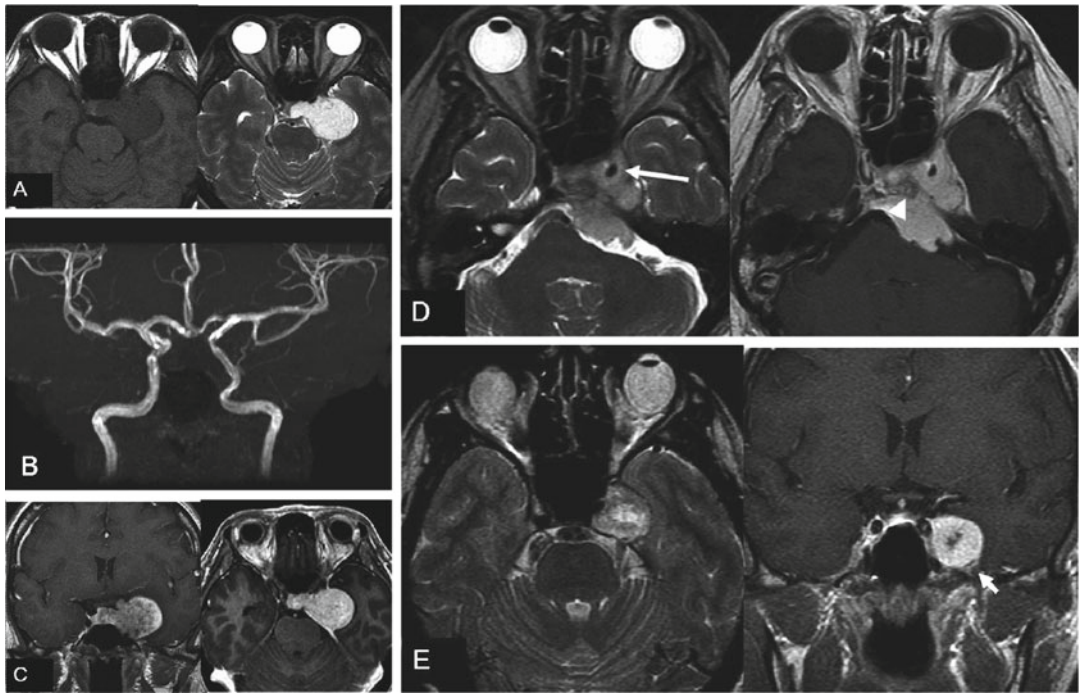

Fig. 25.1 (**a**) to (**c**) are images of a left CS hemangioma from the same patient. (**a**): This CS hemangioma appears on MRI as a well-circumscribed, lobulated mass with hypointense or isointense signals on the T1-weighted image (*left*), and markedly hyperintense signals on the T2-weighted image (*right*). (**b**): The TOF MRA image reveals a normal caliber of the left internal carotid artery despite its encasement by the CS hemangioma. (**c**): On the early post-contrast coronal T1-weighted image, the tumor shows heterogeneous, mottled enhancement (*left*), which turns into strongly homogeneous enhancement on the delayed contrasted axial T1-weighted image (*right*). (**d**): A CS meningioma with an isointense or mild hyperintense signal in the T2-weighted image (*left*), and mild constriction of the left internal carotid artery (*arrow*). Hyperostosis of the dorsum sella (*arrow head*) is noted on the post-contrast axial T1-weighted image (*right*). (**e**): Trigeminal schwannoma shows heterogenous signal intensity on T2-weighted image (*left*) and heterogenous enhancement (*right*) due to the co-existence of solid and cystic components. The lesion arises from the left Meckle's cave with inferolateral displacement of the mandibular branch of the left trigeminal nerve (*arrow in right*)

sequential or dynamic MR images (Salanitri et al. 2004; Jinhu et al. 2008) (Fig. 25.1c).

The imaging diagnosis of CS hemangiomas needs to differentiate these from other more common tumors involving the CS, mainly meningiomas and schwannomas. The meningioma usually appears as a well-demarcated soft tissue mass in the CS with an isointense or mildly hyperintense signal (as the signal of gray matter of the brain tissue) on T2-weighted images. In meningiomas, adjacent hyperostosis, dural tail signs, or encasement and constriction of the cavernous segment of the internal carotid artery are common (Fig. 25.1d). Schwannomas involving the CS usually show heterogeneous signal intensity and contrast enhancement on MRI, due to their heterogeneous distribution of tissue components of Antoni type A and type B, with the appearance of focal cystic degeneration, hemorrhage or calcification inside the tumor (Fig. 25.1e).

Radiosurgery Treatment Methods

Patient Selection and Pre-GKS Evaluation

Patients with a residual CS hemangioma after partial resection or biopsy of the tumor are good candidates for the subsequent GKS. Alternatively,

if patients were found to have a neoplasm inside the CS with the distinctive imaging characteristics of a CS hemangioma, and the estimated risk of hemorrhage or cranial neuropathy after open surgery is high, GKS may be indicated as the first-line treatment (Yamamoto et al. 2010; Chou et al. 2010). Prior to GKS, a thorough clinical evaluation, including a neurological examination, ophthalmological test and neuroradiological study, is mandatory. In some cases, an X-ray cerebral angiography may be indicated for the differential diagnosis with a highly vascular meningioma, but it is not absolutely necessary.

Stereotactic Targeting Procedure

In radiosurgery, a Leksell Gamma Knife model B, C, or Perfexion (Elekta Instruments, Stockholm, Sweden) is used. A Leksell stereotactic G frame is fixed on the patient's head under local anesthesia. After the frame application, 3-dimensional localization of the tumor is accomplished with an MR examination using trans-axial and coronal 3-mm thin-cut images, with and without Gd-DTPA contrast enhancement. Due to the characteristically high signal intensity of the tumor on the T2-weighted image, both trans-axial and coronal T2-weighted images should be included in the examination. The high resolution MR images help to identify critical structures in detail, which allows selective radiosurgical treatment to the tumor while sparing the surrounding normal structures any radiation damage. The contour of the tumor is delineated on the transferred MR images in the GammaPlan treatment program. The surrounding critical structures, such as optic nerves and chiasma, 3rd, 5th and 6th cranial nerves in the cisternal portions, internal carotid artery, pituitary gland and stalk, are also defined.

Radiosurgical Dose Planning

Radiosurgical dose planning in GKS is routinely performed using the GammaPlan software system. The aim of the planning is to achieve effective radiation to the entire tumor target while maintaining a sharp dose gradient outside the tumor margin to spare radiation damage to the adjacent normal structures. In general, a multi-isocenter technique is needed to obtain conformal, selective radiation to the tumor target. For example, the median number of isocenters used in the University of Pittsburgh Medical Center to formulate a conformal radiosurgical plan was 7 (range, 3–13) (Khan et al. 2009). In Taipei, Chou et al. reported an average of 10 isocenters (range, 2–19) to treat CS hemangiomas (Chou et al. 2010). In addition, a suitable CO^{60} plugging pattern was used in selected patients for further optimization of the radiation dose distribution. Most portions of the tumor margin were covered by a 50–70% isodose line. However, the tumor margin adjacent to the optic pathway was slightly underdosed so that the margin of the optic nerve could be touched by a 30–40% isodose line (Fig. 25.2a–f). Such a meticulous adjustment of the radiation field ensures that optic nerves only receive a safe and low dose of irradiation. The internal carotid artery in the CS portion is also intentionally excluded from the high-dose coverage.

In the literature, the reported radiosurgical dose to the tumor margin for CS hemangiomas ranged from 10 to 19 Gy, with a maximum dose ranging from 19 to 38 Gy at the tumor center. The mean and median dose to the tumor margin reported in the Japanese combined study was 13.8 and 14.0 Gy, respectively (Yamamoto et al. 2010). In the report from Pittsburgh, the median dose to the tumor margin was 15 Gy, with a maximum prescription of 19 Gy (Khan et al. 2009). In Taipei, Chou et al. (2010) reported a lower mean margin dose of 12.2 Gy (range, 9.5–16 Gy), with a mean maximum dose of 24.2 Gy (range, 19–32 Gy). Ivanov et al. (2008) also reported a low-dose treatment using Gamma Knife for three CS hemangiomas, with a mean margin dose of 11.7 Gy (range, 10–13 Gy). They advocated that low-dose radiosurgery is also very effective for the treatment of CS hemangiomas, with a lower risk of radiation damage to the cranial nerves. In general, a margin dose around 12–13 Gy, a mean tumor dose of 15.5–17.5 Gy and a maximum

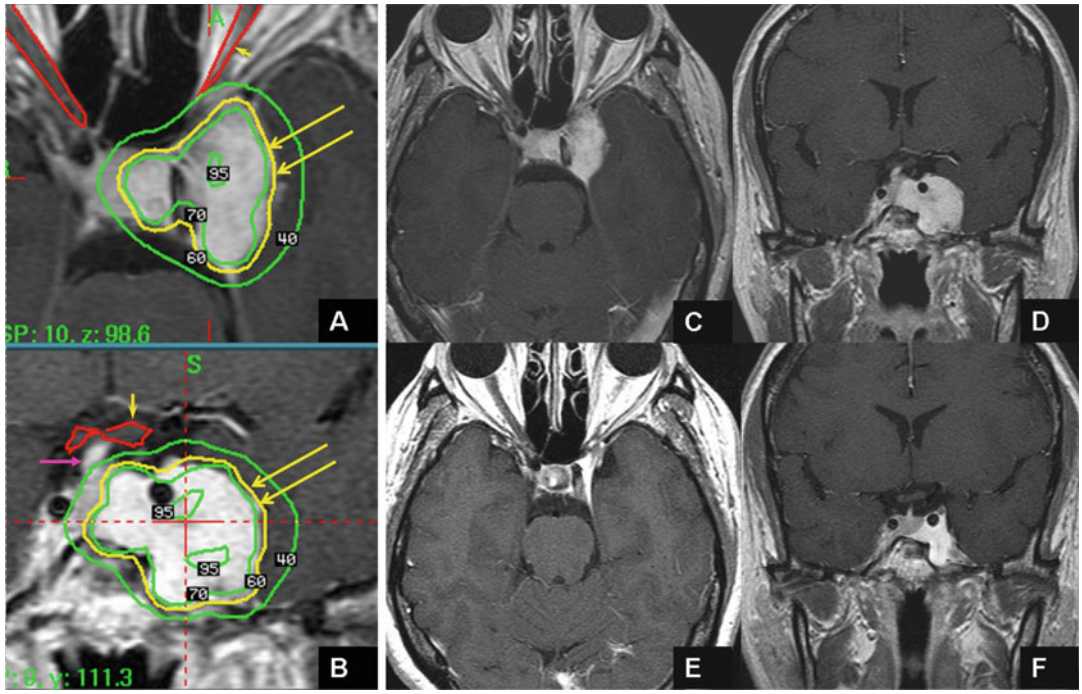

Fig. 25.2 (**a**): Radiation dose plan for a patient with a left CS hemangioma. This 46-year-old woman had double vision and headache before treatment. During radiosurgery, the treatment plan on axial MRI demonstrated a conformal radiation field covering the tumor margin at the 60% isodose level (*yellow line*). The dose to the tumor margin was prescribed as 12 Gy. The optic nerves were outside the 40% isodose level, and received less than 8 Gy of radiation (*yellow arrowhead*). (**b**): Coronal T1-weighted image with contrast enhancement in the same patient showing the optic chiasm was pushed upward and the pituitary stalk was pushed medially by the tumor. The isodose curve covered the tumor adequately and spared the optic apparatus and pituitary stalk (*magenta arrow*). (**c**) and (**d**): Pre-GKS status of the tumor in axial (**c**) and coronal (**d**) MR images. The tumor volume was measured as 9.0 cm^3. (**e**) and (**f**): Post-GKS status at the 12th month follow-up, showing conspicuous shrinkage of the tumor on axial (**e**) and coronal (**f**) MR images. The tumor volume was reduced to 2.3 cm^3. The patient's clinical symptoms of diplopia and headache improved completely

dose of 21–30 Gy are sufficient for the radiosurgical treatment of CS hemangiomas.

Gamma Knife Surgery Treatment Results

Because of the rarity of CS hemangiomas, the series reports of radiosurgery for these hypervascular tumors consist mostly of a small number of patients. After Iwai's first report of a case successfully treated by GKS in 1999, Thompson et al. (2000) published radiosurgical results for four cases, including three CS hemangiomas and one orbital hemangioma, treated at the University of Pittsburgh Medical Center. In this report, the tumor volume ranged from 5.2 to 10.8 cm^3, the tumors were treated with a margin dose of 14–19 Gy, and they were followed for 12–24 months. The follow-up result showed remarkable shrinkage of the tumors, with an average of 54% (range, 14–100%) volume reduction. All patients had symptomatic improvement after radiosurgery, except one who had persistent diplopia. There were no treatment-related complications.

Kida et al. (2001) presented three radiosurgical cases with similar results. The average tumor diameter in this series was 20.5 mm (range, 14.5–28 mm). During the mean follow-up of 27 months after radiosurgery, all of the tumors decreased in size. None of the patients showed any neurological deterioration, and one demonstrated an obvious

improvement in ocular movement. Nakamura et al. (2002) reported three cases with CS hemangiomas treated by GKS. They used a mean margin dose of 13.3 Gy (range, 12–14 Gy) for the treatment of tumors ranging from 3.3 to 9.5 cm^3. Follow-up MRI 3 months later showed a reduction in tumor volume, with improvement in the patients' neurological symptoms. Peker et al. (2004) reported five patients treated by GKS in Istanbul, Turkey; four of them had a previous partial surgical resection. They used a 14–16 Gy margin dose during radiosurgery. During the mean follow-up period of 32 months, all of the patients showed remarkable shrinkage of the tumor size, and two experienced symptomatic improvement.

Khan et al. (2009) published a second report of radiosurgical results for CS hemangiomas treated at the University of Pittsburgh. In this report, seven patients, including four newly treated cases, were enrolled for study and were followed up for an extended time, ranging from 40 to 127 months. In their four more recently treated cases, the margin dose to the tumor was slightly reduced to 12.5–14 Gy. However, the mean tumor volume reduction rate after GKS remained as high as 69% in the series. They concluded that, based on their extended experience, GKS is an effective management strategy for symptomatic CS hemangiomas, with long-term tumor control.

Yamamoto et al. (2010) reported a combined study of seven institutes in Japan, and included 30 cases of CS hemangiomas treated by GKS. The follow-up time in this study ranged from 12 to 138 months. Before radiosurgery, eight patients were asymptomatic, and 22 had symptoms of ocular movement disturbances and/or optic nerve impairment. After radiosurgery, two of the symptomatic patients showed complete remission, 13 showed improvement, and seven had no change in their neurological status. MRI follow-up of the 30 patients after radiosurgery showed remarkable shrinkage of the tumors in 18 (60%), slight shrinkage in 11 (36.7%), and no change in 1 (3.3%). There were no tumors showing transient volume enlargement after GKS, and no patients experienced tumor recurrence.

In 2010, Chou et al. in Taipei reported a consecutive series of seven patients with CS hemangiomas treated by GKS between 1993 and 2008. The tumor incidence was estimated as 2.5% (7/283) among all CS neoplasms treated in the same period at their institute. The follow-up period after GKS for these seven CS hemangioma patients ranged from 6 to 156 months; three of them had been followed for more than 5 years. Data from 84 patients with CS meningiomas treated by GKS during the same period were also analyzed for comparison. The MRI follow-up study of the seven CS hemangiomas revealed an average of 72% tumor volume reduction at the 6th month post-treatment. After 1 year, the tumor volume reduction was 80%. In the three patients who had over 5 years of follow-up, the tumor volume further decreased by 90% of the original size. The mean tumor volume reduction of the CS hemangiomas in this series was 82%. In contrast, the tumor volume reduction of the 84 CS meningiomas after GKS was only 29%. The statistical analysis revealed a significant difference in the radiosurgical responses between CS hemangiomas and CS meningiomas ($P<0.001$). Clinically, five of the six patients who had ophthalmoplegia and two with impaired visual acuity had significant improvement after radiosurgery. The authors suggested that the characteristic tumor response after radiosurgery may also help to differentiate CS hemangiomas from other tumors. If the tumor treated with GKS did not shrink remarkably over time, the diagnosis of CS hemangioma was less likely. In view of the characteristic imaging findings before and after radiosurgery, GKS could be considered as the first choice of treatment for CS hemangiomas.

In conclusion, despite the fact that surgical treatment of CS hemangiomas was considered dangerous in the past, the cumulative data in the recent decade have shown that stereotactic radiosurgery can provide a safe and effective treatment alternative for these hypervascular tumors. Before treatment, the tumors can be readily differentiated from other CS tumors based on their distinctive MRI appearance of hyperintensity on T2-weighted images. During radiosurgery, a highly selective treatment planning with conformal

radiation to the tumor can be achieved under stereotactic MRI guidance. Optic nerves and surrounding vital structures are well protected and away from the high-dose irradiation.

After radiosurgery, the tumors usually show a rapid, marked shrinkage in size, with 50–90% volume reduction during follow-up periods. Improvement of clinical symptoms and signs is also evident. The tumor control rate is high and persists for a long time, with the longest reported follow-up time of 13 years.

Radiosurgery for CS hemangiomas is limited mainly by tumor size. The largest documented tumor successfully treated by GKS was 23.1 cm^3. If the tumor is too large, the optic nerves may be obscured on MRI; thus, protection of the nerves from radiation damage may be difficult. The use of a lower dose, around 12 Gy to the tumor margin and a dose of less than 10 Gy to the optic nerves, permits better protection of the nerves. In conclusion, if a tumor shows the clear neuroimaging characteristics of CS hemangioma without evidence either of meningioma or schwannoma, and the lesion is not too large, GKS can be performed as the primary treatment procedure.

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Linear Accelerator Radiosurgery for Cavernous Malformation

26

Yin-Cheng Huang and Peng-Wei Hsu

Contents

Abstract

Cavernous malformation (CM) is a vascular lesion, characterized by low-flow sinusoidal vessels without any intervening neural tissue. The manifestations of CM include headache, seizure, and focal neurological deficits. CMs have been found to be less hazardous than high-flow vascular lesions. The hemorrhage rate is about 0.5–1.6% per patient-year, but the severity of the hemorrhage is usually milder. However, the re-bleeding rate is higher for patients with a history of hemorrhage. Surgical excision is considered to be the most effective treatment to reduce re-bleeding and seizures caused by CMs. However, for deep-seated or multiple lesions, radiosurgery may be considered as an alternative treatment modality because of possible morbidities associated with surgical excision. Although surgical excision also provides the best seizure control, seizures have been occasionally found to occur even after excision. Radiosurgery, including gamma knife and linear accelerator (LINAC), considerably reduces the rates of hemorrhages and seizures; in addition, it is associated with few radiation-induced complications than conventional radiotherapy. In this chapter, we will discuss the feasibility of treating CM by LINAC radiosurgery.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_26,

Introduction

Cavernous malformation (CM), also known as cavernoma or cavernous hemangioma, is a vascular deformation composed of sinusoidal vessels with no intervening neural tissue. Cavernomas comprise 5–13% of all central nervous system (CNS) vascular malformations. Since the introduction of magnetic resonance imaging (MRI), these angiographically occult cavernomas are diagnosed more frequently. T2-weighted gradient-echo MRI, which is the most sensitive diagnostic test, shows a cavernoma as a lesion with a mixed-signal core and a low-signal rim, sometimes described as a "popcorn" pattern, which forms due to a previous blood leakage. The prevalence of such cavernomas is about 0.5%, as diagnosed on the basis of the results of MRI or postmortem examination (Del Curling et al. 1991; Otten et al. 1989).

Patients may present with diverse neurological symptoms or signs because of hemorrhage, about 30–60% of the patients also present with seizure (Zabramski et al. 1994; Hsu et al. 2007). In addition, headache and progressive neurological deficits are two other common symptoms. Focal neurologic deficits are mostly associated with brainstem cavernomas; Fritschi et al. (1994) reported 139 cases of brainstem cavernomas, with 100% symptomatic patients.

Because cavernomas are low-flow vascular lesions, they are often excised surgically without major complications in order to prevent re-bleeding and epilepsy, except when the lesions are deep-seated or multiple. Some of the multiple or deep-seated lesions are epileptogenic, and some bleed repeatedly. The incidence of uncontrollable seizures or progressive neurological deficits induced by repeated bleeding is the key to determine whether these lesions should be treated aggressively or conservatively.

Considered a safe modality to treat intracranial arteriovenous malformation (AVM), radiosurgery has also been used to treat cavernomas, the low-flow vascular lesions. In the mid-1980s, the tremendous development of linear accelerator (LINAC) made it an alternative platform for radiosurgery. LINAC, with electrons ejecting from cathode tubes, is able to generate high energy particles targeting lesions in all parts of the human body, not just in the brain. Unlike radioactive cobalt, head frame-based gamma knife system, LINAC systems utilized a specialized planning software to deliver the required radiation dosage with satisfactory accuracy (Terao et al. 1992). LINAC radiosurgery is now widely used in many medical centers for the treatment of vascular lesions, benign and malignant brain tumors.

Table 26.1 Radiosurgery results for cavernous malformations

Author (year)	Case no.	Dose (Gy)	Volume (ml)	Median follow-up (months)	Re-bleeding (patient-year) %	Seizure control (*Engle class I/II) %	GKS/LINAC
Kondziolka et al. (1995a, b)	47	16	2.1	43	32	–	GK
Pollock et al. (2000)	17	18	2.1	51	24.8	–	GK
Regis et al. (2000)	49	19.2	2.37	23.7	–	73.4%	GK
Hasegawa et al. (2002)	83	16.2	1.85	52	0.76%	–	GK
Huang et al. (2006)	30	16	1.19	81	0.74	84.5	LINAC

*Engle class: class I: seizure-free, class II: significant decrease of seizure
GKS gamma knife, *LINAC* linear accelerator

This chapter will further focus on the effects of LINAC radiosurgery on the reduction of hemorrhage and seizure rates and discuss the risk of radiation-induced neurological deficits in the cavernomas. Selected series are listed in Table 26.1 showing results for reducing hemorrhage events and seizures.

Reduction of Hemorrhages

Del Curling et al. (1991) reported an overall hemorrhage rate of 0.25% per person-year and a seizure rate of 1.51% per person-year. In a more recent series, 122 patients with cavernomas having typical MRI characteristics were prospectively enrolled and followed-up under a conservative treatment (Kondziolka et al. 1995a). In this cohort study, 50% of the patients were found to have no symptomatic bleeding; however, patients with a history of hemorrhage tended to re-bleed (4.5% vs. 0.6%, annually). In these patients, 41% had 1, 7% had 2, and 2% had 3 bleeding events, and the hemorrhage rate was 1.6% per patient-observation year. Among the nine patients who were diagnosed with new bleeding, 6 had symptomatic neurological deficits. Pozzati et al. (1996) reported that in 16 out of 145 patients with cavernoma, the lesions had an aggressive behavior; ten patients presented with repeated episodes of hemorrhage, and the average hemorrhage interval was 11 months.

Unlike high-flow AVMs, not just lower in hemorrhage rate, cavernomas caused lesser neurological deficits. Even though, a new hemorrhage may still occur and cause new neurological deficits and seizures. The treatment of choice is surgical excision instead of observation. Shih and Pan (2005) reported an almost 0% of re-bleeding rate in surgical excision patients.

However, due to the role in the obliteration of high-flow AVM (Ganapathy et al. 2003), radiosurgery has been also attempted to reduce the hemorrhagic rate of cavernomas. The safety and efficacy of radiosurgery has been described about reducing the rate of hemorrhages (Kondziolka et al. 1995b, 2007; Kim et al. 2002); however, most centers reserve radiosurgery for deep-seated or multiple cavernomas that are associated with higher surgical morbidities. A marginal delivery dosage of 13–20 Gy is advocated in most series (Hasegawa et al. 2002; Regis et al. 2000; Pollock et al. 2000; Kondziolka et al. 1995b). Gamma knife system is a well-established system, yielding favorable results by reducing the hemorrhage rate (Kida et al. 1995; Kondziolka et al. 1995b; Pollock et al. 2000). Lately, LINAC has been included among the radiosurgery modalities. Kim et al. (2002) reported similar results in 22 cavernoma patients who underwent either gamma knife or LINAC radiosurgery. In a later study, a re-bleeding rate of 0.67% per patient-observation year was reported in 30 cavernoma patients who underwent LINAC radiosurgery (Huang et al. 2006). Although the inclusion criteria are different, similar result was obtained in patients who underwent gamma knife or LINAC radiosurgery.

Furthermore, an accurate obliteration rate cannot be determined because of its angiographically occult character in cavernomas; MR imaging usually demonstrates stationary size after radiosurgery.

Reduction in Seizures

The other major consideration for treating cavernomas is to reduce seizures. Patients frequently present with seizures, in addition to major neurological deficits or headache, irrespective of the presence or absence of hemorrhage. Several factors such as hemorrhage, mass effect, ischemia, gliosis, and neuronal loss are known to cause seizures. Hemosiderin deposition and iron release after a hemorrhage may play a role in reduction/oxidation reactions and induce epileptogenic activities (Kraemer and Awad 1994). It has been reported that a series of 62 cavernoma patients in whom seizure was the most frequent presentation (40.8%), and other major neurological deficits comprised 32.6% cases. Regis et al. (2000) studied 49 cases of medically intractable seizures, indicating the epileptogenic property of cavernomas.

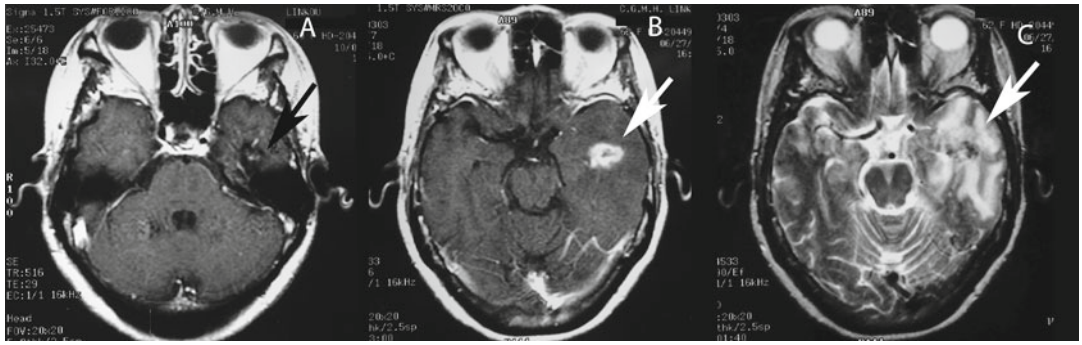

Fig. 26.1 (**a**): 1998, T1WI with enhancement (*black arrow*). (**b**, **c**): 2001 T1WI with enhancement and T2WI (*white arrow*). The left temporal lesion showed enlarged enhancement after LINAC 3 years later. This patient is symptom-free

One of the most important prognostic factors is the duration of seizure history. Patients with a longer seizure history may have a more widespread epileptogenic zone involving the adjacent cortex, which results in poor seizure control (Hsu et al. 2007). Only 37.5% of patients with longer than 12-month seizure history became seizure free, as compared to the 100% control for patients with a shorter history (Cappabianca et al. 1997). Surgical resections achieved relatively significant seizure-free results, with the success rate ranging from 53.3 to 79% (Shih and Pan 2005; Baumann et al. 2006).

However, radiosurgery may be an alternative treatment option for patients with non-resectable lesions that are either deep-seated or located in an eloquent area. Regis et al. (2000) reported 49 medically intractable seizure patients, with Engle class IA/B seizure control achieved in 43% of the patients after radiosurgery (Regis et al. 2000). Similarly, in 3 out of 22 medically intractable seizures patients, seizures ceased completely after radiosurgery (Kim et al. 2002). In another study, the seizure control rates between groups with surgical excision and radiosurgery were compared by Hsu et al.; 86.3% of the patients in the surgical excision group and 64.3% of the patients in the LINAC radiosurgery group achieved Engle class I seizure improvement. The good seizure control outcome with Engle I+II was 100% versus 92.3% (Hsu et al. 2007). Although there is limited knowledge about the mechanisms of radiosurgery, medically intractable seizures, irrespective of the etiologies, can be effectively controlled by radiosurgery with an optimal delivery dosage of 10–20 Gy *(*Dunoyer et al. 2002).

Adverse Effects from Radiosurgery

Complications of radiation therapy, however, remain a major concern. Cases of radiation-induced gliomas and meningiomas have been reported sporadically (Shenoy et al. 2004; Caroli et al. 2005; Prasad and Haas-Kogan 2009). In addition, traditional radiation therapy also induces brain radiation necrosis (Chong and Fan 1997; Kim et al. 2007).

With radiosurgery, the rate of adverse radiation effects is lowered because of the lower dosage employed and precision of delivery. However, still Chernov et al. (2005) reported five out of nine patients with radiation necrosis induced by gamma knife radiosurgery for brain metastasis. As for cavernomas, Huang et al. (2006) reported post-radiation edematous changes in 2 out of 30 cavernoma patients who underwent LINAC radiosurgery. A ratio of 3–18% of radiation-induced edema in patients harboring thalamus and brain stem cavernomas is reported recently (Kida 2009). However, radiosurgery-induced necrosis or edema is not always clinically evident (Fig. 26.1). The adverse effect occasionally is observed during regular image follow-up.

Nevertheless, the incidence of radiosurgery-induced adverse effects may need closer observation with a longer window period. Hasegawa et al. (2002) reported 3 out of 82 patients had permanent prominent neurologic deficits after radiosurgery without rebleeding; all of these cavernomas are located in the medulla and midbrain.

In conclusion, cavernomas may not have any clinical manifestation. However, patients may present with clinical symptoms if a hemorrhage occurs and require aggressive treatment because a higher re-bleeding rate is noted in such cases. Microsurgical excision of cavernomas is the mainstay procedure and provides a very good hemorrhage and seizure control. When considering the surgical risk and complication rates, radiosurgery is an alternative treatment especially for deep-seated or multiple lesions, and it has a good outcome with a relatively low morbidity and effectively reduced rates of hemorrhages and seizures. LINAC provides a similar precision and satisfactory prognosis as gamma knife radiosurgery.

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Treatment of Brainstem Hemangioblastomas

27

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Contents

Abstract

Hemangioblastomas are World Health Organization Grade I tumors of the central nervous system. Hemangioblastomas can present sporadically, and also comprise 5–10% of central nervous system (CNS) tumors in patients with von Hippel-Lindau (VHL) disease. Despite their sensitive location, brainstem hemangioblastomas can be removed safely; they generally should be resected when they become symptomatic or when the tumor has reached a size such that further growth will increase the risks associated with surgery, or in the presence of an enlarging cyst. Magnetic resonance imaging is usually sufficient for preoperative evaluation and presurgical embolization is unnecessary. The goal of surgery is complete resection of the lesion before the patient experiences a disabling neurological deficit.

In this chapter we would describe the clinical presentation, diagnosis and management of brainstem hemangioblastomas

Introduction

Hemangioblastomas are benign vascular central nervous system (CNS) tumors. Hemangioblastoma are frequently associated with peritumoral cysts (cysts arising at tumor edge). Because resection is curative, it is the preferred therapy for symptomatic brainstem hemangioblastomas.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_27,

Nevertheless, surgical removal can present a treatment challenge due to the delicate surrounding anatomic structures in this region of the CNS (Wang et al. 2001; Wind et al. 2011). Here, we describe the salient clinical and management features of brainstem hemangioblastomas.

Epidemiology

Generally, hemangioblastomas account for 12–17% of posterior fossa lesions and approximately 2% of all intracranial tumors (Jeffreys 1975). The reported incidence of brainstem hemangioblastomas ranges from 10 to 26% of all posterior fossa hemangioblastomas (de la Monte and Horowitz 1989; Lee et al. 1989; Zimmermann et al. 1997; Conway et al. 2001; Wang et al. 2001). Over 50% of brainstem hemangioblastomas arise in the medulla (75% occurring at the obex), with the remainder arising in the pons (13–33%) or at the cervicomedullary junction (15–31%) (Wang et al. 2001; Wanebo et al. 2003; Zhou et al. 2005). While approximately 60–80% of brainstem hemangioblastomas will have a surface presentation, 20–40% will be entirely intramedullary (Wang et al. 2001; Wanebo et al. 2003; Zhou et al. 2005).

While most brainstem and other craniospinal hemangioblastomas will arise sporadically, hemangioblastomas are found in von Hippel Lindau disease (VHL). Sixty to 70% of CNS hemangioblastomas will occur sporadically (Neumann et al. 1989) and 30–40% of CNS hemangioblastoma patients have VHL (Huson et al. 1986). VHL is an autosomal dominant transmitted heritable multisystem neoplasia disorder (Lonser et al. 2003). CNS hemangioblastomas in VHL patients (median age of presentation ~32 years) become symptomatic at significantly younger ages than their sporadic (mean age of presentation ~46 years) counterparts (Maher et al. 1990; Takai et al. 2010).

von Hippel Lindau Disease

VHL results from a germline mutation of the *VHL gene*. The *VHL gene* is a tumor suppressor encoding for VHL protein and is found on the short arm of chromosome 3 (Latif et al. 1993; Chen et al. 1996). The estimated incidence at birth of VHL is approximately 1 in 36,000 to 40,000 based on genetic and population studies (Maher et al. 1991). VHL has nearly complete penetrance, with 96% cumulative penetrance at 51–60 years of age and 99% penetrance from ages 61 to 70 years (Maher et al. 1991). There are a number of visceral tumors and/or cysts associated with VHL that arise in the kidneys, pancreas, adrenal glands and adnexal organs (Lonser et al. 2003). VHL-associated CNS tumors include the hemangioblastomas and endolymphatic sac tumors (Butman et al. 2007).

Gross Appearance and Pathology

Hemangioblastomas are intensely vascular lesions that appear bright red or red-yellow grossly. These tumors are histologically recognized as World Health Organization Grade I lesions. They are associated with large abnormal feeding vessels and draining veins. They are thinly encapsulated and can be associated with a peritumoral cyst, which is lined by gliotic tissue. Histological analysis will reveal characteristic lipid-laden stromal cells, as well as endothelial cells that form extensive vascular channels (Fig. 27.1).

Histologically, hemangioblastomas appear similar to renal cell carcinoma (RCC). Thus, immunohistochemical differentiation between the tissues should be performed in VHL patients with concurrent renal cell carcinoma (RCC), as RCC will appear similar and these tumors can metastasize to a co-existing hemangioblastoma (8% of hemangioblastomas resected) (Jarrell et al. 2006). Hemangioblastomas are EMA negative, but positively stain for inhibin, GLUT1, VEGF and CD56. RCCs will show strong EMA immunoreactivity, as well as stain positively for anti-CD10 and anti-AE1/AE3 (cytokeratin) (Jarrell et al. 2006).

Clinical Presentation

Symptoms and signs of brainstem hemangioblastomas can be variable. The presenting signs and/or symptoms that are most frequently associated with

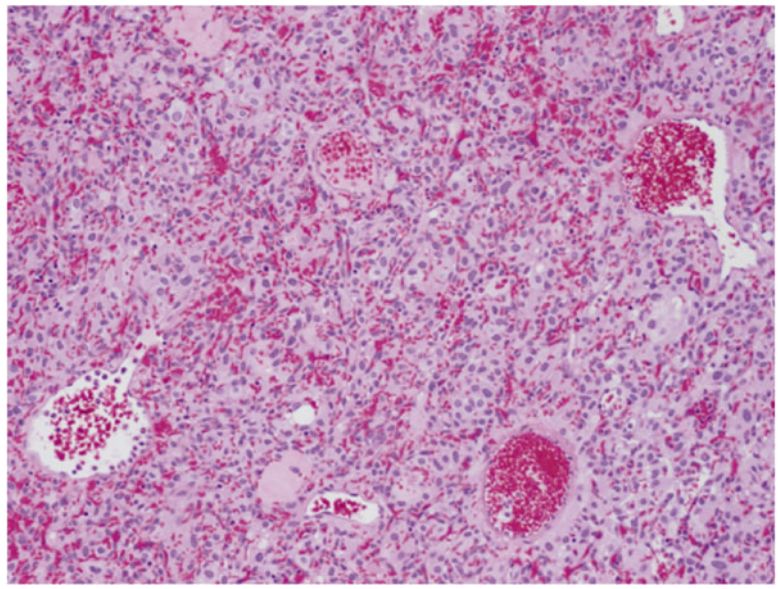

Fig. 27.1 Low power hematoxylin and eosin stained section of a hemangioblastoma, showing numerous thin-walled capillary sized blood vessels and lipid filled stromal cells

brainstem hemangioblastomas include headache, neck pain, swallowing difficulties, singultus, posterior column dysfunction and gait disturbances (Table 27.1) (Wang et al. 2001; Weil et al. 2003; Zhou et al. 2005; Wind et al. 2011). Less frequent presenting symptoms are often related to the anatomical location of these lesions, with lesions disrupting satiety pathways leading to anorexia or gastric ulcer formation (Wind et al. 2011).

Table 27.1 Clinical presentation of brainstem hemangioblastomas in von Hippel-Lindau disease

Symptomatic presentation	No. of cases (%)
Headache	30 (58.8)
Swallowing difficulties	17 (33.3)
Singultus	16 (31.4)
Gait difficulties	16 (31.4)
Ataxia	15 (29.4)
Visual disturbances	13 (25.5)
Limb paresthesias	13 (25.5)
Decreased sensation in upper extremities	13 (25.5)
Decreased sensation in lower extremities	12 (23.5)
Nausea or vomiting	12 (23.5)
Speech difficulties	10 (19.6)
Lower-extremity weakness	9 (17.6)
Vertigo	8 (15.7)
Upper-extremity weakness	7 (13.7)
Fatigue or changes in sleep/wake cycle	6 (11.8)
Coughing	8 (15.7)
Anorexia	2 (3.9)

Adapted from Wang et al. (2001)

Diagnosis

Contrast enhanced magnetic resonance (MR)-imaging provides the most useful information for identifying and characterizing brainstem hemangioblastomas. On non-contrast T1-weighted MR-imaging, these lesions may appear iso- to slightly hyperintense, while T2 weighted MR-sequences reveals a hyperintense lesion. Contrast enhanced T1 weighted MR-imaging typically reveals lesions with strong homogenous contrast enhancement, often with serpentine flow voids depicting their highly vascular nature (Fig. 27.2a–e).

A detailed neurological history and exam is particularly important in the case of VHL patients, as they may have multiple lesions that could account for a patient's symptomatic presentation. Longitudinal study of these lesions reveals that peritumoral cysts are often found associated with

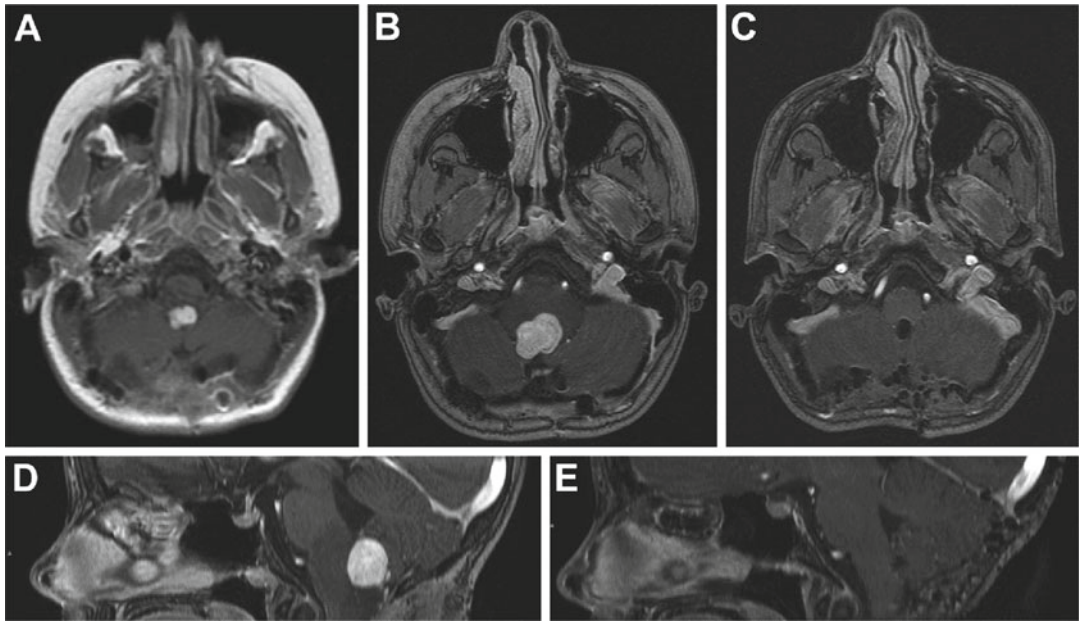

Fig. 27.2 Pre-operative (**a**, **b**, **d**) and post-operative (**c**, **e**) T1-weighted magnetic resonance imaging with contrast revealing an obex hemangioblastoma. The obex hemangioblastoma can be seen to obstruct the fourth ventricle. Associated edema, as shown by a hypointense region of the pons pre-operatively, has resolved on the post-operative imaging

symptomatic brainstem hemangioblastomas and account for over 60% of symptomatic lesions in VHL patients (Wind et al. 2011). As many as 97% of sporadic lesions which require surgery may harbor a cystic component (Wang et al. 2001). Hemangioblastoma peritumoral cysts develop result from the gradual confluence of edema surrounding the lesion (Lonser et al. 2005).

Surgical Treatment

Surgical Indications

Due to their benign nature, CNS hemangioblastomas can be cured by surgical resection. The management approach can be different for sporadic and VHL-associated brainstem hemangioblastoma. Early pre-symptomatic intervention and treatment may be warranted in sporadic brainstem hemangioblastomas if diagnosis is needed. However, in VHL patients, long-term natural history data indicates that neither tumor size or growth rate should necessitate intervention but tumors should be resected once they become symptomatic (Ammerman et al. 2006). In rare instances, VHL patients may undergo resection of a rapidly growing asymptomatic lesion causing mass effect.

Pre-operative Angiography and Embolization

Performing preoperative arteriography can be of use to characterize tumor vasculature. Due to the hyper-vascular nature of these lesions, preoperative embolization by injecting embolic agents into the tumor's feeding arteries has been proposed by some (Montano et al. 2008). While some studies have reported pre-operative embolization of brainstem hemangioblastomas can be helpful to reduce intraoperative blood loss,(Krishnan and Schackert 2006) studies have demonstrated that it is unnecessary for the safe removal of the tumor (Conway et al. 2001; Weil et al. 2003) and can add significant risk including intratumoral hemorrhage, stroke and death (Montano et al. 2008).

Pheochromocytoma Workup

Pheochromocytomas are present approximately 30% of VHL patients (Lonser et al. 2003). Subsequently, it is recommended that VHL patients undergo routine screening for pheochromocytomas with serum and urine testing, together with imaging of the abdomen and pelvis (Eisenhofer et al. 1999; Maher et al. 2011). Studies have shown that patients with a pheochromocytoma exhibit global left ventricular diastolic and systolic dysfunction, and these patients have a risk of developing acute hypertensive crises before or during surgery (Young 2007; Agarwal et al. 2011). While alpha blockade can ameliorate some of these cardiovascular effects and be used in the perioperative period, surgical excision of these lesions causes definitive improvement in heart function and will prevent hypertensive crises in subsequent procedures (Young 2007; Agarwal et al. 2011).

Surgical Technique

Most brainstem hemangioblastomas are located in the posterior brainstem at the obex and a posterior midline approach is typically used to access these tumors. Following induction of anesthesia, patients are positioned prone with head fixed in a mild flexed position at the neck. A midline incision is made starting at the superior edge of the suboccipital region (inion) to the second cervical vertebrae spinous process. Nuchal muscles are dissected from the suboccipital region and upper cervical (first and second cervical) vertebrae and the reflected laterally.

For sporadic patients a suboccipital craniotomy is utilized and a suboccipital craniectomy is used in VHL patients (to facilitate posterior fossa retry for the removal of lesions) to access the brainstem. The craniotomy/craniectomy is created using a drill and/or rongeurs. Often the lamina of the first cervical vertebrae is removed to provide adequate exposure of the foramen magnum and cervicomedullary junctions. Once the craniotomy/craniectomy and/or laminectomy is completed, intraoperative Doppler ultrasound is used to confirm the adequacy of the bony opening around the hyperechoic hemangioblastoma. The dura is then sharply opened (but the underlying arachnoid is initially left intact) and its edges are tacked supero-laterally with sutures to the surrounding musculature. Next, microscissors are used to sharply open the arachnoid, which is then secured to the adjacent dural leaves with titanium vascular clips.

Next, a diamond knife is used to make an incision at the junction between the tumor and pia for tumors that reach the pial surface. Deeper circumferential dissection is performed at the red tumor capsule edge and the immediately adjacent white brainstem tissue. Gentle irrigation during bipolar cauterization of tumor vessels prevents adherence of tumor capsule and small vessels to the bipolar tips. Once vessels are cauterized, they are sharply transected with microscissors. During the course of dissection, the hemangioblastoma will darken and then soften as the feeding vessels are transected. At this point, gentle retraction via compression of the hemangioblastoma is possible using a suction tip placed on a cotton patty on the tumor capsule. This allows of clear deeper exposure during circumferential dissection (Fig. 27.3a–d).

A pial incision and separation of the posterior median raphe is necessary to access deep completely intramedullary hemangioblastomas that do not have a pial surface presentation. After the posterior surface of the hemangioblastoma is identified, circumferential dissection is performed as described above. If necessary, large tumors can be shrunk by coagulating the tumor capsule with bipolar forceps (Lindau 1931). We often try to avoid cauterizing the tumor surface, as this causes blanching of the tumor that can make distinguishing the tumor from brainstem more difficult. While resecting cystic hemangioblastomas, the cyst wall is examined for any signs of residual solid tumor and any additional tumor tissue is removed. The wall of the cyst is not removed, because complete hemangioblastoma (cyst fluid source) resection will cause the cyst to collapse and resolve. After tumor removal, the dura and tissues are reapproximated in standard fashion.

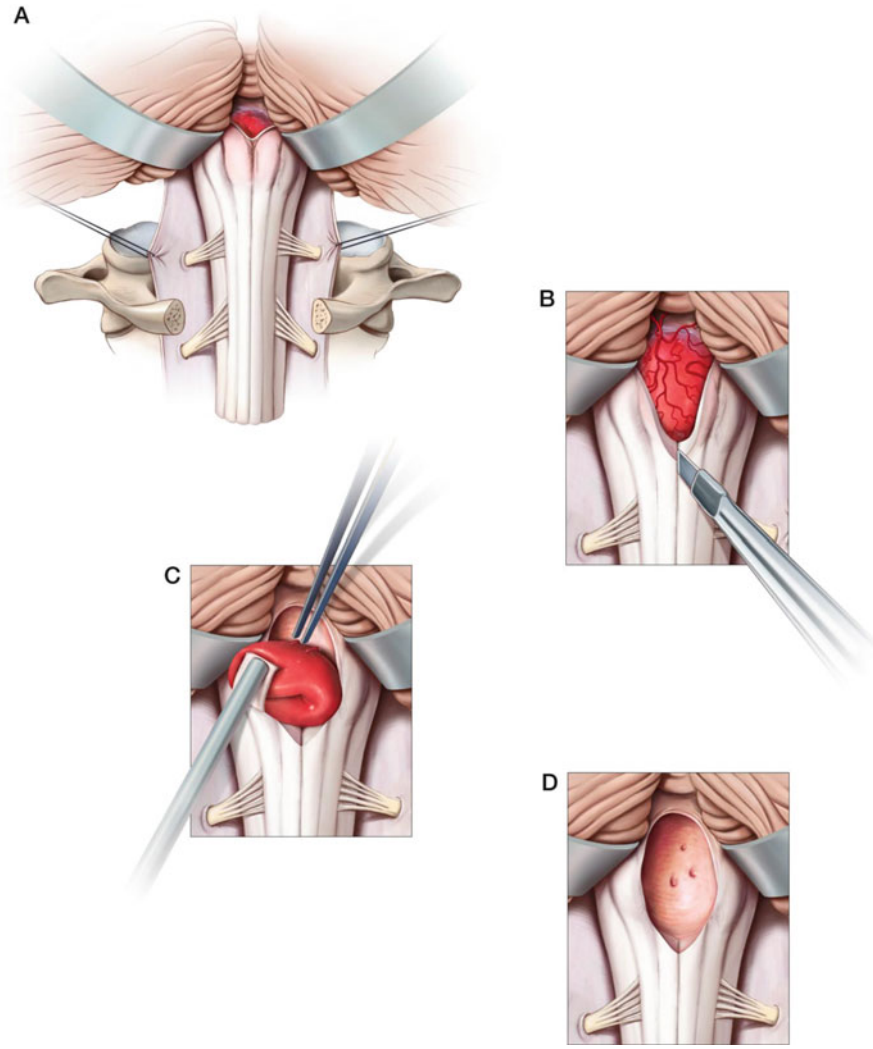

Fig. 27.3 Artist's depiction of the resection of a hemangioblastoma of the obex without a complete surface presentation. (**a**). After craniectomy, a C1 laminectomy and opening of the dura matter and arachnoid membrane is performed. (**b**). A sharp pial incision is made and the posterior median raphe is separated to access the tumor. (**c**). Gentle retraction is performed by placing suction on a cotton patty, allowing the surgeon to bipolar deeper vessels feeding the tumor. (**d**). After the vasculature has been coagulated and circumferentially from the lesion, the tumor softens and can be completely removed

Outcome

Reported outcomes after resection of brainstem hemangioblastomas have improved as surgical technique has been refined. Wang et al. (2001) reported a 23% morbidity rate and 5% mortality after brainstem hemangioblastoma resection. Fukushima et al. (1998) reported in a literature review study an overall mortality rate of 24%. Recently, Wind et al. (2011) described long-term outcome after resection in a large series VHL-associated brainstem hemangioblastomas patients (71 brainstem hemangioblastomas in 44 patients). They found that after

resection 95% of patients either remained at their neurologic baseline or significantly improved. Long-term mortality was due to progression of CNS disease or RCC related complications.

Complications

Wind et al. (2011) reported immediate post-operative complications including pneumonia in 10% of cases, gastro-intestinal ulcerations in 6%, deep vein thrombosis in 2%, cerebrospinal fluid leak in 2% and new onset hydrocephalus requiring a shunt in 2%. Other series have reported cranial nerve dysfunction in over 20% of patients (Zhou et al. 2005).

Adjuvant Treatment

Stereotactic Radiosurgery (SRS)

SRS has been proposed as a non-invasive alternative for treating brainstem hemangioblastomas. Specifically, small, solid lesions (under 3 cm in diameter) in VHL patients, patients medically unfit for surgery, or when there is no tumor-associated mass effect or neurologic symptoms (Smalley et al. 1990) have been consider the candidates for SRS. Nevertheless, determining the long-term efficacy of SRS treatment of CNS hemangioblastomas based on previous reports, including those in the brainstem, has been limited number of patients analyzed and/or limited duration follow-up in most reported studies (less than 5 years).

Recently, Asthagiri et al. (2010) concluded a long-term prospective study of VHL patients with CNS hemangioblastomas that were treated with SRS. They found that SRS has a limited long-term control that may not be different than the natural history of hemangioblastoma progression in VHL (10 years of follow-up control rate of 51%). As there is no method to predict which tumor will grow or be symptomatic, prophylactic SRS is not recommended except in cases that are not resectable. They also noted that there are long term risks to the use of radiation, so given the benign nature of these lesions, these risks must be considered carefully before subjecting asymptomatic patients to a potentially harmful intervention.

Chemotherapy

The high expression of different vascular growth factors and its reciprocal receptors suggest both the origin of these tumors and the potential use of anti-angiogenic drugs for their treatment. There is limited reported information on the use of these putative therapeutics in the treatment of brainstem hemangioblastomas. Vascular endothelial growth factor receptor inhibitor (SI5416) and interferon α-2a (a potent anti-angiogenic agent) have been used to treat VHL-associated hemangioblastomas. Studies using these drugs have demonstrated no effect on tumor vascular proliferation or tumor size.

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Part VIII

Craniopharyngiomas

Craniopharyngiomas: An Overview

28

Tim Korevaar, Georgia Ntali, and Niki Karavitaki

Contents

Abstract

Craniopharyngiomas are rare, mainly sellar/parasellar epithelial tumors diagnosed during childhood or adult life. They may present with a variety of neurological, visual, and hypothalamo-pituitary manifestations. Histologically, they are divided in two main subtypes, adamantinomatous and papillary, but mixed forms have also been reported. Despite their benign histological features, they often show an unpredictable growth pattern, which, combined with the lack of randomized studies, poses significant difficulties in the establishment of an optimal therapeutic protocol. Currently, surgery combined or not with radiotherapy are the most commonly used treatment modalities. Irrespective of the type of primary therapeutic approach, the long-term morbidity (endocrine, visual, hypothalamic, neurobehavioral and cognitive) is substantial compromising quality of life and survival. The identification of clinical and imaging parameters predicting patients with a better prognosis is difficult and central registration of patients may provide correlates between treatments and outcomes.

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Introduction

Craniopharyngiomas are rare epithelial tumours arising along the path of the craniopharyngeal duct. They account for 2–5% of all the primary

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_28,

intracranial neoplasm's (Parisi and Mena 1993) and for up to 15% of the intracranial tumours in children (Karavitaki et al. 2006). Their incidence is reported as 0.13 per 100,000 person-years (Bunin et al. 1998) and genetic susceptibility seems unlikely. Craniopharyngiomas may be detected at any age, even in the prenatal and neonatal periods, (Bailey et al. 1990; Müller-Scholden et al. 2000) and a bimodal age distribution with peak incidence rates of ages 5–14 and 50–74 year has been proposed (Bunin et al. 1998). They display benign histological features, but they can clinically show aggressive and unpredictable behaviour resulting in significant morbidity and mortality. This overview will focus on the presentation, treatment and prognosis of craniopharyngiomas.

Pathology

Craniopharyngiomas are WHO grade I tumors, (Kleihues et al. 1993). Although considered histologically benign, rare cases of malignant transformation (possibly triggered by previous irradiation) have been described (Karavitaki et al. 2006). Their pathogenesis has not been clarified. Two theories have been suggested: neoplastic transformation of embryonic squamous cell rests of the involuted craniopharyngeal duct or metaplasia of adenohypophyseal cells in the pituitary stalk or gland (Karavitaki et al. 2006).

Histologically two primary subtypes have been recognized, the adamantinomatous and the papillary, but transitional or mixed forms have also been described (Crotty et al. 1995; Petito et al. 1976; Weiner et al. 1994). The adamantinomatous subtype bears similarity with the adamantinoma of the jaw and the calcifying odontogenic cyst raising the possibility that this variant may arise from embryonic rests with enamel organ potential. Macroscopically, it shows cystic and/or solid components, necrotic debris, fibrous tissue, and calcification (especially common in children). The cyst contains liquid ranging from "machinery oil" to shimmering cholesterol-laden fluid, which consists mainly of desquamated squamous epithelial cells, rich in membrane lipids and cytoskeleton keratin (Parisi and Mena 1993). Their margins are sharp and irregular often making the identification of the surgical planes difficult; in such cases, forcible removal may be accompanied by severe damage to critical structures. They may also merge into a peripheral zone of dense reactive gliosis with abundant Rosenthal fiber formation in the surrounding brain tissue and the vascular structures that may be easily mistaken for a glioma. The epithelium is composed of a palisaded basal layer of small cells with darkly staining nuclei and little cytoplasm; above this, there is an intermediate layer of variable thickness composed of loose aggregates of stellate cells (termed stellate reticulum) and a top layer facing into the cyst lumen with abruptly enlarged, flattened and keratinized to flat plate-like squamous cells. The flat squames are desquamated singly or in distinctive stacked clusters forming nodules of "wet" keratin, often heavily calcified and apparent grossly as white flecks.

The papillary variety has almost exclusively been described in adults, with the exception of rare paediatric cases (only up to 2% in this age group). Its cellular structure resembles the oropharyngeal mucosa. Macroscopically, it tends to be solid or mixed with cystic and solid components, calcification is rare and the cyst content, in contrast to the adamantinomatous subtype, is usually viscous and yellow (Crotty et al. 1995). It is generally well circumscribed, and infiltration of adjacent brain tissue by neoplastic epithelium is less frequent than in the adamantinomatous type or even absent (Crotty et al. 1995). Microscopically, it is composed of mature squamous epithelium forming pseudopapillae and of an anastomosing fibrovascular stroma without the presence of peripheral palisading of cells or stellate reticulin. The distinction between a papillary craniopharyngioma and a Rathke's cleft cyst may be difficult, particularly in small biopsy specimens, due to the squamous differentiation that may be seen in the epithelial lining of the Rathke's cysts. In such cases, the lack of a solid component and the presence of extensive ciliation and/or mucin production are suggestive of Rathke's (Karavitaki et al. 2006).

Clinical, Hormonal, and Imaging Features at Presentation

Craniopharyngiomas may exert pressure effects to various brain structures (visual pathways, brain parenchyma, ventricular system, major blood vessels and hypothalamo-pituitary system) resulting in multiple clinical features (neurological, visual, hypothalamo-pituitary); headaches, nausea/vomiting, visual disturbances, growth failure (in children) and hypogonadism (in adults) are the most frequently described. The duration of the symptoms until diagnosis ranges between 1 week and 372 months (Karavitaki et al. 2006). A substantial number of patients present with compromised hypothalamo-pituitary function; reported rates for pituitary hormone deficits include 35–95% for GH, 38–82% for FSH/LH, 21–62% for ACTH, 21–42% for TSH and 6–38% for ADH (Karavitaki et al. 2005).

Most of the craniopharyngiomas are detected in the sellar/parasellar region; rare ectopic locations have also been described including the pineal gland, the cerebellopontine angle, the temporal lobe or completely within the 3rd ventricle. A suprasellar component has been reported in 94–95% of the cases (purely suprasellar 20–41%, both supra- and intrasellar 53–75%, purely intrasellar 5–6%), and extension into the anterior or middle or posterior fossa in nearly 30% of them (Karavitaki et al. 2006). The size of craniopharyngiomas has been reported >4 cm in 14–20% of the cases and <2 cm in 4–28% (Weiner et al. 1994; Fahlbusch et al. 1999; Karavitaki et al. 2006). Their consistency is purely or predominantly cystic in 46–64%, purely or predominantly solid in 18–39% and mixed in 8–36%. Calcification has been shown in 45–57% (probably more common in children) and hydrocephalus in 20–38% (also more frequent in childhood populations), as declared by Fahlbusch et al. (1999), Karavitaki et al. (2005), De Vile (2002), Weiner et al. (1994), Van Effenterre and Boch (2002) and reviewed by Karavitaki et al. (2006).

Plain skull X-rays, although seldom used nowadays, may show calcification and abnormal sella. CT is helpful for the evaluation of the bony anatomy, the identification of calcifications and the discrimination of the solid and the cystic components (the cystic fluid is hypodense and the solid portions, as well as the cyst capsule show enhancement following contrast administration). The MRI is particularly important for the topographic and structural analysis of the tumour. A solid lesion appears as iso- or hypointense relative to the brain on pre-contrast T_1-weighted images, shows enhancement following gadolinium administration and is usually of mixed hypo- or hyperintensity on T_2-weighted sequences. Large amounts of calcification may be visualized as areas of low signal on both T_1- and T_2-weighted images. A cystic element is usually hypointense on T_1- and hyperintense on T_2-weighted sequences. On T_1-weighted images a thin peripheral contrast-enhancing rim of the cyst is demonstrated. Protein, cholesterol and methemoglobin may cause high signal on T_1-weighted images, while very concentrated protein, calcification and various blood products may be associated with low T_2-weighted signal as stated by Sartoretti-Schefer et al. (1997) and Byrne (2002). The differential diagnosis includes a number of sellar or parasellar lesions, including Rathke's cleft cyst, dermoid cyst, epidermoid cyst, pituitary adenoma, germinoma, hamartoma, suprasellar aneurysm, arachnoid cyst, suprasellar abscess, glioma, meningioma, sacroidosis, tuberculosis and Langerhans cell histiocytosis (Karavitaki et al. 2006).

Treatment Options

Surgery combined or not with adjuvant external beam irradiation is currently one of the most widely used first therapeutic approaches for these tumours, which remain challenging, even in the era of modern neurosurgery. This is mainly attributed to their sharp, irregular borders and to their tendency to adhere to vital neurovascular structures making surgical manipulations potentially hazardous to vital brain areas. Consequently, the attempted degree of excision has been a subject of a long-standing debate. The surgical

approach should provide wide exposure of all parts of the tumor and minimize the damage to vital structures. Its choice depends on the location, the consistency, the degree of calcification, the shape and size of the tumor, as well as on the surgeon's preference and experience. When large cystic components are present, fluid aspiration provides relief of the obstructive manifestations and facilitates the consecutive removal of the solid tumor portion, which should not be delayed for more than a few weeks, due to the significant risk of cyst refilling that is reported in up to 81% of the cases at a median period of 10 months (Karavitaki et al. 2005). The extent of resection depends on the size (achieved in 0% of lesions >4 cm) and location (particularly difficult for retrochiasmatic or within the 3rd ventricle) of the tumour, the presence of hydrocephalus, of >10% calcification and of brain invasion, as well as on the experience, the individual judgment during the operation and the general treatment policy (aggressive or not) adopted by each neurosurgeon (Fahlbusch et al. 1999; Van Effenterre and Boch 2002). In recent reports this ranges between 1.7 and 5.4% for the primary operations.

Recurrent tumors may arise even from small islets of craniopharyngioma cells in the gliotic brain adjacent to the tumor, which can remain even after gross total removal. The mean interval for their diagnosis following various primary treatment modalities ranges between 1 and 4.3 years and relapses as late as 30 years after initial therapy have been reported (Karavitaki et al. 2006).

Series with radiological confirmation of the radicality of resection show that the recurrence rates following gross total removal range between 0 and 62% at 10 years follow-up. These are significantly lower than those reported after partial or subtotal resection (25–100% at 10 years follow-up). In cases of limited surgery, adjuvant radiotherapy improves significantly the local control rates (recurrence rates 10–63% at 10 years follow-up). Finally, radiotherapy alone provides 10 years recurrence rates ranging between 0 and 23% (Karavitaki et al. 2006). The interpretation of the data on the effectiveness of each therapeutic modality has to be done with caution, since the published studies are retrospective, non-randomised and often specialty-biased.

The growth rate of craniopharyngiomas varies considerably and reliable clinical, radiological and pathological criteria predicting their behaviour are lacking. Thus, apart from significant impact of the treatment modality, attempts to identify other prognostic factors of relapse (age, group at diagnosis, sex, imaging features, pathological subtypes) have not provided consistent data (Karavitaki et al. 2006).

The management of recurrent tumours remains difficult, as scarring/adhesions from previous operations or irradiation make successful removal difficult. In such cases, total removal is achieved in a substantially lower rate when compared with primary surgery (0–25%) and it is associated with increased peri-operative morbidity and mortality (10.5–24%). The beneficial effect of radiotherapy (preceded or not by second surgery) in recurrent lesions has been clearly shown (Karavitaki et al. 2005; Jose et al. 1992).

Intracavitary irradiation (brachytherapy) is a minimally invasive treatment modality involving stereotactically guided instillation of beta-emitting isotopes into cystic craniopharyngiomas. It delivers higher radiation dose to the cyst lining compared with the one offered by external beam radiotherapy and results to damage of the secretory epithelial lining, elimination of the fluid production and cyst shrinkage. The efficacy of various beta and gamma-emitting isotopes (mainly ^{32}phosphate, ^{90}yttrium, ^{186}rhenium, ^{198}gold) has been assessed in a number of studies but given that none of them has the ideal physical and biological profile [i.e. pure beta emitter with short half-life and with tissue penetrance limited to cover only the cyst wall], there is no consensus on which is the most suitable therapeutic agent. In several studies (Pollock et al. 1995; Voges et al. 1997; Van den Berge et al. 1992; Hasegawa et al. 2004), with a mean or median follow-up ranging between 3.1 and 11.9 years, intracavitary irradiation mainly with ^{90}yttrium or ^{32}phosphorus

providing radiation dose of 200–267 Gy, complete or partial cyst resolution was seen in 71–88% of the cases, stabilization in 3–19% and increase in 5–10%. New cyst formation or increase in the solid component of the tumour were observed in 6.5–20% of the cases. Although beta emitters have short range tissue penetrance, lesions in close proximity to the optic apparatus should be approached with caution. The published control rates combined with its reported low surgical morbidity and mortality render brachytherapy an attractive option for predominantly cystic tumors, and particularly the monocystic ones.

A small number of reports have shown that the intracystic installation of the antineoplasmatic agent bleomycin may be an effective therapy for some cystic tumors (Hader et al. 2000). Direct leakage of the drug to surrounding tissues during the installation procedure, diffusion though the cyst wall or high drug dose have been associated with various toxic (hypothalamic damage, blindness, hearing loss, ischaemic attacks, peritumoral oedema) or even fatal effects. The value of this treatment option in the tumor control or even in delaying of potentially harmful surgery and/or radiotherapy, as well as the optimal protocol and the clear-cut criteria predicting the long-term outcome remain to be established in large series with appropriate follow-up.

Stereotactic radiosurgery delivers a single fraction of high dose ionising radiation on precisely mapped targets keeping the exposure of adjacent structures to a minimum. Tumor volume and close attachment to critical structures, as the optic apparatus, are limiting factors for its application. It achieves tumor control in a substantial number of patients with small volume lesions (Chung et al. 2000). It may be particularly useful for well-defined residual disease following surgery or for the treatment of small solid recurrent tumors, particularly after failure of conventional radiotherapy. Studies with long-term follow-up evaluating the optimal marginal dose, its role in the prevention of tumour growth and its effects on the neurocognitive and neuroendocrine functions are needed.

Long Term Morbidity and Mortality

Craniopharyngiomas are associated with significant long-term morbidity (mainly involving endocrine, visual, hypothalamic, neurobehavioral and cognitive sequelae), which is attributed to the damage of critical structures by the primary or recurrent tumour and/or to the adverse effects of the therapeutic interventions. Notably, the severity of the radiation-induced late toxicity is affected by the total and per fraction doses, the volume of the exposed normal tissue and the young age in childhood populations.

The rates of individual hormone deficits range between 88 and 100% for GH, 80–95% for FSH/LH, 55–88% for ACTH, 39–95% for TSH and 25–86% for ADH (Karavitaki et al. 2006). In contrast to anterior pituitary tumors, restoration of pre-existing hormone deficits following surgical removal, is absent or uncommon.

Compromised vision has been reported in up to 63% of the patients treated by surgery combined or not with radiotherapy during an observation period of 10 years. The visual outcome is adversely affected by the presence of visual symptoms at diagnosis, by daily irradiation doses >2 Gy and is more common in those treated by partial removal group, probably as a consequence of their significantly increased recurrence rates (Duff et al. 2000; Karavitaki et al. 2005, 2006).

Hypothalamic damage may result in hyperphagia and uncontrollable obesity, disorders of thirst and water/electrolyte balance, behavioral and cognitive impairment, loss of temperature control and disorders in the sleep pattern. Among those, obesity is the most frequent (reported in 26–61% of the patients treated by surgery combined or not with radiotherapy) and is a consequence of the disruption of the mechanisms controlling satiety, hunger and energy balance. Factors proposed to be associated with significant hypothalamic morbidity are young age at presentation, hypothalamic disturbance at diagnosis, hypothalamic invasion, attempts to remove adherent tumor from the region of hypothalamus, multiple operations for recurrence

and hypothalamic radiation doses >51 Gy (Karavitaki et al. 2006).

The compromised neuropsychological and cognitive function in patients with craniopharyngioma after surgery and radiation therapy contributes significantly to poor academic and work performance, disrupted family and social relationships and impaired quality of life. In a series of 121 patients followed-up for a mean period of 10 years, Duff et al. (2000) found that 40% of them had poor functional neuropsychiatric outcome, while De Vile et al. (1996) in a series of 75 children followed-up for a mean period of 6.4 years, demonstrated that 40% of them had IQ <80. Finally, Karavitaki et al. (2005) in a series of 121 patients, found cumulative probabilities for permanent motor deficits, epilepsy, psychological disorders necessitating treatment and complete dependency for basal daily activities at 10 years follow-up of 11, 12, 15 and 9%, respectively. There is no consensus on the therapeutic option with the least unfavorable impact on the neurobehavioural outcome necessitating prospective studies with formal neuropsychological testing and specific behavioral assessment before and after any intervention. Such data will be particularly important for the young children, in which the uncertainties of whether delaying irradiation is a reasonable policy and the relative contributions of the recurrent disease, the subsequent surgery and irradiation need to be clarified.

The mortality rates of patients with craniopharyngioma have been reported to be 3–6 times higher than that of the general population and reported 10-years survival rates range between 83 and 93% (Fahlbush et al. 1999; Karavitaki et al. 2005). Apart from the deaths directly attributed to the tumour (pressure effects to critical structures) and to the surgical interventions, the risk of cardio-/cerebrovascular and respiratory mortality is increased. It has also been suggested that in childhood populations the hypoadrenalism and the associated hypoglycemia, as well as the metabolic consequences of ADH deficiency and absent thirst may contribute to the excessive mortality. The impact of tumour recurrence on the long-term mortality is widely accepted and the 10-year survival rates in such cases range between 29 and 70%, depending on the subsequent treatment modalities as stated by (Karavitaki et al. 2005).

In conclusion, craniopharyngiomas are rare epithelial tumors diagnosed during childhood or adult life. Given the lack of randomized studies, their optimal treatment remains a subject of debate. Surgery combined or not with adjuvant external beam irradiation is currently the most widely used first therapeutic approach. In cases of limited surgery, adjuvant radiotherapy improves significantly the local control. Intracystic irradiation or bleomycin, stereotactic radiosurgery or radiotherapy and systemic chemotherapy are alternative approaches; their place in the management plan remains to be assessed in adequately powered long-term trials. The long-term morbidity of patients with craniopharyngioma is considerable and it is attributed to the damage of critical structures by the primary or recurrent tumor and/or to the adverse effects of the therapeutic interventions. It mainly involves endocrine, visual, hypothalamic, neurobehavioral and cognitive sequelae, compromising the normal psychosocial integration and the quality of life. Overall, the management is undoubtedly complex: life-long surveillance by a multidisciplinary support team (experienced neurosurgeons, endocrinologists, neuro-oncologists, ophthalmologists, neurologists, neuropsychologists and rehabilitation doctors) is required for better long-term results.

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Radical Removal of Craniopharyngiomas

29

Pietro Mortini, Marco Losa, and Filippo Gagliardi

Contents

Abstract

The optimal treatment of patients with craniopharyngioma remains controversial and continues to be debated because an effective balanced protocol between aggressive therapy and reducing adverse sequelae is still lacking in both children and adults.

Radical resection is usually considered the therapy of choice at any age for primary treatment of craniopharyngiomas. This treatment is associated with the best outcome in terms of survival and recurrence-free survival.

Nevertheless, the location and the frequent involvement of critical neurovascular structures, tumor size, calcifications, and the patient age at presentation may limit the extent of resection. Surgery also carries significant morbidity in terms of visual, hypothalamic, and endocrinological disturbances. Moreover, craniopharyngioma can also recur, despite negative postoperative brain imaging. For these reasons, many authors advocate a less aggressive surgical treatment followed by radiation therapy.

To further elucidate the role of attempted radical resection in the craniopharyngioma, the present study retrospectively investigated the data reported in the literature, the outcome after surgical treatment and the factors affecting the risk of tumor recurrence through a rigorous clinical and radiological follow-up.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_29,

Introduction

Craniopharyngiomas (CFGs) are rare epithelial tumors arising along the path of the craniopharyngeal duct. Clusters of squamous epithelial cells located along the pars distalis and pars tuberalis of the pituitary were first identified by Zenker in 1857. Saxer in 1902 described a tumor consisting of these epithelial cells. The first attempt for surgical removal of such a tumor by Halstead was reported in 1910. However the term craniopharyngioma was introduced by Cushing in 1932. Their incidence is reported as 0.13 cases per 100,000 individuals-years. They account for 2–5% of all primary intracranial tumors and 5.6–15% of intracranial neoplasms in children. They are the most common lesions of the hypothalamopituitary region in childhood. They show a bimodal age distribution with peak incidence rates in children from 5 to 14 years old and in adults from 50 to 74 years old. Population-based studies suggest no gender differences (Karavitaki and Wass 2008).

Pathogenic and Pathological Findings

Craniopharyngiomas arise along the path of the craniopharyngeal duct which is the canal connecting the ectoderm of the stomodeum with the evaginated Rathke's pouch.

Two pathogenetic hypotheses have been proposed: neoplastic transformation of embryonic squamous cell remnants of the involuted craniopharyngeal duct or metaplasia of adenohypophyseal cells in the pituitary stalk or gland. Craniopharyngiomas are histologically benign grade I tumors (World Health Organization [WHO] classification). Rare cases of malignant transformation (possibly triggered by previous irradiation) have been reported. Two main histologic subtypes have been recognized, the adamantinomatous and papillary subtypes, but transitional or mixed forms have also been reported.

The adamantinomatous type predominantly affects young subjects during their first two decades of life but may be diagnosed at all ages. Macroscopically, this type may show cystic and solid components, fibrous tissue, necrotic debris, and calcification. The liquid within the cysts is called "motor oil" and it is mostly composed of desquamated squamous epithelial cells, rich in membrane lipids and cytoskeleton keratin. The borders of the tumor often merge into a peripheral zone of dense reactive gliosis. Furthermore, the margins are sometimes irregular, leading to significant difficulties in surgery for the preservation of neurovascular structures.

The epithelium is composed of a basal layer of small palisaded cells; an intermediate one with aggregates of stellate cells; and a top layer of enlarged and squamous keratinized cells. The flat squames are desquamated in distinctive clusters forming nodules of keratin, which are often calcified. The keratinous debris may elicit an inflammatory and foreign body giant cell reaction.

The papillary variety has been almost exclusively described in adults. Its structure resembles the oropharyngeal mucosa. Macroscopically, it is solid or mixed with cystic and solid components. The cyst content is usually viscous and yellow. Calcification is rare. Infiltration of adjacent brain tissue is less frequent than in the adamantinomatous craniopharyngiomas. Microscopically, it is composed of mature squamous epithelium forming pseudopapillae and of a fibrovascular stroma, which includes chronic inflammatory cells. Small aggregates of keratinized cells may be seen in some tumors (Weiner et al. 1994).

Clinical, Hormonal, and Imaging Features

Craniopharyngiomas may exert pressure to brain structures such as the visual pathways, the brain parenchyma, the ventricular system and the hypothalamopituitary structures, resulting in multiple signs such as neurologic, visual, and hypothalamopituitary impairments; headaches, nausea, vomiting, visual disturbances, growth failure in children, and hypogonadism in adults. The duration of the symptoms until diagnosis ranges between 1 week and 372 months.

A substantial number of patients presents with compromised pituitary function. The reported rates for anterior pituitary hormones deficits range from 38 to 95% and 6 to 38% for the antidiuretic hormone (ADH). Most of the craniopharyngiomas are detected in the sellar and suprasellar region; rare ectopic locations have also been described. A suprasellar component has been reported in 94–95% of the cases. Purely suprasellar has been detected in 20–41% of cases, both supra and intrasellar in 53–75%, and purely intrasellar in 5–6% (Karavitaki et al. 2006).

The size of craniopharyngiomas, as evaluated by CT or MRI, has been reported as greater than 4 cm in 14–20% of the cases, 2–4 cm in 58–76%, and less than 2 cm in 4–28% (Weiner et al. 1994). Rare cases of "giant" tumors with a diameter up to 12 cm have also been described. Their consistency is purely or predominantly cystic in 46–64% of cases, purely or predominantly solid in 18–39%, and mixed in 8–36%. Calcification has been shown in 45–57% of cases, and it is more common in childhood populations (78–100% of cases). Hydrocephalus has been reported in 20–38% of cases and is more frequent in children (41–54% of cases) (Karavitaki et al. 2006).

Surgical Considerations

Surgery is currently the most frequently used first therapeutic approach. Craniopharyngiomas remain challenging tumors, even in the era of modern neurosurgery. This is mainly due to their irregular margins and to their tendency to adhere to vital neurovascular structures, making surgical manipulations sometimes hazardous to vital brain structures. Consequently, the degree of excision to be attempted has been a subject of long-standing debate. The extent of resection depends on the size and location that is particularly difficult for retrochiasmatic or within the third ventricle tumors, the presence of hydrocephalus, the presence of greater than 10% calcification and brain invasion. Notably, in large series, radical surgery has been accomplished in 18–84% of the cases. The perioperative mortality rate currently ranges between 1.7 and 5.4% for primary operations (Karavitaki et al. 2006). Radical excision may or may not associated with substantial perioperative morbidity and mortality (Duff et al. 2000; Karavitaki et al. 2005).

There are many anatomic elements that can obstacle the surgical removal of craniopharyngiomas. The relationships between the tumor and the third ventricle and the hypothalamus are of paramount importance in the surgical treatment of such a complex lesions. The majority of craniopharyngiomas classifications are based on the relationships between the tumor and the sella turcica, the third ventricle and the optic pathways. However form the surgical point of view the most important relationship to consider during surgery is the relationships between the tumor and the walls and floor of the third ventricle. The understanding of these relationships is mandatory to perform a radical resection and to minimize the damages to hypothalamic structures.

According to some authors the intraventricular craniopharyngiomas don't exist at all and some authors defined a group of pseudo-intraventricular craniopharyngiomas (Hoffman et al. 1992; Van Den Bergh and Brucher 1970). According to other the intraventricular tumor exist and are well described as mass that can "arise from an above intact hypothalamic floor and lateral walls, filling some or all the third ventricle" (Sweet 1988).

Craniopharyngiomas (CFGs) can be classified according to the relationships between the tumor, the arachnoid and the pia mater (Ciric and Cozzens 1980). Before the formation of the pia mater the nests of epithelial cells are very adherent to the neuro-epithelium. When the pia mater is forming from the mesoderm these epithelial nests are included into the subpial space. The tumors developed from these clusters in contact with the primitive cerebral vesicle can be strictly intraventricular. These tumor named intrapial-intraventricular are very invasive and are extremely difficult to remove radically (Fig. 29.1a). Sometimes the development of these cells nests is in the direction of the subarachnoidal space.

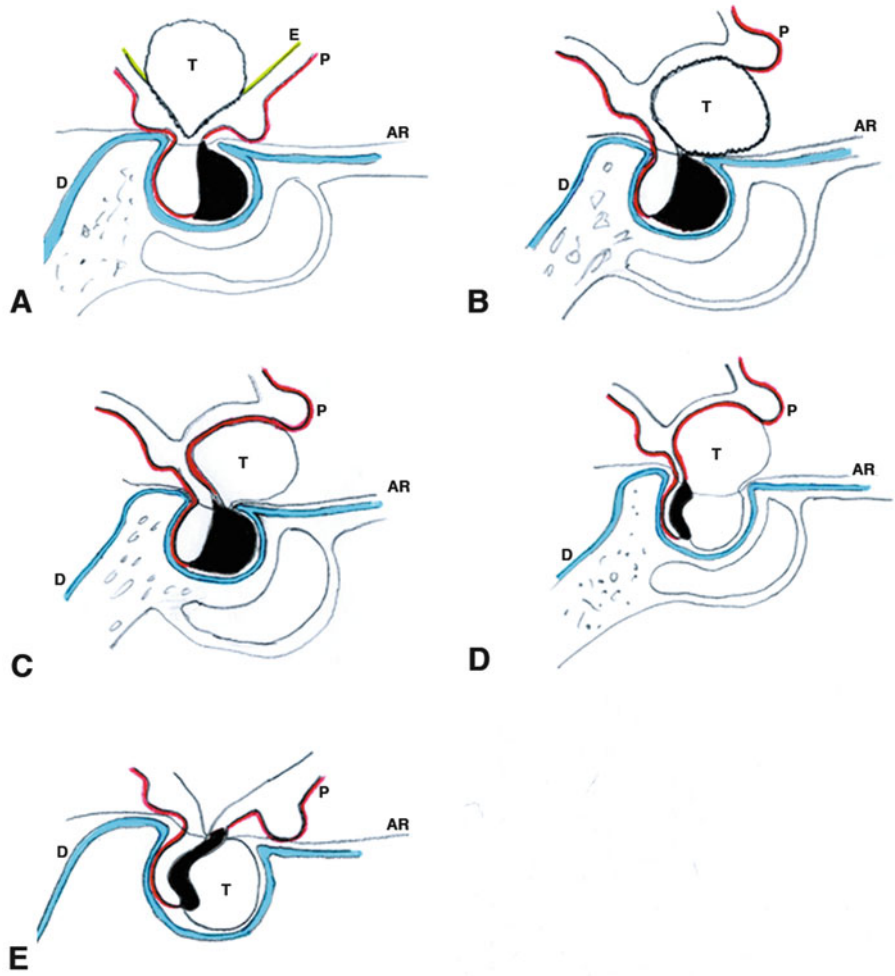

Fig. 29.1 Schematic drawing of the five different variants of craniopharyngiomas. (**a**): Intra-pial, intra-ventricular type; (**b**): Intra-pial, intra-arachnoidal; type; (**c**): Extra-pial, intra-arachnoidal type (Invasive variant); (**d**): Extra-pial, extra-arachnoidal intra-sellar, intra-arachnoidal suprasellar type (Dumbell variant); (**e**): Intra-sellar extra-arachnoidal. *AR* arachnoid, *D* dura, *E* ependyma, *P* pia mater, *T* tumor

The rupture of the pia mater gives origin to an intrapial subarachnoidal extension of the tumor. In this case the growing pattern is invasive, and the tumor is firmly adherent to hypothalamic structures (Fig.29.1b). In other circumstance the epithelial nests developed in contact with the anterior pituitary or remain suspended into the mesoderm far from the infundibulum and have no contact with the neural epithelium. When the pia mater develops the cellular nests remain extrapial and can give origin to extrapial craniopharyngiomas**.** According to its development in relationship with the pituitary stalk they can give origin to CFGs totally intra-arachnoidal or intra and extra-arachnoidal (Fig.29.1c). The extrapial intra-arachnoidal CFGs can be radically removed more frequently than other in this region. When the origin is below the infundibular area the CFG is a bilobated lesion partially intra-arachnoidal in the supradiaphragmatic part and extra-arachnoidal into the sellar part. In this case the sella is enlarged by the tumor (Fig.29.1d). The last variant of the CFG is the intrasellar one that is, of course, fully extra-arachnoidal (Fig.29.1e). Some authors

studied on autopsy specimens the relationships between the CFG and the walls of the third ventricle.

A first type of CFG is located into the sellar and suprasellar region. The superior part of the tumor is formed by a thick capsule separated from the floor of the third ventricle by an arachnoidal membrane. This tumor can be radically removed without any lesion to the ventricular floor.

A second type of CFG is located over the diaphragm sellae and can be extraventricular, intraventricular or both. The suprasellar extraventricular CFGs can be extrapial and are separated from the ventricular floor and are pre-chiasmatic or retrochiasmatic. The suprasellar intraventricular CFGs are very adherent to neural tissue in particular to the mamillary bodies and the infundibulum. In this case the radical resection can be difficult and dangerous. Moreover the location of the tumor is retrochiasmatic.

Other authors observed the tumor is closely adherent to the floor of the third ventricle in the area of the tuber cinereum (Hoffman et al. 1992). Moreover elsewhere is covered with meninges and is completely free of the remainder of the hypothalamus. As a consequence a radical removal is possible in the majority of cases without damages to the ventricular floor. It must be noted that the existence of a reactive tissue between the tumor and the neural structures is very unclear in literature. This is a point of paramount importance in case of a radical resection is attempted.

It has been demonstrated in an electron microscope study that the basal membrane of the epithelial tumor cells is separated from the basal glial membrane by a layer of collagen fibers that can be used as cleavage plane during surgery. However other authors stated that the layer around the tumor could be either too dense or too adherent to the brain or non-existent to be of value as a cleavage plane (Van Effenterre and Boch 2002).

Other studies showed that the relationships between the CFGs and the ventricular floor are different according to the consistence of the upper part of the tumor. In case of cystic tumors they found a layer of connective tissue and gliosis with abundant Rosenthal's fibers between the cist's wall and the hypothalamus tissue. This barrier is not evident in solid CFGs. This could explain the different surgical results according to the tumor characteristics (Kobayashi et al. 2005). Other authors stated that the functionless glia might provide a significant margin of safety between the mass to be excised and the vitally important hypothalamic and visual structures that should be preserved during surgery (Sweet 1988).

Other studies described cases of adherence to the anterior-inferior part of the hypothalamus where is impossible to separate the tumor from the nervous tissue (Yasargil et al. 1990). According these observations the dense finger-like splayed tumor and the gliotic adherent tissue make it impossible to identify a cleavage plane between the tumor and the nervous tissue. However the unilateral invasion of the hypothalamus could allow for a radical removal without postoperative complications.

Other authors stated that the radical removal is possible without significant damages to the hypothalamus because of the absence of adherence between the tumor and the floor of the third ventricle where the connections are limited and are a simple invagination of the tumor capsule into the brain tissue that can be separated by a gentle traction in the majority of cases (Choux et al. 1991). However these authors stated that in case of intraventricular extension the wall of the ventricle are truly infiltrated and the radical removal is impossible without sacrifice of the neural tissue.

The contact with the optic pathways is another main step in surgery for CFGs. Sometimes the chiasm and optic nerves are compressed and stretched. Usually the vascular supply is intact and should be preserved during surgery. The dissection should be started far from the tumor mass. Attention should be paid to preserve the microvascular supply to the optic pathways during the resection. In case of large tumors it could be difficult to distinguish the branches to the optic apparatus and the supply to the tumor mass.

Many authors agree that the pituitary stalk is frequently invaded by the tumor and should be

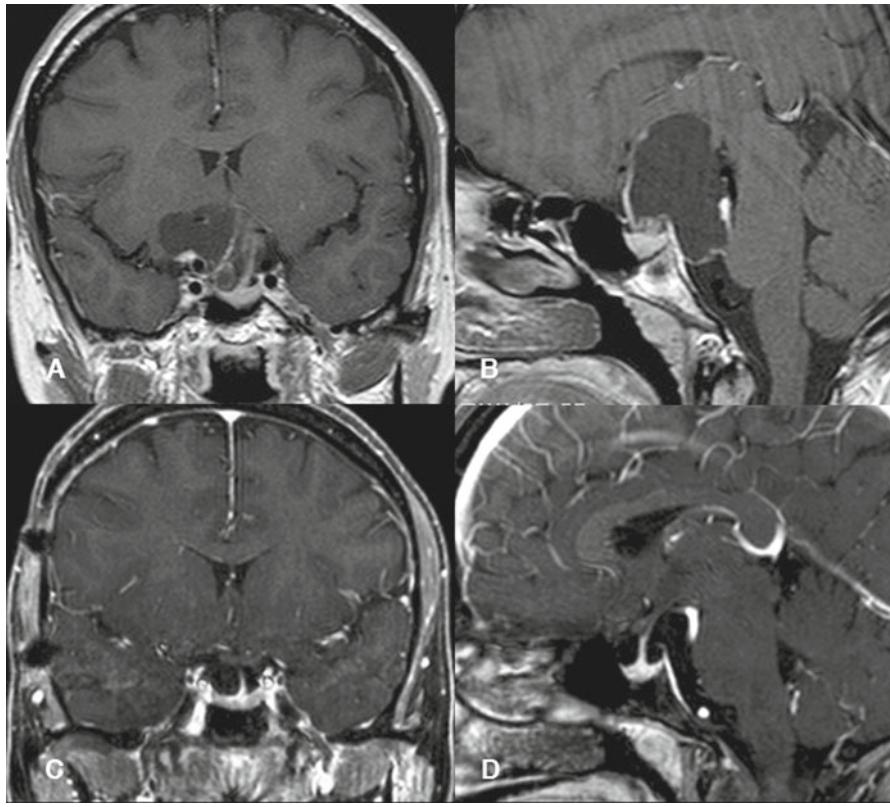

Fig. 29.2 Preoperative and Postoperative MR images. (**a**, **b**): Preoperative MRI study; coronal and sagittal gadolinium enhanced T1-weighted images showing the extension of the craniopharyngioma. (**c**, **d**): Three months postoperative MRI study; coronal and sagittal gadolinium enhanced T1-weighted images showing complete tumor resection with preservation of the pituitary stalk

sectioned in order to avoid potential source of recurrence (Sweet 1988; Mortini et al. 2011). However in patients with preoperative normal pituitary function when the CFG is separated from the stalk without a true dissection it should be preserved. This is a rare occurrence we have in our series (Fig.29.2a–d). The section of the pituitary should not be considered a major consequence of surgery. In fact in our experience the complete removal of the tumor is the most effective method of preventing recurrences. Considering the attending risks of renewed treatments, in both adults and children, we accept the sacrifice of the pituitary stalk to obtain radical resection, as advocated by others. We anticipate to the patients that pituitary replacement therapy is a very likely consequence of surgery, but it must be emphasized that individuals with adequate substitution therapies may have normal life expectancy. Moreover, it has been postulated that the degree of postoperative endocrine deficits depends on the extent of tumor removal, but most studies did not find any significant differences in pituitary function depending on whether patients had received aggressive or conservative surgical procedures. Adherence between CFGs and major vessels is one of the most frequent reasons of subtotal resection as reported in the literature (Choux et al. 1991). The carotid arteries and their branches are the vessels most frequently involved. However this occurrence is rare because the arteries are usually separated from the tumor by an arachnoidal layer. In case of strong adherence the surgical dissection can lead to the intraoperative rupture or formation of fusiform aneurysms few months after surgery.

Treatment Options

It has been proposed that radical surgery may be successful in selected tumors; in reports published during the microsurgical era with radiological confirmation of the operative results, complete removal has been accomplished in 18–84% of the cases. The extent of resection depends on the size and location that is particularly difficult for retrochiasmatic or within the third ventricle of the tumor; the presence of hydrocephalus, calcifications, and brain invasion; as well as on the surgeon's experience and the general treatment policy (aggressive or not) adopted by each neurosurgeon (Karavitaki et al. 2005; Van Effenterre and Boch 2002; De Vile et al. 1996; Mortini et al. 2011).

Reasons for incomplete removal, as reported in a series of patients who underwent primary surgery, include firm adherence to hypothalamus (26.8%), obstructed view (21.4%), major calcifications (14.3%), adherence to perforating vessels (10.7%), adherence to major vessels (7.1%), severe bradycardia during dissection (5.4%) very thin capsule (1.8%), and impression of complete removal (7.1%) (Fahlbusch et al. 1999).

In most studies, the GTR was confirmed by postoperative imaging, because the neurosurgeon's assessment during the operative procedure may not always be accurate. In fact, tumor remnants were detected on postoperative imaging in 18–26% of the cases in which the resection was considered complete by the surgeon. Series with radiological confirmation of the radicality of resection show that GTR is associated with recurrence rates of 0–62% at 10-year follow-up. These are significantly lower than following partial or subtotal removal (SR) (25–100% at 10-year follow-up) (Karavitaki et al. 2005; Van Effenterre and Boch 2002; Fahlbusch et al. 1999; De Vile et al. 1996; Mortini et al. 2011).

The first postoperative MRI showed residual tumor in 37 of the 131 patients of our most recent series who could be evaluated (28.2%), whereas no tumor was demonstrable in the remaining 94 patients (71.8%). In the group of 37 patients with visible residual tumor, radiation therapy was performed in 12 cases (32.4%), was advised but not performed in 6 patients (16.2%). In other 4 patients (10.8%), residual tumor was completely removed by another surgical procedure. The remaining 11 patients (29.7%) were advised to undergo regular neuroradiological monitoring, leaving the choice of radiation at the first demonstration of tumor growth.

Multivariate logistic regression analysis showed that previous surgery for craniopharyngioma (OR, 7.63; 95% CI 2.43–23.91; $p<0.001$) and maximum tumor diameter (OR per unit increase, 1.09; 95% CI 1.03–1.15; $P<0.01$) were associated with persistence of tumor residue after surgery. Other characteristics, such as sex, age at surgery, diabetes insipidus before surgery, type of surgery, histological subtype, and infiltration of the surrounding nervous tissue had no association with surgical outcome.

Recurrence of craniopharyngioma occurred in 30 of the 134 patients (24%) after a mean follow-up of 84.9 ± 5.3 months.

The risk of recurrence was higher in the first 3 years after surgery and then shows a plateau. The recurrence-free survival at 5 and 10 years was 76.2% (95% CI 67.5–84.9%); (Fig. 29.3a) and 64.8% (95% CI 52.5–77.1%), respectively. The presence of residual tumor after surgery was the strongest predictor of late recurrence of the tumor. The 5-year recurrence-free survival in patients with no residual tumor was 84.9% (95% CI 76.6–93.3%) as compared with 48.3% (95% CI 28.3–69.3%; $p<0.001$); (Fig. 29.3b, c) in patients with residual tumor.

Intracavitary irradiation (brachytherapy) is a minimally invasive modality involving stereotactically guided instillation of b-emitting isotopes into cystic craniopharyngiomas. It delivers a higher radiation dose to the cyst compared to external beam radiotherapy and leads to the destruction of the secretory epithelial lining and the elimination of fluid production with a consequent cyst shrinkage. The efficacy of various isotopes (mainly ^{32}phosphate, ^{90}yttrium, ^{186}rhenium, and ^{198}gold) has been assessed in several studies; because none of them has the ideal physical and biologic profile

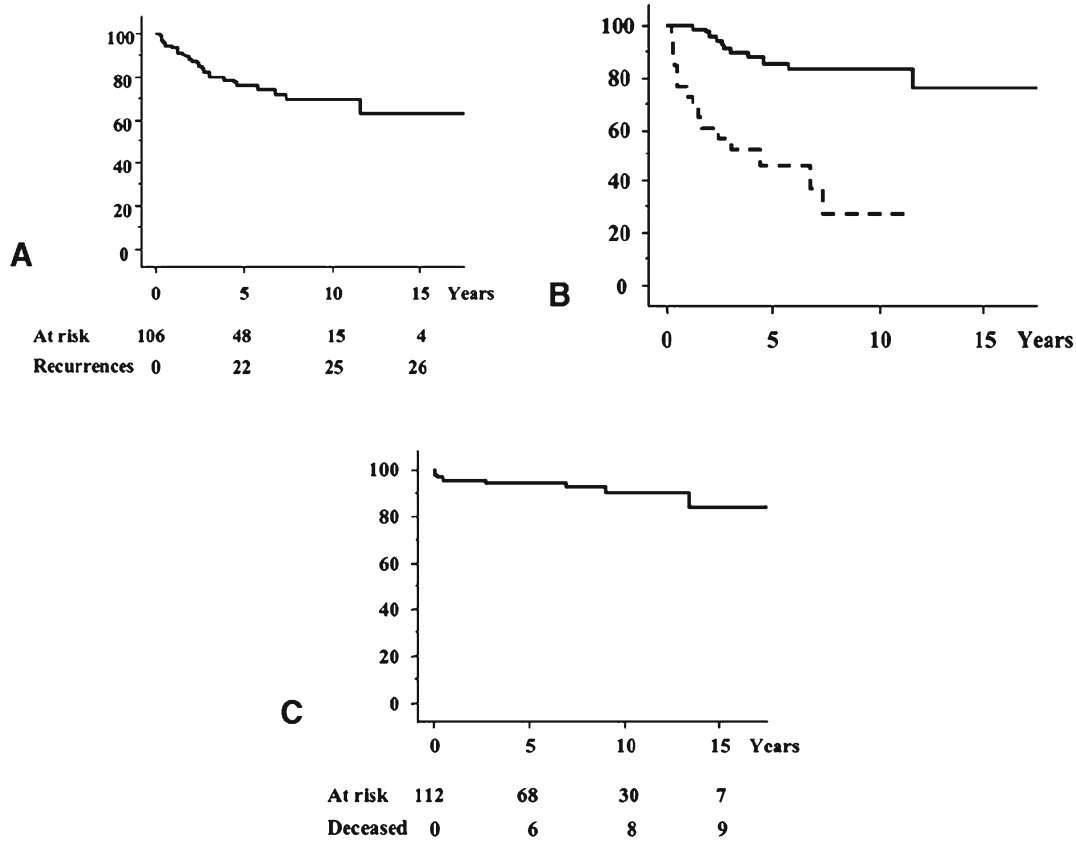

Fig. 29.3 (**a**): Kaplan-Meier analysis of recurrence-free survival in patients undergoing operations for craniopharyngioma. (**b**): Kaplan-Meier analysis of recurrence-free survival according to the absence (*solid line*) or presence (*dashed line*) of residual tumor after surgery. (**c**): Kaplan-Meier analysis of overall survival in 134 patients undergoing operations for craniopharyngioma

(i.e., pure β-emitter with a short half-life and with tissue penetrance limited to cover only the cyst wall) there is no consensus on which is the most suitable therapeutic agent. In several studies with a mean or median follow-up ranging between 3.1 and 11.9 years and intracavitary irradiation complete or partial cyst resolution was seen in 71–88% of the cases, stabilization was seen in 3–19%, and an increase in size was seen in 5–10%. New cyst formation or an increase in the solid component of the tumor was observed in 6.5–20% of the cases. The published control rates, and the reported low morbidity and mortality rates, make the brachytherapy an attractive option for predominantly cystic or monocystic tumors (Karavitaki and Wass 2008).

The intracystic installation of bleomycin results in at least a 50% decrease of the cystic tumor size in 64–86% of children during follow-up ranging from 3 to 12 years. Direct leakage of the drug into the surrounding tissues during the procedure, the possible diffusion though the cyst wall has been associated with serious toxic or even fatal effects (e.g., hypothalamic damage, blindness, hearing loss, ischemic attacks, brain edema). The value of this treatment option remains to be established.

Stereotactic radiosurgery delivers a single fraction of high-dose ionizing radiation on precisely mapped targets, keeping the exposure of adjacent structures minimal. Tumor volume and close attachment to critical structures like the optic pathways are limiting factors for its

application; 10 Gy have been reported as the maximum tolerated doses to the optic apparatus and 15 Gy the other cranial nerves (Karavitaki et al. 2006).

Some authors treated 31 patients, in 6 as primary therapy and in 25 for recurrent disease, with a mean margin dose of 12.2 Gy (range: 9.5–16 Gy). During a mean follow-up of 33 months, the overall response rate was complete (residual tumor volume <20% of the original volume) in 32.3% of the cases and partial (residual tumor volume <20–50% of the original volume) in 32.3%. No change was observed in 22.6%, and uncontrolled tumor progression was observed in 12.8%. 10.3% of the subjects experienced enlargement of the cystic component 5–17 months after radiosurgery. Smaller volume (<4.2 cm^3 or diameter <2 cm) or single-component tumors (solid or cystic) had a better control rate (Chung et al. 2000).

In a large series (Kobayashi et al. 2005) of 100 patients treated with a tumor marginal dose of 11.5 Gy followed for a mean period of 65.5 months (range: 6–148 months), the craniopharyngioma disappeared or decreased in size more than 25% in 67.4% of the cases, remained stable or decreased in size less than 25% in 12.2%, and increased in size in 20%. Based on the published data, stereotactic radiosurgery achieves tumor control in a significant number of patients who have small-volume lesions and it may be particularly useful for well-defined residual tissue after surgery or for the treatment of small solid recurrent tumors.

Systemic chemotherapy has been offered in a limited number of patients, mainly with aggressive tumors, with relative success. Its application remains rather experimental, and its value, particularly in the treatment of aggressive tumors, remains to be established (Karavitaki et al. 2006).

The growth rate of craniopharyngiomas varies considerably. Unfortunately reliable criteria predicting their behavior are lacking. Thus, apart from the significant impact of the treatment modality, attempts to identify other prognostic factors have not provided consistent data.

Age at tumor diagnosis (child or adult) probably does not affect the risk of recurrence; studies with appropriate statistical evaluations on patients who were offered various types of treatment have not confirmed differences in the local control rates between tumors diagnosed during childhood or adult life (Duff et al. 2000). Still, the age at presentation may affect the risk of recurrence when comparisons are performed within childhood populations only. In a study that age less than 5 year was found a significant predictive factor for recurrence (De Vile et al. 1996) but no differences have been detected among males and females (Karavitaki et al. 2005; Rajan et al. 1993).

Some series suggest that large calcified lesions involving many intracranial compartments or causing severe hydrocephalus maybe associated with increased recurrence rates. However, because these features may affect the amount of resection of the tumor, their impact on the recurrence may simply reflect the surgical result achieved (Fahlbusch et al. 1999). On the other hand, some authors did not confirm the effect of tumor size on the prognosis (Duff et al. 2000). Moreover, other studies propose that the location (intrasellar, extrasellar, or both), the consistency of the tumor, the presence of calcification, the hydrocephalus or third ventricular wall/floor invasion are not associated with an unfavorable outcome (Karavitaki et al. 2005).

The prognostic significance of the two pathological subtypes remains controversial. A few series suggest that the papillary type may have a better outcome, whereas others do not support this result. Moreover the small number of papillary tumors in most series, the difficulties in the classification of lesions with intermediate characteristics, and in many cases, the type of treatment make the interpretation of these data difficult (Karavitaki et al. 2006).

In our most recent series the risk of tumor recurrence was significantly associated with the presence of residual tumor on the first postoperative MRI (hazard ratio 9.89; 95% C.I., 3.84–25.50; $p<0.001$), male sex (hazard ratio 4.15; 95% C.I., 1.69–10.19; $p<0.01$), and no postoperative radiation therapy (hazard ratio 5.78; 95% C.I., 1.08–30.84; $p<0.05$). Previous surgery, tumor calcification, infiltration of the nervous tissue, absence of postoperative diabetes

insipidus, childhood onset, and obesity had no significant association with the risk of tumor recurrence. Finally, studies on the prognostic value of the tumor proliferation marker MIB-1 have provided contradictory data. Some authors suggested differences between recurrent and non-recurrent lesions, whereas another study has not reached similar conclusions (Nishi et al. 1999; Losa et al. 2004).

Long-Term Outcome

The long-term morbidity of patients with craniopharyngiomas involves visual, endocrine, hypothalamic, neurobehavioral, and cognitive functions, and compromising the quality of life. These complications are attributed to the damage of critical neural structures by the primary or recurrent tumor and to the adverse effects of the adopted therapies. The severity of the radiation-induced toxicity is associated with the doses, the volume of the exposed normal tissue, and the young age in childhood populations (Karavitaki et al. 2006). It has been proposed that the use of modern machines and irradiation doses of 55 Gy or less at 1.8 Gy per fraction should minimize toxicity (De Vile et al. 1996).

The visual outcome is compromised in a significant number of patients. In a large series was found that 62.5% of patients treated by surgery alone or combined with RT exhibited visual field defects during a mean observation period of 10 year (Duff et al. 2000). Other authors in a series of patients treated with similar modalities estimated that the cumulative probability for major visual field defects at 10-year follow-up was 48% (Karavitaki et al. 2005). Other authors reported deterioration of visual fields/acuity in 36% of 54 patients treated by surgery with or without adjuvant RT and followed up for a median period of 10 year (Pereira et al. 2005). In a series of patients treated with external beam RT either alone or after surgery and observed for 12 year, the pretreatment visual deficits was found worsened in almost one third of the cases. In this study, by using an accurate radiation modality and doses far below the tolerance limit of the central nervous system, visual functions remained unaffected in those with normal sight before radiotherapy (Rajan et al. 1993). The visual outcome is adversely affected by the presence of visual symptoms at diagnosis and by daily irradiation doses above 2 Gy (Karavitaki et al. 2006). Moreover some authors suggested that among patients treated with complete resection or partial resection followed or not by radiotherapy, the deterioration of vision is more common in the group of patients where a partial removal was possible, probably as a consequence of their increased recurrence rates (Karavitaki et al. 2005).

Visual function was impaired before surgery in 95 of the 131 patients of our most recent series (72.5%). Fifty-four out of these 95 (56.8%) had a visual field defect only, while the remaining 41 patients (43.2%) also had an impaired visual acuity. Visual function improved after surgery in 61 (64.2%), remained unchanged in 23 (24.2%), and worsened in the remaining 11 patients (11.6%). Among the 36 patients with preoperative normal visual examination, 32 (88.9%) retained a normal function, while the remaining 4 patients (11.1%) developed a permanent defect of visual field with no impairment of visual acuity.

Partial or complete hypopituitarism is encountered in a substantial number of patients. In series including various treatment modalities and follow-up periods, the frequency of individual hormone deficits ranges from 88–100% for GH, 80–95% for FSH/LH, 55–88% for ACTH, 39–95% for TSH, and 25–86% for antidiuretic hormone. Moreover, at least 3 pituitary hormone deficiencies have been reported in 54–100%.

The long-term endocrine morbidity is not affected by the type of tumor treatment. It should be stressed that restoration of preexisting hormone deficits after surgery, is absent or very uncommon (Karavitaki et al. 2005).

At baseline, normal gonadal, thyroid, adrenal, or somatotroph function was respectively present in 24, 66, 63, and 18 of 134 of patients of our most recent series. A new defect of the corresponding pituitary axis occurred postoperatively in 14 (58.3%), 47 (71.2%), 46 (73.0%), and 15 (83.3%) of the patients, respectively. On the con-

trary, 74, 63, 68, and 27 patients had a preoperative deficit of gonadal, thyroid, adrenal, or somatotroph function, respectively, that did not recover after surgery. Eighty-four patients had normal urinary concentrating capacity before surgery and 28 of them (33.3%) retained a normal function while the remaining 56 (66.7%) had postoperative diabetes insipidus. Of the 47 patients with preoperative diabetes insipidus, 3 patients (6.4%) regained a normal urinary concentrating capacity. Overall, 118 of 131 (90.1%), 110 of 129 (85.3%), 114 of 131 (87.0%), 72 of 75 (96.0%), and 100 of 131 patients (76.3%) had impaired gonadal, thyroid, adrenal, and somatotroph function or diabetes insipidus after surgery, respectively. The mean prolactin level decreased from 23.1 ± 2.8 μg/L to 15.4 ± 1.9 μg/L ($p < 0.01$), but the percentage of patients with hyperprolactinemia decreased only slightly from 26.7 to 16.8% ($p = ns$). Damage of hypothalamic functions may result in hyperphagia and obesity, disorders of thirst and water balance, and cognitive impairment, loss of temperature control, and disorders in the sleep pattern.

Obesity is the most frequent manifestation of hypothalamic damage reported in 26–61% of the patients treated by surgery combined or not with RT (Karavitaki et al. 2006). It results from the loss of the mechanisms controlling satiety, hunger, and energy balance. In a study of childhood craniopharyngioma, all subjects with obesity after surgery had evidence of significant alterations of the normal hypothalamic anatomy, with their MRI showing either complete deficiency or extensive destruction of the wall of the third ventricle. Hypothalamic obesity often results in devastating metabolic and psychosocial complications, necessitating provision of dietary and behavioral modifications.

Diabetes insipidus (DI) with an absent or impaired sense of thirst lead to a significant risk of serious electrolyte imbalance that is one of the most difficult complications to manage. This abnormality was found in 14% of children treated by complete or subtotal tumor excision with or without irradiation; all the identified subjects had other evidence of significant hypothalamic dysfunction (De Vile et al. 1996). Moreover other studies reported absence of thirst in 19% of adults with DI after surgery combined or not with RT. In this group of patients, the maintenance of the osmotic balance has been shown to be precarious, with recurrent episodes of hyper- or hyponatremia contributing to significant morbidity and sometime mortality (Smith et al. 2004).

In the literature factors associated with significant hypothalamic morbidity are young age at presentation in children, manifestations of hypothalamic disturbance at diagnosis, hypothalamic invasion, tumor vertical measure greater than 3.5 cm from the midline, attempts to remove adherent tumor from the hypothalamus, multiple surgical procedures for recurrence, and hypothalamic radiation doses greater than 51 Gy (De Vile et al. 1996). The deterioration of the neuropsychological and cognitive function in patients with craniopharyngioma sometimes contributes significantly to poor academic and work performance, and impaired quality of life (Van Effenterre and Boch 2002; Pereira et al. 2005).

Some authors in a series of 121 patients treated by surgery with or without adjuvant RT and followed up for a mean period of 10 year, found a poor outcome in 40% of cases. In this study the outcome was based on motor deficits, visual function, dependence for daily activities, Karnofsky Performance Scale school and work status, and major psychological or emotional problems (Duff et al. 2000). Another study on a series of patients treated mainly by surgery, found that during a mean observation period of 7 year, 16% of the adults and 26% of the children did not achieve an independent living status with social integration and normal professional occupation or school status (Van Effenterre and Boch 2002). Moreover in a large series of patients treated by surgery with or without RT, the cumulative probabilities for permanent motor deficits was 11%, epilepsy 12%, psychological disorders requiring treatment 15%, and total dependency for daily activities 9% at 10-year follow-up. Moreover 25% of the adults or children were unable to work in their previous occupation or were behind their expected school status (Karavitaki et al. 2005).

In a study on operated patients with or without postoperative RT and followed up for a median time of 10 year, 47% had psychosocial impairment (such as compromised independent living, social integration, professional occupation, and school performance) and 49% had neurological morbidity (defined as the presence of concentration problems, personality changes, short-term memory loss, anosmia, or epilepsy) (Pereira et al. 2005). Other authors in a series of children who had surgical removal followed or not by irradiation and followed up for a mean time of 6.4 year, demonstrated that 40% had IQ below 80 and 23% had severe motor disorders and epilepsy (De Vile et al. 1996).

In a series of 112 patients the data on quality of life, as assessed by mean Wen score were collected in 91 patients both before surgery and at last follow-up after radiation therapies or not. The mean score before surgery was 1.96 ± 0.05. Twelve patients (13.2%) were in Class I (grossly normal and independent patients), 71 (78%) were in Class II (patients with minor deficits and living independently), and 8 (8.8%) were in Class III (only partially dependent patients). No patient was in Class IV (completely dependent on others for self-care). At the last follow-up visit the mean Wen score was slightly increased (2.08 ± 0.05, $p < 0.02$). The number of patients in Classes I, II, III, and IV was 7 (7.7%), 71 (78%), 12 (13.2%), and 1 (1.1%), respectively (Mortini et al. 2011).

It should be noted that the data on the therapeutic option with the least unfavorable impact on the neurobehavioral outcome are inconsistent. Other authors in a study of 20 children who had been operated through a subfrontal craniotomy and were followed up for 38 months, found no difference in the outcome among those treated by PR or GTR (Anderson et al. 1997). In another study 13 adults assessed preoperatively and 3 months after surgery (all patients were treated during the microsurgical era, 10 had transcranial operations, with complete tumor removal achieved in eight cases) no impairment of the overall neuropsychological performance was found (Honegger et al. 1998).

Another study of 40 children treated by surgery combined or not with RT, showed that the group treated by conservative surgery with adjuvant irradiation was the one with the most consistent return to school and achievement of tertiary education or employment (Graham et al. 1992).

The assessment of the treatment option providing the most favorable functional outcome is difficult, because the experience of the neurosurgeon, the recurrences, and the subsequent therapies contribute to the final results. Moreover the comparative evaluation of published studies is further complicated by the variable not validated parameters defining the "good" outcome.

Moreover, most of them assess that patients treated before the advances in neurosurgery, neuroradiologic imaging, and RT techniques, and often they do not take into account the status of the patients at diagnosis. Thus, some authors reported that 5.7% of children and 5.4% of adults who underwent primary microsurgical complete excision had poor outcome (severe deterioration or unchanged poor condition, totally dependent, and with major medical problems). In this study, the outcome was significantly compromised in patients with large tumors or hydrocephalus or in those who underwent second or subsequent craniotomy for recurrence of the original tumor (Yasargil et al. 1990).

The mean morbidity scores were found not different between children who received RT after SR and those who had total removal. However, the morbidity scores of children with additional surgery for recurrence were higher than the ones after the initial surgery and higher than those of children without recurrence (De Vile et al. 1996). Interestingly, others suggested that GTR is associated with better neurological outcome, whereas there is no difference between patients who received or did not receive RT, both children and adults, and patients bearer of the adamantinomatous or the papillary type. In this series, factors associated with poor outcome were lethargy, visual deterioration or papilloedema at presentation, tumor calcification and adhesiveness to sur-

rounding neurovascular structures, as well as hydrocephalus (Duff et al. 2000). In a study no differences was found among patients treated by GTR, PR, or PR combined with RT in the cumulative probability of morbidities not present at diagnosis such as hyperphagia, motor disorders, epilepsy, dependency for basal daily activities, and deterioration of work or school status (Karavitaki et al. 2005).

Long-Term Survival

The overall survival rates in earlier series were 67–69% at 5-year follow-up and 43–77% at 10-year follow-up. The advances in neuroendocrinology, neuroradiology, microsurgery, intensive care, and radiation technologies allowed improvements, so that in the last decade studies, the overall survival rates range between 80 and 91% at 5 year and between 83 and 92.7% at 10 year (Karavitaki et al. 2006; Rajan et al. 1993).

In a more recent study on a large series the reported overall survival rates at 5 years is 94.4% (95% CI 90.0–98.8%) and 90.3% (95% CI 83.4–97.3%), at 10 years (Mortini et al. 2011).

The data on the treatment option with the most favorable impact on survival are not consistent, and often the large studies lack statistical evaluations. Furthermore, the reported mortality rates are probably affected by the different therapies adopted in case of recurrence resulting in a significant heterogeneity among the compared cohorts.

Thus, the 10-year survival rates range from 81.3 to 100% after radiologically confirmed total removal, 25–86% after SR or PR, 77–100% after PR and subsequent RT, and 81–100% after RT alone. It should be stressed that the radiologic confirmation of the removal has been assessed on MRI only in a single series with more than 100 cases. The lower limits of these rates represent data of earlier series (Karavitaki et al. 2006; Mortini et al. 2011).

Selection bias in the choice of treatment, should also be taken into account, in fact less aggressive or small tumors were treated with RT only in many series. Some authors found no significant difference in the 10-year survival rates between operated patients where a GTR was possible (100%), PR (86%), and PR and RT (87%) (Karavitaki et al. 2005). Moreover other authors found comparable 10-year survival rates in patients treated by surgery alone (GTR or SR) (86%) or surgery combined with RT (83%), being the extent of resection not predictive for survival (Stripp et al. 2004). In a large series of 173 patients treated with RT either alone or after surgery, was found that the survival was not influenced by the extension of tumor removal (Rajan et al. 1993).

The unfavorable effect of tumor recurrence on mortality is widely accepted with 10-year survival rates ranging between 29 and 70% (depending on the treatment modalities) (Karavitaki et al. 2006; Mortini et al. 2011). The impact of age at diagnosis as a prognostic factor of survival is controversial; some studies suggest better outcome in younger patients (Fahlbusch et al. 1999), others in older age groups (Rajan et al. 1993), while others have found no difference between children and adults (Karavitaki et al. 2005). With few exception (Pereira et al. 2005), no gender differences have been confirmed.

The histological type and the consistency or location of the lesion (intrasellar, extrasellar, or both) have no prognostic significance (Karavitaki et al. 2005). Finally, no consistent results exist for the tumor size. The interpretation of the data on the effectiveness of each therapeutic modality has to be done with caution, because the studies published to date are retrospective, nonrandomized and often specialty biased. Thus, the favorable outcome of the totally resected tumors or of those treated only with RT could be attributed to the fact that they represent "selected, " less aggressive cases on the basis of size, location, and clinical status of the patient, allowing the radical removal or the adoption of the irradiation alone. The review of the data reported in the literature are summarized in Table 29.1.

Table 29.1 Review of the literature

(Part 1)

Study	No.	Mean age (year)	Follow-up (year)	Children %	Tumor size (cm)	Preop H %
Yasargil et al. (1990)	144	N/A	N/A	49	>3 (62.5%)	N/A
Hoffman et al. (1992)	50	9.39	4.9	100	N/A	48
De Vile et al. (1996)	75	6.6	6.4	100	>3.5 (51%)	54.1
Duff et al. (2000)	121	N/A	10	26	N/A	12
Kim et al. (2001)	36	7.3	4.3	100	>3 (100%)	69.4
Van Effenterre and Boch (2002)	122	32.7	7	24	>3 (11%)	20
Merchant et al. (2002)	30	8.6	6.1	100	>3.5 (51%)	23
Maira et al. (2004)	57	35	6	8.8	N/A	N/A
Stripp et al. (2004)	76	8.5	7.6	100	N/A	N/A
Gonc et al. (2004)	66	4.2	5.1	100	N/A	46.2
Lena et al. (2005)	47	N/A	9.5	100	>2 (97%)	14.9
Minamida et al. (2005)	37	29.7	11.1	22	N/A	N/A
Shirane et al. (2005)	42	N/A	5	50	N/A	N/A
Sosa et al. (2005)	35	7	4.6	100	N/A	N/A
Thompson et al. (2005)	48	N/A	5.6	100	N/A	N/A
Tomita and Bowman (2005)	54	8.2	N/A	100	N/A	50
Zuccaro (2005)	153	10.5	N/A	100	4–6 (mean)	54
Lee et al. (2008)	66	8.02	7.2	100	N/A	N/A
Shi et al. (2008)	309	9/36 (Ch/Ad)	2.1	16.2	3.5 (mean)	37.8
Zhang et al. (2008)	202	9.3	N/A	100	N/A	N/A
Mean	88.5	N/A	6.4	73.6	N/A	37
Current series (2012)	134	34	7.1	27	2.9 (mean)	N/A

Preop vis def %	Postop CT/MRI	Radical removal %	TC surgery %	Surgical mortality %	Major morbidity %	Postop DI %
30.6	CT/MRI	90	90	16.7	N/A	90
58	CT/MRI	90	100	2	6	93
N/A	CT/MRI	40	100	0	13	80
62.5	N/A	57	68	1.7	18.4	21
N/A	CT/MRI	100	100	0	42	94
86.1	CT/MRI	59	92	2.5	8	57
N/A	N/A	27	100	0	10	50
N/A	MRI	56	0	0	0	14
56.6	CT/MRI	62	100	1	N/A	80
N/A	CT/MRI	31	100	2	10.6	52
68.1	MRI	66	98	2.4	N/A	86
N/A	MRI	70	92	0	5.4	N/A
N/A	N/A	71	100	0	6.7	52
N/A	MRI	83	89	0	20	91
58.3	MRI	33	73	0	15	84
42.6	MRI	61	94	0	9	87
43.8	CT/MRI	69	99	3	10	50
N/A	CT/MRI	N/A	100	0	6	67
43	CT/MRI	89	100	3.9	6	53
N/A	CT/MRI	40	99	1	5.4	81
55	N/A	62.8	89.7	1.7	11.3	67.5
74	MRI	72	66	2.2	7	76

(Part 2)

Study	Visual improvement %	Visual worsening %	Postop obesity %	Postop hypopituitarism %
Yasargil et al. (1990)	36	13	N/A	79
Hoffman et al. (1992)	36	41	52	N/A
De Vile et al. (1996)	N/A	N/A	15	99
Duff et al. (2000)	N/A	N/A	35.7	21
Kim et al. (2001)	N/A	25	6	100
Van Effenterre and Boch (2002)	70	11	36	76
Merchant et al. (2002)	N/A	17	N/A	97
Maira et al. (2004)	N/A	0	N/A	32
Stripp et al. (2004)	21	15	49	N/A
Gonc et al. (2004)	N/A	N/A	N/A	100
Lena et al. (2005)	16	16	48	89
Minamida et al. (2005)	N/A	2.7	N/A	97
Shirane et al. (2005)	N/A	N/A	N/A	81
Sosa et al. (2005)	N/A	17	N/A	100
Thompson et al. (2005)	61	N/A	20	96
Tomita and Bowman (2005)	61	13	28	93
Zuccaro (2005)	45	8.5	35	85
Lee et al. (2008)	N/A	N/A	18	N/A
Shi et al. (2008)	42	5.5	N/A	N/A
Zhang et al. (2008)	42	5	22	N/A
Mean	41.2	12.9	27.5	83
Current series (2012)	64	12*	23	90

Ad adults, *Ch* children, *DI* Diabetes Insipidus, *H* Hydrocephalus, *N/A* not available, *PFS* progression free survival,
*any degree of visual worsening. No postoperative blindness was recorded
°referred to 105 pts
^after GTR/STR/STR + RT

Postop RT %	Overall survival %	Relapse %	Relapse after radical removal %	5-year PFS %	10-year PFS %
4	80	7	7	N/A	N/A
0	98	34	29	N/A	N/A
51	80	41	10	N/A	N/A
21	88	24	12	77	N/A
0	89	36	39	55	N/A
21	89	24	13	78	60
77	97	37	38	N/A	N/A
3.5	96	14	N/A	N/A	N/A
56	89	N/A	N/A	63	53
54.5	80	56	41	N/A	N/A
19	94	34	26	N/A	N/A
0	94	30	15	80	75
N/A	93	38	20	N/A	N/A
26	97	34	41	N/A	N/A
73	96	39	50	N/A	N/A
15	90	44	27	62	49
31	88	0/51^	0	N/A	N/A
N/A	97	N/A	N/A	N/A	N/A
N/A	94	14/75^	14	75	N/A
N/A	68	15°	0	N/A	N/A
28.2	89.9	32.8	22.5	70	59.2
9	95	24	13	76	65

Postop postoperative, *Preop* preoperative, *RT* radiotherapy, *TC* transcranial, *y* year

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Part IX

Neurogenesis

Neurogenesis Outside the Central Nervous System (An Overview)

30

Luca Bonfanti and Paola Crociara

Contents

Abstract

Adult neurogenesis in the mammalian central nervous system is restricted to small, embryonic germinal layer-derived neurogenic sites localized in the forebrain. This neurogenic process is sustained throughout life by neural stem cells harboured within well characterized niches. Persistent neurogenesis is also known to occur in various organs of the peripheral nervous system, (e.g., retina, olfactory mucosa, gut, and carotic body). Ongoing research is trying to describe the *atypical* niches in which different types of new neurons are produced, with the aim of unraveling the mechanisms which regulate them at different locations.

Introduction

Adult neurogenesis, namely the capacity of generating new nerve and glial cells throughout life, is a phylogenetically highly conserved feature that challenges the dogma of the nervous system as a static, non-renewable tissue. In invertebrates and non-mammalian vertebrates, neurogenesis persists in wide regions of the central nervous system (CNS). In adult mammals, as reviewed in Gage (2000) and Kriegstein and Alvarez-Buylla (2009), a 'constitutive' genesis of new neurons is mainly restricted to two brain sites: the forebrain subventricular zone and the

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_30,

hippocampal dentate gyrus. The persistence of neurogenesis in these zones depends on stem cells which reside in niches as vestigial remnants of embryonic germinal layers. To a lesser extent, it has been demonstrated to occur even in humans, and recently, neurogenic/gliogenic processes have been shown to exist also in the brain parenchyma of some mammals. This 'parenchymal', non-constitutive cell genesis starts from local progenitor cells not performing as true stem cells, yet further studies are needed to ascertain their real potentialities.

In the last few years, in parallel with intense research on brain neurogenesis, evidence has been accumulated that new neurons can also be produced at several locations outside the CNS. Among these regions, the olfactory mucosa is known since long time, far before the demonstration of adult CNS neurogenesis. More recently, persistent neurogenesis has been observed in sensory organs (e.g., eye, carotid body, taste buds) and visceral organs (e.g., gut). Beside a deep knowledge accumulated in the last 20 years on CNS neural stem cells and neurogenic sites, whether and how neurogenesis also occurs in the neural crest-derived and placode-derived organs of the adult mammalian peripheral nervous system has been studied in lesser detail. In this chapter, the most investigated examples of neurogenesis in the periphery will be briefly reviewed and discussed.

In some cases, a stem cell niche has already been defined (e.g. the olfactory mucosa), whereas in others the search for a niche represents a widely open field of research (e.g. the taste buds). It is well known that the 'niche', namely the microenvironment in which stem/progenitor cells live and are finely regulated, is fundamental in defining their potential. Thus, in addition to specific knowledge on the histological/functional features of each peripheral location of neural stem cells (what could help in understanding stem cell biology in general and pathologies within specific organs), the study of 'atypical' stem cell niches is important under a translational profile, since can reveal substantial insights in the perspective of stem cell manipulation for regenerative medicine. The picture emerging from *in vivo* stem cell studies during the last two decades is that of a theme (the persistence of cell renewal/regenerative processes) with many variations linked to different variables: the cellular and molecular composition of different anatomical locations, the type of tissue, the age, and the species. In this context, the goal could be that of trying to understand if 'atypical niches' are required to allow the neurogenic process to persist at different locations and at different developmental stages through the 'adaptation' of stem cells to highly different tissue environments.

The new insights reported in this chapter come from a field which is gaining increasing interest and unexpected heterogeneity; a sort of new frontier in a highly ramified field spanning through the issues of structural plasticity, adult neurogenesis and brain repair, by focusing on different anatomical contexts with the aim of further understanding the neural stem cell/tissue interactions in such contexts. Nevertheless, the concept of 'atypical' stem cell niches is quite semantic, and only justified by the fact that some 'classic' neural stem cell niches have been discovered firstly, and are particularly active in the brain.

In addition, peripheral neurogenesis is interesting for several reasons: (i) peripheral neurons are more exposed to injury with respect to CNS neurons; (ii) some similarities exist between neural stem cells in CNS neurogenic centers and those of the peripheral nervous system, particularly concerning their glial phenotype; (iii) peripheral stem cells are more accessible than those in the CNS, thus representing a possible source of cells for tissue repair after injury or in the treatment of neurological diseases. Hence, the issues considered in this chapter should be regarded not only as a new, specific knowledge about neurogenesis within peripheral locations, but also as a further approach to understand the variety of interactions among stem/progenitor cells, their niches, and the different tissue contexts, what could contribute to new therapeutic strategies aimed at circumventing the failure in regeneration and repair that characterizes most of the mammalian nervous system.

Olfactory Mucosa

In the most superficial layer of the olfactory mucosa, the sensory neurons of the olfactory epithelium send axonal input to the main olfactory bulb. The epithelium also comprises specialized olfactory glands (Bowman's glands) and bundles of axons of the olfactory sensory neurons that are surrounded by the olfactory ensheathing cells. The axons enter the olfactory bulb where they synapse with mitral/tufted cells and interneurons.

The proximity of olfactory sensory neurons to the external environment increases their risk of death throughout life; e.g., inhalation of several molecules and pathogens can affect sensory neuron survival. Since the 1940s, it is known that continuous mitotic activity occurs in basal cells of the olfactory epithelium, as well as that receptor neurons can regenerate. Replacement of olfactory sensory neurons is a tightly regulated process, in which the number of mature neurons is maintained with a constant surface density of sensory dendrites, as described by Mackay-Sim and Kittel (1991) and Hinds et al. (1984). In addition, neurogenesis in the olfactory epithelium is stimulated by the death of the sensory neurons with recovery of function.

Many studies, reviewed in Calof et al. (1998) and Mackay-Sim (2010), indicate that there is a hierarchical stem cell lineage in the adult olfactory mucosa which normally regenerates the olfactory epithelium if damaged by trauma or toxins, including its neural and non-neural components. The horizontal basal cell is regarded as the stem cell since it proliferates slowly, self-renews, and generates all olfactory epithelial cell types *in vivo* and *in vitro*. This stem cell is in a niche defined by the extracellular matrix of the basement membrane as well as the many growth factors expressed by surrounding cells and hormones from nearby vasculature.

Murrell et al. (2008) showed that several trophic factors contribute to the regulation of these stem/progenitor cells: EGF and TGFa (proliferation of horizontal basal cells), FGF2 (proliferation of globose basal cells). EGF and FGF2 are required to generate multipotent neurospheres from the olfactory mucosa. As proposed by Leung et al. (2007), because the globose basal cell arises from the horizontal basal cell *in vivo*, it is likely that the latter is a *true* stem cell that maintains long-term regenerative capacity of the olfactory epithelium, whereas the former is a multipotent, transit amplifying cell. Recently, a multipotent cell has been isolated from the olfactory mucosa that can give rise to cells of endodermal and mesodermal origin as well as the expected neural lineage. Whether this is an additional stem cell or the horizontal basal cell is still an open question.

Since neural progenitors formed in the subventricular zone migrate forward and join in neural circuits as interneurons in the olfactory bulb, the target for axons from the olfactory sensory neurons is a continuously changing environment. As suggested by Bonfanti (2006), relationships between these two neurogenic system (one central, the other peripheral) should exist, as part of a general structural plasticity involving the entire olfactory pathways, up to their further projections to the piriform cortex and its functional relationship with the hippocampus. Finally, it is worth mentioning that unlike the deep location of brain neural stem cells, the olfactory mucosa could be a source of tissue since it is accessible in living adult humans, thus also representing a source of cells for transplantation repair of the nervous system.

In addition to neurogenesis in the olfactory epithelium, within the nasal cavities new neurons are formed (and can regenerate) from the adult vomeronasal organ. As reviewed in Halpern and Martinez-Marcos (2003), this is a bilaterally symmetrical tubular structure located at the base of the septum containing a pseudostratified columnar epithelium composed of basal cells, intermediate neuronal precursors, mature sensory neurons, and sustentacular cells. The sensory neurons send a long axon that establishes glutamatergic synapses in the accessory olfactory bulb. Two types of stem cells have been identified in the vomeronasal organ: cells in the marginal zone (largely responsible for growth) and cells in the central zone (associated with neuronal replacement). Contrary to prior observations, recent studies indicated that a vomeronasal organ

is present in human adults. Although some observations in humans require confirmation, the vomeronasal system in other mammals is responsible for one of the most striking pheromonal phenomena, the Bruce effect, thus remaining an excellent model for studies on neurogenesis and behaviour.

Retina

The retina of many fish and amphibians continues to grow throughout life and is able to regenerate, due to multipotent, self-renewing stem cells that are located in the ciliary marginal zone. As reviewed by Perron and Harris (2000), these cells became progressively reduced in evolution, from fish to mammals; a few mitotically active cells were also identified in postnatal marsupials but never to date in other mammals, wherein the retina achieve its development by the early postnatal period and no additional retinal cells are produced in the adult. For this reason, and in the absence of repair following damage, the adult mammalian eye was considered to be devoid of retinal stem cells (RSCs).

A decade ago, Tropepe et al. (2000) reported the existence of RSCs in the mammalian ciliary body, which is located between the neural retina and the iris, and contains the ciliary muscles involved in eye accommodation. The ciliary epithelium consists of two cell layers, an inner non-pigmented epithelium, and an outer-pigmented epithelium; single pigmented cells from the ciliary epithelium of mouse retina clonally proliferate *in vitro* to form sphere colonies. As recently reviewed in Locker et al. (2010), when exposed to differentiation conditions, the colony forming cells were shown to display features found in rod photoreceptors, bipolar neurons, and Müller glia, suggesting their multipotentiality. In particular, Coles et al. (2004) proposed that a population of retinal stem cells, mitotically quiescent *in vivo*, exists in the ciliary body of the adult mammalian eye, including humans. Accordingly, it was recently reported that in physiological conditions, ciliary body stem cells might contribute to retinal cell turnover of adult primates, by producing retinal neurons. Discrete heterogeneous populations of cells endowed with innate neural stem/progenitor properties might also occur in the iris epithelium and in Müller glia.

In contrast to brain-derived neural stem cells, iris- and ciliary body-derived cells display the unusual property to proliferate as neurospheres in serum free media without exogenous growth factor addition, although EGF and/or FGF2 or bFGF do increase the number of neurospheres formed from dissociated cells. Anyway, the proliferation of retinal-derived cells is more limited in comparison with those isolated from the brain. No more than 0.2–2% seem to be endowed with proliferative capacities and their self-renewal and proliferation rates gradually decrease with subsequent passages. Among the genes and molecules studied in retinal-derived stem cells, *Pax6* seems the most involved in the regulation of their capacity in generating neurospheres and in their maintenance in vivo.

Some authors suggest that neurospheres formed from the ciliary epithelium retain epithelial features. Thus, the mammalian ciliary epithelium would not contain actual RSCs, but instead a population of differentiated cells that can proliferate, self-renew and express some neuronal markers, while retaining features of pigmented epithelial cells. Accordingly, recent studies on regeneration indeed suggest that the term "stem cell" should be used to refer to a biological function that can be inherent to or induced in many distinct cell types, even differentiated cells.

The discovery of ciliary body-derived stem cells generated several research directions aimed at characterizing their *in vitro* properties, molecular signature, *in vivo* ability for tissue repair and potential for cell-transplantation medicine. In retinal degenerative diseases, such as age-related macular degeneration and retinitis pigmentosa, photoreceptor cells are damaged or lost, with consequent visual impairment. At present, the best source for therapeutic approach seem to be cells already engaged towards a photoreceptor fate. Human RSCs, genetically modified to promote their photoreceptor differentiation into murine eyes, exhibit higher level of retinal integration compared with unmodified RSC progeny.

Yet, as indicated by Locker et al. (2010), a major difficulty in translating such strategies into clinical applications relies on the limited availability of adult RSCs and their reduced proliferative potential. An alternative approach to treat retinal dystrophies, reviewed by Karl and Reh (2010), could be that of endogenous retinal stem cell mobilization.

Enteric Nervous System

The enteric nervous system, namely the largest division of the autonomic nervous system, represents the highly organized intrinsic innervation of the gastrointestinal tract and plays a critical role for all stages of postnatal life. As showed by Le Douarin and Teillet (1973), it is formed by a population of multipotent stem cells deriving from the neural crest. Gut colonization by vagal neural crest cells is completed by E15 in mice and after 7 weeks gestation in humans. Shortly after these cells have reached the hindgut sacral cells, they start to migrate into the gut wall, and after complete colonization they generate a complex network of differentiated neuronal and glial cells. All these cells are arranged in interconnecting ganglia within the longitudinal and circular smooth muscle layers (myenteric plexus) as well as the connective tissue beneath the mucosa (submucosal plexus) of the gut. On the whole, this system is estimated to contain more neurons than the spinal cord (i.e. up to 10^{10} cells in humans) sharing many neural subtypes and neurotransmitters with the CNS, consisting mainly of intrinsic primary afferent neurons. Nevertheless, in contrast to the highly protected CNS, these neurons are more exposed to injury.

Enteric glial cells, which largely exceed neurons in number, are also an important component of the neuronal circuitry. They resemble astrocytes of the CNS and are different from the Schwann cells of the peripheral nervous system. Enteric glial cells form a widespread network at all levels of the gastrointestinal tract with neurons, epithelial cells, mesenchymal cells and immune cells.

The fully mature enteric nervous system circuitry develops soon after birth and allows a largely independent control of gut peristalsis and secretory activity. However, it is well connected to the CNS via motor and sensory pathways of the sympathetic and the parasympathetic nervous system which is necessary for fine tuning of diverse functions.

As recently reviewed in Metzger (2010), a subpopulation of enteric glia maintain the ability to divide showing a great plasticity during pathological processes (e.g., inflammation), with upregulation of neurotrophic factors (GDNF, NGF and others) and expression of neural stem cell markers (nestin, GFAP). Whether these cells can act as *true* stem cells is still unclear, yet many parallels exist to the CNS neural stem cells. As for the CNS, also in the enteric nervous system until the early 1990s neurogenesis was believed to end shortly after birth. Young et al. (2003) demonstrated that some neuronal subtypes of the gut (e.g., CGRP neurons) appear in the very late fetal and postnatal stage, suggesting that ongoing adult neurogenesis could also occur. At birth, up to 5% of cells within enteric ganglia still remain negative for pan-neuronal and glial markers, depending on the gut region. This value further decreases (to less than 1%) in the adult gut, but the one could not rule out the presence of undetected immature cells. Neuroplasticity and reversibility of plexus disruption have been described by histological and electronmicroscopical observations. In addition, Pham et al. (1991) earlier, and Liu et al. (2009) more recently, showed postnatal neurogenesis in the gut of rodents. The stem cells would be localized in germinal niches between the myenteric plexus and the longitudinal muscle layer in adult mice.

Kruger et al. (2002), by adapting protocols from neural crest stem cell cultures were able to demonstrate multipotent neural stem cells isolated from postnatal rat gut. Significant progresses in the identification and harvesting of enteric nervous system stem and progenitor cells from postnatal gut, including humans, are reviewed in Metzger (2010).

Severe disturbances of function in this system can significantly influence life quality or, in

severe cases, can have acute life-threatening effects. Enteric stem cells have been proposed as an appropriate cell source to provide an alternative therapeutic option for a number of neurogastrointestinal diseases, although a better understanding of these cells would be crucial for the translation of cell-based therapies into clinic. At present, the functional significance of neural crest-derived stem cells in the postnatal gut remains unclear, especially about the question whether these cells permanently perform neurogenesis and gliogenesis or whether, and how, they can be affected by injury, ageing or external stimuli.

Carotid Body

The carotid body, a paired organ located at the carotid bifurcation, is a principal component of the homeostatic acute oxygen sensing system required to activate the brainstem respiratory center to produce hyperventilation during hypoxia. This organ is one of the most irrigated in the body; its parenchyma is organized in glomeruli, clusters of cells in close contact with capillaries and afferent sensory fibers joining the glossopharyngeal nerve. The most abundant cell types are the neuron-like, glomus or type I cells, which are enveloped by processes of glia-like, or type II cells. Glomus cells, the chemosensory components of the organ, are electrically excitable: when exposed to hypoxia, they detect the decreased level of blood oxygen and release neurotransmitters to activate the adjacent nerve fibers, which in turn carry the information to the respiratory centers to trigger the appropriate responses.

Recent experimental data obtained by Pardal et al. (2007) of the group of J. Lopez-Barneo, have shown that the adult carotid body is a functionally active germinal niche where type II cells might act as dormant stem cells that proliferate and differentiate into new glomus cells in response to physiological hypoxia. Evidences for the discovery of these neural crest-derived progenitor cells in the carotid body are reviewed in Pardal et al. (2010).

Few days after exposure to the hypoxic environment, the carotid body undergoes a marked hypertrophy due to an increased number of chemosensitive type I cells, enhanced vascularization and neo-vascularization. By using the thymidine analog BrdU, which is incorporated to DNA and marks proliferative cells and their derivatives, it has been demonstrated that progenitor cells in the carotid body can proliferate and differentiate into new neuronal cells, thus explaining the marked growth of the organ.

When dissociated carotid body tissue are cultured in a medium designed to allow the growth of neural crest progenitors and maintained under moderate hypoxia that mimics the hypoxic stimulation *in vivo* (3% O2), about 1% of the plated cells give rise to neurospheres. Unlike the typical spherical shape of CNS-derived neurospheres, most of these neurospheres have large blebs budding out of the main core, containing TH + neuronal cells and resembling in shape the characteristic carotid body glomeruli. If the neurospheres are plated, some progenitors can differentiate into another typical derivative of neural crest stem cells: the smooth muscle actin-positive myofibroblasts. At present, it remains to be elucidated whether the multipotency demonstrated in vitro also occurs *in vivo*, and particularly if carotid body stem cells can contribute to vasculogenesis by undergoing differentiation into smooth muscle cells, in addition to neurogenesis.

Other studies from the group of Pardal et al. (2007) showed that the GFAP staining of sustentacular type II cells progressively vanishes as the number of proliferating BrdU + cells increases upon exposure to hypoxia. Then, GFAP + cells reappear in normoxic atmosphere, when the carotid body resumes to its original size, thus suggesting that GFAP-expressing type II cells might function as progenitors. By using a transgenic mouse model in which both GFAP + cells and their derivatives are marked, the same authors showed that newly formed BrdU + type I cells actually derive from GFAP + type II cells. Hence, it is suggested that stem/progenitor cells are present in the carotid body in the form of quiescent (or slowly dividing) GFAP + type II cells that can be reversibly converted to intermediate

progenitors. These latter, upon exposure to hypoxia, are able to give rise *in vivo* to TH + glomus cells.

It is interesting to note the similarities existing between neural stem/progenitor cells in neurogenic centers of both the peripheral and central nervous system, particularly concerning their glial phenotype (see the Introduction). Because understanding the *in vivo* regulation of different adult neural stem cell niches is crucial to elucidating the cell biology of neural stem cells and ultimately defining their therapeutic potential, the ability of carotid body (neural crest-derived) stem cells to revert their behavior upon physiological stimulation could be an excellent model, complementary with respect to CNS (radial glia-derived) germinal niches. Beyond physiology, the existence of stem cells in the carotid body raises the question of their possible role in the paragangliomas affecting the autonomous nervous system (e.g., chemodectomas), whose incidence increases in high-altitude residents. Future studies are needed in order to ascertain if disruption of carotid body stem cell homeostasis can lead to tumor transformation.

Taste Buds

As reviewed in Roper (1989), taste is a primary sense of all vertebrates, reliably conveying important chemical information from the oral cavity to the brain to regulate ingestion. The ability of animals to make this distinction between nutritional, versus potentially lethal, or fermented or unripe food items, respectively, may mean the difference between survival and death. The taste system consists of several anatomical and functional components of the oral and pharyngeal cavities, including a distributed array of taste buds, namely multicellular end organs of roughly 50–100 fusiform cells, which transduce sapid stimuli into electrochemical signals.

These cells comprise a heterogeneous population including taste responsive cells (for particular taste modalities, such as sweet, sour, bitter, umami, or salty) which communicate via neurochemical signals with afferent nerve fibers of pseudobipolar gustatory sensory neurons. From the cell bodies located in the cranial ganglia (VII, IX or X) the distal neurites extend to peripheral taste buds, whereas the proximal neurites project centrally, to the brainstem. As showed by Beidler and Smallman (1965), cells within taste buds continually turnover throughout adulthood such that ~10% of cells are new to each bud each day, yet the percept of taste is relatively constant over time.

As reported by Roper (1989), taste receptor cells are electrochemically excitable and release neurotransmitter onto afferent nerve fibers upon excitation, thus sharing features with neurons. However, as shown by Stone et al. (1995), unlike neurons the origin of these chemosensory cells is epithelial, and not from ectoderm. Thus, continual regeneration of taste cells may be driven by cellular and molecular mechanisms which reflect their function (neural) and their origin (epithelial).

In rodents, there are three types of cells: type I, II, and III. Type I cells are the most numerous, representing ~50% of cells per bud, and are believed to function as support cells. Type II and III cells are less common, contributing 15–20% each. As recently reviewed by Miura et al. (2006) and Miura and Barlow (2010), cells within taste buds are postmitotic, since they do not express markers of cycling cells (e.g., Ki-67, PCNA, and phosphohistone3A). Birthdating studies employing injections of BrdU then revealed at different survival times, have revealed that epithelial cells immediately adjacent to taste buds are in S phase within 1–6 h of nucleotide labeling. At 12–24 h of BrdU, however, post-mitotic labeled cells are evident within taste buds, and by 48–72 h, these immature cells differentiate and express specific taste cell markers.

Very likely, mitotically active perigemmal (adjacent to taste buds proper) and basal epithelial cells correspond to the true stem cells, namely a proliferative pool from which immature taste cells are generated in a process similar to that providing cell renewal of general epidermis. Stone et al. (2002) have estimated that each mouse taste bud is populated by 7–13 putative stem cells. However, as for stem cells and progenitors of the interfollicular epidermis,

to date, a molecular discrimination of taste bud stem cells from transit amplifying cells remains elusive.

Some information on the genesis of taste cells comes from studies of embryonic development of the taste epithelium. In mice, these structures are specified at midgestation from epithelial thickenings, or placodes which express Sonic Hedgehog (Shh). Thirumangalathu et al. (2009), by treating pregnant females with tamoxifen precisely when Shh is focally expressed in the taste placodes of the embryos showed that these cells did not contribute to taste papilla epithelium. In addition, taste bud cells descendent from Shh-expressing placodes were gradually lost postnatally, and were absent 4 months after birth. Thus, the Shh-expressing placodal cells could function as a signaling center in embryos and youngs, but additional progenitor cells are recruited in adult mice to continuously replenish mature taste buds, similarly to what happens in murine hair follicles.

Under normal conditions, taste cell regeneration occurs, yet these sensory cells are sensitive to insult, and taste buds themselves are impacted in a number of relevant human health problems. The most used experimental model is that of denervation. It is known since long that differentiated taste buds are dependent upon an intact innervation; when either the chorda tympani branch of the VIIth nerve, or the glossopharyngeal nerve most taste buds are reduced and disappear. By contrast, as showed by Miura et al. (2004) and Yee et al. (2005), in the case of nerve regrowth the taste buds will regenerate. Nevertheless, that of taste bud cells degeneration and regeneration remains a widely open field of research. In human health, both the glossopharyngeal and chorda tympani nerves can be damaged inadvertently during oral surgery and chronic otitis media can result in concomitant taste sensitivity problems. Finally, in patients with head and neck cancer that receive a daily radiotherapy over several weeks, a reduction in taste sensitivity is possible, resulting in reduced food intake and weight loss, and therefore an overall reduced quality of life.

Sensory Ganglia

A true process of adult neurogenesis in spinal (or cranial) ganglia has not been clearly demonstrated. Nevertheless, this research topic is part of a more general question regarding the potentialities of various types of satellite cells. GFAP and vimentin expressing satellite cells have been described in some sympathoadrenal structures like the adrenal medulla or the sympathetic ganglia. Furthermore, Li et al. (2007) showed that some of these populations of satellite glial cells, like those in the dorsal root ganglia, behave as progenitors *in vitro*, being activated *in situ* in response to injury. In dorsal root ganglia explants, cells that express nestin and p75 neurotrophin receptor form secondary and tertiary neurospheres in cloning assays, and can differentiate into neurons, glia, and smooth muscle cells. These results, along with the observation that after peripheral nerve injury the number of sensory neurons in the adult dorsal root ganglia is initially reduced but recovers to a normal level several months later, strongly suggest the possibility for neurogenic processes in a subpopulation of ganglionic cells.

Many reports indicate that primary sensory neurons of the dorsal root ganglia do increase the number in the adult. B-type cells are the most affected population, although A-type cells also increase in number. Yet, it is still debated whether the increase is attributable to postnatal neurogenesis or maturation of dormant, postmitotic precursors. In studies carried out on sensory ganglia of adult rats by Farel (2003) and Lagares et al. (2007), it was concluded that a protracted maturation process can be responsible for the neuronal addition in juvenile and adult animals. It was proposed that the new neurons in adult dorsal root ganglia derive from differentiation of cells that at younger ages could not be recognized as neurons. These cells are positive to neuronal markers but are not traceable when HRP is applied to the periphery suggesting that they had not yet extended their peripheral axons. In the adult trigeminal ganglion some populations of Nestin+

and DCX+cells were identified, both markers being related to neuronal maturation of neuronal precursors, and in some cases to neurogenesis.

What is not yet clear is whether neurogenesis could occur as a consequence of certain types of damage. Experimental manipulations or pathological conditions of the peripheral nerves result in phenotypic changes within the ganglia. Thus, such an issue is of primary interest to understand the functional and structural reorganizations in the system. Neuronal loss does occur in the dorsal root ganglia after target removal or irreversible damage to a peripheral sensory nerve. For instance, a subpopulation of sensory neurons undergoes apoptosis after peripheral nerve injury in the adult, resulting in a loss of 20–30% of dorsal root ganglion neurons in the first 2–3 months, then recovering to normal levels several months later. However, reported quantitative data show large variability, consistent with the multifactorial dependence of neurons for survival after axotomy, such as animal age, nerve type, distance of tran-section from the soma, availability of trophic factors, and postlesion survival time.

In conclusion, it remains to be clarified whether satellite glial cells are indeed adult peripheral neural stem cells with the capacity to undergo neurogenesis, at least in pathological conditions. For such a reason, these cells, along with those described in this chapter within various contexts outside the CNS, do represent a widely open field of research in the topics of peripheral stem cells and neurogenesis.

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Neurogenesis and Reproduction

31

Wui-Man (Benson) Lau and Kwok-Fai So

Contents

Abstract

Continuous generation of new neurons in adulthood, namely adult neurogenesis, could be found in two neurogenic regions in the brain, the subventricular zone and hippocampus. Neurogenesis is considered as a specific form of neuroplasticity, and it ultimately influences the behavior of an individual. While neurogenesis in the hippocampus is widely accepted to contribute to memory functions, subventricular zone neurogenesis is suggested to have roles in olfactory, social and reproductive functions. This chapter reviews recent studies which examine the interrelationship between neurogenesis and reproductive behaviors including mating, pregnancy and parental behaviors. The regulation of neurogenesis by reproductive behaviors is widely observed across different species, and the regulation is under the control of gonadal or adrenal hormones. As the new born neurons require a few days to mature, the increase in cell proliferation usually shows a delayed functional significance at later reproductive stages. Blocking neurogenesis by cytostatic compounds confirms the necessity of neurogenesis in reproductive functions. These findings exemplified the modification of neurogenesis by experience, and provide a novel perspective on the function of gonadal hormones in modulation of neuroplasticity. Future studies on the mechanism of neurogenesis regulation

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1_31,

will be needed for the understanding and potential applications of neuroplasticity in reproduction.

Introduction

Continuous production of new neurons in adulthood occurs in two regions in the mammalian brain: the subgranular layer (SGZ) of hippocampus and subventricular zone (SVZ) (Gross 2000; Lee et al. 2011). The phenomenon, namely adult neurogenesis, is a complex process involving different phases of neuronal maturation including cell proliferation, differentiation, migration and integration into the existing neural circuitry. In the hippocampus, neural progenitor cells proliferate in the SGZ and migrate through a short distance (two to three cell layer thick) to the granule cell layer. In that region the survived new cells differentiate and establish synapses with mature neurons in the CA (Cornus Ammonis) three region of hippocampus. Neural progenitor cells in the SVZ, being different from their counterpart in the SGZ, differentiate into neuroblasts and migrate over a long distance (up to 5 mm long in rodents, (Racekova et al. 2009)) to the olfactory bulb through the rostral migratory stream (RMS). The neuroblasts then migrate radially towards the outer border of the olfactory bulb and differentiate into granule or periglomerular neurons (Huang and Bittman 2002; Lau et al. 2011b).

The discovery of adult neurogenesis has challenged a 'dogma' in neuroscience, that is, no new neurons are added into the adult mammalian brain (Gross 2000). As a specific form of neural plasticity, neurogenesis provides the insight that the matured brain could be modified by experience, pharmaceutical treatment and other forms of stimulations at the cellular level. The discovery is inspiring because endogenous neural progenitor cells are potential cellular sources for neuronal regeneration in neurological disorders like cerebral vascular accident and Parkisonian disease. On the other hand, the persistent addition of neurons to the adult brain in physiological conditions implies that the new neurons may play important roles in daily functioning, which is still a matter of debate. Due to its potential application value and obscure significance, adult neurogenesis has been investigated intensely since the past decade.

The functional impact of new neurons was cued by the site of integration. As the hippocampus is involved in memory formation and cognitive functions, the new neurons were found to be important for specific forms of hippocampal-dependent memories, including trace memory conditioning (in which an animal is needed to associate the unconditioned and conditioned stimuli separated for a relative long period) and trace fear conditioning (Shors et al. 2001). On the other hand, the new cells are possible to be involved in sensorimotor gating (Lau et al. 2009), which is related to symptoms of psychosis.

Comparing to the SGZ, behavioral significance of the SVZ neurogenesis is obscure. Until recently, it was shown that SVZ/olfactory bulb neurogenesis is involved in the social and reproductive behaviors (Lau et al. 2011b; Mak et al. 2007; Mak and Weiss 2010). When the SVZ neurogenesis was blocked by anti-mitotic drugs, disruption of normal reproductive behaviors was observed, which includes suppressed male sexual behavior, disruption in female mate preference and disrupted paternal behavior. Since reproduction of rodents relies heavily on pheromones or olfactory cues, the findings mentioned above show the importance of neural plasticity in reproductive functions. This review will discuss recent findings disclosing the involvement of adult neurogenesis in reproduction, specifically sexual behavior, pregnancy and parenting behaviors.

Neurogenesis and Sexual Behavior

Olfactory cues related to sexual behavior and mating experience act as stimuli to affect neurogenesis. In general, sexual stimulation increases neurogenesis in the SVZ or SGZ and it is associated with changes in gonadal or adrenal hormones. This phenomenon was shown across different species. Female prairie voles, unlike laboratory rats or mice, lack spontaneous estrous cycle (Smith et al. 2001). They remain sexually

immature until exposure to a novel male vole, which is followed by an increase in serum estradiol level and induction of behavioral estrus (i.e., sexual receptivity). After an exposure to novel male for 24 h, the number of newly proliferative cells in the RMS of female vole increased by 90 %, which is likely to be mediated by the estrogen surge (Smith et al. 2001). Although not confirmed yet, the newly generated neurons may be required to form the olfactory memory of the mate, as prairie vole is a monogamous species. Being similar to voles, ewes remain reproductive quiescent until they are exposed to an unfamiliar ram (Hawken et al. 2009). Exposure to unfamiliar male induces ovulation in ewes, and it is also shown that the sociosexual cues rapidly increase SGZ neurogenesis, together with a luteinizing hormone surge, within several hours. As the reproductive significance of increase in hippocampal neurogenesis or alteration in memory in ewes still remains unknown, it could not be denied that the changes may be simply associated events.

Several studies explored the causal relationship between mating experience and neurogenesis. In female laboratory mice, mating with male increases SVZ, but not SGZ, neurogenesis at gestation day seven (Shingo et al. 2003). As expected, an increase in new granule and periglomerular neuron production is also observed in the olfactory bulb. Because the increase was also induced in female mice mated with vasectomised male, it could be concluded that the mating process but not the fertilization or embryo implantation led to the increase in neurogenesis. Infusion of prolactin, but not estradiol or progesterone, in either female or male mice increased SVZ neurogenesis to an extent similar to that after mating (Shingo et al. 2003), which suggested that prolactin may be a mediator of SVZ neurogenesis. This was further confirmed by later studies (Larsen and Grattan 2011; Mak et al. 2007): in prolactin-knockdown female mice, exposure to a dominant male did not bring an increase in SVZ and SGZ neurogenesis. A recent study showed that whether a female rat could control the rate of the mating process could affect the neurogenesis (Corona et al. 2011): neurogenesis in the accessory olfactory bulb increased when a female rat was mated in a paced chamber. The paced chamber was designed to contain a small hideout which allowed the female to freely move in and out during the session, in which the female could control the rate of sexual contacts. Interestingly, no change in neurogenesis was found in this study when the female was mated to a male in a non-paced manner, and no change in neurogenesis in the main olfactory bulb was observed in paced mating, non-paced mating or exposure to male rat. The discrepancy between these studies may be due to species difference, methodology or other confronting factors, which suggest that neurogenesis is regulated by numerous interacting and intricate factors.

Comparing to investigations using female rodents, studies of male neurogenesis and reproduction are relatively scarce. Leuner et al. (2010) reported that hippocampal neurogenesis in male rats increased robustly after mating. The increase could be found after single (sacrificed after 2 h) or multiple (for 2 weeks) exposure to sexually receptive female rats. The increase came along with a decrease in anxiety-like behavior, which is hypothesized to be regulated by neurogenesis. It was supposed that the rewarding nature of mating increases the hippocampal neurogenesis and this is comparable to that of free running to rodents. SVZ neurogenesis was not studied in this study, while further investigation about SVZ neurogenesis in male mating behavior may provide valuable information about sexual dimorphism in neurogenesis.

The incorporation and activation of the newly generated neurons into the existing neural circuit was shown in a study utilizing BrdU-birth dating technique and c-fos expression assay (Huang and Bittman 2002). Male golden hamsters were injected with the thymidine analogue BrdU, and then the labeled new neurons in the SVZ were allowed to mature and incorporate into the olfactory bulb circuitry for 3–7 weeks. By the end of experiment, the hamsters were allowed to copulate with a receptive female for 30 min and followed by sacrifice. Coimmunostaining showed that a certain proportion of BrdU-labeled cells in the olfactory bulb co-express c-fos protein.

As c-fos is a protooncogene product expressed rapidly in activated neurons, the colabeled cells indicate the activation of new olfactory bulb neurons due to sexual stimulation and the integration of them into the olfactory circuitry. No co-labeled cells was found in mating-related regions such as medial preoptic area (MPOA), medial nucleus of amygdala (MeA) and bed nucleus of stria terminalis (BNST), although proliferative cells could be found at these regions. Furthermore, the cell proliferation and survival in the medial amygdala and MPOA were not altered by mating experience (Antzoulatos et al. 2008). In short, proliferative cells in the mating circuit are unlikely to integrate into the existing circuitry, and they are not under the regulation by sexual stimulation.

Blocking neurogenesis is one of the direct approaches to study the necessity of neurogenesis in behaviors, and this technique was also used to delineate the role of neurogenesis in sexual behavior (Lau et al. 2011a; Mak et al. 2007). Under normal situations, exposure to a dominant male mouse with limited physical contact would increase SVZ and SGZ neurogenesis. The increase was hypothesized to form the olfactory memory for the male mouse and to induce the preference to choose a dominant mate over a subordinate one. When the SVZ and SGZ neurogenesis was abolished by intracerebroventricular infusion of a cytostatic compound, cytosine arabinoside (Ara-c), the preference for the dominant male was eliminated (Mak et al. 2007). Under this context, the increase of neurogenesis facilitates the choice for a mate which is advantageous in claiming resources for survival, and which is likely to provide better genetic traits for the offsprings. Another study utilized pharmaceutical agents to regulate neurogenesis and observe its influence on male sexual behavior (Lau et al. 2011a). When high dose of corticosterone was administrated chronically, the sexual performance of the male rat was suppressed. This is associated with a decrease in SVZ and SGZ neurogenesis. Both the suppressed sexual performance and neurogenesis could be reversed by administration of an selective serotonin reuptake inhibitor (SSRI, an antidepressant). When the neurogenesis was abolished by Ara-c, the animals showed a suppressed sexual performance in the mating test. What is more, the decreased neurogenesis was associated with a reduction of c-fos expression in the mating-related neural circuit. Collectively, abolishing neurogenesis in the CNS showed the importance of neurogenesis in successful reproductive behaviors in both male and female rodents, and the new neurons may participate in the transduction of signals in the mating-related circuitry. Although the detail mechanisms of how neurogenesis is regulated in mammals remain largely unknown, the new neuron production is likely to be regulated by gonadal and adrenal hormones in the reproductive behaviors.

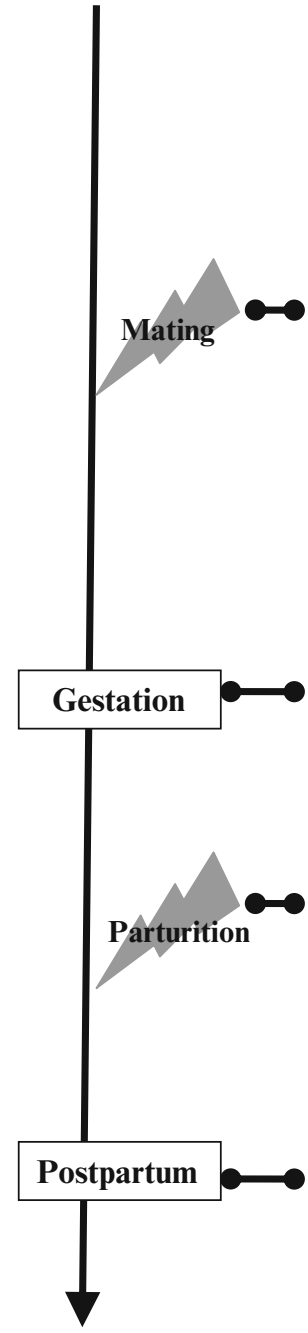
Neurogenesis and Pregnancy

The spatial memory of pregnant rats was impaired during gestation, and this observation elicited the study of change in hippocampal neurogenesis during pregnancy (Pawluski et al. 2010). In the breeding season of meadow voles, captured female voles showed a decreased level of neurogenesis than those captured during non-breeding season, which suggested that pregnancy may decrease hippocampal neurogenesis (Galea and McEwen 1999). Unexpectedly, no alternation of SGZ neurogenesis was found in mice during early or late gestation period under controlled laboratory conditions (Furuta and Bridges 2005; Levy et al. 2011; Pawluski et al. 2010). Reproductive experience (i.e., number of parturition) also did not affect the cell proliferation and survival. However, pregnant rats showed fewer pyknotic cells in the CA3 of hippocampus than the virgin rats. Lower level of cell death and unaltered level of neurogenesis means that the number of neurons in the hippocampus may be higher in the pregnant female. Thus there is no robust evidence to support the hypothesis that hippocampal neurogenesis decreases during the gestation period (Levy et al. 2011), and the choice of species and conditions for study may greatly affect the conclusion being drawn.

Unlike the hippocampus, increased SVZ neurogenesis was reported in pregnant laboratory rats and mice (Furuta and Bridges 2005; Shingo et al. 2003). An increase was exhibited by female pregnant rats at gestation day 21 but not earlier at gestation day seven (Furuta and Bridges 2005). This finding is different from mice since activation of SVZ cell proliferation was observed in pregnant mice at gestation day seven but not in later stage. The discrepancy between the two species is interesting when considering the similar gestation period and gonadal hormone fluctuation during the gestation period. Prolactin, which is known to promote SVZ neurogenesis (Larsen and Grattan 2011), rises rapidly around parturition and increase in neurogenesis is expected. It is puzzling that mice did not show a rise in cell proliferation at late gestation stage. Considering that new born neurons take 2 weeks to mature and be responsive to stimulation, the increase in neurogenesis at gestation day seven in mice may provide new functional neurons at the time of parturition, which is the time of the onset of maternal behavior and pup recognition (Levy et al. 2011). Paradoxically, the increase of SVZ neurogenesis in rats at late gestation period could not be interpreted from this perspective. Thus although pregnancy is known to increase SVZ neurogenesis, species difference should be taken into account. Although the specific functions of the newly proliferative cells remains elusive, it is likely that their production will exert functions in later stages: parturition and display of maternal behavior.

In contrast to mating and pregnancy, parturition brings a decrease in neurogenesis in the SVZ and SGZ. Cell proliferations in the SVZ and SGZ of ewes 24 h after parturition were decreased when compared to non-pregnant ewes, but the decrease in the SVZ could be reduced by isolating the ewes from the lambs (Brus et al. 2010). Female rats face a similar situation, in which the SGZ neurogenesis was suppressed in the early postpartum period (Darnaudery et al. 2007; Leuner et al. 2007) which is associated with an impaired spatial memory. The reduction of neurogenesis could be observed in both primiparous and multiparous mothers (Pawluski and Galea 2007), while the ratio of surviving cells at post-partum day 21 is higher in multiparous mothers. Reduction of the decrease was achieved by either isolating the mother from the pups or by adrenalectomy, which reduced the circulating glucocorticoid level. While high glucocorticoid is known to suppress neural precursor cell proliferation (Chen et al. 2011), the rise in glucocorticoid level may be the main mechanism of SGZ neurogenesis reduction at postpartum period. It is interesting that pup exposure to postpartum mother decreases neurogenesis rather than increases it; while the reduction was suggested to allow re-organization of the neural circuitry by reducing competition for cellular survival and enhancing the integration of new neurons (Brus et al. 2010).

A study conducted by Larsen and Grattan (2010) suggested the potential implication of new born SVZ neurons in the prevention of postpartum anxiety. When mice was injected with bromocriptine (which blocks prolactin secretion from the anterior pituitary gland) during early pregnancy, SVZ neurogenesis was suppressed. Behavioral data showed an elevated anxiety level at the early postpartum period followed the SVZ neurogenesis down-regulation when compared to virgin mice. Interestingly, the display of maternal behavior was also hampered by the bromocriptine injection. On the other hand, when SVZ neurogenesis was abolished by cytostatic methylazoxymethanol (MAM) injection, the female pregnant mice showed an elevated anxiety level similar to those received bromocriptine injection. Although the MAM-treated mice showed normal maternal behaviors in a familiar environment, the behaviors were impaired when they were placed in an unfamiliar, anxiogenic situation. These results suggested that the increase neurogenesis may be involved in reducing/preventing postpartum anxiety and consequently the induction of maternal behavior.



Region	Sex /Species	Neuro-genesis	Condition	Ref.
SVZ	♀ Prairie vole	↑	After exposure to ♂	(Smith et al., 2001)
	♀ Mice	↑	After mating/ exposure to ♂	(Larsen et al., 2008; Shingo et al., 2003)
SGZ	♀ Sheep	↑	After exposure to ♂	(Hawken et al., 2009)
	♀ Mice	--	After mating	(Shingo et al., 2003)
	♀ Mice	↑	After mating	(Leuner et al., 2010)
SVZ/ SGZ	♀ Mice	Blocked by Ara-c	Mate preference disrupted	(Mak et al., 2007)
	♀ Rat	Blocked by Ara-c	Sexual performance inhibited	(Lau et al., 2011a)
SVZ	♀ Mice	↑	Early postpartum	(Shingo et al., 2003)
	♀ Rat	↑	Late postpartum	(Furuta and Bridges, 2005)
SGZ	♀ Mice	--	During pregnancy	(Pawluski et al., 2010)
SVZ/ SGZ	Mice	Blocked by MAM	Postpartum anxiety induced	(Larsen and Grattan, 2010)
SVZ	♀ Sheep	↓	24 hr after Parturition	(Brus et al., 2010)
SGZ	♀ Sheep	↓	24 hr after Parturition	(Brus et al., 2010)
SVZ	♂ Mice	↑	After pup exposure	(Makand Weiss, 2010)
SGZ	♂ Prairie voles	↑	After pup exposure	(Ruscio et al., 2008)
	♀ Rat	↓	During early postpartum period	(Darnaudery et al., 2007)
	Mice (Virgin)	↑	After pup exposure	(Pawluskiand Galea, 2007)
SVZ/ SGZ	♂ Mice	Blocked by Ara-c	Puprecognition disrupted	(Mak and Weiss, 2010)

Fig. 31.1 Summary of the relationship between reproductive process and neurogenesis

Neurogenesis, Maternal and Paternal Behavior

To investigate the effect of maternal behavior on neurogenesis, an experimental handling termed maternal sensitization was adopted (Pawluski and Galea 2007). Non-pregnant rats were exposed to neonatal pups to induce maternal behavior. Such handling could isolate the effect of maternal behavior from that due to pregnancy and parturition. Opposite to postpartum dams, sensitized rats showed increased SGZ cell proliferation and cell death compared to nulliparous or postpartum female, while the number of surviving cells is higher in the sensitized rats than the postpartum mothers. The pup exposure may increase neurogenesis by serving as a novel enrichment to the sensitized rats. Interestingly, exposure to an unfamiliar male mouse also induced increase in SVZ neurogenesis in virgin female mice, which is associated with the onset of maternal behavior (Larsen et al. 2008). The difference in neurogenesis upon pup exposure in sensitized and postpartum dams may be caused by various factors, such as physical demands during pregnancy, necessity of lactation and hormonal fluctuation during pregnancy and parturition. Collectively, these factors illustrate the differential effects of a stimulus in different situations.

Recent studies showed that pup exposure not only affect maternal but also paternal neurogenesis. Prairie vole is a biparental species which fosters pups by both parents (Ruscio et al. 2008). Exposure of pups to male vole, regardless of displaying paternal behaviors or not, induced an increase in SGZ neurogenesis. Laboratory mice, albeit not being a monogamous species, also demonstrate paternal behavior if they mate with a female and are kept with the partner throughout the pregnancy and early postpartum period (Mak and Weiss 2010). The induction of paternal behavior (including covering and retrieval of the pups) was associated with an increase in SVZ and SGZ neurogenesis. Interestingly, the newly generated neurons in the olfactory bulb were responsive to the pups being exposed to the male mice. Similar to the female mice, the increase is likely to be mediated by prolactin.

Disruption of neurogenesis during early pregnancy caused impaired maternal behavior when the mother was placed in a novel environment, but not in the original home cage (Larsen and Grattan 2010). This may be the consequence of increased anxiety when neurogenesis was blocked, but elucidating the detailed mechanisms requires further investigations. In transgenic mice without prolactin receptor, exposure to pups did not induce an increase in neurogenesis (Mak and Weiss 2010). Simultaneously the pup recognition behavior was also abolished. Interestingly, brain infusion of luteinizing hormone allowed the increase in cell proliferation after pup exposure, which is accompanied by the restoration of pup recognization. This finding supports the regulatory role of paternal behavior by neurogenesis, and the importance of gonadal hormone in reproduction through the regulation of neurogenesis.

To conclude, increasing lines of evidence support the roles of neurogenesis in reproductive behaviors including mating, pregnancy and parental behavior (Fig. 31.1). Different studies demonstrate the reciprocal relationship between gonadal hormones and neurogenesis, which provide a novel perspective to consider the effect of these hormones on reproduction: the hormones may affect reproductive behavior via the regulation of adult neurogenesis and neuroplasticity. These findings also provide novel information on sexual dimorphism of the CNS (Cahill 2006), which shows the functional and structural difference between the two sexes. The detailed mechanism underlying the regulation of neurogenesis remains largely elusive and further evidence will definitely improve the understanding of reproductive functions, and the progress in reproductive medicine.

Acknowledgements The work from the authors are supported by funding from the Jessie Ho Professorship in Neuroscience (The University of Hong Kong for Educational Development and Research Limited) and the Fundamental Research Funds for the Central Universities, No. 21609101.

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 9*,
DOI 10.1007/978-94-007-5488-1, © Springer Science+Business Media Dordrecht 2012