Pineal Region Lesions

Management Strategies and Controversial Issues

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Foreword

If I dared to explore a remote, exotic location, I would certainly like to have a detailed map or an elaborate guide to disclose the many secrets and mysteries of that land. The pineal region is such an exotic locale, an area that for eons has nourished the imaginations of thinkers and philosophers, from ancient to modern times alike. From the mythical "third eye," to the "seat of the soul" of the post-Renaissance period, or from "unapproachable lesions" to the myriad options that current neurosurgical techniques offer, the pineal region and the gland nestled at its core have proven a fountain of inspiration for professionals of various fields of knowledge and experimentation. The book that you hold in hour hands was designed to be a well-documented guide, the authors of each chapter acting as a chaperon on this path cobbled by challenges and controversies, in a region whose pathology, albeit rare, is extremely diverse. It is precisely the underscoring of the controversial aspects within all of the chapters that represent a peculiarity of this volume, raising not only problematic questions but also answers borne out of the proficiency of their experienced authors, while even leaving the reader able to discern the best available solution in light of their understanding.

Assembled logically and didactically, the scope of this book is a systematization of the key features regarding the pathology of the pineal region. Considering that in the last few years, there has been a scarcity of books principally dedicated to the pathology of this area, and those mostly focused on the oncological aspect, the current tome encompasses almost the entire range of lesions encountered in the pineal region. Divided into seven parts, this volume takes the reader on a broad. Yet, a coherent journey is beginning with the history regarding specific interest for the pineal gland and its surroundings, as well as anatomical data with practical applicability. Pathological data is preceded by clinical aspects, the reader then being ushered toward imaging features, as well as the importance of biomarkers with an emphasis on oncological diseases.

Naturally, a section dedicated to surgical approaches to the pineal region follows, as presented by eminent neurosurgical figures in their respective fields, offering not only detailed description of these approaches but also tips and tricks inherited from their experience. Moreover, the controversial aspects concerning these surgical routes are linked with an abundance of illustrative radiological studies, preoperative, intraoperative, and postoperative alike.

Therapy for the majority of oncological lesions in this region is multimodal. As such, specialists in this field present the available options in terms

of radiotherapy and chemotherapy according to the various tumor types encountered.

Oncological therapy, the subject of the ensuing section, sets the stage for renowned neurosurgeons to share their knowledge concerning the common tumors encountered in this area, in combination with the current therapeutic options available, and illustrated with instructive personal cases.

The part on vascular pathology embodies three separate chapters, namely cavernous malformations, the vein of Galen aneurysms, and arteriovenous malformations, respectively, as imparted by figures with an unanimously recognized experience. The pineal region can also play as the site for cysts, whether simple or malformative, the aspects of these lesions being presented in a distinct section.

Last but not least, the treatment algorithm that brings this volume to a close proffers a concise synthesis of current diagnostic means and management solutions presently available.

I consider this book not only a beneficial foray in pineal region pathology, but even more so an opportunity to visit, and on occasion revisit from different perspectives, the diagnostic tools and therapeutic choices of a diverse set of ailments in a diminutive area. Even though the pineal gland and its surroundings sometimes display a frightening aura, this is effectively shattered by the remarkable effort of the authors, whom the editor had the distinct pleasure to unite in an ambitious scientific endeavor.

I am sure that the editor of this book took a lot of effort to gather all this information and offer the reader a complete source. Beyond that, he interpreted the information with years of experience, and he hid his real experience between the lines of the book. For this reason, I strongly recommend this book not only to young colleagues who are interested in neurosurgery but also to colleagues with years of experience. In short, colleagues from all disciplines dealing with pineal region lesions “trust the guidance of Professor Florian!”

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Preface

A good book is one which keeps the reader enthralled and coming back for more; if it also opens up the pathway to previously untapped knowledge, and if it holds your hand during the most difficult steps, then that book becomes part of one's soul. I hope that this, dear reader, will be the case for you as well since this volume is fostered not only by current and precise scientific data but also by the trials and endeavor of many talented neurosurgeons. Its pages are garnished with the fruit of several decades of experience, commitment, hopefulness, achievements, and disappointments alike. Thus, each page from the tome you are holding has its very own soul. Peruse it as an intimate dedication from a team of professionals who wish to impart onto you their beliefs as well as doubts attained from a vast personal experience. I remember being a first-year resident when I was presented with the opportunity to witness and discover the provocations posed by the pineal region alongside a coauthor of this very book. Ever since, I have never ceased in my pursuit of refining the surgical techniques involved in the approach of this perplexing area of the brain and the treatment of its ailments. For this reason, when the Springer Nature publishing house offered me the task of leading a project on this subject, I did not hesitate for a moment, even though such an assignment involves countless challenges. However, I had the opportunity of collaborating with exceptional figures in the neurosurgical society, personalities who not only epitomize the pillars of contemporary neurosurgery but also whose kind support and friendship have honored me through the years. Alongside them, younger and very enthusiastic colleagues brought their own valuable contribution, demonstrating a keen understanding of such an opportunity for their professional development. I would like to address my warmest gratitude to all of my collaborators in this endeavor, with the added conviction that our combined effort managed to assemble a book that is comprehensive and up-to-date, a bibliographical resource that we hope will prove useful to both current and future generations of neurosurgeons. I also offer Mrs. Ioana Robu, assistant editor, my sincerest appreciation for her decisive contribution in tying this project together. We collectively give thanks to the Springer Nature publishing house for their constant professional support that has honored us during the demanding course of this enterprise. And on behalf of all contributors to this book, I would like to thank you, dear reader, for choosing to peruse this book, which we genuinely wish will become a prized companion in your very own journey into the fascinating and mysterious world of the pineal region.

Cluj-Napoca, Romania — Ioan Stefan Florian

Contents

Part I

Overview

1 Historical Landmarks in Pineal Region Surgery

Ioan Stefan Florian and Cristina Caterina Aldea

The central element of the pineal region, namely the pineal gland, has intrigued scholars for centuries, the first known accounts of this structure being documented in Ancient China in 2600 BC [1, 2]. Despite this prolonged interest, surgery of the pineal region is barely more than a century old. Owing to its location, arguably one of the most difficult areas to access surgically even today, attempts of approach were not made until the beginning of the twentieth century [1, 3, 4].

1.1 Leading up to Surgery: Defining the Pineal Gland and the First Reports Related to its Pathology

The pineal gland has been surrounded by a mystical aura since the beginning of civilization; it has been the symbol of the all-seeing eye from ancient Egypt to the one-dollar bill. This pinecone shaped gland was considered the most powerful source of ethereal energy. We can find the pine symbol in almost all religions, starting with the Sumerian civilization to the Christian church, Hinduism, the Masonic lodges, and Buddhism [5, 6]. Galen of Pergamon (130–200 AD) acknowledges Herophilus (325–280 BC) as the first not only to report the existence of the gland and to study it scientifically, but also to theorize its role as a valve regulating the flow of pneuma from the third to the fourth ventricle. Seventeenth-century French rationalist Descartes considered that the mind and body were connected through the pineal gland, thus iconically naming it the "seat of the soul" [7]. The true understanding of the role of this structure came with describing the pathology in this area. The first to report a pineal tumor was French physician Charles Drelincourt, as stated in a treatise published in Geneva in 1717. He presented the case of a young woman with a lesion the size of a "fowl's egg" [8]. This was followed by several other case reports throughout the nineteenth century, the definition of the syndrome known today as Parinaud's in 1883 [9], but little was known about the histology, due to the underdevelopment of pathology techniques. Surgery on this area was terra incognita. In 1904, Harvey Cushing reported performing one of his famous bitemporal decompressive craniectomies on a patient in whom autopsy later found a quadrigeminal plate tumor [10]. This report established the necessity of surgical exposure of the pineal region and also foreshadowed its advent.

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1.2 Description of Surgical Approaches

Owing to the deep-seated location, in the proximity of major venous and vital structures, as well as to the fact that anesthesia and intraoperative monitoring were still in their early stages of development, the initial period of attempting to approach the pineal region was defined by extremely high mortality and morbidity rates. The very first description of a direct approach was unsuccessful. This was done by none other than Sir Victor Horsley, who in 1905 attempted to remove a pineal tumor using an infratentorial approach. His patient died due to surgical complications [11]. In 1910, Howell reported to the Royal Academy that, discouraged by his poor results, Sir Horsley proposed a supratentorial approach coupled with splitting the tentorium from a centro-posterior position in order to expose the region. He thought that his approach through the posterior fossa was the root of his unfavorable outcomes [12]. It is interesting to note that the discussion about whether the supratentorial or infratentorial approach is best remains relevant up to the present. Encouraged by this, in 1910, Pussep resected a pineal tumor using a transverse transtentorial approach with splitting of the transverse sinus and tentorium, with survival of the patient up until the third postoperative day [13]. Seeing these results, some started proposing more tempered management strategies: Rydyngier from Poland recommended a puncture through the corpus callosum in order to reduce intracranial pressure, while, in Germany, Anxenfeld and Marburg described a palliative approach through a supracerebellar route—both their patients were lost [1]. Not at all bothered by his colleagues' results, the man rightfully named father of German neurosurgery, Fedor Krause (1857–1937) performed the first reported successful resection of a pineal tumor (Fig. 1.1).

He operated on a 10-year-old boy with a 4-cm-diameter lesion, in sitting (!) position using an infratentorial supracerebellar approach. He took advantage of the natural plane between the tentorium and cerebellum given by this position and managed to preserve the venous system surrounding the lesion, damage of which was the major cause of the high surgical morbidity [14, 15] (Figs. 1.2 and 1.3).

Fig. 1.1 Fedor Krause. (Photo Courtesy of the History of Medicine Division at the U.S. National Library of Medicine)

Krause foreshadowed this approach in 1911, and in 1926, he reported an additional three cases with no mortality [16]. On the other side of the ocean, Walter Dandy (1886–1946) reported the supratentorial parieto-occipital transcalossal approach with antero-posterior exposure of the tumor in 1921, publishing a series of three consecutively treated patients. He began developing this approach on canines in 1915 and it took him years to apply it to humans, with the note that his morbidity rates remained quite high [17]. By 1936, he had mastered this approach which became the preferred route to the pineal region in that era [18]. In 1931, Van Wegenen from the University of Rochester described an unconventional supratentorial transcortical, temporo-parietal approach to reach pineal lesions through the dilated lateral ventricle. Later in 1937, Horrax proposed occipital and temporo-parietal lobectomies to resect

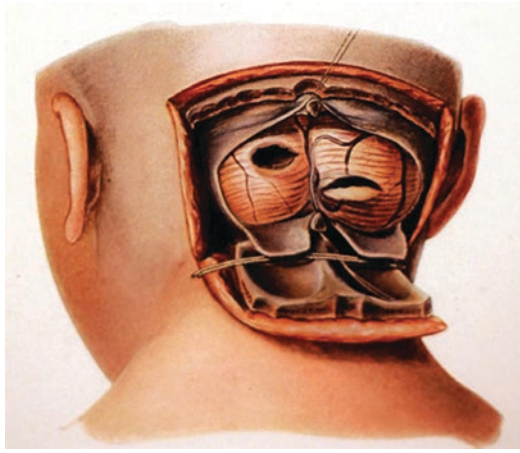

Fig. 1.2 An illustration of Fedor Krause's infratentorial approach similar to the one used for pineal region tumors using an osteoplastic flap [14]. (*From Krause F. Surgery of the Brain and Spinal Cord Based on Personal Experiences [Haubold H, Thorek M, Trans.]. New York: Rebman Co.; 19-1912)*

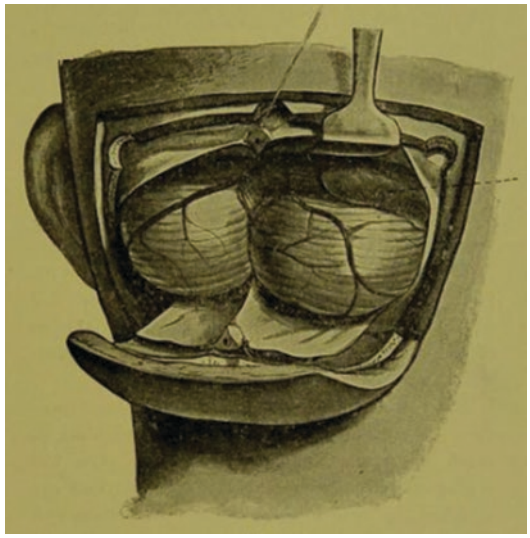

Fig. 1.3 Krause's supracerebellar infratentorial approach [15]. (*From Krause F. Surgery of the Brain and Spinal Cord Based on Personal Experiences, London: HK Lewis; 1910)*

large pineal lesions. These approaches were associated with high rates of postoperative visual field defects and seizures, thus being abandoned. The occipital transtentorial approach, still used today, was first described by Heppner in 1959 and popularized by Poppen in 1966 [17].

1.3 Abandonment of Large Surgical Approaches in Favor of Palliative Procedures

In 1948, Torkildsen argued that "attempts at the removal of neoplasms in regions of the pineal gland (…) are associated with such a grave mortality rate that, if possible, such operations should be avoided" [19]. Indeed, most neurosurgeons of that era took the following management strategy: diagnosis by ventriculography, treatment by radiation therapy if radiosensitive tumor suspected. Cerebrospinal fluid diversion was used to treat significant hydrocephalus, if present. Torkildsen even described his own method for this palliative procedure (passing a catheter from the lateral ventricle into the cisterna magna) [17, 19].

1.4 Rediscovery and Refinement of Surgical Approaches

Together with the advent of microneurosurgery and progression of neurocritical care, interest in direct and radical approaches returned—this time with significant reduction in mortality and morbidity rates. In 1971, Bennett M. Stein, revisited Krause's approach using the microscope and reported six patients with no perioperative mortality and little morbidity [3]. In 1976, Voigt and Yasargil described the paramedian variant of the supracerebellar infratentorial approach [20]. Fukushima is noted as the pioneer of using endoscopic techniques in this area starting with the 1970s, and this method was later on perfected by Robinson and Cohen, in 1997 [4], who described an endoscopic biopsy combined with third ventriculostomy as an alternative to biopsy and separate ventriculoperitoneal shunting.

Even though surgery of the pineal region remains difficult, the rate of major morbidity and mortality ranges between 0 and 2% in modern series [3]. We have come a long way from the beginning of the century and, undoubtedly, will continue to evolve in the years to come—possibly by revisiting the past as well.

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Pineal Region Anatomy

2

Pablo González-López, Javier Abarca-Olivas, Enrique Luna, Carlos Martorell-LLobregat, and Verónica de los Santos

2.1 Introduction

Etymologically, "pineal" is derived from its conical shape, as "pinea" is a Latin word meaning "pinecone". It has also been referred as epiphysis, and its anatomical and physiological exploration has been challenging due to its deep location [1].

Regarding its embryological development, the pineal gland starts to develop during the fourth week as a median evagination of the epiphyseal end of the diencephalon roof. In the following weeks, the walls of this pineal process are thickened and become a compact mass, incorporating vascular mesoderm to form the definitive gland. In its anterior aspect, a vestige of the hollow diverticulum of the ventricular cavity persists, called the pineal recess [1, 2].

Two types of cells can be observed during its development: cells with dense and small cytoplasm nuclei and small pale cells. The former will develop into pinealoblasts, which represent the characteristic gland population. During the eighth month begins the differentiation to pinealocytes, which secrete melatonin. The second population are spongioblasts that will subsequently differentiate into astrocytic glial cells. Meanwhile, a meningeal structure coats the epiphysis and crosses septal architecture of the gland to form its blood vessels [1, 3].

The pineal gland is a neuroendocrine organ with regulatory duties. It modifies the activity of the adenohypophysis, neurohypophysis, parathyroids, endocrine pancreas, gonads, adrenal cortex, and medulla. The pineal gland synthesizes the sleep-promoting neurohormone called melatonin, which is secreted into the bloodstream and cerebrospinal fluid where it modulates brainstem circuits that control the circadian rhythm. This secretion is nocturnal and is inhibited by light. It also influences mammalian reproduction, immune system, aging, and thermoregulation. The secretion is controlled by the circadian clock located in the suprachiasmatic nuclei of the hypothalamus [2].

Considering the pineal gland's functions, its highly complex anatomy, and the advances in neurosurgical approaches, it may be useful to describe in detail the anatomy of the pineal gland, its blood supply, and its relationships with the surrounding structures.

2.2 External Morphology, Location, and Intrinsic Connections

The pineal body belongs phylogenetically to the diencephalon. The diencephalon lies above the

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midbrain and in between the cerebral hemispheres, closely related to the lateral and third ventricles. Thus, it remains hidden deep in the cerebral substance, and only a few parts face the external aspect of the brain. For practical purposes, the diencephalon is divided into the following: thalamus, which is the largest; subthalamus, which lies above the midbrain; hypothalamus, in front of the subthalamus and anteroinferior to the thalamus; epithalamus, which will be the object of study of this chapter; and the metathalamus, which consists of the medial and lateral geniculate bodies.

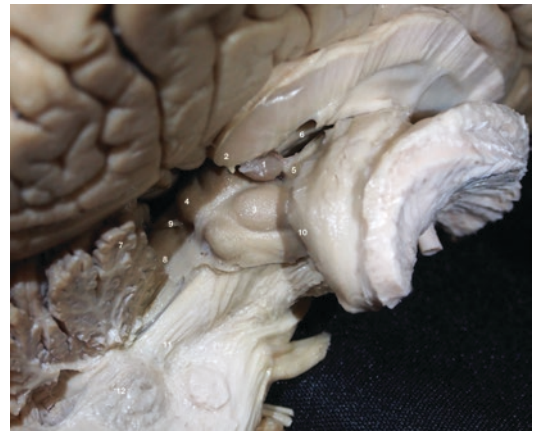

Fig. 2.1 Posterolateral view of the pineal region in a brain specimen treated by Klinger's method and in which the right cerebral and cerebellar hemisphere have been dissected. (1) pineal gland; (2) splenium of the corpus callosum; (3) right superior colliculus; (4) left inferior colliculus; (5) habenular trigone; (6) stria medullaris; (7) vermis; (8) cerebello-mesencephalic fissure; (9) IV cranial nerve; (10) pulvinar thalamus; (11) superior cerebellar peduncle; (12) dentate nucleus

2.2.1 Pineal Region

The pineal region or epithalamus occupies the caudal roof of the diencephalon. It is located above the tectal plate in close relationship with the posterior incisural space, supratentorial ventricles, basal cisterns, the deep venous system, and distal posterior arteries.

The pineal region, together with the pulvinar, mammillary bodies and the pituitary stalk and gland, represents the only diencephalic structures that directly face the external aspect of the human brain. It is directly related with the posterior aspect of the third ventricle, with which it shares a natural anatomic corridor. Thus, the accurate knowledge of these relationships remains crucial to perform some selected surgical routes to approach this area (Fig. 2.1).

The pineal region consists of the two habenular trigones, habenular commissure, pineal body, posterior commissure, and the superior and inferior laminae of the epiphyseal stalk. The gland and trigones present a well-established and defined output and input connections circuit. The most relevant connections are represented by the fasiculus retroflexus of Meynert (or "habenulointerpeduncular tract") and the striae medullaris thalami in terms of habenular connections. The pineal body shows a special histologic cytoarchitecture with different microscopic fiber bundles responsible for its more specific circadian functions.

The habenular trigone is a paired small triangular depression (one on each side) lying medial to the pulvinar and superomedial to the posterior commissure. This bilateral depression limits laterally the narrow communication between the quadrigeminal cistern and the posterior aspect of the third ventricle. It is a small accumulation of grey matter medial to the pulvinar below the ventricular surface of the diencephalon. The habenular trigone is composed by the so-called medial and lateral nuclei. The habenular commissure is represented by a transverse band of axons between the two sides of the epithalamus, connecting both habenular complexes and crossing the midline in the superior lamina of the pineal body stalk [4].

Although the role of the habenula is not clearly known, the nuclei are supposed to play a crucial role about how the brain responds to a large variety of stimuli such as anxiety, pain, rewards, stress, and, especially sleep.

The posterior commissure is a transversely oriented commissural tract connecting both hemispheres along the midline. It is located slightly inferior to the habenular commissure, thus crossing the midline in the inferior lamina of the stalk. Understanding a coronal orientation, it crosses the median plane behind the upper end of the cerebral aqueduct.

From a surgical point of view, it may be interesting to understand the pineal region as an oblique

midline plate located in the center of the posterior incisural space, just below the splenium of the corpus callosum, above the quadrigeminal plate, posterior into the third ventricle, and laterally bounded by the pulvinar nuclei. Seen from inside the third ventricle, this oblique plate is composed from superior to inferior by the tela choroidea and choroid plexus, suprapineal recess, habenular commissure (and trigone laterally), pineal recess (which projects posteriorly into the pineal body between the two laminae), posterior commissure, and superior ostium of the cerebral aqueduct. From a posterior extraventricular view, most of these structures are not visible. Thus, the classic picture shows the pineal body in the center, superolaterally related to the habenular trigone and tela choroidea through which the internal cerebral veins exit, and the posteromedial choroidal arteries enter the third ventricle to form the vascular layer of the velum interpositum (Fig. 2.1).

2.2.2 Pineal Gland

The pineal body represents the pivotal point of the epithalamus. It is a midline and single encapsulated structure, located in a deep position near the geometric center of the human brain. In adults, this body is a relatively small conical structure located between the superior colliculi and the suprapineal recess, which projects as a dorsocaudal extension of the third ventricle containing the choroid plexus and the vascular layer of the velum interpositum. Various authors have highlighted its size, being an organ measured between 5 and 10 mm in longitudinal length, 5 and 9 mm in transverse width, and 1.5 and 4 mm in thickness [5, 6].

The pineal gland is bordered by the posterior commissure ventrally, the habenular commissure dorsally, and the corpus callous superiorly. Below it overhangs the depression between the two superior colliculi on the posterior surface of the midbrain. It is connected to the caudal diencephalon by a stalk. Thus, the pineal gland may be grossly divided into an apex, a body, and a stalk. The stalk presents a couple of paired roots (superior and inferior). Each of these roots or laminae is firmly adhered to the habenular (superior) and posterior (inferior) commissures. This capricious architecture gives rise to the so-called pineal recess of the third ventricle, which represents the intraventricular stem of the pineal gland being lined by ependymal cells (Fig. 2.2).

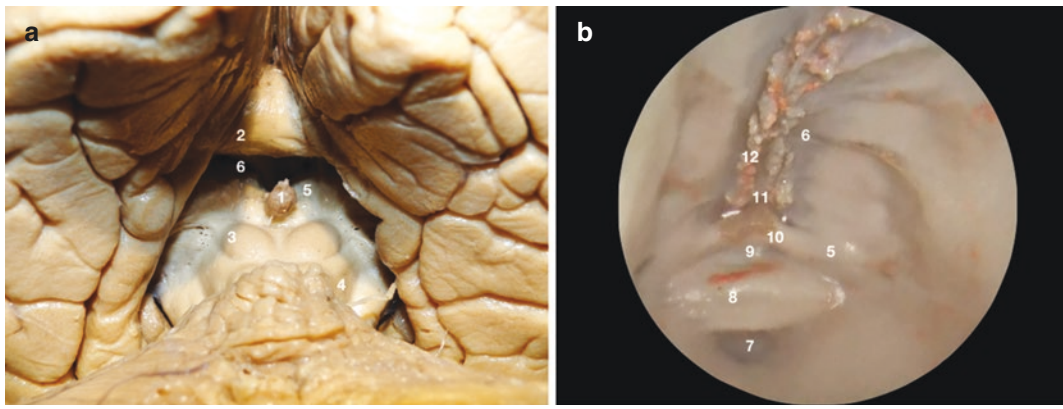

Fig. 2.2 Different views and schematic diagrams of the pineal region and related structures. (**a**) Posterior supracerebellar midline view of the pineal gland in a human brain specimen; (**b**) anterior endoscopic view through the right foramen of Monro of the inner aspect of the pineal region; (**c**) schematic diagram showing the different anatomical relationships of the pineal region structures, as well as its connections. (**d**) pineal gland schematic drawing. (1) Pineal gland; (2) splenium of the corpus callosum; (3) left superior colliculus; (4) right inferior colliculus; (5) habenular trigone; (6) stria medullaris; (7) cerebral aqueduct of Sylvius; (8) posterior commissure; (9) pineal recess of the third ventricle; (10) habenular commissure; (11) suprapineal recess; (12) choroid plexus; (13) mammillothalamic tract; (14) mammillary body; (15) fornix; (16) anterior commissure; (17), habenulointerpeduncular tract; (18) anterior nuclei of thalamus; (19) thalamus

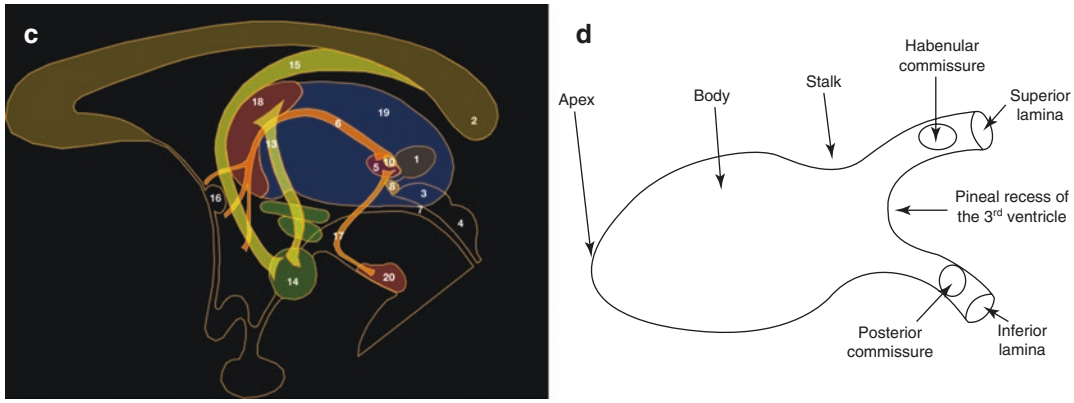

Fig. 2.2 (continued)

Histologically, the pineal body is divided into capsule, trabeculae, and parenchyma. The latter is composed of pinealocytes or "chief cells," peptidergic cells, astrocytes, phagocytes, interstitial cells, blood vessels, and nerve endings. The pinealocytes represent more than 90% of the cells. Moreover, these cells are responsible for the majority of the primary parenchymal tumors. However, the presence of other cell populations explains the different tumors that this small organ can present. The pineal gland capsule is composed of pia mater. Some septa of connective tissue extend into the gland from the capsule, dividing it into small regions. Blood vessels and nerve fibers enter the gland through those septa [4, 7].

The pineal gland is essentially an extra-axial structure. Considering the variety of cellular populations it is made of, the different structures to which the gland is attached and closely related to, and its central location in the posterior part of the third ventricle, surgical approaches to this region are specially challenging and require an adequate neuroanatomical knowledge and careful preoperative planning.

2.2.3 Internal Organization and Connections of the Pineal Gland and Surrounding Structures

The intrinsic cytoarchitecture is represented by a complex network of cells and axons, being the basis to understand the large variety of functions with which this small part of the brain has been related. This complex axonal system is not fully understood, but roughly, and with the aim of creating a comprehensive classification, the involved fibers can be divided in afferent, commissural, and efferent.

The main *afferent* system is composed by olfactory fibers that run within the stria medullaris thalami. The habenular complex receives these fibers, which are derived from the septal region, hypothalamus, and the amygdala. The stria medullaris thalami is a band of fibers arching on the upper part of the medial surface of the thalamus, passing along the taenia thalami to the habenula. Some of these axons cross the midline through the habenular commissure reaching the contralateral habenula. Another important *afferent* system is the one originating from the superior cervical ganglion, which receives input from the suprachiasmatic nucleus and is mainly related with the sleep-wake cycle [4].

As a gross bundle representing the *efferent* system, the habenulointerpeduncular tract or fasciculus retroflexus of Meynert projects axons from the medial nuclei of the habenula to the interpeduncular nucleus in the ventral midline of the midbrain, reticular formation of the midbrain, and medial nucleus of the thalamus [8] (Fig. 2.2).

The *commissural* group are mainly represented by the habenular and posterior commissures, also known as cranial and caudal commissural bundles. The habenular commis-

sure is mainly composed of fibers from the stria medullaris thalami that cross the midline and connect both habenular complexes. It crosses the midline in the upper lamina of the stalk of the pineal body. On the other hand, the posterior commissure connects bilaterally the superior colliculi, pretectal nuclei, as well as the medial longitudinal bundle. The fibers composing the posterior commissure derive from the grey matter of the interstitial nuclei of Cajal, Darkschewitsch, and posterior commissural nuclei. Furthermore, these nuclei cover the posterior commissure laterally. The transverse decussating fibers of the posterior commissure cross the midline in the lower lamina of the stalk and can be grossly appreciated in the posterior wall of the third ventricle, just above the aqueduct of Sylvius.

2.3 Ventricular Relationships

The pineal region has shown relevant relationships with the supratentorial ventricular spaces. The posterior portion of the third ventricle and the cerebral aqueduct are anterior and the atrium and occipital horns of the lateral ventricles are lateral to the posterior incisural space and pineal body [9, 10].

The upper aperture of the cerebral aqueduct has a ventrocaudal relationship with the pineal gland, situated just in front of the posterior commissure, and passing ventral to the anterior wall of the posterior incisural space. It may be compressed by pineal lesions with anterior extension causing a triventricular obstructive hydrocephalus.

Cranially, the gland is in close relationship with the two third ventricle recesses. The first one, an embryological residue of the diencephalic dorsal evagination, constitutes the pineal recess which is an extension of the third ventricle.

The second recess is the suprapineal and extends posteriorly between the pineal body and the inferior wall of the velum interpositum toward the posterior incisural space and contains the choroid plexus in the roof of the third ventricle [1]. This roof is triangular with a posterior base and extends anteriorly between the two thalami. It is essentially formed by an ependymal membrane condensed into two formations: (Fig. 2.2)

- The *tectorial membrane* which is fixed laterally on both habenulae and limited anteriorly by the anterior part of the habenula and posteriorly by the habenular commissure.
- The *superior choroidal tissue* overlies the tectorial membrane. This lamina presents two layers: the inferior layer adhered to the tectorial membrane and the superior adhered to the inferior face of the atrium. The velum interpositum is defined in between the two layers, where the choroid plexus runs over the third ventricular cavity. It also includes the posteromedial choroidal arteries and the internal cerebral as well as multiple veins converging from the pineal region. This choroidal tissue separates the pineal body from the splenium of the corpus callosum.

The atrium is separated from the posterior incisural space by the crus of the fornix as it passes posterior to the pulvinar and the cortical gyri located in the lateral wall of the posterior incisural space. The choroid plexus, which forms a large tuft, the glomus, is attached along the choroidal fissure, between the crus of the fornix and the pulvinar.

2.4 Arachnoid Membranes and Cisternal Relationships

The posterior incisural space contains several cisterns and arachnoid membranes with complex relationships. These compartments and their neurovascular contents must be mastered by neurosurgeons to safely approach the pineal region. In addition, the pathology located in this region will use these cisterns as a way of expansion.

2.4.1 Arachnoid Membranes

There are three main arachnoid membranes in the posterior half of the incisural space, forming a complex arachnoid net:

- The upper or *posterior perimesencephalic membrane* (PPM). It arises at the tentorial edge and attaches to the pulvinar, dorsal, and lateral midbrain. It can be divided into horizontal and ascending parts.
- The lower or *cerebellar precentral membrane* (CPM). Posteriorly, the CPM has a common origin with the PPM. It attaches anteroinferiorly to the anterior aspect of the cerebellar vermis medially and the cerebellar hemisphere laterally.
- The third one or *quadrigeminal membrane* (QM) lies within the quadrigeminal cistern. This membrane may have two parts: sagittal and axial. However, in rare cases, this membrane is complete and shows a cruciform appearance. It attaches anteriorly on the vertical ramus of the cruciform sulcus (the one dividing the quadrigeminal plate into four colliculi) when it lies in the sagittal plane (70%), or on the horizontal ramus when it lies in the axial plane (30%). Therefore, the QM subdivides the quadrigeminal cistern in two parts, left and right, or superior and inferior [11].

2.4.2 Basal Cisterns and Contents

The most relevant cistern related with the pineal region is the *quadrigeminal cistern (QC)***.** It contains the quadrigeminal plate, pineal gland, and the vein of Galen. The QC is related with other cisterns:

- Superiorly with the *posterior pericallosal cistern* that runs close to the splenium between the two cerebral hemispheres. It contains the splenium and the splenial veins.
- Inferiorly with the *cerebello-mesencephalic cistern* related with the cerebello-mesencephalic fissure, running through the recess created between the posterior aspect of the midbrain and the superior and anterior aspects of the cerebellum and vermis. It contains the exit of both IV cranial nerves and the precentral veins.
- Inferolaterally with the posterior part of the *ambient cistern* (AC). It connects anteriorly with the *crural cistern* and is located between the lateral aspect of the midbrain and the parahippocampal gyrus. It contains the posterior cerebral and superior cerebellar arteries, basal vein of Rosenthal, and the cisternal segment of the IV cranial nerve.
- Laterally with the *retrothalamic cistern* running close to the pulvinar. It contains the pulvinar and the medial and lateral posterior choroidal arteries.
- Anteriorly with the *velum interpositum* that projects anteriorly to the roof of the third ventricle between the splenium above and the pineal body below. The upper and lower walls of the velum interpositum are formed by the two membranous layers of tela choroidea in the roof of the third ventricle. The upper is formed by the layer attached to the lower surface of the fornix and hippocampal commissure. The lower is attached to the striae medullaris thalami, habenular commissure, and pineal body. The internal cerebral veins exit the velum interpositum above the pineal body to enter the quadrigeminal cistern and join the great vein. The velum interpositum is widest posteriorly where it extends from the lower margin of the splenium to the upper margin of the pineal. It may infrequently have an opening situated between the splenium and the pineal body that communicates with the quadrigeminal cistern to form the cisterna velum interpositum. It mainly contains the internal cerebral veins.
- Posteriorly, the *superior cerebellar cistern* appears below the tentorial apex and is located between the CPM anteriorly and the outer arachnoid membrane below the tentorium posteriorly. It communicates with the quadrigeminal cistern anteromedially and with the cerebello-mesencephalic cistern inferolaterally without arachnoid separation. Superolaterally, it communicates with the AC through the openings along the anterior attachments of the ascending part of the PPM [9, 10].

2.5 Posterior Incisural Space

2.5.1 Location

The area between the upper brainstem and the edges of the tentorial incisura is divided into

anterior, middle, and posterior incisural spaces. This notch provides the only communication between the supra- and infratentorial spaces. It is roughly triangular and has its anterior edge or base at the dorsum sellae and its apex dorsal to the midbrain, just posterior to the pineal region [9]. The size is variable, with a distance between its posterior boundary and the pineal body ranging from 10 to 30 mm. This variation in distance could influence the choice of whether or not to make a tentorial incision during a surgical approach to the pineal region [1, 6] (Fig. 2.3).

The posterior incisural space is located posterior to the midbrain and corresponds to the pineal region. The venous anatomy in this space is extremely complex, as it contains the convergence of the internal cerebral and basal veins and many of their tributaries into the vein of Galen [9].

2.5.2 Limits and Relationships

The posterior incisural space has roof, floor, anterior and lateral walls and extends backwards to the level of the tentorial apex.

The quadrigeminal plate is located in the center of the anterior wall. The part of the anterior wall rostral to the colliculi is formed by the pineal body and the habenular trigones and commissure. The area of the anterior wall below the colliculi is formed in the midline by the lingula of the vermis and laterally by the superior cerebellar peduncles as they ascend beside the lingula.

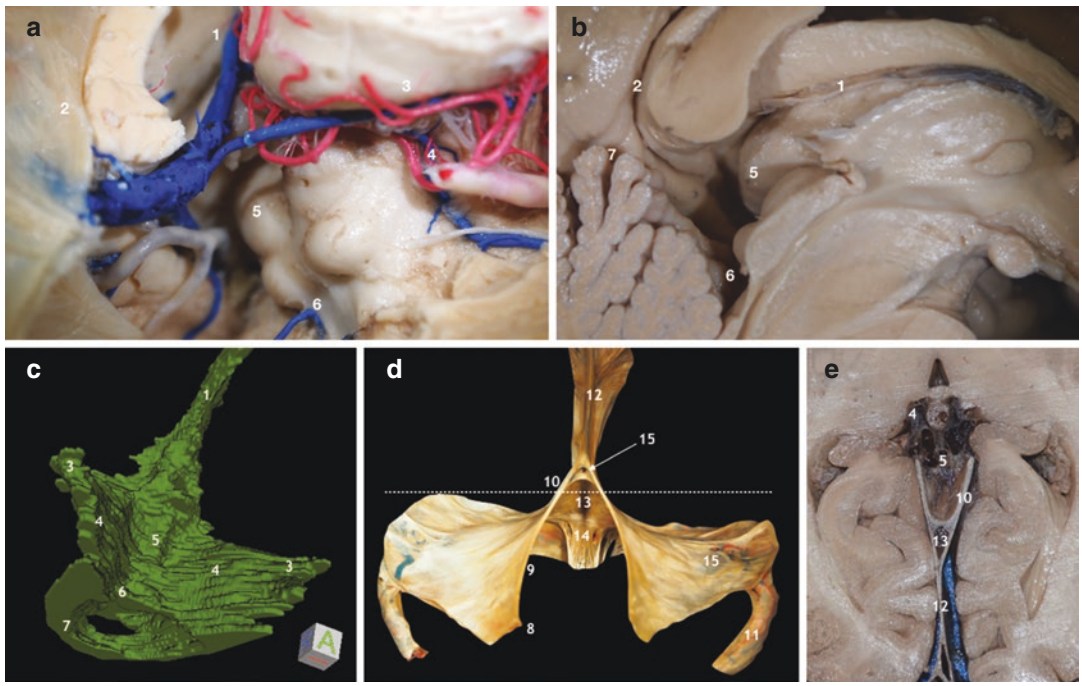

Fig. 2.3 Different anatomic views, dissections, and schemes representing the pineal region spaces, cisterns, limits, and dural relationships. (**a**) Posterolateral oblique view of the right aspect of the pineal region and its relationship to the posterior basal cisterns; (**b**) midline sagittal view of the posterior diencephalon and pineal region; (**c**) oblique antero-inferior view of the quadrigeminal cistern and its prolongations; represented as a volumetric reconstruction; (**d**) pure anterior view of the incisural space and falcotentorial junction; (**e**) superior axial view of the pineal region and its relationship to the basal cisterns and surrounding structures. (1) Velum interpositum cistern; (2) pericallosal cistern; (3) retrothalamic cistern; (4) ambient cistern; (5) quadirgeminal cistern; (6) cerebellomesencephalic cistern; (7) superior cerebellar cistern; (8) anterior incisural space; (9) middle incisural space; (10) posterior incisural space; (11) transverse sinus; (12) fax; (13) straight sinus; (14) torcula; (15) falcotentorial junction and entry of the great vein into the dural folders to form the straight sinus

The roof of the posterior incisural space is formed by the lower surface of the splenium, the terminal part of the crura of the fornices, and the hippocampal commissure.

The floor of the posterior incisural space is formed by the anterosuperior part of the cerebellum and consists of the culmen of the vermis in the midline and the quadrangular lobules of the hemispheres laterally. This space extends inferiorly into the cerebello-mesencephalic fissure, the cleft opening inferiorly between the culmen and quadrangular lobules and the colliculi.

Each lateral wall is formed by the pulvinar, crus of the fornix, and the medial surface of the cerebral hemisphere. The anterior part of the lateral wall is formed by the part of the pulvinar located just lateral to the pineal body. The lateral wall, posterior to the pulvinar, is formed by the segment of the crus of the fornix that wraps around the posterior margin of the pulvinar. The posterior part of the lateral walls is formed by the cortical areas located below the splenium on the medial surface of the hemisphere. These areas include the posterior part of the parahippocampal and dentate gyri [9, 10] (Fig. 2.3).

2.6 Vascular Relationships and Intrinsic Vascularization

2.6.1 Venous Relationships (Fig. 2.4)

The complexity of the venous relationships of the pineal gland is based on the convergence of the

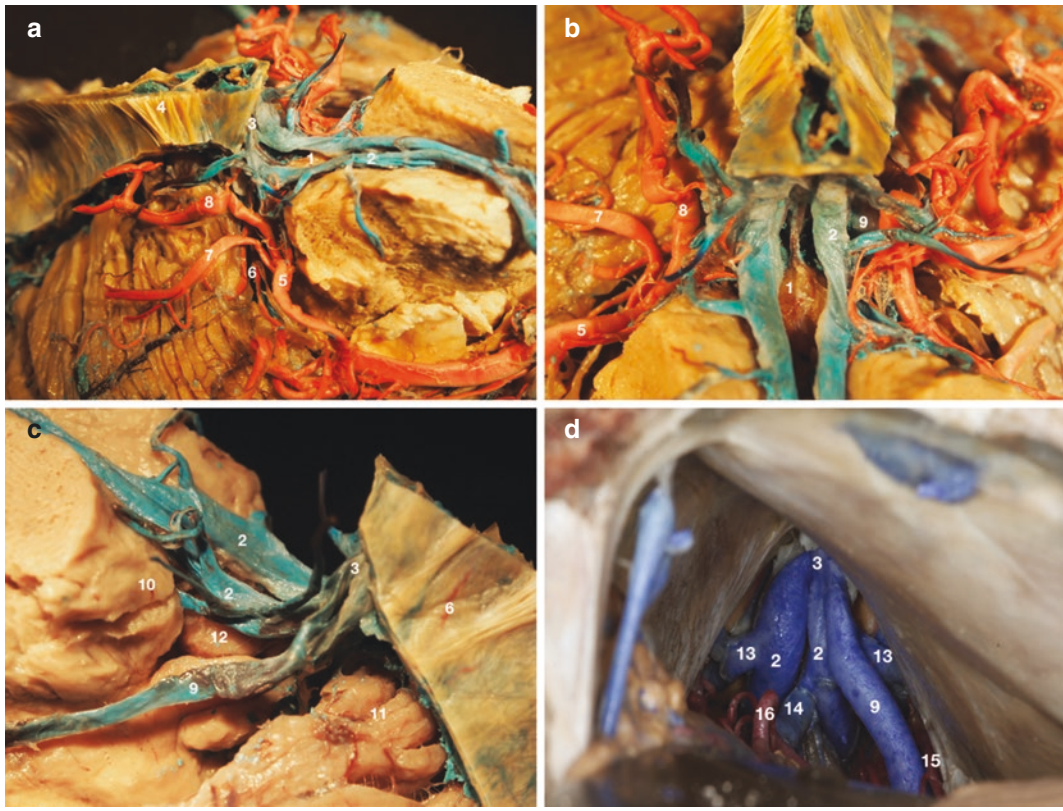

Fig. 2.4 Vascular anatomy of the pineal region. (**a**) lateral view of a cadaveric dissection showing the arterial and venous anatomy of the pineal region. (**b**) anterosuperior view. (**c**) left posterolateral view of the venous anatomy. (**d**) supracerebellar infratentorial right-sided view of the venous complex. (1) pineal gland; (2) internal cerebral vein; (3) great vein of Galen; (4) straight sinus; (5) posterior cerebral artery; (6) superior cerebellar artery; (7) parieto-occipital artery; (8) calcarine artery; (9) basal vein of Rosenthal; (10) pulvinar; (11) vermis; (12) superior colliculus; (13) internal occipital vein; (14) superior vermian vein; (15) medial posterior choroidal artery; (16) vermian branches of superior cerebellar artery

internal cerebral, basal veins, and many of their tributaries into the vein of Galen within this area. This complex net makes up the final route of the deep venous system of the brain. The venous structures are located superomedially in the quadrigeminal cistern, in contrast to the arterial ones that are located inferolaterally [12].

- *Internal Cerebral Veins*. The internal cerebral veins course posteriorly along the roof of the third ventricle within the velum interpositum. They access the posterior incisural space superolateral to the pineal gland and posteroinferior to the splenium, joining later into the vein of Galen in the suprapineal recess [12, 13].
- *Basal Veins*. The basal veins originate in the anterior perforated space and pass through the anterior and posterior incisural space, receiving their tributaries. The posterior segment begins in the posterior margin of the midbrain, where they pass from the AC to the QC, ending in the internal cerebral or the great veins [13].
- *Vein of Galen.* It originates in the suprapineal recess by the junction of both internal cerebral veins, extends posterosuperior below the splenium, and reaches the straight sinus at the tentorial apex [1, 13].
- *Straight Sinus*. It comes from the junction of the inferior sagittal sinus and the vein of Galen, and continues posteroinferiorly, following the falcotentorial line, to reach the torcula.
- *Tributaries*. The tributaries of the internal cerebral, basal, and great veins within the quadrigeminal cistern appear as follows:
  - **Galenic draining group of the veins of the posterior fossa** draining the tentorial surface of the cerebellum, part of the roof of the fourth ventricle, the cerebello-mesencephalic fissure, and midbrain. It includes the tectal veins that drain the quadrigeminal plate, and the superior vermian vein, which receives the superior hemispherical veins of the adjacent tentorial surface of the cerebellum, and the vein of the cerebello-mesencephalic cleft or vein of the precentral cerebellum [1, 13, 14].
  - **Medial and lateral atrial veins** from the atrium and occipital horn of the lateral ventricle. They can appear as a single trunk called a *common atrial vein* [12].
  - **Epithalamic or pineal veins** which drain the posteromedial part of the thalamus and the adjacent epithalamic areas, including the pineal body and posterior and habenular commissures.
  - **Internal occipital veins** which drain the medial surface of the occipital lobe, particularly the calcarine sulcus.
  - **Thalamic veins** from the superior and medial portions of the thalamus.
  - **Posterior pericallosal veins** which run through the posterior surface of the splenium.
  - **Posterior longitudinal hippocampal vein** that drains the posterior hippocampus.
  - **The most posterior of the medial temporal veins** which drains the posterior sector of the parahippocampal and occipitotemporal gyri.
  - **Medial occipitotemporal veins** which drain the lingula and the occipitotemporal gyrus.

2.6.2 Arterial Relationships (Fig. 2.4)

Important arterial trunks are found in close relationship with the pineal region. The most relevant are the posterior cerebral artery (PCA), the superior cerebellar artery (SCA), and the branches that originate or transit through this region. The PCA vascularizes the posterior incisural space above the level of the lower margin of the superior colliculi, while the SCA supplies the structures below it [9].

Posterior Cerebral Artery. The main segment related to the pineal is P3 or quadrigeminal segment of the PCA, which begins lateral to the posterior border of the midbrain where it leaves the AC to reach the lateral part of the QC and ends at the anterior limit of the calcarine sulcus. It is in the posterior incisural space where it divides into

two terminal branches: the calcarine and the parieto-occipital arteries [9, 15]. The change of direction of the artery at the level of the quadrigeminal plate is called the collicular point, which represents the point of maximum proximity between the arteries on both sides and represents the transition from P2 to P3.

- *Branches of the Posterior Cerebral Artery in the Quadrigeminal Cistern*
  - **Lateral Posterior Choroidal Artery:** It arises in the posterior incisural space and enters through the choroidal fissure to supply the choroid plexus in the atrium, giving branches to the thalamus on the way [9].
  - **Medial Posterior Choroidal Artery:** It originates from P2 or P3 segments, and ascends laterally to the pineal gland to enter the velum interpositum at the level of the suprapineal recess. It supplies the choroid plexus in the roof of the third ventricle and body of the lateral ventricle. It sends branches along its course to the cerebral peduncles, colliculi, pulvinar, pineal gland and medial thalamus [9, 15].
  - **Long Circumflex or Quadrigeminal Arteries:** They originate from P1–P2 and reach the QC to vascularize the quadrigeminal plate. Its terminal branches form an anastomotic arterial network with branches of the superior cerebellar artery on the colliculi [15].
  - **Posterior Temporal Artery**: This artery occasionally arises in the QC and supplies the inferior temporal and occipital surfaces.
  - **Splenial Arteries:** They branch from P3 and transit over the splenium forward to anastomose with the distal pericallosal artery.
  - **Terminal Branches**: The parieto-occipital artery that runs through the parieto-occipital sulcus and the calcarine artery that runs in the calcarine sulcus, supplying it.

Superior Cerebellar Artery. The SCA is related to the posterior incisural space at the level of its cerebello-mesencephalic and cortical segments. The cerebello-mesencephalic segment originates from the precerebellar branches destined to the quadrigeminal plate that ascend and anastomose with PCA branches [9].

2.6.3 Vascularization

Arteries. The pineal gland is vascularized by three main arterial systems: the lateral, medial, and rostral pineal arteries. The *lateral pineal artery* represents the main artery of the pineal gland, supplying its lateral aspect and apex. It generally arises from the posteromedial choroidal artery, but it can also originate from the superior cerebellar artery or from the posterolateral choroidal artery. It also feeds the habenular trigone and pretectal area. The *medial pineal artery* achieves the pineal apex after a long medial course on the inferior aspect of the pineal region. The r*ostral pineal artery* reaches the superior and lateral pineal surfaces. It arises more frequently from the A4 and A5 arteries, but it can also originate from the posteromedial choroidal artery [1, 16, 17].

Veins. The blood supply of the pineal gland is drained through the *pineal veins.* They run along the lateral aspect of the epiphysis, sometimes converging and forming the medial pineal vein that drains into the vein of Galen or into the internal cerebral veins. Their tributaries are the so-called *upper and lower lateral pineal veins* that drain the superior colliculus, pretectal area, and suprapineal recess [9, 16, 18].

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3 Histopathology of the Pineal Region Tumors

Sergiu Susman, Bobe Petrushev, and Doinița Crișan

3.1 Pineocytoma

3.1.1 Definition/Cell of Origin

According to the 2016 WHO classification of brain tumors, pineocytoma is a well-differentiated neoplasm, consisting of cells whose monomorphic appearance is similar to that of normal pinealocytes, which form pineocytomatous rosettes, and/or to that of pleomorphic cells with gangliocytic differentiation (pleomorphic variant) [1].

Given the phenotypic similarity and the molecular expression profiles, the origin of this type of neoplasm is considered to be in the pinealocytes. The expression of CRX and ASTM, molecular markers involved in pineal lineage and melatonin synthesis, supports the idea that pineocytoma origin is to be found in the pineal cells [2, 3]. It is interesting to note that during morphogenesis, the pineal gland consists of cells arranged in rosette-like structures, with the morphogenesis of this tumor remaking the ontogenetic development of the gland [4].

3.1.2 Grading

Pineocytoma is a WHO grade I tumor [1].

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3.1.3 Macroscopy

These tumors are well-delineated from the adjacent parenchyma. On the cut section, they appear to be white-gray and granular. Cystic degeneration, hemorrhage areas, or calcification may be noted [5].

3.1.4 Microscopy

From a phenotypic point of view, the tumor cells are well differentiated, being similar to normal pinealocytes. A diffuse or vague lobular pattern may be seen [6]. A characteristic of this type of tumor is the presence of pineocytomatous rosettes of variable size which are not associated with vascular structures. They consist of cells disposed concentrically around a center consisting of neutrophil-like neuritic processes [7]. Cell density is moderately high. The cells are of medium size and look uniform. The nuclei are round or oval, have finely dispersed chromatin and inconspicuous nucleoli. The scant eosinophilic cytoplasm shows short processes ending in club-shaped expansions, more visible in immunohistochemistry (IHC) for Neurofilament protein (NFP). A variant characterized by this neuronal differentiation with large ganglion cell or multinucleated cell formation has been described. The tumor stroma is represented by a reduced number of reticulin fibers. The vascular structures are of the capillary type. Mitotic activity is reduced or

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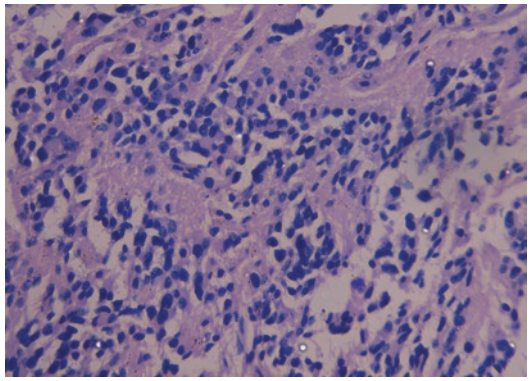

Fig. 3.1 Pineocytomas are composed of uniform, differentiated cells resembling normal pinealocytes. The pineocytomatous rosettes, a characteristic feature of this tumor, are formed of large fibrillary areas surrounded by neoplastic cells. (Hematoxylin-eosin, 200×)

absent (<1/10 HPF) in both classical and pleomorphic variants. Necrosis is absent. Calcifications are present, but they are structures normally present in the pineal gland [8] (Fig. 3.1).

3.1.5 Molecular Tests

3.1.5.1 Immunohistochemistry

Pineocytomas are positive for neuronal markers such as synaptophysin, neuron-specific enolase, NFP, tau protein, Ubiquitin C-Terminal Hydrolase L1 (UCHL1), and neurotransmitters (5-HT). They express chromogranin-A and class III β-tubulin variably. They can also express markers of photosensory differentiation, such as rhodopsin and S-arrestin. They are also positive for S100 and MAP2. In the pleomorphic variant, ganglion cells express NFP. They are negative for OLIG2 and GFAP. The proliferation index evaluated by Ki-67 expression is low (1–2%) [9, 10].

3.1.6 Genetic Tests

There are no genetic events that are characteristic of pineocytoma, and the results obtained by conventional cytogenetic studies and those obtained by comparative genomic hybridization (CGH) are discordant. Karyotyping performed on a very small number of pinealocytomas highlighted chromosome number and chromosome structure anomalies: gain of Chr 19 and 5; loss of Chr 14, 11, and 22; and partial loss of Chr 22 or partial deletion of Chr 11 [11]. These data could not be confirmed by CGH analysis. A single case of familial pineocytoma has been reported in the literature [12]. Studies that analyzed the gene expression profile confirmed the dual phenotype (neurosecretory and photosensory) of tumor cells, high expression profiles being present for the genes involved in melatonin synthesis (TPH1 and ASMT) and phototransduction (OPN4, RGS16, CRB3) [13].

3.2 Pineal Parenchymal Tumor of Intermediate Differentiation

3.2.1 Definition/Cell of Origin

A tumor of the pineal gland with histopathological appearance and malignancy degree ranging between pineocytomas and pineoblastomas [1, 14].

The cell of origin is a fully differentiated pinealocyte or a pinealocyte in an intermediate stage of differentiation. As in the case of normal pinealocytes, the tumor is positive for CRX and ASMT [2, 3].

3.2.2 Grading

This histopathological entity corresponds to WHO grades II or III. The criteria for differentiation between grades II and III are not clearly defined, the biological evolution may correspond to either of these two grades. A number of 6 mitoses per 10 HPF and NFP positivity may be considered to be suggestive of a second-grade tumor, but the importance of these criteria remains yet to be established [15].

3.2.3 Macroscopy

The aspect on the cut section is similar to that of pineocytomas, being white-gray, soft at palpation, and well circumscribed.

3.2.4 Microscopy

Two architectural patterns may be present: diffuse or pseudolobular. The diffuse pattern (neurocytoma or oligodendroglioma-like) is characterized by cellular areas consisting of monomorphic, medium-sized cells that may form small pseudo-rosettes. Pineocytomatous rosettes are absent. Cell density is moderate or high. Neoplastic cells have "salt and pepper"-like nuclei [10]. Cytoplasm is less visible than in the case of pineocytoma. In the pseudolobular pattern, lobules are vaguely delineated by vascular structures. Atypia and mitotic activity vary from low to moderate. Similar to pineocytomas, the histological variant described shows bizarre ganglion-like cells with atypical, single, or multiple nuclei [16]. Necrosis may be present in high-grade forms of pineal parenchymal tumor of intermediate differentiation (PPTID). A certain degree of vascular proliferation, as well as meningeal infiltration may be present in some cases. The absence of the "small blue cell" appearance differentiates these cases from PB (Fig. 3.2) [17].

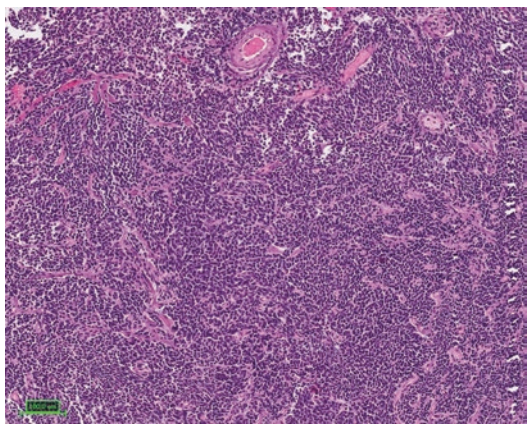

Fig. 3.2 Pineal parenchymal tumor of intermediate differentiation with high cellularity and mild to moderate cellular atypia. Tumor cells have distinguishable pale eosinophilic cytoplasm. Tumor showed less than 6 mitoses per 10 high-power microscope fields and an MIB-1 (KI-67) proliferation index of approximately 10%. (Hematoxylin-eosin, 100×)

3.2.5 Molecular Tests

3.2.5.1 Immunohistochemistry

The immunohistochemical profile of tumor cells is characterized by positivity for synaptophysin, chromogranin, MAP2, and NFP. Tumor cells are negative for GFAP, Olig2, and NeuN. Interstitial cells of astrocytic phenotype can express GFAP and S100. In the pleomorphic variant, ganglion cells express neuronal markers such as NFP and S100 [16]. Differently from pineoblastomas, PPTID has more cells that are positive for ASMT. The Ki-67 proliferation index is increased (between 3.5 and 16%), ranging between PC and PB [10].

3.2.6 Genetic Tests

The gene expression profile of POU4F2, CD24, HOXD13, and PRAME may be correlated with the degree of malignancy, being increased in high-grade PPTID and pineoblastoma and decreased in low-grade PPTID and pineocytoma. The most common genetic alterations are Chr 22 loss and Chr 4 gain [1]. PPTID is characterized by recurrent KBTBD4 small in-frame insertion and the absence of mutually exclusive DICER1 mutation and DROSHA homozygous deletion [18]. Another study showed the presence of mutations in TSC1L388P and IKZF3F206C (targeted exome sequencing), while high-resolution array cytogenetics highlighted the Chr 2, 3, 4, 8, 10, 11, 17, and 20, resulting in single-copy loss of PTEN and TP53 [19].

3.3 Pinealoblastoma

3.3.1 Definition/Cell of Origin

Poorly differentiated embryonic neoplasm with increased cellularity and originating from the pineal gland cells. It is believed that the cell of origin is either the completely differentiated pinealocyte that may undergo a dedifferentia-

tion process, or a pinealocyte that is being differentiated [1].

3.3.2 Grading

Pineoblastoma is a WHO grade IV tumor [1].

3.3.3 Macroscopy

Unlike other tumor entities originating from the pineal gland parenchyma, pineoblastoma is a poorly delineated tumor, and the invasion of adjacent structures is very common. It has a dark pink aspect on the cut section and low consistency. Necrosis and bleeding are present. Unlike pineocytomas and PPTID, it does not show calcifications [20].

3.3.4 Microscopy

The tumor architecture consists of high-density cell sheets of no particular pattern. Pineocytomatous rosettes are absent. Neural and retinoblastic differentiation is highlighted by the presence of Homer-Wright and Flexner-Wintersteiner rosettes, as well as by the presence of rare fleurettes [10, 20]. The small-size cells are of high-grade appearance: high nucleo-cytoplasmic ratio and large, hyperchromatic nuclei. Cytoplasm is reduced, with poorly visible cell boundaries. The overall appearance is similar to that of the "small blue round cell tumor." There may be areas of low-grade histopathological appearance of the type present in pineocytomas and PPTIDs. In this case, the pineocytoma component should be differentiated from a normal pineal gland area with invasion. Necrosis is present. Significant mitotic activity is highlighted by the presence of numerous mitoses and by a Ki-67 proliferation index of 23–50%. Tumor vessels are thin-walled. The invasion of the adjacent structures is also present at microscopic level [5, 7] (Fig. 3.3).

The pineal anlage tumor is an extremely rare tumor of the pineal region whose morphological characteristics make it a separate entity. At tumor level, both neuroectodermal elements (sheets of small blue round cells, but also neuronal and glial differentiation) and mesenchymal elements (rhabdomyoblasts, cartilage, and striated muscles) can be noted [21].

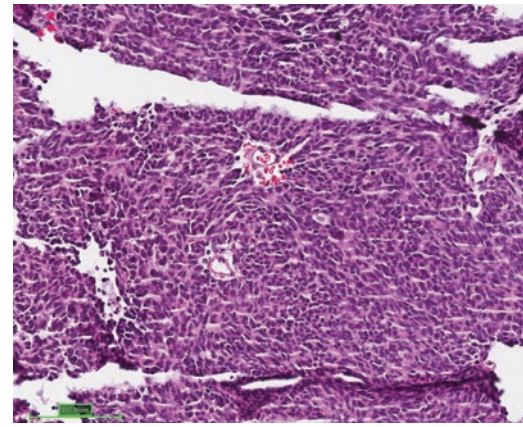

Fig. 3.3 Pineoblastomas are composed of small, undifferentiated cells with hyperchromatic nuclei having the appearance of a small blue round cell tumor. Tumors have extensive mitotic activity and increased proliferation indices (over 20%). (Hematoxylin-eosin, 200×)

3.3.5 Molecular Tests

3.3.5.1 Immunohistochemistry

The immunohistochemical profile of the tumor is similar to that of the PC, being positive for synaptophysin, chromogranin-A, NFP, class III beta-tubulin, and negative for Neu-N, OLIG2, GFAP. In contrast, in pineoblastomas SMARCB1 (INI1) is constantly expressed. The NSE and Syn expression is poor compared to PPT. MIB-1 index is increased (between 25 and 50%) [9].

3.3.6 Genetic Tests

One study reported differences in the methylation profile of adult and pediatric PB. In pediatric PB, the methylation profile is not homogeneous, which suggests the existence of several entities in this group. It is also the first study that highlighted the molecular drivers as recurrent homozygous deletions of DROSHA and the microduplication of PDE4DIP, a molecular driver different from medulloblastoma or CNS-PNET despite the morphologically similar appearance [18]. Also 22q

loss and gains of 14q211, 6p12, 5p13, 1q12, and 5q21 have been reported. Regarding gene expression profile, microarray analyses showed upregulation of UBEC2, SOX4, TERT, TEP1, PRAME, CD24, POU4F2, and HOXD135.6 [13]. Most cases are sporadic. However, there are cases where germline mutations in the RB1 and DICER1 genes increase the risk for developing PB [22]. Also, trilateral retinoblastoma syndrome or familial adenomatous polyposis can lead to the appearance of this type of tumor [23].

3.4 Papillary Tumor of the Pineal Region

3.4.1 Definition/Cell of Origin

A tumor with solid and papillary architecture made up of cells with a neuroepithelial phenotype and cytokeratin positivity, especially for CK18. It has been suggested that the origin of the tumor cells may well be the subcommissural organ ependymocytes, having the same immunohistochemically and gene expression profile (ZFHX4, CALCA, TTR, RFX3, SPDEF), and the same electron microscopic appearance. Also, the expression profile of claudin (Claudin 1 and 3 positive) is similar to the subcommissural organ during morphogenesis [1].

3.4.2 Grading

The WHO grade may be II or III. The criteria for differentiation in terms of biological evolution are yet to be established [1].

3.4.3 Macroscopy

These are well-circumscribed tumors with respect to the adjacent structures, which makes it difficult to differentiate it from the PC. They may have cystic structures containing cerebrospinal fluid. On the cut section, they appear in grey to yellowish color. Calcifications and necrosis are absent.

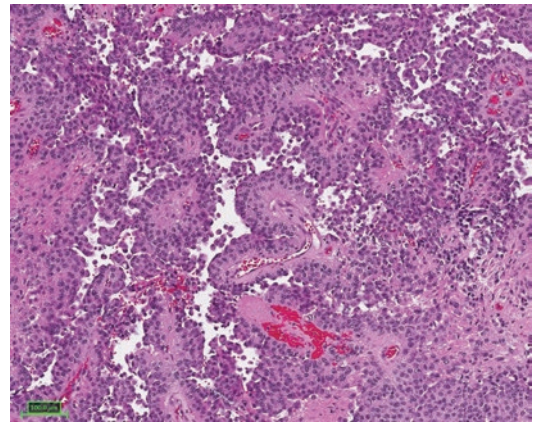

Fig. 3.4 Papillary tumor of the pineal region exhibits a papillary architecture with vessels covered by layers of columnar tumor cells with round/oval nuclei with stippled chromatin patterns. (Hematoxylin-eosin 100×)

3.4.4 Microscopy

The microscopic appearance is that of epithelial-like tumor-presenting areas with both papillary and solid architecture. The papillary structures consist of a fibro-vascular axis, covered with eosinophilic, cubic, multi-layered or cylinder cells. Ependymal-like differentiation may be present in some cases. The nuclei are round or oval with stippled chromatin. The nucleoli are prominent. There may be rare nuclei with pleomorphism, hyperchromasia, but also many multinucleated cells. In the solid areas, round or oval cells may present clear, vacuolate, or signet-ring cytoplasm. There may be necrosis. As for the mitotic index, it can vary greatly (between 0 and 12 mitoses/10 HPF), and in some cases many mitoses can be observed. Tumor vessels have a pseudo-angiomatous appearance and are frequently hyalinized. Microvascular and endothelial proliferation is rarely observed (Fig. 3.4) [15].

3.4.5 Molecular Tests

3.4.5.1 Immunohistochemistry

A feature of this type of tumor is the expression of cytokeratin, especially at the level of the papillary structures. The positive cytokeratins in this type of

tumor are: CK18, AE1/AE3, KL1, and CAM5.2. Expression is cytoplasmic, dot-like, and may lead to diagnostic errors being mistaken for a metastasis of carcinoma. However, in carcinoma, the marked expression of cytokeratins and EMA is not supported by the expression of other markers such as vimentin, S100, NSE, MAP2, NCAM1, and transthyretin. Also, carcinoma metastasis never expresses nestin. The focal expression of EMA observable in ependymoma is absent. Although PTPR has a molecular profile similar to the choroid plexus tumors, KiR7.1, E-cadherin-1 and claudin-2 are always negative. Synaptophysin and chromogranin may be present at times, but their expression is focal. GFAP is absent [24].

3.4.6 Genetic Tests

PTPR has chromosomal alterations, characteristic gene expression, and methylation profiles, which facilitate diagnosis. With regard to chromosomal alterations, the most characteristic modification is loss of Chr 10. Other less characteristic alterations are loss of Chr 3 and Chr 22 and gains of Chr 8 and Chr 12. The gene expression profile determined by the cDNA array method is similar to that of the subcommissural organ, the genes with the most important expression being ZFH4, CGRP, RFX3 and TTR. Expression of SPDEF can help differentiate it from ependymal and choroid plexus tumors at the PTPR level being overexpressed. The methylation profile determined by Illumina 450k arrays allows differentiation from ependymoma, but at the same time has a predictive role, as a higher methylation profile is associated with a reduction in PFS [25, 26]. Genetic profile but also other criteria like clinical features, macroscopy, histology and immunohistochemistry could improve the differential diagnostic of the pineal gland tumor lesions (Table 3.1).

Table 3.1 Differential diagnostic of pineal gland tumor lesions

Pineocytoma (I)	Adult	Well-delineated White-gray Granular Hemorrhage areas or calcification	Well differentiated cells Pineocytomatous rosettes +/− Ganglion and multinuclear cells <l/10M HPF	(+) Syn, NSE, NFP (+++) (gangliocytic variant), UCHl 1, chromogranina-A, class III-tubulin, rhodopsin si S-arrestin, S100 si MAP2 (−) OLIG2 si GFAP Ki67 1–2%	Gain of Chr 19 si 5, loss of Chr 14, 11 si 22, partial loss of Chr 22 (??) Gene expression Melatoninsynthesis (*TPH1 si ASMT*) and phototransduction (*OPN4, RGS16, CRB3*)
Pineal parenchymal tumour of intermediate differentiation (II/III)	Adult	Well-delineated White-gray Hemorrhage Calcification	Moderate atypia Pseudorosettes No pineocytomatous +/− ganglion cells <6M/HPF gr II, >6M/HPF gr III	(+)Syn, Chr-A, MAP2, NFP si SJOO (pleomorphic variant) ASMT (ddPB) (−) OLIG2 si GFAP Ki67 5%	Losses ale Chr 2, 3, 4, 8, 10, 11, 17, and 20 Gene expression: POU4F2, CD24, HOXD13, PRAME KBTBD4 small in-frame insertion DICER1 mutation DROSHA homozygous deletion Mutations in TSCIL388P and IKZF3F206C

Table 3.1 (continued)

Pineoblastoma (IV)	Children	Poorly delineated Rose Hemorrhage No calcification	Important atypia "smal1 blue round cells" Homer-Wright si Flexner-Wintersteiner rosettes, fleurettes High mitotic index Necrosis	(+)Syn, Chr-A, NFP, class III beta -tubulin (−) Neu-N, OLIG2, GFAP (+)SMARCB1 (INI1) Ki67 25–50%	22q loss and gains of 14q211, 6p12, 5p13, 1q12, 5q21 Upregulation of UBEC2, SOX4, TERT, TEP1, PRAME, CD24, POU4F2, and HOXD135,6 Homozygous deletions of molecular drivers DROSHA and microduplication of PDE4DIP Methylation profiles different adult/children
Papillary tumour of the pine.al region (II/III)	Children/ Adult	Well-delineated Cysts Yellowish No calcification	Epitelial-like, areas with papillary and solid architecture Moderate atypia, signet ring, multinucleate cells Necrosis-possible Mitotic index 0–12M/HPF	(+)CK18, AE1/ AE3, KL1, CAM5.2,vim, S100, NSE, MAP2, NCAM1 si transthyretin, Nestina (−)EMA, KiR 7.1, E-cadherin- 1 si claudin-2, GFAP	Loss of chromosome 10 losses of chromosome 3 and 22 and gains of 8 and 12 Gene expression ZFH4, CCRP, RFX3, TTR si SPDEF

Other tumor entities that may occur in the pineal region whose diagnostic must be considered are not only gliomas (including tectal plate glioma, pylocytic astrocytoma, and ependymoma) but also meningiomas, choroid plexus tumors, teratomas, and metastases. Also, cystic lesions (epidermoid cyst, dermoid cyst, arachnoid cyst, and pineal cyst) may be encountered in this location.

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Clinical Presentation

4

Zoltan Zs. Major

4.1 An Evolutionary Perspective

The pineal gland or epiphysis is a neuroendocrine organ, part of the epithalamus, along with the habenula, habenular commissure, and stria medullaris. Its role overlaps with melatonin function, a methoxyindole derivative, widely expressed, from algae to humans. In mammals, the gland is the principal site of production [1] .

In low-order vertebrates, the pineal gland has direct sensitivity to light [2] through the parietal eye, which protrudes on the skull, being covered by skin. It directly regulates the circadian rhythm and metabolic functions, and contributes to thermoregulation [3].

In mammals, there is no direct photosensitivity, the response to light-darkness alternation being given by a multi-synaptic pathway, a modulating pace-maker for the rhythmic secretion of melatonin involving the melanopsin secreting retinal ganglion-cells, retinohypothalamic tract, the suprachiasmatic nucleus of the hypothalamus, the paraventricular nucleus, the intermediolateral column of the spinal cord, the sympathetic cervical ganglia, and the pineal gland [4].

4.2 Pineal Gland Function

Melatonin is secreted during the night, being a signal for day-night cycle. In humans, this photoperiodic behavior is represented by sleep regulation. Daytime melatonin supplementation induces a sleepy, near soporous effect, during nighttime it favors sleep. Melatonin influences hormone secretion and through this acts on puberty, infertility and hypogonadism. This also contributes to its oncostatic, antitumoral effect in breast and prostatic cancer, besides its potent antioxidant and free-radical scavenging as well as the immune-modulating function [2]. Increased levels of melatonin promote immune responses, the opposite suppression [1]. Early pinealectomy in animals reduces thymic cell proliferation [5]. Low peripheral leucocyte and lymphocyte counts were reported with low melatonin levels. A cyclic modulating effect can be observed in hemostasis and glucose metabolism regulation [6], in an attempt of the body to adapt to stress [5].

Melatonin has definite effects on neurological functions. An inhibitory effect on long-term potentiation in neurons of the hippocampal dentate gyrus influences memory. Secretion rhythmicity changes in age-related calcification of the gland and in various degenerative diseases like Alzheimer's and Parkinson's, but there is no evidence yet about a causative effect.

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4.3 Systemic Pathology with Clinical Features Related to the Pineal Gland

Various systemic diseases involve at least a functional disturbance of the pineal gland. The clinical presentation in such circumstances is characterized by the signs and symptoms of the underlying disease; nevertheless, the evaluation of melatonin levels or favoring its function has a beneficial effect.

Neurological and psychiatric illnesses are frequently accompanied by circadian rhythm disturbances. Structural and imaging differences of the pineal gland along with altered function are described in schizophrenia [7]—early calcification of the gland and reduction of melatonin secretion rhythmicity. Pineal volume and evening melatonin secretion seem to be reduced in patients with affective disorders [8]. In Alzheimer's disease, the circadian timing system is deactivated in concomitance with fading memory [9].

Autism spectrum disorders might also be influenced by pineal dysfunction, namely overproduction of N,N-dimethyltryptamine in the gland leads to abnormal neuroplasticity, cortical overgrowth, and dendritic spine dysgenesis, seemingly key features in the pathogenesis of the disease [10].

In critically ill patients, as in traumatic brain injury [11], there are frequent circadian rhythm disturbances caused by a reduction of melatonin production, the exogenous supplementation having a protective effect through several pathways. The anti-inflammatory [12] and antioxidative [13] effects of melatonin and its close links with the endocrine system reveal pineal dysfunction in several diseases and represent a primary pathological finding.

These metabolic pathways, together with others involved in oncogenesis, are disturbed in malignancies, the melatonin dysfunction being well established. There is no proven causal link, still, reduced circadian modulation is yet to be characterized in breast, ovarian, prostatic, skin (melanoma) [14], colorectal and non-small cell lung cancer [15] and also in primary malignancies of the central nervous system like gliomas. In malignancies of the female reproductive organs, pineal function has also a direct effect on hormone homeostasis. Supplementation of melatonin shows promising results in both breast [16] and ovarian [17] cancer. In gliomas, there are not only reduced melatonin levels, but also altered expression of melatonin receptors in different areas of the brain [18].

4.4 Clinical Presentation in the Primary Pathology of the Pineal Region and Gland

Pineal region tumors show increased histopathologic diversity, the neuroepithelial tumors [19] being the primary lesions of the gland [20]. Until now, no biomarkers are available to assess the diagnosis of primary lesions [21].

Pineal lesions produce a variety of clinical signs and syndromes. A controversial issue is the type and timing of treatment, considering that the vast majority of lesions are asymptomatic for a long time and are discovered incidentally [22]. Invasive treatment in these cases is applied using intermittent signs of high intracranial pressure as criteria [23]. Regression of lesions is seen in many cases, although there are almost always possibly contributing factors like steroid treatment, hydrocephalus treatment, diagnostic irradiation, pineal apoplexy, immunological mechanism, or surgery for other causes ([24]. Serial imagery might be the answer to establish the necessity of interventions in case of improving clinical features.

Visual phenomena are quite characteristic. The classically described Parinaud syndrome is characterized by vertical gaze palsy, mostly the upward movement, caused by compression of the rostral interstitial nucleus of the medial longitudinal fasciculus. This syndrome is characterized also by pseudo-Argyll Robertson pupils, conjugate down gaze, the so called setting-sun sign, eyelid retraction and convergence-retraction nystagmus. The syndrome frequently associates signal enhancement in the midbrain on MRI findings [25]. Other

visual signs are presented by visual field deficits, paroxysmal pupillary dilatations, and contractions [26]. Deficits are seen for both intra- and extra-axial lesions [27]. Minor features and rarer syndromes are also seen, according to the topography of the tumor, like isolated rectus inferior paresis [28], or the wall-eyed bilateral internuclear ophthalmoplegia—WEBINO syndrome [29].

Another key clinical finding in lesions of the pineal gland is headache, either associated with hydrocephalus, when it also presents the signs of the latter, such as nausea and vomiting, or caused probably by intermittent stenosis of the aqueduct [30]. A rarer cause of headache is represented by pineal gland apoplexy [31]. The symptom is severe and it rapidly might present signs of hydrocephalus or other clinical signs and frequently becomes a surgical emergency [32].

Auditory symptoms are another frequently reported sign of pineal region lesion. Usually, the patients present sometimes reversible hearing loss, of various degree [33, 34], and tinnitus [35], caused either by compression of inferior colliculi or by conduction deafness due to hydrocephalus [36]. More limited signs are also reported, like pure word deafness [37], either caused directly by the tumor or as an effect of the surgery, controversially present even with normal brainstem auditory evoked responses [38].

Endocrinological features occur mainly with germ cell tumors of the pineal region, showing frequently multiple topographies also involving the pituitary. According to this, patients show diabetes insipidus and various pituitary deficiences [39] or even hypothalamic-pituitary disconnection syndromes [40], according to the tumor topography. Another observed endocrinological feature involves the pineal gland itself; increased melatonin secretion associated with lesions, tumors of the gland, is seen in cases of male hypogonadotropic hypogonadism [41] or primary amenorrhea in women [42].

Around one-third of patients with pineal lesions might present primary generalized seizures or pathologic EEG morphology, represented by paroxysmal discharges of ≥3 Hz spike-and-wave complexes [43]. Frequent tumor removal solves this symptom. Frequently, tumor removal solves this symptom. Melatonin was attributed with anticonvulsive effect [44]. The lesion might compress the vasculature, causing deficient perfusion, or erodes vessels, producing hemosiderin deposits. Hydrocephalus is caused by compression on the aqueduct. In cases of giant cell astrocytomas of the region, associated with tuberous sclerosis and seizure, the prognosis is influenced by the evolution of the base disease [45].

A rarer, although reported, clinical feature of pineal lesions are extrapyramidal signs, mainly resting tremor, which rapidly subside and disappear after the tumor has been removed [46].

Finally, but of considerable importance, are psychiatric signs associated with pineal lesions, sometimes leading to their discovery [47]. Circadian rhythm disturbances are frequent due to melatonin dysfunction [48], though cognition is rarely affected [49]. Memory might be affected by compression of the nearby fornix [50], usually being reversible after removal of the lesion. Rarer psychiatric signs are also reported, such as obsessive-compulsive disorder [51] or anorexia nervosa ([52].

4.5 Controversial Issues and Conclusion

Several categories of signs were presented in the above sections, characterizing the pineal lesions from a clinical point of view. However, the picture is not complete; controversial issues are identified in almost each of the presented fields. Among these, we consider a few of key importance, with practical impact on the prognosis of these lesions. The role of melatonin is understandably important, but its supplementation for such a high number of diseases—see neoplasias—is questionable and lacks sufficient support (such as multicenter trials). Another practical question is whether to perform surgery or not when patients are asymptomatic; different approaches are suggested in the literature. Finally, but not least important, is the use of neurophysiological intraoperative monitoring during surgery. There are only limited data among these reports about the development of a new functional deficit, although brainstem auditory evoked potentials or visual evoked potentials

were kept normal during surgery. Hopefully, controversies will contribute to the development of new research toward a better understanding and consensus.

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Imaging Diagnosis

5

Horia Pleş

5.1 Introduction

Pineal region tumors are closely connected to the deep venous system. Using magnetic resonance angiography (MRA) venous sequence, the neurosurgeon can plan the surgery. Digital subtraction angiography (DSA) may be used in tumors with rich vascularization [1] (Fig. 5.1).

According to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), the pineal region tumors are: pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, and papillary tumor of the pineal region [2].

Within the same classification, in the category "germ cell tumors" which are commonly found in the pineal region, there are: germinoma, embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, teratoma, immature teratoma, teratoma with malignant transformation, and mixed germ cell tumor [2].

Depending on these classifications, there is a clinical incidence of pineal tumors and pineal region tumors. Common tumors are germinoma (50%), glioma (20–30%), teratoma (10–25%), and pineal region tumors (<20%). Rare tumor lesions are embryonal cell carcinoma, dermoid cyst, metastasis, lipoma, meningioma, arachnoid cyst, and epidermoid [3].

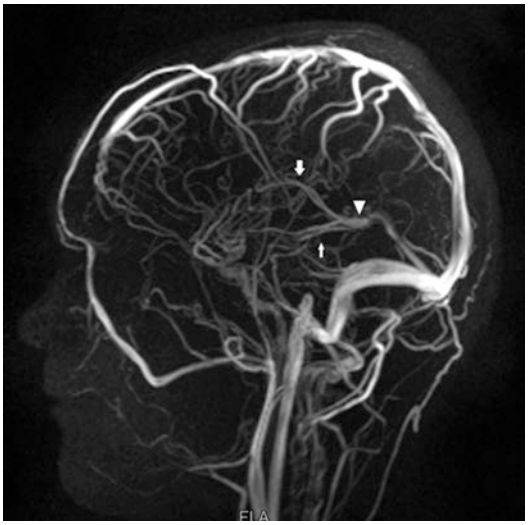

Fig. 5.1 Magnetic resonance angiography (MRA) venous sequence, deep cerebral veins. Tip of arrow—galenic vein; large arrow—internal cerebral veins; narrow arrow—basal veins of Rosenthal

Data about parenchymal tumors of the pineal region are based on small series; therefore, they should be interpreted with some caution. Imaging does not have such a high diagnostic accuracy to differentiate between different types of pineal tumors and pineal region tumors [4].

Pineal parenchymal tumors can be differentiated from the normal pineal gland on the basis that the latter calcifies with aging (thin calcium

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concretions called corpora arenacea, or brain sand). Intratumoral calcifications can also be found in pineal parenchymal tumors [4].

The imaging diagnosis methods are as follows: X-ray—it can detect a highly calcified pineal gland, but it is not enough to make a diagnosis; computed tomography (CT)—it can be helpful in detecting a level of hydrocephalus and calcification of the gland, also being used for guiding during biopsy; magnetic resonance imaging (MRI)—it is the method of choice for diagnosing pineal gland tumors; usually high-resolution MRI with gadolinium is used (Ammar Haouini & Frank Gallard).

5.2 Germinoma

Germinoma is a tumor originating in the primordial germ cells, and it is the equivalent of seminoma or dysgerminoma in the gonads or the mediastinum, respectively [5].

Germinoma presents as a tumor mass that encloses the pineal gland. Its size varies between 1 and 3 cm, and it is commonly associated with ventricular obstruction [5].

Some authors consider that germ cell tumors represent 60% of pineal region tumors. The pineal gland is hosting 53% of all primary germinomas of the central nervous system (CNS). This category can be subdivided into germinomas and nongerminomatous germ cell tumors. The incidence of germinomas is up to eight times higher in Japan and East Asia compared to the Western world [6].

Pure germinomas represent 55–65% of all intracranial germ cell tumors, and they are found in the pineal gland and also in the suprasellar region in 10% of cases [6].

Germinomas present as a non-encapsulated brittle mass, and they may occur inside cystic areas; necrosis, calcifications, and hemorrhage are unusual [5].

Germinomas does not secrete tumor markers in the serum, but it causes an increase in the levels of β-subunit of human chorionic gonadotropin (β-hCG) in the cerebrospinal fluid (CSF) to up to 50 U/mL, due to the syncytiotrophoblastic cells, and increase of the placental alkaline phosphatase (PLAP). The absence of the alpha-fetoprotein (AFP) in the serum and CSF is mandatory for the diagnosis of a pure germinoma [6].

Generally, the tumors are radio- and chemosensitive, and this leads to a good overall prognosis, with a 5-year survival rate of over 90% [6].

Computed tomography—it reveals a hyperdense tumor mass in native examination compared to the grey matter, which is well delimited and surrounds the pineal gland or is growing around the posterior part of the third ventricle, and which usually enframes the calcifications of the pineal gland. The tumor has an intense uptake of the contrast medium. Iodophilic subarachnoid metastases can be revealed [5].

Magnetic resonance imaging—it reveals a round or lobulated tumor mass, in T1, T2 isosignal/hypersignal compared to the grey matter, which can contain cystic or necrotic areas in T2 hypersignal. Intratumoral spots can be present in T2 hypersignal, suggesting bleeding or calcifications, but seldom. The tumor is in hypersignal on the fluid-attenuated inversion recovery (FLAIR) sequence and shows restriction on the diffusion-weighted imaging (DWI) sequence. After the administration of the contrast medium, of note is the intratumoral intense uptake of the contrast medium. In spectroscopy, there is an increase of choline, and a decrease of NAA (N-acetyl aspartate) ± lactate. MRI examination is the best technique approach for assessing pineal gland germinomas. It is also required to evaluate the entire spine in order to reveal meningeal metastases in the spinal canal [5].

The CT and MRI images in Figs. 5.2 and 5.3 are from the same patient, operated 10 years ago, currently with a relapse of the germinoma.

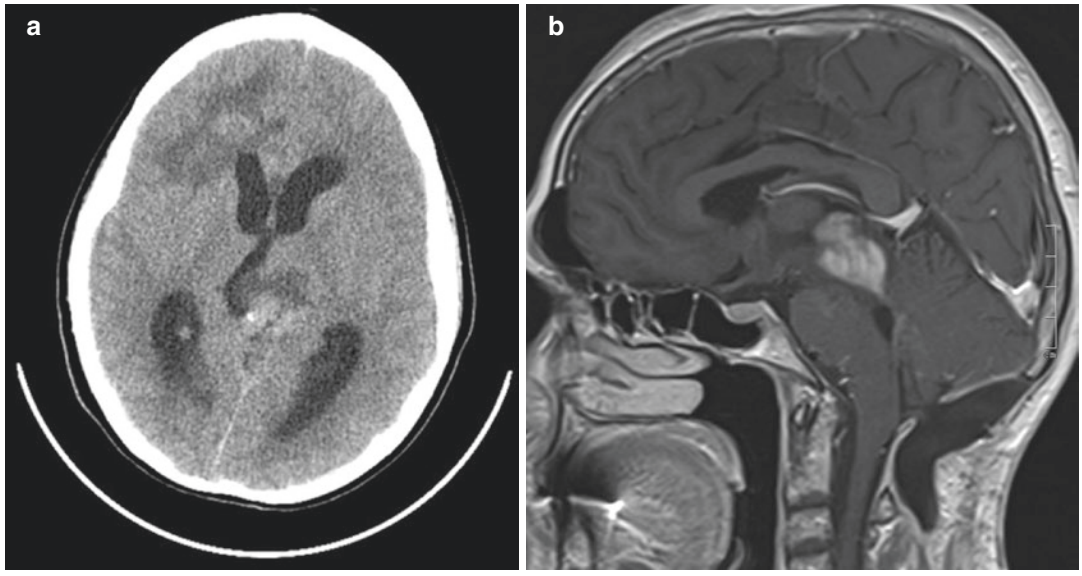

Fig. 5.2 Solid cystic tumor mass (germinoma confirmed via histopathology) in the pineal region. (**a**) CT native with the presence of a millimetric intratumoral calcification, mass effect on the third ventricle, with secondary hydrocephalus, right frontal periventricular secondary lesion infiltrative in the corpus callosum; (**b**) CT sagittal with contrast present iodophilia in the solid parts

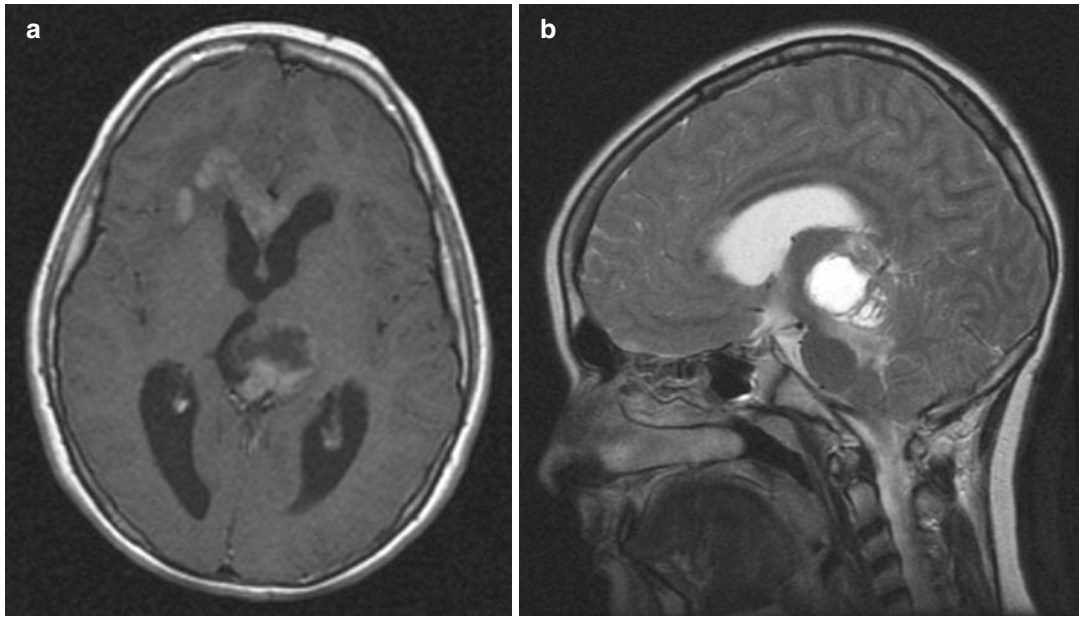

Fig. 5.3 MRI—solid cystic tumor mass in the pineal region (germinoma confirmed via histopathology). (**a**) Axial T1 with contrast, right frontal periventricular secondary lesion with infiltration of the corpus callosum, of note is the edema around the lesion. Contrast uptake in the pineal region with mass effect exercised on the third ventricle and secondary hydrocephalus; (**b**) Sagittal T2, of note is the cystic mass adjacent to the tumor, with imprint on the third ventricle

5.3 Embryonal Cell Carcinoma

It is a malignant tumor which consists of undifferentiated epithelial cells. It presents as a tumor mass with heterogeneous structure in the pineal or suprasellar region in adults [5].

Computed tomography—it presents as a heterogeneous mass which can contain cystic and hemorrhagic areas in native examination and has a variable proportion of contrast medium uptake [5].

Magnetic resonance imaging investigation—in the T1 weighted sequence, the mass is in hyposignal/isosignal compared to the grey matter, with a shorter T1 (hypersignal) due to the hematic, lipomatous, or proteic content. In the T2 weighted sequence, the tumor appears in isosignal or in a mild hypersignal compared to the grey matter. In the GRE T2* sequence, the hemosiderin deposits in the tumor are revealed. The DWI sequence uncovers the solid tumoral component with reduced restriction. The T1 sequence with contrast brings out a variable uptake of the medium. In brain spectroscopy, there is an increase of choline, lipids, and lactate, and a decrease of NAA. As a method of choice, MRI of the brain and of the entire spine is to be performed [5].

5.4 Gliomas

Histologically, the human pineal gland consists mainly of pinealocytes, with few astrocytes with a supportive role, and is subdivided into lobules by the pial layer [4].

A number of non-pineal types of tissue are located in the pineal region and can grow other tumor types, and this category constitutes an additional percentage of 10–14% of the tumors of this region [6]. There are astrocytomas, glioblastomas, ependymomas, and gangliogliomas.

Although there are astrocytes in the pineal gland, it is more common for gliomas to originate in the glial tissue from the vicinity of the pineal gland rather than in the pineal gland itself; most pineal region gliomas originate in parapineal structures such as the corpora quadrigemina of the posterior thalamus [3].

In Figs. 5.4 and 5.5, we present CT and MRI images of an astrocytoma GII.

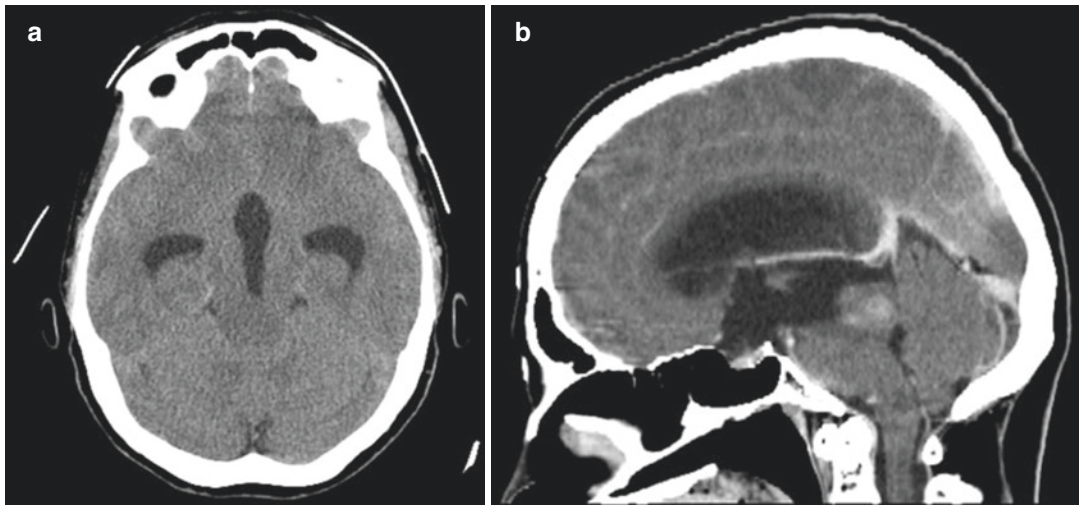

Fig. 5.4 Tumor mass—astrocytoma GII confirmed via histopathology, post-biopsy aspect. (**a**) CT native axial image, tumor mass mildly hypodense native, without calcifications in the pineal region with infiltration of the mesencephalic tectum; (**b**) CT post-contrast sagittal image, of note is the uptake after administration of contrast medium. Of note is the presence of hydrocephalus

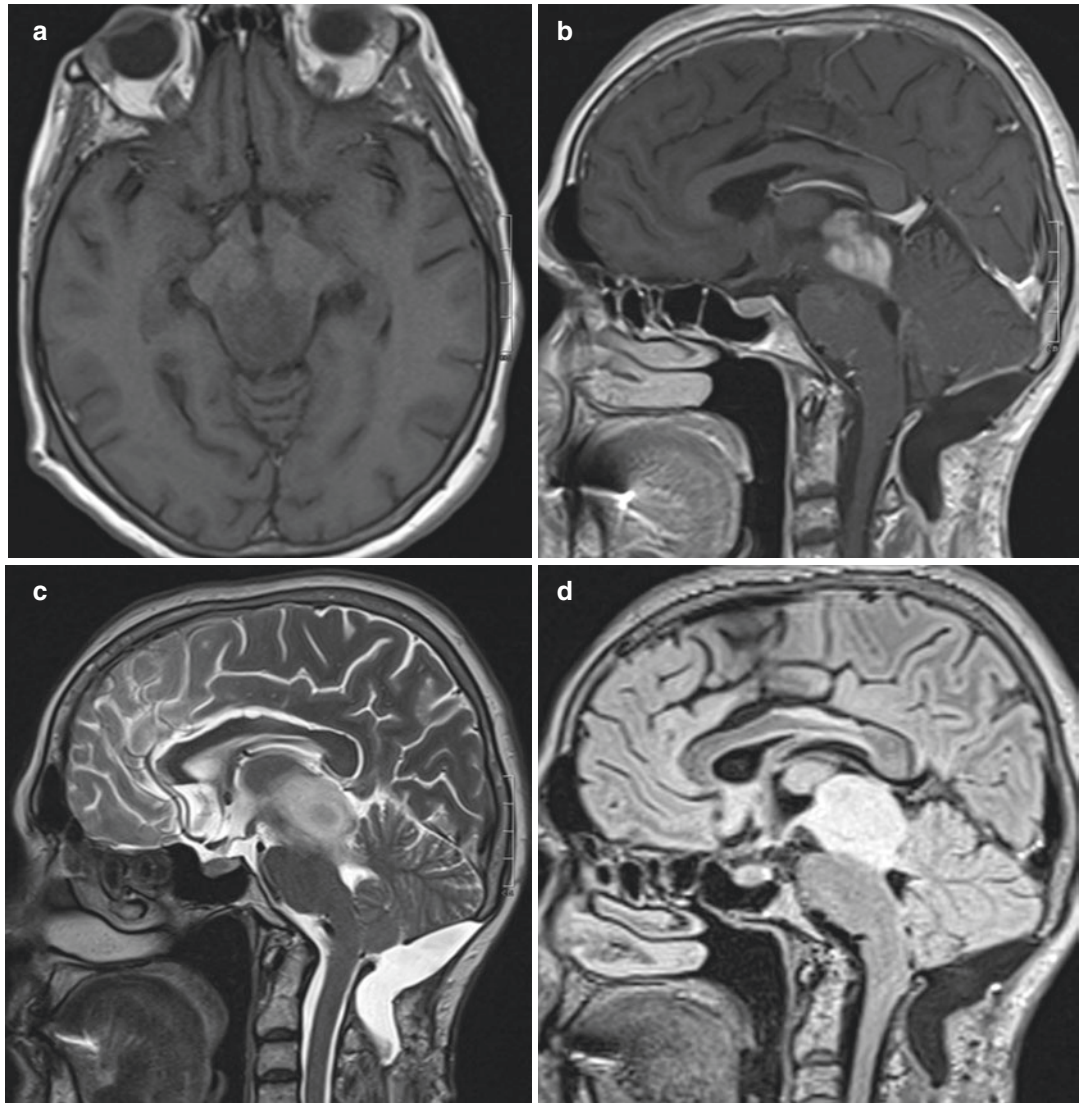

Fig. 5.5 MRI—tumor mass—astrocytoma GII confirmed via histopathology. (**a**) Axial T1 native.; (**b**) Sagittal T1 after administration of contrast medium; (**c**) Sagittal T2; (**d**) FLAIR sagittal. Of note is the absence of hydrocephalus

5.5 Teratoma

Non-germinomatous germ cell tumors are a heterogeneous collection of tumors which include mature teratoma, immature teratoma, teratoma with malignant transformation, yolk sac tumor, embryonal cell carcinoma, and choriocarcinoma [6].

Teratomas represent 4% of germ cell tumors of the CNS and include both the mature and the immature version. They are derived from all three germ cell strata (endoderm, mesoderm, and ectoderm). They are well-circumscribed, multilobulated, often cystic, and, unlike germinomas, they can be associated with malignant degeneration. Teratomas constitute 50% of all congenital neoplasias. Mature teratomas are formed of elements of completely differentiated tissue, while immature teratomas have incompletely differentiated tissues, such as neuroepithelial or stromal tissue, and usually have a high mitotic activity [6].

Immature teratomas tend to have higher recurrence rates than mature teratomas. Ten-year survival rates were reported as 90% for mature teratomas and 70% for immature teratomas [6].

Generally, teratoma is less sensitive to radio- and chemotherapy. Surgical resection is generally the main therapy for both mature teratoma and immature teratoma. The addition of chemotherapy to radiotherapy radiation actually leads to improvements in case of immature teratoma [6].

The pineal region is the most common intracranial location for benign teratoma. A significant proportion of cases occur in young men [3].

Computed tomography seems to reflect the gross pathological features of these tumors. They have densities of −70 to −30 Hounsfield units, especially in fatty parts. Small pieces of bone or teeth can be found; the soft tissue can be isodense with the brain, and it has a contrast uptake [3].

Quite frequently, teratomas do not invade the surrounding tissue. Spontaneous ruptures of the cystic tumors in the subarachnoidian space and in the ventricle have been described [3]. Figure 5.6—Immature teratoma.

Differential diagnosis is performed with a dermoid cyst [3].

After germ cell tumors, pineal parenchymal tumors are most common. They represent less than 20% of pineal region tumors. Pineal parenchymal tumors constitute a morphologic continuum from the benign pineocytomas (WHO grade I) through pineal parenchymal tumors of intermediate differentiation (low and high grade, respectively WHO grade II and III) to pineoblastomas (WHO grade IV) [4].

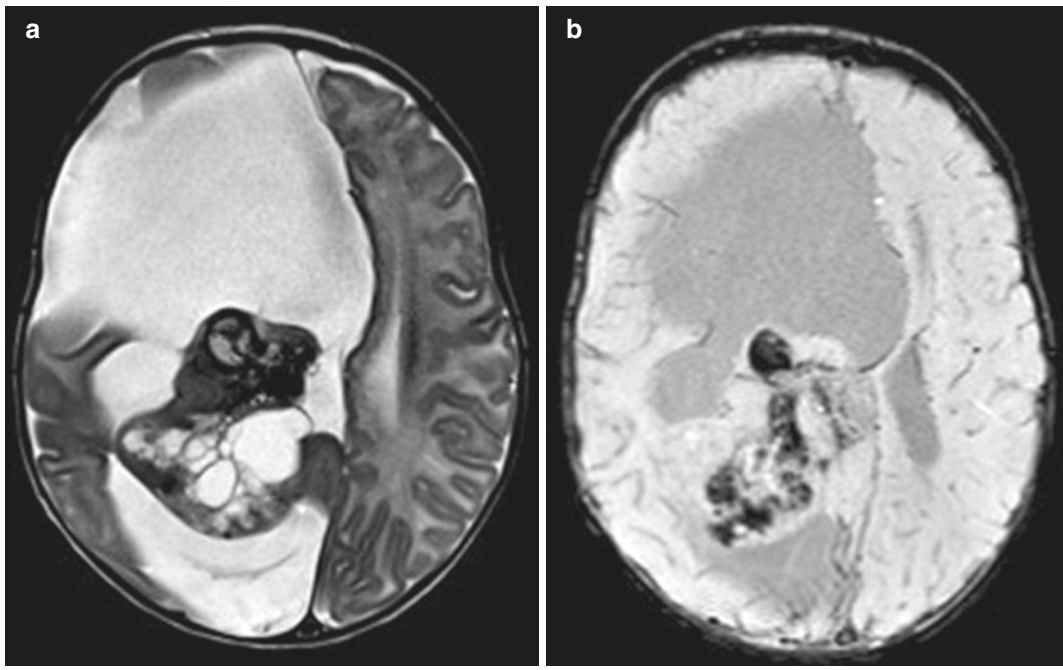

Fig. 5.6 Tumor mass of large size (confirmed via histopathology—immature teratoma) in the right cerebral hemisphere and pineal region with intensely heterogeneous structure, with cystic areas, calcification, and exercising a discreet compressive effect on the contralateral hemisphere. (**a**) Axial T2; (**b**) Axial SWI; (**c**) Axial T1 with contrast; (**d**) Axial T2

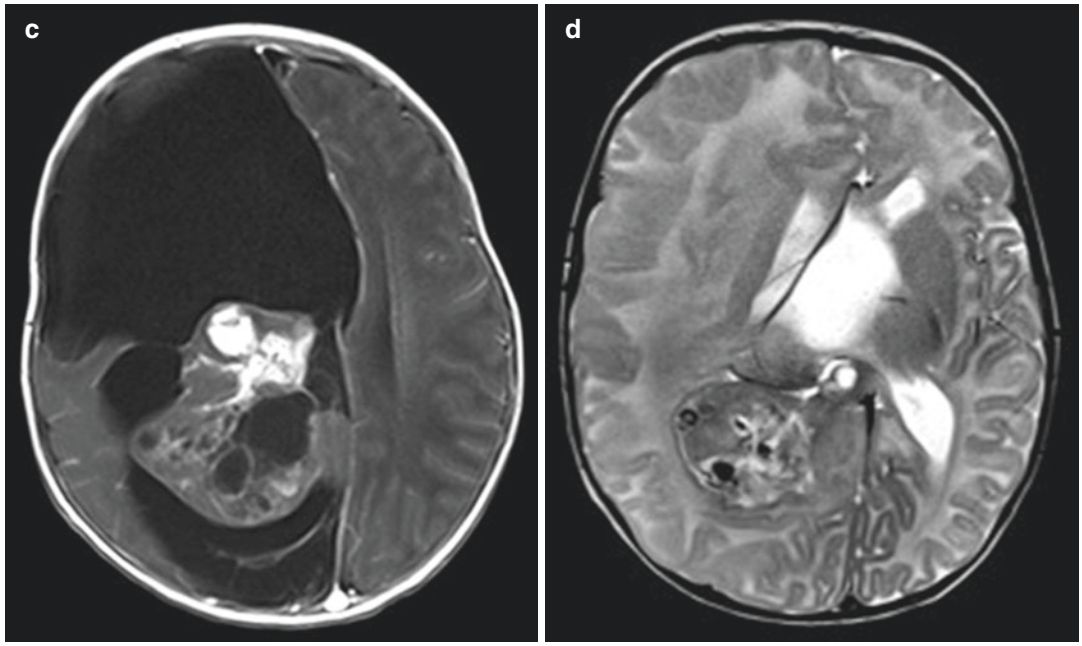

Fig. 5.6 (continued)

5.6 Pineocytomas

The average age of occurrence is 10 years. Generally, a pineocytoma is of size less than 3 cm, and it has a capsule. Rarely it extends in the third ventricle, it can compress the adjacent structures, respectively the aqueduct, leading to hydrocephalus. Occasionally it bleeds [3].

In tomographic investigations, tumors are hypodense with central or peripheral calcifications, with peripheral or nodular contrast activity. In MRI, pineocytomas appear in T1 iso-/hyposignal and in hypersignal in T2 and FLAIR. They have an intense and homogeneous contrast intake [4, 7].

5.7 Pineoblastomas

Pineoblastomas are soft brittle tumors, grey, with hemorrhagic or necrotic areas. They appear more infiltrative, with irregular margins or lobulated form [4]. Pineoblastomas frequently disseminate via CSF pathways and may also metastasize outside the CNS [3].

In CT, pineoblastomas appear as interpose tumors, hyperdense, with calcifications. In MRI, they appear as hypo-/isointense tumors in the T1 sequence and hypo- to hyperintense in T2. In CT and in MRI, they have a moderate contrast uptake with heterogeneous or patchy aspect [4].

In the group "pineal parenchymal tumors of intermediate differentiation," the neuroimaging criteria are not clearly established [4].

5.8 Ependymoma

They are neoplasms with slow growth originating in the ependymal cells. These tumor types have a bimodal distribution on age groups with a peak at 1–5 years, and the other peak around the age of 25–30 years, respectively. The male gender is more affected compared to the female gender [8].

At the MRI examination, ependymomas appear as heterogeneous masses, usually in T1 hypo- or isosignal, with intermediate signal or hypersignal in T2, containing inside cystic areas, calcifications, and blood products. Post-contrast, there is an intratumoral heterogeneous contrast uptake, in the solid areas. In MRI spectroscopy, an increase of choline and a peak of lactate, with decreased levels of NAA can be detected [8] (Fig. 5.7).

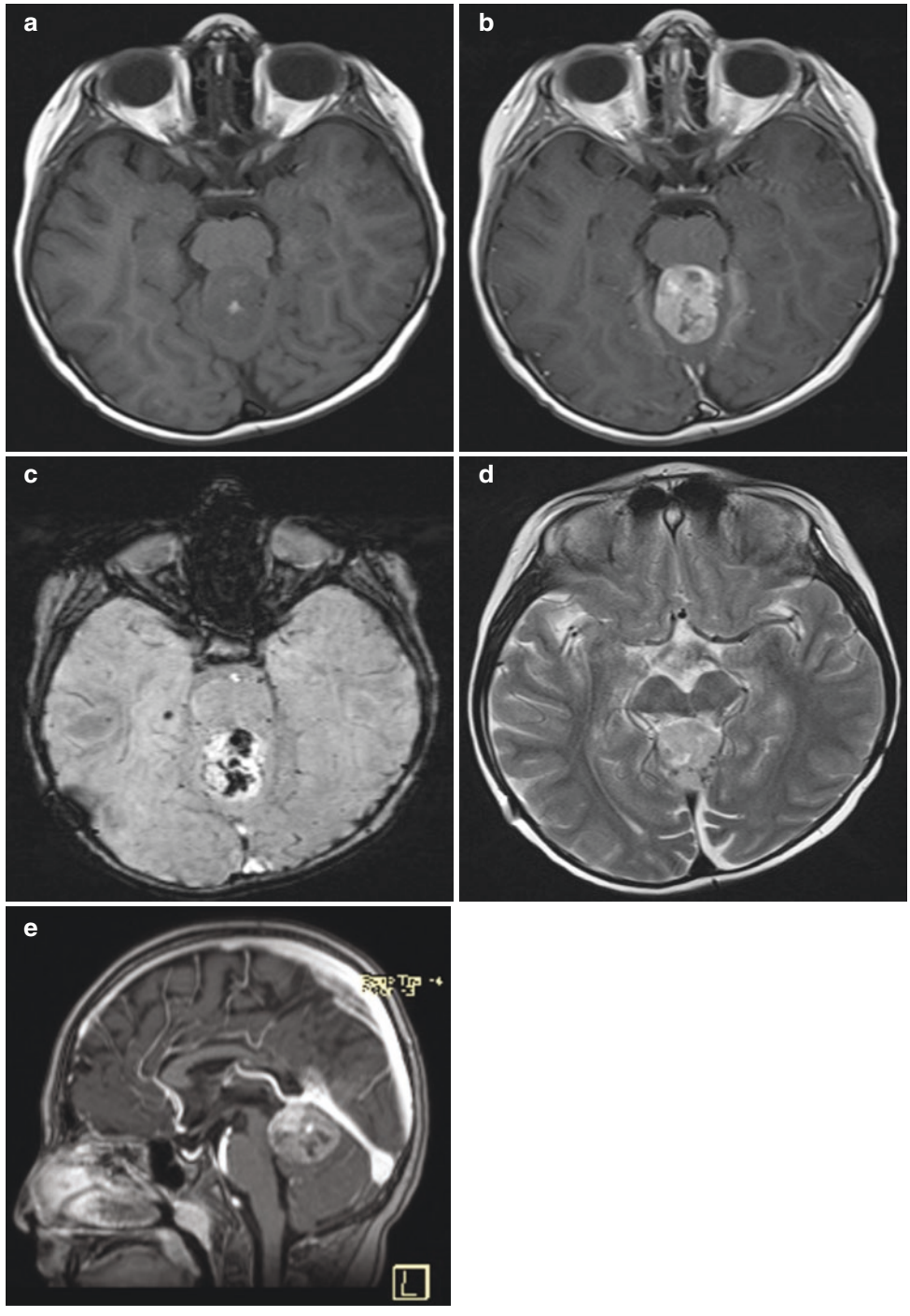

Fig. 5.7 MRI—tumor mass of approximately 3 cm with heterogeneous structure. (**a**) T1 native axial: contains inside bleeding; (**b**) T1 axial post-contrast: non-homogeneously gadolinophilic; (**c**) SWI axial: hemosiderin deposits and calcifications; (**d**) Axial T2: the mass is in hypersignal compared to the grey matter; (**e**) Sagittal T1 post-contrast

5.9 Lipoma

They are rare lesions representing 10% of all intracranial lipomas. They are benign mesenchymal tumors and affect both males and females in equal proportion [8].

At MRI examination, pineal lipomas in the T1 sequence native show a homogeneous hypersignal with disappearance of the fatty signal in the T1 sequence fat-sat (hyposignal in the T1 sequence with fat suppression), and show a hyposignal in T2. Lipomas are non-gadolinophilic on the post-contrast acquisitions [8].

Computed tomography – it reveals homogeneous mass with fatty densities (between −50 and −150 UH), without contrast uptake [8].

5.10 Meningioma

It is a meningothelial tumor originating in the cells of tela choroidea, velum interpositum, and falx tentorium junction. It represents 6–8% of pineal region tumors. MRI investigation shows a hyposignal in T1 and a moderate hypersignal in T2. It has an intense contrast uptake, typical for a meningioma [6, 7].

5.11 Arachnoid Cyst

It is a congenital lesion. Arachnoid cysts and glial cysts of the pineal region share similar CT characteristics. The cyst may be either developmental or acquired secondary to post-inflammatory or post-hemorrhagic adhesions. The cysts may involve the cistern of the velum interpositum, the quadrigeminal plate cistern, or both [3].

5.12 Pineal Cyst

It is common in adult women. As a general imaging characteristic, it is a mass that occurs between the velum interpositum and the internal cerebral veins. The mass is small, less than 1 cm, occasionally over 2 cm, is round-ovoid; in 95% of cases, it does not compress the tectum or the aqueduct; 5% have a compressive effect occasionally. In case of cystic apoplexy, a hydrocephalus occurs [5].

Brain CT reveals a well-delimited mass, homogeneous, cystic, behind the third ventricle, hyperdense compared to the cerebrospinal fluid; 20% show wall calcifications. After the administration of the contrast medium, it has peripheral or nodular uptake. In rare cases of pineal apoplexy, an acute hemorrhage can occur [5].

In MRI investigation, a slice with a 3 mm thickness is recommended. In the T1 sequence, 60% of cysts occur in mild T1 hypersignal compared to the CSF, 40% in T1 isosignal compared to the CSF, and 1–2% heterogeneous signal due to the hemorrhage. In the T2 sequence, we have iso-/mild hypersignal in T2 compared to the CSF. The proton density (PD) sequence shows a hypersignal compared to the SCF. The FLAIR sequence shows a hypersignal depending on the content: proteinaceous, bleeding, or calcifications. The DWI sequence is without signal restriction. At the injection of the contrast medium, 90% have peripheral uptake for masses less than 2 cm, more rarely nodular uptake. In late sequences, cysts can become homogeneous with the contrast medium and they occur as solid tumors. In spectroscopy, we have the absence of neuronal markers [5] (Fig. 5.8).

Pineal cysts can be typical or atypical.

The typical ones are unilocular, well-delimited, round-oval, with homogeneous content, with a thin peripheral wall less than 2 mm. These are different of pineoblastoma, teratoma, and pilocytic astrocytoma [5].

Atypical pineal cysts are multilocular, with a thick wall of over 2 mm, with contrast uptake. They are septated, lobulated, and are not differentiated via imaging of pineoblastoma, germinoma, and teratoma [5].

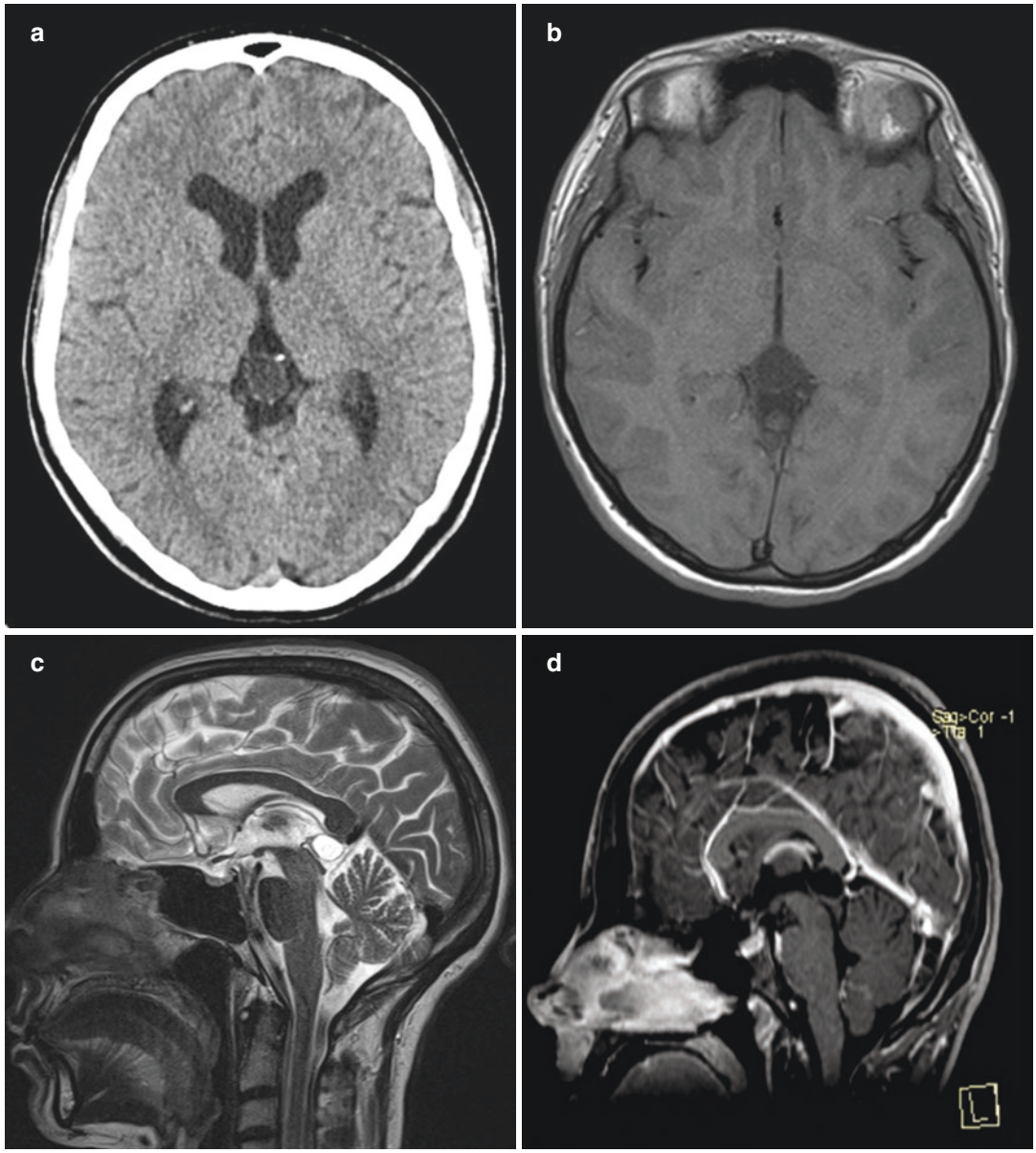

Fig. 5.8 CT—(**a**) oval cystic mass with a net contour in the pineal bed measuring 15/13.5 mm in axial plane native, with thin walls, with left paramedian internal microcalcification. MRI—(**b**) axial T1 native, cystic lesion of 1.5 cm, well-delimited; (**c**) Sagittal T2 with a different signal compared to the CSF; (**d**) Sagittal T1 with contrast

5.13 Other Tumor Types

Choroid plexus papillomas can originate from the choroid plexus. Falx cerebri, tentorium and velum interpositum originate tumors of mesenchymal origin, including the previously mentioned meningioma, hemangiomas, and hemangiopericytomas [6].

5.14 Conclusion

There are tumors originating from the pineal gland tissues and tumors originating from the tissues of the pineal region. Some radiologists reported that they can distinguish the tumors of the two categories. In reality, it is very difficult to distinguish pineal tumors from tumors originating in the pineal region from an imaging point of view.

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6 The Usefulness of Biomarkers for Diagnosis

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6.1 Introduction

Modern cancer classification is aimed at establishing adequate prognosis in order to select the best therapeutic option available and help researchers design clinical trials with comparable criteria, given that an inadequate prediction could cause unnecessary harm to patients or could significantly increase the healthcare costs. Proteomics are very stable in blood and other bodily fluids, even if the major drawback is that their expression patterns do not seem to be very tissue-specific, making them not ideal candidates for non-invasive cancer evaluation. Pineal region cancers are usually diagnosed too late, when the sensitivity and specificity of biomarkers are not acceptable, but in order to improve the therapeutic ratio of these patients, an excellent biomarker should alert the clinician about the possibility of a malignancy even before it can be detected via conventional imaging techniques. The most commonly used potential biomarkers are alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG).

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6.2 Alpha-Fetoprotein

Even if AFP is commonly used all over the world as a serum tumor marker for the screening of hepatocellular carcinoma (HCC), american association for the study of liver diseases (AASLD) strongly recommends against its use as a sole marker for screening, unless ultrasonography is available [1], supporting the acute need for efficient markers. In patients diagnosed with colorectal or liver cancers, adequate prognoses are important for an effective therapy because biochemical markers such as carcinoembryonic antigen (CEA) or CA-19-9 are very non-specific. For the pineal gland region, AFP was reported to be a potential useful biomarker. AFP is a fetal protein which is part of an albuminoid gene family together with albumin, vitamin D-binding protein, and alpha-albumin (also known as afamin in humans) [2]. The levels of serum AFP were found to correlate with several defects and malformations of the fetus and negative pregnancy outcomes in general [3]. In addition, high concentrations of AFP were linked to the presence of neoplastic processes in both children and adults [4, 5].

Structurally, AFP is a glycoprotein with a molecular mass of 68–72 kDa [6]. The molecule is composed of three domains which form a single-chain polypeptide, and which are dictated by various disulfide-bridging patterns [7, 8]. The result is a U-shaped molecule [9, 10]. This cysteine-bridged structure is characteristic of the

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whole albuminoid family [11]. The genes of the four members of the albuminoid family are located on chromosome 4, in the 4q11–q22 region [12].

As albumin, AFP also binds and transports different molecules, such as retinoids, bilirubin, steroids, fatty acids, dyes, phytoestrogens, flavonoids, dioxin, and several drugs [13]. AFP is generally known to be a fetal protein that promotes growth processes. Normal concentrations of AFP during pregnancy are associated with successful pregnancies [14]. However, this protein also stimulates growth in tumors at certain levels, in an autocrine fashion [15, 16]. On the other hand, in certain situations, after going through a conformational change, AFP is also able to inhibit growth and differentiation in cells [17, 18]. Thus, AFP is considered to be a dual cell-proliferation regulator, and the main mechanisms through which it exhibits its effects are apoptosis, cytoplasmic signaling, and G-coupled signal transduction [19]. In adults, high levels of serum AFP (>5 ng/mL) have been identified, especially in malignant processes. However, some benign hepatic disorders, such as cirrhosis or viral hepatitis, have also been linked to increased serum AFP [20]. Various tumors are associated with higher levels of AFP, such as hepatocellular carcinoma, testicular germ cell tumors, ovary yolk sac tumors, stomach and pancreatic tumors, and pineal/pituitary tumors [19].

AFP seems to be produced by tumor cells, but not secreted. After synthesis, it remains inside the cell, bound to an intracytoplasmic protein [21]. In addition, circulating AFP is uptaken by cancer cells through receptor-mediated endocytosis [22]. The ability to internalize AFP is an attribute of cells which are undergoing differentiation. By contrast, undifferentiated or fully differentiated cells do not have this ability. Malignant cells express membrane-surface receptors for AFP, showing that these cells exert properties typical for immature cells [19]. Thus, AFP is a potential target for anti-cancer drug therapies, as binding certain molecules to it might help in incorporating them into neoplastic cells. When referring to pineal gland tumors, AFP is particularly increased in both serum and cerebrospinal fluid (CSF), in several histological types. These include embryonal carcinomas, immature teratomas, and endodermal sinus tumors [23, 24].

Studies show that in pineal gland tumors, serum AFP levels can range between 29 and 27,100 ng/mL, whereas CSF levels range between 26 and 15,700 ng/mL. However, it has been shown that serum levels <1000 ng/mL do not influence prognosis and outcome. On the other hand, a measured serum or CSF AFP >1000 ng/mL seems to have a negative impact on 5-year progression-free survival. This group of patients are considered to have a significantly worse outcome and therefore need a different approach when it comes to treatment options and cycles of chemotherapy [25].

6.3 Human Chorionic Gonadotropin

Besides AFP, human chorionic gonadotropin (hCG) is another potential biomarker used for the monitoring of pineal gland tumors. Structurally, hCG is formed from two subunits: alpha and beta. The alpha subunit is common between glycopeptides used in signaling, while the beta subunit offers different structures and functions between these molecules. The crystal structure of hCG shows not only that the two subunits have a similar topology, but also that the heterodimer formed is stabilized by the beta subunit wrapping around the alpha subunit, a feature essential for receptor binding [26, 27].

The term hCG is used to depict four distinct entities: hCG, hyperglycosylated hCG, pituitary, hCG and beta hCG. hCG is produced by the syncytiotrophoblast cells, while hyperglycosylated hCG is mainly produced by the cytotrophoblast cells. These two aforementioned forms explain why it is commonly known that hCG is present in higher levels in the case of a pregnancy. Pituitary hCG, as the name suggests, is produced by the pituitary gland and acts as a mimic for the luteinizing hormone (LH). Beta hCG represents the free beta chain of hCG and is frequently produced in malignancies, specifically in choriocarcinomas, germinomas, and embryonal

carcinomas [28]. Structurally, beta hCG is formed from 145 amino acids and presents 6 homologs clustered in the subband 19q13.3. These homologous genes are depicted as CGB1, CGB2, CBG3, CBG5, CBG7, and CBG8 and differ by three amino acids situated in positions 2, 4, and 117. Because of these differences, they have been categorized as type 1 proteins, represented by CGB7, and type 2 proteins, represented by CGB3, CGB5, and CGB8 [29].

Functionally, hCG is known to manifest its effects through the TGF beta pathway and through protein kinases, especially protein kinase A and protein kinase C. These effects have been used as an explanation for the effects of hCG on uterine wall angiogenesis and pregnancy immunomodulation. What can be observed is that the aforementioned effects overlap with some of the hallmarks of cancer, specifically angiogenesis induction and immune escape [30–32]. Considering that beta hCG has been shown to promote malignant cell proliferation and inhibit apoptosis, other two hallmarks of cancer can be added to the latter ones: sustained proliferative signaling and resisting cell death. This can be also predicted from the structure of beta hCG, which presents a cysteine knot, a motif generally shown to occur in growth factors [26]. Thus, activation of the aforementioned hallmarks of cancer can explain, in part, the results from clinical studies, where it has been shown that higher levels of beta hCG associate with a reserved prognosis [33–35]. A good question to be asked is: "Is beta hCG produced by the malignant cells or by the stroma?"

The answer has repeatedly been shown that beta hCG is produced by the malignant cells and either secreted or present on their surface [36–40]. Nagasawa et al. have shown that there is an association between beta hCG expressed on the surface of malignant cells and the level of beta hCG in serum or cerebrospinal fluid (CSF) [41]. Thus, these results show that malignant cells secrete and express beta hCG on their surface, which leads to survival advantage.

When focusing on pineal gland lesions, beta hCG is generally secreted by choriocarcinomas, germinomas, and embryonal carcinomas. In the case of choriocarcinomas, beta hCG levels are known to be consistently elevated. This is not always true for germinomas or embryonal carcinomas, where beta hCG is not consistently elevated, but, when elevated, is associated with a worse prognosis. Thus, beta hCG can be used as a biomarker for the presence of a choriocarcinoma, but, because of inconsistencies, it is better suited as a prognostic marker in the case of germinomas and embryonal carcinomas. Because of the easier access, serum is generally used as the source assessing biomarker levels, although it has been shown that assessing CSF for beta hCG offers a higher sensitivity for diagnosis. This can be explained through the central nervous system (CNS) localization of the aforementioned malignancies [24], [42–50]. It has to be noted that biomarkers complement clinical examination, imaging, and pathology, being useful for a differential diagnosis, and they should not be used to replace more classical approaches. As mentioned before, because of the CNS localization of these tumors, it can be expected that CSF levels of beta hCG are higher compared to serum levels. This is generally the case, but, in situations where there exists a discordance in this logic, the clinician should expect the disease to have metastasized. If this is the case, surgical intervention presents no benefit [24].

6.4 Conclusion

The main biomarkers identified in pineal gland tumors are AFP and beta HCG. Their levels are usually increased in both serum and CSF. Higher levels of these markers can give a clue regarding the type of tumor, as each of them is encountered in different histological types. Also, their levels can be used as a predictive factor for the extent of the disease and also for the approach that should be taken. However, these markers should not be used for diagnosis alone, but should be complementary to the other methods such as imaging and pathology.

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7 Surgical Adjuvants for the Pineal Region Approach

Vincenzo Paternó

7.1 Introduction

The pineal gland is an endocrine intracranial gland, located centrally and posteriorly, which lies below the splenium of the corpus callous, above and medial to the thalamus, considering the dorsal wall of the posterior rim of the third ventricle.

The gland represents the main structure of the "epithalamus," which is able to synthesize the amine hormone, melatonin, from the paraneuronal cells called pinealocytes. The pinealocyte cells are grouped into cords and separated by connective tissue while being supported by glial cells.

Different groups of lesions may involve the pineal region arising from the pineal parenchymal cells or from the glial cells of the midbrain and/or of the medial walls of the thalamus. Most of these lesions are tumors, which are mixed in nature, simultaneously containing benign as well as malignant elements.

Despite the enormous advances in high definition of neuroradiological images, as well as the accuracy of several tumor markers, the histological nature of the lesion is, in most of the cases, an obviously crucial point for their further medical treatment, as the preoperative diagnostic tests are insufficient to determine the nature of the tumor.

Considering that the pineal gland is outside the blood-brain barrier, there is a good response to the oncological treatment for the malignant tumors due to better access for chemo- and radiotherapy.

Nevertheless, one-third of pineal lesions are benign, for which surgery alone is usually curative. Different routes to the pineal region have been developed during the last decade, from supratentorial to infratentorial approaches. An experienced neurosurgeon should be able to analyze the advantages and disadvantages of those approaches according to each single clinical case. The knowledge of the conventional and surgical anatomy of the pineal region as well as the surrounded structures is mandatory in order to increase the rate of successes and steady decrease of mortality and the morbidity.

7.2 Pathology

Different pathological lesions may involve the pineal region, from benign cystic lesions, which are normal variants of the pineal gland, consisting of cystic structures surrounded by normal pineal parenchymal tissue, to benign tumors like meningioma, teratomas, hemangioblastoma, and choroid plexus papilloma, or to malign tumors like germ cell, astrocytoma, chemodectoma,

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adenocarcinoma, teratocarcinoma, and metastatic tumor.

Additionally, a variety of vascular lesions may occur, including cavernous malformations, arteriovenous malformations, and vein of Galen malformations.

7.3 Clinical Features

Most of the pineal region tumors are asymptomatic for quite a long period. In the majority of the cases, a diagnosis of a lesion in the pineal gland region is an occasional finding. Lesions in the pineal region normally become symptomatic through different mechanisms: first of all, the increase of intracranial pressure, and second the direct or indirect cerebellar or brain stem compression [1].

(a) The increase of the intracranial pressure consequently leads to an obstruction of the third ventricle outflow at the level of the sylvan aqueducts, which become responsible for the hydrocephalus state with symptomatic headache, nausea, and vomiting in the beginning phase. In case of no acute surgical treatment of the hydrocephalus, you may face papill-edema, important cognitive deficits, and coma.
(b) Direct and indirect brain (cerebellar and brain stem) compression and dislocation lead to motor and sensory dysfunction, ataxia, and dysmetria as well as Parinaud's syndrome with vertical gaze palsy and nystagmus. This syndrome is well known and caused by compression of the tectal region of the midbrain in the majority of the cases by tumors of the pineal region and tectal plate.

Pressure at the level of the inferior colliculi may be responsible for the loss of downward gaze and convergence.

The possibility to develop diabetes insipidus is a frequent occurrence with all types of pineal tumors.

7.4 Imaging Studies

The technological advances in the neuroradiological field, with the almost standard diagnostic examination nowadays through a high-field MRI, have revealed an enormous number of patients who are suffering from pineal region lesions. In most of the cases, the patient appears to be asymptomatic.

Radiographically, the pineal cyst can mimic a pilocytic astrocytoma, even in case of contrast medium examination. Tumors can be also distinguished by their increased tendency to be progressive and symptomatic.

Neuro-radiological follow-up with high-field brain MRI and angio-MRI images provide useful details for right diagnosis as well as correct interpretation, which are fundamental for the presurgical planning.

The decision-making process for the surgical approach should be made considering the tumor size and extension (cranio-caudally) as well as the angle of the straight sinus and tentorium [2].

The correct study of the Galenic venous draining group and the superficial bridging veins of the cerebellum may guide in choosing the correct surgical approach, but unfortunately, very often they cannot be recognized on the brain MRI images. In many cases, brain angio-MRI sequences should be performed, and in selected cases, a cerebral angiography may be helpful for pre-operative planning and intra-operative surgical strategy [3].

Last but not least, the presence of a tendency to an obstructive hydrocephalus should always be evaluated in order to plan for an initial external ventricular drainage or a third ventriculostomy followed by microsurgical tumor removal.

7.5 Laboratory Diagnosis

All the pineal region tumor patients should undergo, preoperatively, a MIRATE laboratory biochemical tumor markers control in the serum and cerebrospinal fluid (CSF). The alpha-fetoprotein (AFP)

and beta-human chorionic gonadotropin (ß HCG) are markers of germ cell malignancy.

In case of high levels of those markers, histological verification is unnecessary as surgery does not improve the outcome.

An immediate oncological treatment with chemotherapy and radiotherapy is, at this point, mandatory.

Those markers are also helpful in already oncologically treated patients with high-grade pineal tumor in order to follow any possibility of tumor recurrence.

Nevertheless, the under-range level of those markers does not guarantee the absence of malignity due to the fact that malignant germ cell tumors could not be always ruled out.

Lumbar puncture and cerebrospinal fluid cytology rarely indicate the tumor type preoperatively.

Unfortunately, laboratory diagnosis will still not achieve a complete autonomy.

7.6 Conventional and Surgical Anatomy

Any surgeon should take into consideration the difference between so-called conventional anatomy and surgical anatomy. Conventional anatomy is the anatomy of the human body in normal health condition, while surgical anatomy takes into consideration the relationship between the conventional anatomy and the pathological findings.

Conventionally, the pineal gland is a midline structure, part of the epithalamus; it develops from the roof of the diencephalon, posteriorly positioned between the two cerebral hemispheres in the center of the brain and located behind the third ventricle attached by a stalk to the posterior wall. Its name is derived from its shape, which is similar to that of a pine cone.

Essentially, it is an extra-axial gland; therefore, the lesions involving, directly or indirectly, the gland are resectable through a surgical plane established between the adjacent structures.

Ventrally, the pineal gland is strongly anatomically related to the posterior border of the third ventricle by a stalk, being primarily part of the epithalamus, including the habenula and the habenular commissure and the stria medullaris. In a sagittal section, we may differentiate an antero-superior relation, with thalamus and the habenular commissure, and an antero-inferior relation, with the cerebral aqueduct of Sylvius, the posterior commissure and the cerebral peduncle.

Inferiorly, the quadrigeminal plate, also known as the tectal plate or tectum, is strongly related to the pineal gland through the superior colliculi.

Superiorly, there is a closer anatomical relationship between the pineal gland and the splenium of corpus callosum through the closed space called velum interpositum, in which arise the internal cerebral veins. Among the two internal cerebral veins, in some cases the basal vein of Rosenthal on both sides, the pre-central cerebellar vein, and superficial vermian vein drain directly into the vein of Galen, others into the torcular Herophili [4].

The arterial blood supply originates from the posterior cerebral artery via posterior choroidal branches and the venous drainage is mainly to the basal veins of Rosenthal and the great cerebral vein.

Surgically, due to the fact that most of the tumors arise from and are attached to the undersurface of the velum interpositum, which includes the choroid plexus, deep venous system, and choroidal arteries, the blood supply comes from within the velum interpositum, mainly through the posterior medial and lateral choroidal arteries. In rare instances, the internal cerebral veins are ventral to the tumor. More frequently, however, the vein of Galen, the internal cerebral veins, Rosenthal's vein, and the precentral cerebellar vein surround or cap the periphery of these tumors [5].

The quadrigemina plate may give rise to an exophytic astrocytoma or be infiltrated by the more malignant tumor of the pineal region, encompassing the aqueduct in the course of tumor growth.

7.7 Surgical Approaches

The deep location of pineal region lesions and their relationships with important neuro-vascular anatomical structures have resulted, before the advent of microsurgical techniques, in significant operative morbidity and mortality rates [6, 7]. These unsuccessful surgical results and the improving of microsurgical skills prompted neurosurgeons to develop safer approaches for removing pineal region lesions.

There are several approaches suitable for reaching the pineal region and the most common are the infratentorial supracerebellar, occipital transtentorial, posterior transcallosal, and posterior subtemporal routes [2, 8].

In the last 50 years, all around the world, all these approaches have been studied and improved for daily use. Some of these approaches have been even used together in a so-called combined supra/infratentorial approach in case of extended and large pineal region lesions [9, 10].

After a careful evaluation of our series in the last 10 years and reviewing the entire international literature, there is no doubt that the "infratentorial supracerebellar approach" is the most commonly used approach nowadays, even reminding that the infratentorial supracerebellar approach was introduced the first time by Krause before the development of microsurgical techniques. Even at that time it was described as an excellent approach allowing easy orientation and providing a good visibility of important veins [11–13].

Recently, the neuroendoscopic approach has been added as a microsurgical endoscopy-assisted surgical approach [2].

7.8 Anesthesia, Patient Positioning, and Monitoring

There is no doubt that the development of anesthetic and intensive care techniques has led to an improvement in surgical results.

The sitting or the Concorde position can be both used in this approach in order to get a fallen cerebellum inferiorly and for a wider surgical view.

It is well known that the sitting position entails the risk of air embolism, which can be reduced by using a semi-sitting position and also by a good experience of your dedicated anesthetists. The enormous advantage of this position is evident in minimizing the venous congestion and a having a blood-free operating field.

Nowadays, unfortunately not all the anesthetists, all around the world, use the semi-sitting position, therefore prone position "Concorde" could be an alternative. Nevertheless, this position is contraindicated in case of high-vascularized lesions due to the amount of blood accumulation in the surgical field [14].

The implementation of intraoperative electrophysiological neuromonitoring in neurosurgery has demonstrated a great degree of recent success in clinical outcomes. The somatosensory-evoked potential (SEP) and the motor-evoked potential (MEP) are routinely used for intraoperative neuro-functional evaluation.

7.9 Clinical Cases

In the last 4 years, from January 2015 to October 2019, we operated 32 cases of pathological lesions involving the entire pineal region.

Starting from benign cystic lesion, going through benign tumor and malignant tumor, ending with vascular lesion, we can schematically distinguish: arachnoidal cystic lesion (1 case), pilocytic astrocytoma (3 cases), germinoma (5 cases), low-grade glioma (2 cases), ganglioglioma (2 cases), high-grade glioma (3 cases), pineoblastoma (2 cases), and cavernous malformation (14 cases).

Benign cystic lesions are nearly always asymptomatic and generally do not require treatment unless they are causing aqueductal obstruction [15].

In the majority of the cases, we have chosen and used a pure supracerebellar infratentorial approach. In extreme selected cases, we used a combined supracerebellar infratentorial/occipital

transtentorial approach; once a huge tumor was extended extremely caudally, in order to reach the tumor via two different trajectories, or, occasionally, we have chosen a combination between the infratentorial and telovelar approach through the fourth ventricle, but only in tumors with very low extreme caudal extension of the lesion. In one case, we approached the pathology through a posterior subtemporal route.

7.10 Surgical Considerations

The pure "supracerebellar infratentorial approach" remains, in our opinion, the first choice and the most common access route to the pineal region [16].

We normally use a semi-sitting position which helps us in gaining better access to the region. A very steep tentorium required correct positioning of the patient's head with sufficient ventral flexion.

A long midline incision is used, extending from the occipital region, 2–3 cm above the level of the external occipital protuberance, down into the second vertebral body spinal process. A wide bilateral suboccipital craniotomy is performed including the superior margin of the transverse sinus on both sides. The opening of the foramen magnum is not necessary. The upper board of the craniotomy is prepared with four holes in order to fix the elevated and retracted opened dura with the inferior board of the transversus sinus. This maneuver allows us to add more space between the tentorium and the superior cerebellar surface. To avoid excessive downward retraction of the superior cerebellar vermis, we used the paraculminal route either on one side or bilaterally. The side of the monolateral approach depends on the presence of thick bridging veins of the tectorial surface of the cerebellum. In case of small caliber of veins, which are significantly obstructing the access view to the pineal region, it is possible to transect one of these while single hemispheric bridging veins should be preserved during the entire surgical procedure. In most of the cases, they may be easily inadvertently damaged, with potentially serious consequences, during the maneuver of introducing the micro instrument while the deep microscope focuses on the pineal region [4].

In order to avoid this risk, we recommend, before starting with the exposure of the pineal region tumor, a U-shaped piece of Gelfoam, which is used to enforce the venous wall at the entry point into the tentorium and covered with fibrin glue.

The cerebellum hemispheres gradually descended after incising the thick arachnoid membrane around the Galenic venous draining group, releasing the cerebrospinal fluid from the dorsal mesencephalic, quadrigeminal, or ambient cisterns, offering a wide exposure of the vein of Galen and tributaries. Their anatomical relationship to the underlying tumor should be clearly visualized. It is crucial to avoid any mechanical damage to the tributaries of the vein of Galen [17].

Pineal cell tumors have a strong tendency to seed, in the majority of the cases, in the third ventricle and infundibulum; therefore, long microinstruments are mandatory. In case of firm consistency of the tumor, the use of Micro-Cavitron would be recommended for a primary tumor debulking procedure.

In those cases where the tumors had encased part of or the entire Galenic venous draining group, the tumor debulking procedure should be done without the use of Micro-Cavitron, starting in the center or lower part of the tumor in order to avoid any kind of conflict with these veins.

The second step would be the dissection of the deep-seated veins away from the tumor. Unfortunately in those cases where the tumor extends behind the Galenic veins draining group, leaving a small piece of tumor could be an option, avoiding the high risk of damage to the tributary veins. Nevertheless, one should keep in mind that a subtotal removal increases the risk of postoperative bleeding; therefore, a meticulous hemostasis is crucial for minimizing the risk of bleeding from the residual tumor and achieving a successful good post-operative course. Despite these cases, a complete tumor removal is achieved in the majority of the cases.

One of the most critical maneuvers in the pineal region tumor removal is the approach to

the inferior tumor portion. In case of lower extension and adhesion to the dorsal surface of the midbrain, a combined approach with occipital transtentorial route could be necessary in order to avoid an excess of cerebellum retraction, which can be the cause of a post-operative cerebellar swelling. Therefore, in case of a tight posterior fossa, this can be highly dangerous for an extremely fast brainstem compression [18, 19].

7.11 Complications of Surgery

In the semi-sitting position, there is a well-known risk of air embolism, which can be handled by an expert anesthesiologist.

One of the uneventful early postoperative courses is the "acute cerebellar swelling" which may require an emergency decompressive craniectomy. Apparently, the most frequent pathomechanism is a combination of venous obstruction, sometimes combined with post-operative local hemorrhage [18].

7.12 Controversial Issues

- In case of obstruction, the patient should be treated either by endoscopic ventriculostomy, if possible, or by placement of an external ventricular drain or insertion of a permanent ventriculoperitoneal shunt. The decision-making process depends, first of all, on the acuity of the obstruction as well as on the pathological behavior of the lesion and the size of the tumor.
- The use of a cerebellar self-retaining retractor during surgery may significantly increase the risk of local ischemia leading to cerebellar contusion and venous congestion, or even be responsible for the rupture of superficial bridging veins. In almost all cases, there is no need of using a brain retractor as the cerebellum almost always descends by gravity after releasing, as first step of the intradural procedure, the cerebrospinal fluid from the quadrigeminal or ambient cistern.
- Surgical biopsy versus oncological treatment has always been a crucial discussion point. Nowadays, due to the fact that either cytological examinations of alpha-fetoprotein and beta-hCG in serum and CFS or neuro-radiological images are able to give us a reliable diagnosis, there is no doubt that in the majority of the cases, a histological diagnosis is mandatory. Additionally, the wide pathological variations that may occur in the pineal region do not help in obtaining a clearer diagnosis than through a surgical procedure. The final histological result will guide in the further management of the patient. Most of germ cell tumors do not need to be operated on, as they are most sensitive to radiation.
- Surgical biopsy versus aggressive tumor removal is a controversial point for many lesions around the pineal region. The reason why a first surgical biopsy was in the past the major management tendency in many neurosurgical departments is that the deep-seated anatomical location as well as the high risk of intra- and post-operative complications was considered easier for the hand of less experienced neurosurgeons. Nowadays, we know that an aggressive surgical treatment can be performed by many neurosurgeons all over the world.
- Low-grade gliomas remain an important discussion topic in neurosurgery. It has been demonstrated in the literature that early surgery in brain supratentorial low grade represents a better prognosis for the patient. Of course an asymptomatic small tumor around the pineal region should not be operated on immediately, especially in those cases with no significant increase in size over time.
- The utility of conventional radiotherapy versus Gamma Knife as multimodality treatment in conjunction with or without surgery should always be discussed in tumor board meeting for a high-grade tumor as well as for subtotal removal of low-grade glioma [20–22].

7.13 Conclusions

The wide histopathological types and subtypes of lesions involving the pineal gland region compelled us to get a clear diagnosis in order to optimize the management decision even in case of germinoma, where the oncological rate of success is extremely high [LO AC].

The natural history of pineal cysts is often a static anatomic variant that does not always require treatment. Benign tumors should be always surgically treated and complete tumor removal should be achieved whenever possible. Subtotal removal should be taken into consideration only in case of extreme adhesion of the tumor to the tributaries of the vein of Galen. Post-operative conservative follow-up should be taken first into consideration before deciding on post-surgical conventional or stereotactic radiotherapy.

High-grade malignant tumors should be surgically treated, while the patients are certainly benefited from a combined management with surgical/adjuvant oncological therapy.

The infratentorial supracerebellar approach as a single method is enough for almost all the lesions involving the pineal gland region.

Originally, this type of surgery used to have a high rate of morbidity and mortality, which is nowadays minimized due to the expertise and experience of surgeons. High-level experience in microsurgical techniques is required in order to achieve a tumor removal with preservation of the venous flow of the Galenic draining system, as well as the preservation of the thick bridging veins of the tentorial surface of the cerebellum.

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Part II

Surgical Approaches for Pineal Region Lesions

8 A Supracerebellar-Infratentorial Approach in Pineal Region Lesions

Vladimir Beneš and Martin Majovsky

8.1 Introduction and General Remarks

Microsurgical supracerebellar-infratentorial (SCIT) approach is one of the essential neurosurgical approaches. Traditionally, SCIT has been credited to Fedor Krause, who described it in 1911 [1]; however, Sir Victor Horsley is most likely the first to use this approach [2]. With the rapid progress of neurosurgery in the 1930s and 1940s, many other approaches to the pineal region have been popularized, including the lateral transcortical-transventricular, occipital transtentorial, and subtemporal approach [3]. The SCIT was reintroduced by Stein in 1971 who used a surgical microscope with the patient in the sitting position [4].

With the advent of neuroendoscopy, endoscope-assisted [5–7] and fully endoscopic techniques [8–11] of SCIT were introduced. Fully endoscopic techniques are usually performed through the lateral and third ventricle and the target is most often cyst fenestration and mass lesion biopsy.

The SCIT is a very versatile approach and, in addition to the pineal region, it addresses several other pathologies, including those in the superior aspect of the cerebellum, tectum, lateral mesencephalon, posterior third ventricle, upper fourth ventricle, anterior rectus sinus, posterior thalamus, upper cerebellopontine angle (CPA), and petroclival area up to the posterior clinoid process [12]. Also accessible is the cavum Meckeli [13]. Tentorial resection enables access to the medial and inferior aspects of the temporal lobe [13].

In general, six directions are available (lesion examples in brackets):

(a) Midline
   1. Anterior—to the pineal gland and posterior third ventricle (posterior third ventricle ependymoma) (Figs. 8.1, 8.2, and 8.3).
   2. Anterior–superior—to the vein of Galen complex (posterior thalamic pilocytic astrocytoma) (Fig. 8.4).
   3. Anterior–inferior—to the upper part of the fourth ventricle (fourth ventricle cavernoma) (Fig. 8.5).

(b) Lateral
   1. Lateral–anterior—petrous bone apex, superior clivus, and tentorial edge (petroclival meningioma) (Fig. 8.6).
   2. Lateral—superior (upper tentorial edge or upper petrous ridge meningioma) (Fig. 8.7).
   3. Lateral–inferior—clivus, cerebellopontine angle (chordoma, fifth nerve schwannoma).

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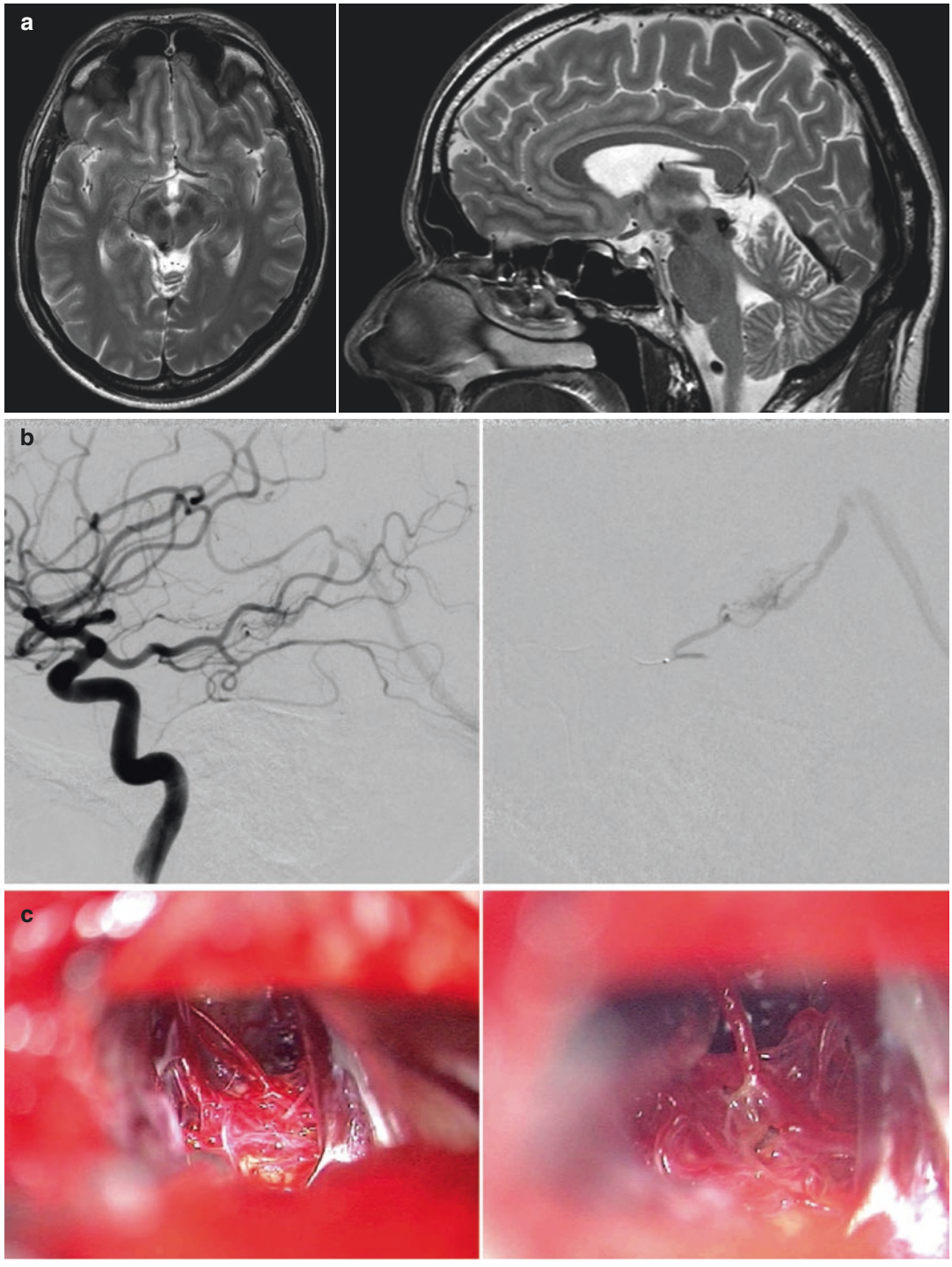

Fig. 8.1 Mesencephalic AVMs resected using SCIT. (**a**) Preoperative MRI; (**b**) preoperative DSA; (**c**) intraoperative image; (**d**) postoperative DSA showing complete removal of AVMs

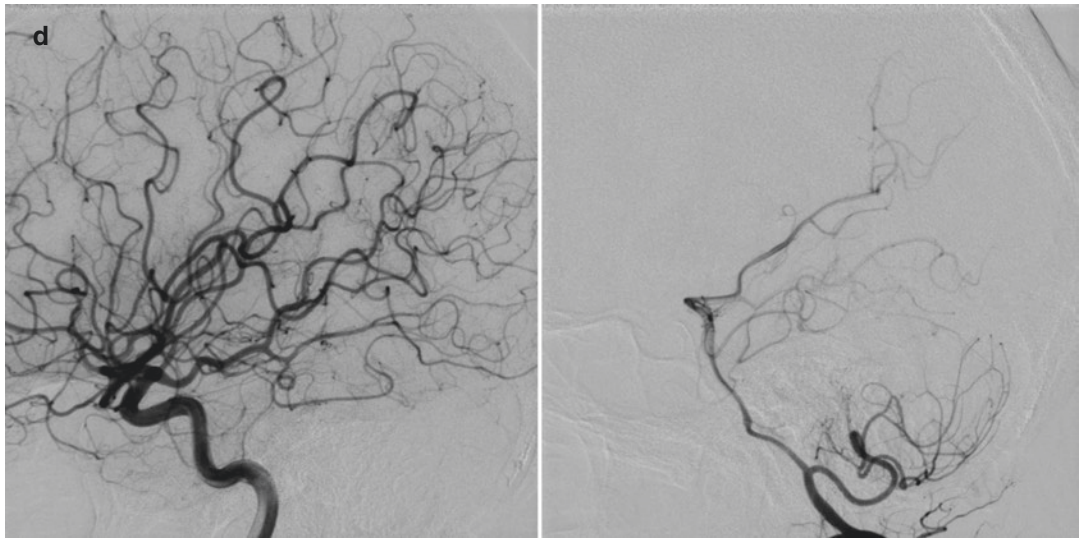

Fig. 8.1 (continued)

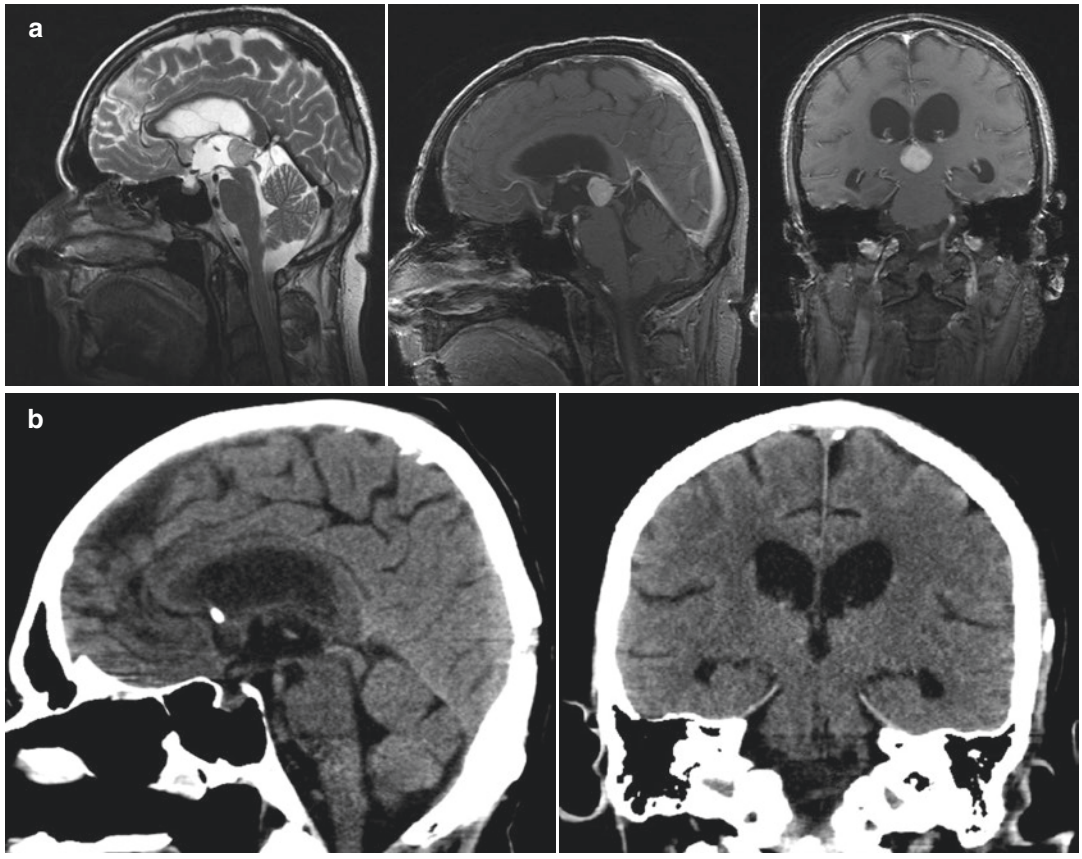

Fig. 8.2 Pineocytoma GII in the posterior third ventricle resected by SCIT. (**a**) Preoperative MRI. Note that the lesion is located below the deep cerebral veins. (**b**) Postoperative CT showing radical resection. Note that the ventricular catheter of the VP shunt was implanted because of hydrocephalus

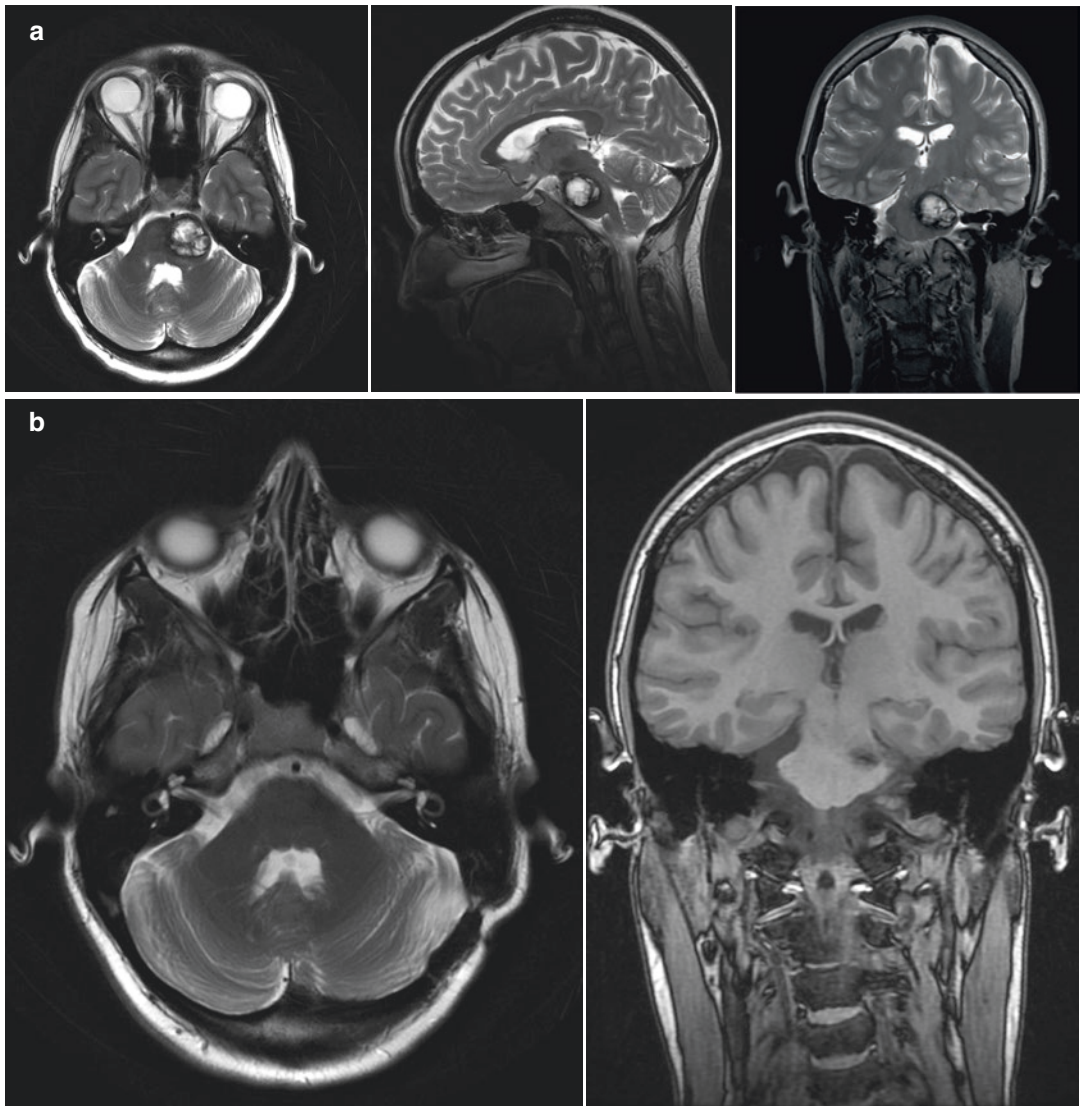

Fig. 8.3 Brainstem cavernoma resected with SCIT. (**a**) Preoperative MRI. Note that the cavernoma is reaching the surface of the brainstem near the tentorium (arrow). (**b**) Postoperative MRI showing complete resection of the lesion

Technically, an extreme lateral SCIT or lateral SCIT (described below) [14] approach does not differ from a modified retrosigmoid approach [15]. The lowermost accessible point in SCIT is the internal auditory meatus, which can be reached from above. We recommend craniotomy that is individually tailored to the patient and lesion, regardless of traditional approaches, as such approaches may overlap (Table 8.1).

Magnetic resonance imaging (MRI) is often insufficient to provide a comprehensive diagnosis and hence biopsy is recommended for further histological evaluation. Before surgery, all patients with a tumor in the pineal region should be examined for the presence of hCG (human chorionic gonadotropin) and AFP (alpha-fetoprotein) in serum and cerebrospinal fluid (CSF), which may help in the diagnosis of germi-

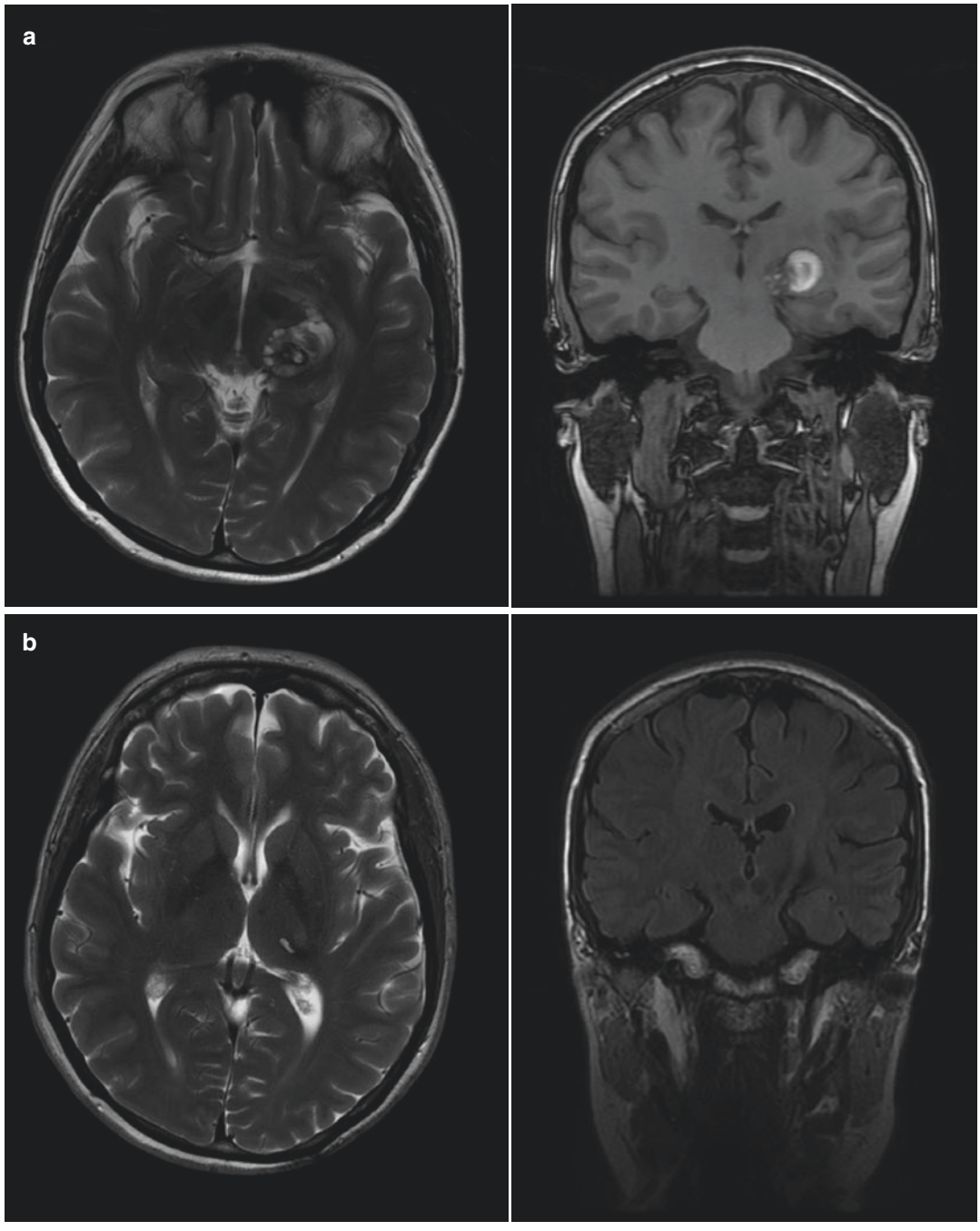

Fig. 8.4 Cavernoma of the posterior thalamus resected by SCIT. (a) Preoperative MRI; (b) postoperative MRI illustrating complete resection of the lesion

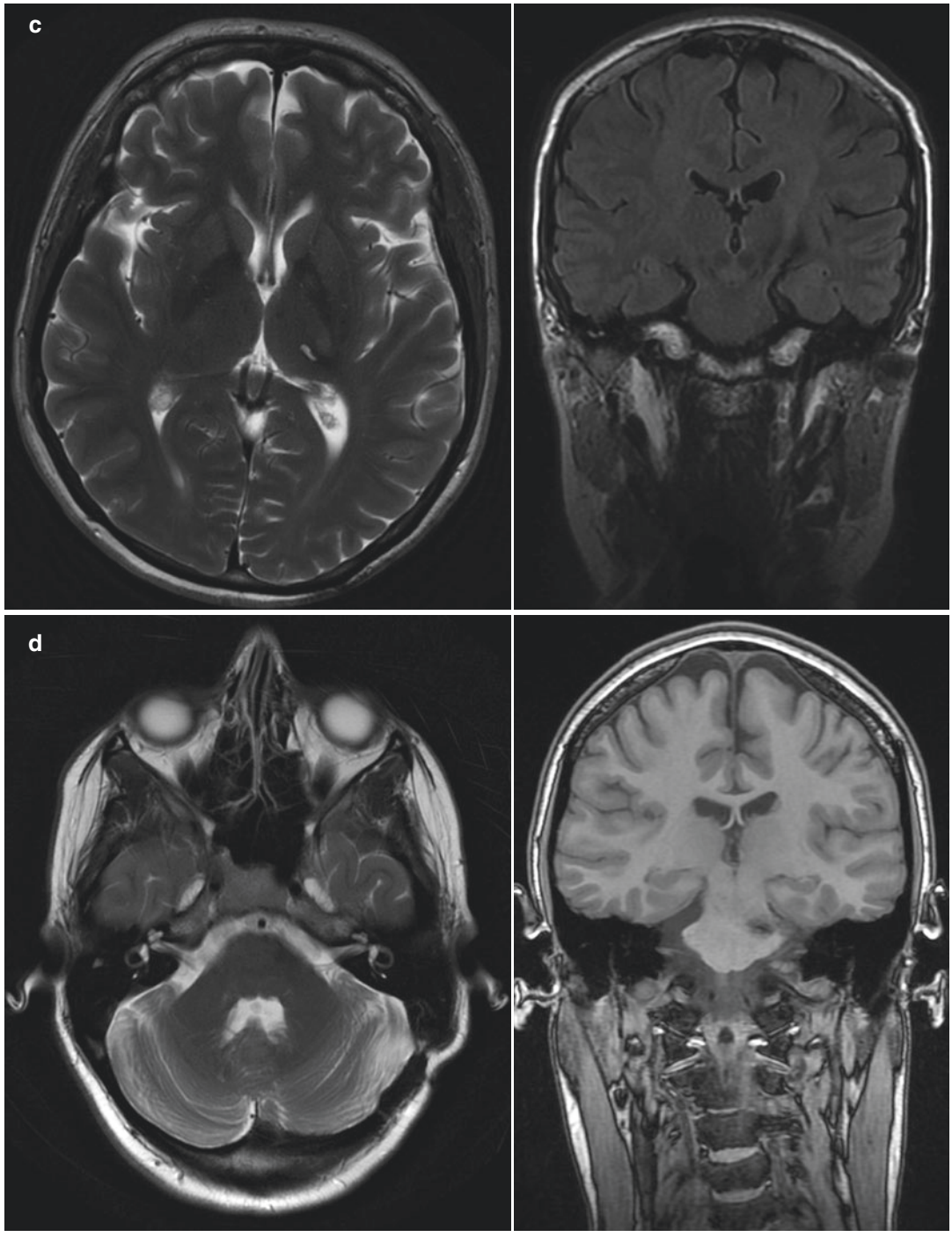

Fig. 8.4 (continued)

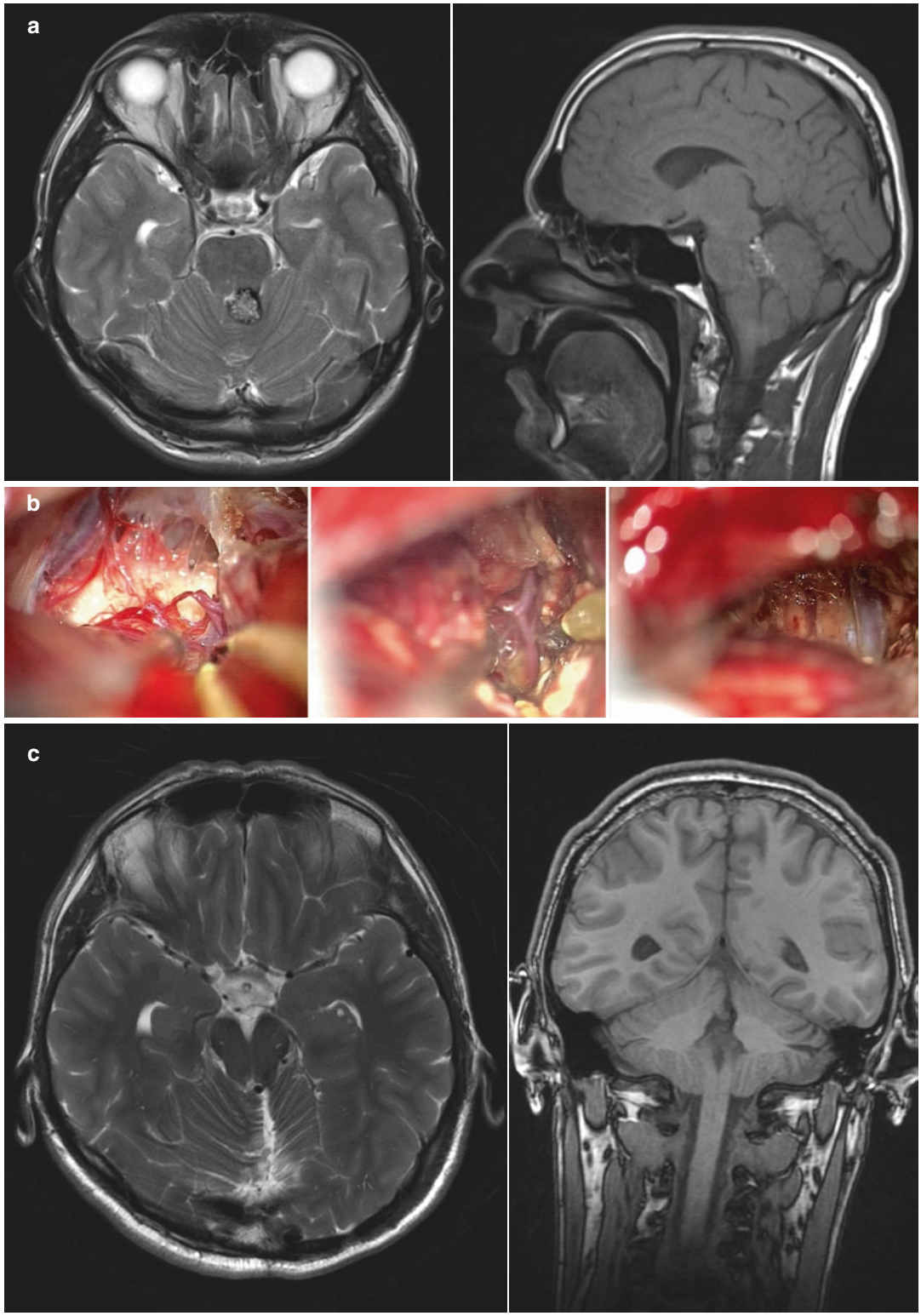

Fig. 8.5 Cavernoma of the fourth ventricle resected by SCIT using a paravermian incision. (**a**) Preoperative MRI; (**b**) intraoperative image; (**c**) postoperative MRI showing complete resection of the lesion. Note the paravermian incision

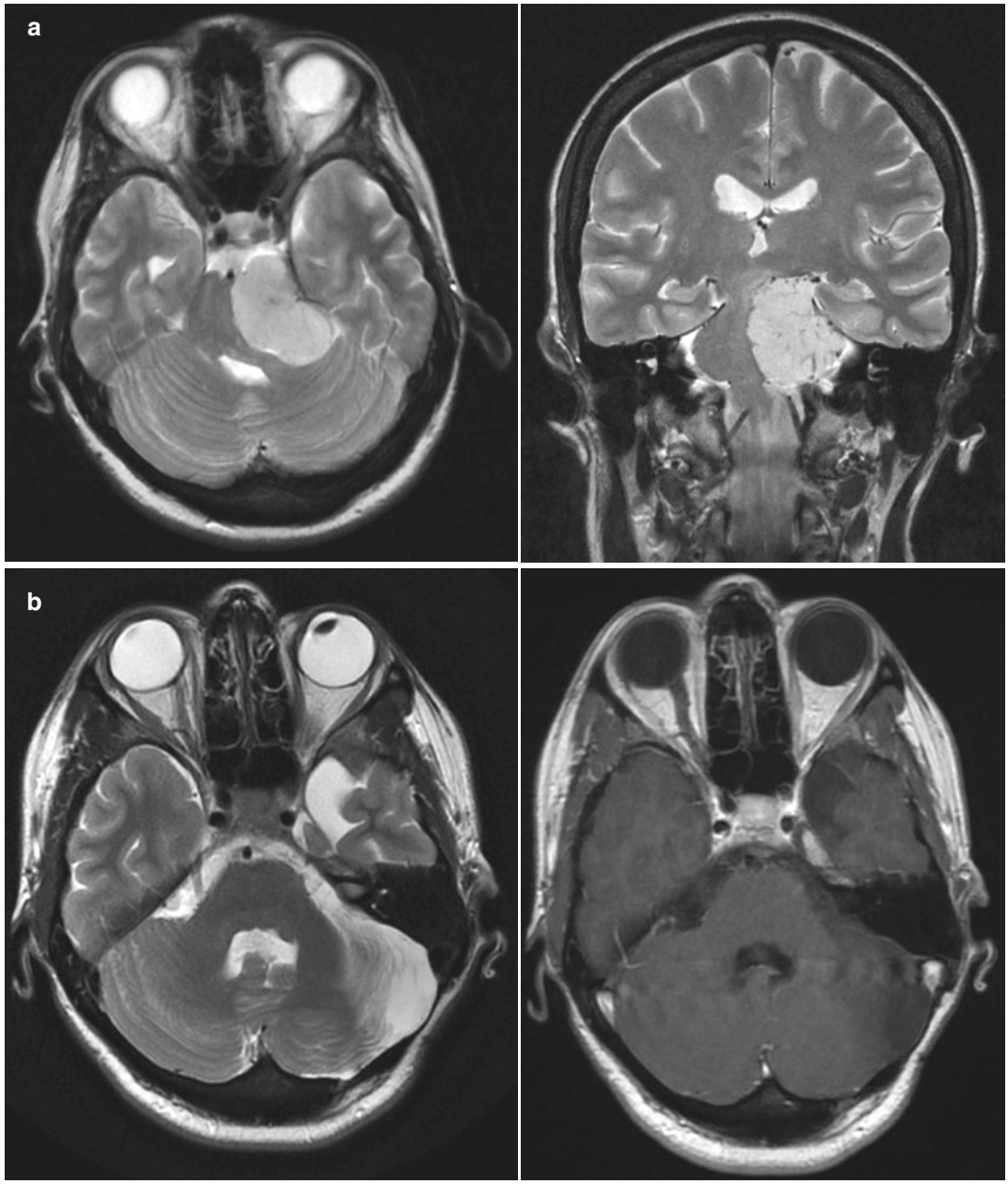

Fig. 8.6 Petroclival meningioma resected with SCIT. (**a**) Preoperative MRI; (**b**) postoperative MRI showing complete resection of the lesion

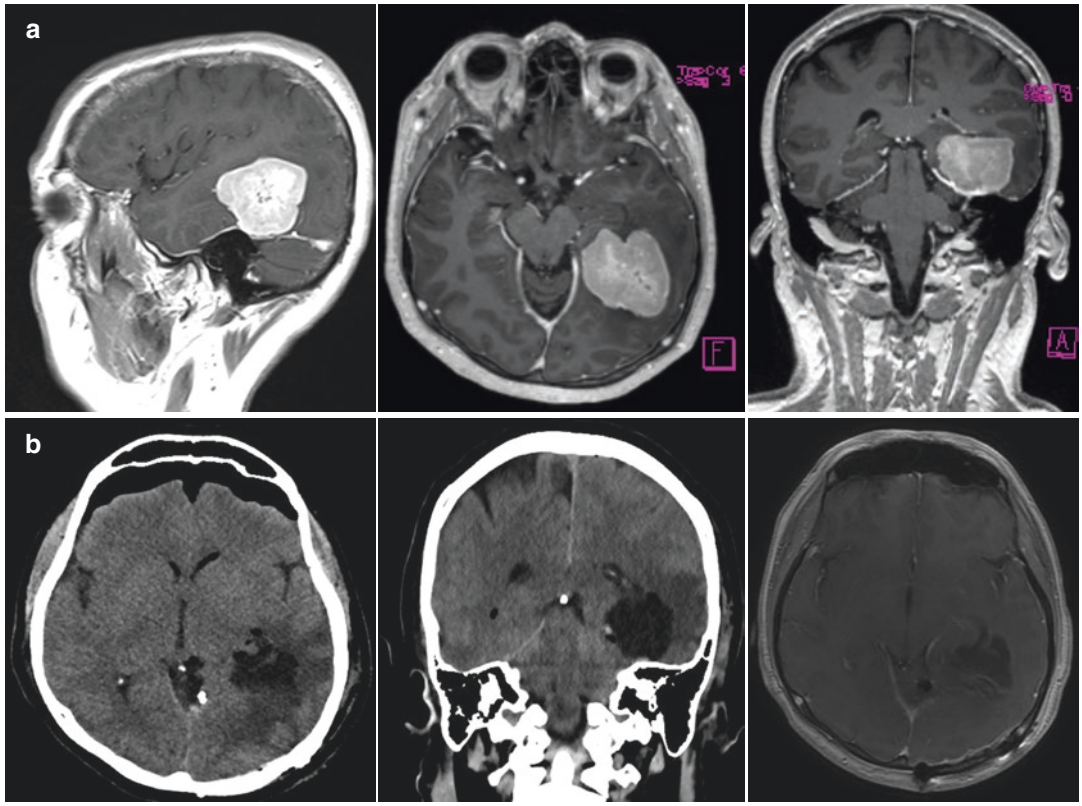

Fig. 8.7 Supratentorial meningiomas of the tentorium. (**a**) Preoperative MRI; (**b**) postoperative CT and MRI showing complete resection of the lesion

Table 8.1 Structures accessible using the SCIT approach

• Cp angle
• Pineal
• Upper fourth ventricle
• Posterior third ventricle
• Posterior thalamus
• Posterior clinoid
• Above the meatus

nomas even without surgery. When germinoma is ruled out, radical resection of the lesion is the surgical goal. In some patients, a wait-and-see policy is a reasonable option given that, for example, some pineal cysts regress and some tumors do not grow.

For patients with preoperative hydrocephalus, external ventricular drainage or endoscopic third ventriculostomy could be performed as a first step before tumor resection. At the beginning of surgery, a lumbar drain is introduced to allow for CSF drainage, which affords the cerebellum some relaxation and opens space between the cerebellum and tentorium.

8.2 Positioning of the Patient

A sitting position is preferred to a prone position when using SCIT (Fig. 8.8). Still, a main drawback of the sitting position is the risk of venous air embolism, which might be a potentially fatal complication. Preoperative echocardiography is performed to rule out patent foramen ovale, which represents a contraindication for the sitting position [16, 17]. Placement of a central venous catheter (CVC) before surgery is mandatory. The patient's legs should be kept at approximately the same level as the heart to balance central venous pressure.

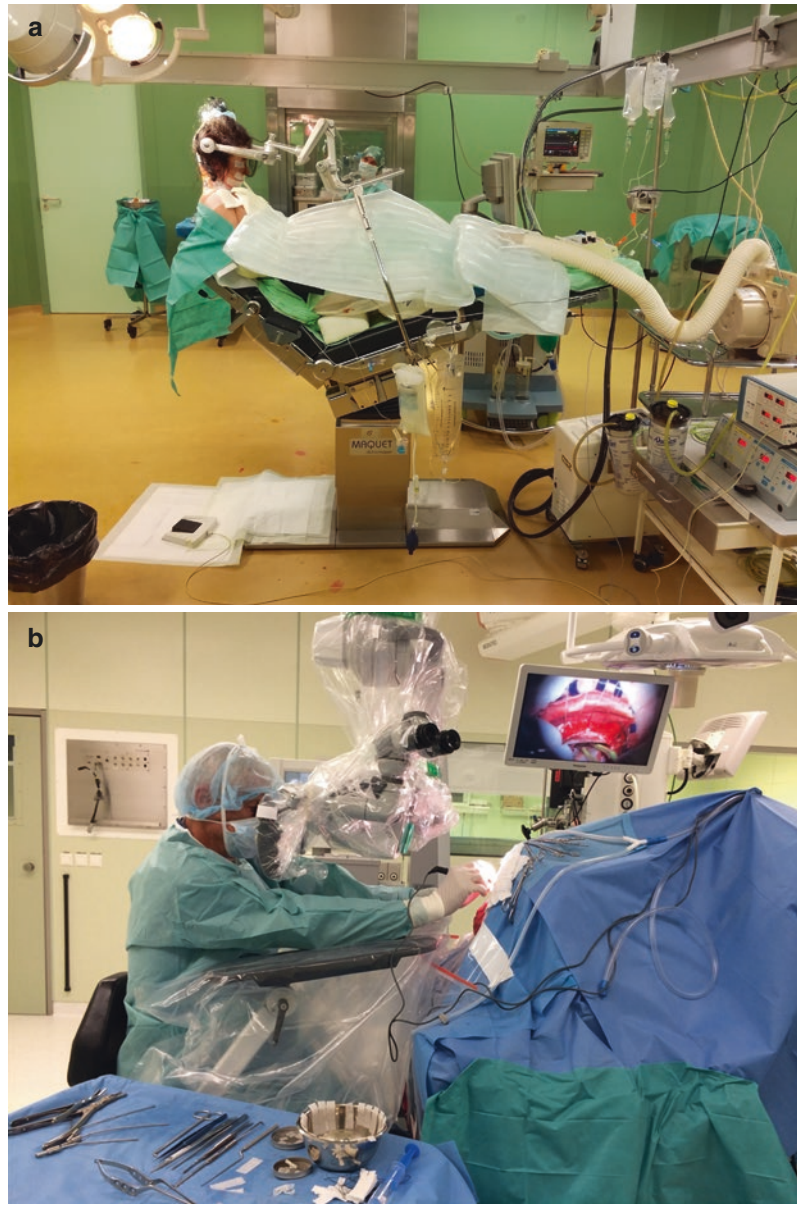

Fig. 8.8 Sitting position. (**a**) Semi-sitting position. Note that the knees of the patient are at approximately heart level. (**b**) Surgeon's position during the SCIT procedure

During surgery, air embolism should be monitored using transthoracal or transesophageal echocardiography [17, 18]. The patient's head is placed in a Mayfield head holder and flexed enough to make the tentorium parallel to the floor but still allowing two fingerbreadths between the chin and sternum to avoid jugular vein compression. The most comfortable position is then achieved by surgical table inclination or rotation, or both.

8.3 Skin Incision

For midline SCIT (mSCIT), a linear skin incision is extended from approximately 2 cm above the inion to the level of C2. Muscles are split with monopolar electrocautery in the midline along the ligamentum nuchae to minimize muscle damage. When the procedure is properly performed, only minor or minimal bleeding occurs. Bleeding

from emissary veins is controlled using bone wax. For paramedian and lateral SCIT (see below), the vertical skin incision runs approximately in the middle between the occipital protuberance and external auditory meatus.

8.4 Three Types of Supracerebellar-Infratentorial Craniotomy and Target Areas

Basically, three types of SCIT craniotomy are available: midline SCIT, paramedian SCIT (pSCIT), and lateral SCIT (lSCIT).

8.4.1 Midline Supracerebellar-Infratentorial Approach

Burr holes are placed above and below the transverse sinuses, with the upper ones lateral to the superior sagittal sinus, and the dura is carefully detached. A craniotome is then used to connect the burr holes to create bone flap. After removing the bone flap, the torcular Herophili and both transverse sinuses are exposed in the superior aspect of craniotomy. Caudally, craniotomy extends some 3–4 cm below the transverse sinuses. Epidural bleeding is stopped by using a gelatin sponge and routine dural tack-up sutures. mSCIT is reserved for complex midline lesions.

8.4.2 Paramedian Supracerebellar-Infratentorial Approach

A craniotomy is situated on one side lateral to the torcular Herophili and approximately 4 cm of transverse sinus is exposed (Fig. 8.9). This approach allows for the protection of a dominant transverse sinus and to spare bridging veins from the opposite side of the cerebellar hemisphere and

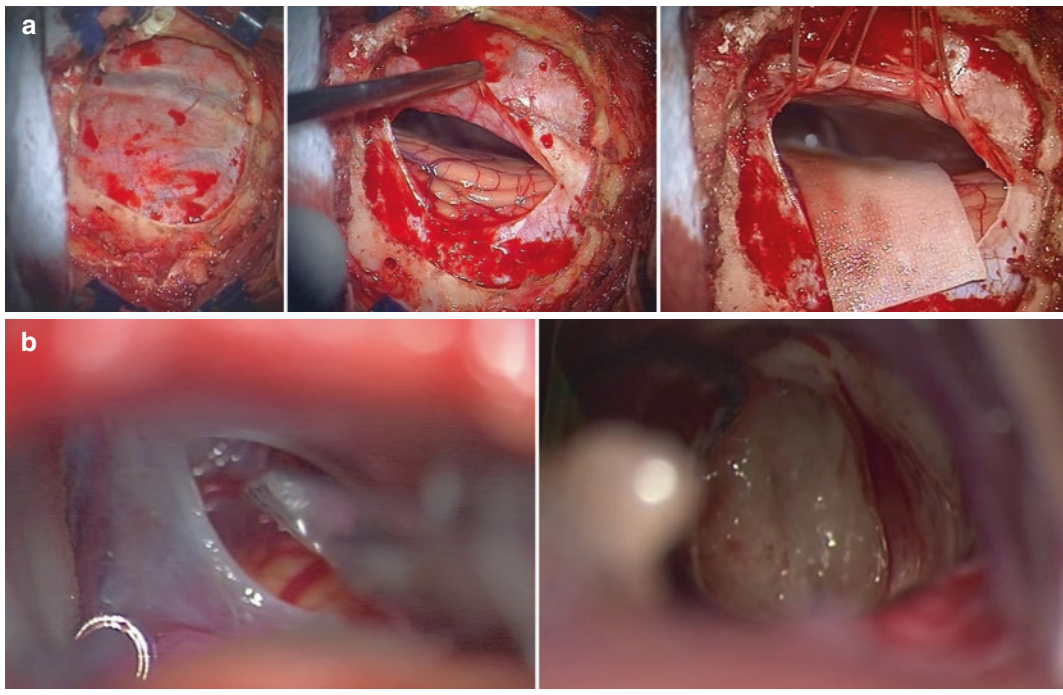

Fig. 8.9 SCIT approach. (**a**) Extent of craniotomy and durotomy. Note the tack-up sutures pulling the tentorium upwards to improve the line of sight. (**b**) Dissection of arachnoid layer in the pineal region and pineal cyst; (**c**) deep structures in the pineal region

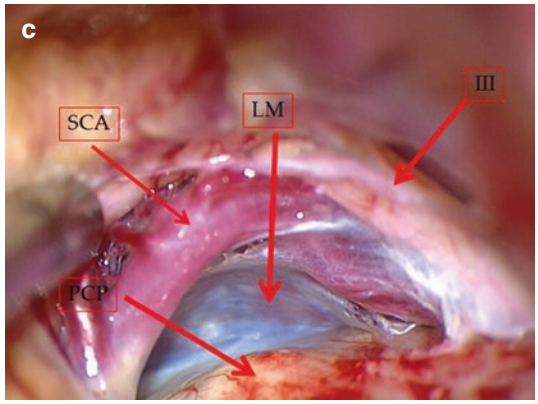

Fig. 8.9 (continued)

posterior ascending veins from the vermis. pSCIT is suitable for simple pineal tumors and dorsal mesencephalic and posterior thalamic lesions.

8.4.3 Lateral Supracerebellar-Infratentorial Approach

Craniotomy exposes the lateral portion of the transverse sinus and the upper segment of the sigmoid sinus. This approach is used for the upper CPA: the superior petrous sinus, petroclival area, and lateral mesencephalic lesions. Inferiorly, the limit of lSCIT is the internal acoustic meatus. If necessary, cavum Meckeli can be entered and the petrous apex resected.

Over the past 10 years, the midline approach has virtually been abandoned in favor of lateral approaches.

For all types of craniotomy, close cooperation with an anesthesiologist is crucial throughout the entire procedure. Moreover, if an air embolism occurs (detected by a decrease in end-tidal CO_2), the neurosurgeon needs to react promptly. Steps to be taken include wound irrigation with saline, waxing of bone edges, lowering of the patient's head, compression of the jugular veins, and aspiration of air from the right atrium by way of a CVC [19].

8.5 Dural Opening

Starting laterally, dura is usually incised in a standard curvilinear fashion. The occipital sinus, if exposed, is ligated, then cut, and the resulting dural flap is reflected upwards, exposing the superior aspect of the cerebellum. The occipital sinus is sometimes large and bleeding is prevented by a combination of metal clips, suturing of the dura, and hemostatic materials. For lesions in the petroclival area and CPA, an additional short dural incision in the caudolateral direction can be performed to expose the upper lateral aspect of the cerebellum. In all approaches, the dura is opened 15–20 mm below the transverse sinuses to prevent prolapse of the cerebellum.

8.6 Approach to the Pineal Region

Bridging veins often involve blocking the surgical corridor in the midline, and most authors agree that some of these might be sacrificed [20]. On the other hand, cases of cerebellar venous infarction and swelling have been described after occlusion of a single bridging vein [21]. Thickened arachnoid overlying the pineal gland is sharply dissected from a lateral to a medial direction and deep cerebral veins are exposed (Fig. 8.9). The lesion is identified and dealt with accordingly. Extreme care must be taken in preserving the integrity of the vessels. Superior cerebellar arteries and numerous perforators are encountered on the arterial side. On the venous side, the following veins are exposed: basal veins of Rosenthal, internal cerebral veins, tectal and pineal veins, internal occipital veins, and the vein of Galen. It is crucial to protect and preserve all these veins [22]. The upper vermian veins can be sacrificed, except for the most anterior one, namely the cerebellomesencephalic vein. In unilateral approaches, usually, one ascending vein from the upper cerebellar hemisphere entering the tentorium is present. The vein is coagulated and cut. The petrosal vein is preserved laterally, except for cases of meningiomas in which the superior petrous sinus represents the tumor origin.

The upper limit of SCIT is the basal veins while the lowermost limit is the inferior colliculi. The fourth nerve origin is generally below the line of vision; however, the nerve is well exposed

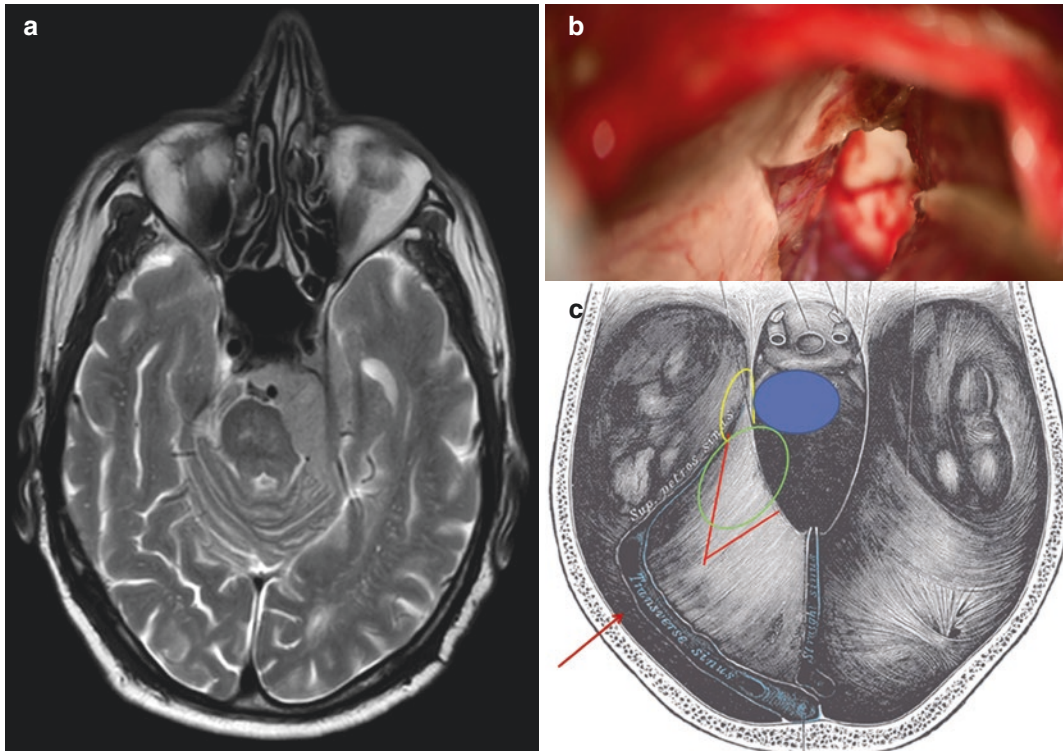

Fig. 8.10 Petroclival meningioma with SCIT using tentorial incision. (**a**) Preoperative MRI; (**b**) intraoperative image showing extent of tentorial resection; (**c**) schematic depiction of steps taken during petroclival meningioma resection: (1) resection of the tumor in the CPA, (2) tentorial incision, (3) resection of the tumor part located infratemporally and (4) resection of the mediobasal parts of the tumor

on the lateral aspect of the mesencephalon. The upper portion of the fourth ventricle can easily be approached by making a short incision in the paravermian area.

The potential of all three approaches may be enhanced by tentorium resection, which is typically performed unilaterally (Fig. 8.10). The first tentorial incision runs anterior to the transverse sinus, turns anteriorly parallel to the rectus sinus, and parallel to the superior petrosal sinus, ending posterior to the fourth nerve entry into the cavernous sinus. However, ordinarily, only a limited tentorial resection is sufficient—a V-shaped incision with the apex approximately in the middle of the tentorium and the anterolateral extension tailored according to the target lesion. Tentorium resection allows attacking much more superiorly localized brainstem lesions and resection of the lesions located in the basal medial parts of the occipital and temporal lobes [13]. Laterally, it allows an approach as far as the Liliequist membrane and posterior clinoid area. In petroclival meningiomas, the tentorium opening permits very early control of the brainstem at the upper medial limit of the tumor. The most extensive resections are done in the anteriorly located rectus sinus meningiomas, where the rectus sinus is occluded. The tentorium is resected on both sides along the rectus sinus and then the falx is cut anterior to the lesion and down to the inferior sagittal sinus. It is important to note that reversed flow in the inferior sagittal sinus may be the only deep venous drainage. When incising the tentorium, extreme care should be directed toward frequent venous lakes within the tentorium. These venous lakes must be recognized and dealt with accordingly. The bleeding can be massive and difficult to control once it starts.

The steps taken to remove large petroclival meningiomas using tentorial incision are as fol-

lows: First, the portion of the tumor along the petrous ridge and in CP angle is removed, the positions of VII/VIII, V, VI, and IV nerves are ascertained and the petrous vein is either cut or preserved depending on the condition of the superior petrosal sinus. Next, the tentorium is cut triangularly and part of the tumor in the medial temporal region is resected. Above and medially to the tumor, the brainstem, and especially the dissection plane between the tumor and the brainstem, is carefully defined. After this step, the major tumor bulk is resected along the brainstem downwards as far as the VII/VIII complex. Throughout the surgery, all the nerves are under direct visual control of the surgeon and not a single nerve is "behind" the tumor. In addition, the dissection plane between the tumor and the brainstem is found very early on in the procedure.

NB: In cases of tentorial section, the position of vein of Galen above the lesion on sagittal MRI certainly is not mandatory. This rule strictly applies to true pineal lesions. The attacked lesions in, for example, the posterior thalamus will be above the vein of Galen on sagittal plane, yet easily accessible by SCIT.

8.7 Duraplasty and Wound Closure

The dura is closed with a running 3-0 suture and reinforced with a fibrin glue or a dural graft. The bone flap is replaced and fixed with bone sutures or miniplates. Covering the bone defect with autologous bone flap or polymethylmethacrylate implant is desirable to prevent postoperative headache [23]. The wound is then closed in anatomic layers, usually without a drain. After surgery, the patient stays at the intensive care unit, where slow awakening from anesthesia is ensured before an extubation attempt is made. A lumbar drain is usually left in place until the first postoperative day.

8.8 Pitfalls

The most important pitfall is insufficient knowledge of the regional anatomy. Technical errors are not that frequent, largely because SCIT normally is in the hands of experienced neurosurgeons. A rather frequent error concerns too low dural opening and ensuing cerebellar herniation; less common are venous sinuses and venous injury with ensuing venous infarction and perforator injury on the mesencephalic surface. In older patients, a sitting position and thorough CSF drainage may lead to massive pneumocephalus. In some patients, disturbances in CSF flow may be seen and managed postoperatively. It is not uncommon that hydrocephalus develops even after mass lesion resection. The most endangered cranial nerve in petroclival meningiomas is the fourth, which is usually directly in the middle of the surgical corridor posterior to the tumor.

8.9 Tips and Tricks

Introduce more stitches into the dural flap and gently lift the dura mater along with the transverse sinus (Fig. 8.9). Such a maneuver opens the surgical corridor considerably. Tack-up sutures may be introduced directly into the tentorium as well, a maneuver that opens up the surgical corridor even more. Start the cisternal dissection well away from the midline and continue in an upward direction toward the midline. Cut the arachnoid sharply; do not use blunt dissection. The arachnoid in the pineal region is dense, firm, and is often not very translucent. Dissect the veins in the area, taking extreme care not to injure them. Restrict your coagulation and coagulate only vessels associated with the tumor. Deploy navigation for lesions below the surface. Be prepared to use endoscopic assistance, customarily for inferior parts of the lesion hidden by the cerebellum. In the event of typical petroclival meningioma, the third nerve is superior to the tumor, the fourth nerve is dorsal to the tumor, the fifth nerve may be split on the inferior dorsal surface of the tumor, the sixth nerve is located medio-caudally and seventh/eighth nerve inferior to the tumor. Opening the tentorium allows early detection of the brainstem-tumor interface; then, tumor resection, from superior to inferior, is easier and rather straightforward. Do not lift the tumor upwards before identification and dissection of the seventh/eighth nerve within their

arachnoid covering. Identify and preserve all perforators. In case of brainstem and thalamic cavernomas, be sure to identify the entry point with great care. At all times, be aware of the location of the deep veins on both sides.

8.10 Clinical Experience

Apart from cerebellar lesions, the SCIT method has been used in more than 150 cases in our institute over the past 20 years. At the beginning, the present authors used a midline approach; however, as the technique became more routine and we gained considerable experience, the midline approach was abandoned and, more recently, only the unilateral approach has been used. We do not see much difference between the paramedian and lateral approach. Routine craniotomy starts some 2 cm lateral to the torcular and reaches the angle between the rectus and sigmoid sinus. Only in the case of petroclival meningiomas will the upper portion of the sigmoid sinus be exposed to allow for additional CPA exposure.

The SCIT method can be used to approach a variety of pineal lesions. The majority (>50 cases) were petroclival and petrous apex meningiomas but also pineal region meningiomas and meningiomas in the anterior part of the rectus sinus. The second larger groups were pineal cysts (>20), mesencephalic, pontine, and thalamic cavernomas (>20). More than ten brainstem and thalamic gliomas were approached using the SCIT method and another ten pineal tumors. Less frequent diagnoses were ependymomas, cholesteatomas, cysts, fifth nerve schwannomas, and metastases. Infrequent lesions included hemangioblastoma, chordoma, plexus papilloma, colloid cyst, high grade glioma, and arteriovenous malformation. Additionally, certain upper cerebellar lesions, such as gliomas, metastases, and arteriovenous malformations (AVMs), were approached using SCIT craniotomy.

Infrequent complications related to the SCIT approach were observed. We have seen one severe air embolism, and once the procedure for relapsing tumor had to be abandoned because of a rectus sinus injury with ensuing severe bleeding. We have noted our proper share of CSF complications, leaks, and pseudocysts, and we already have mentioned hydrocephalus development even after proper lesion resection.

8.11 Controversies

8.11.1 Supracerebellar-Infratentorial Versus the Occipital Transtentorial Approach

Both SCIT and the occipital transtentorial approaches enable access to lesions in the pineal region. In general, the most important landmark in decision making is the vein of Galen. All lesions located below the vein of Galen are indicated for resection using a SCIT approach. Deep cerebral veins are usually displaced cranially and laterally in true pineal gland lesions and therefore extend away from the surgical corridor [5]. In lesions located above the vein of Galen, an alternative to the SCIT approach is either the occipital transtentorial (Fig. 8.11) or the interhemispheric transcallosal approach. The SCIT approach is a direct extracerebral route with cerebellum falling away by simple gravity, and therefore, there is no need for manipulation. In the supratentorial approach, the occipital lobe needs some manipulation and retraction with all possible risks associated with such a procedure.

8.11.2 Sitting Versus Prone Position for Supracerebellar-Infratentorial Approach

Sitting position is preferred to the prone position when using the SCIT approach (Fig. 8.8) as it allows caudal displacement of the cerebellum by gravity without the need of additional retraction. In addition, this position prevents the pooling of blood in the surgical field. Still, there is a risk of venous air embolism in the sitting position, which might be a potentially fatal complication (see above).

The prone position, on the other hand, diminishes the risk of venous air embolism, but an

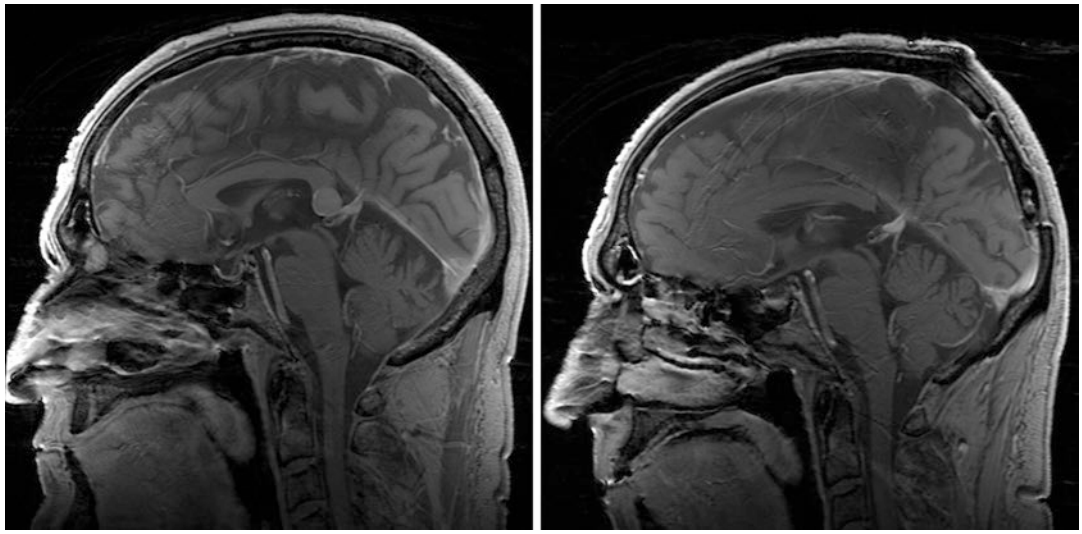

Fig. 8.11 Colloid cyst of the posterior third ventricle resected by the occipital transtentorial approach. **Left:** Preoperative MRI. Note that the lesion is located above the deep cerebral veins, and therefore, the occipital transtentorial approach is indicated. **Right:** Postoperative MRI showing complete resection of the lesion

objection to this approach has been the need for cerebellar retraction. Another limitation of the prone position concerns compromised ergonomy for the surgeon. Even with maximum head flexion of the patient, the approach might be somewhat troublesome for a surgeon positioned behind the patient. The line of sight is still angled toward the surgeon, especially in higher located lesions (e.g., thalamic cavernomas).

8.12 Conclusion

The unilateral supracerebellar-infratentorial approach is a highly versatile and safe option for microsurgical resection of a variety of lesions in the pineal and related regions. The method is represented by routine convexity craniotomy that allows direct access to brainstem and skull base lesions. The approach is irreplaceable in an armamentarium of any neurosurgical department.FundingThis work was supported by grant no. NV19-04-00272, grant no. 15-32791A, funded by the Ministry of Health of the Czech Republic, and grant no. Q25/LF1/2, funded by Charles University. The sponsors had no role in the design or conduct of this research.

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9 The Suboccipital Transtentorial Approach: How and Why We Do It—the Lyon Experience

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9.1 Introduction

The surgical approach to pineal region tumors still remains a difficult challenge for surgeons. Different approaches have been described, all being conditioned by the position and inclination of the tentorial plane, and so, they can be divided into the supratentorial or infratentorial avenue. The choice of the surgical approach is conditioned by the axis of growth of the tumor and its extension, but mainly by the operative experience of the surgeons.

In Lyon, we prefer the suboccipital transtentorial approach, which has been used in most of our cases and we try to describe its advantages over the infratentorial approach. Generally, the suboccipital transtentorial approach is shorter than other pineal approaches and permits more space at the beginning of the dissection. The opening of the tentorial plane allows to work under the venous arch represented by the basilar veins and the Galen vein. The vision of the two internal cerebral veins, which are generally located in a plane anterior to the pineal tumors, sometimes elevated but rarely enveloped by the tumor, represents a key point of all the approaches of the pineal region and this seems to be facilitated by the suboccipital transtentorial avenue [1].

The axis of view offered by the transtentorial suboccipital approach allows a better visualization of the floor of the third ventricle, which can be obtained by elevating the lower pole of the lesion. In general, tumors of the pineal gland do not invade the tectal plate, which facilitates the opening of the posterior wall of the third ventricle (Fig. 9.1a, b).

In this approach, the control and the dissection of the ipsilateral wall of the thalamic structure require a very lateral movement of the microscope to the contralateral direction, while the control of the opposite structures is easier. This situation can sometimes be uncomfortable for the surgeon.

9.2 History of the Suboccipital Transtentorial Approach

The narrow access to the pineal region pushed Heppner, as reported by Pendl (1985), to describe the suboccipital transtentorial approach in 1959 [2]. Theoretically this approach was mentioned by Tandler and Ranzi in 1920 in their Textbook of Surgical Anatomy (in Pendl, 1985). The variation proposed by Poppen, in 1966, with the opening

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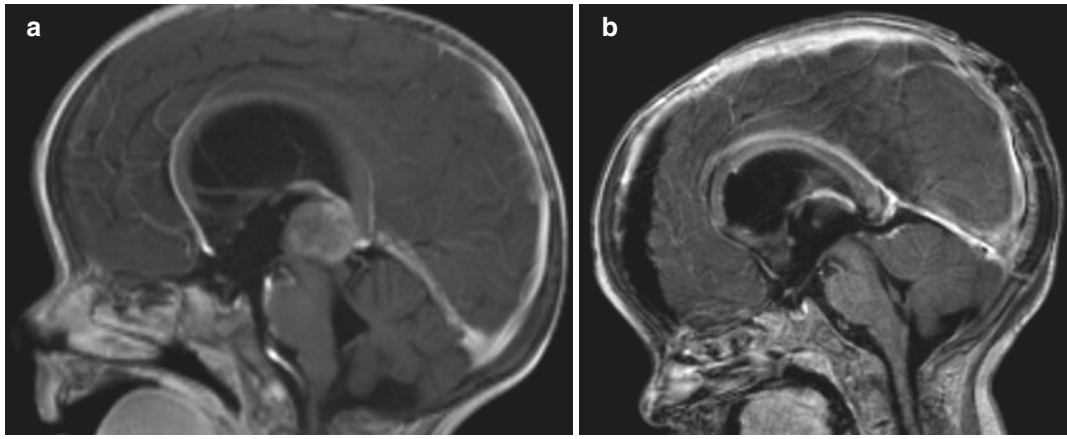

Fig. 9.1 MRI appearance of a pineal tumor in a child before (**a**) and after (**b**) surgery on T1 gadolinium-enhanced sequences

of the tentorium was intended to have a larger space for the approach of lesions in this deep area [3, 4]. Jamieson modified it again with a more medial exposition [5]. Many other surgeons used this approach, such as Negrin [6], Glasauer (1970) (in Pendl, 1985), Lazar and Clark (1974) (in Pendl, 1985).

Claude Lapras revisited the occipital transtentorial approach by proposing some technical modifications to facilitate a better exposure of the pineal region, in order to obtain a better control during surgery and to increase the rate of complete removal [7]. In the light of this heritage, we describe this approach as used in Lyon.

9.3 Positioning

We advocate for the surgical procedure in the sitting position, even if it requires experimented anesthesiologists. According to Hernesniemi [8], the deep location of the pineal structure justifies this position even in patients with an opened *foramen ovale* because air embolism, the most severe complication of this position, is in fact very rare [8].

The advantages of the sitting position have largely been discussed in literature but it is necessary to remember that the sitting position calls for an experienced team of anesthesiology to reduce the rate of complications [9] related to the air embolism and to the pneumocephalus. It also requires postoperative management in intensive care unit to manage and to facilitate the resorption of pneumocephalus.

Particularly important is the monitoring of patients during anesthesia. Patients are normally equipped with a central venous line, an invasive blood pressure catheter, and a cardiac output monitor with an esophageal Doppler and capnography monitor to detect gas embolism [9, 10].

In seated position, it is important that the hips are placed against the operative table, the lowers arms have to be bent and raised at level of the heart, paying attention to avoid an elongation of the sciatic nerve that may be responsible of postoperative sciatic pain, which can be very disabling for patients (Fig. 9.2a). The operative table has to be inclined at 90° to favor the good patient position (Fig. 9.2b).

The headrest is mandatory for a proper position of the head. Generally, the single pin of the Mayfield headrest is used at level of the frontal region of the side of the approach while the other two pins of the headrest are positioned on the contralateral side. The head is rotated by 15° on the right side and tilted down at an angle of at least 45°. The operative table is tilted forward in a way to obtain the tentorial plane parallel to the floor of the operative room. This position facilitates the opening of the tentorium, which becomes

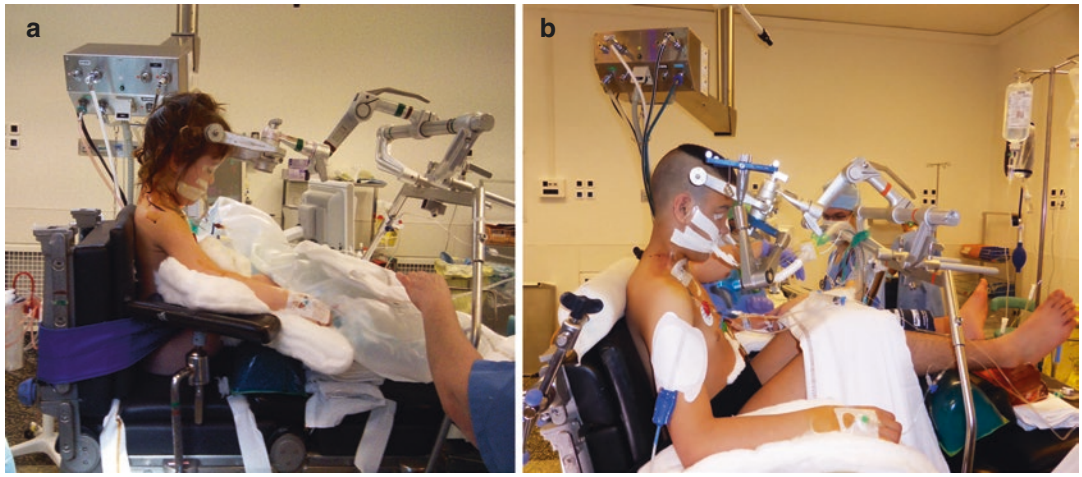

Fig. 9.2 (**a**) Young patient in sitting position with the head fixed in pin holder that can be used starting from the age of 3 years. Note the position of the back and of the head; (**b**) patients are positioned with the legs elevated at level of the heart being careful not to stretch the sciatic nerve during the operating period. A pediatric headrest is useful for children and adults. The head is flexed in order to expose the occipital region

easier to control with better exposition of the pineal region.

The neck has to be flexed, paying attention to leave a distance of two fingers between the chin and the neck in order to avoid respiratory problems. As in all sitting positions, the operative draping should not impede the access for a jugular compression by anesthesiologists at level of the neck in case of air embolism or for routine control of the venous hemostasis.

Generally, we do not use a lumbar drainage as proposed by some authors in literature [11, 12]. However, if the patients present with hydrocephalus, we treat it at the beginning with a third endoscopic third ventricle cisternostomy, which also allows us to study the CSF markers and, if necessary, to obtain a biopsy.

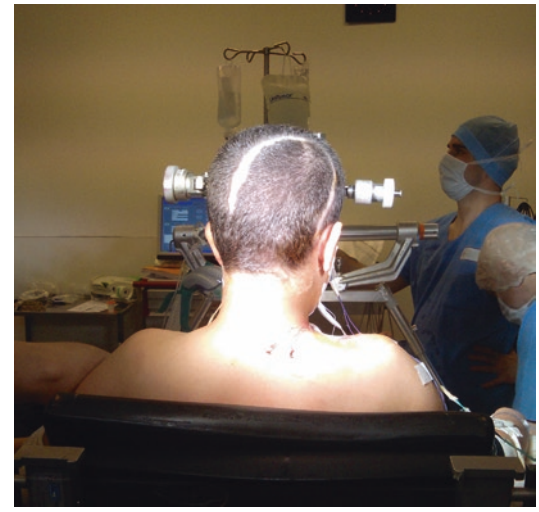

Fig. 9.3 Aspect of the skin incision allowing exposure of the posterior parieto-occipital region. The skin flap should be wide to assure good exposure in front of the parietal hump

9.4 Scalp Incision

The suboccipital transtentorial procedure needs, in our opinion, a large approach. Over the years, we have tried to reduce the size of the approach to lessen the brain exposure, but we have concluded that a larger approach decreases the rate of complications related to the potential lesions of the venous system when the occipital cerebral pole has to be elevated and spread [1].

The incision in horseshoe shape is extended to the level of the parietal bossing and descends laterally down to 1 cm medial to the mastoid bone. Medially, the skin incision is extended to the inion 1 cm away from the middle line (Fig. 9.3).

The skin flap is dissected in a subperiosteal plane down to the superior nuchal line. Generally, the exposition of the inion and of the superior nuchal line may give an idea of the projection of the venous confluence (Torcula) and of the transverse sinus.

Hemostasis control of the skin flap and of the bone must be rigorous to avoid air embolism complications. During the procedure, the surgeon can ask the anesthesiologist to perform a jugular compression to discover any venous source that could cause an air embolism.

The bone flap should be made by cutting the medial border parallel to the longitudinal sinus and the inferior edge at level and parallel to the transverse sinus. The first burr hole is made in front of the parietal hump. The second burr hole is drilled paramedian at the middle line in the parietal region 4 cm up from the lambda point.

The third burr hole is made on the middle line on the lambda point to discover the longitudinal sinus, and the fourth one is done at level of the asterion to visualize the point where the transverse sinus becomes the sigmoid sinus. The fifth and last burr hole is drilled to the inion in order to ensure a good vision of the torcula (Figs. 9.4 and 9.5). In our philosophy, it is always better to expose the venous structures to avoid their opening during the removal of the bone flap but also to improve exposure by dural folding.

The final form of the bone flap should be rhomboid. This shape has been adopted because it avoids the compression of the brain against the superior and lateral bone edges [1].

In order to prevent the lesion of the dura mater, a cautious dissection of the bone with a large dissector is necessary before cutting the bone flap, mainly at level of the sinuses with risk of hemorrhage but also air embolism, particularly in children. In this regard, it is preferable, in our opinion, to discover the dura mater by performing a small craniectomy with a gouge punch to expose the venous structures and the plane of the dura mater before using a saw. A careful dural dissection prevents dural tearing with cerebral contusions and venous lesions, especially in older patients with a more adherent dura.

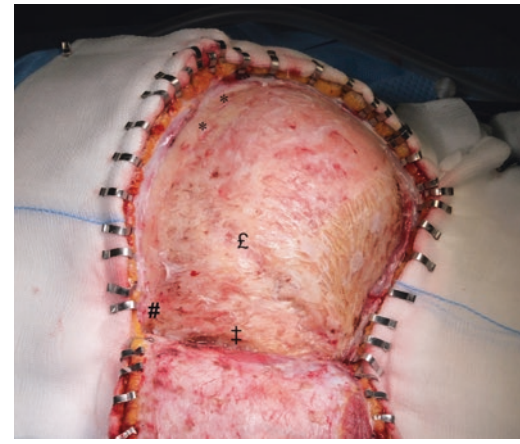

Fig. 9.4 The parieto-occipital region is exposed. Note the sagittal (*) and the lambda (£) sutures, the inion (#), and the superior nuchal line (‡). All are important landmarks for the bone flap

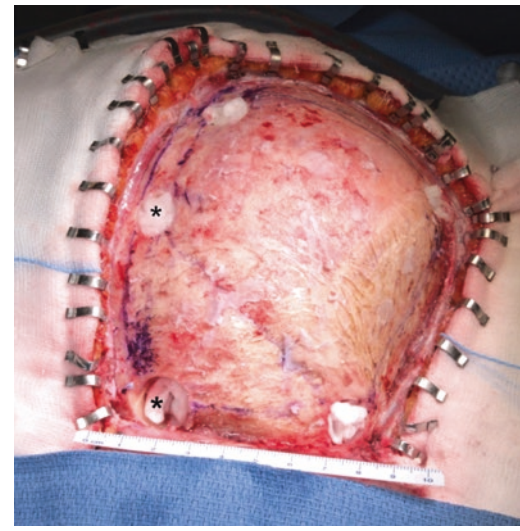

Fig. 9.5 The position of the burr holes has been studied to diminish the risks of dural and venous sinus lesions. The two burr holes in the lower middle line (*) show the exact position of the posterior portion of the sagittal sinus and of the torcula

When the bone flap is removed, the wax is generously used to obtain a good bone hemostasis. Dural suspensions are made with a 4-0 sticks before opening of the dura. The median suspensions are on the longitudinal sinus while inferiorly are done parallel to the transverse sinus (Fig. 9.6).

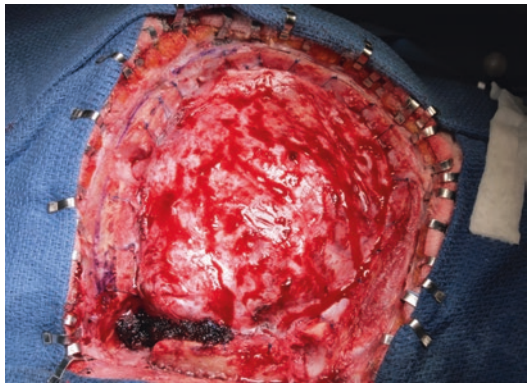

Fig. 9.6 The dural suspensions with stitches. Note the generous use of bone wax in order to prevent air embolism in sitting position

Before opening of the dura mater, a systematically jugular compression is requested to the anesthesiologist to ensure hemostasis. In addition, the space between the bone and the dura is covered with a hemostatic gauze to reduce the risk of air embolism.

9.5 Opening of the Dura Mater

The opening of the dura mater is started generally in the superior and lateral parietal region. Generally, in sitting position, the brain is depressed and it is very easy to control the dural opening. We usually do a dural flap with a base at the longitudinal sinus. The upper transverse incision is started laterally and directed to the superior longitudinal sinus, careful not to damage the superior afferent parietal veins that drain into the sagittal sinus. Laterally, the incision is extended downwards at 1 cm from the edge of the bone, taking care to avoid injuring the bridging veins which are also found in the middle part of the parietal region. These veins can sometimes be too large to be coagulated without consequences. Similarly, if a very large venous sinus is found in the dura, the opening has to be adjusted to preserve it.

The inferior dural opening is made, leaving a margin of more than 5 mm away from the transverse sinus to allow sufficient space for the dural inferior suspension and closure. This incision must be parallel to the transverse sinus to the torcula and observing a distance of at least 2 mm or 3 mm to avoid opening it.

If necessary, in the case where the dural opening is higher compared to the plane of the tentorium, two incisions perpendicular to the transverse sinus allow the eversion of the flap of the dura mater, favoring a better vision.

In cases of venous dural bleeding, we recommend to avoid aspiration but to control hemorrhage with hemostatic agents, exerting a pressure with cottonoids on the hemorrhagic source, and to close the tears with stiches and dural suspensions, especially in very young patients.

The dura mater flap is suspended by stitches that are ligated at the periosteal plane. Superior and lateral dura mater discharge incisions can be made before the dural suspension to avoid any compression of the brain against the free edge of the craniectomy later. When the dural suspension is complete, the surgeon must take the time for CSF aspiration to promote brain collapse, to collect CSF for the research of tumoral cells and for the study of tumoral markers.

During this phase, it is important to localize the superficial venous anatomy and the distribution of the bridging cerebral veins in order to adapt the movement of elevation and external rotation of the cerebral hemisphere necessary for exposure of the tentorium. At this moment, it seems important to remember that the suboccipital approach allows access to the pineal region passing under the occipital lobe, offering a different exposure than the inter-hemispheric approach. This point is very important to us and explains why the occipital lobe is elevated and pushed and not only pushed aside.

It is important to preserve the parietal superior veins that are always located at a point above the projection of the lambdoid suture. Between this point and the occipital pole, it is very rare, according to our experience, to find median bridging veins draining into the superior longitudinal sinus, as rare as bridging veins located between the inferior medial surface of the occipital pole and the tentorium or the transverse sinus (Fig. 9.7). Sometimes arachnoid adhesions may be cut to free these parietal veins from the dura

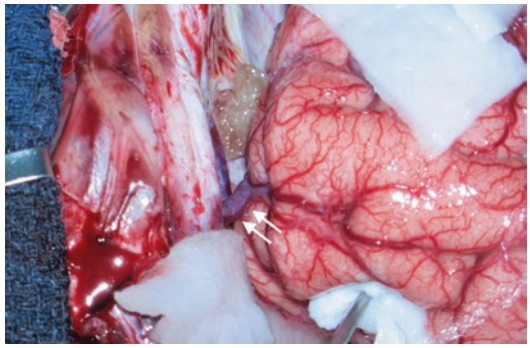

Fig. 9.7 Bridging veins in the inferior parietal region are very rare (arrows). In case they are present, it is necessary to preserve them in order to avoid ischemic venous injury

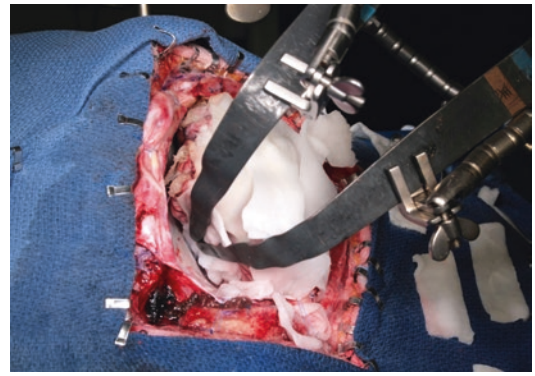

Fig. 9.8 The elevation and lateral push of the cerebral hemisphere permits the exposure of the tentorial plane to its free edge

mater and improve elevation and rotation of the cerebral hemisphere. For this dissection, a microscope may be useful.

More frequently, bridging veins are located inferior to the temporo-occipital and lateral region draining to the tentorium. These veins can tear with bleeding or ischemic lesions. To avoid this, the elevation of the occipital lobe must be donne leaving the lateral portion of the occipital lobe in contact with the tentorial plane. Therefore, the pressure to elevate the occipital lobe must be applied in a more median region always with a progressive cautious force.

Before starting the maneuvers of elevation and lateral rotation of the occipital lobe, the brain is covered with a silastic sheet and water-soaked cottonoids to prevent it from being in contact with the internal parietal bone edge in the upper part. A continuous irrigation is necessary to avoid brain dehydration.

With prudence, when the brain is sufficiently slack and covered with silastic sheets and water soaked cottonoids, we slowly begin to lift the occipital with a spatula in the median region of the inferior part of the occipital lobe to avoid compression of the calcarine region. It is very important to respect this technical point to reduce the risks of postoperative hemianopia, which is the main criticism of this approach.

When the exposition of the tentorial plane seems satisfactory, the occipital lobe is supported by the Yasargil retractor. The spatulas must not exert a force against the brain parenchyma, but they only have to support it (Fig. 9.8).

When the free edge of the tentorium is well exposed, before the incision of the tentorium, the superior parietal and the inferior temporo-occipital veins are coated with a hemostatic tissue and glue to preserve their integrity. The opening of the tentorium increases the exposition and the vision of the pineal region (Fig. 9.9a).

The exploration of the tentorial plane is necessary to visualize the presence of venous lakes found in a large number of cases. The incision of the tentorium begins posteriorly at least 5 cm from the free edge and at least 1.5 cm lateral and parallel to the straight sinus. The tentorium is incised with a blade knife No. 11 (Fig. 9.9b).

When the incision of the tentorium is made throughout its thickness, cotton is pushed between the tentorium and cerebellum and the incision is completed to the free edge. Attention should be paid to the free edge to avoid cutting the occipital internal vein, which is sometimes covered by the tentorium. The injury of the occipital internal vein can be responsible for sequalae, mainly in the case of the dominant hemisphere.

When the opening of the tentorium is completed, the medial edge is suspended with two 4-0 stiches, allowing a good exposure of the middle line (Fig. 9.9c). The lateral edge can be retracted with the bipolar forceps to improve the vision.

The presence of venous lakes at the level of the tentorium represents a risk of major bleed-

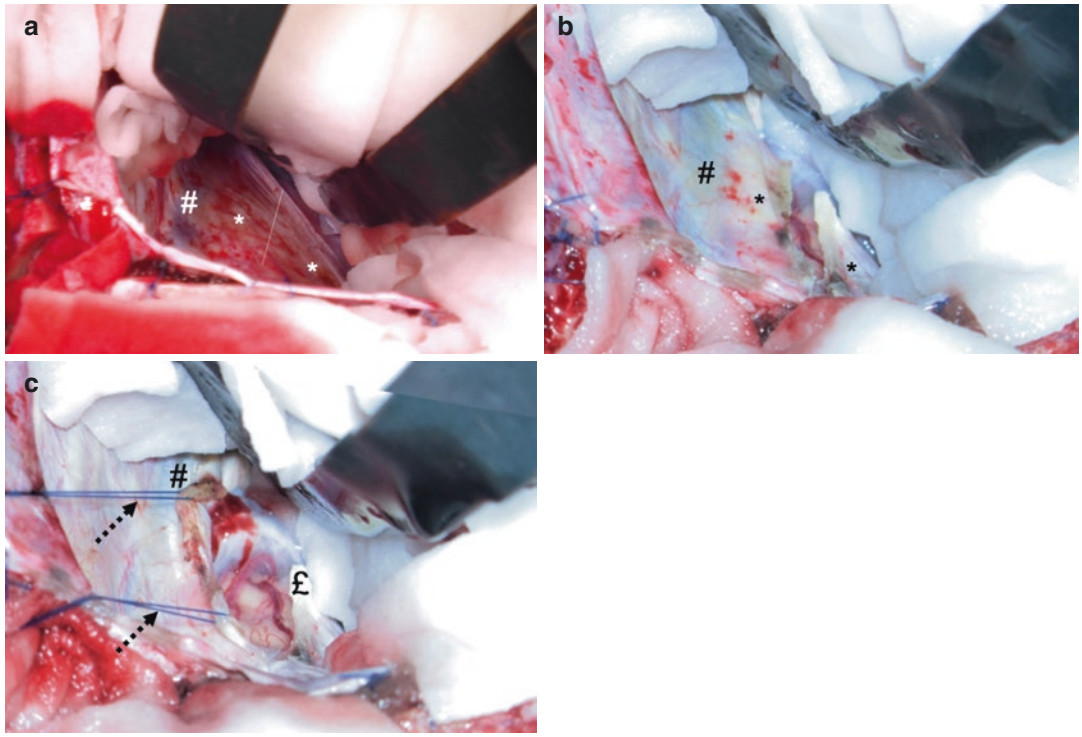

Fig. 9.9 (**a**) The opening of the tentorium plane (*) from the back to the free edge, 1.5–2 cm away from the straight sinus (#), allows a very great vision of the pineal region; (**b**) the incision starts from posterior toward the free edge of the tentorium avoiding venous lakes; (**c**) the two stiches (arrows) allow the exposure of the region, and the retraction of the lateral edge (£) is obtained by coagulation

ing. In this case, it is useful to perform two incisions, one posterior and the other in front of the venous lake, to close it with two clamps, to cut and finally to close both edges with a continuous suture. Keeping a distance of 1.5 cm from the straight sinus is necessary in order to prevent it's opening. In case of major venous bleeding, it is imperative not to aspirate blood, especially in young children, but to control the hemorrhage using hemostatic clamps or stiches. In this respect, we prefer to use stiches rather than definitive hemostatic clips.

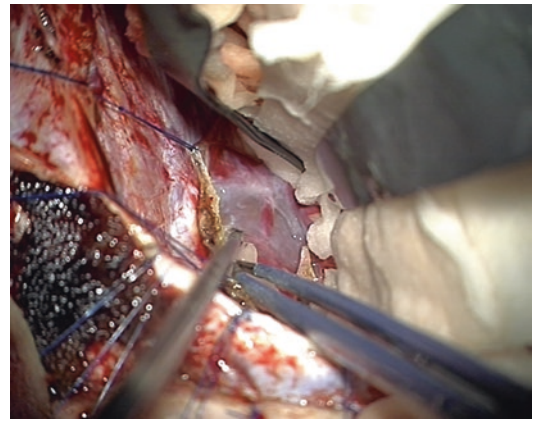

Fig. 9.10 The opening of the arachnoid space is made near the superior part of the vermis of cerebellum because it is very rare to find vascular structures at this level

9.6 The Approach to the Pineal Region

Once the tentorium is fully open and suspended, the surgical microscope is mandatory to continue the dissection of the lesion. At this moment, the tentorial notch and the Galen vein are perfectly visible with the arachnoid of the posterior part of the tectal plate (Fig. 9.10).

Under the surgical microscope, the opening of the posterior wall of the quadrigeminal cistern is

started close to the culmen of the cerebellum because, generally, at this level, there is space and it is easier to avoid lesions of the vascular structures as the basilar vein and the superior cerebellar artery.

The arachnoidian sheet should be widely opened from lateral to the medial region and continued along the left side to visualize the inferior part and the free edge of the contralateral tentorium. With the opening of the arachnoid, the venous and the arterial structures are visualized, like other anatomical structures. The lesion is localized generally below the venous arch of the basilar veins and the Galen vein and in a plane superior to the tectal plate.

When the venous arch is completely exposed, the surgery is performed under this arch keeping in mind that it is imperative to individualize the two internal cerebral veins which, generally, at beginning of the dissection, are masked by the lesion and it is very important to respect them.

If seen, the contralateral tentorium is very usefull during the dissection because the surgeon can always control the extreme margin of the contralateral surgical field.

In general, pineal lesions are located on the middle line, covered by the precentral cerebellar vein. Sometimes, the precentral cerebellar vein can be constituted by a multiple venous channels system and it is therefore necessary to coagulate one or more of these veins to approach the lesions. In the case of a single precentral vein, the dissection can be performed on either side (Fig. 9.11).

In our experience, coagulation of a single precentral cerebellar vein does not have great consequences on the neighboring structures or for patients. However, the coagulation has to be made far from the Galen vein to avoid harmful bleeding at his section and to prevent venous thrombosis as reported by Kano, who observed extensive thrombosis of the Galen vein after the coagulation of the precentral venous system [13].

When venous problems are controlled, it is preferable to start the dissection of the tumor from the inferior pole and to expose the tectal plate because, generally, true pineal tumors do not infiltrate the quadrigeminal plate, thus allowing an easier opening of the third ventricle. The opening of the third ventricle facilitates the CSF exit and the localization of the floor of the third ventricle, which, in our experience, is a key point for achieving a large or

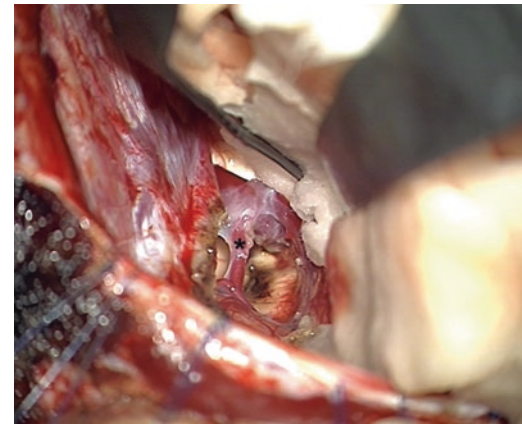

Fig. 9.11 In case of a single precentral vein (*), surgical dissection of the pineal lesions can be performed on either side and the vein can be spared. If the precentral cerebellar system consists of different venous channels, it is necessary to sacrifice certain veins

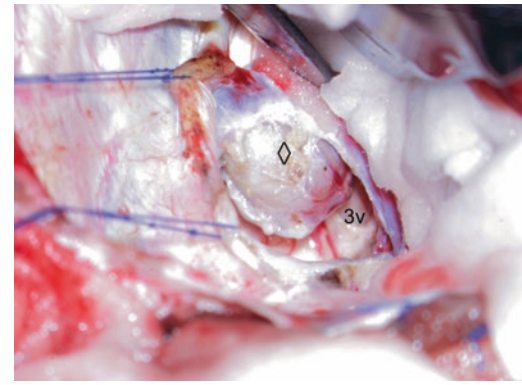

Fig. 9.12 The dissection always begins at the inferior pole of the lesion (◊) of the pineal region to access the posterior part of the third ventricle (3v)

complete removal by avoiding lesions of important surrounding anatomical structures. The opening of the third ventricle facilitates CSF evacuation, cerebral depression, and better understanding of the relationship between the lesion and the lateral walls of the third ventricle (Fig. 9.12).

If the tumor is smooth, it can be aspirated by ultrasonic aspiration set to low power after tumor sampling for histology or molecular and genetic studies.

If there is a clear plane, dissection of the tumor is followed around the left and right sides ensuring coagulation of the tumoral pedicles by avoiding lesions of the main arterial system of the posterior medial and lateral choroidal arteries and posterior

cerebral arteries. The control of feeding arteries of pineal tumors is one of the main advantages of a posterior surgical approach and, consequently, of the suboccipital transtentorial approach, since the arterial feeders generally originate from the posteromedial or posterolateral choroidal arteries located in a plane posterior to the tumor.

The dissection can be facilitated by the reduction of the volume of the tumor with the ultrasonic aspirator. This strategy permits to better individualize the interface of dissection between the tumor and the anatomical structures. Special attention should be paid to dissection of the superior pole of the tumor where some pineal veins must be coagulated and cut.

Attention should be paid to the dissection of the cerebral internal veins, which are usually elevated or pulled back by the tumor if one considers the approaching view. Rarely, the tumor envelops the internal cerebral veins. In this case, it is important to find and follow the plan of dissection between the tumor and the venous structures. The lateral approach of the superior part of the tumor facilitates, in our opinion, the vision and dissection of the internal cerebral veins in a plane more anterior to the tumor in order to permit a complete removal respecting their integrity. It is important to remember that the occlusion of one of the internal cerebral veins may be tolerated, but its sacrifice must be an extreme solution [14, 15].

It is difficult, at the upper pole of the tumor, to find the arachnoid plane of the *velum interpositum* cistern which, in general, is completely displaced by the tumor. During the dissection of this part of the tumor, the surgeon must pay particular attention to the dissection of the posterior commissure to reduce the incidence of the Parinaud's syndrome, which, once the posterior commissure has been spared, can be found at the beginning of the postoperative period and recovers usually in 6 months.

In case of lateral extension of the tumor in the lateral wall of the third ventricle, the use of cottonoids makes the dissection easier reducing damages to the thalamic structures. In this case, use of the ultrasonic aspirator set to low power can increase the rate of complete removal while decreasing the incidence of sequalae.

In case of the right suboccipital transtentorial approach, which is generally used in right-handed patients, lateral dissection of the left side of the tumor is easier because the field of vision is larger to control the tumor and the vascular and anatomical structures of the area. In contrast, ipsilateral dissection is more difficult and requires a very lateral left position of the microscope to visualize the right edges of the lateral extension of the tumor in the right thalamus or also in the medial part of the atrium of the *lateral ventricle.*

When the tumor is removed, the hemostasis is performed with the bipolar forceps and with cottonoids. In general, we do not leave hemostatic agents in the operative field to avoid confusing radiological images with misleading interpretation of the postoperative MRI performed in the first 48 h. At the end of the tumoral resection, we would inspect the operative field with a 30° lens rigid endoscope to ensure that no residual tumoral nodules are left in place and to be sure of the quality of the surgical resection.

For us, pure endoscopic resection of pineal tumors is limited to only small, non-vascularized selected lesions that can be approached within a transventricular avenue. Therefore, we prefer the endoscopic-assisted microsurgical resection at the end of the surgery to increase the rate of complete removal of tumors [1, 12, 16].

In case of extension of the tumor into the lateral ventricle, the splenium of the *corpus callosum* can be retracted or split to allow a better control of the removal [16, 17]. We do not recommend this approach variant, which may be responsible for a posterior disconnection syndrome more severe than in anterior callosotomy ([18]. If this route is realized, the dissection is performed between the internal cerebral veins and the lateral part of the fornix at higher risk of damage with a possible severe postoperative morbidity.

At the end of the surgery, the Yasargil retractors and the cottonoids are removed with abundant irrigation of saline solution to avoid damages to the cerebral parenchyma. For the closure of the dura mater, we use a large patch of synthetic dura sutured in a watertight fashion.

When the entire dural edges are sutured except for the upper edge, the subdural space is filled with saline solution to prevent a postoperative pneumocephalus. This maneuver is repeated until the dura

mater is completely closed. Double stiches are used for the central dural suspension. The bone flap is positioned and fixed with rivets or stiches. Bone powder is used to fill the burr holes to favor bone healing. The muscle plane is closed with separated stiches and the skin flap is closed with separated stiches with a modulated skin drain.

At the end of the procedure, the surgeon participates in laying the patients slowly in dorsal position under the supervision of the anesthesiologist. When the patient is in the dorsal position, the headrest is removed and the nurse can do the dressing.

9.7 Experience of Lyon with the Suboccipital Transtentorial Approach

Out of 365 patients followed up in the period between 1982 and 2012 for a pineal region tumor, 267 were operated through a suboccipital transtentorial approach (73%). Considering the patients of the French Register for pineal tumors, suboccipital transtentorial approach was used only in 33% of cases, while the infratentorial approach was used in 67% of cases, which confirms our preference for treatment of pineal tumors [1]. We have used the infratentorial supracerebellar approach in only 13% of cases [19].

The histological classification confirmed: pineal parenchymal tumors in 63 patients, germ cells tumors in 59 patients, pineal gliomas in 62 patients, papillary tumors of the pineal region in 47 patients, and pineal cysts in 36 patients.

The rate of survival is related to the histological nature (Fig. 9.13) of lesions, confirming that benign lesions have a long free survival with a good quality of life [20].

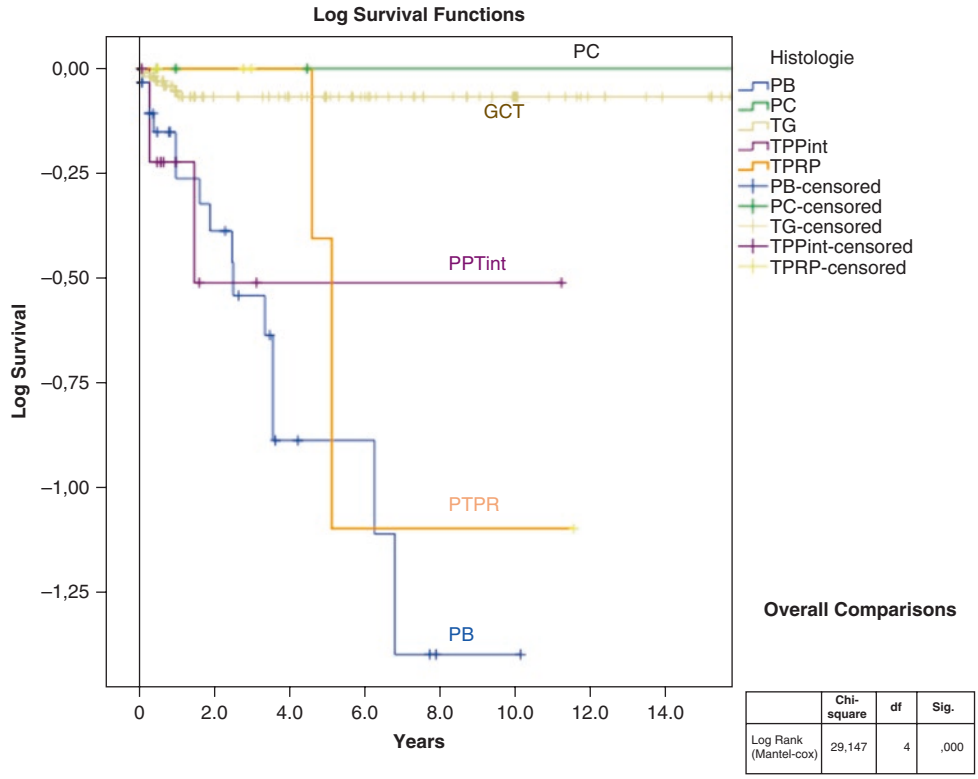

Fig. 9.13 Kaplan-Meier survival curve of most frequent pineal gland region tumors according to the histology from the French pineal register. *PC* pinealocytoma, *GCT* germ cell tumors, *PPTint* pineal parenchymal tumor, *PTPR* papillary tumor of pineal region, *PB* pinealoblastomas

9.8 Controversial Issues

The rate of complications of the suboccipital transtentorial approach for pineal region tumors has diminished during the last years with the progress of radiology, anesthesiology, and surgical techniques. Overall, an incidence of subdural hematoma was observed in 1.7% of patients. We had only one case of extradural hematoma, on the postoperative CT-scan the day after the surgery, which did not need a surgical removal because it was well tolerated.

A motor deficits was observed in less than 2% of patients and could be related to the deep dissection at level of the thalamic structures.

The incidence of epilepsy has been 5% in the postoperative period, and in all patients, a medical treatment for a least of 1 year has been insured before discontinuation in the absence of epileptic crisis and without electrical signs of ictal discharges. We recommend the administration of antiepileptic drugs from the preoperative period, which we stop at least 6 months after the surgical procedure if the EEG does not show abnormal critical activity.

A conjugate gaze palsy was observed in 3% of cases and is related to the dissection of the superior part of the tumor that is in contact with the posterior commissure responsible for the Parinaud syndrome. When the posterior commissure is respected, the patients recover from the Parinaud in the first 3 or 6 months after the surgical procedure.

The incidence of lateral homonymous hemianopia, which for a long time has represented the main criticism of this approach, has declined to less than 0.7% [1]. In this respect, it is of paramount importance to avoid prolonged pressure with the retractors at the calcarine fissure to prevent ischemic injury or visual cortex contusions.

Regarding this precaution, if visual field deficits are present in the early postoperative period, they should improve with time. This improvement can be observed even a year after the surgery. This fact highlights the importance of the ophthalmological follow-up for the patients. The visual troubles were, in our experience, observed only in 0.9% of cases and does not represent a real postoperative complication. We recommend the use of silicon sheets between the cerebral parenchyma and cottonoids to prevent their adhesions to the cerebral cortex with hemorrhagic lesions, when they are removed, at the end of the surgical procedure. With a watertight dural closure and a good filling of the intradural space with saline solution, the incidence of pneumocephalus was less than 4%. The perioperative mortality due to surgical complications has been 1% and has decreased lately with the development of microsurgical and anesthesiologic techniques [1].

9.9 Conclusion

The suboccipital transtentorial approach for the treatment of tumors or lesions of the pineal region is recommended because it seems to offer a larger space at beginning of the surgical resection in comparison with others approaches to the region. The exposition of the pineal region is large and the control of the venous and arterial structures easier.

This approach permits to control the floor of the third ventricle with a direct vision and more perpendicular approach, which, for us, represents a key point for the dissection of all kinds of lesions. In case of tumors, it is very rare that the inferior pole of lesions give infiltration at the level of the tectal plate and the important vessels can be easily controlled and spared because they are located in a more posterior and lateral plane.

The control of the homolateral of the lateral wall of the third ventricle is more difficult to obtain than the contralateral, but it can be achieved by pushing the microscope far laterally in the other side.

The low rate of complications observed in our series makes this approach safe, in our experience, even if it requires experienced hands.

In our school, the approach of choice remains the suboccipital transtentorial way, even though we think that all neurosurgeons should be familiar with different surgical approaches for the treatment of pineal region lesions.

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The Transcallosal Approach to Pineal Region Lesions

10

Krešimir Rotim and Tomislav Sajko

Interhemispheric approach is used to access lesions within the ventricular system and pineal and suprasellar regions. Lesions in the pineal region may also be reached via infratentorial supracerebellar, occipital transtentorial, transventricular, and interhemispheric transcallosal approach.

Walter Dandy, in 1921, performed and described the interhemispheric transcallosal approach to lesions in the third ventricle and pineal region [1]. Krause, van Wegenen, and Poppen described other surgical approaches to pineal region [2–4].

Different interhemispheric approaches to the pineal region and ventricular system are described and performed in both adult patients and children [5–9].

The transcallosal approach is recommended for lesions of the posterior part of the third ventricle and the pineal region with a predominantly superior growth involving the splenium of the corpus callosum and displacing the deep venous system [10] (Fig. 10.1). This approach follows the shortest route to the lesion and has the advantage of working anterior to the confluence of the deevp venous system [1].

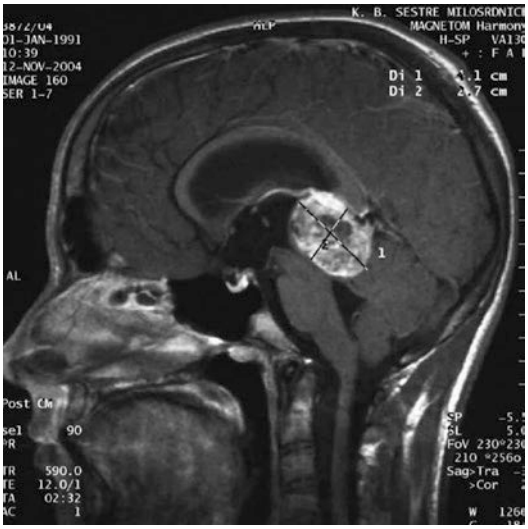

Fig. 10.1 Preoperative sagittal T1 contrast-enhanced MRI demonstrates a heterogeneously contrast-enhancing pineal mass with superior displacement of the internal cerebral veins

10.1 Anatomy Relevant to the Transcallosal Approach

The pineal region or posterior incisural space is also known as the quadrigeminal cistern [11]. The roof is the lower surface of the splenium of the corpus callosum. The anterior wall of the pineal region is divided into superior, middle, and inferior parts. The superior part of the anterior wall is formed by the pineal body, the habenular

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trigones, and the habenular commissure medially and by the medial portion of the pulvinar laterally. The middle part of the anterior wall is formed by the collicular plate of the quadrigeminal cistern and the pineal gland is situated between the paired superior colliculi. The inferior part of the anterior wall is built by the lingula of the vermis on the midline and by the superior cerebellar peduncle laterally. The floor is constituted by the superoventral portion of the cerebellum. The lateral walls are formed by the crus of the fornix and by the medial surface of the occipital cortex below the splenium of the corpus callosum [12–18].

Interhemispheric transcallosal approach reaches the roof of the posterior incisural space with the splenium visualized anteriorly, the falcotentorial junction with the straight sinus medially, medial surface of the parietooccipital cortex laterally, and the deep venous system posteroinferiorly (Fig. 10.2).

The confluence of the deep venous system is situated in the posterior incisural space. The vein of Galen originates behind the pineal body. The vein of Galen runs posterosuperiorly to drain into the straight sinus located around 10 mm from the tip of the pineal body [13]. Several important veins drain into the vein of Galen. The paired internal cerebral veins course inferior to the splenium of the corpus callosum and lateral to the pineal body and turn upward before joining to form the vein of Galen.

The union of the internal cerebral veins may be located above or posterior to the pineal body and inferior or posterior to the splenium (Fig. 10.3).

The basal veins of Rosenthal drain into the vein of Galen more inferiorly than the convergence of the internal cerebral veins. The precentral cerebellar vein and superior vermian vein drain into the vein of Galen separately or as a single trunk. Internal occipital vein terminates in the lateral part of the vein of Galen [14, 18–22]. Posterior incisural space houses medial and lateral posterior choroidal artery, quadrigeminal artery, and medial occipital artery [16].

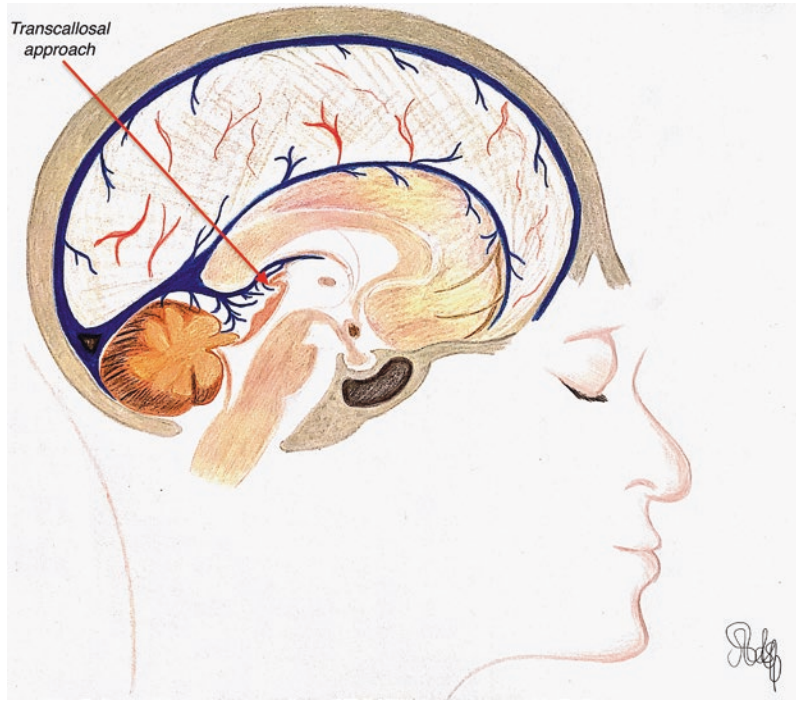

Fig. 10.2 Interhemispheric approach to the posterior part and splenium of the corpus callosum

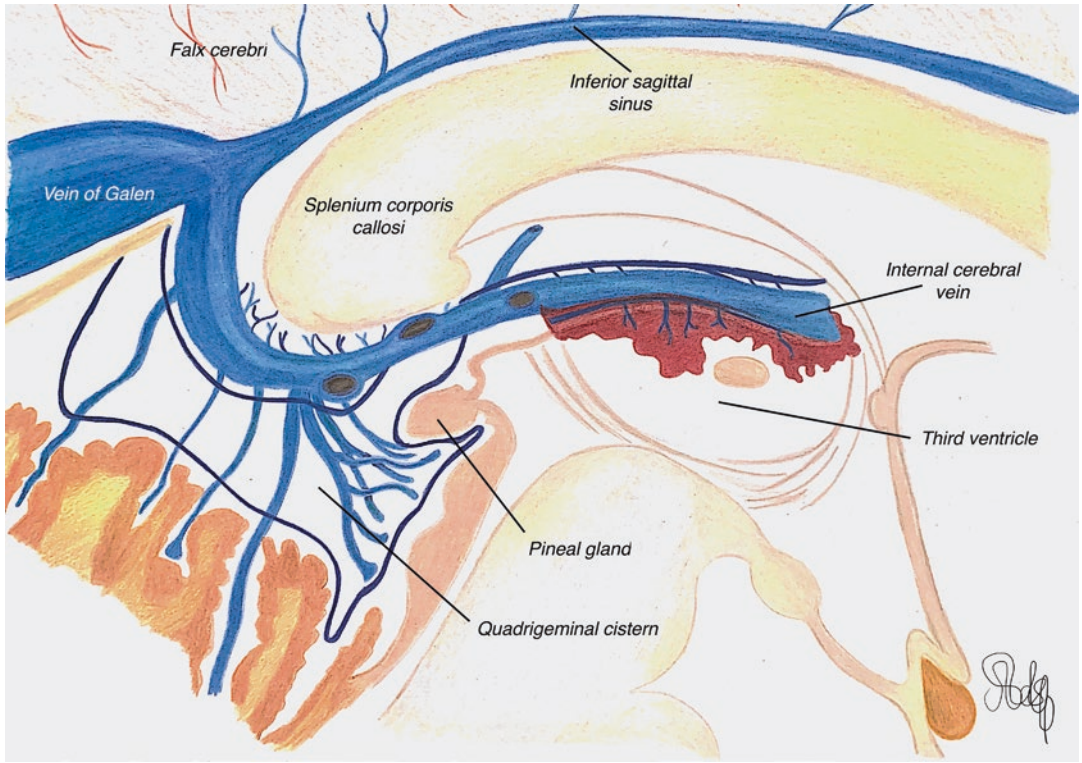

Fig. 10.3 Sagittal view of the anatomy of the pineal region

10.2 Interhemispheric Transcallosal Approach Surgical Technique

The *posterior interhemispheric transcallosal approach* is recommended for lesions in the posterior portion of the third ventricle and the pineal region, especially when there is a superior extension of the tumor involving the splenium of the corpus callosum [10]. The positioning of the bone flap depends upon tumor location. For the posterior interhemispheric transcallosal approach, the patient is placed in a prone position (Fig. 10.4). The right-sided approach is used in most cases, except for dominant left-sided tumor extension. Neck flexion should be avoided during positioning to facilitate brain relaxation and venous drainage. Neuronavigation system and neurophysiological monitoring are installed and the patient is dressed in an orderly fashion.

C-shaped or linear skin incision is made in the parietal or occipital region (Fig. 10.5).

Two burr holes are made over the superior sagittal sinus and a craniotomy extending to the contralateral side is performed. In case of concomitant hydrocephalus and brain swelling, an external ventricular drainage is inserted into the ipsilateral ventricle under neuronavigation or ultrasound guidance. Dura is opened with the base toward the superior sagittal sinus.

With the use of cottonoids, the brain is gently pulled away in order to visualize the falx. In case of veins running toward the midline and being adherent to the dura, it is recommended to spare the larger ones. Brain retractors are used for mild retraction of the ipsilateral brain and for contralateral retraction of the falx. The longitudinal cerebral fissure is followed to the posterior portion of the corpus callosum and to the angle between falx and tentorium. In most cases, the

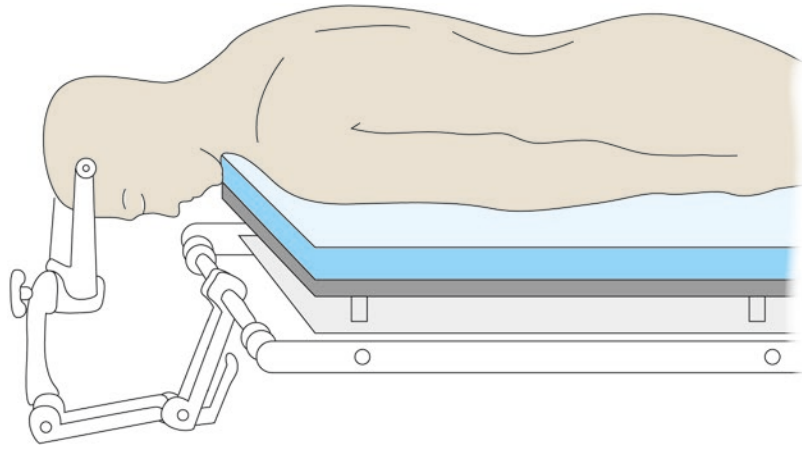

Fig. 10.4 The prone position used for interhemispheric transcallosal approach

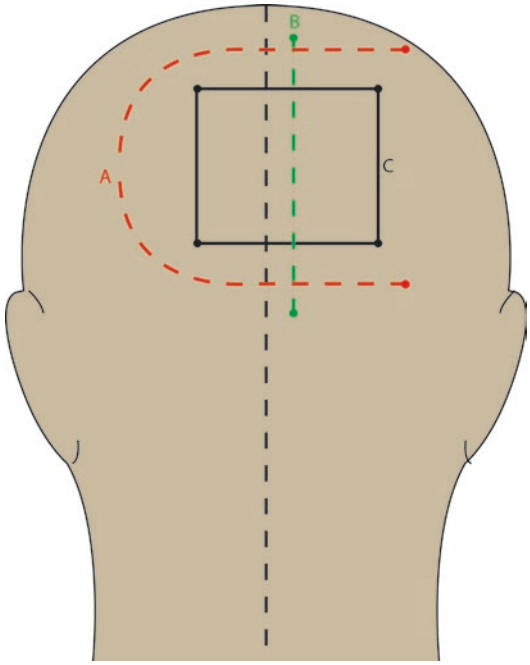

Fig. 10.5 Illustration of the C-shaped (**a**) and linear skin incision (**b**). Craniotomy (C) is in most cases done on the right side with over the midline extension

tumor can be seen bulging the splenium corporis callosi and occupying the angle between falx and tentorium (Fig. 10.6).

Pineal tumors start to grow inferiorly to the internal cerebral veins displacing the veins superiorly and the vein of Galen posteriorly. To improve visibility, a small portion of the tentorium can be cut parallel to the straight sinus. To gain more access to the tumor and its anterior border, the section of the corpus callosum can be performed in two different areas (Fig. 10.7).

Complete section of the splenium corporis callosi allows a clear view of the pineal region, vein of Galen, and quadrigeminal cistern. Opening the splenium is useful for pineal lesions with a superior growth. Section of the splenium bears no risk in injuring the fornix since no fornix exists at this level. Section of the posterior part of the corpus, sparing the splenium, allows a clear view of the posterior part of the third ventricle in the area between the massa intermedia and pineal gland [10]. With opening of the corpus callosum's posterior part, the hippocampal commissure is frequently sectioned before reaching the third ventricle. Nevertheless, callosotomy and subsequent dissection should be performed directly in the midline because this maneuver will lead the surgeon to the avascular membrane separating the internal cerebral veins [23]. Natural separation of the internal cerebral veins just proximal to their confluence with the vein of Galen allows the separation of the veins which is carried out anteriorly. After extracapsular circumferential dissection and visualization of the anterior, superior, and posterior tumor border, tumor is debulked and, if possible, resected. Tumors are often adherent to the deep venous system, especially both-sided internal cerebral veins and vein of Galen; therefore, meticulous care is necessary to separate the veins from the tumor. In case of strong venous bleeding, compression using the sponge and hemostatic mate-

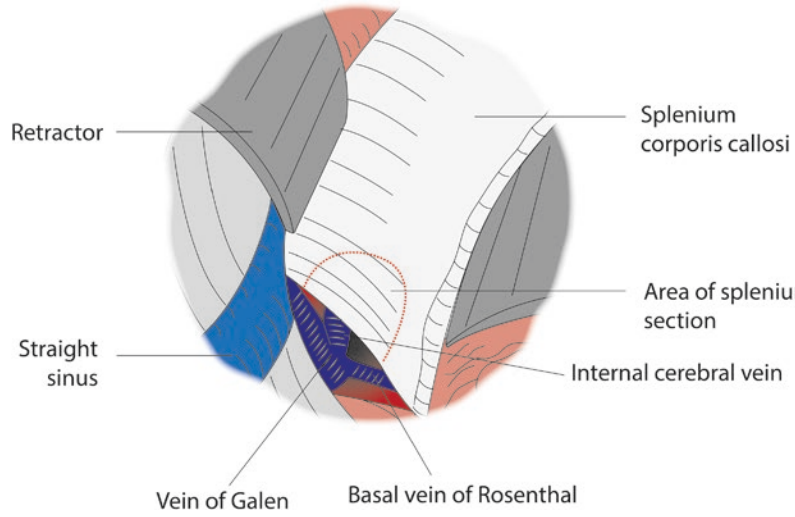

Fig. 10.6 Interhemispheric approach to the posterior incisural space with area of possible splenium corporis callosum section

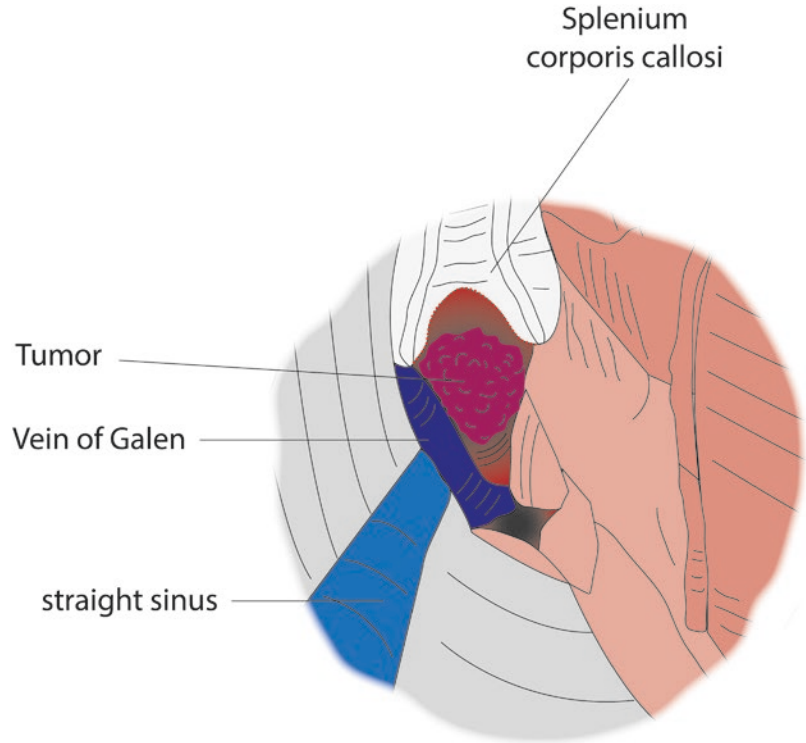

Fig. 10.7 Interhemispheric transcallosal approach with splenium section that allows better visualization of the pineal tumor and its relationship with the deep venous system

rial is performed rather than cautery. Total resection of the tumor can be achieved if a plane between the tumor and surrounding normal structures can be identified. Upon total resection, the posterior third of the third ventricle, the quadrigeminal cistern, superior colliculi, and the deep venous system can be identified.

10.3 Discussion

Walter Dandy introduced the transcallosal approach in 1921 [1]. In 1965, Suzuki et al. used the transcallosal approach in 19 patients. They reported death in three cases and concluded that pineal tumors can be excised safely through this

approach [24]. In 1973, Hoffman and Hendrik presented a series of nine pineal tumors in children operated mostly via transcallosal approach with good results [25]. Nevertheless, the transcallosal approach was gradually abandoned due to the opinion that it fails to provide proper exposure of the lateral extent of the third ventricle and carries the risk of damage to the deep venous system. Subsequently, the interhemispheric transcallosal approach to the pineal region has mostly been replaced by the occipital-transtentorial and the infratentorial-supracerebellar approaches. In a series of 700 patients with pineal region tumors, Konovalov et al. used occipital-transtentorial, supracerebellar-infratentorial or combined approaches [26]. In their series of 119 patients, Hernesniemi et al. used supracerebellar-infratentorial approach in 111 patients and parietooccipital-transtentorial approach in 8 patients, respectively [18].

In pediatric patients, Jia et al. reported the use of transcallosal interforniceal approach to pineal region in 150 children [27]. Soleman et al. reported using interhemispheric posterior approach in 6 out of 28 patients in their series [9]. Recently, Patel et al. reported their experience with transcallosal approach in 22 patients with tumors located within the pineal regions, posterior third ventricle, and thalamus [23].

The interposition of the deep venous system between the corpus callosum and pineal region has been the main reason why transcallosal approach has been progressively replaced by other approaches [10] The importance of the deep venous system and the degree of venous collaterals is still discussable as consequences of venous sacrifice in the posterior fossa are not well-reported in the literature. There is some evidence that one vein can be sacrificed safely in several instances, but interruption of two would likely greatly increase the risk of a devastating infarction [4, 28].

Brain damage or infarction after an interhemispheric approach due to venous infarction or brain retraction has been described [9, 29, 30]. Kanno et al. described radiologically evident brain damage in 17.8% of patients undergoing the interhemispheric approach, while clinically relevant symptoms were seen in only 3.6% [29]. In the parietal region, brain retraction during the transcallosal approach may lead to contralateral sensory deficits or to hemiparesis. Occipital lobe retraction may result in cortical visual field deficits. Brain retraction should be avoided and held to a minimum through opening of the interhemispheric cisterns or placing an external ventricular drainage.

The sacrifice or injury to some bridging veins is sometimes unavoidable. Sacrifice of bridging veins may lead to cortical infarction, particularly if more than one vein is taken [31].

The most significant immediate complications include bleeding within the tumor bed, hydrocephalus, shunt malfunction, and pneumocephalus.

Neurological sequelae represent the major disadvantages of transcallosal approach. Most patients display some degree of impairment of extraocular movements, particularly upgaze and difficulty with convergence [32]. In a study of 26 children operated via interhemispheric approach, Soleman reported that hemianopsia did not occur in any of the patients undergoing a posterior interhemispheric approach [9]. Davidson and colleagues analyzed the safety and efficacy of the posterior interhemispheric approach in the pediatric population for lesions in the pineal region and the posterior fossa [5]. Approach-related complications occurred in 7.1%. No patient developed a stroke, even though veins were sacrificed in six cases.

Posterior transcallosal approach bears the risk of involving the hippocampal commissure, which may cause serious intellectual sequelae. Transecting the posterior half of the corpus callosum can involve the posterior and habenular commissures, resulting in memory dysfunction and disconnection syndrome [33–35].

Section through the splenium, although acceptable in most patients, may result in hemialexia. Splenial section combined with a left occipital injury or any lesion producing a right hemianopsia leads to alexia without agraphia, a severely disabling disconnection syndrome for patients with any degree of literacy [36]. Disconnection syndromes may occur if the

splenium is divided [36]. Studies analyzing the neuropsychological outcome of the interhemispheric approach in adults showed that the transcallosal interhemispheric approach might lead to memory deficits, executive cognitive and behavioral syndrome, and disturbance in interhemispheric transfer of learning [37, 38]. In a study by Mazza, transverse dissection of the callosal fibers led to better neuropsychological outcome than sagittal dissection/retraction of the callosal fibers, which was described by Yasargil [37, 39]. One of the most serious sequelae is mutism. The pathophysiological mechanism of mutism is unknown, but it may be associated with a psychological disturbance. Another serious symptom of the disconnection syndrome is the frequent, but temporary loss of recent memory, which may occur when the connecting pathways from the temporal lobes are damaged [34, 40].

Winkler et al. have reported that although the loss of verbal learning and recognition is difficult to quantify, it occurs in up to 25–33% of patients after the transcallosal approach [41].

Friedman et al. found that there was a significantly increased frequency of cognitive impairment relative to normative values in memory, executive functioning, and fine manual speed and dexterity [42].

10.4 Controversial Issues

When approaching the pineal region using the posterior interhemispheric transcallosal approach the tumorous lesion is occupying most of the operative field and it is interposed between the surgeon and inferior structures of the pineal region. Veins of Galen and internal cerebral veins are scarcely visible at the posteroinferior margin of the tumor and usually adherent to the lesion. Gaining a wider view of the tumor requires section of the splenium and the posterior part of the corpus callosum, which is connected with a high incidence of neurological consequences. An attempt to completely remove the tumor bears a risk of damaging the deep venous system.

10.5 Conclusion

The transcallosal approach is recommended for lesions of the pineal region and posterior part of the third ventricle with a predominantly superior growth involving the splenium of the corpus callosum. Although a section of the splenium and posterior part of the corpus callosum are associated with neuropsychological complications, the transcallosal approach to pineal region lesions is safe and, in certain patients, superior to other surgical approaches.

Careful planning, including assessing the tumor dimensions and its relationship to the surrounding neurovascular structures, is crucial in determining the optimal approach for tumors in the pineal region.

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Endoscopic Approach for Pineal Region Lesions

11

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11.1 Introduction

The approaches of tumors in the pineal region that have been described and used throughout the time have each their own set of advantages and limitations. From a historical point of view, the pineal region tumors were most often approached via stereotactic biopsy or via open posterior fossa microscopic approaches [1]. Nowadays, there is still some debate regarding the best management of pineal region tumors, and about the role of surgical resection, especially in the case of high-grade lesions, due to high postoperative surgery-related morbidity [2]. Recently, the surgical endoscope has gained an important role in many fields of neurosurgery, especially in skull base surgery, proving to be a great instrument which improves illumination and visualization within a deep and narrow surgical corridor, thus decreasing the approach-related morbidity [3]. Along with the increase in the experience with this type of view, the use of endoscopic approaches to the pineal region has advanced from simple cyst fenestrations and tumor biopsies to large tumor resections and removal of vascular lesions, using posterior keyhole endoscopic approaches, with excellent postoperative outcomes. In the past decade, several specialist teams have described endoscopic posterior approaches for resection of pineal region tumors, with minor differences between them [4].

The use of the paramedian supracerebellar infratentorial (SCIT) keyhole approach for pineal region tumors is described using an endoscope for the entire length of the procedure. The presentation is based on the pending-publishing case series of 11 patients with pineal region tumors, operated using a fully endoscopic technique. All surgical procedures were performed by the same surgical team, composed of two senior doctors: a neurosurgeon and an ENT (Ear, Nose, and Throat) surgeon. Their 10-year experience with endoscopic skull base surgery started with anterior skull base, sellar and suprasellar tumors, and now transitioned to deep intraventricular and pineal region tumors, with good results.

The aim is to demonstrate the feasibility and safety of endoscopic techniques compared to the classical microscopic approaches for pineal region tumors, with better results regarding grading of resection, lower surgery-related morbidity, and faster patient recovery.

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I. S. Florian (ed.), *Pineal Region Lesions*, https://doi.org/10.1007/978-3-030-50913-2_11

11.2 Case Presentation

An 18-year-old previously healthy female presented to a community hospital with a 6-month history of headache, and sudden onset of nausea and vomiting. The headaches started gradually, and the family had noticed some vague cognitive changes, including memory disturbances, during the previous month. On neurological examination, she was found to have bilateral papilledema. A subsequent non-contrast computed tomography (CT) scan showed hydrocephalus and suggestions of a pineal region mass. The patient was immediately transferred to the University Hospital, where an external ventricular drain (EVD) was placed in emergency to control her intracranial pressure and then a brain magnetic resonance imaging (MRI) was obtained.

11.3 Diagnosis and Assessment

The MRI scan of her head demonstrated the presence of a tumor located in the right thalamus and mesencephalon, with an important exophytic component in the posterior region of the third ventricle, with associated obstructive hydrocephalus. She had a ventriculo-peritoneal (VP) shunt placed in the same neurosurgery department with no further treatment planned. Postoperative evolution was favorable with complete resolution of symptoms for the next 2 years. On arrival in our clinic, she complained of nocturnal headaches accompanied by nausea and vomiting. The head MRI scan was repeated, revealing the volumetric progression of the tumor. Serum and cerebrospinal fluid (CSF) were searched for alpha-fetoprotein and beta-human chorionic gonadotropin. The differential diagnosis for the tumor included germ cell tumors and a wide variety of other tumors, including pineal parenchymal tumors, gliomas, meningiomas, metastases, and miscellaneous other tumor types. Both tumor markers were negative in this patient. Had the tumor marker been positive, it would have confirmed a malignant germ cell tumor and further surgical considerations would have been abandoned because these tumors are better treated with chemotherapy and radiation [5]. The absence of tumor markers, as in this patient, does not rule out a germ cell tumor and thus it mandates an endoscopic biopsy to guide further management, or open biopsy and surgical resection of the tumor, the latter being the decision made in this case.

11.4 Preoperative Management

Upon admission, the patient was alert and oriented, the neurological examination revealing only a left incomplete Parinaud syndrome. In the preoperative setting, it is important to take care of the associated obstructive hydrocephalus, but in our case, this had already been resolved at the previous institution where the patient was admitted. Because the sitting position is used, a precordial echocardiographic examination is paramount in order to detect any patent foramen ovale, which would place the patient at risk for a paradoxical air embolism. Also, during the procedure, all patients require transesophageal Doppler monitoring, as well as a central line in the right atrium to detect and treat venous air embolism.

11.5 Anatomical and Imaging Considerations

The preoperative MRI scan (Fig. 11.1) demonstrated a large (3 × 2.5 × 2 cm) heterogeneously gadolinium-enhancing mass in the pineal region, originating from the right thalamo-mesencephalic junction, with mild perilesional vasogenic edema and compression and deformation of the contralateral wall of the third ventricle. It enlarged the aqueduct of Sylvius and displaced the tectal plate posteroinferiorly. The mass was mainly in the posterior half of the third ventricle, and it was easy to appreciate that the tumor was engulfed by the veins of the Galenic complex, being situated between the basal veins, located laterally, internal cerebral veins, located superiorly, and vein of Galen, located posteriorly. There was no sign of obstructive hydrocephalus, given the presence of the VP shunt; the ventricular catheter and also the

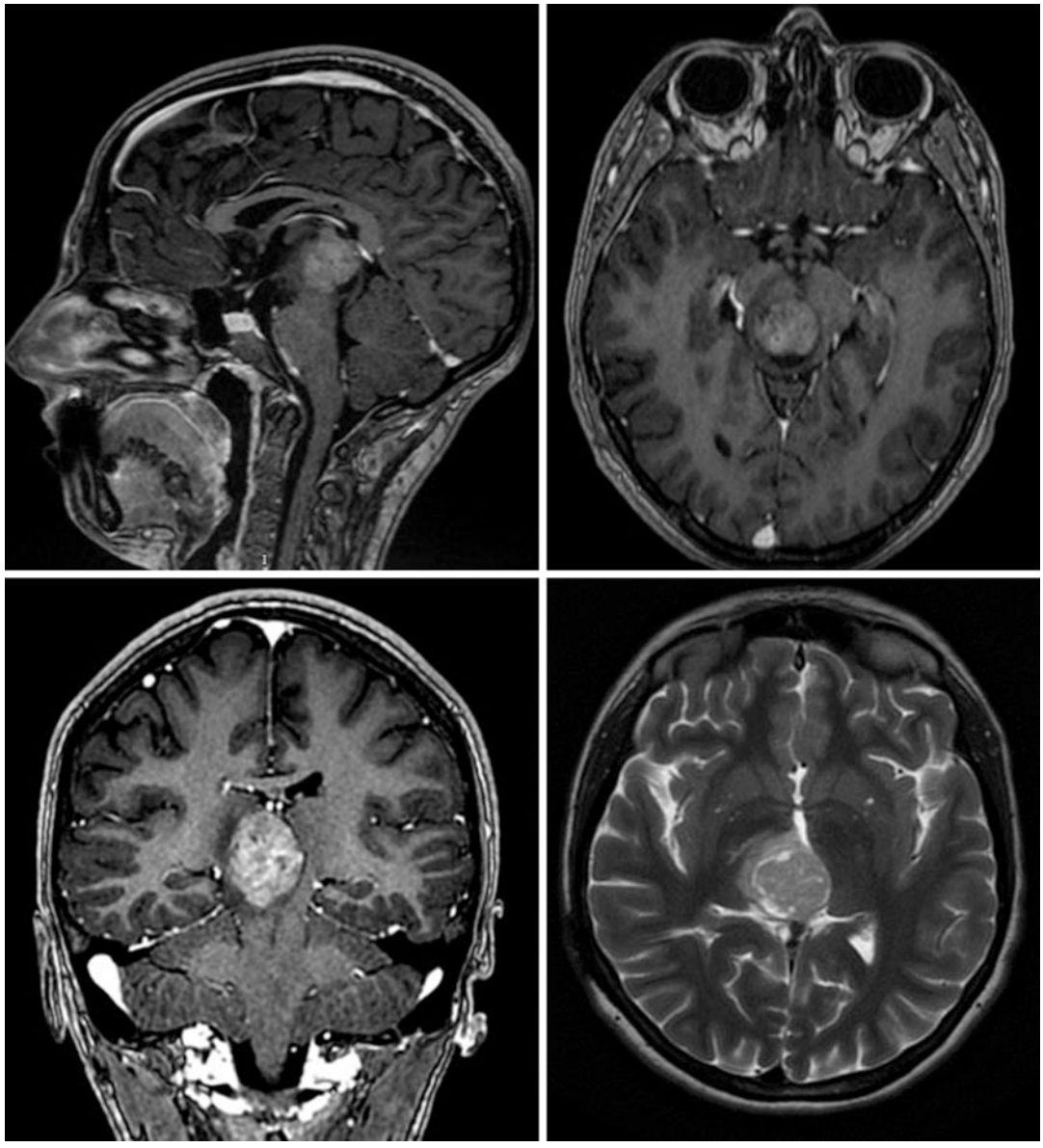

Fig. 11.1 Preoperative 3-plane gadolinium-enhanced magnetic resonance imaging (MRI) and axial T2 sequence demonstrating an enhancing right thalamo-mesencephalic tumor

valve can be seen on this scan. Given the young age of the patient, the absence of CSF/serum markers and the presence of the symptomatology, gross total resection appeared to be the best indication. Some may consider that the tentorium is too steep for a supracerebellar infratentorial approach, but as further discussed, with the aid of the sitting position, and with the use of the paramedian trajectory and the endoscope, all of these make SCIT the ideal approach [6]. Therefore, in this case, the recommendation was a paramedian endoscopic supracerebellar infratentorial approach with a keyhole craniotomy for resection of this mass.

11.6 Surgical Technique

The surgery was performed under general anesthesia in sitting position, with the head flexed forward and transesophageal echocardiographic monitoring was performed throughout the entire length of the surgery. The sitting position was preferred for the patient, because it has some advantages over other types of positioning, improving the visualization through gravity retraction of the cerebellum and lowering of the venous pressure; thus, it decreases bleeding from the resection cavity and allows blood to be drained away from the surgical field [7].

Stryker Nav3i Neuronavigation System (Stryker Instruments, Kalamazoo, MI, USA) was used. Optical magnification was achieved using a rigid 0°, 30°, 45°, 70°, and 90° Karl Storz endoscope (Karl Storz, Tuttlingen, Germany). Standard endoscopic and microsurgical instruments were utilized and the CUSA (CUSA Excel Ultrasonic Tissue Ablation System, Integra Life Sciences, San Diego, USA) aided in tumor resection. The routine of this surgical team does not include irrigating sheaths, which are commonly used for endonasal procedures, because they increase the diameter of the instrument, making the microsurgical technique more difficult, given the keyhole approach. Prior to beginning the surgery, the externalization of the ventricular catheter of the VP shunt was performed.

Neuronavigation and the operating microscope were used in order to place the incision and the craniotomy. A 4-cm-long skin incision was performed, starting at the level of the transverse sinus and pointing down, and a bone flap with the diameter of 2 cm was cut, exposing the inferior edge of the transverse sinus and the dura mater overlying the upper cerebellum, lateral to the torcula.

The approach used was a left paramedian SCIT, and the side of the approach was determined by the laterality of the tumor's origin, which was in this case the right thalamomesencephalic junction. Midline approaches are avoided due to increased number of bridging veins from the tentorium to the cerebellum that are located in this region, as well as due to obstruction of the pineal region by the high-riding culmen of the cerebellum in the midline. The contralateral approach provides a better view and microsurgical control of the tumor insertion on the lateral wall of the third ventricle.

The surgical endoscope was brought in starting with the dural incision, incision done in a curvilinear fashion at the lower border of the craniotomy. The dura mater was suspended at the upper border of the craniotomy with tackling sutures, retracting also in this step the left transverse sinus. The supracerebellar infratentorial subarachnoid space was entered, with careful preservation of bridging veins, until we reached the profound pineal region. The arachnoid membranes of the supravermian and quadrigeminal cisterns were incised, preserving at this level the superior vermian vein.

The Galen venous complex was identified together with a grey-yellowish tumor, bulging medially into the third ventricle from the right pulvinar. The tumor dissection and resection were done in a circumferential fashion, starting with the superior pole, and preserving at this level the venous complex of Galen. The next move was laterally, where the posteromedial choroidal arteries and the basal veins are usually identified and preserved. In the end, the inferior pole of the tumor from the tectal plate was detached.

The tumor debulking started with the sessile part of the tumor, going toward the tumor insertion, located in the right lateral wall of the third ventricle (Fig. 11.2). CUSA was used for debulking, given the favorable soft consistence and moderate vascularization of the tumor. The CUSA was also used to resect the tumor in the proximity of the normal cerebral tissue of the thalamic nuclei, given the fine power variations of the aspiration/cavitation, and also the tissue selectivity. The dissection was continued at the superior pole of the tumor, detaching it from the third ventricle roof, continuing with the ependymal surface of the left lateral wall, and, in the end, the permeability of the sylvian aqueduct (Fig. 11.3) and foramen of Monro, using endo-

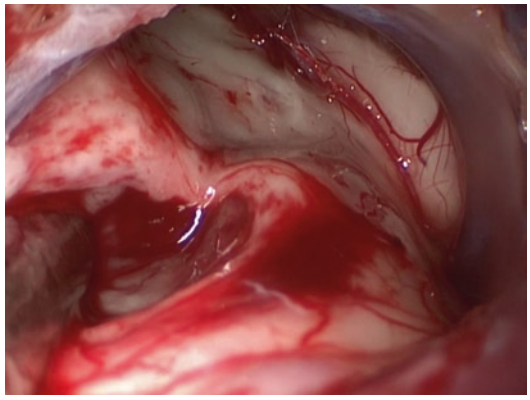

Fig. 11.2 Intraoperative bidimensional endoscopic view (0°) of the quadrigeminal cistern, left and right basal veins, posteromedial choroidal artery, tectal plate inferiorly, the right pulvinar and the tumor bulging into the third ventricle cavity

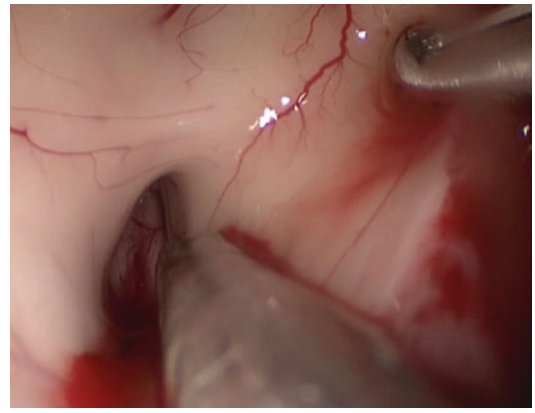

Fig. 11.3 Intraoperative bidimensional endoscopic view (30°) of the third ventricle floor and the Sylvius aqueduct which is permeable

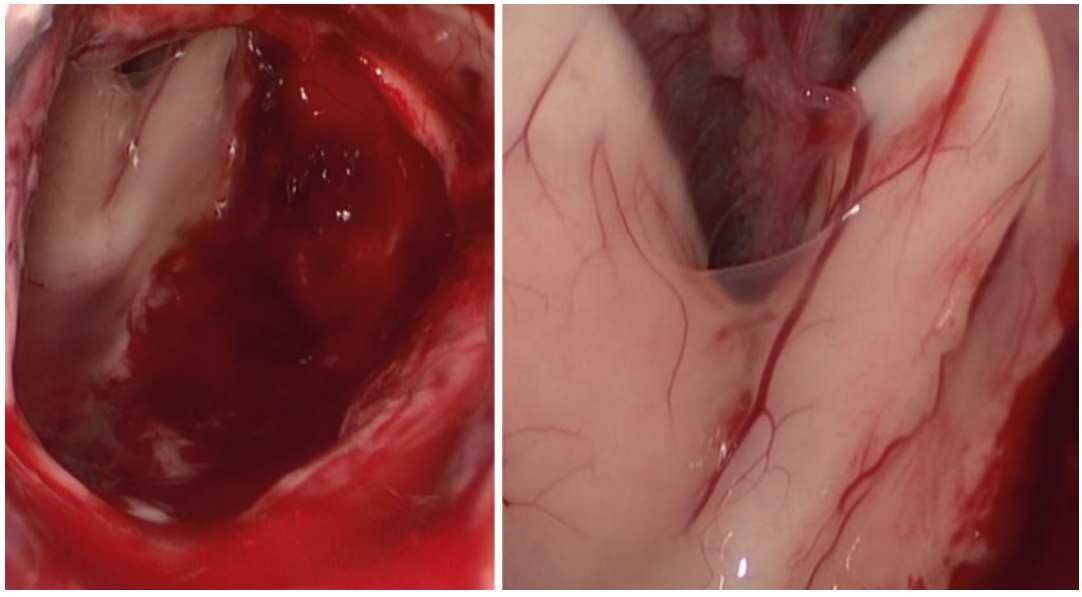

Fig. 11.4 Intraoperative bidimensional endoscopic view (0°) of the third ventricle, interthalamic adhesion and the tumor origin in the right thalamus (left-sided picture). The right-sided picture shows a closer view of the interthalamic adhesion and also of the roof of the third ventricle with the posteromedial choroidal arteries, choroid plexus, and internal cerebral veins

scopes with various angulation, were checked. Anteriorly, the columns of the fornix, anterior commissure, and lamina terminalis were identified (Fig. 11.4).

Immaculate hemostasis was obtained using saline irrigation, bipolar coagulation, and Avitene (fibrillary collagen). The dural margins were approximated, never attempting for a watertight closure, and Avitene was placed on the epidural space. The bone flap was secured with titanium plates and screws. Resorbable sutures were used to close the skin incision.

11.7 Postoperative Management/ Complications

In the first postoperative 24 h, a contrast-enhancing MRI was performed (Fig. 11.5), confirming the gross total tumor removal and the permeability of the Sylvian aqueduct, given by the flow artifact; no ischemic or hemorrhagic complications were encountered, only mild increase in the area of vasogenic edema from the right thalamus and mesencephalic tectum.

The external ventricular drain was removed after 48–72 h of ICP (intracranial pressure) monitoring.

The postoperative clinical evolution was favorable, with no new neurological deficits,

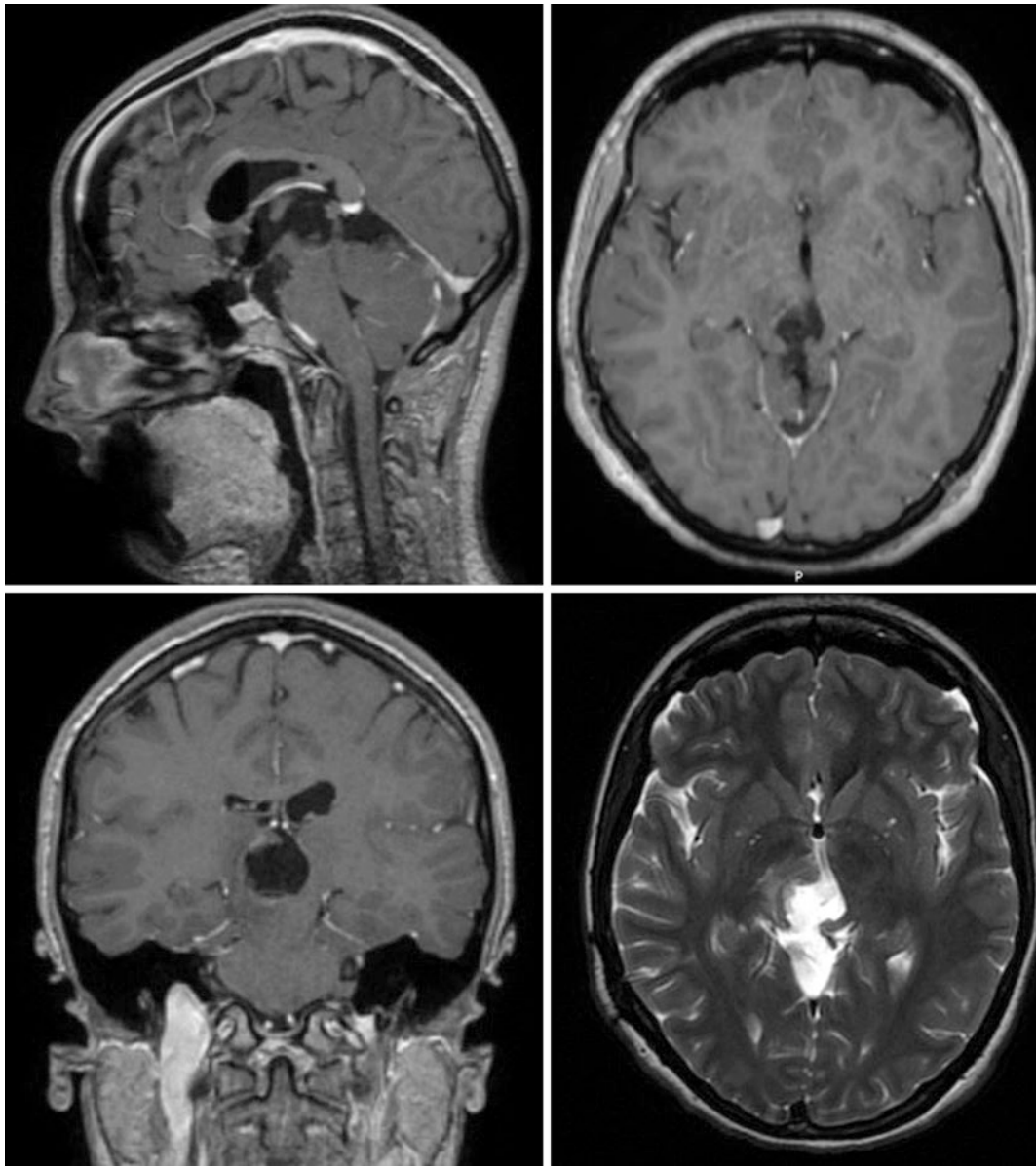

Fig. 11.5 Postoperative 3-plane gadolinium-enhanced MRI and axial T2 sequence confirming the gross-total resection of the enhancing tumor

except for a bilateral Parinaud Syndrome. The patient was discharged on the fifth postoperative day, and at 3-month-follow-up, she presented with complete resolution of symptomatology.

The histopathological and immunohistochemical examination was consistent with the diagnosis of ganglioglioma, WHO grade I.

The long-term follow-up (1.5 years) demonstrated favorable evolution, with no imaging signs of recurrence.

11.8 Discussion and Controversial Issues

Along with the integration of the new technology and new surgical tools, it is essential to be open to new and apparently unconventional techniques, but which may ultimately minimize the potential morbidities for patients. Neurosurgeons should actively pursue advancements in surgical approaches for overall improvement in all aspects of patient care, ensure the continuous development of their skills, the understanding of anatomy, and pathology, and thus of the specialty. One of the main goals in any brain surgery is to damage as little brain tissue as possible, regardless of whether the tissue is placed at risk during the approach by retraction or direct surgical manipulation.

In the case described in this section, the paramedian endoscopic supracerebellar infratentorial approach with a keyhole craniotomy in sitting position minimizes these risks, exemplifying the advantages of using an endoscope and deviating from the traditional midline open microscopic approaches.

With the patient in a sitting position, the cerebellum will relax with the force of gravity, the drainage of CSF, and the use of osmotic diuretics. The natural corridor reveals itself almost effortlessly as we make our way toward the pineal region without unnecessary injury to veins, torcula, sinus, or cerebellum. Before the beginning of the operation, all precautions to prevent an air embolism should be made, and the surgeon should be familiar with managing any intraoperative air emboli.

The neuronavigation system improves the anatomical orientation, helping in precise placing of the skin incision and craniotomy.

We use a paramedian approach, which allows for a better visualization of the pineal region because the view is unobstructed by bridging veins and the vermis; more than that, it provides a better view and better microsurgical control of the tumor insertion on the lateral wall of the third ventricle, when using a contralateral paramedian approach.

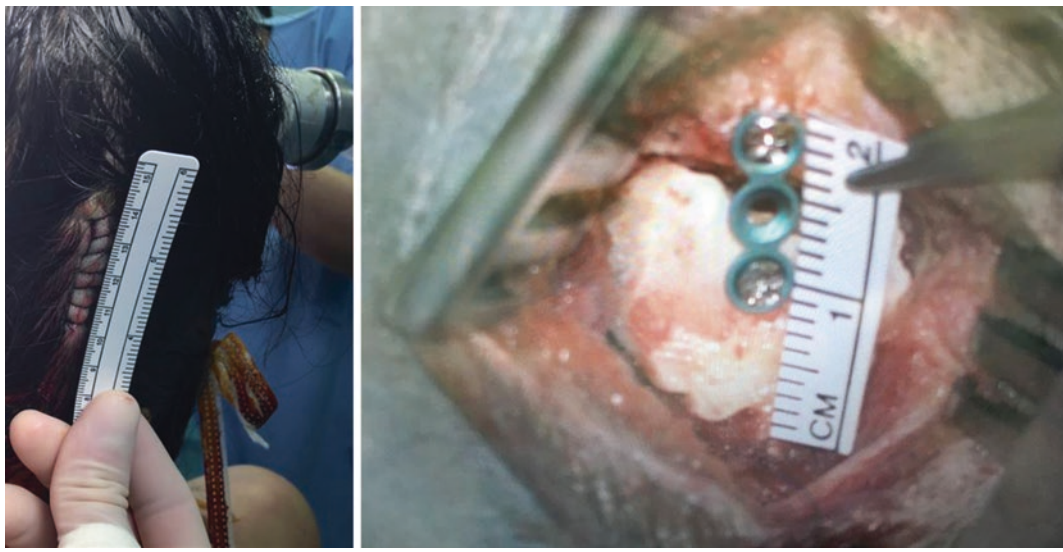

Fig. 11.6 The length of the skin incision (4 cm) and the diameter of the bone flap (2 cm)

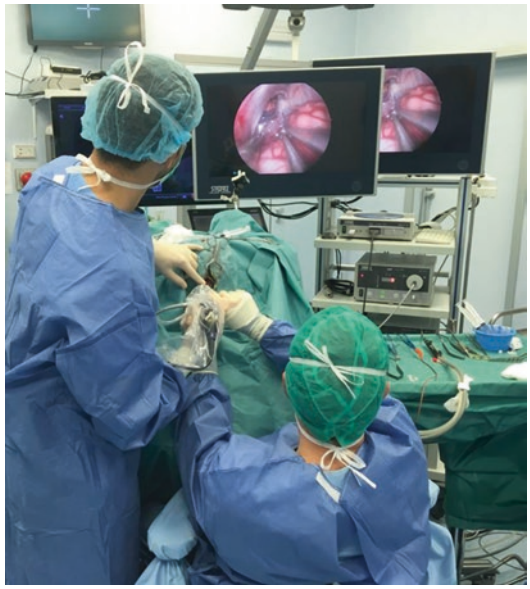

Fig. 11.7 The less demanding position of the operating surgeons and the operative setup

In this minimally invasive approach, the small skin incision (3–4 cm) and the keyhole craniotomy (1.5–2 cm) are important factors that contribute to the rapid postoperative recovery of the patient (Fig. 11.6).

Regarding the endoscopic variation of the approach used, there are some advantages compared to the standard techniques that use the operating microscope.

First of all, compared to the surgeon's demanding position when using the operating microscope, the endoscopic approach of the pineal region in sitting position is much more ergonomic, decreasing the surgeon's intraoperative fatigue (Fig. 11.7).

Second, the use of the endoscope provides a much better illumination, compared to the operating microscope whose luminosity is restricted by distance, the light source being located outside the cranial cavity. Even with a much smaller craniotomy, the surgical corridor is wide enough for almost any resection and the field is well-illuminated with the endoscope. Unlike in open microsurgical approaches, the relatively small craniotomy used in endoscopic approaches does not compromise the degree of visualization of the surgical corridor because the light source and camera are located within the cranial vault.

Although two-dimensional, the dynamic view of the operative field compensates for the lack of stereoscopy, and the magnification and the extended panoramic view afforded with the use of the endoscope generally provide a better visualization and close observation of the anatomical and pathological structures, facilitating a safe surgical dissection, regardless of the shape or structure of the tumor. More than that, the use of the angled endoscope is better for the visualization and control of critical anatomical areas that are nearly impossible to view through the operating microscope (like the Sylvius aqueduct), allowing for an extension of the surgical indications of this approach.

A multihanded approach is used, with the assistant surgeon holding the endoscope while the primary surgeon operates with both hands using standard microsurgical instruments and techniques. With regard to this approach, the emphasis is on the importance of collaboration between surgeons of different specialties, like in this case, where the surgery was performed with the aid of an ENT surgeon, who is much more familiar with the endoscopic techniques. The learning curve is understandably steep, as it includes not only the development and refinement of endoscopic skills, but the acquisition of new anatomical understanding as one sees the structures from unconventional angles.

Also, the smaller the craniotomy, the greater the risk of instrument conflict; the assistant holding the endoscope has to be an active participant in the surgical procedure, frequently advancing and retracting the endoscope as the primary surgeon is moving instruments in and out of the surgical field. As they are advancing on the learning curve and their experience is growing, they can anticipate better and better each other's movements, they can coordinate better, they know when and how to get out of each other's way, and learn how and when to help each other.

Therefore, there is no ideal or "correct" approach as yet, but the paramedian endoscopic supracerebellar infratentorial approach with a

keyhole craniotomy in sitting position, presented here (Video 11.1), can be an excellent option, for surgeons and patients, creating the best conditions for safe and accurate pineal region tumor resection, while minimizing surgery-related morbidity and maximizing the speed of postoperative recovery of patients.

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Management of Hydrocephalus

12

Horațiu Stan and Ionuț Olteanu

12.1 Introduction

Hydrocephalus is defined as a pathological increase of cerebrospinal fluid (CSF) inside the ventricles of the brain. Despite the relatively basic description of hydrocephalus, this pathology results from a disturbance in the intricate balance between CSF secretion and absorption. Obstructive hydrocephalus occurs when there is a blockage in the normal CSF flow, causing a progressive buildup of fluid in the ventricle(s) superior to the obstruction, whereas the nonobstructive designation is given when there is no discernible impediment of CSF flow. Typically, pineal region lesions produce a barrier at the level of the posterior portion of the third ventricle or Sylvian aqueduct, resulting in a triventricular obstructive hydrocephalus. In pediatric patients, these lesions account for almost 90% of such cases [1]. The surgical management of hydrocephalus, in principle, is associated with the diversion of the flow of CSF in order to restore the intracranial fluid equilibrium. To this purpose, several possible choices are taken into consideration: preoperative endoscopic third ventriculocisternostomy [1–3], ventriculoperitoneal shunt drainage, the treatment of the lesion itself and subsequent resolution of hydrocephalus, or even placement of a shunt between the third ventricle and cisterna magna after tumor resection [4].

12.2 Endoscopic Third Ventriculocisternostomy

Endoscopic third ventriculocisternostomy (ETV) refers to a small perforation made in the floor of the third ventricle in a neuroendoscopic procedure. It should be considered the first choice of treatment in all patients with pineal region lesions with dilated ventricles [5]. The main objectives of this surgery are:

(a) Obtaining a CSF sample for analyzing tumoral markers
(b) Creating a passage between the third ventricle and the interpeduncular cistern so as to divert the CSF away from the obstruction
(c) Performing an endoscopic biopsy of the tumor

The procedure is performed under general anesthesia, with the patient placed in a semi-sitting position and the head positioned in such a way that the burr hole is the highest point of the cranium. Thus, the risk of postoperative pneumocephalus is diminished. After careful consideration of imaging studies, preferably magnetic resonance imaging (MRI), we can choose between drilling one [6, 7] or two burr holes, depending on multiple factors: the size of the

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massa intermedia, the aim of surgery, the degree and severity of hydrocephalus, as well as the relationship between the tumor and massa intermedia [7]. If a biopsy is planned, ETV should take precedence due to the high risk of hemorrhage during tumor manipulation. Any intraoperative hemorrhage during this procedure blurs vision, is difficult to control, and can even endanger the patient's life.

Single Burr Hole Procedure. The procedure should be performed on the nondominant side of the brain. If the tumor is placed anteriorly enough, a single burr hole can be drilled, either in the usual site for an ETV, or even slightly more anterior to this point (Fig. 12.1). The skin is incised in an arch with the concavity pointing posteriorly to preserve scalp vasculature, cover and close the burr hole without risking CSF fistula, and promote wound healing. The burr hole will then allow the creation of the stoma and also the approach of the tumor for biopsy.

The 0° endoscope is inserted in its sheath and driven into the nondominant (usually right) lateral ventricle. Then a CSF sample is collected to test for biological markers (α-fetoprotein and human chorionic gonadotrophic hormone subfraction β for germ cell tumors; carcinoembryonic antigen for teratomas; placental alkaline phosphatase for germinomas, etc.). ETV is then resumed by carefully passing the endoscope through the foramen of Monro and into the third ventricle, so as not to damage the thalamostriate vein resulting in venous stroke or intraoperative hemorrhage. Once the infundibulum and mammillary bodies have been identified, a stoma is made on the midline at the halfway point between the aforementioned structures, that is, between the dorsum sellae and the tip of basilar artery. The opening in the third ventricle floor can be enlarged with dedicated forceps or with a Fogarty balloon. This specific sequence is important for symptom relief; otherwise, the signs of increased intracranial pressure may persist. If the membrane of Liliequist is visible, it needs to be opened to ensure a more adequate flow of CSF.

If intended, the biopsy of the lesion may then ensue. In certain cases, the tumor can be adequately inspected with the same 0° endoscope

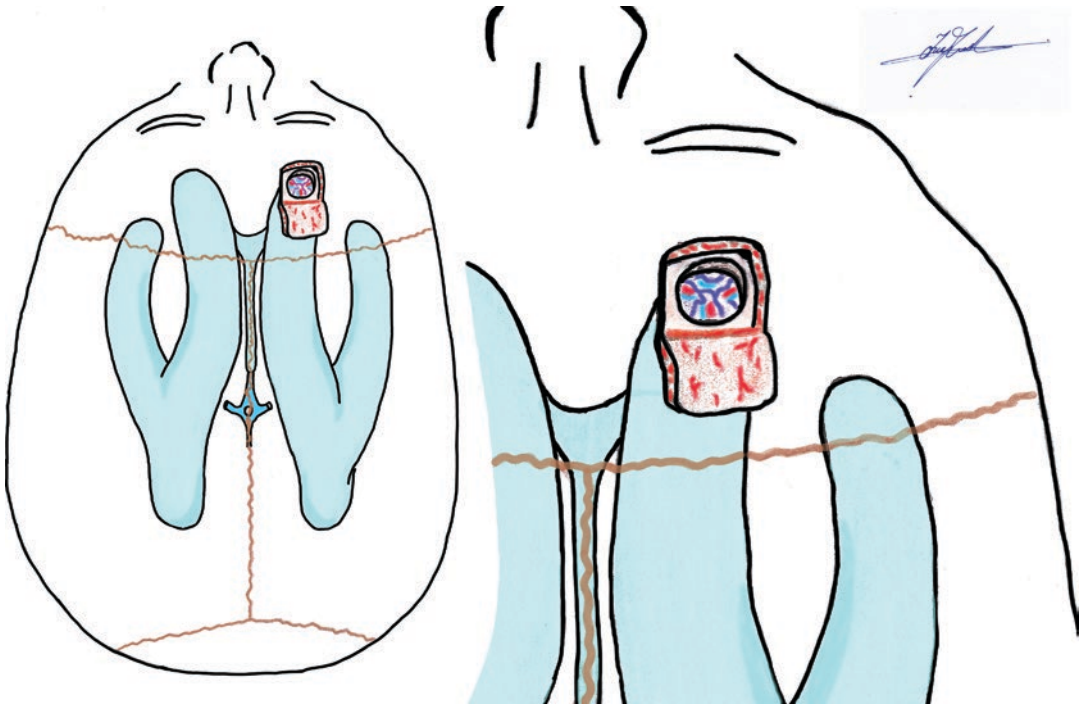

Fig. 12.1 Incision and burr hole position in one-burr hole procedure

previously used for ETV, or one with a 30° visual angle. The operator must always be mindful of the blind angle in which the endoscopic instruments are out of the sheath but have yet to appear on-screen. Any misstep while the instruments are off-screen can result in irreparable damage to sensitive neurovascular structures and irreversible neurological deficit. After clear visualization of the tumor, a location needs to be selected for biopsy, either with or without previous coagulation or incision of the capsule (Fig. 12.2). Sufficiently large forceps are needed in order to collect an adequate sample for pathology, with 4–5 individual pieces of the tumor usually being taken. A positive histologic sample is obtained in approximately 85% of patients, but the heterogeneous nature of these tumors may lead to an error rate in the initial diagnosis of approximately 21% of cases [8]. After obtaining the tissue sample, we can also strive to coagulate the surface of the tumor, if it is small and hypovascular enough. This act may alleviate tumor resection in an ulterior phase. In some cases, complete excision of the tumor is also feasible [5].

Two-Burr Hole Procedure. If the anterior portion of the tumor is situated in the posterior third ventricle, the tasks can be conducted through two separate burr holes [5, 9]. The preferred incision is linear in the sagittal plane on the nondominant side, at around 2–2.5 cm lateral to the midline (Fig. 12.3).

The first burr hole is usually made just anteriorly to the coronal suture, which allows collection of the CSF samples and conduction of ETV in the same manner as described earlier. The second burr hole needs to be drilled anterior to the first one, being designated for biopsy (Figs. 12.3 and 12.4). Biopsy of the lesion can be performed

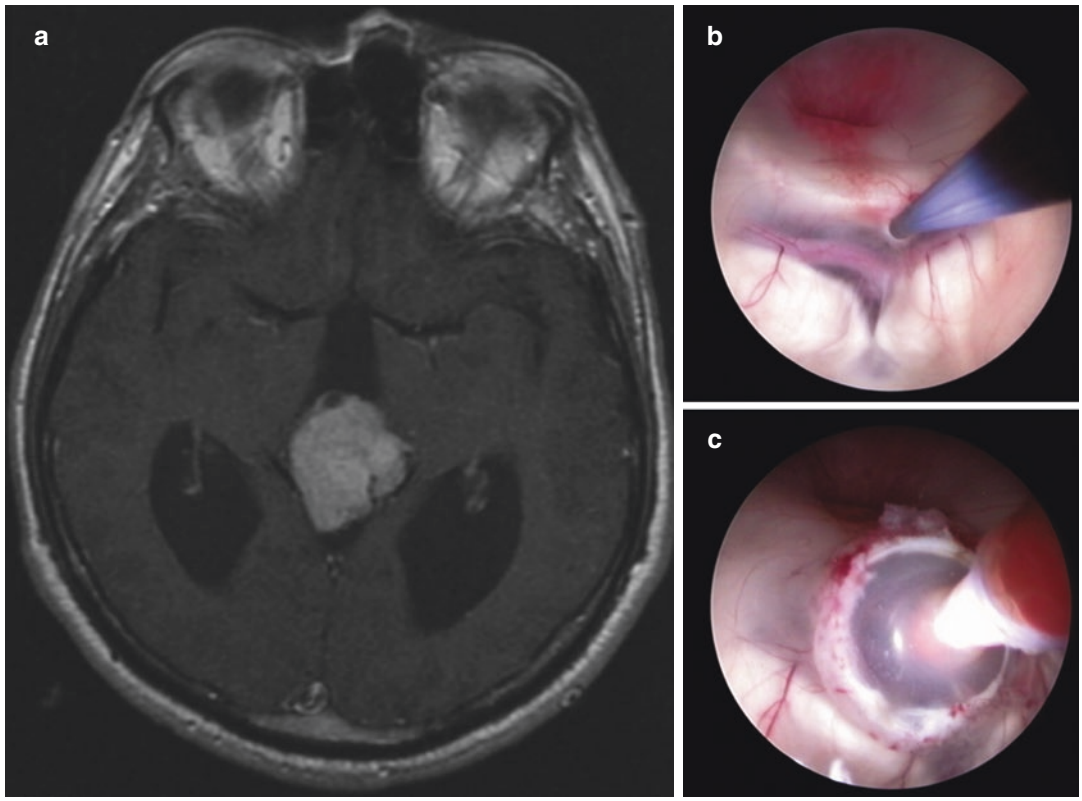

Fig. 12.2 Endoscopic biopsy of a pineal region tumor with previous coagulation; (**a**) preoperative T1 sequence Gd-enhanced MRI demonstrating the pineal region lesions; (**b** and **c**) endoscopic visualization of the tumor during coagulation

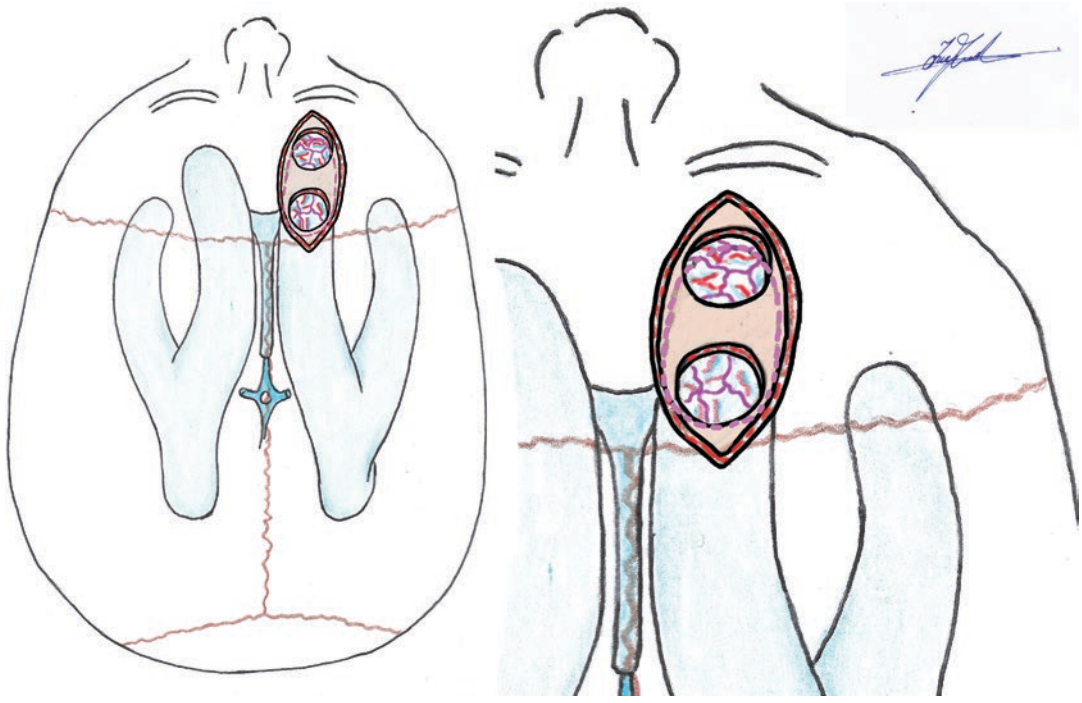

Fig. 12.3 Incision and burr hole positioning in two-burr hole procedure

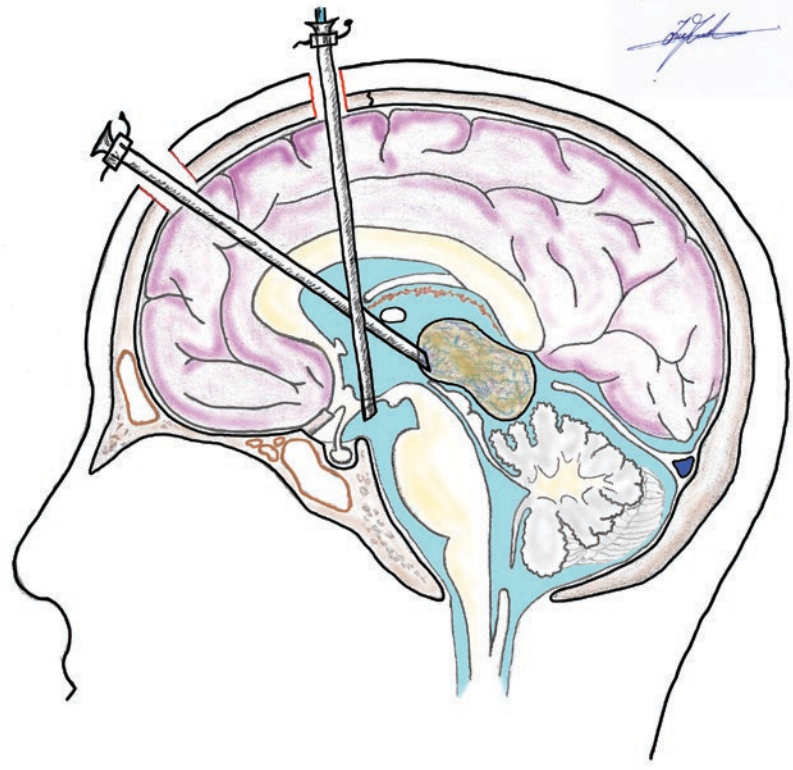

Fig. 12.4 Tumor removal and ETV using the two-burr hole procedure

after completion of ETV, following the same steps and principles as for the single burr hole technique. Regardless of the procedure, if the markers and the histological examination show the presence of a germ cell tumor, the patient must be transferred to the oncology department for appropriate treatment.

12.3 Ventriculoperitoneal Shunt

The ventriculoperitoneal (VP) shunt is the most common CSF diversion procedure performed using a permanent subcutaneous implant. In principle, it offers an alternative path for the CSF flow, while the peritoneum handles the resorption of excessive fluid. For pineal region lesions, the frontal approach is considered the most preferred method for insertion of a ventricular catheter, as it preserves the occipital region for tumor resection [2]. Compared to endoscopic surgery, this option does not allow collecting tumor tissue samples, it inserts non-biological materials into the organism, and it carries a predisposition to shunt failure and complications such as infections and over-drainage [1]. Tumor surgery performed after shunt insertion may increase the risk of shunt-related problems. Thus, some surgeons are in favor of delaying the treatment of hydrocephalus after the resection of the tumor.

12.4 Tumor Surgery

The main goal of surgery of the pineal region tumor is the complete removal of the lesion, which also, most often, results in the re-permeabilization of CSF pathways. If this is not possible, then a satisfactory intratumoral debulking has to be achieved at the very least. Once the tumor has been resected, symptoms of increased intracranial pressure may ameliorate or completely remit.

However, this strategy has a series of theoretical disadvantages. During the approach of the tumor, until the CSF from the third ventricle has been evacuated, the pressure gradient between the supratentorial and infratentorial compartments can generate surgical difficulties (e.g., narrow spaces, edema) or complications (e.g., downward heernia-tion and even respiratory failure). The relatively quick decompression of the ventricular system may also lead to important pneumocephalus, especially if the patient is placed in the sitting position. In turn, this may cause the patient to suffer from headache and nausea until the resolution of pneumocephalus. Rarely, a frontal burr hole may be required if the pneumocephalus degree is significant. If resolution of the hydrocephalus is not obtained by the resection of the tumor, the postoperative course may become challenging, marked by the symptoms of increased intracranial pressure and almost certainly requiring a second surgical intervention. Some surgeons [4] prefer placing the shunt generally after tumor resection if required, unless there is an acute obstructive hydrocephalus.

Another option is to perform an external ventricular drainage (EVD), either by classical approach or by puncture with a needle, and decompress the ventricular system before or during tumor resection surgery. In this situation, surgeons must be aware of the possible complications of EVD, especially infections [1].

12.5 Third Ventricle to Cisterna Magna Shunt

If no specific surgical procedure was performed to treat hydrocephalus (ETV or VP shunt), and the suspicion of persistent hydrocephalus remains at the end of the tumor resection, there is a possibility to place a catheter between the third ventricle and cisterna magna in order to bypass the non-functional Sylvian aqueduct [10]. This procedure has been only recently described; therefore, data regarding its effectiveness and longevity is limited.

12.6 Controversial Issues

Each of the described techniques is applicable for patients harboring pineal region lesions that cause obstructive hydrocephalus. Selecting the treatment course depends on the patient's clinical status, MRI findings, experience, and preference of the neurosurgeon. Nevertheless, ETV has gained a steady foothold because of its relative

accessibility and lack of implanted materials. It also offers the possibility for tumor biopsy during the same procedure. ETV has some drawbacks related to possibility of obstruction of the fenestration and the risk of bleeding during biopsy. In centers unable to perform this technique, a good valuable option is intraoperative EVD before dural opening, anticipating that complete removal of pineal tumor will solve the obstructive hydrocephalus. Whether EVD could lead to central brain herniation is a matter of debate. In our experience, we did not encounter such an event. VPS remains the standard therapy for persistent obstructive hydrocephalus. Additionally, neurosurgeons may simply opt for internal third ventricle cisterna magna shunt [8, 10], being aware that this method poses a similar risk of complication to VPS (mainly obstruction and infection).

12.7 Conclusions

Hydrocephalus is a common occurrence in pineal region pathology; however, there is a series of interventional strategies that may alleviate morbidity caused by increased intracranial pressure. ETV should be considered as the first step in the treatment of triventricular obstructive hydrocephalus, but neurosurgeons must be mindful that complete tumor resection often results in resolution of CSF blockage. Nevertheless, for patients in a critical neurological state, proper management of hydrocephalus may be lifesaving.

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Part III

Adjuvant Therapies

13 Radiosurgery

Fery Stoica

13.1 Introduction

Radiosurgery is a relatively new method of treating cerebral lesions and is defined as a single, high dose of focused radiation delivered precisely to the target in order to create a desired radiobiologic response within the target with minimal effects to the surrounding healthy structures or tissues. In contrast with conventional fractionated external beam radiation therapy (EBRT) which exploits the higher radiosensitivity of malignant tissues relative to normal brain, stereotactic radiosurgery (SRS) is capable of selectively affecting (destroy) the target, mainly with sharply focused radiation and steep dose gradient fall outside the treatment volume. The desired radiobiologic response consists in DNA strand breaks with irreparable cellular damage and delayed vascular occlusion by endothelial and myofibroblast proliferation.

Stereotactic neurosurgery emerged many years before Leksell's pioneering activity in Karolinska Institute, when, in 1908, Sir Victor Horsley and Robert Clark had described an instrument for localizing structures in the brain that they named as a stereotactic device [1]. Leksell's own prototype, presented in 1949, was using a rectilinear coordinate system and an arc-centered principle to deliver a probe to an intracranial target defined by radiographs of the skull [2]. Only 2 years after this invention, in his landmark paper of 1951 [3], Leksell coined the term "stereotactic radiosurgery" by conceiving the idea of replacing the surgically inserted probe with multiple narrow cross-fired beams of ionizing radiation stereotactically guided through the intact skull.

In the twenty-first century, technological improvements in medical imaging and computing have led to the increased clinical adoption of SRS. Stereotactic radiosurgery has been redefined as a distinct neurosurgical discipline that utilizes externally generated ionizing radiation to inactivate or eradicate defined targets without the need for a surgical incision [4].

13.2 Other Radiosurgical Techniques

In the last decades, in addition to the Gamma Knife, several other technological platforms developed radiosurgical capabilities, some of them being dedicated to radiosurgery, such as the CyberKnife or the proton-based radiosurgical equipment. At the same time, many other clinical and industrial improvements dramatically increased the spectrum of indications for radiosurgery and frame-based or frameless, single-session or multi-session treatments. Today, SRS is defined as the single-session, precise delivery

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of a therapeutically effective radiation dose to an imaging-defined target [5].

13.3 Stereotactic Radiosurgery in Neuro-Oncology

Pineal region lesions are a very challenging category of targets for neurosurgery because of their deep-seated location in the brain and the extreme risk that all surgical approaches encounter. In these conditions, SRS may be considered due to its highly conformal treatment plans which are capable to minimize the risk of damaging the surrounding critical structures. In this chapter, we will present the role of Gamma Knife radiosurgery (GKRS) in the treatment of pineal region lesions: indications, results, complications, using data from personal experience and literature review, as well as future developments.

The wide variety of tumor histologies and the lack of large series with significant outcome data irrespective of adult or pediatric literature render the use of SRS in the treatment of pineal region lesions very difficult to compare with other therapies in terms of efficiency. Nonetheless, there is no doubt about the very low incidence of complications, most of them being transitory.

In our center, in a time span of 15 years, we performed single-session frame-based SRSs using a Leksell Gamma Knife unit upon 27 pineal region lesions in 25 patients, representing 0.46% of total indications and consisting of 1 astrocytoma (pilocytic), 1 arteriovenous malformation (AVM), 2 ependymomas, 1 germinoma, 1 hemangiopericytoma, 2 metastasis, 12 meningiomas (all grades), 1 choroid plexus papilloma, and 4 pineocytomas.

Pineal parenchymal tumors are, along with **germ cell tumors**, common histologies in this area. **Primitive neuroectodermal tumors** and **tumors of glial origin** can also be encountered in the pineal gland [6]. Even though the treatment should be dependent on tumor histology, many times it is dictated by the complex anatomy of the adjacent organs at risk: the tectal plate of the midbrain with the superior colliculi, the interstitial nuclei of Cajal, and the central veins. In these conditions, the achievement of satisfactory results of SRS on the selected pineal tumors (Fig. 13.1) was surprising because in all these cases, the marginal dose was decreased to a value supported by the organs at risk, which is often lower than the therapeutic dose.

According to an early 1996 pioneering series from France [7] and another more recent report from 2006 [8], all treated tumors responded to SRS and no significant complications were observed, with mild and temporary radiation-induced reactions being controlled with steroids. The well-documented report of the French National Register on 452 patients with pineal tumors published in 2014 [9] emphasizes the role and effectiveness of SRS in both residual tumors

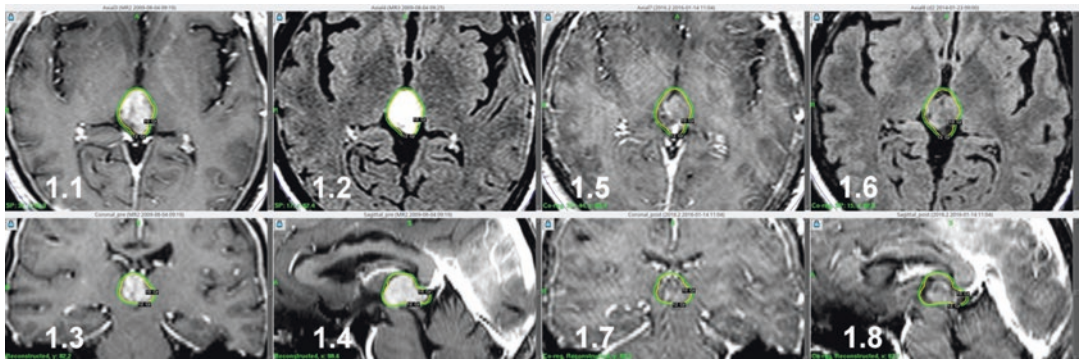

Fig. 13.1 MRI images (1–4) of a pineocytoma diagnosed in a 39-year-old woman at the time of GKRS treatment; follow-up images (5–8) after more than 6 years reveal stable remnant tumor with significant reduction in volume and without contrast enhancement

after surgery or EBRT and, in selected cases, as primary therapy.

In another study, from the University of Pittsburgh, Hasegawa and co-workers reported the results of 16 patients with pineal parenchymal tumors (pineocytomas and pineoblastomas) treated with GKRS [10]. The local tumor control rate was 100% [10].

A larger series from Japan presents the more eclectic results of their experience on 30 patients with pineal and related tumors treated with GKRS: only 73.3% response rate and tumor progression was observed in 26.7% of patients, of which 23.3% died as a consequence [11]. Comparing histologies, the authors observed that germinomas (Fig. 13.2) and pineocytomas showed response and control rates of 100%, and neither progression nor death occurred after GKRS treatment. In contrast, malignant germ cell tumors and pineoblastomas showed a more unfavorable response and prognosis, both being at 50%.

In 2012, Yianni et al. reported outcomes of 50 GKRS treatments on 44 patients with a great variety of pineal lesions, of which 20 were without a prior histological diagnosis [12]. For these patients, overall progression-free survival (PFS) results were 93% at 1 year, 77% at 5 years, and 67% at 10 and 20 years. Worse outcomes were noted in patients with higher initial tumor grade, previous EBRT, or radiological evidence of intratumoral necrosis. One patient developed transient diplopia, which disappeared within a year.

In 2017, the International Gamma Knife Research Foundation issued a report about Histology-Stratified Tumor Control and Patient Survival After SRS for Pineal Region Tumors [13] using data from five centers about 70 patients treated between 1989 and 2014 with a median follow-up of 47 months. Excellent local control and survival rates around 80% at 20 years were obtained for pineocytomas and germinomas. The results of patients with a high-grade tumor were significantly less favorable, with the worse outcome being recorded in patients with pineoblastomas: as little as 27% local control and 48% survival rates at 5 years. Complications, consisting of new focal neurological deficit, Parinaud syndrome, and hydrocephalus, occurred in 9%, 7%, and 3% of cases, respectively. The report concludes that SRS is a safe treatment for pineal region tumors, but its efficiency is highly dependent on tumor histology.

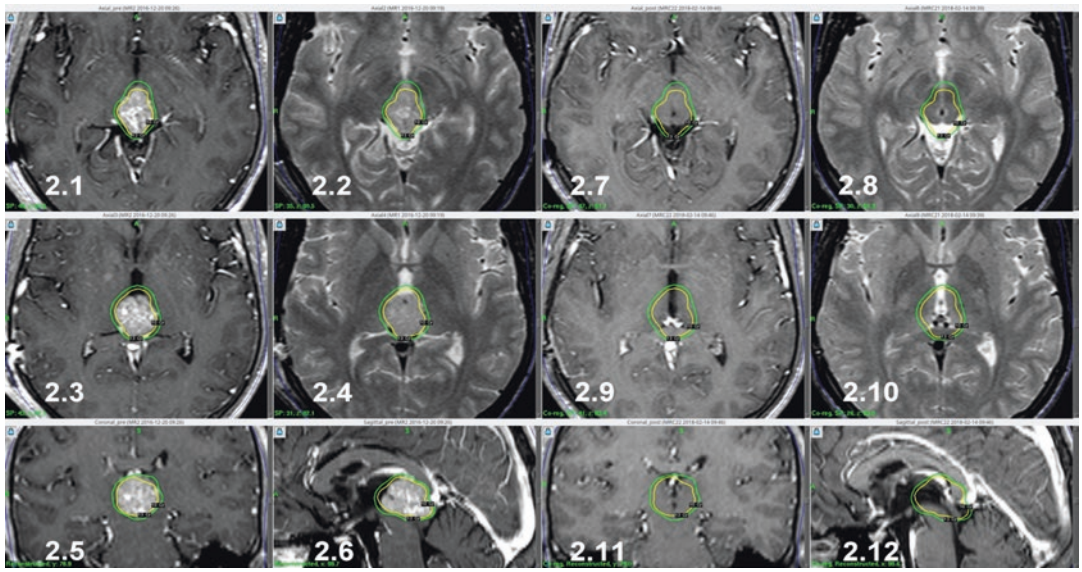

Fig. 13.2 Germinoma of the pineal region in a 27-year-old man treated by GKRS (1–6) with 13 Gy on the 50% isodose, with complete remission after 14 months (7–12)

Meningiomas are, at the same time, the most common intracranial benign tumors encountered in our neurosurgical practice and the most frequent indication for GKRS treatment. On the other hand, in our experience, even though meningiomas represent 22.3% of all indications, the falcotentorial ones with extension in the pineal region count for less than 1% (Fig. 13.3). Fortunately, these tumors have many ideal characteristics for radiosurgery: they are easily visualized on magnetic resonance imaging (MRI) and enhance well with contrast because they are richly vascularized. This means that meningiomas will benefit from both radiobiologic effects of SRS: irreparable cellular damage and delayed vascular occlusion.

It is well known that the best prevention of meningioma recurrence is the completeness of surgical resection, as Simpson demonstrated in his classic paper of 1957 [14]. In 2003, in another classical paper, Pollock et al. [15] showed that there is no statistical difference between the actuarial PFS rate, at 3 and 7 years, of patients with Simpson grade I resection and those with SRS. In contrast, the PFS rate of patients with SRS was significantly better than those with Simpson grade II, III, and IV resections with a much lower incidence of complications.

Over the last three decades, many major series about the result of SRS treatment of meningiomas were published: beginning with the experience of Pittsburgh University in 1991 [16], updated in 2008 [17], continuing with Malik et al., in 2005, presenting 309 patients from Sheffield [18], or Pollock et al., in 2012, who provided updates on the Mayo Clinic experience on 416 patients treated with the Gamma Knife [19]. All these studies concluded that local control rates after SRS on intracranial WHO grade I meningiomas ranged between 93 and 96% at 5 years and between 87 and 91% at 10 years with 3–8% radiation-induced complications. In contrast, atypical tumor control was only in the range of 50% and, for malignant meningiomas, as little as 17%.

Probably the most consistent retrospective observational analysis of SRS treatments for meningiomas is the study of Santacroce et al. [20] of 4565 patients with at least 2 years of follow-up from 15 European Gamma Knife centers. Their conclusion, based on excellent long-term results (control rates of 95% at 5 years and 89% at 10 years with radiation-induced morbidity of less than 7% of patients), is that radiosurgery is a safe and effective treatment for benign meningiomas even in the medium to long term.

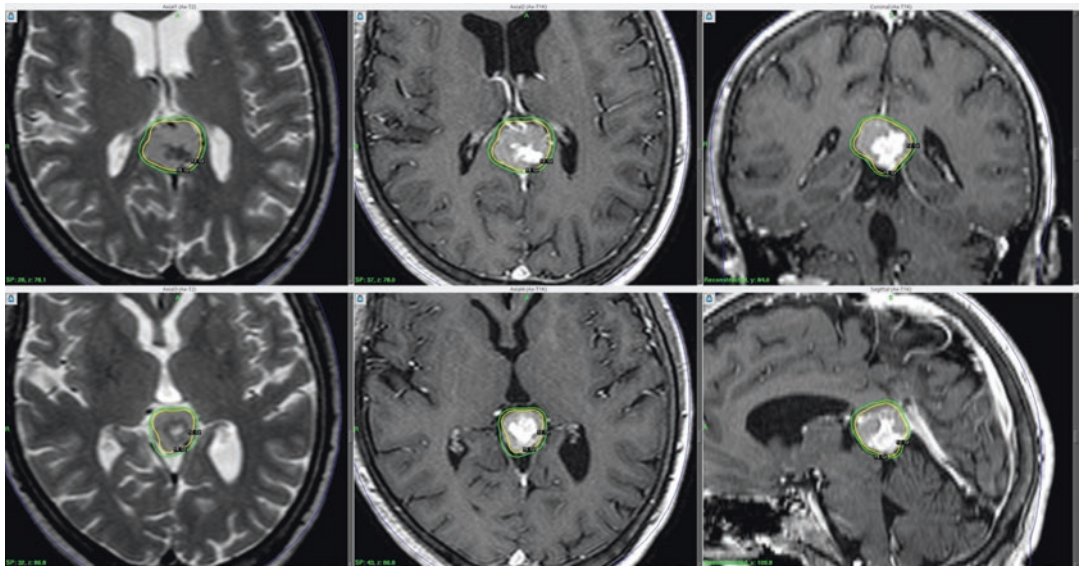

Fig. 13.3 GKRS treatment of a partially calcified meningioma of the pineal region in a 67-year-old woman

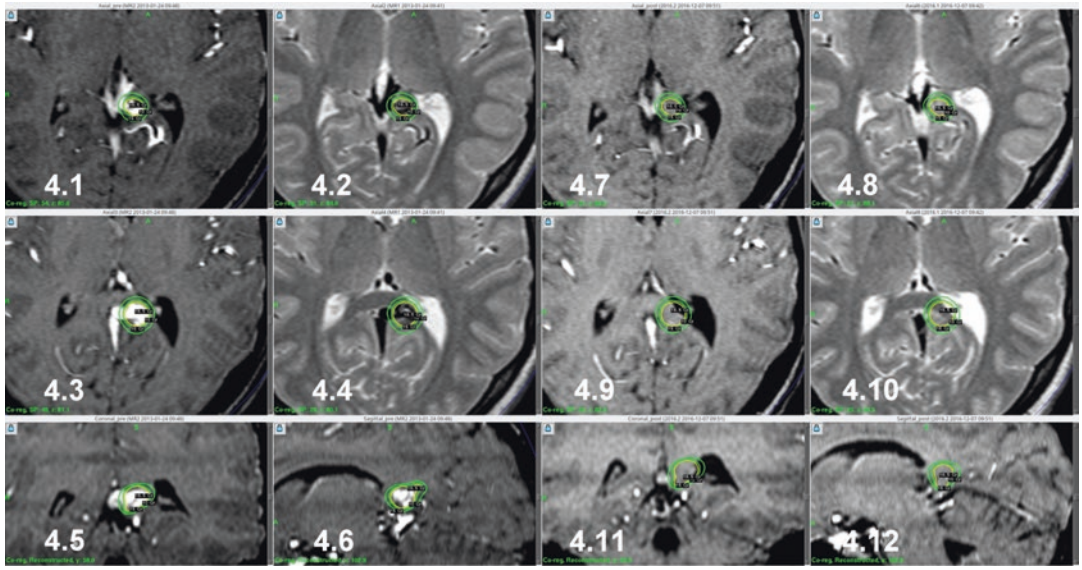

Fig. 13.4 A 29-year-old woman with an unruptured AVM located in the pineal region irradiated with the Gamma Knife (1–6) with 18.5 Gy on the 55% isodose, which shows complete obliteration of the nidus (7–12) after almost 4 years of follow-up

13.4 Stereotactic Radiosurgery in Vascular Lesions

Vascular disorders, such as **arteriovenous malformations** (AVMs) and **cavernomas**, with almost 7% of our total radiosurgical practice, represent one of the most common indications for GKRS treatment. Nonetheless, the pineal region location of AVMs is, even in these circumstances, so rare that not only in our experience (only one patient), but also in neurosurgical literature, there are very scarce reports with not more than individual case presentations [21]. The annual risk for spontaneous bleed from brain AVMs is well documented and ranges from 2 to 4% [22], with approximately 1% annual death risk. At the same time, excellent results of GKRS in this very challenging pathology are very well documented, from classical papers published in the early 1990s [23], to the most recent ones [24], and all of them depict 81–82% complete obliteration of treated AVMs at 10 years with significant reduction of intracranial hemorrhage to approximately 1.1% per year for those with incomplete obliteration within 3 years after radiosurgery. Complications after radiosurgery are rare [25], being quantified to less than 8% with only 1.6% of disabling sequelae. Nowadays, these figures are constantly decreasing by use of late technological developments in SRS techniques, which allows practitioners to perform staged-volume radiosurgery [26] or hypofractionated SRS [27] on large AVMs. Our own series confirm this statement, the obliteration rate being approximately 91% at 3 years of follow-up (Fig. 13.4) with only 1.9% of radiation-induced complications.

13.5 Controversial Issues

Glial tumors represent in all, and especially in the pineal region, a much less fitted pathology for SRS because of their characteristics which often contradict all criteria favorable for radiosurgery: they are not well circumscribed, they are generally over 3 cm in diameter, they have subependymal spread, and they are too close to organs at risk such as the tectal plate of the midbrain, optic radiation, or even the brainstem [28]. Pilocytic

astrocytoma is one of the very few indications for SRS against glial tumors of the pineal region in both pediatric [29] and adult patients [30]. After a median follow-up period of 55.5 months, Kano reported a PFS rate of 91.7% at 1 year and 70.8% at 5 years [29]. The prospective randomized trial RTOG 93-05, after investigating the benefits of adding radiosurgery to conventional therapy for the initial treatment of malignant gliomas, found no survival benefit for the addition of a targeted boost to conventional radiation therapy and chemotherapy [31]. Nowadays, the decision of accepting or rejecting the use of SRS treatment in these individual challenging cases is made mostly at the clinician level and is influenced more by personal experience than by institutional guidelines or imperfect literature reviews [32].

Even though **brain metastases** are an increasingly more frequent pathology treated by neurosurgeons, due to the fact that 20–40% of cancer patients will develop brain metastases which, untreated, have a very poor outcome, with only 1–2 months of life expectancy, they are not so numerous in the pineal region, being reported sporadically, usually as leptomeningeal metastases with a poor prognostic factor [33]. Also, in our practice, despite the fact that brain metastases represent the most frequent indication with almost 29% of all cases, in 15 years we have treated only one metastasis in the pineal gland.

13.6 Future Developments

In the near future, in addition to the technological advances already presented, which allow us to perform staged-volume or hypofractionated SRS in order to minimize radiation injury to healthy surrounding brain, we will definitely see a vigorous "strike-back" of the particle treatments, not only because the protons were the first used radiosurgical modality [34], but mainly due to the exceptional recent developments in accelerating heavy ions (carbon et al) and especially based on the proliferation of clinical proton and carbon therapy facilities which are carrying out SRS [35]. Besides, there are more and more opportunities to perform proton imaging and even "proton microscopy" and to incorporate them into the so-called theranostic strategies, [36] which aim to improve cancer treatment efficiency by nanomedicine-mediated drug targeting [37]. The place and contribution of SRS in this intriguing multidisciplinary field remain yet to be determined, but it is of mutual benefit to exploit the selectivity of new molecular agents in conjunction with the extreme precision of radiation delivery performed by stereotactic radiosurgical techniques [38] in order to maximize the destructive effects on target and minimize adverse effects to healthy surrounding tissues.

13.7 Conclusions

In conclusion, radiosurgery of pineal region lesions appears to be an appropriately safe and effective treatment modality for selected patients, with many promising future developments.

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14 Other Radiotherapeutic Techniques

Dana Michaela Cernea

14.1 Introduction

Tumors arising in the pineal region are rare, representing 2–4% of the pediatric central nervous system (CNS) tumors and less than 1% of adult CNS tumors [1]. They can have local extension or can develop leptomeningeal or spinal metastases. More than 60% of pineal tumors are germ cell tumors (GCTs): germinomas and non-germinomatous germ cell tumors (NGGCTs). Evaluation and staging of the disease are very important for treatment planning and should include magnetic resonance imaging (MRI) of the entire neural axis, lumbar puncture with cerebrospinal fluid (CSF) cytology, and CSF alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG) determination. Serum AFP and beta-HCG values must also be assessed [2].

Radiation therapy is part of a multidisciplinary treatment depending on the histological type and disease extension. Taking into account that this tumor occurs predominantly in younger age, overall treatment strategy is extrapolated from children to adults. Tumors have a different grade of radiosensitivity, with pure intracranial germ cell tumors being the most radioresponsive. Target volumes, total dose, and dose at organs at risk are important parameters of treatment planning [3].

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14.2 Target Volumes and Treatment Planning

Pure germ cell tumors are highly curable: overall survival at 5 years is 60–90% with radiotherapy only. Whole ventricular radiotherapy (WVRT) plus boost on primary tumor is recommended for localized disease, if radiation therapy is not associated with chemotherapy. Total dose (TD) recommended on WVRT is 24 Gy/1.8–2 Gy/fraction (fr) with boost on primary tumor to 45 Gy/1.8–2Gy/fr. Focal radiation therapy of the residual tumor after surgery or cavity of resection is indicated if the combination with chemotherapy is decided [4].

Disseminated disease (leptomeningeal or spinal metastasis) at the time of diagnosis is treated by craniospinal irradiation. The whole brain and the entire spinal cord represent the target volume. A boost on primary tumor and on bulky disease of the spinal cord is done. For patients treated only with radiotherapy, a total dose of 24 Gy/1.8–2 Gy/fr on the entire craniospinal axis and a boost with 21 Gy/1.8–2Gy/fr on whole measurable disease are indicated. When chemotherapy is used, the TD on craniospinal axis is lowered to 21 Gy/1.8–2Gy/fr with a boost with 30 Gy/1.8–2Gy/fr on measurable disease. Patients with NGGCT, metastatic disease, are treated with CSI and chemotherapy: 36 Gy/1.8–2Gy/fr on craniospinal axis with boost to TD = 45 Gy/1.8–2Gy/fr on measurable disease [5]. Parenchymal pineal tumors are treated with

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surgery and adjuvant radiotherapy. A prescribed dose of 50.4–54 Gy/1.8–2Gy/fr is generally used. High percentages of local failures are reported when doses less than 50 Gy/1.8–2Gy/fr are prescribed [6].

Delineation of target volumes for treatment planning is achieved using a simulation computer tomography scanning with contrast. A fusion with preoperative or postoperative MRI is indicated when possible. The following parameters are defined: gross tumor volume (GTV) as cavity of resection, or the macroscopic disease in postoperative or preoperative MRI; clinical target volume (CTV) as the expansion of GTV with 1.5–2 cm depending on the histological type, areas at risk at diagnosis, and aspects of resection cavity; planned target volume (PTV) as the expansion of CTV with 0.3–0.5 cm for set-up margins [7–9].

Extended disease requires CSI. The scanning during simulation procedure starts from the vertex to the sacral vertebrae S2–S3 with thin slices (2–5 mm depending on the region of interest). Fusion with preoperative or postoperative MRI is recommended when possible. A cranial CTV including whole brain, frontal lobes, cribriform plate, and a 5–10 mm inferior expansion below the base of the skull is delineated. The spinal CTV is the entire thecal sac (inferior lower limit on MRI), extended laterally to cover the intervertebral foramina. PTV is defined as the uniform expansion of CTV with 0.3–0.5 cm set-up margins. A boost on tumor resection cavity, postoperative residual tumor, or metastatic spinal disease is required. GTV, CTV, and PTV are defined taking into account MRI examinations prior and post surgery or chemotherapy, depending on the treatment protocol [8–10].

Organs at risk must be carefully identified and delineated because of the cognitive and functional deficits, hormonal impairments, and neurological alterations which can be late effects of radiation treatment, especially when total doses admitted are exceeded. The following should be delineated: lens, lacrimal gland, optic nerves, retina, optic chiasma, cochlea, hippocampus, brainstem, pituitary gland, temporal lobes, and cerebellum. Dose constraints for intracranial organs at risk must be respected [11–13].

14.3 Treatment Delivery

Increasing the conformity of treatment is important in order to augment the tumor dose while minimizing the dose to normal tissues. Methods of radiation delivery in photon techniques include three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT).

Three-dimensional conformal radiotherapy uses fields with the same radiation intensity conforming to the shape of the tumor, avoiding normal tissues. Important parameters like isocenter location, beam energy, gantry, couch position, collimator, field size, field modifiers, and dose prescription are specified by the planner to develop a treatment plan (forward treatment planning) (Fig. 14.1a–c).

Inverse Planning Algorithms are used in IMRT techniques to generate treatment plans, taking into account the pre-specified target volume goals and organs at risk constraints. Multiple beam arrangements, coplanar or non-coplanar, with non-uniform beam fluence are generated. A highly conformal treatment plan in which high-dose regions can be shifted away from critical structures, but with a lower dose in uninvolved tissues, is can be obtained [14]. Volumetric modulated arc therapy (VMAT) is based on delivery of coplanar intensity-modulated arcs, in which the linear accelerator gantry rotates around the patient. The treatment plan is highly conformal with regard to target volume coverage, homogeneity, and normal tissue sparing. A major advantage is the speed of treatment delivery: 10–15 min treatment time for VMAT compared with 30–45 min for IMRT. The technique is very advantageous for CSI [6, 9, 10].

Proton Beam Therapy (PBT) is used based on the physical properties of particle beam dose deposition (Bragg peak). The possibility to deliver RT with minimal exit dose, protecting the normal tissues is one of the main advantages of PBT. The dosimetric advantages of PBT are best seen in CSI. The spinal cord, as target volume, is homogeneously covered by the dose prescribed with minimal dose spread anteriorly into critical organs (thyroid, lungs, heart, gastrointestinal

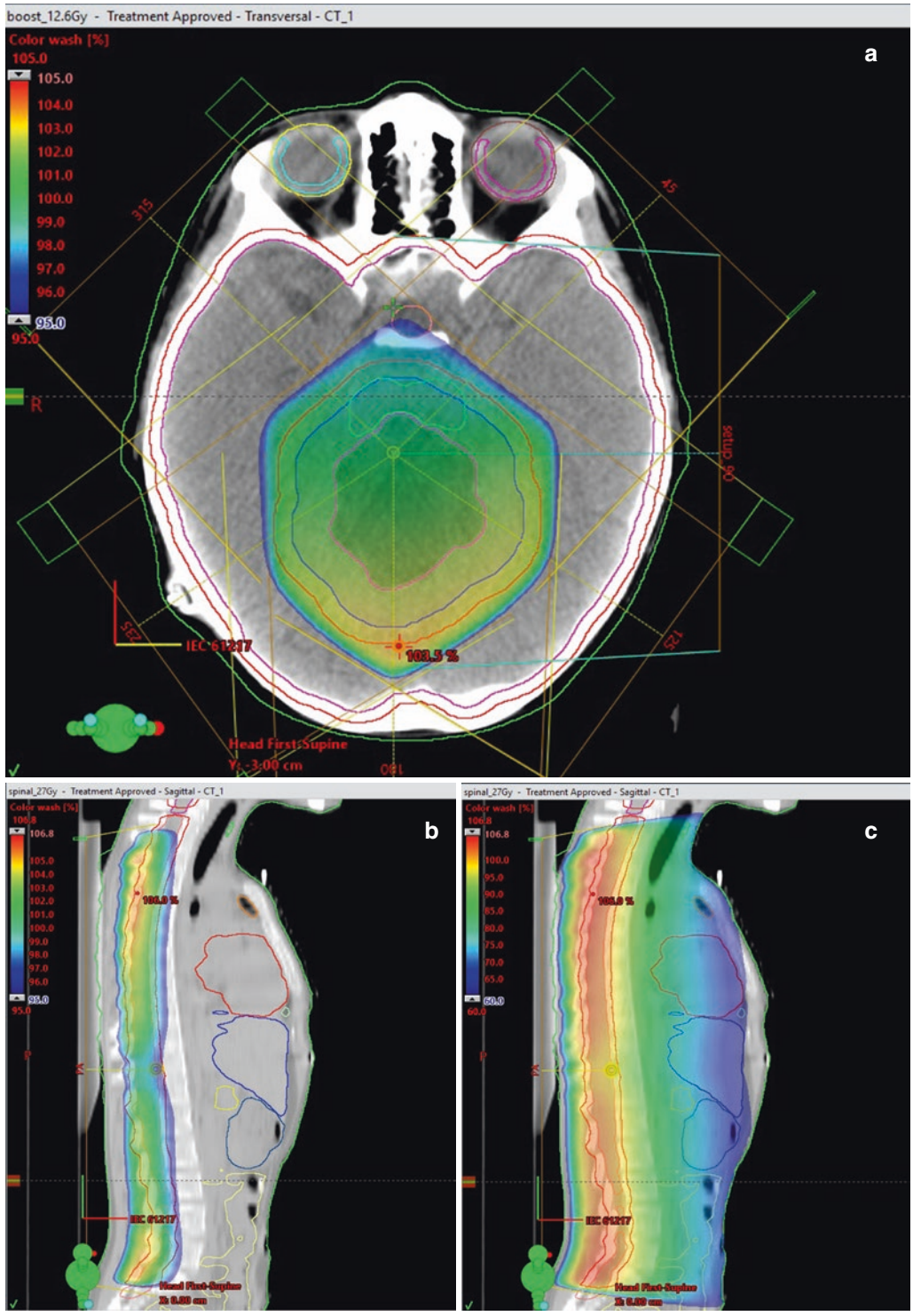

Fig. 14.1 3D-CRT for a pineal germ cell tumor, CSI technique; prescription dose 27 Gy, entire craniospinal axis with boost on primary tumor with 12.6 Gy: (**a**) axial slice of 5 beams arrangements for boost, 95% isodose blue color wash; (**b**) sagittal slice of spinal irradiation, 95% isodose in blue color wash; (**c**) sagittal slice of spinal irradiation, 60% isodose in blue color wash

structures). Protons also have greater linear energy transfer in the matter and are estimated to have a greater radiobiological effectiveness for cell killing than photons. Dosimetric distribution of energy and probably a better radiobiological effectiveness could be associated with high local control and low rates of late effects, but with expensive treatment costs [14, 15].

14.4 Conclusions

Fractionated radiation therapy is an important part of the multidisciplinary treatment of pineal region tumors. Highly conformal radiation techniques can be used in order to obtain a better local control with lower rates of acute and late effects. The increase of overall survival and quality of life are goals in choosing treatment methods.

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15 Chemotherapy

Mihaela Aldea and Elena Diana Olteanu

15.1 Introduction

Pineal region tumors include a broad spectrum of tumor histologic subtypes that can be assigned to four main categories: germ cell tumors, pineal parenchymal tumors, glial cell tumors, and other miscellaneous tumors and cysts. The most common tumors of the pineal region are germ cell tumors and pineal parenchymal tumors [1].

Systemic treatment with chemotherapy has shown variable tumor responses depending on histology. Historically, germ cell tumors have proven a higher sensitivity to chemotherapy than pineal cell tumors. Chemotherapy is usually employed as an adjuvant treatment, in addition to radiotherapy, in selected cases of high-volume disease in the preoperative setting, or in case of tumor relapse.

15.2 Germ Cell Tumors

The therapeutic management of germ cell tumors (GCTs) consists of a multimodal approach. Chemotherapy alone was shown to have a high rate of disease relapse, while radiation alone provided good local control rates but increased neurotoxicity. Chemotherapy has evolved as an attractive means to decrease the neurotoxic effects of radiotherapy by minimizing the amount of radiation needed to effectively treat children with pineal region tumors [2]. This resulted in the decreased risk of long-term toxicities, including neurocognitive effects, hypopituitarism, and second malignancy [3]. Germinomas are efficiently treated with chemotherapy and radiotherapy, whereas nongerminomatous germ cell tumors usually require surgical resection, chemotherapy, and radiotherapy. Mature teratomas are often curable by surgery alone [2].

Localized germinomas: Neoadjuvant chemotherapy has been explored in patients with localized intracranial germinomas, followed by a reduced dose and volume of radiotherapy, in an effort to minimize toxicity. The prospective, nonrandomized SIOP CNS GCT 96 trial, which included 190 children and adults with localized germinomas, proved that chemotherapy followed by reduced-field radiotherapy was non-inferior to reduced-dose craniospinal irradiation in terms of 5-year event-free survival and overall survival (OS). However, there was a benefit in 5-year progression-free survival (PFS) for craniospinal irradiation (97% vs. 88%, $P = 0.04$). In the combination chemoradiation arm, 7 out of 65 patients relapsed, with 6 patients having ventricular relapse, outside the primary radiation field. This suggests the need for enlarging the radiation field by including the ventricles. The chemotherapy regimen used was two courses of carboplatin/etoposide alternating with etoposide/ifosfamide [4]. Although germinomas are highly chemosensitive,

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the use of chemotherapy alone in this setting led to relapse in fairly half of the patients treated [5–7], despite a risk-adapted use of the chemotherapy regimens.

Metastatic germinoma: In 45 patients with metastatic germinoma included in the SIOP CNS GCT 96 study, patients received craniospinal radiotherapy (24 Gy) with focal boosts (16 Gy) to primary tumor and metastatic sites, with or without chemotherapy before irradiation. The administration of chemotherapy before radiotherapy failed to provide any clinical benefit, compared with craniospinal radiotherapy alone. Radiation therapy provided a 5-year event-free and overall survival of 98% [3].

Recurrent germinoma remains sensitive to chemotherapy and radiotherapy; however, re-irradiation in a previously irradiated field is often difficult to perform due to the risk of severe acute and long-term toxicities [8]. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) is a promising therapy for recurrent intracranial germinoma, but the optimal high-dose chemotherapy regimen is unknown, although the majority of groups have used thiotepa-based regimens [9]. Recently, a Japanese group reported excellent results using a melphalan-based conditioning regimen administered in either a single cycle or multiple sequential cycles; they attributed the success of the study to the fact that all patients achieved complete remission after platinum and ifosfamide–based chemotherapy (at least one cycle of iforfamide-carboplatin-etoposide (ICE)) before HDC [10].

Nongerminomatous GCTs (NGGCTs) include yolk sac tumors, choriocarcinoma or embryonal carcinoma, or mixed histologies with germinoma and/or with teratoma [1]. Although primary intracranial NGGCTs are less radiosensitive and have poorer prognosis compared to germinomas, they are highly responsive to platinum-based chemotherapy, with response rates of 68–78% in prospective studies utilizing chemotherapy alone [6, 7]. However, chemotherapy alone was associated with relapse rates of 50–70% [6, 11]. Because of such a high risk of local recurrence and metastasis, a combined treatment of radiotherapy and chemotherapy is strongly supported, as it has been proven to increase the chance of cure. In non-randomized studies, the addition of cisplatin at a minimum cumulative dose of 400 mg/m^2 had a favorable impact on the patients' prognosis, and platinum-based chemotherapy followed by radiotherapy improved survival rates [11–13]. The most frequently used chemotherapy involved standard children's oncology group (COG) and SIOP agents (platinum agents, etoposide, and ifosfamide) [14].

15.3 Pineal Parenchymal Tumors

According to the World Health Organization (WHO) classification of tumors in the central nervous system, which was revised in 2007, PPTs are subdivided into well-differentiated pineocytoma (PC), pineal parenchymal tumor (PPT) with intermediate differentiation (PPTID), and poorly differentiated pineoblastoma (PB). A standard treatment strategy for these tumors has not yet been established. Various treatments from surgery or radiotherapy and chemotherapy alone to radiotherapy and chemotherapy in combination have been applied. Chemotherapy is usually used for aggressive pineal tumors, while pineocytomas are treated with surgery alone (gross tumor resection) or stereotactically guided iodine-125 seed implantation [15, 16].

Pineoblastomas correspond to WHO grade IV tumors. Similar to the central nervous system primitive neuroectodermal tumors, they are highly aggressive malignant infiltrative tumors with a significant potential for dissemination and a poor prognosis that account for approximately 5% of childhood brain tumors [17]. Gross total resection has been shown to improve overall survival, while prognosis was negatively impacted by a partial tumor resection [18]. In cases of partial tumor resection, craniospinal irradiation and adjuvant chemotherapy are recommended. However, the clinical benefit of chemotherapy added to surgery and radiotherapy seems marginal [19]. One study performed on 41 children with pineoblastoma supports the administration of neoadjuvant chemotherapy for larger or bloody tumors in order to achieve a complete tumor resection. Two courses of chemotherapy, consist-

ing of carboplatin, cyclophosphamide, and etoposide, resulted in a decreased tumor vascularity and a change in the consistency of the tumor, which became soft and friable, thus facilitating the aspiration of the tumor [18]. In the prospective multicentric HIT 2000 trial, 11 children with pineoblastoma with a median age of 11.9 years (4.0–20.7) received hyperfractionated radiation therapy with concomitant vincristine administered on a weekly basis and followed by eight cycles of maintenance chemotherapy with lomustine, cisplatin, and vincristine. The study obtained a 5-year PFS and OS rate of 64% [20].

Papillary tumor of the pineal region (PTPR) is a rare grade II–III neuroepithelial tumor that was introduced in the WHO classification of CNS tumors in 2007. These tumors occur mostly in adults, and their prognosis is uncertain, being characterized by frequent local recurrences [21, 22]. In a multi-institutional retrospective review of 31 cases, complete surgical resection was the only clinical factor that tended to be associated with overall survival and to decrease the recurrence rate. Local relapse was reported in 70% of patients and cerebrospinal fluid dissemination in 7% [23]. The higher local relapse rate suggests the potential clinical benefit of the additional radiotherapy boost to the tumoral bed after surgery. However, a recently published analysis of the medical databases for case series and reports on 177 patients with PTPRs showed no significant benefit of gross tumor resection or adjuvant therapies. Small lesions and surgery were the only factors that significantly improved survival at 36 months [24]. Adjuvant chemotherapy after surgery and radiotherapy mainly consisted in temozolomide, platinum and etoposide, or vincristine combinations [22]. In a young patient that could not undergo surgery due to an extensive disease, more aggressive therapy was proposed, consisting of ifosfamide, cisplatin, and etoposide, but with poor response [25]. Bevacizumab could also be considered in case of inoperable tumors, or in case of favorable response to irradiation or standard chemotherapy [26]. Currently, there is no standard treatment for this rare and relatively recently described entity. Clinical trials are needed to establish an efficient therapy.

15.4 Gliomas

They are rare tumors that can arise from astrocytes in the pineal gland, but more commonly, they grow from the adjacent brain parenchyma [27]. Prognosis is dismal, with a median overall survival of 15 months (range: 2–24 months) from the time of diagnosis, despite surgery and adjuvant radio-chemotherapy [28].

15.5 Conclusion and Controversial Issues

Pineal tumors are highly heterogeneous, with chemotherapy usually administered as a complement to radiation therapy in cases of partial tumor resection, with the aim of decreasing the radiation dose or in case of relapsed disease. Currently, there are no clear recommendations because of the rarity of the tumors and the difficulty of performing randomized clinical trials. Management may greatly vary depending on each center experience and experts' opinion, especially in case of relapse disease. Further research should be performed in order to better define the most appropriate chemotherapy regimen according to histology and risk factors, as well as the optimal therapeutic sequencing in the multimodal approach.

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Part IV

Pineal Region Tumors

Tumors of Pineal Cell Origin

16

Victor Volovici, Ruben Dammers,
and Marie-Lise C. van Veelen

16.1 Introduction

Pineal tumors are rare pathological entities that present with a broad spectrum of clinical, imaging, and histopathological characteristics that make them sometimes difficult to define. Tumors of pineal cell origin (TPCOs) are the second most common entity, after tumors of germ cell origin [1]. Unlike in other regions of the brain, gliomas in this region account for 14–22% of all tumors [2].

TPCOs are classified according to their differentiation, from best differentiated to anaplastic, into pineocytomas, pineal parenchymal tumors of intermediate differentiation (PPTIDs), papillary tumors of the pineal region (PTPRs), and pineoblastomas. Pineocytomas are considered World Health Organization (WHO) grade I tumors, PPTIDs and PTPRs WHO grade II or III, and pineoblastomas grade IV [1].

16.2 Epidemiology

TPCOs are the second most common tumors of the pineal region, accounting for a median prevalence of roughly 30–40% [3]. However, owing to the very low overall incidence (0.8 in 100,000 patient years), the prevalence in individual studies varies widely between 5.6% [4] and 41.6% [5]. There appears to be a slightly higher incidence in the Asian population [3]. The existing prevalence data are extremely heterogeneous, given the small series, and should be interpreted accordingly.

Pineocytomas typically appear in the young and middle-aged adult population, whereas in children they make up less than 10% of the pineal region tumors reported [6, 7]. The male-to-female ratio is 0.6:1. **PPTIDs** have a prevalence of roughly 33% among all pineal region tumors [8], appearing equally often in the young adult (second and third decades of life) as well as in the pediatric population [9]. A slight female preponderance is noted, with a male-to-female ratio of 0.8:1. **PTPRs** are reported in both the adult and pediatric populations. Because the entity was unrecognized until recently, and due to only 181 cases reported so far in the literature [1], no data on the incidence is

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available. One study included patients aged 5 to 66, with a median age of 30 [10]. In this case the male-to-female ratio is 1:1. **Pineoblastomas** amount for about 24–50% of all pineal region tumors and are primarily a pediatric tumor [6], with some reports describing adult patients with pineoblastomas as well [8, 11]. The male-to-female ratio is 0.7:1.

Data pertaining to the Brain Tumor Registry of Japan [12] database show a cumulative 5-year survival rate of 84.1% for pineocytomas and 46.1% for pineoblastomas.

16.3 Clinical Presentation and Diagnostics

The most common reported clinical presentation was raised intracranial pressure due to obstructive hydrocephalus [7]. Given the location, eye movement disturbances, in particular vertical gaze palsy ranging all the way to a complete Parinaud syndrome, were present in as many as 75% of the patients [7]. Because of its regulatory endocrine function, diabetes insipidus (18%), hypopituitarism (5%), and pubertas praecox (2%) were also reported [5–7]. Lesions that infiltrate or compress the thalamus and the posterior limb of the internal capsule cause hemihypesthesia, hemiparesis, and dyscoordination.

Diagnostic workup includes imaging studies, usually an (angio) computed tomography (CT), magnetic resonance imaging (MRI), or both, cerebrospinal fluid (CSF) sampling, and a biopsy or resection to confirm the histological diagnosis.

Pineocytomas appear on CT as intermediate density lesions, similar to the surrounding white matter. The essential feature distinguishing pineocytomas from germ cell tumors is that they "explode" the calcifications of the pineal gland and displace these to the edge of the lesion, as opposed to germ cell tumors that "engulf" the calcifications [13, 14]. Given that they are slow-growing tumors, a thin-slice, contrast-enhanced 3 Tesla MRI is necessary to differentiate them from pineal cysts. On T1-weighted imaging they appear hypointense or isointense to brain parenchyma, with vividly enhancing solid components, and on T2-weighted imaging they appear isointense to brain parenchyma with multiple cysts [13, 15].

Pineoblastomas appear on CT hyperdense to the adjacent white matter, due to their hypercellularity. They also characteristically show the "exploded" pineal calcifications, lining the periphery of the lesion. On MRI, they appear isointense or hypointense to adjacent parenchyma, with vivid patchy enhancement and restricted diffusion on apparent diffusion coefficient (ADC)/diffusion weighted imaging (DWI) due to hypercellularity (ADC usually around 400–800 mm^2/s). T2-weighted imaging shows a tumor isointense to adjacent brain with cysts and necrosis [13–15].

PPTIDs and **PTPRs** are virtually indistinguishable from pineocytomas on CT and MRI. What differentiates **PPTIDs** from **pineocytomas** is the rapid growth of the latter on serial MRIs and sometimes the low ADC values [13], whereas **PTPRs** may have a high T1 signal owing to secretory inclusions [16].

For **PPTIDs**, **PTPRs**, and **pineoblastomas,** complete neuraxis scanning is necessary, as these lesions have been reported to exhibit cerebrospinal fluid (CSF) dissemination in between 7% and as much as 45% of cases [14]. Figures 16.1 and 16.2 show MRI images of two patients from the Erasmus University Medical Center (Erasmus MC).

In the diagnosis of pineal germ cell tumors, biochemical markers such as alpha-fetoprotein

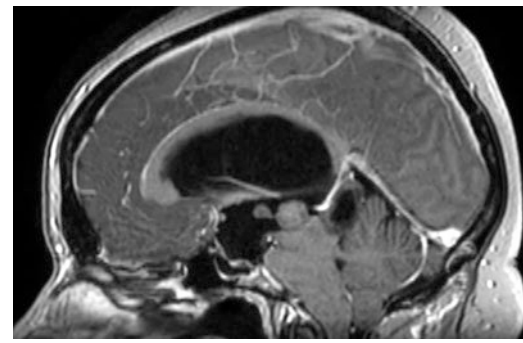

Fig. 16.1 Sagittal MRI, T1 sequence, gadolinium-enhanced. A T1 isointense circular mass is visible just above the tectal plate. Contrast enhancement is scarce. The vein of Galen is draped on its upper side en route toward the sinus rectus. The patient received a third ventriculocisternostomy and biopsy, which revealed a probable PPTID

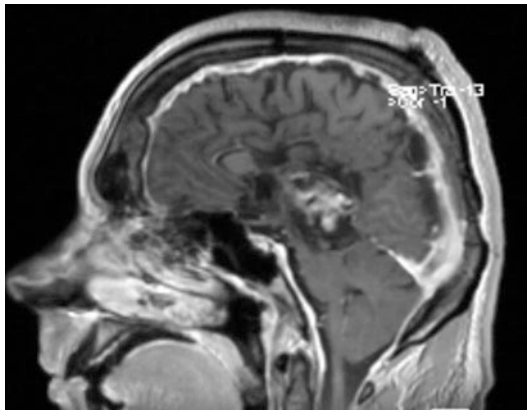

Fig. 16.2 Sagittal MRI, T1 sequence, gadolinium-enhanced. A T1 heterogeneous hypointense and isointense lesion is visible posteriorly to the mesencephalon with compression on the tectal plate and culmen. The tumor was previously operated on via a transcallosal approach. The pathology revealed a pineocytoma

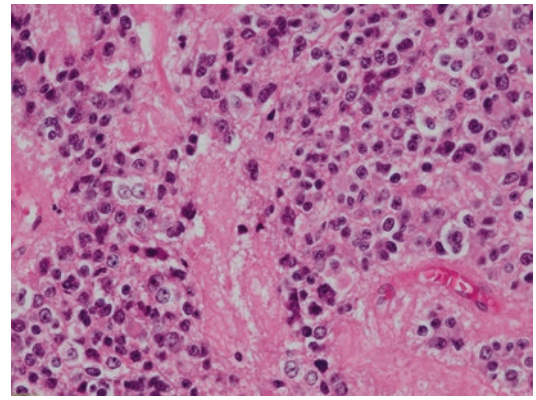

Fig. 16.3 (Hematoxylin–Eosin [H–E] staining, 400×) A patient of the Erasmus Medical Center, MRI depicted in Fig. 16.2. Pineocytoma. The tumor is moderately cellular, composed of sheets of slightly variable cells with moderate amounts of eosinophilic cytoplasm. The nuclei are round—oval, with inconspicuous or regular small nucleoli and fine chromatin. Cell processes form typical pineocytomatous rosettes

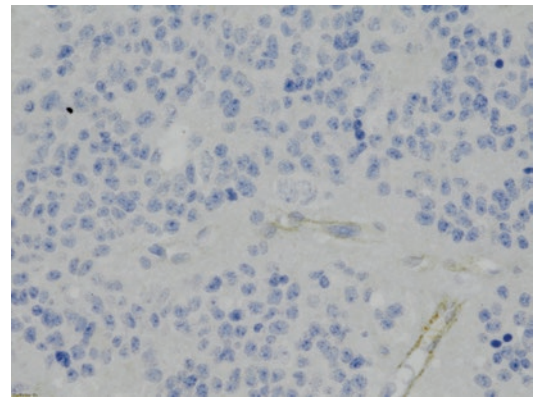

Fig. 16.4 (Immunohistochemistry [IHC], Ki-67 staining, 400×) Same patient as in Figs. 16.2 and 16.3. Ki-67 staining of the nuclei is below 1%, indicating very low proliferative activity. (Courtesy of Dr. R. M. Verdijk, Neuropathologist, Erasmus MC, Rotterdam)

and beta-human chorionic gonadotropin are helpful; there are no biomarkers that help the diagnosis of TPCOs, but biomarkers can help in the differential diagnosis with primary germ cell tumors. Other markers for germ cell tumors that might add to the diagnosis are placental alkaline phosphatase [17] and lactate dehydrogenase isoenzyme 1 [18], but these are not part of the routine screening in all centers. The absence of these markers does not rule out a germ cell tumor, however, and a ventriculostomy and biopsy soon after presentation are recommended.

To date, melatonin levels [19] and hydroxyindole-O-methyltransferase (HIOMT) enzyme levels (which catalyzes the final step in melatonin secretion) [20] in serum and CSF have been suggested to aid the diagnosis of TPCO, but no proper, adequately powered studies have been conducted.

A biopsy, either stereotactic or open, or resection material will be used to acquire the histopathologic diagnosis.

16.4 Pathology

Pineocytomas are circumscribed, grayish-tan tumors well delineated from brain parenchyma. Cystic or hemorrhagic changes are sometimes present macroscopically. Microscopically, they are composed of cells reminiscent of pinealocytes, with characteristic pineocytomatous pseudorosettes [1]. In stark contrast, **pineoblastomas** are macroscopically poorly defined, infiltrative tumors with a pinkish-gray hue. Microscopically, they exhibit small, round, blue cells, with a high nuclear-cytoplasmic ratio, and also exhibit rosettes, but unlike pineocytomas, these are the Homer Wright (pseudo) rosettes also seen in medulloblastoma or olfactory neuroblastoma [1] (Figs. 16.3 and 16.4).

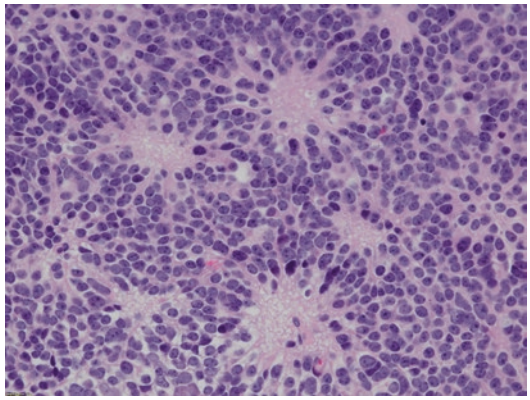

Fig. 16.5 (H–E, 400×) Pineocytoma. The tumor is moderately cellular, composed of sheets of uniform cells with moderate amounts of eosinophilic cytoplasm. The nuclei are round to oval, with inconspicuous or regular small nucleoli and fine chromatin. Cell processes form typical pineocytomatous rosettes

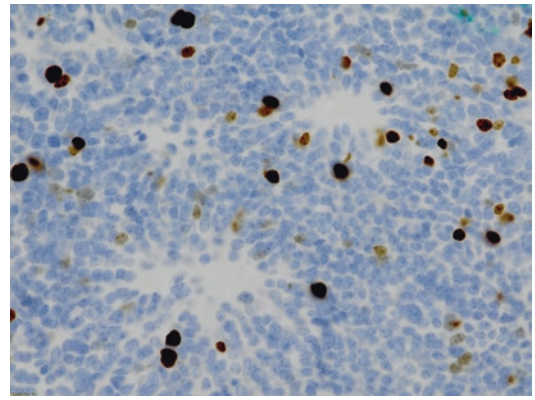

Fig. 16.6 (IHC, Ki-67 staining) Same patient as depicted in Fig. 16.5. Ki-67 staining of the nuclei in this case is around 5%, indicating slight proliferative activity, which is still acceptable for pineocytoma. Pineocytomatous rosettes are not expected to be present in pineal parenchymal tumor of intermediate differentiation or pineoblastoma. (Courtesy of Dr. R. M. Verdijk, Neuropathologist, Erasmus MC, Rotterdam)

PPTIDs and **PTPRs** show intermediate forms, even though they most often microscopically resemble pineocytomas without rosettes. **PPTIDs** exhibit either a lobulated pattern, in which lobules are divided by vessels, or a diffuse pattern, reminiscent of oligodendrogliomas [1]. **PTPRs** range microscopically from solid to predominantly papillary, with areas of necrosis, in a pattern suggestive of an ependymoma [9, 10].

Immunohistochemistry is used to look at tissue-specific antigens (neuronal and glial- neurofilament, glial fibrillary acidic protein (GFAP), synaptophysin, nestin), proliferation (Ki-67), and apoptosis markers and specific pineal markers hydroxyindole-O-methyltransferase (HIOMT). A wealth of markers is currently being studied for diagnosis and prognostic purposes, but consensus remains lacking as to the proper combination. Ki-67-positive nuclei are a well-known and often-used method to determine the proliferation index that usually aids diagnosis. **PTPRs** have a fairly characteristic immunohistochemical profile [21] (Figs. 16.5 and 16.6).

16.5 Management

Surgery, radiation, and chemotherapy are all tools used in the management of TPCOs. Pineal tumors, given their location, should only be treated in centers with considerable neurosurgical experience [7, 22, 23].

The workup of a new TPCO includes: serum and CSF biomarkers, through either the lumbar tap, if deemed safe, or during ventriculostomy procedures (alpha-fetoprotein and beta–human chorionic gonadotropin), contrast-enhanced MRI and T1, T2, DWI, ADC, time-of-flight (TOF) sequences, and CT venography (CTV) or MRI venography (MRV) for preoperative planning.

A benign pineal cyst with negative CSF markers may be followed up without intervention. The same holds true for asymptomatic, small tumors with negative CSF markers (incidental findings), which may be first followed up with serial MRIs. Very often, however, these patients present when they are already symptomatic, usually with obstructive hydrocephalus [7], in which case the primary goal is to resolve the hydrocephalus and to obtain the proper diagnosis. We most often resort to an endoscopic third ventriculocisternostomy with subsequent endoscopic biopsy when feasible. Reports suggest that this approach enjoys low morbidity [24, 25]. It can be argued, however, that, when feasible, a direct approach to the tumor might accomplish both objectives and help avoid a second surgery. If germ cell tumors are still in the differential diagnosis, then a biopsy

should be performed and a first craniotomy avoided, since germinomas, but not non-germinomatous germ cell tumors (NGGCTs), are most effectively treated with chemotherapy and radiation [26].

For both benign as well as malignant TPCOs, an approach that maximizes the extent of resection should be chosen. Reports so far suggest that for benign tumors, surgery alone may be curative [23, 27], while for malignant tumors it might slightly improve the outcome [5, 27]. Obviously, given the infiltrative nature of malignant tumors, a gross total resection cannot be achieved, and adjuvant therapies need to be employed.

The choice of approach for resection depends on the displacement of the surrounding neurovascular structures by the tumor and on certain characteristics of the anatomy of the patient. The pineal stem is continuous with both the habenular (dorsally) as well as the posterior commissure (ventrally). The tip projects in the quadrigeminal cistern, where it is surrounded by the quadrigeminal plate. The principal vessel that provides vascularization is the middle posterior choroidal artery (MPChA) en route to the velum interpositum in the roof of the third ventricle. The main obstacle to approaches of this area is the vein of Galen, which originates 3–5 mm behind the pineal gland and runs in a superoposterior angle to drain in the straight sinus. Dorsally, the superior vermian and precentral cerebellar veins join the vein of Galen. Ventrally, the internal cerebral veins and pineal vein join the vein of Galen.

Taking these anatomical aspects into account, as well as the changes brought about by the tumor (the vein of Galen is usually pushed upward, the internal cerebral veins are either displaced laterally together or apart, the MPChA and the lateral posterior choroidal artery are also pushed laterally), the proper surgical corridor is defined.

The three approaches used for this region are occipital transtentorial [28], infratentorial supracerebellar [29], and interhemispheric retrocallosal [22]. The occipital transtentorial approach is preferred for tumors that extend more cranially or more laterally, into the aqueduct, or more towards the thalamus, where visualization of the walls of the third ventricles is essential. For smaller tumors growing more caudally or which displace the quadrigeminal plate caudally, but without much lateral extension, an infratentorial supracerebellar approach (possibly in the sitting position) offers a relatively unobstructed pathway to the tumor, except for the precentral and anterior vermian veins. The interhemispheric retrocallosal approach offers a wide exposure and excellent visualization, at the cost of potential venous injury (internal cerebral vein or vein of Galen) and hemialexia, pure word blindness, or visual agnosia if the splenium is injured.

Radiotherapy, either stereotactic or fractionated, together with chemotherapy [30, 31] should be used in conjunction with surgery, especially for higher-grade tumors and/or incomplete resections. Spinal irradiation should only be carried out in cases of documented spinal seeding. The decision regarding the proper treatment regimen should be taken in a multidisciplinary team with neuro-oncologic expertise [23].

16.6 Controversies

The two main controversies in the treatment of TPCOs are the timing of surgery and the choice of approach.

Nowadays, most centers choose an endoscopic third ventriculocisternostomy together with an endoscopic biopsy in the same session in order to establish the diagnosis. Ideally, the burr hole should be planned in such a way as to allow achieving both goals (ventriculostomy and biopsy) without damage to the fornix or other neurovascular structures due to the angle of the endoscope. This is often a daunting task. Reports in the literature so far also suggest the possibility of placing two burr holes to achieve the same outcome, but if one is deemed safe, then it is the approach of choice [32, 33]. Some reports suggest the possibility of CSF seeding through the procedure [24]. Another issue is the possibility of sampling errors, especially in germ cell tumors with mixed cell populations. All of these issues must be taken into account when deciding on the surgical strategy.

In large tumors with specific imaging characteristics of a pineocytoma and negative markers, in which a gross total resection is expected, resection will also resolve hydrocephalus, thus avoiding two surgeries. The balance, however, is still in favor of a more conservative approach [23].

The second controversy regards the choice of approach. This choice depends on the anatomy of the individual patient, the displacement of anatomy by the tumor, and last but not least, on the experience of the surgeon. The risk of damage to the surrounding structures, such as contralateral hemi-neglect after lesions of the pulvinar, hemialexia, pure word blindness, or visual agnosia after lesions of the splenium, visuospatial dyscoordination after lesions of the quadrigeminal plate, and vertical gaze palsy after injury of the posterior commissure, should be taken into account. In the pediatric population, surprisingly, despite conventional wisdom deterring neurosurgeons from damaging the internal cerebral vein—vein of Galen complex—sacrifice of these veins or of bridging veins did not lead to any deficit [22, 34]. The authors postulate that this is due to the extended network of valveless veins allowing massive redistribution of flow when one vein is sacrificed. They also speculate that venous infarctions attributed to the sacrifice of bridging veins is actually due to brain retraction and venous congestion. Proper preoperative workup should therefore include either a CTV or an MRV.

Ultimately, the approach that delivers the most direct route to the tumor, allowing for maximum removal without damage to surrounding structures, should be chosen. More often than not, this is the approach the surgeon is most familiar with.

16.7 Conclusion

Tumors of pineal cell origin are rare tumors originating in the cells of the pineal gland itself. Differentiating them from germinomas is essential, and the surgical approach needs to be tailored to the symptomatology of the patient and the anatomical relations of the tumor. The approaches used to maximize resection and minimize the chance of surgical morbidity are highly complex, and these tumors should be treated in centers with plentiful experience in dealing with pineal region lesions.

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Tumors of Germ Cell Origin

17

Douglas R. Taylor, Richard J. Edwards, and Frederick A. Boop

17.1 Introduction

Intracranial germ cell tumors (GCTs) are predominately a pediatric disease, with the majority of diagnoses occurring within the first two decades of life [1, 2]. Histopathologically, germinoma is the most common diagnosis; however, non-germinomatous germ cell tumors (NGGCTs) include five other histologically distinct tumors which we discuss later. These are rare tumors that classically present in midline structures, namely the pineal region or suprasellar region. Geographically, the proportion of primary brain tumors comprising GCTs vary among the pediatric populations: 0.5% in India [3, 4]; 2–5% in North America and Europe [1, 5–8]; and up to 9–15% in Japan, Taiwan, and Korea [2, 8–11]. Uncommon in adults, less than 10% of central nervous system germ cell tumors occur between ages 30 and 45 [1, 12, 13].

During the initial stages of development, primordial germ cells of the embryo travel from the yolk sac to the genital ridges along the dorsal mesentery of the hind gut. At 4 weeks of embryogenesis, they incorporate into the developing gonads. Extragonadal GCTs occur when there is a derangement in the process of germ cell migration [14]. There are two theories that describe the origin of GCTs. The first and more classic teaching is that GCTs arise from reprogrammed primordial germ cells. The second states that while germinomas originate from primordial germ cells, NGGCTs develop from embryonic stem cells where embryonal carcinoma cells are the pluripotent neoplastic precursors [15].

Patient presentation is largely related to tumor location. Germ cell tumor growth in the pineal region, adjacent to the posterior third ventricle and cerebral aqueduct, carries the risk of obstructive hydrocephalus. Common manifestations include headache, vomiting, papilledema, increasing head circumference in the very young, and even decreased consciousness. Additionally, direct compression of the quadrigeminal plate may result in Parinaud's syndrome, up-gaze palsy, convergence nystagmus, and light-accommodation dissociation [16, 17]. Alternatively, some cases present with endocrinological dysfunction. For example, choriocarcinoma and certain human chorionic gonadotropin (HCG)-producing germinomas may stimulate Leydig cells to produce testosterone which can result in precocious puberty in males [18].

GCTs are a heterogeneic group of tumors, and different parts of the world vary in methods of categorization, prognostication, and treatment

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approaches. This chapter discusses the characteristic features of germ cell tumors, including important diagnostic and clinical considerations for the treating physician.

17.2 Germ Cell Tumor Demographics

17.2.1 Germinoma

Germinomas are the most common GCT, making up 0.5–3% of all central nervous system (CNS) tumors [16, 19, 20]. They are the most undifferentiated type of germ cell tumor and arise from primordial germ cells (Fig. 17.1) [8, 21]. Germinomas typically arise between ages 7 and 30 and have a peak incidence at 10–12 years, with 90% of cases diagnosed before the age of 20 years [12, 16, 22–24]. As discussed, germinomas typically result from aberrant embryologic development, and thus are often found in midline structures. While about two-thirds of germinomas are recognized in the pineal region, they can occur elsewhere. For instance, they may occupy the suprasellar region (30%), be bifocal (i.e., both suprasellar and pineal), or infrequently may occur in ectopic regions such as the basal ganglia or thalamus (4–10%) [25, 26].

Gender disparity plays a role in pineal region germinomas, where the male-to-female incidence is 2.5–22:1 [17, 27–29]. Sano's embryologic theory hypothesizes this relates to early closure of the anterior neuropore in males during development. Effectively, embryonic cells become enfolded into the neural tube at the pineal region in males as opposed to the suprasellar region, which occurs more often in females [17, 27, 30].

Bifocal, or multicentric, germinomas occur simultaneously in the pineal and suprasellar region, with an incidence of 2–20% in reported cases (Fig. 17.2) [16, 17, 31, 32]. This phenomenon is highly suggestive of germinoma; however, it is not pathognomonic for this diagnosis, because mixed GCTs may also occur in a bifocal pattern [2, 33, 34]. Similarly, there are case reports of metachronous germinomas. This entity

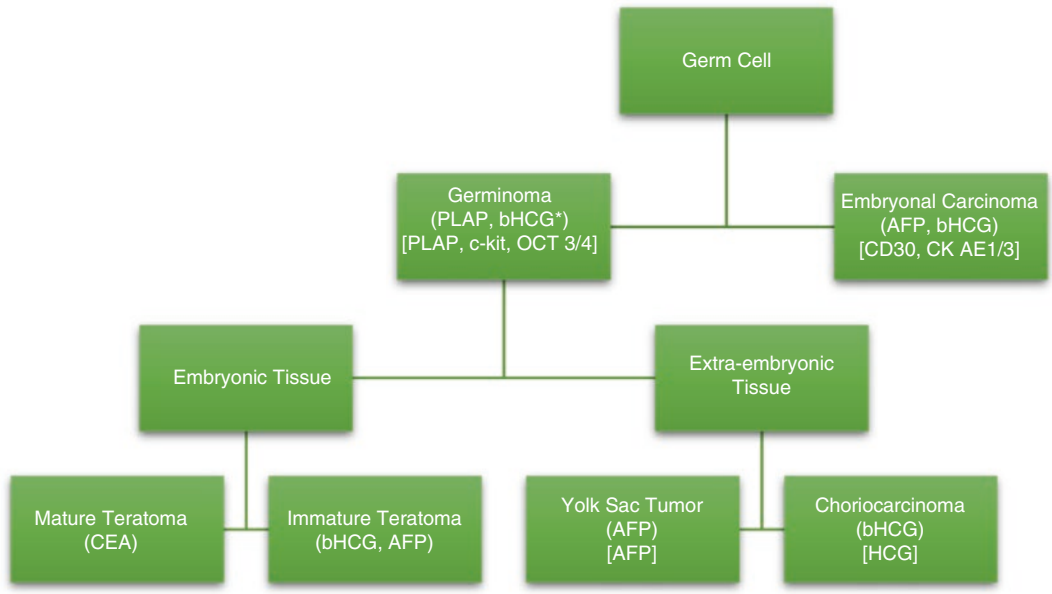

Fig. 17.1 Germ cell tumor divergence. Diagram depicting the maturation deviation of developing germ cell tumors. () indicates serum and/or cerebrospinal fluid tumor marker secretion; [] indicates immunohistochemical tumor markers; * indicates only when syncytiotrophoblasts present; *PLAP*, placental alkaline phosphatase; *bHCG*, beta human chorionic gonadotropin; *AFP*, alpha fetoprotein; *CEA*, carcinoembryonic antigen

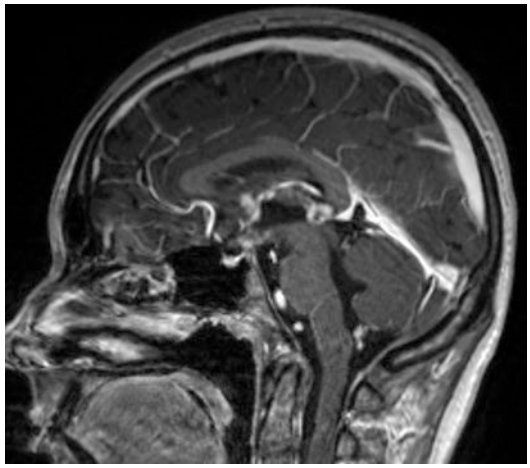

Fig. 17.2 Sagittal T1-weighted magnetic resonance imaging (MRI) post gadolinium, depicting bifocal germinoma. Heterogeneously enhancing tumor is seen simultaneously in the pineal and suprasellar region

is described as a histologically different tumor that develops at a different site and time than the primary diagnosed tumor, i.e., pineal germinoma that arose years after treatment for sellar teratoma [35–37]. All documented cases have been males, with a mean age of 12.5 years and a primary tumor diagnosis of mature teratoma. Overall, metachronous germinomas are treated as a second primary rather than recurrence [35].

The World Health Organization (WHO) classifies germinomas as malignant grade IV tumors [38]. However, because these tumors are highly sensitive to chemoradiation treatment, current therapies have improved prognostication for patients with germinoma. The 10-year overall survival rate (OS) of patients with pure germinoma reaches as high as 90% [2, 39, 40].

17.2.2 Non-germinomatous Germ Cell Tumor

Non-germinomatous germ cell tumors (NGGCTs) include embryonal carcinoma, endodermal sinus or yolk sac tumor, choriocarcinoma, and both mature and immature teratoma. Compared to germinomas, they evolve from differentiated cells of embryonic or extraembryonic tissues [15]. Most NGGCTs occur between birth and 20 years of age [24, 41], and are more common than germinomas from 0–3 years of age [42]. In fact, the majority of infantile GCTs are composed mainly of teratoma and yolk sac tumors [15]. Embryonal carcinomas, on the other hand, occur in prepubescent children but are rarely seen in children less than 4 years of age [42].

Teratomas comprise the second most common pineal germ cell tumor, making up 15% of cases [42]. Histopathologically, they are comprised of elements from all three germ layers: ectoderm, mesoderm, and endoderm [43, 44]. They can be classified as mature teratomas when samples contain fully differentiated tissue, or immature when they contain mostly embryonic or fetal tissues [45]. Teratomas can also arise from non-progenitor germ cells and undergo malignant transformation [46, 47].

Except mature teratoma, which is a surgically curable disease with 86–100% survival [15, 43], NGGCTs are considered malignant tumors that have a poorer prognosis than germinomas. They typically require a higher dosing regimen of chemotherapy and radiation, and have a 10-year overall survival of 60–70% [1].

17.2.3 Mixed Germ Cell Tumor

Occasionally, GCTs in the pineal region may be derived from more than one subtype of germ cell tumor. This takes place in approximately 10–30% of cases [15]. Typically, the components involved are germinoma and teratoma, which carry a relatively good prognosis after chemoradiation and surgery, respectively; however, if other malignant subgroups are involved, the prognosis is degraded [15]. The overall prognosis as well as management is based on the most malignant component within the tumor [48].

A phenomenon known as "growing teratoma syndrome" (GTS) is a unique representation of these cases. GTS manifests when treatment of presumed germinoma or NGGCT with chemotherapy or radiation therapy (RT) produces paradoxical growth of mature teratoma components despite normal or decreased tumor markers

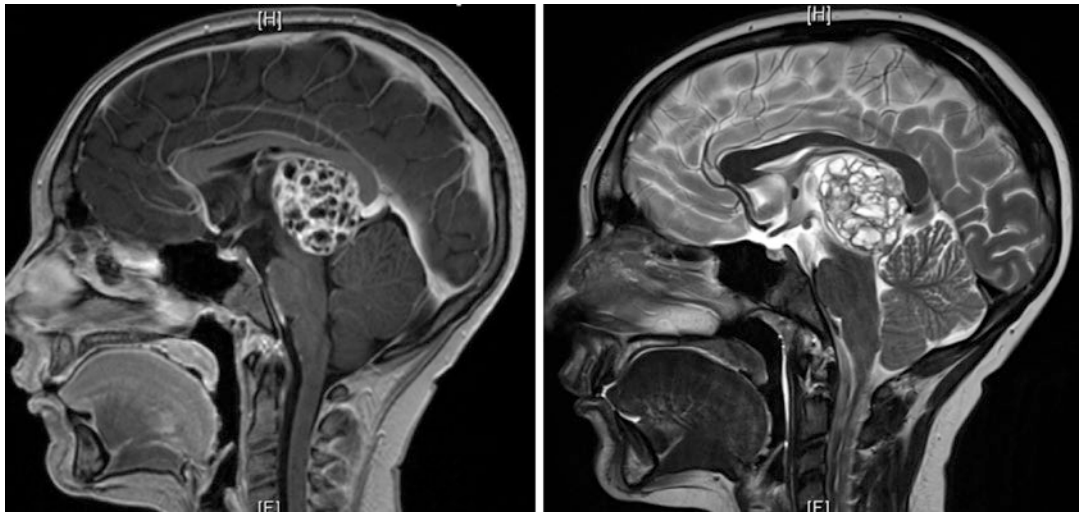

Fig. 17.3 Classic "honey-combed" appearance of growing teratoma syndrome represented on T1-weighted MRI post gadolinium (left) and T2-weighted MRI (right)

[49, 50]. It has a characteristic honeycomb appearance with multiple cysts on magnetic resonance imaging (MRI) (Fig. 17.3) [49, 51]. Unlike malignant GCTs that typically respond to chemotherapy and RT, mature teratoma does not [52]. Hence, the benign components of the tumor may endure while the malignant parts are eliminated [52]. Several hypotheses have been formulated to account for this paradox. One suggests that mature teratoma may experience uninhibited growth after the malignant, more rapidly dividing tumor components are selectively eradicated [53]. Another proposes that the chemotherapy may induce differentiation of immature germ cells to a mature teratoma phenotype [49]. A final theory claims that the tumor growth is secondary to microcyst and macrocyst formation promoted by chemotherapy and/or RT [49].

17.3 Germ Cell Tumor Diagnosis

17.3.1 Imaging

Initial evaluation of patients with suspected germ cell tumor should include a head computed tomography (CT) followed by magnetic resonance imaging (MRI) of the brain and spine. While many features are nonspecific, there are certain characteristics of each modality that, when present, infer certain histological types of GCTs compared to other common tumors in the pineal region such as pineal parenchymal tumors (PPTs) and pineal cysts. Even so, given the vast array of imaging presentations of GCTs, especially NGGCTs, the distinction from other pineal tumors is typically made based on tumor markers.

Regardless, screening head CT upon patient presentation allows for quick recognition of hydrocephalus, hemorrhage, and calcifications. Basic tenants of imaging depict hemorrhage and calcification as hyperdense lesions on CT. Similarly, blood products and calcifications are seen as hypo-intensities on T2-weighted MRI. On the contrary, T1-weighted MRI hyperintensities can signify hemorrhage (methemoglobin), high protein cyst fluid, or fat. Fat is a low-density characteristic on CT. Thus, this can be useful when narrowing the differential, for example: choriocarcinomas are often hemorrhagic; teratomas have mixed solid and cystic components, often with calcifications and fat (Fig. 17.4).

In children less than 10 years of age, pineal region calcifications are infrequent and suggestive of a pathology such as germ cell tumor [54]. Several studies revealed that a localized, clumpy

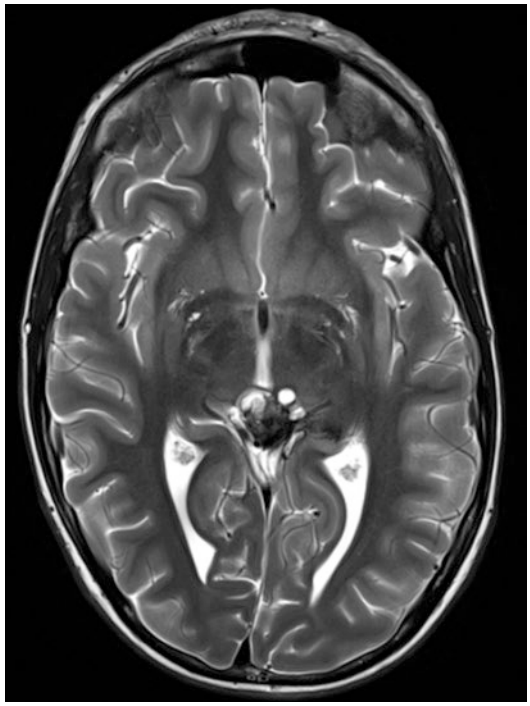

Fig. 17.4 Axial T2-weighted MRI of residual mature teratoma in the pineal region after treatment of mixed germ cell tumor. Note the mixed solid and cystic tumor with small focus calcium posteriorly

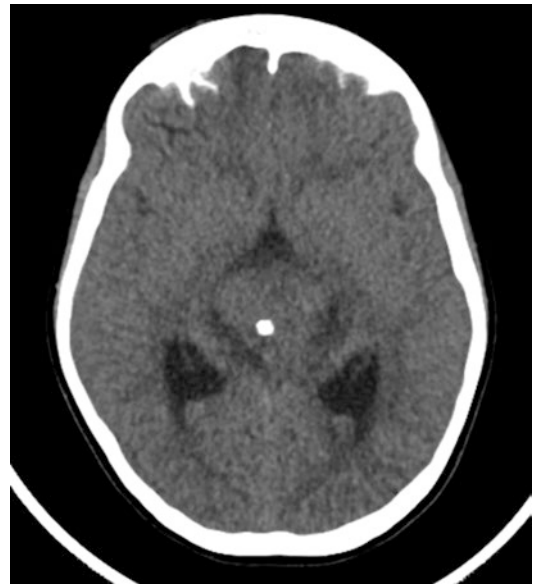

Fig. 17.5 Axial CT of the head showing focal calcification of pineal region germinoma

calcification pattern is more likely to be seen in germinomas and NGGCTs (88.5% and 72.7%, respectively, in one study), while a scattered pattern is more likely to occur in a pineal parenchymal tumor (PPT) (Fig. 17.5) [55, 56]. This is likely the result of abnormal enfolding of primordial germ cells into midline structures during development, versus the dispersion of calcifications seen in PPTs where growth occurs outward from pineal parenchymal tissue [38, 55, 57].

In order to avoid invasive procedures, attempts have been made to quantify image characteristics that specifically diagnose GCT in tumor marker–negative cases. Pineal germinomas are high-density lesions on CT with homogeneous enhancement, clear margins, frequent calcifications, and rarely peritumoral edema [17]. They are often smaller than NGGCTs and less cystic than other pineal tumors [55]. 43 to 78% of pineal germinomas exhibit bi-thalamic extension, resembling a "V" or heart shape, which has been termed by some as the "butterfly sign" [54, 58]. MRI demonstrates the solid portions of germinomas to be iso-hypointense on T1 and iso-hyperintense on T2 with homogeneous enhancement (Fig. 17.6) [1, 54, 55, 58]. MRI imaging of NGGCT is more varied, with mixed signal intensities and cystic components. Germinomas tend to show restricted diffusion reflecting their high cellularity [55, 59]. Additionally, the presence of lipid peaks on magnetic resonance (MR) spectroscopy in combination with low apparent diffusion coefficient (ADC) may be characteristic of germinoma [33, 60]. In general, GCTs tend to have high lipid peaks as a result of apoptosis of tumor cells and infiltrating lymphocytes which can resemble lymphoma [60–62]. ADC inversely correlates with tumor cellularity and grade, such that a low signal indicates malignant lesions like GCTs [63, 64].

Multiple lesions may occur in combination with pineal region tumors at the time of diagnosis. Previous sections discussed that bifocal lesions can be characteristic of germinoma and mixed GCT (Fig. 17.2). Further, however, Awa et al. found that pineal cases with multiple other lesions on presentation tend to be indicative of germ cell tumors when compared to PPTs and other miscellaneous tumors [55]. Typically, ger-

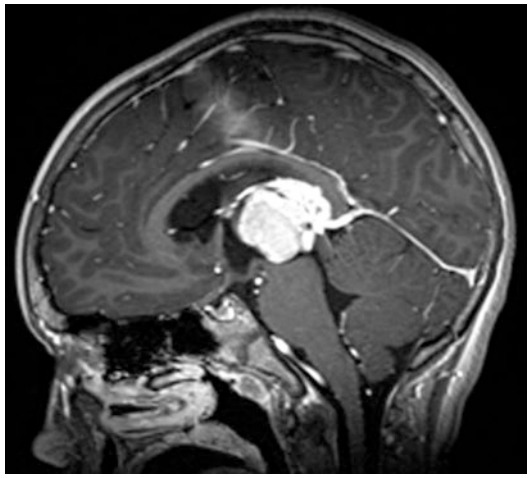

Fig. 17.6 Homogeneously enhancing pineal region germinoma seen on sagittal T1-weighted MRI post gadolinium

minomas invade locally to the ventricles and seed the subarachnoid space with a frequency reaching four times that of NGGCTs [55]. MRI of the entire neuroaxis guides therapy as well as prognostication when disseminated metastasis is identified.

17.3.2 Biomarkers

Patients with suspected GCT must have serum and cerebrospinal fluid (CSF) analysis to evaluate tumor marker status as well as CSF cytology. Nonetheless, negative tumor markers do not exclude the presence of GCT from diagnosis. A complete representation of the tumor markers associated with each histological type of GCT can be found in Fig. 17.1. Yolk sac tumors, immature teratomas, and embryonal carcinomas can secrete alpha-fetoprotein (AFP). Choriocarcinomas secrete beta-human chorionic gonadotropin (b-HCG). Mature teratomas may have elevated serum levels of carcinoembryogenic antigen (CEA), while immature teratomas can be mildly positive for b-HCG or AFP.

Germinomas are classically PLAP-positive. Additionally, some germinomas secrete b-HCG in serum or CSF when syncytiotrophoblastic cells are present [65]. Syncytiotrophoblastic cells produce b-HCG in germ cell tumors [54, 66]. Often, these levels are higher in CSF than serum [67]. Although it can dictate prognosis and guide intensity of therapy, there is debate on the threshold value of b-HCG that distinguishes pure germinoma from NGGCT. In North America and Europe, a b-HCG value of less than 100 IU/L is typically used for germinoma, while in Asia, specifically Japan, a much higher cutoff of 2000 IU/L is used [2, 16, 65]. Hence, there is no standardized value that clearly defines diagnosis.

After treatment, b-HCG levels are routinely followed and will drop to 0 IU/L. To facilitate monitoring, an Ommaya reservoir is often left in place after endoscopy, which creates easy access for CSF sampling. When recurrence is suspected, tumor markers can be elevated in CSF as well as serum.

17.3.3 Molecular Genomics

Advances in adjuvant treatment in today's era relies heavily on molecular pathology and gene-specific investigations. Various mutations of certain proteins involved in cell signaling have been linked to the pathogenesis of GCTs. For example, the tyrosine-protein kinase/rat sarcoma (KIT/RAS) or protein kinase B-mammalian target of Rapamycin (AKT-MTOR) signaling pathway appears to be overactive in more than half of the intracranial GCTs [15, 68]. One study comparing the components of germinoma and NGGCT in mixed GCTs found common KIT/RAS mutations but a profile of hypomethylation in germinoma versus hypermethylation in the NGGCT constituents [69].

It appears variations in the KIT pathway are more specific for germinomas. For example, activating mutations in the tyrosine kinase receptor c-KIT are frequent in germinomas and implicate its importance in tumor development [70, 71]. Thus, the proto-oncogene c-KIT (CD 117) is a useful cell surface marker for immunohistochemical staining of germinomas [17, 72]. In fact, c-Kit is said to be an even more reliable marker than PLAP in germinomas with or without syncytiotrophoblasts [72–74]. S-Kit is its soluble

form that can be found in CSF [72]. Other cell membrane and nuclear stains that have been studied with specificity for germinoma include OCT3/4 and D2–40 [16, 19, 54, 75]. There are also common immunohistochemical stains identified for embryonal carcinoma, which include CD 30 and CK AE1/3 [41].

On the landscape of tumor genetics, investigations show that a gain of chromosome 12p is a common event in gonadal GCTs but plays a less important role in intracranial GCTs [15]. However, other chromosomal aberrations, such as gain of the X and 21 chromosome in Kleinfelter's and Down syndrome, respectively, have been associated with intracranial GCT [15, 17, 76]. Studies of the human genome have identified a susceptibility gene involved in coding for histone demethylase (JMJD1C) among intracranial GCT patients [1, 68]. This germline variant is a chromatin modifier that appears to be prominent in Japanese patients and also interacts with the androgen receptor, which may account for the increased incidence in the male and Asian populations [68, 77].

Molecular and genetic studies will allow for more targeted treatment in the future. For example, tyrosine kinase inhibitors such as imatinib mesylate and dasatinib have shown efficacy in other KIT-activated human malignancies [15]. In fact, dasatinib has shown promise and ability to cross the blood brain barrier, which is currently under review as an adjunct to treatment [70].

17.3.4 Tissue Sampling

While most Western medicine advocates beginning RT and/or chemotherapy for patients with suspected GCT as indicated by positive tumor markers and consistent image findings, the Japanese rely more on surgical biopsy prior to starting treatment [11]. However, surgical biopsy is necessary in cases of negative markers [1, 16]. One potential deviation from this practice may be cases of negative marker, bifocal or multifocal intracranial tumors where the diagnosis of germinoma is highly likely [16].

Biopsy can occur via various techniques, including open craniotomy, stereotactic needle, or neuro-endoscopy. The pineal region can be a challenging surgical location, but technical advances in neuro-endoscopy and microneurosurgery have improved the risk profile of biopsy [17, 65]. Endoscopic third ventriculostomy (ETV) and biopsy is favored as the intervention of choice, with decreased morbidity and mortality compared to stereotactic options [78, 79]. The risk of sampling error, however, is a consistent problem associated with any type of biopsy, especially for mixed GCT cases.

Another important prognosticator that affects intensity of treatment is the propagation of tumor cells in the CSF at the time of diagnosis. CSF cytology can be obtained either by lumbar puncture or at the time of biopsy, often via endoscopy. Europe and North America, but not Japan, acknowledge positive cytology as well as disease at distant CNS sites (excluding bifocal disease) to be considered metastatic [1]. The diagnosis of CSF spread is an important guide for the field and dose of radiation prescribed for treatment.

17.4 Germ Cell Tumor Treatment

17.4.1 Radiation and Chemotherapeutic Strategies

Treatment of pineal germ cell tumors requires a multimodal approach and is typically similar for adult and pediatric patients [80, 81]. GCTs are relatively unique among intracranial oncology in that the combination of imaging findings and presence of tumor markers allows for presumptive chemoradiation treatment without tissue confirmation. While the Japanese require initial biopsy prior to therapy for germinoma and GCT [33], Western countries proceed expectantly with treatment if there are elevated levels of serum or CSF b-HCG or AFP. Survival outcomes of GCTs (except mature teratoma, which is a surgical disease) are correlated with the radiosensitivity of these tumors, which is the mainstay of treatment. While different institutions have varied protocols for chemotherapy and RT based on marker status and disseminated disease, there are commonly accepted recommendations we will discuss.

Regarding germinoma, therapies today are geared largely toward preserving quality of life for patients, since their survival after RT is so high. Germinoma is not a surgical disease and requires RT for cure. Thus, late treatment effects of radiation, such as secondary malignancies or neurocognitive and neuroendocrine sequelae, are balanced with adjuvant chemotherapy in order to decrease the RT dose with sustained survivability without recurrence. Today, the recommended treatment for germinoma includes four cycles of platinum-based chemotherapy, including carboplatin or cisplatin with etoposide and ifosfamide, followed by whole ventricular volume radiotherapy (20–24 Gy) plus boost radiation (12–16 Gy) to the tumor bed [15, 41, 81–85]. The ventricular system is usually included in the treatment field, because germinomas often recur by seeding the ventricles, as opposed to spreading to leptomeningeal or spinal sites. If metastases are present, whether CSF dissemination or tumor seeding, then craniospinal irradiation (CSI) is also administered [15, 41, 80, 83, 86]. Bifocal germinoma is generally treated similar to localized germinoma and is controlled with extended focal RT [87]. However, the treating physician should consider the possibility of disseminated disease with potentially poorer prognosis and maintain high suspicion on routine monitoring, especially if the tumor has positive b-HCG markers.

Non-germinomatous germ cell tumors (barring mature teratoma) carry a worse prognosis than germinomas and require a more intense chemotherapy and RT regimen. Neoadjuvant chemotherapy often includes four to six cycles of carboplatin or cisplatin with etoposide and ifosfamide; however, it may also include other agents such as vinblastine, taxanes, or gemcitabine [41, 84, 88, 89]. In contrast to germinomas, chemotherapy is used to increase survival rather than decrease RT dose [90]. Following this, radiation treatment is administered either with CSI (>36 Gy) and boost radiation (>54 Gy) to the tumor bed or whole brain or whole ventricular radiation (24–40 Gy) with a boost to the tumor bed (15–30 Gy) [41, 89, 91, 92]. After completion of chemoradiation, most clinicians advocate surgical resection if there is evidence of remaining tumor [82, 90]. Similarly, immature teratomas respond poorly to cisplatin; thus, for improved outcome, they require a combination of chemoradiation and best surgical resection where possible [93].

Investigations continue for different treatment modalities to improve survival and decrease recurrence. As an example, one study experienced increased 5-year survival of NGGCT with the addition of Gamma Knife radiosurgery [93]. Proton beam therapy is another method used to concentrate treatment doses to the tumor and spare surrounding tissues while reducing late neurologic and hematologic toxicities [2, 94–96]. Additionally, autologous stem cell rescue has been explored as an adjunct to chemotherapy, with the similar goal of reducing RT dose and long-term adverse effects [41, 97]. Often, more experimental treatments and protocols are used in cases of relapsing malignant tumors. However, there is consensus that recurrent malignant NGGCT should be treated with high-dose chemotherapy, hematopoietic stem cell rescue, as well as surgery and radiation when possible [41, 90].

17.4.2 Surgical Intervention

In all cases of pineal GCT, surgical intervention is fundamental to management of obstructive hydrocephalus. This can be addressed with external ventricular drainage (EVD) or endoscopic third ventriculostomy (ETV) and subsequent endoscopic biopsy, which may be most beneficial in appropriate patients. Initially, ventriculoperitoneal shunting was used to decompress the ventricles in the 1970s; however, this has fallen out of favor due to reports of shunt-related peritoneal metastasis and is no longer recommended [8, 98, 99]. There has, however, been a documented 70% success rate of ETV in treating tumor-related hydrocephalus in pediatric patients [100].

Residual radiologic abnormalities are seen in up to 30% of GCTs after initial treatment [1]. Second-look surgery is considered when lesions persist after completion of RT. In reported cases, the majority of lesions had components of teratoma or scar tissue [15, 101, 102]. When surgical

resection is warranted, cranial approaches to the pineal region often include the suboccipital supra-cerebellar infratentorial approach or the occipital interhemispheric trans-tentorial approach. In these instances, the patient is typically positioned prone in Mayfield head pins, and stereotactic neuro-navigation is used for operative planning. These cases can be challenging, given the long surgical corridor to the tumor and surrounding venous anatomy. Referral to tertiary centers with a high volume of these complex cases is likely to improve outcomes.

17.4.3 Prognosis and Monitoring

Prognosis of GCTs and long-term treatment outcomes have been based on histological subtype as well as levels of tumor marker positivity. A study of 373 pineal GCTs found a 5-year overall survival of 80%, with worse prognosis associated with the female sex, those of age greater than 18 years, NGGCT, and lack of RT [103]. In general, Europe and North America use a dichotomous scheme of germinoma versus NGGCT, delineating a good versus poorer prognosis, respectively [15]. Further, a serum or CSF AFP level greater than 1000 ng/mL is considered a poor prognostic factor [104]. There are mixed reports concerning poorer prognosis for b-HCG secreting germinomas, which may require more intense therapy for similar outcomes as pure, non-secreting germinomas.

Another prognostication strategy was developed by Dr. Matsutani of Japan in 1997. It is a three-pronged scheme wherein germinoma and mature teratoma have good prognosis, immature or malignant teratoma, as well as mixed GCT (germinoma/teratoma), comprise the intermediate group, and the remaining malignant NGGCTs (embryonal carcinoma, choriocarcinoma, yolk sac tumor, mixed tumor of these subtypes) have a poor prognosis [48].

By virtue of the malignant nature of this group of tumors, initial staging should occur with MRI of the brain and entire spine, CSF cytology, and tumor markers. After treatment, appropriate monitoring includes serial imaging and evaluation of tumor markers. Residual or recurrent tumor on imaging or continued elevated tumor markers can indicate recurrent disease that requires additional treatment. In the instance of germinoma patients, late recurrences have been reported, which suggests the need for continued follow-up for more than 10 years after therapy [2]. Management of the germ cell tumor patient population should include a multidisciplinary team of hematology oncologists, radiation oncologists, neurosurgeons, and potentially endocrinologists and neuropsychiatrists. In preparation for long-term care, appropriate discussions should be held with the family regarding treatment effects, quality of life, and continued monitoring.

17.5 Controversial Issues

Despite the availability of new technology and the evolution of treatment modalities, there are several topics that continue to be debated regarding germ cell tumors. Alluded to previously, there is a geographical disparity regarding tumor markers and the threshold values that define certain diagnoses. For example, NGGCTs are distinguished from b-HCG-producing germinomas at a much lower level in Western countries (>100 IU/L) when compared to the East (>2000 IU/L). This, in turn, determines the intensity and modality of treatment the patient receives. Secondly, there are no clear guidelines for best treatment of germ cell tumors (except surgery for mature teratoma) that maximizes survival while reducing treatment-related complications from radiation and chemotherapy. Often, treatment algorithms are institution-based or trial-related. Certain practitioners may advocate for radiation alone, while others use combination therapy with chemotherapeutic agents. Similar to dose variations, there are contrasting opinions on the radiation field to be used, be it whole ventricular, focal, whole brain, or craniospinal. Lastly, cases of enhancing residual tumors beg the question whether treatment with focal radiation or surgical resection becomes the most appropriate course of action. History being the

best indicator, future advances will continue to decrease morbidity and improve quality of life in the growing number of survivors as these controversies are reconciled.

17.6 Conclusion

Germ cell tumors of the pineal region are composed of multiple diverse subtypes of tumors originating from the primordial germ cell. Diagnostic imaging and analysis of serum and cerebrospinal fluid for tumor markers are integral for treatment. Management of these patients requires a multimodality approach including radiation, chemotherapy, and surgery. Given the rare and complex nature of these tumors, patient care can benefit from specialty center referral. Future technical advances and therapeutic investigations aim to provide improved survivability and quality of life for this patient population.

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Tumors of Glial Origin

18

Ioan Stefan Florian and Eduard Tronciu

18.1 Introduction

Tumors of the pineal region encompass a large variety of histopathological types. Tumors arising in the pineal region represent approximately 1% of all primary brain tumors (0.1–1.2% by some authors) [1–5], and up to 3.2% in the pediatric population (0–18 years) [3, 5]. Tumors of this particular location are rare, and even more so are gliomas. As such, it is difficult to have a large series of patients to evaluate peculiar characteristics, treatment options, and outcome. Also, because of the scarcity of data (mostly because gliomas of the pineal region are reported as case reports or as limited case series), there are some variations regarding patient characteristics. Therefore, best treatment options, outcome and prognosis in these patients represent an ongoing debate, and recently a number of reviews have emerged trying to address this issue.

18.2 Epidemiology

Gliomas of the pineal region are the third most frequent group of tumors of this location, representing 5–22% of all pineal tumors [1, 4] and about 0.1% of all gliomas of the central nervous system (CNS) [5]. This large variation is probably due to the different understanding of the pineal region in itself, with papers reporting the highest incidence being in gliomas of the vicinity that secondarily invade the pineal region. Mean age at presentation is estimated to be between 26 years (Literature Review, Magrini et al., 2013) and 38 years (SEER Database review, Al-Hussaini et al., 2009), and males are more affected than females. In our experience of 15 pineal region gliomas (representing 1.1% of the 1353 gliomas operated by the first author), the mean age was 33 years (range: 4–56 years), with a peak incidence in the third decade of life, males being represented in 73.3% (11) cases.

Glial cell tumors may arise from astrocytes within the pineal gland, while ependymomas can develop from ependymal cells from any location along the ventricular system and will usually grow posteriorly, into the pineal region (Fig. 18.1) [6].

From a histological perspective, all types of gliomas can be found in this location, from non-invasive World health Organization (WHO) grade I pilocytic astrocytomas to WHO grade IV glioblastomas. There is a new entity being researched

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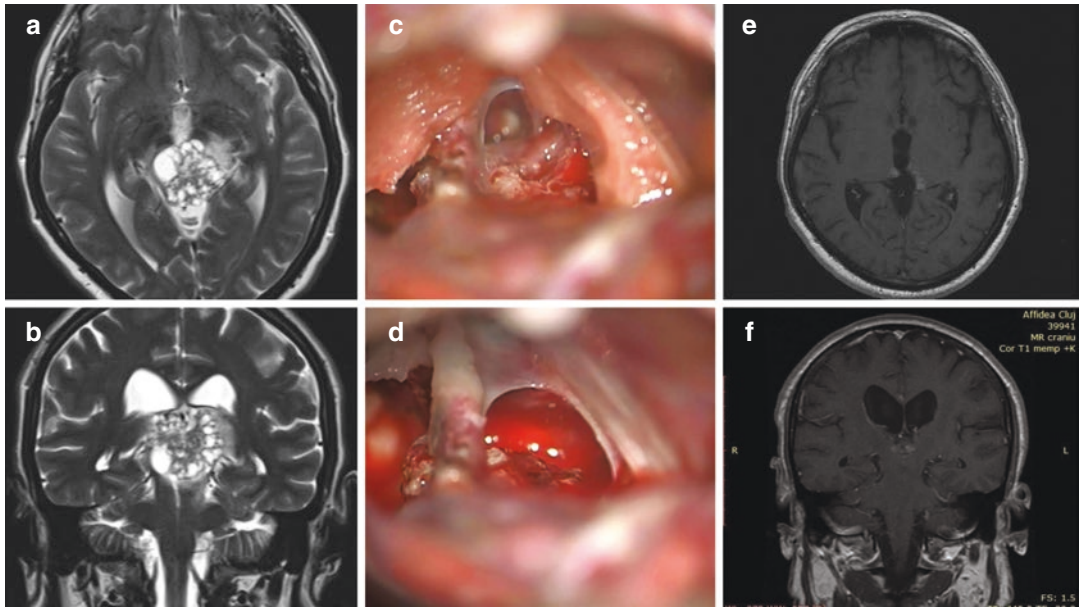

Fig. 18.1 Preoperative T2 weighted (T2W) images in axial (**a**) and coronal (**b**) planes of a pineal region ependymoma in a young male. A supracerebellar infratentorial (SCIT) approach in a semi-sitting position was performed. Please note the large supracerebellar corridor of this approach without any brain retraction (intraoperative images (**c**) and (**d**)). A near-total removal of tumor was obtained with intentional remnant infiltrating both thalami, as demonstrated by contrasted T1W sequences in axial and coronal planes (**e**) and (**f**)

that is represented by diffuse midline glioma H3-K27M mutant (DMG-K27M), which seems to have a predilection for the pineal region and has a poor outcome and limited treatment options, with only two cases described in literature [7, 8]. Regarding the distribution of pineal gliomas by histological type, available data suggest a predominance of grade II diffuse astrocytomas (approximately 24% of all pineal gliomas), followed by glioblastomas, ependymomas and pilocytic astrocytomas [4]. In our series of 15 pineal region gliomas, pilocytic astrocytomas are equally distributed with glioblastomas (five cases of each—33.3%), followed by anaplastic astrocytomas and ependymomas (two cases of each type—13%), with only one case of diffuse glioma (Fig. 18.2).

Regarding pineal region glioblastomas, it seems that these have a rather high rate of cerebrospinal fluid (CSF) dissemination into the leptomeninges, ventricular system, and "drop metastases" into the lumbar region [9–11]. There are some conflicting data regarding the total number of pineal region glioblastomas published in literature, from as low as 26 cases to as high as 65 cases [4, 12, 15]. Nevertheless, these numbers show how rare this pathology is. This is also true for our experience, where pineal region glioblastomas represent 1% out of 503 new cases of operated glioblastomas (Fig. 18.3). Gliosarcomas of the pineal region were reported in only three adults and one pediatric patient [17], and all cases had a poor outcome despite the best available treatment (gross total resection, followed by radio-chemotherapy). There was one case report of a pineal glioblastoma following radical subtotal removal of pineal parenchymal tumor of intermediate differentiation (PPTID), this being the only such case in the reported literature [15].

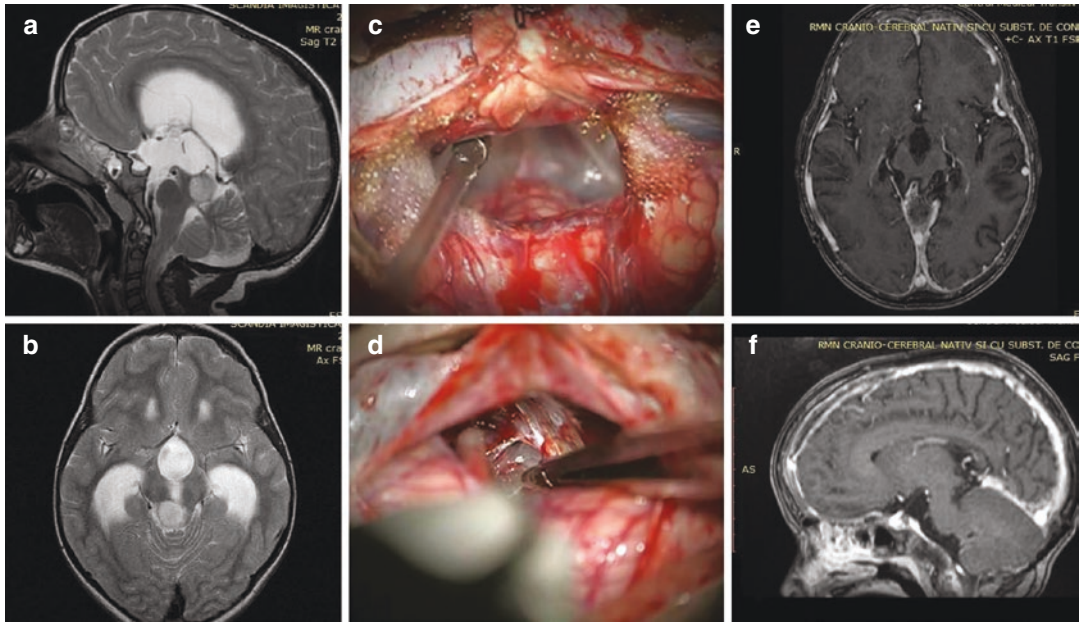

Fig. 18.2 Preoperative T2W images in sagittal (**a**) and axial (**b**) planes of a 4-year-old boy. In semi-sitting position, after dural opening and cerebrospinal fluid (CSF) release from cisterna magna, a large supracerebellar space is developed tensioning both supracerebellar veins. Surgicel patties were used to reinforce their walls in order to prevent intraoperative laceration and, as a consequence, intraoperative venous air embolism (VAE) (**c**); after the opening of the thick arachnoidal plane, the tumor is visible as a grayish-white hypovascular mass (**d**). The tumor was completely removed, as demonstrated by the contrasted T1 weighted (T1W) sequences (**e**) and (**f**) at 6 months postoperative follow-up MRI

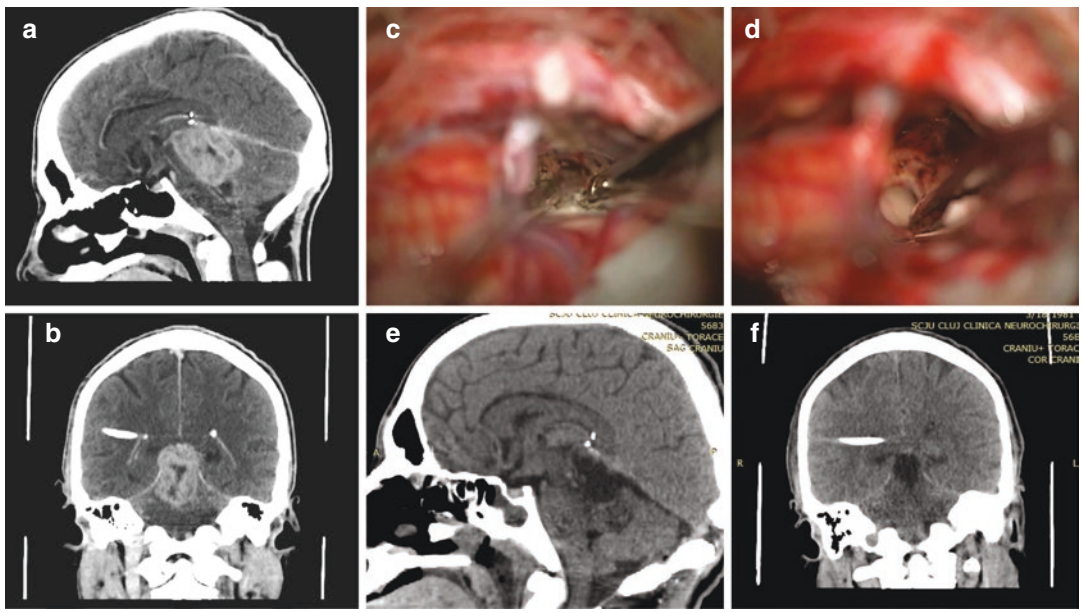

Fig. 18.3 Contrasted CT scan in sagittal (**a**) and coronal (**b**) reconstruction of a patient with glioblastoma of pineal region. A preoperative ventriculoperitoneal shunting (VPS) was previously placed in emergency in another neurosurgical service; through an SCIT median approach, a gross total removal was achieved with preservation of superior vermian vein—intraoperative images (**c**) and (**d**); postoperative CT scans (**e**) and (**f**) demonstrate the complete removal of the tumor

18.3 Clinical Features

Pineal region tumors become symptomatic through four main mechanisms [14]: (a) increased intracranial pressure due to obstructive hydrocephalus; (b) direct compression on cerebellum or brainstem; (c) endocrine dysfunction; and the rarest, (d) pineal apoplexy [13]. Details about all clinical features of pineal region tumors are discussed in the clinical presentation, Chap. 4 of this book.

It seems that, because of the pattern of growth, the tissue from which these tumors arise and their location, the only symptoms of pineal region gliomas, belong to either increased intracranial pressure (ICP) (from hydrocephalus) or direct compression on cerebellum or brainstem. There were no reported cases in the literature of patients with pineal region gliomas that presented with endocrine dysfunction.

The most prominent presenting symptoms in gliomas of the pineal region are represented by headaches (more than half the cases), followed by nausea and vomiting—the signs of obstructive hydrocephalus. A lower number of patients (approximately 12%) present with visual disturbances such as decreased visual acuity, Parinaud's syndrome, and diplopia/coordination extraocular muscles, and only a small number of patients complain of dizziness/drowsiness, behavioral changes, extrapyramidal disorders, and seizures [4, 12, 16].

18.4 Diagnosis

As for all pineal region tumors, magnetic resonance imaging (MRI) is the gold standard diagnosis test for pineal region gliomas, as this imaging technique provides data regarding tumor type, size, extent, and relationship to surrounding anatomical structures. Additionally, angiographic sequences provide valuable information concerning tumor vasculature. It is also recommended to perform spine MRI for patients with pineal region tumors in order to evaluate the presence of drop metastases.

The imaging features of pineal gliomas appear to be the same as in other regions. As such, it is important to assess T1 weighted images (T1WI), T2 weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR), and contrast-enhanced images. Diffuse astrocytomas will appear as hypointense, homogenous masses in T1WI and as hyperintense in T2WI and FLAIR (Fig. 18.1). T2WI and FLAIR will also be important in postoperative assessment, as these sequences are a part of response assessment in neuro-oncology (RANO) criteria for assessment of response of gliomas to therapy [18].

Another important diagnostic tool is magnetic resonance spectroscopy (MRS). MRS will not only differentiate between tumor types but also between tumor grades. The most important metabolites are choline (Cho), creatine (Cr), myo-inositol (mIns), N-acetylaspartate (NAA), lipids (Lip), and lactate. It is important to know that higher levels of mIns and NAA are associated with low-grade gliomas [19–22]. Cho levels correlate with protein Ki-67 positivity, and thus high levels of choline are seen in high-grade gliomas [23]. Cr is a stable marker of cellular metabolism and is usually expressed as a ratio to compare it to other neuronal metabolites. Thus, NAA/Cr is higher in low grade-gliomas, and Cho/Cr is higher in high-grade gliomas (decrease in creatine corresponds to higher energetic demands of continuously dividing malignant cell) [24].

An important contribution of MRS in the light of the new WHO Classification 2016 is the opportunity to differentiate the isocitrate dehydrogenase (IDH) mutation status in gliomas, using 2-hydroxyglutarate as a surrogate of its presence. IDH mutation leads to the enzyme losing its ability to produce α-ketoglutarate, while at the same time gaining the new capability to convert α-ketoglutarate to D-stereoisomer of 2-hydroxiglutarate (2HG) [25]. This will give rise to the formation of aberrant dioxygenases with consequent neoangiogenesis and abnormal gene expression [26]. MRS techniques were perfected to identify 2HG at 2.25 ppm [27].

As part of the diagnostic workup of pineal region gliomas, as in all pineal tumors, the neuro-ophthalmological examination assesses the degree of invasion/compression of the mesencephalon. This examination is also of great importance in the postoperative follow-up.

Like in other types of pineal region tumors, the evaluation of CSF biomarkers (alpha-fetoprotein, beta-HCG, placental alkaline phosphatase [PLAT], cytokeratins) is routinely recommended before surgery in order to differentiate gliomas in which the biomarkers are absent from other tumors (germinomas, choriocarcinomas, papillary tumors) [28].

Concerning stereotactic biopsy, it is generally discouraged because of the increased risk of causing vascular lesions of the region, difficulty in controlling hemorrhages, insufficient pathologic material for a clear definition of lesion, and, as a consequence, inconclusive results. On the other hand, there is the possibility of biopsy under direct vision during endoscopic third ventriculostomy (ETV) with flexible endoscope [4] or via the supracerebellar infratentorial endoscopic approach [29]. Progression of neurosurgical and anesthesiologic techniques greatly reduced the risk of direct approach of pineal region tumors, making the stereotactic biopsy more hazardous than any of the previously mentioned surgical techniques [30].

18.5 Surgical Treatment

Treatment of the pineal region is essentially a multidisciplinary endeavor, with surgery playing a pivotal role. Surgical treatment has the main goals of decompressing the neurovascular surrounding structures, restoring the CSF flow, alleviating the intracranial pressure, obtaining conclusive pathologic material in order to establish the histopathological, molecular, and genetic profile of the tumor, and creating favorable conditions for adjuvant radio-chemotherapy. In current practice, the preferred surgical routes are supracerebellar infratentorial (SCIT) and occipital transtentorial (OTT) [31]. The posterior transcallosal approach is reserved for tumors invading this part of corpus callosum and in selected cases of posterior third ventricular tumors. All these approaches are presented in detail within the dedicated chapters of the present book. We will only underline some principles based on our experience.

- The decision of surgical approach is more dependent on the relationship of the lesion with the venous complex of the pineal region than on the angle of tentorium; tumors predominantly located above the venous complex are easily approached via an OTT approach, while tumors located below the veins are best approached via the SCIT route.
- The semi-sitting position for SCIT offers some advantages: it enlarges the supracerebellar natural corridor toward the pineal region, reducing the need for brain retraction; it favors the dissection of veins, which are usually descending below the angle of tentorial incisura; the gravitational flow of fluids offers a clean operating field; and there is normal anatomical orientation in the field. All these advantages outperform the overly blamed disadvantages and risks such as venous air embolism (VAE) (preventable with an accurate surgical technique and permanent collaboration with the anesthesiology team), postoperative pneumocephalus (usually the symptoms subside without specific treatment in 3–4 postoperative days), or surgeon arm fatigue (preventable with a specially designed chair with armrest).
- Regarding the veins, we attempt to preserve them from the superior surface of the cerebellum by reinforcing their walls with patties of Surgicel® (Fig. 18.2c) [32]. Special attention is given to protect the vein of precentral cerebellum, a central median vein that should be preserved by working on both of its sides. (Fig. 18.1b, c).
- Over the last few years, we moved our surgical strategy toward a unilateral SCIT approach that offers the same working space in the pineal region but avoids sacrificing the superior cerebellar veins at least on the contralateral side (Fig. 18.4 and Video 18.1 presentation).
- A frozen sample is always taken at the beginning of tumor removal to grossly evaluate the character of the tumor (benign or malignant); according to the quick pathological result, in benign tumors every effort should be made for a gross total removal of the tumor, which will possibly cure the patient

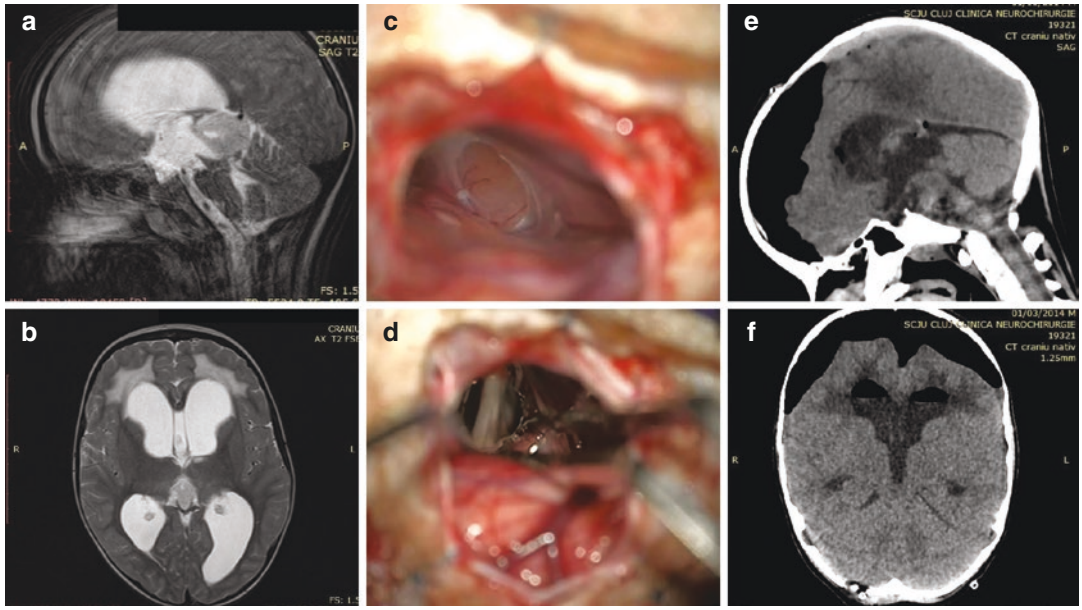

Fig. 18.4 Unilateral SCIT approach in a 5-year-old boy with low-grade glioma of the pineal region. The tumor is well demonstrated on preoperative native T2-weighted MRI in sagittal and coronal sections (**a**) and (**b**); the unilateral SCIT offers enough working space without any venous interference (**c**); after dissection of the arachnoid, the postero-superior surface of the tumor is in direct vision; removal starts from this portion, and with progressive reduction and mobilization it is completely removed (**d**); immediate postoperative follow-up CT scans demonstrate gross total removal of the tumor, reduction of hydrocephalus, and an important pneumocephalus, a frequent consequence of the semi-sitting position (**e**) and (**f**)

(Fig. 18.4). In malignant tumors the goal is safe maximal reduction.

- Internal debulking, piecemeal reduction of tumor through aspiration, bipolar coagulation and ultrasonic aspiration, and progressive dissection of the tumor margins (easily identifiable in pilocytic astrocytomas and at least from some parts in malignant ones) will finally lead to gross total removal in most of the cases.
- At the end of the procedure, a thorough check of hemostasis with bilateral jugular vein compression is mandatory, especially for cases operated in the semi-sitting position.

Complications related to surgery are not different from other types of tumors. In most of the cases an impairment of extraocular muscle movements and an aggravation of preoperative oculomotor deficit are noted. Some specific complications related to surgical corridor are mentioned in the literature. For example, for SCIT approach in prone position, retraction of cerebellum could result in postoperative ataxia, as for the semi-sitting position pneumocephalus is the rule. In both positions, sacrificing the large supracerebellar veins may sometimes lead to venous infarction. Concerning the OTT approach, the most commonly reported complication is represented by lesions on the occipital lobe, with some visual field impairment and the risk of seizures, whereas for the damage of the bridging vein, the venous infarction could be a devastating complication [33].

Concerning the histopathological grade of gliomas, postoperative mortality of HGG seems to be higher in the pineal region than in other supratentorial locations [4]. Indeed, we lost one of our five cases of glioblastomas in the immediate postoperative period due to multiple local and general complications.

Data regarding specific chemotherapy in glioma cases are scarce, with a review of literature published a few years ago [4] identifying only 17 cases in which chemotherapy was utilized. Radiotherapy is more frequently reported, being recommended for gliomas of this location [1] even for the pediatric population [8]. More details

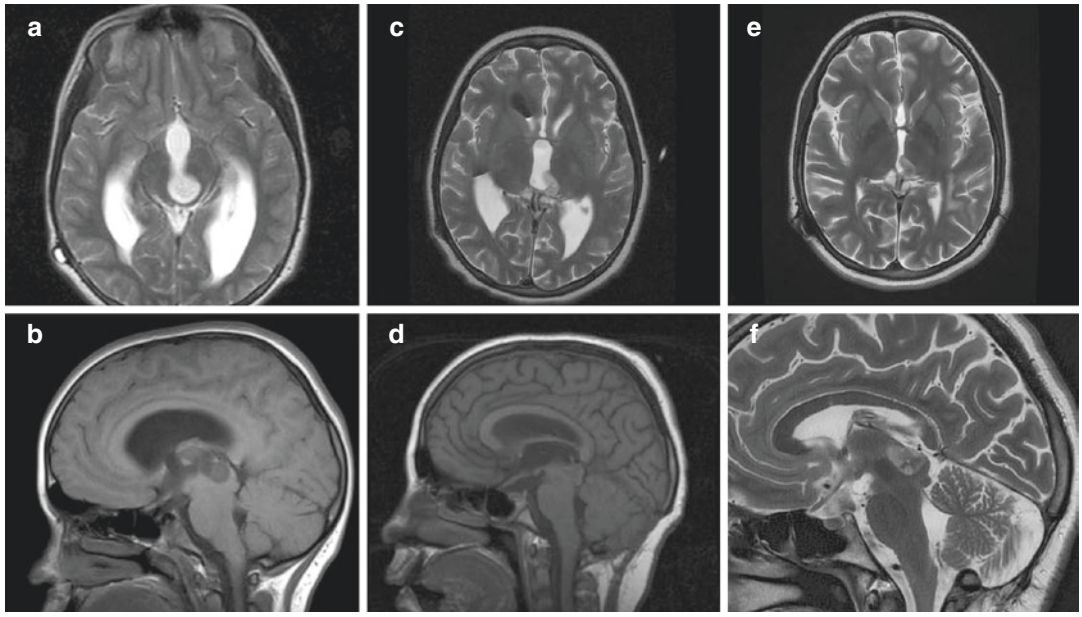

Fig. 18.5 Pilocytic astrocytoma with subtotal resection. Preoperative examination in axial T2WI (**a**) and sagittal T1WI (**b**) reveal a hypointense mass in the pineal region producing an obstructive hydrocephalus. During surgery, a subtotal resection was obtained with an infiltrative remnant in the left thalamus and persistence of symptomatic hydrocephalus, for which reason a VPS was inserted (**c**) and (**d**); The lesion was quite stable at the 10-year postoperative follow-up, without any additional complaints (**e**) and (**f**)

regarding chemotherapy, radiotherapy, and radiosurgery are presented in the respective chapters of the present book.

The prognostic of pineal region gliomas is largely related to pathology. Since for the pilocytic astrocytomas long-term survival (Fig. 18.5) and even cure is reported in the majority of publications, concerning HGG and, especially, glioblastoma, the natural course appears to be more aggressive here than in any other location [4]. There are some studies reporting a median overall survival (OS) of 11–20 months in patients who underwent surgery and radiotherapy [15, 16]. Some other studies report increased OS, up to 20 months, in patients who underwent radiochemotherapy without surgery [8, 34–36].

18.6 Controversial Issues

SCIT in the semi-sitting position is an appropriate route for the large majority of cases. Minimal VAE in this position is frequently encountered, but with meticulous technique, good collaboration with the anesthesiology team, rapid occlusion of venous bleeding sources, and copious lavage of the suspected zone with saline solution, the dreaded VAE can almost always be prevented. The selection of the approach is equally a matter of tumor position and surgeon preference [37]. In terms of minimal invasiveness, whether an endoscopic SCIT is superior to a unilateral microsurgical approach is debatable. Total removal is the main goal, but this should not be achieved at any cost, as, sometimes, the cost could be the patient's life.

18.7 Conclusions

Pineal region gliomas are rare tumors, and until now there is no relevant preoperative diagnostic data in order to discriminate them from other pineal region tumors. Low-grade gliomas seem to appear more frequently in this region, affecting predominantly young-adult males. Open surgery in experienced hands offers sufficient pathologi-

cal material for definitive diagnosis and poses lower risks than stereotactic surgery. SCIT and OTT are both valuable options for tumor removal, and the selection of the route is largely related to surgeon preference. Surgery represents the first and the most important step for multimodal treatment of malignant pineal region gliomas, while for benign tumors, radical surgery may offer the cure.

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Meningiomas of the Pineal Region

19

Gheorghe Ungureanu and Ioan Stefan Florian

19.1 Epidemiology of Pineal Meningiomas

Meningiomas represent only 3–8% of the tumors located in the pineal region, where about 0.4–1% of all brain tumors in adults are located [1–4]. Understandably, the literature regarding these lesions is exceptionally scarce and made up exclusively of case reports and small case series. There is a female dominance, which is in a similar trend with meningiomas in other locations [5]. Meningiomas tend to appear in older patients, unlike other tumors located in this region, with patients being mostly in their fourth to sixth decade of life [6–8].

19.2 Definition and Origin of Pineal Region Meningiomas

What exactly constitutes a pineal region meningioma is still debatable. Some authors include only meningiomas that originate at the level of the velum interpositum (VIM), without any dural attachment, while others also include the superior, anterior, and inferior projecting subtype of falcotentorial meningiomas (FTMs) [2, 8–11]. There are also literature reports describing meningiomas in the pineal region which do not originate from either of the mentioned sites [12]. We agree with the definition given by Konovalov et al., who identified three types of meningiomas in the pineal region: free-lying tumors, without dural attachment, tumors with a minimum attachment to the falx/tentorium, which do not functionally compromise the venous system, and tumors that attach to the falx/tentorium and compromise the venous system [2]. Arachnoid cap cells that give rise to VIM come from the dorsal tela choroidea, and those that occupy the qudrigeminal cistern arise from the posterior tenia fornicis [9, 12, 13]. While the exact origin of FTM has not been described, they may arise from arachnoid membranes located at the falcotentorial junction.

19.3 Clinical Presentation

The average patient age of presentation for FTM is 42–56 years, consistent with the mean age at diagnosis for other posterior fossa meningiomas (44.4 years), while a review of case series concerning VIM showed a mean age of 32.6 ± 19.6 years [8, 9, 14], suggesting that these tumors occur at younger ages.

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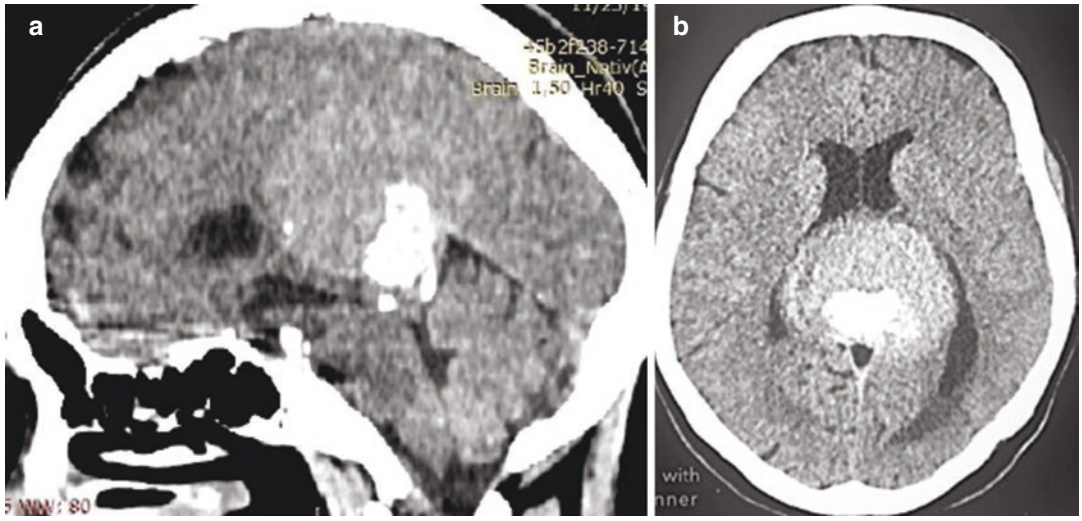

Fig. 19.1 (**a**, **b**) Native CT in sagittal (**a**) and axial (**b**) plane of a falcotentorial meningioma. The posterior aspect of the tumor is calcified. The calcified pineal gland, visible on the sagittal plane, can be seen at the anteroinferior pole of the tumor. The large volume of tumor produces a partial obstruction of the aqueduct with consecutive ventriculomegaly

Headache is the most commonly presenting symptom, followed by ataxia, bradypsychia, and personality changes, and homonymous hemianopia [14]. Symptoms are due to hydrocephalus and increased intracranial pressure and occur insidiously, over long periods, with a mean of more than 2 years [5, 6, 10]. The presence of mental deterioration in up to 37% of patients, together with the uncommonness of Parinaud syndrome or other cranial nerve abnormalities, which occur at a significantly lower rate than in other pineal region tumors, was considered a differential diagnosis trait by some authors [8].

19.4 Neuroimaging Studies

19.4.1 Computed Tomography and CT Angiography

The wide availability and ease in performing the investigation have made computed tomography (CT) the investigation of choice in emergency settings. Meningiomas are isodense or slightly hyperdense lesions, with homogenous contrast enhancement. Intratumoral calcifications are easily recognized. CT can show a small calcification at the periphery of the lesion, with a higher density than the tumor, still present at the postoperative examination, which is the calcified pineal gland (Fig. 19.1a, b) [2]. 3D CT angiography (3D CTA) is useful in evaluating the venous system and identifying how the tumor interacts with the various components of the Galenic system [15, 16].

19.4.2 Magnetic Resonance Imaging

Meningiomas in this region have similar findings to meningiomas in other parts of the central nervous system (CNS), which makes the diagnosis an easy one [4]. The vast majority of meningiomas have a hypointense/isointense appearance on T1 sequences and isointense/hyperintense appearance on T2 sequences and display intense, homogenous enhancement after gadolinium administration. Intratumoral low signal intensity can be caused by calcifications or flow voids, and differentiating between the two can be difficult and requires additional imaging techniques. The development of magnetic resonance (MR) techniques allows a better identification on the origins of meningiomas, adhesion,

and invasion of the tentorial dura and the assessment of an arachnoidal plane between the tumor and the cerebrovascular structures. This is one of the most significant factors in predicting the possibility of total tumor removal [17]. MR angiographic techniques tend to replace digital subtraction angiography (DSA) for the evaluation of the vascular system in meningiomas, and various contrast-enhanced and time-of-flight (TOF) MR venographies can show the displacement of the deep venous system and assist in choosing the surgical approach [15]. MRI can also demonstrate the existence of obstructive hydrocephalus when present [18].

19.4.3 Digital Subtraction Angiography

The use of DSA in investigating meningiomas located in the pineal region has decreased over the years, and most authors do not recommend performing it routinely [19]. Others consider that the occlusion of the Galenic venous system and development of collateral venous channels can only be shown by using DSA [18]. The displacement of the posterior choroidal arteries identified by DSA can help distinguish the various entities in this area: in FTM the arteries are displaced anteriorly, while in VIM these arteries are displaced postero-superiorly [18]. In the venous phase, DSA can identify the displacement of major veins, occlusion of the vein of Galen (VoG) or straight sinus (frequently occluded in FTM), and collateral venous channels, all of which are factors that influence surgical conduct [5, 11, 18].

19.5 Surgical Management

Because novel imaging techniques allow a reliable preoperative differential diagnosis between meningiomas and other pineal region tumors, and since biopsy in this region carries significant risk, we advise a complete surgical resection as the initial treatment step. We recommend confirming the diagnosis using an intraoperative histologic examination, because of the high variability of tumors in this region and since other histologies could guide the surgeon towards a more conservative surgical attitude.

There are several surgical corridors described in the approach for pineal region tumors, infratentorial, supratentorial, or combined, the most critical aspect in their selection being the displacement of the venous complex by the tumor [5–7, 9, 10, 14, 19–22]. As a general rule, we chose our approach by considering the displacement of the venous complex: if displaced dorsally, we favor an infratentorial supracerebellar approach which allows for tumor resection from below the deep venous complex, while in tumors causing inferior displacement of the venous complex, we recommend a supratentorial approach. Nevertheless, a combined approach could be of interest in selected cases. Several approaches were described, including the occipital transtentorial/transfalcine, its bilateral variant, and a combined supratentorial and infratentorial transsinus technique [5, 23]. The specific description of surgical approaches, the related technique, and complications, can be found in other chapters of this book, but there a couple of particular characteristics of meningioma surgery that should be kept in mind.

Firstly, because in a large proportion of patients the VoG or straight sinus are occluded or severely stenosed, collateral venous channels play a crucial role in meningiomas, and their coagulation can have serious complications, while the sacrifice of some of the deep venous structures can be well tolerated in those cases [9]. Therefore, the surgeon should carefully investigate the radiological images and sacrifice collateral veins as conservatively as possible.

Secondly, unlike other tumors in the region, meningiomas often have an excellent arachnoidal plane separating them from the surrounding structures. Like in any other location, the importance of the arachnoid in meningioma surgery cannot be overstated (Fig. 19.2) [17]. Goto et al. classified FTM as superior or inferior relative to the VoG [13]. The outcome of patients with superior FTM is far better, since the thick arachnoid membrane located between the pericallosal and quadrigeminal cistern (which hosts the deep

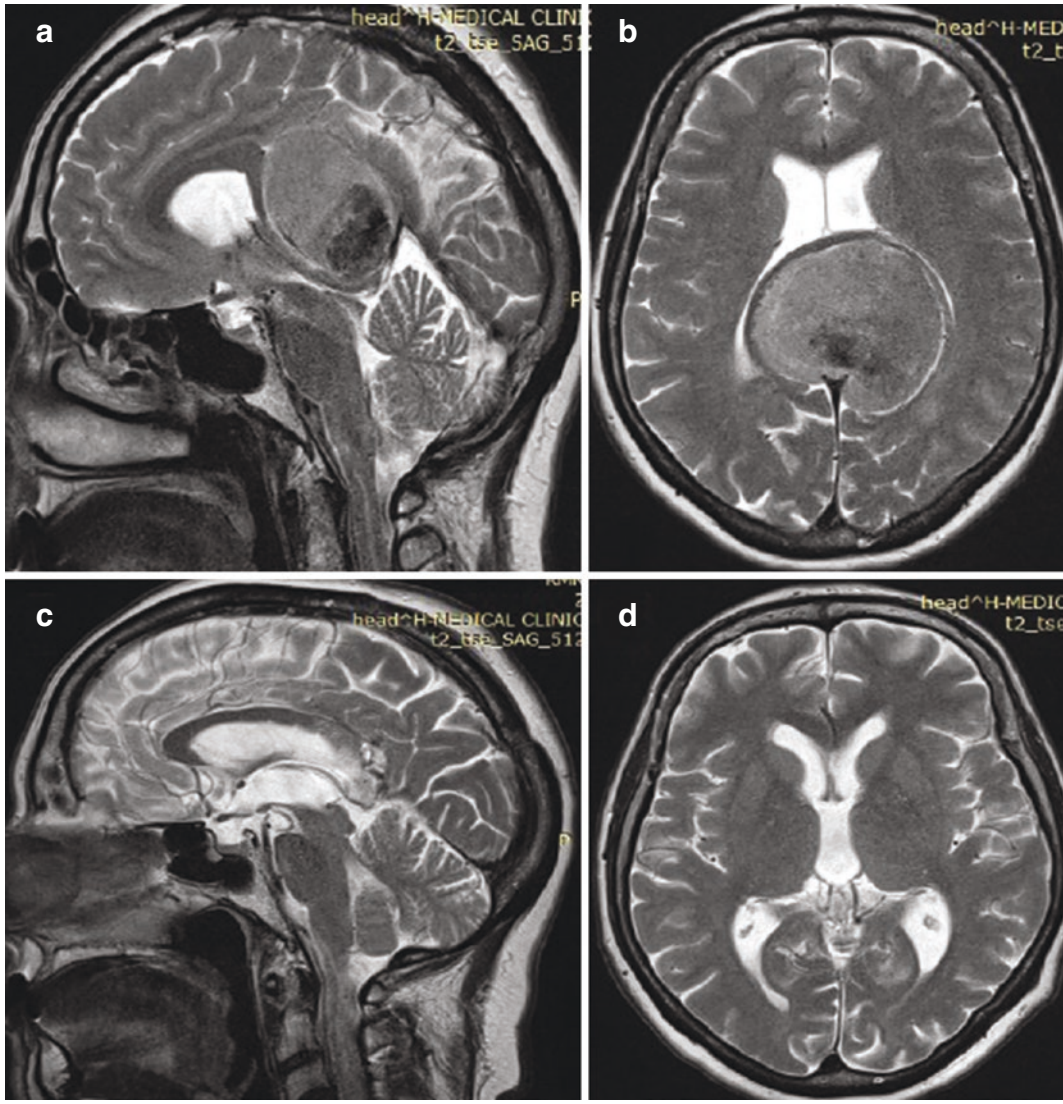

Fig. 19.2 (**a**–**d**) Native T2 sequences in the sagittal and axial planes of a giant falcotentorial meningioma (**a**, **b**). T2 sequences are useful for surgical planning and in identifying the arachnoidal plane separating the tumor from the surrounding structures. Despite the large tumoral dimensions, the presence of this plane facilitates dissection of the tumor from the neurovascular structures, creating a surgical corridor. Through a supratentorial interhemispheric approach using progressive debulking and arachnoidal dissection, total removal is possible. Images (**c**) and (**d**) show complete resection of the meningioma.

venous complex and dorsal midbrain) separates the tumor from these structures, while the inferior tumors closely adhere to these vital structures.

Thirdly, some technical aspects should be underlined. In small- and medium-sized meningiomas, the surgeon should select an approach that brings him/her closer to the base of the tumor, which allows devascularization and progressive removal through internal debulking, and mobilization of the tumor, while the surface of the tumor is gradually coagulated. Preserving the arachnoid is of utmost importance in order to keep away the venous complex and arteries. In large meningiomas, despite an impressive appearance, surgery can be more facile, since the tumor creates a surgical corridor (Fig. 19.3). In

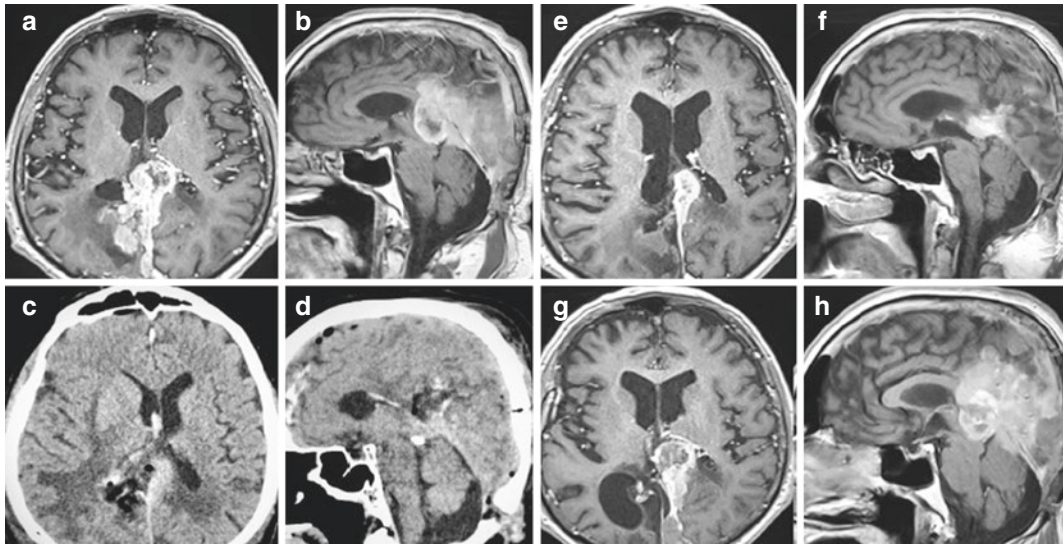

Fig. 19.3 (**a**–**h**) Enhanced T1-weighted (T1W) MR examination in the axial and sagittal plane (**a**, **b**) of a case with an atypical falcotentorial meningioma infiltrating the adjacent right occipital lobe and pineal region. A subtotal resection was obtained through an occipital transtentorial approach (**c**, **d**); after the operation the patient underwent radiotherapy—enhanced T1W MR sequences (**e**, **f**) demonstrating a small remnant at the tentorial notch; at 2 years after the multimodal treatment an important regrowth was observed (**g**, **h**); the patient refused any additional treatment

these cases, an approach that brings the surgeon closer to the most superficial part of the tumor could be more appropriate. Shrinking the surface of the tumor by bipolar coagulation, internal debulking, and progressive mobilization of the capsule inside the arachnoidal plane will allow a complete removal. Bleeding from the tumor in this large meningiomas is usually limited and can be reduced by cottonoid tamponade inside the tumor, coagulation of surface feeders, and division of tentorial insertion (Video 19.1).

Outcome after surgery for pineal region meningiomas is generally a good one, with total resection being possible in a majority of cases, while the invasion of the brainstem or deep venous system is the most important predictor for a subtotal resection [6, 9, 14, 18, 19].

19.6 Controversial Issues

– The definition of pineal meningiomas: Although some authors consider only VIM as pineal meningiomas, as already mentioned, we use the description of Konovalov et al., which also includes a subgroup of falcotentorial tumors [2].
– Supratentorial versus infratentorial approaches: Various authors recommend different approaches for these lesions. We disapprove of the "one-size-fits-all" attitude in any neurosurgical procedure. Each case should be approached by considering its particularities. As described previously, the displacement of the venous system can orient the neurosurgeon towards the better option. Importantly, there is no difference in outcome determined by the surgical approach, apparent in the literature.
– Sitting versus prone position for the infratentorial supracerebellar approach: Although there are several described complications associated with the sitting position, we consider it the best option for the infratentorial approaches. The anatomic orientation, the contribution of gravity, which eliminates the need for any traction and allows for a clear surgical field, are all benefits that cannot be matched. We also find that experience in using

this position makes its use safer over time and minimizes the rate of complications.

19.7 Conclusions

Meningiomas in the pineal region represent a small minority of tumors in this location. Their exact definition, origin, and approach are still subject to debate in the sparse literature concerning this topic. The surgical approach depends on surgeon preference and experience, and a total resection with a good outcome is achievable. The major factors which should be considered in deciding the surgical attitude should be the state and displacement of the deep venous structures.

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Metastatic Tumors

20

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20.1 Introduction

Cerebral metastases are brain tumors that originate in organs outside the central nervous system which then subsequently metastasize to the brain without invading the brain per continuitatem. Therefore, cerebral metastases share certain basic features with their primary tumors, such as cancer cell type. Comprising 50% of the cases, the most frequent primary tumors are lung cancers, either non–small cell lung cancer (NSCLC) or small cell lung cancer (SCLC), followed by breast cancers and malignant melanoma (each 20%). The rest include primary sites in the urogenital and gastrointestinal tract.

Cerebral metastases are the most common cerebral neoplasms, with an estimated yearly incidence of 200,000 cases in U.S.A. and 375,000 cases in Europe [14, 34]. However, only few studies are available calculating exact incidence rates, which range from 2.8 to 14.3 per 100,000 habitants [4, 9, 11, 15, 30, 35, 38, 44, 45]. Nevertheless, the actual incidence of occult cerebral metastases might even be higher, as autopsy studies revealed [3, 8, 37].

20.2 Epidemiology

Although cerebral metastases are the most common brain tumors, metastases in the pineal region are a rare occurrence. Förster described the first case of a pineal metastasis in the nineteenth century [12]. Most publications are case reports; there is one study including ten patients suffering from pineal metastases, representing the largest study of its kind to date [28]. The estimated frequency of metastases to the pineal region was 0.3% in a large Japanese survey [41]. However, the actual frequency might be higher in autopsies and radiological series [33].

Various primary sites of pineal metastases have been reported, including lung cancer (NSCLC and SCLC), breast cancer, malignant melanoma, and cancers of the urogenital (kidney and prostate cancer) and gastrointestinal tract

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(esophagus, stomach, and colorectal cancer). Frequencies of primary sites of pineal metastases might be similar to those of cerebral metastases in general.

While most patients with primary pineal tumors are younger than 30 years of age, most patients suffering from pineal metastases are older than 60 years [31]. The gender ratio is likely to be balanced.

20.3 Clinical Presentation

Almost all patients with symptomatic pineal metastases suffer from obstructive hydrocephalus. Therefore, signs of hydrocephalus, such as severe headaches, change of consciousness, increasing confusion, and finally, coma, are most common and cause high symptom burden for patients and their relatives, and may need the support of specialized palliative care [28]. Additionally, patients might suffer from signs of compression of the dorsal midbrain. About 75% of patients present with Parinaud's syndrome: paralysis of upwards gaze, a pupillary light-near dissociation and a convergence-retraction nystagmus. Other signs, such as the Sylvian aqueduct syndrome indicating periaqueductal dysfunction, might occur [28].

Next to symptomatic pineal metastases, an unknown number of pineal metastases might clinically be silent and only be detected during autopsy as incidental findings.

20.4 Diagnostic Considerations

Diagnosis includes a detailed patient's history and clinical-neurological examination, as well as documentation of neurological deficits. Furthermore, evaluation of patient's therapy goal within shared decision-making and/or patient's advance directive is essential. However, the standard method for the diagnosis of a pineal tumor is a contrast-enhancing magnetic resonance imaging (MRI). Pineal metastases appear as ring-shaped or homogenous contrast-enhancing lesions [13]. The MRI should furthermore be carefully evaluated for signs of obstructive hydrocephalus.

Incidental benign pineal cysts should be ruled out. They occur with a frequency of up to 4% [2]. Since primary pineal tumors are more common than pineal metastases, a routine determination of serum and cerebrospinal fluid (CSF) biomarkers, including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), and placental alkaline phosphatase, might help exclude endodermal sinus tumor/yolk sac carcinoma, embryonal carcinomas, choriocarcinomas, germinoma, and immature teratoma [7].

If malignancies have previously been diagnosed, diagnostic workup includes staging examinations to evaluate systemic cancer distribution, as well as the evaluation of cancer-specific mutations such as, e.g., epidermal growth factor receptor mutations, anaplastic large cell lymphoma receptor tyrosine kinase and proto-oncogene tyrosine-protein kinase ROS rearrangement for NSCLCs, and molecular features of the tumor microenvironment, including expression of PD-1/PD-L1/CTLA4. Leptomeningeal disease might be present at the time of diagnosis of pineal metastases in up to two-thirds of the patients [13]. Therefore, a leptomeningeal spread should be excluded if pineal metastases are suspected. One has to be extremely cautious, since obstructive hydrocephalus occurs in nearly all patients with symptomatic pineal metastases due to the location of the gland. Lumbar puncture should be avoided in case of obstructive hydrocephalus.

20.5 Therapeutic Considerations

Since pineal metastases are rare, evidence for therapeutic concepts is lacking and general recommendations cannot be given [39]. Thus, the therapy concepts of pineal metastases remain individualized, and management of pineal metastases is usually an interdisciplinary approach that involves surgery, radiotherapy, oncology, and palliative care. The selection of the best treatment should carefully consider the patient's clinical presentation and declared intention, the expected tumor histology and its central nervous system (CNS) distribution, a potential systemic cancer spread, and the availability of therapeutic and/or supportive methods. In

particular, a potential leptomeningeal spread should be investigated and, if present, be taken into account during treatment planning [29].

Because patients with pineal metastases frequently suffer from hydrocephalus, management of hydrocephalus is urgent: mild and asymptomatic hydrocephalus might be treated—if necessary—by an external ventricular drain. Mild hydrocephalus frequently resolves after removal of the pineal mass. Symptomatic and severe obstructive hydrocephalus often requires an instant CSF diversion. Endoscopic third ventriculostomy combined with a tumor biopsy enables an effective treatment of the hydrocephalus and a histopathological diagnosis in most patients [36]. However, endoscopic third ventriculostomy and biopsy might not be feasible in all patients or be available in all neuro-oncological centers.

Surgical resection of pineal metastases should be considered in patients presenting with a single cerebral metastasis exerting a huge mass effect, in a good clinical condition with a controlled primary tumor and without further metastases to provide a correct histopathological diagnosis, including the determination of tumor-specific markers. Surgical resection of pineal metastases should be performed by experienced neuro-oncologic neurosurgeons, and the complex anatomy of the pineal region should be taken into account. Main standard approaches to the pineal region are the infratentorial supracerebellar as an intratentorial approach and the occipital transtentorial and the transcallosal interhemispheric as supratentorial approaches (Fig. 20.1) [6, 27, 40, 42].

Figure 20.1 illustrates the case of a female patient suffering from a large pineal metastasis. MRI imaging (a—axial T1-weighted images with contrast agent, b—sagittal T2-weighted images) shows mass of the pineal region. The metastasis was operated using an infratentorial, supracerebellar approach. Figure 20.1c shows the intraoperative finding, and Fig. 20.1d illustrates the corresponding anatomy just before starting the resection.

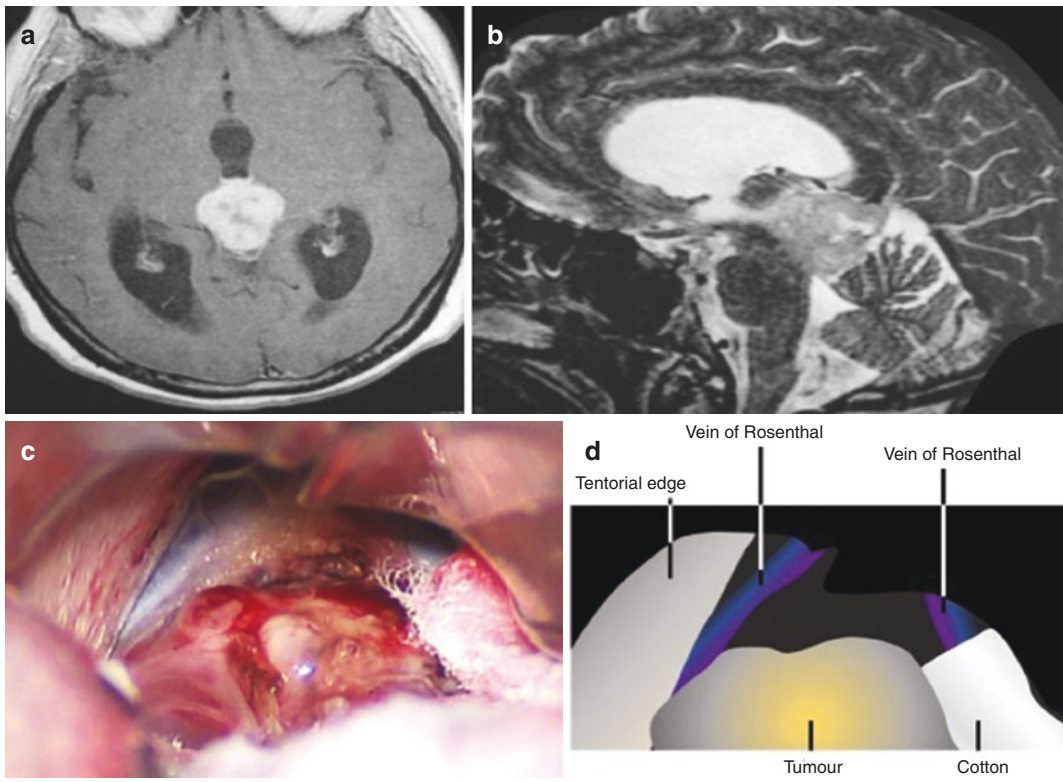

Fig. 20.1 Surgical treatment of a pineal metastasis

The surgical techniques are described in detail in section two of this book. For a better differentiation of the tumor from the surrounding tissue, 5-aminolevulinic (5-ALA) staining of cerebral metastases might be beneficial [22]. However, not all cerebral metastases show 5-ALA-derived fluorescence [21, 23]. Furthermore, use of intraoperative neurophysiological monitoring (INM) is warranted to intraoperatively monitor motor, oculomotor, and visual functions. INM might help prevent severe neurological deficits caused by the surgery. Other concepts for metastases surgery, such as supramarginal resection, might hardly be applicable for pineal metastases [18–20, 23, 25, 26]. An early postoperative MRI within 72 hours is warranted to evaluate the degree of surgical resection [24, 32]. For histopathological diagnosis and determination of tumor-specific markers only, stereotactic biopsy of the tumor is a feasible alternative.

Radiation therapy is an important modality in the treatment of pineal metastases. The selection of irradiation protocol should consider the tumor histology, the patient's clinical condition, the size of the lesion, and if there are additional cancerous lesions present in the CNS. In the case of neuroendocrine small-cell cancer metastases, whole brain radiation therapy (WBRT) should be considered. For single non–small cell cancer metastases, different concepts of irradiation have been reported [1, 5, 10, 16, 28, 31]. Generally, as with all brain metastases, a favorable alternative to WBRT is local (fractionated stereotactic) radiation of the pineal region [16, 31].

Finally, patients with malignancies and cerebral metastases profit from an integration of palliative care early in the disease trajectory [43]. Therefore, an early offer of palliative care is warranted in all patients.

20.6 Prognosis

Most of the older case studies of patients with pineal metastases describe a poor prognosis with a very limited overall survival not exceeding 6 months [1, 10, 17, 46]. However, most of these case presentations did not involve modern oncologic treatments, and some newer reports suggest a better prognosis in some cases [31].

20.7 Conclusion

Metastases are a very rare differential diagnosis of pineal masses, occurring mainly in elderly patients. Diagnostic workup includes visualization of the tumor by a contrast-enhanced MRI, the search for a leptomeningeal spread, and exclusion of more common pineal tumors, for example, by using specific biomarkers. Because patients with pineal metastases frequently suffer from hydrocephalus, management of hydrocephalus is urgently needed. Evidence for any therapeutic concepts of pineal metastases is lacking, and general recommendations cannot be given. Therapeutic management of pineal metastases is usually carried out as an interdisciplinary approach that involves surgery, radiotherapy, oncology, and palliative care.

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Part V

Vascular Lesions of the Pineal Region

21 Arteriovenous Malformations of the Pineal Region: Management and Controversies

Ioan Alexandru Florian, Teodora Larisa Timiș, and Ioan Stefan Florian

21.1 Definition and Epidemiology

Arteriovenous malformations (AVMs) represent an allegedly rare congenital vascular pathology that the highest number of hemorrhagic strokes in the young population [1–5]. They are either focal or diffuse, and can be located anywhere along the central nervous system. AVMs comprise arterial feeders, a nidus of malformed and entangled vessels, and a variable number of drainage veins. Within the nidus, arterial blood passes directly into the venous system at high flow and pressure, since there is no interposing capillary network. It is important to differentiate pineal AVMs that drain into the great vein of Galen from the malformations of this vein, which are direct arteriovenous fistulas with the aneurysmal dilation of the vein of Galen and are covered in another chapter.

The incidence of yearly diagnosed AVMs is around 1–1.5 in 100,000 persons, the estimated prevalence ranging from 5 to over 600 per 100,000 persons across different studies [1, 6]. As many of these lesions remain asymptomatic and undiagnosed, the true prevalence is currently unknown. Pineal region AVMs are exceedingly rare among reported series, accounting for around 1–7% of treated cases [5, 7–11]. In the experience of the senior author of this chapter, of 212 AVMs treated surgically between 2000 and 2018, five such cases have been encountered. However, these lesions may be underreported, due to the poor definition of the pineal region. Purportedly, the first such case reported in the literature belonged to Jaeger et al. in 1937, followed by a number of surgical and anatomical case studies [12, 13]. Because of their rarity, complex vascular framework, and deep location, these lesions represent a veritable challenge, regardless of the treatment method.

21.2 Anatomical Considerations

Arterial feeders of pineal AVMs may emerge from the vertebrobasilar system or tectal arteries such as the meningo-hypophyseal trunk, or the pericallosal or posterior choroidal arteries [7, 14, 15]. These vessels encircle the cerebral peduncles to form a nidus posterior to the pineal gland, which can be mainly supratentorial or infratentorial [12]. This nidus can be either intraparenchymal and surrounded by gliotic tissue or entirely extra-axial and located in the subarachnoid cisterns, such as the quadrigeminal, velum interpositum, or posterior callosal cistern. The nidus is then usually drained into the straight sinus via enlarged tectal and superior cerebellar veins, or within the basal vein of Rosenthal and the vein of Galen [7, 14]. It

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has been reported that tectal AVMs can be associated with a possibly reversible acquired type I Chiari malformation and syringomyelia, as a result of posterior fossa venous congestion [14].

21.3 Clinical Presentation

Although AVMs can be often asymptomatic and discovered incidentally, the most common and severe form of presentation is hemorrhagic stroke with sudden focal neurological deficit or alterations in the state of consciousness [1–3, 16]. Epilepsy, headache, and progressive neurological deficit unrelated to hemorrhage are other possible forms of manifestation. Regarding pineal AVMs, clinical signs can vary from patient to patient. A rupture can result in tetraventricular hemorrhage with acute hydrocephalus and signs of increased intracranial pressure (ICP), the patients generally presenting with an altered state of consciousness or comatose (as was also the case for the patient in Fig. 21.1) [16]. A less severe hemorrhage can lead to headache and vertigo [17]. Neurological deficits, such as visual impairment, diplopia, dyslexia, acalculia, and difficulty concentrating, have been described [7, 14]. Headache can occur as a result of increased ICP from chronic hydrocephalus [15, 18, 19]. Rarely, an AVM in this region may manifest through endocrine disturbances and precocious puberty [20]. Increased ICP from these lesions in infants results in macrocephaly, bulging fontanel, and a delay in mental development [17]. It is obvious that a severe clinical presentation mandates swift interventional therapy, whereas mildly symptomatic AVMs are treated electively.

21.4 Imaging Studies

Digital subtraction angiography (DSA) remains the gold standard for the diagnosis and detailed evaluation of cerebral AVMs, in spite of the advancements of cross-sectional imaging techniques [1–3, 21]. This method defines the exact number and origin of arterial feeders, the location and size of the nidus, the placement of the draining veins, as well as any associated aneurysms. It also represents the first step in endovascular

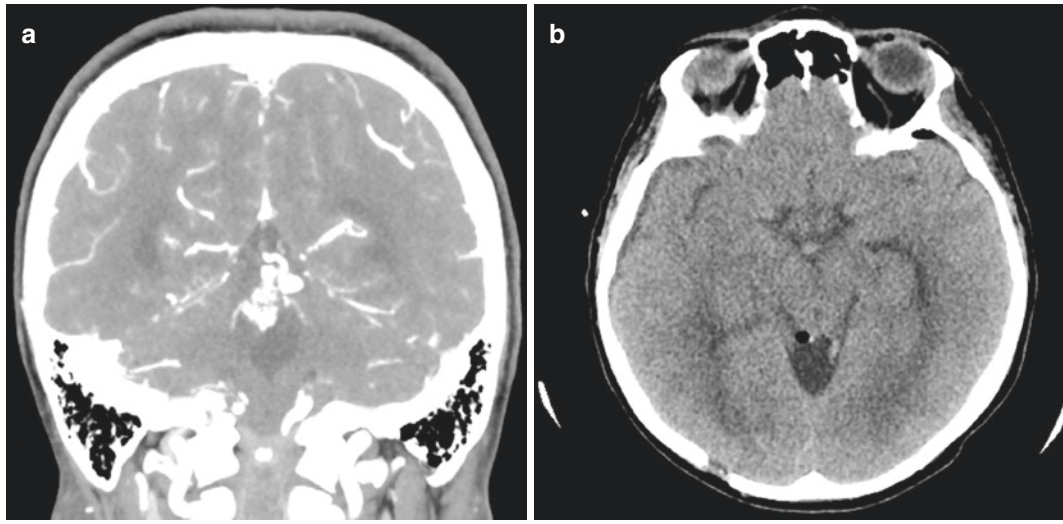

Fig. 21.1 A 45-year-old female patient presented comatose. Preoperative computed tomography (CT) (not shown) revealed massive intraventricular hemorrhage. We performed an external ventricular drain (EVD), and the control CT angiography (CTA) (**a**) demonstrated a large pineal AVM. Using a supracerebellar infratentorial (SCIT) approach, we completely removed the lesion, as shown in the immediate postoperative CT scan (**b**). She was later discharged with minimal deficit

treatment. Computed tomography (CT) and CT angiography (CTA) are valuable replacement tools that can be performed in an emergency setting and easily identify intracranial hemorrhages (subarachnoid, intraparenchymal, intraventricular, etc.). CTA can distinguish blood from intravascular contrast and should be performed whenever there is a suspicion of a ruptured aneurysm or AVM. Even so, in some cases, the hematoma itself can mask the presence of the nidus. In the absence of a hematoma, a non-contrasted CT scan may reveal a seemingly normal brain [21]. Magnetic resonance imaging (MRI) and angio-MRI are superior to CTA in terms of demonstrating the exact size and location of the nidus and also being able to localize the adjacent eloquent structures. However, CTA is apparently more sensitive in identifying associated aneurysms than MRI [1]. Pineal region AVMs are thus identified as being in close proximity to the pineal gland or the quadrigeminal plate, receiving arterial feeders from the posterior circulation or tectal vessels and draining into the great vein of Galen. The nidus can be predominantly supratentorial or infratentorial, deciding the surgical approach. AVM rupture in this region is often associated with tetraventricular hemorrhage, also discernible on CT and CTA.

21.5 Endovascular Treatment

Endovascular procedures can be used as a preoperative adjunct for high-risk AVMs, such as those with intranidal or feeder artery aneurysms, to reduce intraoperative hemorrhage [1, 22]. Alternatively, they can be used as a curative method for small and inoperable symptomatic AVMs, aiming to obtain an angiographic obliteration of the shunt. The two substances generally used, Onyx (ethylene-vinyl alcohol copolymer) and NBCA (N-butylcyanoacrylate), have comparable associated morbidities [23], yet Onyx is the preferred choice for AVMs due to its superior penetration and longer injection time [1, 22]. NCBA is applied through perforating and small cortical arteries, whereas Onyx is applied via larger arteries [24].

Before the start of the procedure, an adequate angiogram has to be performed to facilitate planning. Typically, endovascular procedures are performed via transarterial embolization under general anesthesia, alongside continuous electrophysiological monitoring. In the course of the procedure, anticoagulants have to be administered intravenously (a heparin bolus of 3000 IU, followed by 1000 IU every hour) [27]. Depending on the origin of the feeder arteries, the approach is made through the vertebral arteries and the branches of the posterior cerebral artery (PCA) or the superior cerebellar artery (SCA) [27, 28]. If a presurgical embolization is desired, then proximal arterial occlusion is sufficient to decrease nidus flow [24]. If, however, the endovascular procedure precedes stereotactic radiosurgery or is the sole therapy, the embolic material should be driven all the way up to the first centimeter of the drainage vein. To avoid post-procedural rupture, the vein should only be approached after every single arterial feeder has been occluded. A dual-lumen balloon-augmented Onyx embolization has also been described as a safe and effective option in reducing AVM nidus size prior to surgical procedure, yet it requires further validation [28].

The transvenous route, previously used only in dural arteriovenous fistulas, has been utilized for certain AVMs, although it is still labeled as experimental [24]. It may be attempted for an AVM with a single and readily accessible draining vein, which cannot be effectively approached via the arterial pathway. However, due to the perceived risk of surmounting intranidal pressure, its usage has been largely discouraged before the introduction of Onyx, which can spread inside the AVM against the blood flow.

Apart from preoperative or curative aims, endovascular embolization can also be used as a symptomatic treatment in carefully selected cases, with the goal of alleviating a neurological symptom [24]. The majority of these patients have symptoms due to venous compression on the parenchyma or a cranial nerve, and the procedure helps reduce the high flow within the venous system. However, it is not applicable for epilepsy or migraine.

The complications of this procedure include ischemic incidents that usually develop after an embolic fragment migrates beyond the AVM into the normal vasculature [24]. Hemorrhagic complications, however, are the most often and severe [24, 25]. They are a result of premature venous occlusion and subsequent retrograde pressure buildup, or of arterial perforation during microcatheterization or retrieval of the microcatheter. Consequently, thalamic or temporo-occipital hemorrhagic or ischemic lesions may arise from such an incident within a pineal region AVM. The patients may present cognitive deficit of various degrees, visual disturbances, paresthesia, and even acalculia, as described in one case [26]. As a general drawback, the efficacy of endovascular treatment is generally lower than that of surgery. According to Bradac et al., the obliteration rates were generally lower than 50% among reported case series, with significant recanalization rates [4]. As Steiger et al. have stated, endovascular therapy represented the principal risk factor for the exorbitant event rate after intervention [29]. Regardless, it remains a valuable therapeutic tool in the multimodal arsenal for hard-to-reach AVMs, such as those of the pineal region.

21.6 Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is also a commonly used treatment option for these lesions, although there are only a handful of reported pineal AVMs managed through this method [9–11, 30]. The principal aim of SRS is the complete obliteration of the nidus while avoiding possible adverse radiation effects (AREs). The thrombo-obliteration rates following a single procedure vary between 60% and 80%, this event occurring after a period of 4–5 years [9–11, 31]. During this period of "obliteration expectancy," patients remain at risk for hemorrhage. However, it is currently unknown whether the risk of hemorrhage remains the same or gradually lessens as time passes [32, 33]. Complete obliteration seemingly decreases the cumulative residual lifetime risk of hemorrhage to 1% or below [9–11, 32]. Previously, AVMs larger than 10 cm^3 were not amenable to SRS; however, staged-volume radiosurgery makes treatment of large lesions possible and with acceptable obliteration and morbidity rates [31]. It is also possible to embolize a large AVM before SRS, although an improper endovascular technique may hinder proper radiosurgical obliteration.

AVM marginal doses are typically between 18 Gy and 25 Gy, with maximal doses ranging from 36 Gy to 50 Gy at the AVM borders [30]. Selection criteria for the final dose include AVM volume and location, which are also of great help in predicting the risk for adverse events. The presence of preexisting neurologic pathologies, age, and prior history of hemorrhages should also be taken into account. To reduce the risk of periprocedural seizures, the patients should be given 20–40 mg of methylprednisolone or dexamethasone, coupled with anticonvulsants, before or at the conclusion of the intervention [9–11, 30, 31].

Staged radiosurgery is recommended for AVMs over 10 cm^3, with two consecutive stages usually planned at 3 months from each other [30, 31]. For smaller lesions, single-stage radiosurgery is generally sufficient. Imaging follow-up at regular intervals is crucial.

As complications following SRS, AREs can manifest through focal neurological deficits, epilepsy, and headache as a result of increased ICP [31]. Structural changes such as radionecrosis occur more frequently as the interval from the intervention increases, and if symptomatic may be treated surgically. Malignancies after SRS are exceedingly rare, and even more so for AVMs. In short, radiosurgery is also a viable option for pineal region AVMs that are not acceptable candidates for surgery.

21.7 Surgical Resection

To this day, surgical resection remains the definitive treatment method for intracranial AVMs [2, 3, 34–36]. When compared to natural history, surgical intervention offers clear advantages in survivability and low morbidity rates [37, 38]. Compared to the other treatment choices, it is the only one which can immediately and permanently remove the lesion in its entirety, while also being able to swiftly evacuate

any ensuing hematoma, and greatly reduce the future risk of bleeding [2–5, 36]. Despite these facts, AMV surgery is fraught with difficulties, especially if the lesion is deep-seated and large.

For pineal region AVMs, the preferred surgical route is the supracerebellar infratentorial (SCIT) approach; however, the occipital or parietooccipital interhemispheric (OIH/POIH) approach can also be considered for certain cases [7, 8, 14, 39]. For AVMs situated at the far anterior portion of the pineal region, the falcotentorial approach has also been described [7]. In our operated cases, we used either the SCIT or the OIH approach, according to specific AVM characteristics and surgical experience.

Before planning surgery, careful consideration of the clinical features and imaging studies is mandatory. Bearing in mind the number of arterial feeders, the characteristics of the venous drainage, the exact location and size of the nidus, as well as the possible resulting hematoma, a certain approach may become more suitable. If the AVM presents with intraventricular hemorrhage and acute hydrocephalus, we recommend placing an external ventricular drainage first, moving on to surgical resection of the lesion only after the patient is stable and the signs of increased ICP have receded. Repeated imaging studies, such as CTA, disclose whether the hematoma has been evacuated, and may even reveal the AVM far more clearly once there is no surrounding hematic content. If the nidus compresses the sylvian aqueduct and causes chronic hydrocephalus, an endoscopic third ventriculocisternostomy (VCS) is also a valuable strategy [15, 18, 19].

A particular situation is that of a ruptured AVM during pregnancy, which represents a veritable management dilemma [40]. As was the case for the patient seen in Fig. 21.2, this event can occur at any time during pregnancy, endangering both the mother and the fetus. If the hemorrhage arises during the third trimester, we prefer to stabilize the patient and deliver the child as soon as feasible via cesarean section, only intervening to remove the AVM electively after a "hemorrhagic cooldown" period. However, if the pregnancy is only in its first weeks and the perceived risk of rupture is significant, we can opt to terminate the

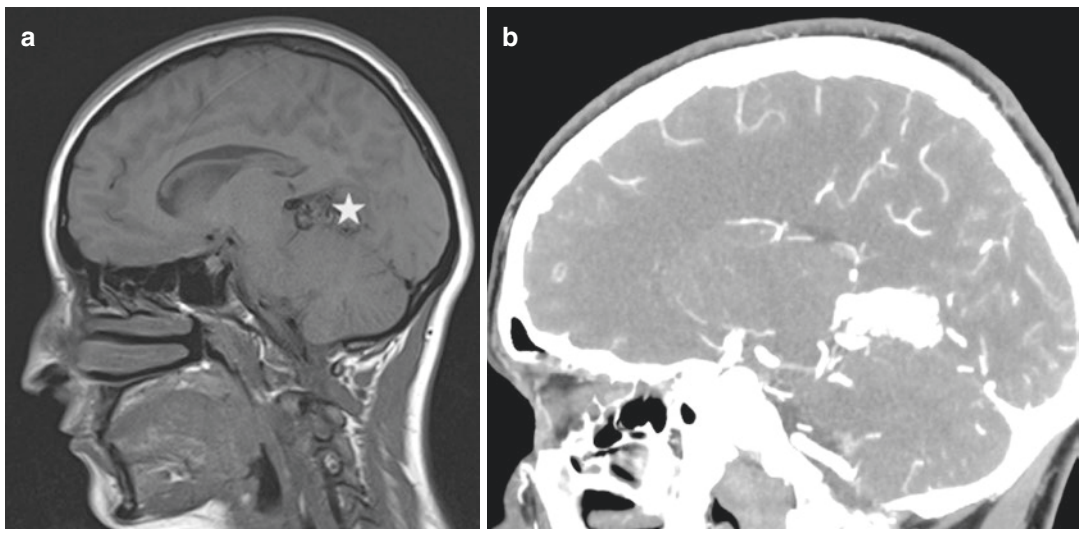

Fig. 21.2 A 27-year-old pregnant woman with a ruptured pineal AVM; (**a**) preoperative T1 gadolinium (Gd)-enhanced MRI presented for somnolence and headache. Given that her pregnancy was in its 30th week, we stabilized her in the intensive care unit (ICU), and then transferred her to an obstetrics and gynaecology (Ob-Gyn) department for a cesarean section. We repeated the CTA to establish the optimal approach (**b**). Afterwards, we performed a complete removal of the AVM via a left occipital interhemispheric (OIH) approach. The postoperative CTA (**c**) shows the complete removal of the lesion and moderate pneumocephalus. She was discharged a week later with no deficit

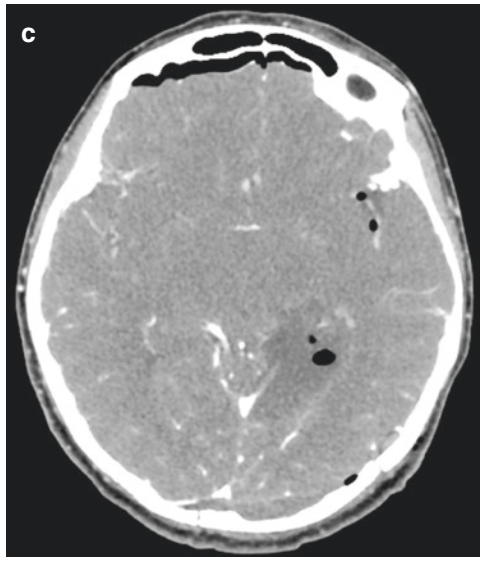

Fig. 21.2 (continued)

pregnancy after explaining the choices to the family in order to obtain consent.

For the SCIT approach, the patient is placed in the sitting, concorde, or park-bench position [8, 14]. We advocate the sitting position, since it offers a wide surgical field, lower intracranial pressure, gravitational retraction, and adequate venous drainage, and also facilitates intraoperative orientation [41]. Although there is a general anxiety in the neurosurgical community, in no small part due to assumptions of an increased risk of venous air embolism, this complication can be readily avoided by meticulous hemostasis and an attentive anesthesiology team. The head is flexed anteriorly and fastened in a three-pinned head holder, making sure that there is an acceptable distance between the chin and manubrium (two or three finger-widths). We incise the skin on the medial line, between 3 cm above the occipital protuberance and the craniocervical region. Using two autostatic retractors, we expose the occipital bone and then cover all emissary vein foramens with bone wax to avoid air embolism. A single burr hole superior to the occipital protuberance is generally sufficient for craniotomy, but more burr holes can be inserted in the case of increased dural adherence. The craniotomy should be performed attentively, as there is a chance of damaging the transverse sinuses or the confluens sinuum. The dura is incised in a "Y" shape, and the flap is reflected upward. If a small midline sinus is present at this level, it must be ligated in order to avoid air embolism. The bridging veins between the cerebellum and tentorium can be coagulated and cut to increase exposure, preferably closer to the cerebellum [8], although we generally discourage this act if not entirely necessary. The quadrigeminal and velum interpositum cisterns are then opened and the cerebrospinal fluid (CSF) within them evacuated, further widening the surgical field and exposing the pineal AVM.

Regarding the OIH approach, it has been mainly used to treat meningiomas and AVMs of this region [7, 8, 39]. Patients are placed in a sitting, semi-sitting, or lateral position on the side of the dependent ipsilateral hemisphere to allow gravitational retraction. The skin incision can be made either in the inverted "U" shape, as described by Yasargil, or a linear paramedian incision of 7–8 cm in length. The craniotomy is made with a single burr hole (or multiple in case of dural adherence) over the sagittal sinus. Typically, a bone flap of 3 cm or 4 cm in diameter is sufficient. We favor a curved incision of the dura mater, with the convexity pointing away from the superior sagittal sinus. If the venous sinus is accidentally notched, the breach must be quickly closed with atraumatic sutures, augmented with hemostatic material (Surgicel®, Gelfoam®). Using cottonoids and a bipolar coagulator, the occipital lobe is gently retracted. The posterior portion of the pericallosal cistern and the quadrigeminal cistern is then opened to evacuate the CSF and obtain a wide surgical field and brain relaxation. Care must be taken when opening the falx cerebri and the tentorium (using microscissors or a no. 11 scalpel) so as not to damage the veins draining into the great vein of Galen. According to Greenblatt et al., a partial section of the splenium results in minimal neurologic deficit [42]. However, should the splenium be completely divided, even if the body of the corpus callosum is intact, disturbance of interhemispheric visual transfer may occur, presenting as visual field deficit and dyslexia. There is

also the possibility of accidentally compromising arterial supply to the occipital lobe [7]. Once adequately exposed, AVM resection may commence.

Regardless of approach, once the AVM is exposed, the surgical principles remain the same. The first step in AVM removal is the identification of the draining vessels [2, 3, 36, 43, 44]. If the veins draining the AVM are compromised before all of the feeder arteries have been coagulated, the retrograde pressure buildup will result in a difficult-to-manage and profuse hemorrhage. Identifying the vein is not as easy as one might think; because of the high-flow arterial blood inside these vessels due to a lack of capillary network, the walls of the draining veins become "arterialized" and problematic to discriminate from feeders. There are, however, a number of hints that neurosurgeons can follow. Firstly, the draining veins always lead to either a larger vein or a venous sinus. Secondly, through the operating microscope, the blood flow may be visible; the vessel through which the blood moves away from the nidus is obviously a drainage vein. Thirdly, placing a temporary clip on the vein for a brief period of time will lead to bulging of the nidus, though we generally do not recommend this gesture unless the vein cannot be identified otherwise. Once the vein is identified and carefully preserved, pial dissection commences, and the arterial feeders should be separated and carefully coagulated at the point of contact with the AVM. One must pay attention to where the bipolar coagulator is placed; if the feeder is coagulated more proximally, it may result in cerebral infarction by damaging normal arteries. On the other hand, a more distal occlusion can provoke bleeding from the nidus [43]. All feeders must be coagulated before the AVM can be safely removed. One definite indication of this is the shrinkage of the nidus; another is the "blue shift" of the draining vein, meaning that arterial blood no longer flows through it.

Circumferential dissection represents the next step in AVM resection, wherein the lesion is separated from the brain parenchyma. This is undoubtedly the lengthiest portion of the resection; nevertheless, the surgeon must never lose patience or become frustrated. A progressive spiraling motion around the nidus exposes the lesion effectively. If rupture occurs, it should not be regarded as a catastrophe, as it can also result in some degree of parenchymal dissection [2, 3, 43]. Constant use of the aspirator, cottonoids, and continuous and attentive dissection will reveal the site of rupture, where the bipolar coagulator can close the breach. After the circumferential dissection is complete and the nidus is coagulated and dark, the apex dissection can ensue. This is probably the most difficult portion of the surgery, as the apex of the nidus is the farthest point of the lesion from the surgeon [2]. Surgeons should proceed by respecting the same microsurgical principles as before. Afterwards, once there are no remaining feeders, the draining vein can be coagulated and cut. The final stages of the surgery are always ensuring proper hemostasis, with the use of the bipolar and hemostatic materials. In order to evaluate the efficacy of hemostasis, the anesthesiologist may raise the patient's blood pressure slightly. The surgical field should be bloodless at this point. If not, the sites of bleeding should be thoroughly resolved.

The dura is suspended to the bone margins for the OIH approach and closed in a watertight fashion, regardless of craniotomy. For this, we usually employ autologous aponeurosis or fascia collected before performing the craniotomy. Depending on the equipment at hand, the bone flap is then placed back with either titanium screws and plates, a titanium cranial fixation system (CranioFix®), or sutures passed through small burr holes in both the skull and the flap (at least four). The skin is sutured layer by layer, leaving a subaponeurotic drainage for at least 24 hours to evacuate any residual CSF or blood.

Once surgery is complete, we recommend performing an immediate CTA if possible, with the patient still sedated and intubated. Thus, we ensure that the normal cerebral perfusion has not been affected and also verify whether the nidus and feeders have been entirely removed. If there are any signs of hemorrhage, vaso-

spasm, or obstruction of large cerebral vessels, it is safer to return the patient to the operating theater straightaway and repair any damage, rather than waiting for them to awaken from anesthesia and reopening them later. In the immediate postoperative period, maintaining a slight arterial hypotension is advisable in order to prevent the bleeding from previously coagulated feeders, but for no more than 48 hours. We typically verify the local aspect with a non-contrasted CT scan at 48–72 postoperative hours, even if the patient is without any neurological impairment. If the postoperative evolution is favorable, we typically discharge our patients 1 week after surgery and remove their sutures either then or at a later day. In case the patient develops hydrocephalus, our procedure of choice is the ventriculoperitoneal shunt. It is our belief that with proper microsurgical gestures and a sufficient amount of patience, any disastrous intraoperative hemorrhage can be avoided (Fig. 21.3).

21.8 Controversies

Because of the deep location of the pineal region, as well as the rarity of reported pineal AVMs, it could be argued that endovascular embolization and radiosurgery could eventually replace surgical removal for these lesions, at least for the smaller ones. Despite the fact that surgery remains the only definitive curative option for AVMs, the intricate vasculature of the pineal region poses many conundrums regarding the optimal approach and proper microsurgical technique. Damage to the veins could be catastrophic, whereas the arteries supplying the area could lead to severe visual impairment if mistreated. As a result, more minimally invasive procedures such as embolization and radiosurgery should, in our opinion, have a stronger foothold in this particular pathology. Meanwhile, microsurgical techniques and instruments should be improved in order to allow better access, visualization, and manipulation of the structures found therein.

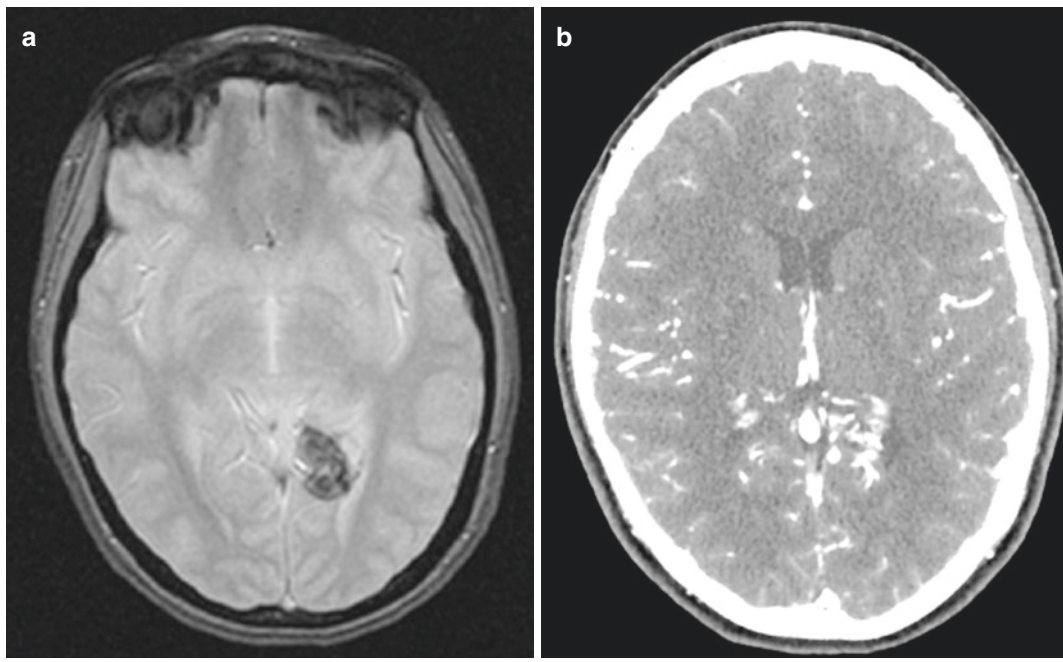

Fig. 21.3 A 19-year-old female patient with a pineal AVM, treated conservatively since 2005 for epilepsy, was admitted in our department for refractory seizures, headache, and nausea. Gradient recalled echo-sequence (GRE)-sequence MRI (**a**), corroborated with the preoperative CTA (**b**), show a left parenchymal pineal AVM. We intervened via the SCIT approach and removed the AVM entirely, as evidenced by the control CTA scan (**c**). She was discharged a week later with no deficit

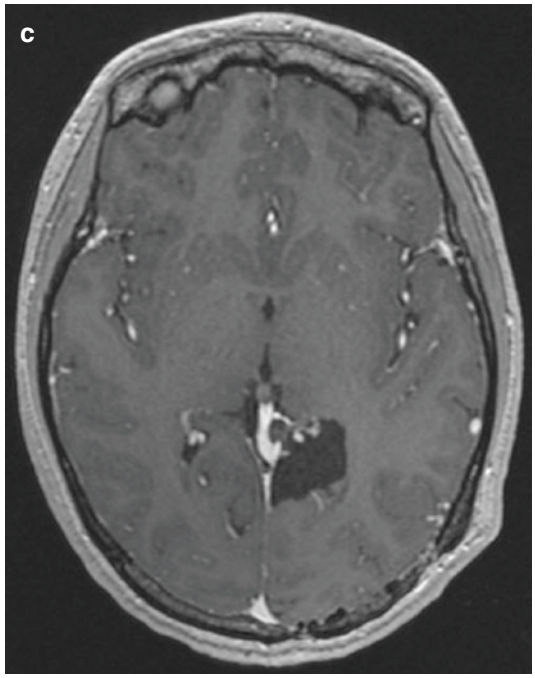

Fig. 21.3 (continued)

The two most widely used approaches are SCIT and OIH, alongside their variations. There is no clear indication as to which one is superior; however, we recommend using the SCIT approach for pineal AVMs that descend infratentorially, whereas the OIH approach is more convenient for the lesions residing predominantly above the tentorium.

Another controversy is tied to patient positioning, the sitting position being banned across several territories for its widely known risks. In our experience, we have not encountered significant air embolism due to this position or events that could not be mended by calculated gestures and an experienced neurosurgeon-neuroanesthesiologist team.

As the nidus or its rupture can cause hydrocephalus, it is imperative to also reestablish proper CSF flow as soon as possible. Both external ventricular drain (EVD) and VCS are viable options, surgeons electing either of them according to experience or preference. If the hydrocephalus persists or occurs after removing the AVM, a ventriculoperitoneal shunt on the non-dominant side is a valuable choice. In short, a dedicated center for pineal region pathology, possessing all the facilities and enough expertise to deal with either vascular or non-vascular lesions of this area, could offer the highest chances for an appropriate management of this extremely challenging pathology.

21.9 Conclusions

Pineal AVMs are a rare but nonetheless challenging pathology. Clinical presentation may be varied and inconsistent from one patient to another. Imaging studies such as CTA or angio-MRI are crucial in establishing the correct diagnosis and instigating proper treatment. As patients may present with hydrocephalus due to sylvian aqueduct compression, an EVD or a VCS should be performed before any other therapeutic approach. Although endovascular procedures and radiosurgery are viable alternatives, resection remains the gold standard, since it is able to completely remove the lesion and permanently decrease the risk of bleeding. However, microsurgical resection should be performed by an experienced team with delicate and calculated gestures and judgments.

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22 Cavernous Malformations of the Pineal Region: Overview, Management, and Controversies

Helmut Bertalanffy, Ioan Alexandru Florian, and Teodora Larisa Timiș

22.1 Background

Cavernous malformations (CMs) of the brain, also referred to as cavernomas or cavernous angiomas, are well delineated, proliferative, low-flow vascular anomalies comprised of a heterogeneous mass of thin-walled blood vessels [1–5]. They contain either blood or clots at various stages of degradation, with no interposing cerebral tissue. CMs are histologically characterized by a single endothelial layer and lack the structural features of mature vessels, while aberrations within the endothelial tight junctions cause them to leak or hemorrhage [1, 6].

Although once considered rare, it is now estimated that CMs account for 5–16% of intracranial vascular malformations, being the second most common brain vascular malformation causing hemorrhage [1, 7–9]. Varying considerably across populations, the incidence of CMs has been assessed at around 0.15–0.56 per 100,000 persons per year, while the prevalence stands between 0.39% and 0.53% [1, 5, 7, 8, 10]. The majority of identified lesions are solitary; however, up to 30% of sporadic and as many as 84% of familial cases are multiple. Mutations found in three genes, namely CCM1, CCM2, and CCM3, are incriminated to cause the grand majority of cases with the familial form [1]. The de novo appearance of brain cavernomas has been linked to irradiation, viral infections, and biopsy [11]. Whichever the case, symptoms are usually the result of a CM in an eloquent area of the brain, often manifesting through epileptic seizures or headache. The risk of hemorrhage has not been properly established, although small asymptomatic bleeds are a common trait, either within the lesion itself or in a limited area around it. Significant or life-threatening hemorrhage is encountered less frequently than in other vascular lesions, such as arteriovenous malformations. Nevertheless, the location within the posterior fossa, particularly in the brain stem, has been proven to carry a higher risk of bleeding than in other regions of the brain; then being associated also with a worse prognosis for this incident [3–5, 10, 12–14].

CMs arising within the pineal gland are extremely rare lesions, and only very few cases have been described in the literature [5, 15]. However, CMs located in the vicinity of the pineal gland (in the pineal region) most commonly have their origin within the dorsal midbrain and/or the pulvinar thalami [3, 16]. Sometimes, they can mimic other lesions, such as pineal region tumors (pineocytoma, pineoblastoma or germinoma) or cysts, especially when presenting with hemorrhage or calcifications on

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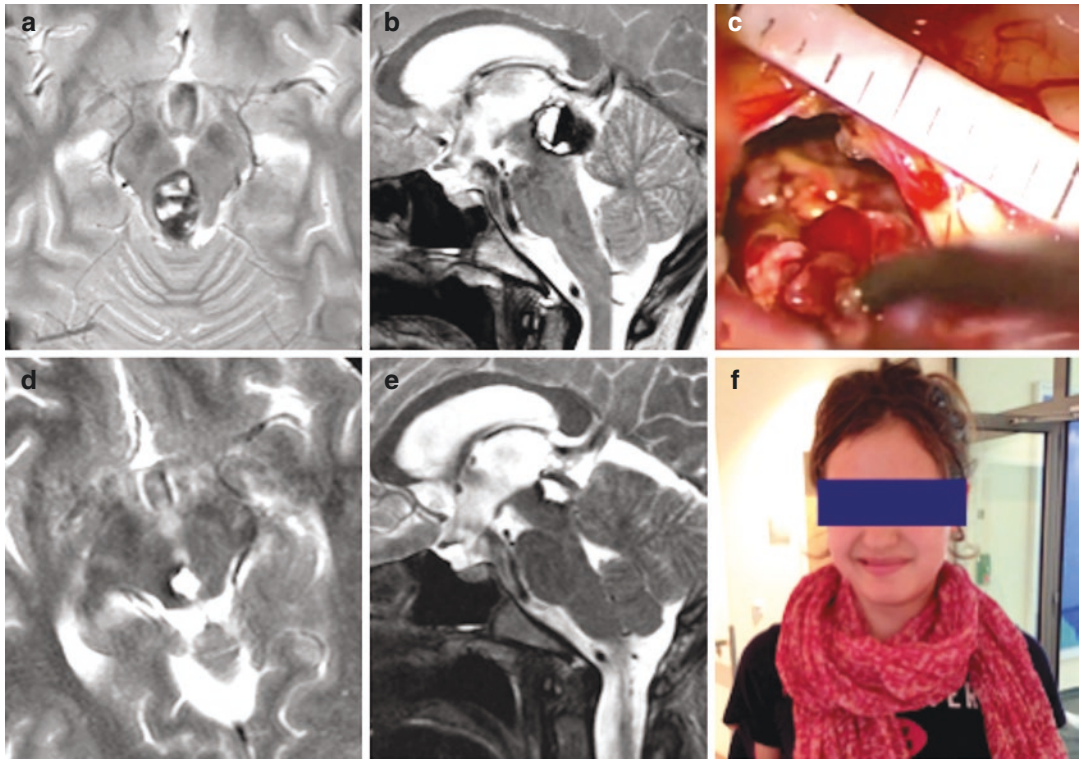

Fig. 22.1 This 14-year-old girl suffered from recurrent absence seizures of unknown origin since the age of 3 years. Two months prior to surgery, the patient suddenly developed status epilepticus that required emergency therapy, and further diagnostics were initiated. Magnetic resonance imaging (MRI) revealed a hemorrhagic tectal plate lesion and occlusive hydrocephalus. Following immediate endoscopic third ventriculostomy, the patient remained symptom-free, while no additional epileptic seizures occurred. Preoperative T2w axial (**a**) and sagittal (**b**) MRI showed the hemorrhagic space-occupying tectal lesion. Surgical exposure via the supracerebellar infratentorial approach revealed a typical cavernous malformation, containing fresh intralesional hemorrhages (**c**). Complete resection of this vascular malformation was documented on postoperative MRI (**d** and **e**). There were no perioperative complications, and the patient remained neurologically intact after surgery (**f**)

imaging studies. Given their relative rarity and deep location, these lesions constitute a surgical challenge (Figs. 22.1 and 22.2).

22.2 Clinical Presentation

As most of cerebral CMs remain asymptomatic over a long period of time, one can assume that this feature also extrapolates to those of the pineal region. According to the pertinent literature, the most common form of presentation is progressive headache, ranging from mild to severe, with the onset usually a few months prior to diagnosis [9, 17–21]. Sudden and severe headache has been described as a result of significant hemorrhage and Sylvian aqueduct occlusion [9]. The risk of bleeding increases in the presence of certain factors such as a deep-seated location, pregnancy, advanced age, or a personal history of previous hemorrhage [1]. Re-hemorrhage rates can be as high as 30%, especially for cavernomas of the brain stem. Nausea, vomiting, lethargy, confusion, and papilledema may occur in the case of increased intracranial pressure (ICP) from acute obstructive hydrocephalus [18–21]. As pineal region CMs involve the tectal plate, visual disturbances, such as diplopia, blurred vision, upward gaze palsy or Parinaud syndrome, have also been frequently documented [9, 15, 18, 20–22].

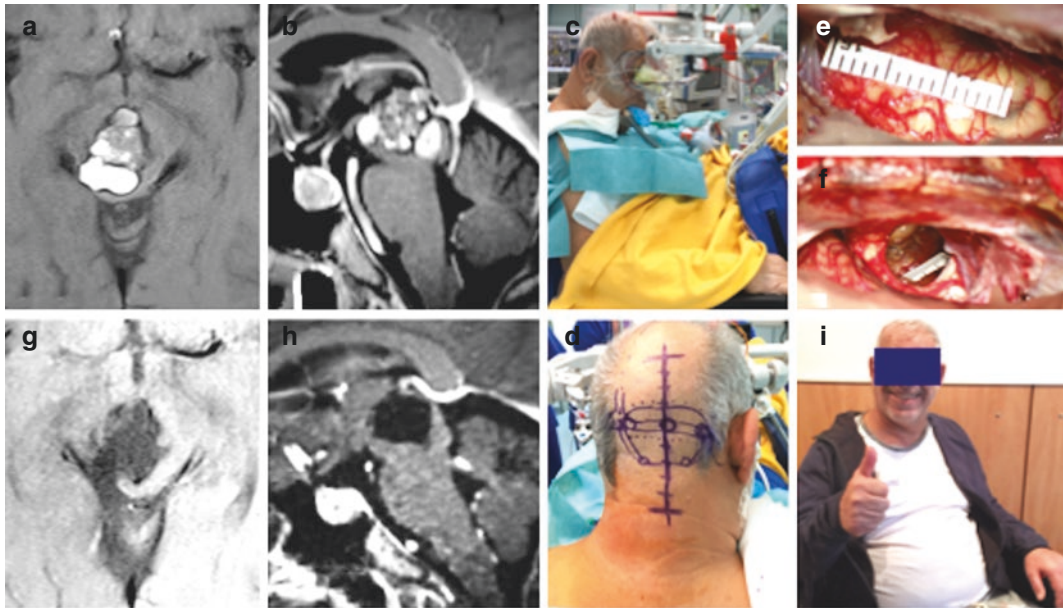

Fig. 22.2 Due to obstructive hydrocephalus, this 61-year-old male underwent placement of a ventriculoperitoneal shunt 8 years prior to the present surgery. Despite repeated intraaxial midbrain hemorrhages from a suspected cavernous malformation seen on magnetic resonance imaging (MRI), no other treatment was offered to the patient in his home country. The latest preoperative T1w contrast-enhanced MRI taken in the axial (**a**) and sagittal plane (**b**) showed a huge hemorrhagic cavernous malformation. The lesion that also involved the pineal gland, primarily distorted and expanded the midbrain, which explained the patient's multiple neurological deficits; severe headache, left-sided hemiparesis and hemihypesthesia, bilateral oculomotor paresis with complex eye movement disorder, gait ataxia, and mesencephalic dysarthria. The patient underwent surgery in the semi-sitting position (**c**). A midline skin incision and symmetric midline suboccipital craniotomy that also exposed the transverse sinus were planned (**d**). Exposure of the midbrain tectum via the supracerebellar infratentorial route revealed an apparently intact, only slightly dorsally bulging, brainstem surface (**e**), despite the considerable size of the underlying lesion. Complete resection of the cavernous malformation was documented intraoperatively (**f**) and on postoperative MRI (**g** and **h**). The patient tolerated the surgical intervention well, and there were no perioperative complications. In the early postoperative period, only accentuated gait ataxia was noted; otherwise, no additional neurological deficits occurred postoperatively, and the patient was discharged after 12 days in good clinical condition (**i**)

Thalamic pain, defined as a treatment-resistant and distressing post-stroke pain in the contralateral side of the body, was also present in a small number of our cases. Pineal apoplexy is described as a series of poorly defined symptoms subsequent to an acute hemorrhage within the pineal gland [20, 23]. As such, any bleeding resulting from a pineal CM can be considered a case of apoplexy, due to the lack of symptom specificity. A small number of pineal CMs presented with endocrinological anomalies such as diabetes insipidus, serum hormone irregularities and amenorrhea, whereas one patient also complained of circadian rhythm inversion [15, 21]. Although no direct relationship between pathology and symptoms could be established, an individual presented with nocturnal and diurnal bruxism, as well as chronic bilateral orofacial pain, predominantly on the left side [24]. As the authors of this case presentation concluded, this was likely due to a neurotransmitter imbalance or disruption in the trigeminal system. Such reports make it understandable that pineal CMs can likewise manifest through unspecific symptoms that are rather typical for tumors of the pineal region (Fig. 22.3).

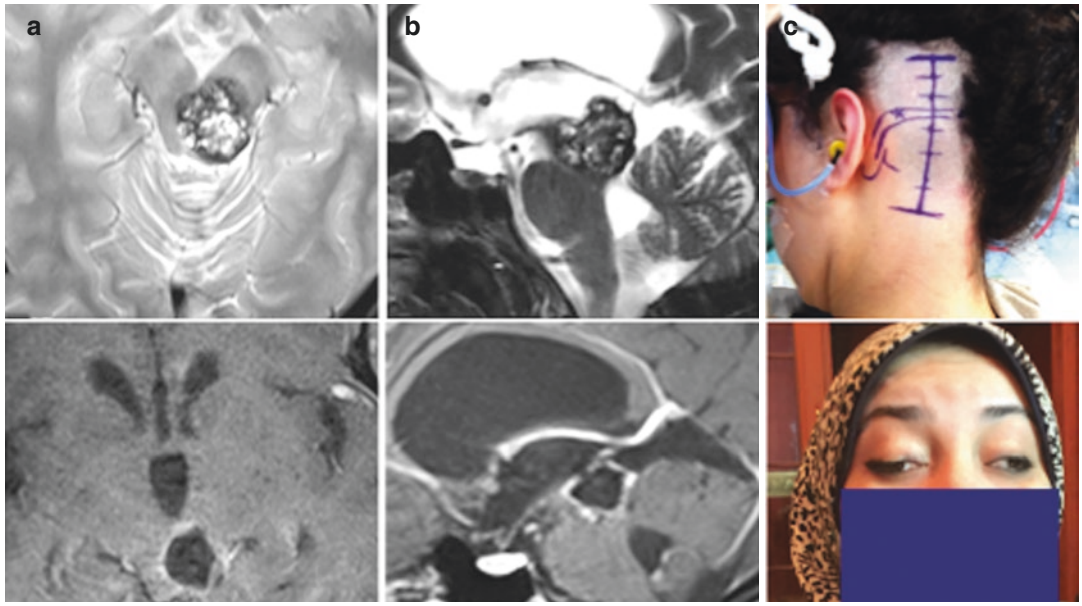

Fig. 22.3 This 22-year-old female suffered a first hemorrhagic episode with left-sided oculomotor palsy at the age of 7 years. Magnetic resonance imaging (MRI) taken by that time only revealed a minimal left-sided tectal plate lesion. Over the following years, this lesion gradually increased in size and developed into a compact, voluminous cavernous malformation as seen on preoperative T2w axial (**a**) and sagittal MRI (**b**). Concomitantly, the lesion has caused occlusive hydrocephalus (**b**), which, however, was not treated in the patient's home country. Contrary to our expectations, there were no other neurological deficits before surgery than intermittent left-sided oculomotor palsy. Surgery was indicated because of the lesion's previous continuous growth. Lesion exposure was planned with the patient in the semi-sitting position via a left-sided suboccipital craniectomy, using a straight-line skin incision (**c**). Complete resection of the cavernous malformation was achieved via the lateral supracerebellar infratentorial route without perioperative complications, documented on postoperative axial (**d**) and sagittal MRI (**e**). Initially after surgery, gait ataxia and bilateral incomplete oculomotor paresis were noted. The patient recovered well from this surgical intervention, but bilateral incomplete oculomotor palsy with partial bilateral ptosis remained as late neurological sequelae (**f**)

22.3 Imaging Diagnosis

When diagnosing cerebral CMs, the most sensitive study and current gold standard is magnetic resonance imaging (MRI), particularly the T2-weighted (T2WI) and gradient-echo (GRE) sequences [1–5, 25]. It is also the imaging technique of choice when managing these lesions expectantly. The appearance of CMs on MRI is very characteristic; the lesion forms a reticulated pattern of both hyperintensity and hypointensity, surrounded by a hypointense ring-shaped area, best visualized on T2WI or GRE. Asymptomatic pineal CMs can be easily diagnosed or followed by MRI scans, showing a popcorn- or mulberry-shaped lesion with the aforementioned features in the vicinity of the pineal gland and regional vascular structures.

Computed tomography (CT) is not as sensitive in diagnosing unruptured CMs, yet it can be useful in an emergency setting in the event of symptomatic hemorrhage, or when evaluating lesion calcifications [1–5, 25]. Bleeding from pineal CMs appears as a large hyperdensity in this region, compressing against adjacent structures (mesencephalon, thalamus, splenium of corpus callosum). This is usually accompanied by an acute and symmetrical enlargement of the two lateral and third ventricles, and it can also present subtle signs of subarachnoid hemorrhage.

Because of low flow, internal thrombi, and the lack of large feeding arteries or draining veins, CMs are typically invisible on angiograms.

22.4 Nonsurgical Management of Pineal Cavernous Malformations

Treatment of CMs found within the pineal region is, in principle, identical to the treatment of cavernomas, arising in any other location. Small asymptomatic lesions that do not obstruct the Sylvian aqueduct can be managed by simple observation. Headache may respond to minor analgesics. For symptomatic CMs, surgical resection is the method of choice. Some authors favor stereotactic radiosurgery (SRS), but this method appears less efficient in preventing future bleeding. Only complete surgical resection permanently eliminates the risk of subsequent hemorrhage from the respective lesion and may control other symptoms.

When employing an expectant strategy, it is preferable to perform MRI scans once every 1–2 years [1–4, 6]. One should take particular notice of recent hemorrhage, cavernoma growth, or enlargement of the lateral ventricles. If any of these are evident, a surgical intervention might be indicated. If the patient may not support resection or a prolonged surgery, a ventriculoperitoneal shunt (VPS) or third ventriculocisternostomy (VCS) will alleviate the symptoms of increased ICP.

Medical therapy in CMs is rather limited, offering only symptomatic relief in case of headaches or seizure control [1–3, 6]. With an increasing comprehension of the pathogenesis of CMs and certain knowledge gained from animal models and in vitro studies, a series of pharmaceutical contenders have been recommended for human clinical trials [6, 26–28]. Among promising medications are statins, tempol and vitamin D [26], sulindac [27], fasudil [28], as well as antiangiogenesis and anti-inflammatory agents [6]. Despite the perceived enthusiasm for testing various substances in human clinical trials, the scarcity of symptomatic cases renders such a prospect somewhat arduous.

Stereotactic radiosurgery (SRS), although controversial for CMs, is propagated by some authors as an appealing substitute to surgery for patients considered unsuitable for surgery or in the case of a lesion regarded as inaccessible [1–5]. Several authors state that SRS significantly reduces the rebleeding rate at 2 years [29–33]. However, there is no unequivocal evidence in our opinion for such a claim [34]. Moreover, this treatment modality bears a significant risk of radiation-induced morbidity and even for the well-documented possibility of developing a de novo lesion [35–37]. Apparently, this is especially the case in familial CMs or in the presence of a venous malformation [37]. The theory of temporal clustering of CM hemorrhage, included in the natural history, would entail a greater rebleeding rate during the first 2 years after the initial episode, followed by a significant decline thereafter [12, 33, 38]. Consequently, it is likely that the latency period observed in the bleeding reduction rate after SRS overlaps with this phenomenon. As such, the actual long-term effect of SRS in brain cavernomas is yet to be effectively demonstrated. For this reason, we believe that SRS cannot be considered a first-line therapy for pineal CMs, as it fails to significantly decrease or even eliminate the risk of hemorrhage.

22.5 Surgical Treatment of Pineal Cavernous Malformations

Microsurgical resection stands as the single curative treatment option for CMs, with the aim of removing the lesion entirely and without producing damage to the surrounding nervous tissue [1–5, 25, 34]. On the one hand, a successful surgical intervention both eliminates any further risk of hemorrhage from that lesion and, depending on the location of the lesion, achieves seizure control in as many as 80% of patients. However, it is also the most perilous treatment method, being associated with the risk of causing severe and permanent neurological deficits or even death. For pineal region CMs, the indication for surgery depends on the presence, severity, and evolution of symptoms; the estimated risk of

further bleeding; the number of previous hemorrhagic episodes; the presence of occlusive hydrocephalus; and even on the patient's own preference.

According to Muzumdar et al., the first description of a surgically treated pineal CM appeared in the literature in 1961; the lesion was only partially resected, and the patient deceased after suffering repeated subarachnoid hemorrhages [17]. Afterwards, only a limited number of surgical cases have been reported (Fig. 22.4).

The supracerebellar infratentorial (SCIT) approach is widely used in pineal region surgery, being a secure, speedy, and easily applicable route that allows excellent visualization of anatomical components [1, 3, 18, 22, 38–43]. It is also a virtually atraumatic route, minimalizing brain retraction and manipulation, thus decreasing the risk of neurovascular injuries. The procedure is performed in the sitting or semi-sitting position, the patient's head placed in a three-pinned headholder and tilted forward at an angle of 30°, and with his back in a slightly kyphotic angulation (Figs. 22.1 and 22.2). This renders the tentorium in a horizontal position and facilitates orientation. The skin incision is made in the median line (occasionally paramedian) from above the inion and down to the spinous process of the C2 vertebra. Using the monopolar coagulator is helpful in detaching the suboccipital muscles to allow proper bone exposure. The craniotomy is carried out only after carefully detaching the dura mater from the bone using a flexible dissector, while avoiding damage to the

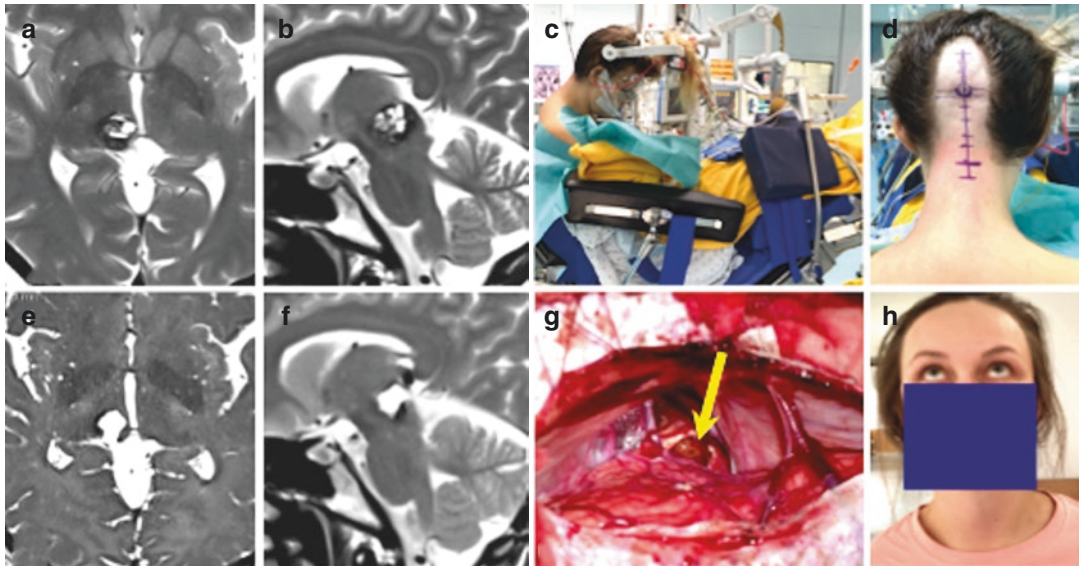

Fig. 22.4 This 37-year-old female was known to harbor a cavernous malformation located in the pineal region since 7 years, but the lesion remained so far untreated. As in other similar cases, a gradual increase in size was observed over the past years. Moreover, the patient gradually developed a sensory disturbance of the left side of her body including the face, dysbalance, and slight dysarthria. Preoperative T2w magnetic resonance imaging (MRI) in axial (**a**) and sagittal plane (**b**) demonstrated a typical cavernous malformation, measuring 15 mm in diameter, located in the upper part of the midbrain and the right pulvinar of the thalamus. Surgery was indicated, and the patient underwent the procedure in the semi-sitting position with the upper part of the body and head flexed anteriorly, and the legs elevated up the level of the heart (**c**). A midline occipital/suboccipital skin incision was marked on the skin (**d**). Complete resection of the cavernous malformation was documented on axial (**e**) and sagittal T2w MRI (**f**). The surgical field can be seen on the intraoperative photograph (**g**). The lesion was exposed via a supracerebellar infratentorial approach. A left-sided paraculminal access route offered an appropriate oblique viewing trajectory to the lesion. Vermian bridging veins remained intact until the end of the intradural stage despite significant descent of the cerebellum. No residual portions of the cavernous malformation were visible within the resection cavity (arrow). There were no additional neurological deficits after surgery, and the patient was discharged after 10 days in excellent clinical condition (**h**)

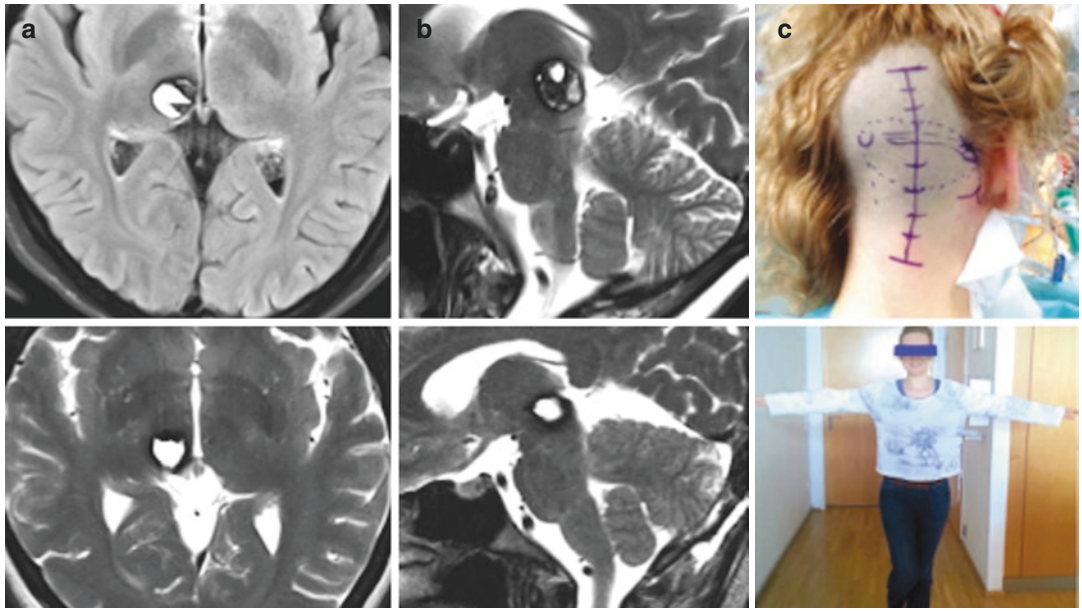

Fig. 22.5 Three years before surgery, this 35-year-old female patient experienced for the first time temporary sensory disturbances within the left hand and left side of her face. A second clinical episode with similar symptoms occurred 1 year later. Three months before surgery, a third clinical episode with exacerbation of the previous symptoms convinced the patient to undergo surgery with the aim of removing the underlying vascular malformation. Preoperative magnetic resonance imaging (MRI) in axial (**a**) and sagittal plane (**b**) demonstrated a hemorrhagic cavernous malformation in the upper midbrain and right pulvinar of the thalamus. For the surgical intervention, the patient was placed in the semi-sitting position, and a right-sided paramedian occipital/suboccipital craniotomy was planned (**c**). Axial (**d**) and sagittal T2w postoperative MRI (**e**) documented complete resection of the vascular malformation. There were no additional neurological deficits, and the patient was discharged after 9 days in excellent clinical condition (**f**)

transverse sinus. The opening should ideally expose the dura mater down to around 3 cm below and 1 cm above the transverse sinus (Figs. 22.5, 22.6, 22.7, 22.8, 22.9, 22.10)

The dura is opened below the transverse sinus from laterally to medially, and the occipital sinus, if present, is ligated and transected together with the falx cerebelli. The dura is then sutured to burr holes placed in the superior margin of the craniotomy, thus elevating the transverse sinus and tentorium to a certain extent [3, 44, 45]. Bilateral jugular compression performed by the anesthetist can help identifying small lesions of the transverse sinus and constitutes an important maneuver to avoid air embolism. By utilizing the sitting position and evacuating a sufficient amount of cerebrospinal fluid (CSF) from the quadrigeminal cistern, the cerebellum will shift inferiorly only by gravity, permitting a retractor-less access to the pineal region. Depending on the local venous pattern (superior cerebellar bridging veins), either a left-sided or a right-sided paraculminal approach can be used. Once the dorsal mesencephalic area is exposed, the pineal region CM must be identified, and lesionectomy can ensue.

Another commonly used access route is the occipital transtentorial (OTT) approach (Fig. 22.3) [9, 10, 19, 23], a modification of the occipital interhemispheric (OIH) as described by Poppen in 1966 [17, 39, 41, 47]. Despite the advantage of providing a wide exposure, this route possesses the glaring drawback of having the deep venous system directly in the path toward the tumor. This hinders complete surgical removal of certain lesions, and it also risks causing significant neurovascular damage. Nevertheless, some authors prefer this approach

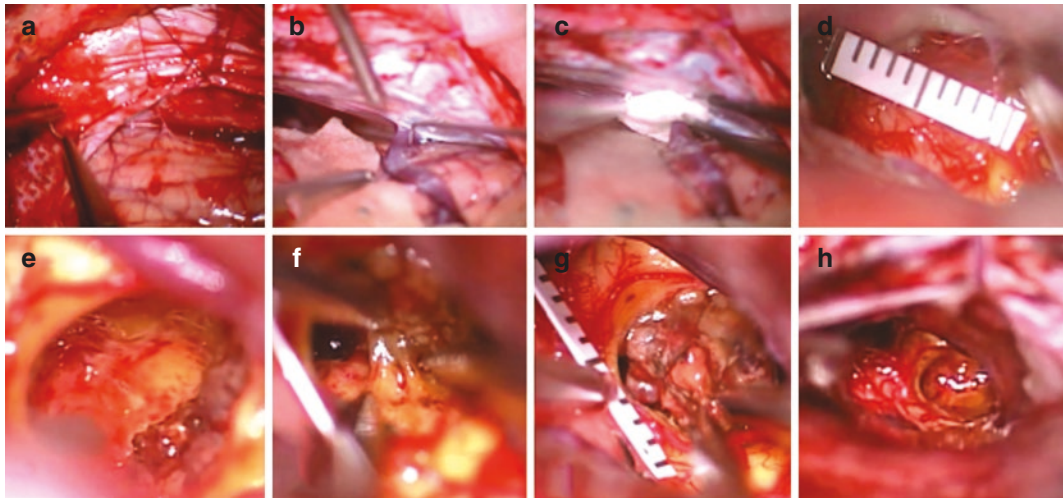

Fig. 22.6 Intraoperative photographs of the patient shown in Fig. 22.5 demonstrate the most important surgical steps. The superior craniectomy rim was situated above the transverse sinus, while the dura was incised below the sinus and then sutured to this upper rim, where burr holes have been placed for this purpose; the sinus and tentorium were elevated by these tenting sutures, while the cerebellum slightly descended just by gravity; there was no need for using a brain retractor (**a**). A bridging vein of the cerebellar quadrangular lobule that drained into the tentorium was gently freed from its surrounding distal arachnoid membrane using a sharp hook (**b**) and was then protected from traction injury by placing a piece of gel foam around its entry point into the tentorium (**c**); the latter was thereafter fixed with fibrin glue. At initial exposure, the dorsal surface of the midbrain showed no abnormalities (**d**). The entry point into the parenchyma was chosen at the transition between midbrain and right pulvinar of thalamus, and the lesion was thus exposed and dissected free from the thalamus (**e**). During dissection, the ependymal wall of the posterior third ventricle was opened to create an additional CSF connection between third ventricle and quadrigeminal cistern (**f**). The opening of the mesencephalic and thalamic parenchyma on the surface measured not more than 5–6 mm in diameter and was smaller than the initial diameter of the lesion (**g**). Meticulous hemostasis by gentle bipolar coagulation and complete resection of the cavernous malformation were documented at the end of the intradural stage (**h**)

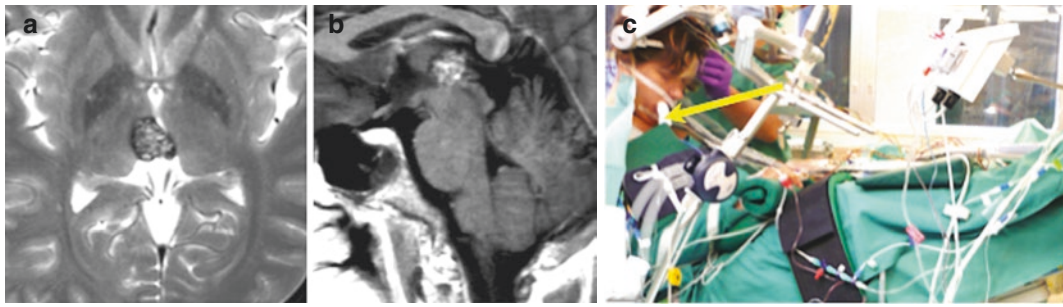

Fig. 22.7 This 32-year-old female patient suffered from severe headache and mild gait ataxia. Preoperative axial (**a**) and sagittal magnetic resonance imaging (MRI) (**b**) furnished evidence of a pineal region cavernoma that extended into the posterior portion of the third ventricle. The right thalamus appeared as the origin of this vascular lesion (**a**). Surgery was undertaken with the patient in the semi-sitting position (**c**); a transoral transesophageal tube *(arrow)* was placed for continuous intraoperative cardiac ultrasonography to monitor and avoid air embolism during surgery (**c**). Complete resection of the lesion was documented on postoperative axial (**d**) and sagittal MRI (**d**). The lesion was exposed, using a routine occipital/suboccipital midline skin incision (**f**), via a supracerebellar paraculminal exposure. There were no additional postoperative neurological deficits (**g**); unfortunately, local wound infection was noted after 5 weeks, requiring surgical wound revision. Thereafter, the patient remained symptom- and recurrence-free

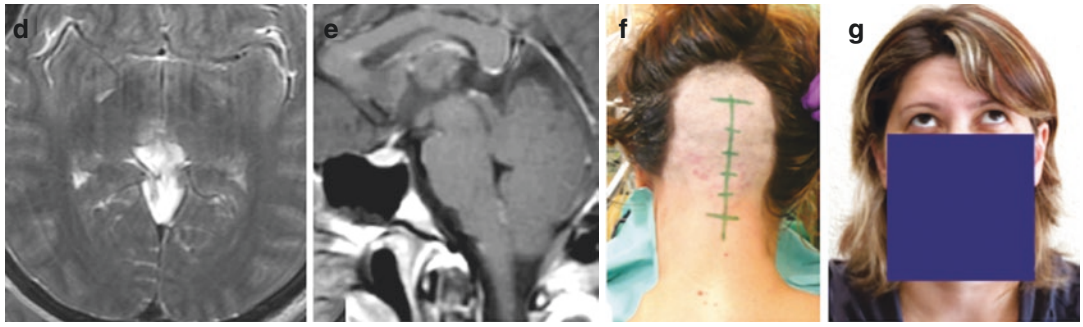

Fig. 22.7 (continued)

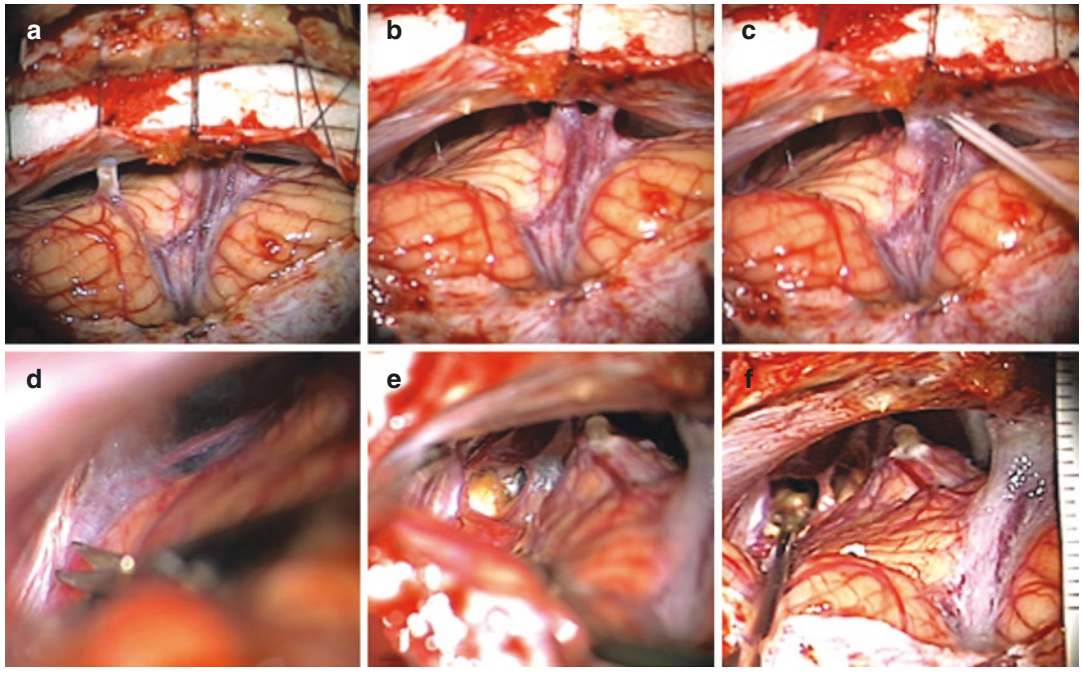

Fig. 22.8 Intraoperative photographs of the patient are shown in Fig. 22.7. To obtain a retraction-free supracerebellar exposure, the craniotomy was extended superiorly above the level of the transverse sinus; burr holes were placed into the upper bony rim to allow for tenting sutures after dural opening below the sinus. Thus, sinus and tentorium were elevated by 4–5 mm (**a**). Bridging cerebellar veins were considered important structures that must be preserved by all means to avoid postoperative cerebellar congestion (**b**). Reinforcing the dural entry point of the bridging veins into the tentorium with fibrin glue rendered them more resistant to downward traction after the cerebellum descended by gravity (**c**). Exposure of the quadrigeminal plate and posterior thalamus was obtained by sharp incision of the thick arachnoid membrane first on the left (**d**), then also on the right side. A left-sided paraculminal trajectory led directly to the pineal region and the thalamic cavernous malformation (**e**). Obviously, there was no need for using a brain retractor, as there was sufficient space for microsurgical dissection between cerebellar surface and tentorium (**f**)

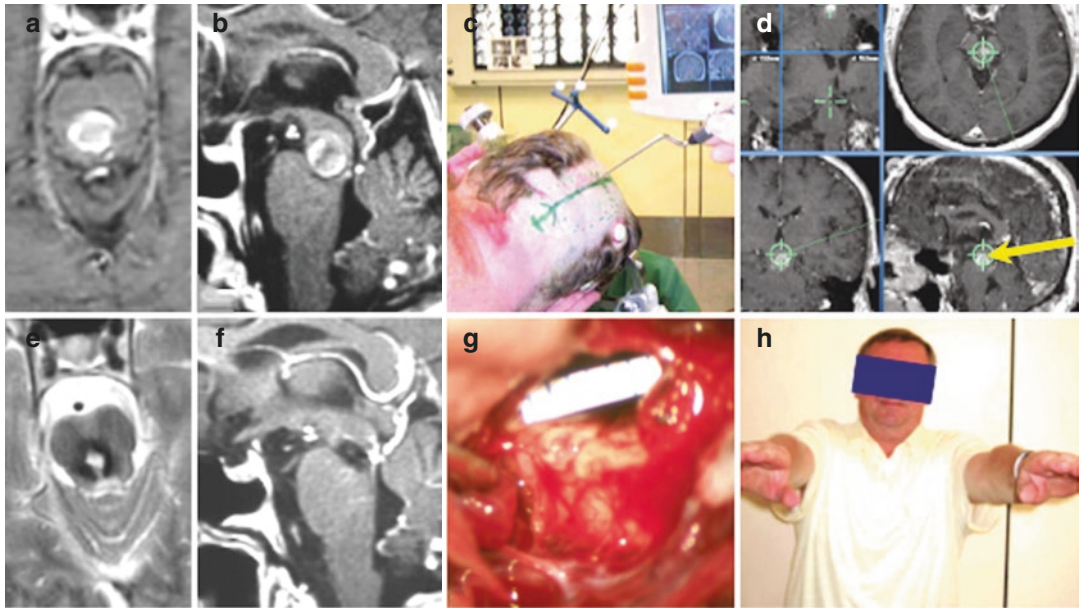

Fig. 22.9 Two years prior to surgery, this 66-year-old male experienced, for the first time, progressive gait ataxia, paresthesia in both legs, and a slight right-sided motor weakness. Gradually, his gait became spastic and ataxic. Preoperative T1w contrast-enhanced magnetic resonance imaging (MRI) (**a**, **b**) demonstrated a hemorrhagic midbrain lesion that did not completely reach the brainstem surface. Surgery was indicated, and an occipital trans-tentorial access route was chosen. The patient was placed in the right lateral park-bench position, with the head slightly tilted to the right side (**c**). We preferred this approach because it offered a straight-line viewing trajectory not only to the superior but also to the inferior portion of the lesion as could be seen on the preoperative screenshot (**d**, *arrow*) of the neuronavigation system (*BrainLab AG, Germany*). Complete extirpation of the lesion was succeeded without perioperative complications, as documented on postoperative MRI (**e**, **f**). Although used less frequently than the supracerebellar approach, this access route was readily feasible and offered an equally good view of the tectal plate and targeted vascular lesion (**g**). There were no additional neurological deficits postoperatively (**h**)

because of a broader exposure, less strenuous patient positioning, and greater operating comfort for the surgeon [48]. According to the description in the literature, the patient is placed preferably in a lateral or three-quarter prone position, with the head set so that the nose is rotated 30° toward the floor. The skin incision is made paramedially, usually on the right side, having the shape of a horseshoe with the base downward. The lambdoid suture is identified, along with the insertions of the cervical muscles. Two burr holes are made on the midline with great care not to damage the superior sagittal sinus (SSS), the dura mater is detached from the bone, and the occipitoparietal craniotomy is performed in such a manner that the posterior segment of the SSS is revealed just cranial to the upper margin of the torcular. The dura mater is incised in a C-shape with the pedicle toward the SSS. Optionally, an extraventricular drainage (EVD) can now be placed in the occipital horn of the lateral ventricle on the same side to obtain additional brain relaxation. Afterward, the occipital lobe is effortlessly retracted laterally and superiorly without sacrificing the bridging veins, advancing until the free edge of the tentorium is visible. This is the safest way to avoid direct damage and perfusion insufficiency around the calcarine cortex and optic radiations near their termination [49]. The tentorium is then dissected in a line alongside the straight sinus, at around 1 cm lateral to it. Alternatively, a wedge-shaped resection of the tentorium further improves exposure. Once in view, the arachnoid membranes of

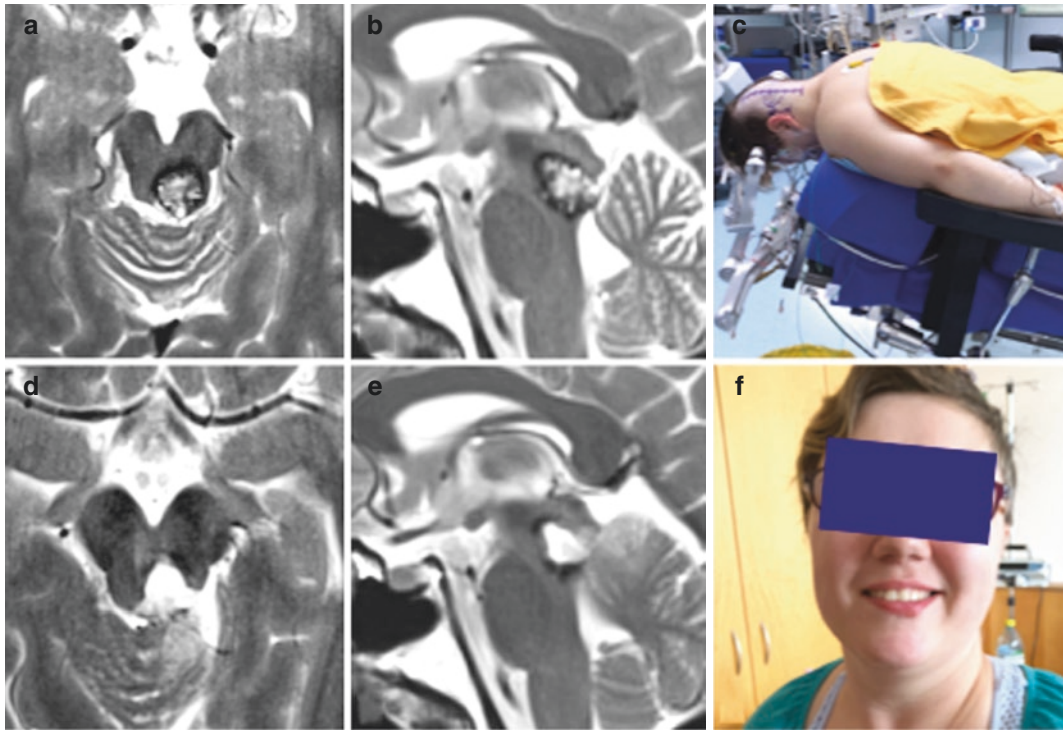

Fig. 22.10 This 36-year-old female patient suffered from progressive headache, diplopia, and slight gait ataxia. A midbrain cavernoma was detected on magnetic resonance imaging (MRI) in her home country, but this lesion was estimated as inoperable deep-seated vascular malformation (**a**, **b**). Contrary to this opinion, we considered the lesion well accessible and resectable, and offered the patient microsurgical removal. Initially, the semi-sitting position was planned, since it appeared as the most suitable for such kind of lesion. However, this position was not applicable because of high risk of paradoxical air embolism, as the patient's routine preoperative cardiac examination revealed a patent foramen ovale of the heart. Under these circumstances, the procedure was carried out with the patient in the prone position (**c**). A left-sided paramedian skin incision enabled a slightly lateralized suboccipital craniectomy, and surgery was carried out via the lateral supracerebellar approach. Although complete resection of the cavernous malformation was achieved as demonstrated on postoperative MRI (**d**, **e**), the microsurgical exposure and parenchymal dissection were significantly more difficult and time-consuming than in other patients because of cerebellar venous congestion in the prone position. Usually, we never encounter such kind of obstacles in similar procedures in which patients were placed in the semi-sitting position. Fortunately, there were no perioperative complications in this patient, and she did not experience additional neurological deficits after surgery (**f**)

the quadrigeminal cistern are cut, just underneath the vein of Galen.

A third and a more infrequently used approach is the occipital interhemispheric transcallosal (OITC), which is accompanied though by a higher morbidity and is therefore less optimal than the previously mentioned routes [39, 46, 49, 50]. This approach utilizes the natural corridor along the junction between the parietal and occipital lobes. Both sitting and prone positions are equally favorable. The skin may be incised either in a horseshoe shape, as for the previous craniotomy, or in a linear fashion (coronal or sagittal). The craniotomy is made in the same manner as for the OTT, with the mention that for the OITC, it is centered over the vertex as to reduce occipital lobe retraction and manipulation. The dura is cut in a C-shape with the base toward the SSS and reflected medially using atraumatic sutures. As soon as the medial aspect of the hemisphere is visible, the route involving the least number of veins is selected. It is preferable not to sacrifice more than one bridging vein, if possible. The ipsilateral hemisphere is gently retracted,

and the falx cerebri can also be cut inferiorly for a wider exposure. Using the operating microscope, the corpus callosum is then identified, with the two pericallosal arteries running just above this structure. Retracting the pericallosal arteries may be done either on the same side apart from one another. The corpus callosum is then cut in its posterior segment. The incision should be made as little as feasible, in order to avoid a disconnection syndrome. Having penetrated through the corpus callosum, the anatomical structures and cavernoma of the pineal region may be visualized.

We prefer a modification of this access route without the necessity of splitting the splenium, namely the combined occipital interhemispheric supracerebellar infratentorial approach [3, 43].

The transcortical transventricular approach is seldom used for the microsurgical removal of pineal region lesions due to the limited visibility and possible damage it may cause to the cortex [42, 50]. This route utilizes a trajectory made via the right lateral ventricle through a cortical incision, evidently in a noneloquent area of the brain. Although neuronavigation is a valuable tool that can be employed in any of the discussed approaches, it is probably the most useful here. To the best of our knowledge, this approach has never been used in resecting a pineal region CM.

Once the pineal region has been exposed and the cavernoma is accessible via any of the aforementioned routes, proper lesionectomy may commence. Some CMs may readily appear on the parenchymal surface of the midbrain or thalamus, others may be located more deeply intraaxially. In the latter instances, the mesencephalic or thalamic surface may show an apparently normal aspect. This certainly renders the choice of the entry point into the brainstem or thalamus more difficult. A limited pial opening is performed where the CM or hematoma is nearest to the surface. Under microscopic magnification, the cavernoma is carefully dissected from adjacent parenchyma using microinstruments. In order to minimize damage to normal neurovascular structures, the bipolar coagulator is usually set to a low current intensity. Preserving the gliotic pseudocapsule around the lesion facilitates maintaining a safe circumferential surgical plane. It is desirable to avoid en bloc resection in this region so as to reduce the risk of unwanted retraction and injury. We recommend employing microinstruments and performing a piecemeal excision, being cautious when removing the pseudocapsule so as not to trespass with the resection into normal cerebral tissue. If any portions of a venous malformation are encountered along the surgical route, it is best to preserve them to avoid venous infarcts.

Under certain circumstances, it is possible to address only the hydrocephalus, resulting from an enlarging pineal CM obstructing the Sylvian aqueduct. Toward that purpose, there are multiple available methods, including temporary CSF release (extraventricular drainage—EVD), ventriculoperitoneal shunt (VPS), and VCS. In the case report of Feletti et al., the cavernoma of the cerebral aqueduct was left untouched while they performed a VCS [51]. The patient had an uneventful postoperative course and a favorable neurological outcome at controls. In case that intuitive methods of diminishing ICP and its symptoms caused by obstructive hydrocephalus are considered, great caution should be taken when indicating these procedures. A recently ruptured pineal region CM may produce additional hemorrhage, should the ICP drop too rapidly or under a certain threshold. This may occur at a variable point in time, but most likely shortly after CSF flow diversion, with a sudden aggravation of symptoms and neurological deterioration. Apparently, even a VPS with a high-pressure valve is at risk of this phenomenon, rendering the ICP threshold uncertain [9, 23]. Under these circumstances, it appears more favorable to remove the pineal CM as early as feasible after the CSF diversion. Furthermore, as these lesions are histologically benign, and since they are expected not to recur in case of complete removal, CSF diversion surgery can effectively be avoided after lesionectomy.

22.6 Controversies

The main controversial issues concerning pineal region CMs are optimal clinical management and surgical strategies. Since asymptomatic CMs are

typically maintained under observation, and with regard to the less easy accessibility of this area, incidentally discovered lesions are best managed expectantly with repeated MRI scans, usually at a yearly interval. Minor or moderate-intensity headaches in the absence of significant hemorrhage on imaging studies and without signs of increased ICP should also be treated conservatively with mild analgesics. The risk of bleeding in this region is not well established; accordingly, we do not recommend removing the lesion in the absence of a higher perceived possibility of hemorrhage (previous stroke, multiple CMs, increased arterial pressure).

SRS is a noninvasive procedure that is claimed to reduce the chances of hemorrhage from cavernomas. Regarded objectively and based on our own observations in several patients, its results are inferior when compared to surgical removal, as this method does not remove the lesion, nor does it completely eliminate the risk of bleeding [3–5, 29–33]. Certain authors and centers may frequently opt for this management strategy due to the fewer complications and lower mortality, especially for patients unable to undergo surgery [1, 15]. Because of the implied low surgical accessibility of the pineal region, it may become an enticing choice for some physicians, specifically if there are no signs of recent hemorrhage or lesion expansion. If acute hydrocephalus is present, this method alone becomes irrelevant. SRS is also discouraged for asymptomatic cavernomas or familial cases, applicable to CMs of this region as well. The authors of this chapter do not recommend radiosurgery for the treatment of CMs because they cannot recognize sufficient evidence for the efficiency of the method in these vascular malformations (Fig. 22.11).

Another controversial topic is the treatment of hydrocephalus in the case of pineal CM hemorrhage. The choice between VPS and VCS has been widely debated; however, neither method is

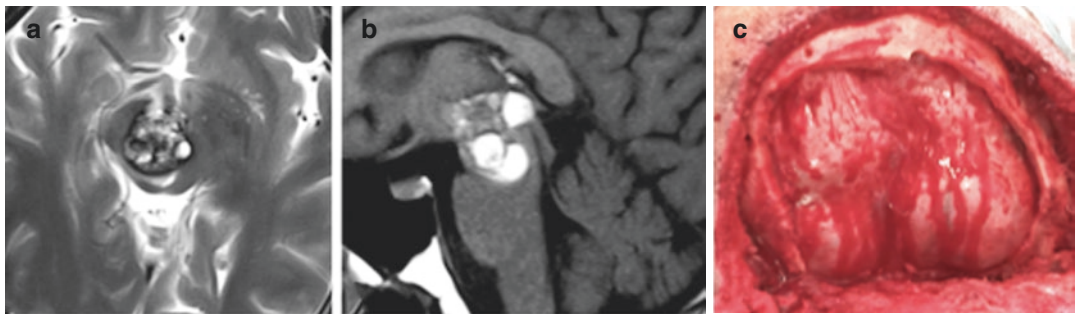

Fig. 22.11 This 36-year-old male patient suffered for the first time from diplopia 4 years prior to surgery. By that time, a rather small mesencephalic cavernous malformation was diagnosed. The only treatment the patient received by that time was placement of a ventriculoperitoneal shunt due to concomitant obstructive hydrocephalus. As the deep-seated vascular lesion was considered inoperable in his home country, the patient underwent gamma knife treatment 2 years prior to the current surgical intervention. Already 1 month after radiosurgery, another hemorrhage from the midbrain cavernoma occurred, causing a temporary left-sided hemiparesis. The patient suffered a second post-radiosurgical hemorrhage several months later; this time, he developed several neurological deficits: right-sided incomplete oculomotor palsy with diplopia, left-sided hemiparesis and hemihypesthesia, as well as gait ataxia. In the meantime, the midbrain lesion has significantly increased in size despite the previous radiosurgery, now measuring 30 mm in largest diameter as can be seen on preoperative axial (**a**) and sagittal MRI (**b**). The patient agreed to undergo surgery, and a right-sided posterolateral occipital/suboccipital craniectomy was performed to also allow for occipital transtentorial exposure if deemed necessary during surgery (**c**). The microsurgical extirpation was carried out via a supracerebellar transtentorial exposure, and complete resection of the lesion was succeeded as documented on postoperative axial (**d**) and sagittal magnetic resonance imaging (MRI) (**e**). The surgical intervention was undertaken with the patient placed in the semi-sitting position under continuous electrophysiological monitoring; for this rather extensive exposure, we used an occipital/suboccipital musculocutaneous flap (**f**). There were no perioperative complications. Postoperatively, temporary exacerbation of the sensory deficits and gait ataxia were noted. Fortunately, 1 year after surgery, the patient presented in excellent clinical condition, mentioning only minimal diplopia and hemisensory deficit (**g**)

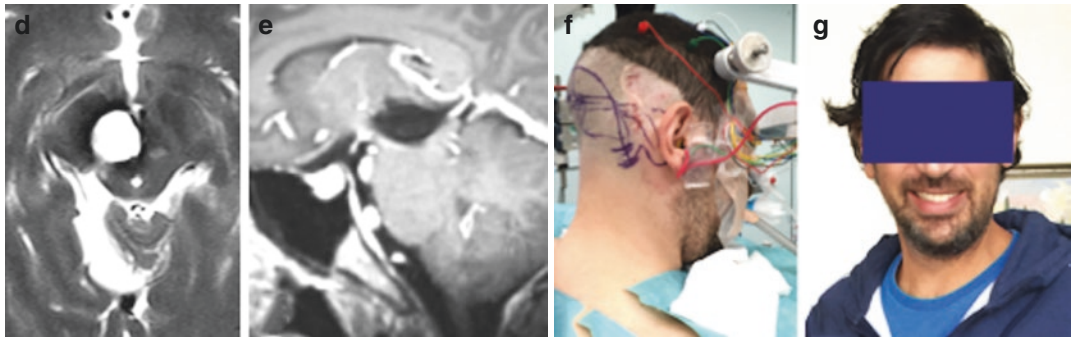

Fig. 22.11 (continued)

the obvious superior alternative [52]. Although VPS has a higher short-term success rate of nearly 100%, it carries a higher risk of postoperative infections and overdrainage, while also being a "blind procedure," Additionally, VPS, through the undesired process of overdrainage, may initiate a second hemorrhagic episode, worsening the patient's neurological prognosis [9, 23]. Alternatively, acute hydrocephalus can be treated via an EVD placed before surgery. VCS, in turn, requires appropriate equipment and training [50, 52]. The final choice is made according to experience, preference, and availability. Regardless of the method, treatment of an occlusive hydrocephalus should be initiated as early as possible, in order to avoid permanent deficit or even death.

As for the surgical technique, the surgical approach should be short, allowing proper exposure of the lesion and the regional vasculature, while also minimizing the need for brain retraction. According to our experience, the supracerebellar infratentorial approach is possibly the most versatile [3]. Also very useful is the occipital transtentorial approach, [41, 48–50], as well as the combined supracerebellar/occipital transtentorial. The supratentorial interhemispheric route is an alternative, but it is more rarely used [15]. Selection of the optimal access route depends on the anatomical characteristics of the patient, as well as the presence, size, and exact location of the hemorrhage. Regardless of the approach, the only way to effectively eliminate the risk of rebleeding is to remove the lesion in its entirety.

22.7 Conclusions

Pineal region CMs can be regarded as rare occurrences that may remain clinically silent or present with nonspecific symptoms. The definitive imaging diagnosis is made on an MRI scan, preferably T2 sequence; however, non-contrasted CT scans can be valuable in an emergency setting. Acute hydrocephalus should be addressed before lesion removal, either via an EVD or a VCS. Complete surgical removal, preferably via the supracerebellar infratentorial approach, ensures curability of the disease and prevention of subsequent hemorrhages, as we have experienced in our own patient series. Our management strategy, continually refined during the past three decades, has yielded excellent clinical results in pineal region CMs.

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Vein of Galen Aneurysmal Malformation

23

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23.1 Part A: Outline of the Literature

In **Part A**, the body of the literature is summarized with a focus on clinically relevant aspects. The chapter can be regarded as a narrative review of published vein of Galen aneurysmal malformation (VGAM) characteristics.

23.1.1 Historical Aspects and Definitions

The entity VGAM has its roots in a cerebral vascular malformation draining into the vein of Galen that was first described by Steinheil in 1896 [1]. In 1923 and 1937, Wohak and Jaeger et al. reported on aneurysms of the vein of Galen; however, the interpretation and understanding of these lesions changed when embryological considerations were taken into account [1]. Normally, the median prosencephalic vein of Markowski (MPV) transforms into the vein of Galen before birth, whereby the anterior portion regresses upon formation of the internal cerebral veins, and the posterior portion persists as the vein of Galen [2]. Strictly speaking, VGAM is a misnomer because it is actually the MPV that persists and fails to develop into a normal vein of Galen [3–5]. Currently, the definition of a VGAM is as follows: an arteriovenous fistula/malformation between the MPV and different arterial feeders (e.g., choroidal arteries, thalamoperforating arteries, and pericallosal arteries) [3, 4].

23.1.2 Epidemiology and Clinical Presentation

VGAMs are uncommon, and their exact incidence and prevalence are not known, but they are estimated to be about 1% of all pediatric congenital anomalies and up to 30% of all pediatric vascular malformations [6]. The published age distributions of patients with VGAMs is listed in Table 23.1 [3].

The clinical presentation of patients with VGAMs depends on age. In a case series with fetus presenting with cardiac enlargement diagnosed by applying prenatal ultrasound, the

Table 23.1 Age distribution of patients with VGAM

Age group	Age	Percentage
Fetus	Before birth	29%
Neonates	Birth–1 month	38%
Infants	1 month–2 years	26%
Children	2–16 years	7%

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mortality rate was 100% [7]. Neonates who survive present with high-output cardiac failure due to severe arteriovenous (AV) shunting (see also **Part B: Indications for Treatment**) [8]. Infants and young children present with hydrocephalus due to malabsorption of cerebrospinal fluid and venous hypertension. The patients can be identified having an overly broad skull in proportion to the size of the face (so-called macrocranium) [9–11]. In children, intracranial hemorrhage, headache, seizure, and developmental delay are further clinical hallmarks [12, 13].

23.1.3 Pathophysiology and Pathoanatomy

Raybaud et al. postulated that VGAMs develop between week 6 and week 11 of gestation [14]. Representing a low-resistance pathway for the blood flow, shunting from the arterial to the venous side of the VGAM results. The combination of high flow with additional recruitment and dilatation of arterial feeders worsens the sump phenomenon, and this *circulus vitiosus* induces cardiac failure [15]. The inability of the right and left ventricles to handle the venous overload is aggravated by the steady decrease of resistance in the pulmonary circulation of the neonate. Because of those two low-pressure systems (the VGAM itself and the maturing pulmonary circulation), high-output cardiac failure develops and worsens [16]. Multi-organ failure is a consequence because of compensating severe vasoconstriction in the region of the splanchnic nervi (e.g., resulting in renal failure) as well as venous congestion (e.g., resulting in hepatomegaly and liver failure). VGAM-associated intracranial hemodynamic changes cause secondary alterations of the venous drainage, with persistence or enlargement of the fetal falcine sinus, stenosis of the straight sinus, development of persisted accessory straight sinus or accessory torcula, and/or atypical drainage via internal cerebral veins or facial veins [17].

23.1.4 Classification of Vein of Galen Aneurysmal Malformation Subtypes

Different classification systems exist, and, to date, four different classification systems evolving over time should be noted. In 1960, Litvak et al. published categories A (aneurysms of the great vein of Galen), B (racemose conglomerations of blood vessels deep in the cerebral structures with dilated deep venous structures), and C (translational types of midline arteriovenous shunts), describing vascular malformations connected to the vein of Galen [1]. We do not further specify this classification system because of the current lack of clinical impact. In 1988, Yasargil et al. proposed a classification system with differentiation into pure arteriovenous fistula (type I–III) and arteriovenous malformations with or without arteriovenous fistulae (type IVA–C) [7]. The Yasargil classification can be regarded as a surgical classification with important functional differences, regarding the venous drainage. (In Yasargil type I–III VGAMs, the internal cerebral veins are not opacified when applying diagnostic angiograms, whereas in Yasargil type IVA–C VGAMs the internal cerebral and mesencephalic veins are opacified on early-phase angiograms such as the vein of Galen and straight sinus.)

On the basis of broad clinical experience in the management of VGAM, Lasjaunias et al. proposed an alternative classification system, which is potentially more suitable for the endovascular therapy [18]. The two different types, classified under consideration of the origin of the arterial feeders using diagnostic angiograms, are the so-called choroidal type (Lasjaunias type I VGAM) and the mural type (Lasjaunias type II VGAM) [1].

In 2013, Mortazavi et al. analyzed the available classification systems and recognized the need for revision [1]. In their new proposal, not only are the morphological and functional VGAM aspects considered, but the clinical symptoms are also taken into account.

Finally, secondary enlargement of the true vein of Galen, and not of its precursor (MPV),

exists, which needs to be distinguished from a VGAM. Vein of Galen dilatation (VOGD) and vein of Galen varix (VOGV) are those entities that result secondarily due to adjacent venous obstruction, arteriovenous shunt, and/or vascular malformation [13, 19–21].

23.1.5 Treatment and Outcome

Morbidity and mortality rates of untreated VGAMs in neonates with high-output cardiac failure reach 100% [5, 22–25]. In the early postnatal period, primary and secondary goals of treatment are hemodynamic and neurological stabilization, respectively [1, 6, 26]. In infants and children, the primary goal of treatment is neurological stabilization, with control of hydrocephalus, avoidance of developmental delay and intracranial hemorrhage, and control of seizures and headache [1, 6, 26]. The Bicêtre neonatal evaluation score was published to enable the quantification of illness severity in patients with VGAMs [17]. A score of <8 indicates a patient who is too critically ill for treatment, a score of 8–12 indicates a patient who should undergo emergency treatment, and a score of >12 indicates a patient who is medically stable and should undergo delayed treatment not earlier than the age of 5 months [17]. According to a systematic review and meta-analysis, the clinical decision making following the Bicêtre neonatal evaluation score results in a higher rate of survival with good neurological outcome [27].

23.1.5.1 Conservative Treatment

The key pillar of hemodynamic stabilization constitutes the aggressive therapy of cardiac failure and pulmonary hypertension. Reduction of the preload (e.g., with diuretics and volume restriction) and increase of the contractibility (e.g., with digitalis, dopamine, and dobutamin) represent options to obtain cardiac stabilization [1]. Pulmonary hypertension is managed with nitric oxide, vasopressors, alkalinization, and ventilation [2]. Even though conservative treatment is fully exploited, the condition of an essential part of patients still worsens progressively. Then, invasive therapy, or, in the strict sense, endovascular therapy, is the only option to prevent hemodynamic decompensation. Optimization of liver and kidney function are other treatment goals; however, this is strongly connected to the success of hemodynamic stabilization [21]. The diverse conservative treatments with the goal of neurological stabilization can be obtained from the relevant literature; however, also in this context, it must be emphasized that concomitant endovascular therapy is the key to optimizing the neurological outcomes (see also **Part B: Indications for Treatment**) [28–31].

23.1.5.2 Surgery and Radiotherapy

Although there are reports describing the microsurgical and radiotherapeutical treatment of VGAMs, the concepts are currently mostly disregarded either due to the high procedure-related morbidity and mortality rates or to the lack of high evidence [26, 32, 38, 39].

23.1.5.3 Endovascular Therapy

The implementation of endovascular therapy marks a milestone in the interdisciplinary management of VGAMs. In 2015, Chow et al. published the mortality rates of different VGAM treatment approaches and noted the superiority of endovascular therapy [32]. Accordingly, the mortality rates of endovascular therapy, microsurgery, and no treatment are 15%, 84.6%, and 76.7%, respectively [5, 33–36]. In 2017, Brinjikji et al. summarized and analyzed the results of endovascular therapy in a systematic review and meta-analysis [27]. Demographically, neonates, infants, and children account for 41.9%, 45.0%, and 13.1%, respectively, of the VGAM patients undergoing endovascular therapy. For the entire collective, all-cause mortality is 14.0% (95% CI, 8.0–22.0%). Overall, a good neurological outcome (defined as normal development) rate is published as being at 62.0% (95% CI, 57.0–67.0%), whereby age (neonate) and presence of congestive cardiac failure are predictors of poor neurological outcome. In 2019, two larger retrospective series were published. Sivasankar et al. treated Lasjaunias type I and II VGAMs with transarterial embolization, and they could achieve a good outcome in 85.0% of patients [6]. For the entire collective, complication and fatal

outcome rates are reported with 26.9% and 12.0%, respectively. The Texas Children's Hospital (TCH; Houston, USA) experience regarding VGAM is published by Wagner et al. who emphasized the importance of modern embolization equipment such as dual-lumen balloon microcatheters, coils and onyx, and their combinations [26]. In their series with repeat endovascular therapy, the procedure-related complication rate is 24%, 66.7% of patients feature normal or near-normal neurological development, and 16.7% of patients have a fatal outcome. The methodology for implementing a new embolization technique, the combined transvenous and transarterial approach with kissing microcatheters, in the clinical routine was published in 2012 by the lead author of this book chapter [37]. Eight neonates and six infants, children, or young adults underwent repeat endovascular therapy, with normal or near-normal outcome in 69.2% of patients. Further study benchmarks are procedure-related complication and mortality rates of 8.8% and 0%, respectively; an angiographic complete or >90% VGAM occlusion rate of 78.6%, and a control of cardiac failure rate of 100%. In Fig. 23.1, a case of one-stage endovascular therapy of a Lasjaunias type II-like VGAM is demonstrated.

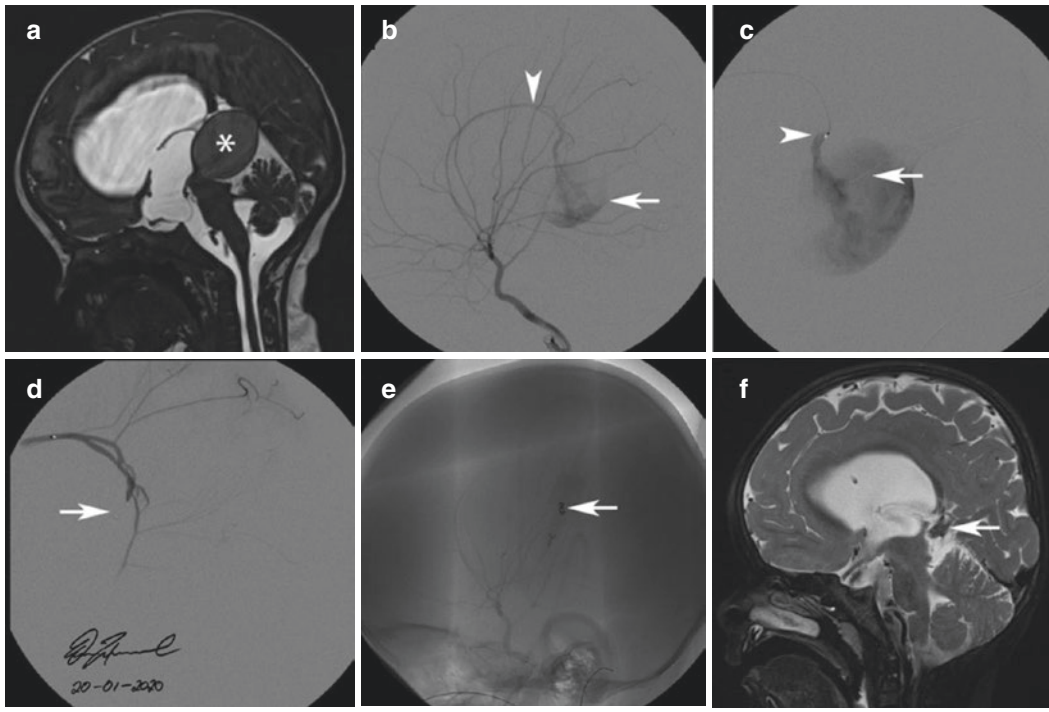

Fig. 23.1 Endovascular therapy of a Lasjaunias type II-like VGAM in a 4-month-old infant with hydrocephalus in stable general condition and without obvious neurodevelopmental alterations. (**a**) baseline MRI (sagittal T2OffPh) at month 4 of life, showing hydrocephalus, delayed brain development, and space-occupying VGAM with a dilated MPV (white asterisk); (**b**) right internal carotid artery angiogram (digital subtraction angiography in lateral projection), showing Lasjaunias type II-like VGAM with supply of the dilated MPV (white arrow) from the distal pericallosal branches (white arrowhead); (**c**) superselective pericallosal artery angiogram (digital subtraction angiography in lateral projection), showing single-hole arteriovenous fistula (microcatheter via the transarterial route, white arrowhead) into the dilated MPV (microwire advanced over the microcatheter via the transvenous route, white arrow); (**d**, **e**) superselective pericallosal artery control angiogram (digital subtraction angiography in lateral projection) and selective right internal carotid artery control angiogram (digital non-subtraction angiography in lateral projection) immediately after embolization, showing occlusion of the single-hole arteriovenous fistula (D - white arrow) after positioning of two coils (E—white arrow); (**f**) Control MRI (sagittal T2OffPh) at month 26 of life showing persistent occlusion of the single-hole arteriovenous fistula, shrinkage of the formerly dilated MPV (white arrow), and regular brain development.

23.2 Part B: Controversial Issues and Dedicated Management Strategies

In **Part B**, the perspective and proceedings in a VGAM high-volume center are presented. In the Clinic of Radiology and Neuroradiology, Duisburg Hospital, Germany, > 100 patients with different types of VGAMs underwent >500 endovascular therapies during the last 20 years with the intention of cure or palliation. Multiple articles involving the institutional VGAM data have already been published, and issues such as angioarchitecture, dedicated embolization technique, radiation exposure, interdisciplinary management, predictors of technical and clinical success, and long-term outcome are in the process of review, analysis, and/or preparation for publication [37, 43–52]. Considering our experience, we believe that the generally accepted VGAM management strategies can be optimized, and therefore this chapter is in accordance with that belief.

23.2.1 Indication for Treatment

In the era of modern interdisciplinary treatment, 40% of neonates with VGAM do not survive [53]. Of the survivors, 50% show poor neurocognitive results (e.g., neuromotor function, language development, cognitive development, and emotional development) [53]. In the multivariate analysis, only a Bicêtre neonatal evaluation score < 12 but with no brain injury (in particular, white matter injury) on early imaging is the predictor of poor cognitive outcome [53]. For long-term survivors, by the time of school age, 57.6% present with good neurological outcome (evaluated using the King's Outcome Scale for Childhood Head Injury [KOSHI] score and eight neurological and behavioral items from the Rivermead Post-Concussion Symptoms questionnaire); however, the majority of individuals suffer from neurodevelopmental alterations [54]. These data point out that the current management of VGAM, inclusive of endovascular therapy, must be optimized. The Bicêtre neonatal evaluation score is commonly recognized as the most important classification system for the decision-making in neonates with VGAMs [17, 18]. At present, however, different high-volume centers deviate from this older concept and choose emergency and staged endovascular management in an alternative way [25, 26, 37, 43]. We believe that there is a bias against patients with low Bicêtre neonatal evaluation scores, who should not be treated, or, in other words, there is a very high probability of morbidity according to the original recommendation. In the Duisburg Hospital, however, parents of concerned neonates and infants regularly insist on treatment. Medical professionals are confronted with the dilemma of treating severely ill patients showing a poor prognosis, based on previous clinical evaluation, according to the Bicêtre neonatal evaluation score. In these cases, interdisciplinary reevaluation of all treatment options and informed consent discussion must be realized as quickly as possible. Both transferring patients to centers with the necessary expertise and consideration of the highest ethical standards should be given utmost priority. Lasjaunias type II-like VGAM is seldom an indication for emergency intervention, and, therefore, not surprisingly, neonates and infants can remain asymptomatic until they grow to be children with clinical signs such as hydrocephalus, macrocrania and prominent subcutaneous cranial and facial veins. These patients rarely suffer from cardiac failure or systemic venous congestion and steal phenomenon. Once detected, staged endovascular therapy is strongly recommended with the intention to avoid impairment of brain development. In contrast, Lasjaunias type I-like VGAM is a neonatal emergency. The concept of patient stabilization over weeks or even months by applying the best conservative and intensive care management with the intention of identifying the "appropriate" therapeutic window for endovascular therapy leads to a significant loss of patients and is therefore regarded in our institution as inacceptable. Severely ill Lasjaunias type I-like VGAM patients require urgent endovascular therapy. The staged occlusion of the VGAM stabilizes the cardiac function and avoids multi-organ failure. Furthermore, the "as early as possible" normalization of the intracranial hemodynamic, in

particular, the optimization of cerebral capillary perfusion, is a prerequisite of normal or near-normal brain development. In patients with an inadequately treated VGAM, brain parenchyma (in particular, white matter) is progressively destroyed due to the severe venous congestion, a phenomenon also observed in other types of brain arteriovenous fistulae and is known as "melting brain syndrome" [32, 55]. From this perspective, patients should not be denied access to treatment controlled by consideration of a controversially discussed classification system alone. Rather, there should be a joint decision that includes the families involved. When the decision to treat a severely ill patient outside of the Bicêtre neonatal evaluation score recommendations is made, there is no 100% guarantee that the best outcome could be achieved. This reality should be made obvious to everyone concerned. A case of endovascular therapy (Lasjaunias type I-like VGAM) performed outside of the Bicêtre neonatal evaluation score recommendations and with favorable outcome is presented in Fig. 23.2.

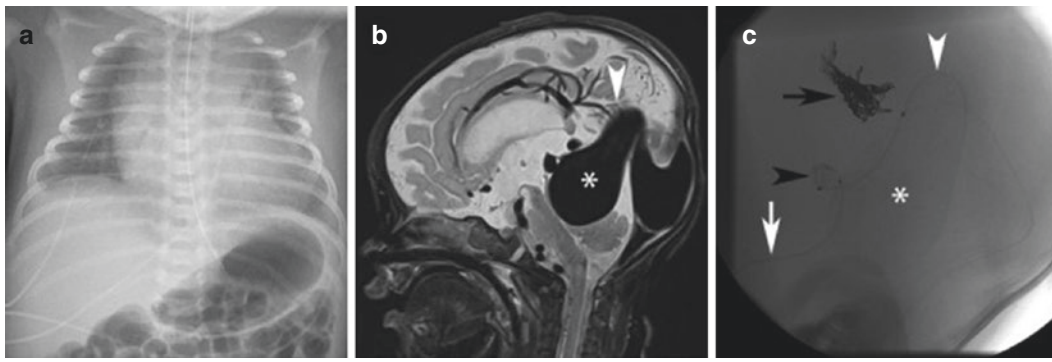

Fig. 23.2 Repeat endovascular therapy of a Lasjaunias type I-like VGAM in a 1-day-old infant with cardiac decompensation, showing a Bicêtre neonatal evaluation score of 7 (see also Figs. 23.3, 23.4, 23.5, and 23.6.). (**a**) Baseline chest X-ray (anterior-posterior projection) on day 1 of life showing cardiomegaly and signs of cardiopulmonary decompensation; (**b**) Baseline MRI (sagittal T2OffPh) on day 1 of life showing a prominent pericallosal artery, multiple arteriovenous fistulae (white arrowhead), a space-occupying VGAM with a dilated MPV (white asterisk), and a persisted and stenosed accessory straight sinus; (**c**) Retrograde superselective angiogram (digital non-subtraction angiography in lateral projection) on day 1 of life, applying the microcatheter via the transvenous route (white arrowhead), showing an arteriovenous fistula (black arrowhead) and the dilated MPV (white asterisk); annotations: microcatheter via the transarterial route (white arrow) and condition after embolization of another arteriovenous fistula with coils and Onyx, according to the "ferroconcrete" concept (black arrow); (**d**) Retrograde embolization (road-map fluoroscopy in lateral projection) of the arteriovenous fistula as demonstrated in C on day 1 of life, applying the microcatheter via the transvenous route and Onyx (black arrowhead); (**e**) Selective left vertebral artery control angiogram (digital non-subtraction angiography in lateral projection) on day 1 of life, immediately after embolization of two arteriovenous fistulae with coils and Onyx, according to the "ferroconcrete" concept; (**f**) Superselective angiogram (digital subtraction angiography in lateral projection) on day 11 of life, showing an arteriovenous fistula (black arrowhead); (**g**) Selective left internal carotid artery control angiogram (digital non-subtraction angiography in lateral projection) on day 11, immediately after embolization with coils and Onyx, according to the "ferroconcrete" concept; (**h**, **i**, **j**, **k**) Selective control angiograms (digital subtraction angiography in lateral projection) at month 6 of life showing persistent occlusion of the multiple arteriovenous fistulae ((**h**) left internal carotid artery angiogram; (**i**) left vertebral artery angiogram; (**j**) right internal carotid artery angiogram; (**k**) right vertebral artery angiogram); (**l**) Control MRI (sagittal T2OffPh) at month 6 of life, showing persistent occlusion of the multiple arteriovenous fistulae, shrinkage of the formerly dilated MPV (white arrow), normalization of the caliber of the pericallosal artery, and regular brain development

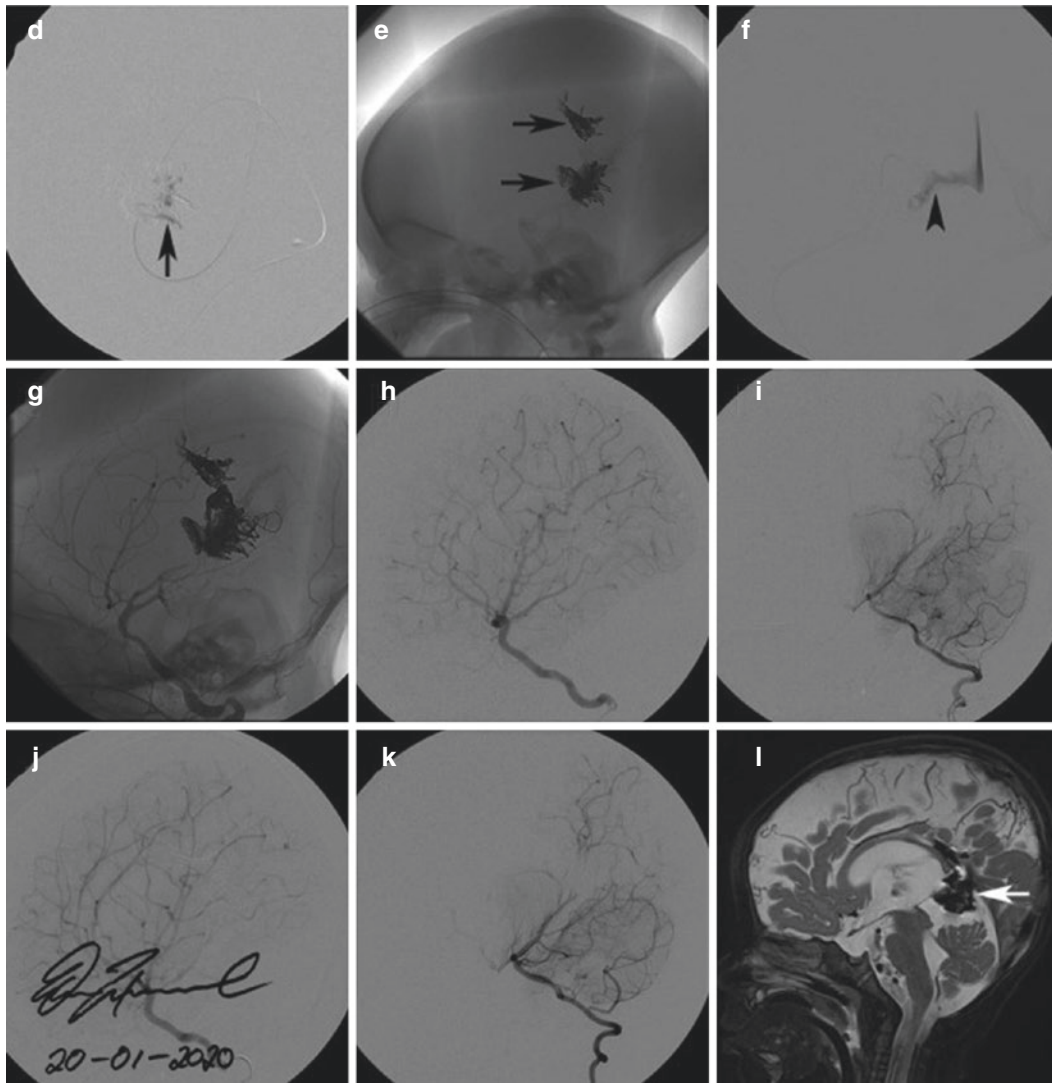

Fig. 23.2 (continued)

23.2.2 The Angioarchitecture of Vein of Galen Aneurysmal Malformation and Strategy of Endovascular Therapy

The adequate description of the VGAM angioarchitecture is challenging. We believe that the true VGAM angioarchitecture is probably better described as a pathoanatomical continuum rather than distinct lesion types or subtypes, according to the classifications as Yasargil type or Lasjaunias type VGAMs. In Fig. 23.3, our interpretation of the VGAM angioarchitecture is illustrated.

Up to the present, the complete extent and functional aspects of VGAMs cannot be captured succinctly. It is more likely that the different arterial feeders and arteriovenous fistulae, and their collateral network, only demarcate, and, potentially, this is still, in part, after major arteriovenous fistulae have been occluded. Applying diagnostic angiography at baseline, arterial feeders and arteriovenous fistulae with high flow are visualized. Arterial feeders and collaterals with smaller calibers and low flow, however, can hardly be visualized. The following reflection of contrast material flow could help to explore the

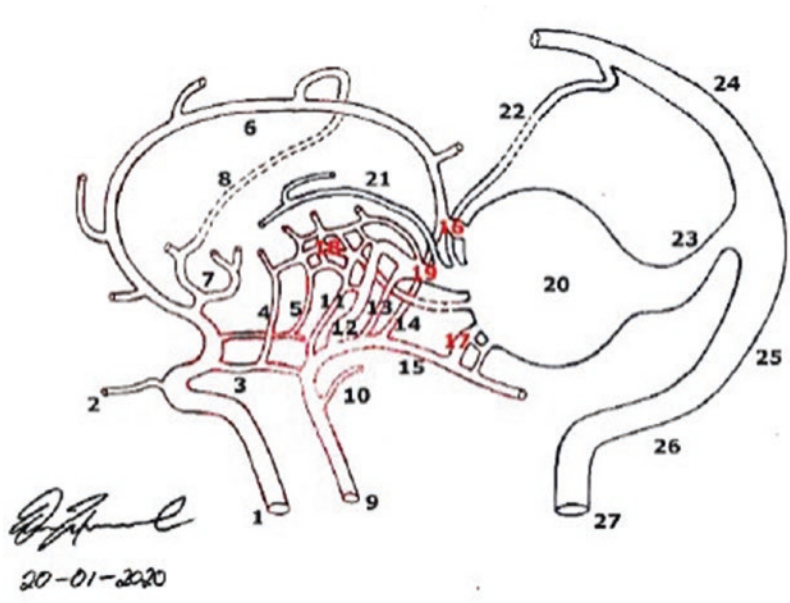

Fig. 23.3 Interpretation of the VGAM angioarchitecture, according to our pool of experience. Note 1: The true VGAM angioarchitecture is probably better described as a pathoanatomical continuum rather than distinct lesion types or subtypes, according to classifications such as Yasargil type or Lasjaunias type VGAMs; Note 2: 1: Internal carotid artery; 2: Ophthalmic artery; 3: Posterior communicating artery; 4: Anterior thalamoperforating artery; 5: Anterior choroidal artery; 6: Pericallosal artery; 7: Middle cerebral artery; 8: Steal-forming cortical anastomosis between the middle cerebral artery and the pericallosal artery; 9: Basilar artery; 10: Superior cerebellar artery; 11: Posterior thalamoperforating artery; 12: Medial posterior choroidal artery; 13: Lateral posterior choroidal artery; 14: Posterior pericallosal artery; 15: Posterior cerebral artery; 16: Lasjaunias type II-like VGAM with single-hole arteriovenous fistula arising from posterior pericallosal artery; 17: Lasjaunias type II-like VGAM connected with second minor Lasjaunias type II-like VGAM; 18: Choroido-thalamic collateral network of the Lasjaunias type I-like VGAM; 19: Lasjaunias type I-like VGAM with fistulous and plexiform components; 20: Dilated MPV; 21: Internal cerebral vein; 22: Anastomosis with a cortical vein; 23: Falcine sinus; 24: Superior sagittal sinus; 25: Transverse sinus; 26: Sigmoid sinus; 27: Internal jugular vein

dynamic visualization patterns during the different steps of endovascular therapy. Initially, the contrast material is guided toward the largest channels of the vascular network, supplying the largest arteriovenous fistulae and, ultimately, toward the major venous collector (in particular, the MPV). Small-caliber arterial feeders, arteriovenous fistulae, and their collateral network contain only little contrast material and therefore are invisible when applying baseline angiography. In fact, these small-caliber arterial feeders and collaterals reduce the contrast material concentration within both the major arterial feeders and the major venous collectors. After the occlusion of the major arteriovenous fistulae, a higher contrast material concentration is available to visualize the initially occult collateral network adjacent to the now-occluded major arteriovenous fistulae. These observations are especially prevalent in complex VGAMs, consisting of multiple arterial feeders, mixed with plexiform arteriovenous fistulae (choroido-thalamic collateral network), such as in Lasjaunias type I-like VGAM. Even in Lasjaunias type II-like VGAM, the so-called mural type with primarily expected single arteriovenous fistula, initially existing smaller separate arteriovenous fistulae in the neighborhood of the major and primarily visualized high-flow fistula demarcate only after the occlusion of the initially visualized mural arteriovenous fistula. The dynamic hemodynamic changes after occlusion of the major arteriovenous fistulae are illustrated in Fig. 23.4.

Appropriate endovascular therapy of VGMAs must consider these dynamic hemodynamic changes that can only be properly recognized

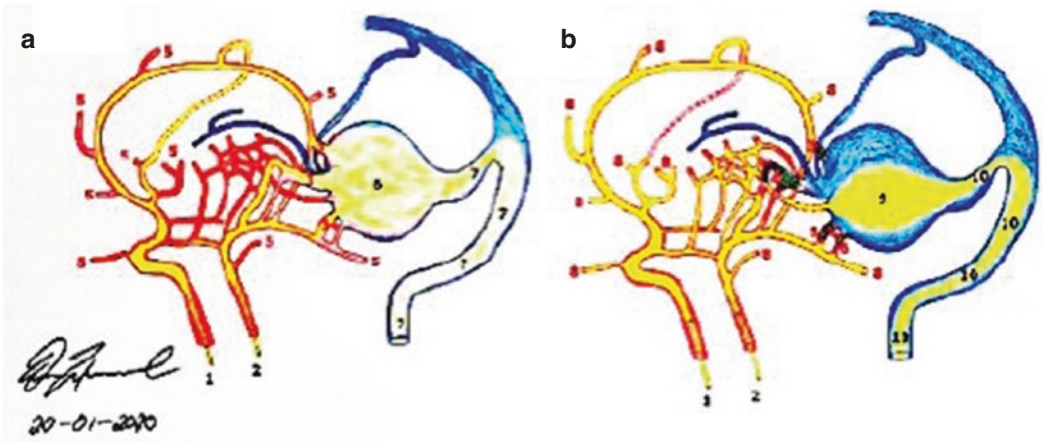

Fig. 23.4 Hemodynamic changes after the occlusion of the major arteriovenous fistulae as the first step of endovascular therapy. (**a**) Baseline selective internal carotid artery (1) and basilar artery (2) angiograms demonstrating the contrast material flow in yellow (annotation: the brighter the yellow, the higher the contrast material concentration); Note 1: The high-flow arteriovenous fistulae (3) are visualized during baseline angiography; however, the small plexiform arteriovenous fistulae (choroido-thalamic collateral network) with low flow (4) supplying the VGAM, displayed in red, cannot be visualized due to the lack of contrast material in these territories. Accordingly, the low-flow arteriovenous fistulae of the VGAM are occult on baseline angiograms; Note 2: Also normal arteries supplying the brain (5) cannot be visualized due to the lack of contrast material in these territories; Note 3: Dilution and off-stream of contrast material in the MPV (6) and other venous collectors (7); (**b**) Control selective internal carotid artery (1) and basilar artery (2) angiograms after the occlusion of 4 high-flow arteriovenous fistulae; Note 1: 3 Occlusion of a high-flow fistula between the posterior pericallosal artery and the MPV (Lasjaunias type II-like VGAM with single-hole arteriovenous fistula); 4" Occlusion of a high-flow central arteriovenous fistula (choroido-thalamic collateral network of a Lasjaunias type I-like VGAM); 5 and 6: Occlusion of two high-flow arteriovenous fistulae of the VGAM (Lasjaunias type II-like VGAM connected with second minor Lasjaunias type II-like VGAM); Note 2: Due to the hemodynamic changes after the occlusion of the high-flow arteriovenous fistulae, the initially occult small plexiform arteriovenous fistulae (choroido-thalamic collateral network) (7) supplying the VGAM, now displayed in bright yellow, are visualized due to the redistribution of flow/high contrast material concentration; Note 3: Due to the hemodynamic changes after the occlusion of the high-flow arteriovenous fistulae, the initially occult normal arteries supplying the brain (8), now displayed in bright yellow, are visualized due to the redistribution of flow/high contrast material concentration; and Note 4: After the occlusion of the high-flow arteriovenous fistulae, there is significant flow reduction in the MPV (9) and other venous collectors (10)

over the course of time. Also for this reason, repeat endovascular therapy is justified or even necessary to obtain the best clinical results. Diagnostic angiography via the transvenous route is a promising option for the better visualization of the different high- and low-flow arterial feeders and arteriovenous fistulae, as it was described previously [37]. The injection of contrast material against the blood stream induces turbulences that also distribute the contrast material in a retrograde fashion into the smaller arterial feeders and collaterals. The transvenous route to the arteriovenous fistula feeding arteries can help to visualize low-flow arterial feeders and collaterals at an early stage of endovascular therapy. As in all embolization procedures, definition of the adequate embolization endpoint is crucial. Different studies have noted that hemodynamic and neurological stabilization with good clinical outcome, the primary endovascular goal of therapy, does not necessarily require complete VGAM occlusion [6, 26, 27, 37]. Although generally accepted hard parameters do not exist, embolization endpoints could be defined as discussed previously. In their 17 years of experience in the management of neonatal arteriovenous brain malformations accompanied by cardiac failure, Giorgi et al. defined the goal for the first endovascular therapy as reduction of the fistula by at least one-third, based on the size of the aneurysm, number of arterial feeders, and hemodynamic status [56]. Earlier, Moersdorf and

Lasjaunias proposed an opportunity to assess objectively the necessary fistula reduction to relieve cardiac failure in an infant with a VGAM [57]. By applying a 0.014″ Doppler guidewire, a 40% morphological reduction of the VGAM was associated with a decrease of the diastolic velocity in the basilar artery by about 50%. Single-step occlusion of too large territories of the VGMA might result in a normal perfusion pressure breakthrough or, in other words, in a procedure-related complication in the form of a hemorrhagic infarction [58–61].

23.2.3 Modern Techniques in Diagnostic and Interventional Neuroradiology

23.2.3.1 Pre-Interventional Imaging

Ultrasound and magnetic resonance imaging (MRI) are essential imaging modalities for the pre-interventional assessment of VGAMs [58–61]. In transfontanellar Doppler ultrasound, pathologic high systolic (up to >1.0 m/s), very high diastolic velocities (up to >0.5 m/s), and low RI (<0.6) can be diagnosed in nearly all cases of untreated VGAMs [48]. As a cost-effective, widely used and noninvasive imaging modality, ultrasound can be used not only for screening but also for the process of making the indication for endovascular therapy. MRI helps to visualize the VGAM angioarchitecture [45]. The most important sequences are non-contrast-enhanced arterial time of flight (TOF) and thin T2WI without flow compensation (T2OffPh), which define the origin of the arterial feeders and arteriovenous fistulae with the highest flow [45]. Compared with standard T2 sequences, T2OffPh allows the markedly better visualization of VGAM angioarchitecture and, furthermore, the identification of pulsation artifacts of the cerebrospinal fluid [45]. The use of intravenous contrast material adds no further information, and therefore contrast-enhanced MRI is also not useful to visualize low-flow and small-caliber arterial feeders, collaterals, and fistulae.

23.2.3.2 Endovascular Therapy

All embolization procedures are performed in interdisciplinary consensus and under general anesthesia.

23.2.3.3 Embolization Technique

In many centers, embolization via the transarterial route is regarded as the standard approach [1]. According to different studies, occlusion or significant flow reduction of the arteriovenous fistulae can be obtained with transarterial embolization alone [6, 26, 55]. In the body of literature, embolization via the transvenous route is discussed as a bailout approach for patients in whom transarterial embolization is technically infeasible [1]. The fact that transvenous embolization of the dilated venous collector (or the MPV) can also be feasible and safe in complex VGAMs was published by Casasco et al. in 2001 [58]. From the seven patients, five and two patients showed complete and partial occlusion of the VGAM, respectively, and there were no major complications. In 1990, Dowd et al. published the first retrograde catheterization of arterial feeders of the VGAM via the transvenous route and through the arteriovenous fistula [62]. In 2012, our concept of combined embolization via the transvenous and transarterial route with kissing microcatheters was published [37]. The promising technical and clinical outcomes of the small series are summarized earlier (see **Part A:** Endovascular Therapy). Technically, the concept allows the precise occlusion of high-flow arteriovenous fistulae at the point of shunting by the simultaneous embolization with coils and/or Onyx via the transvenous and/or transarterial route (Fig. 23.5).

At a later stage, the initially occult collateral network (choroido-thalamic collateral network) adjacent to the now-occluded major arteriovenous fistulae can be visualized during angiography and embolized (Fig. 23.6).

Because the retrograde catheterization via the transvenous route through the arteriovenous fistula into the target high-flow arterial feeder can be extremely challenging, refined neurointerventional techniques are under development. Consequently, our understanding of embolization

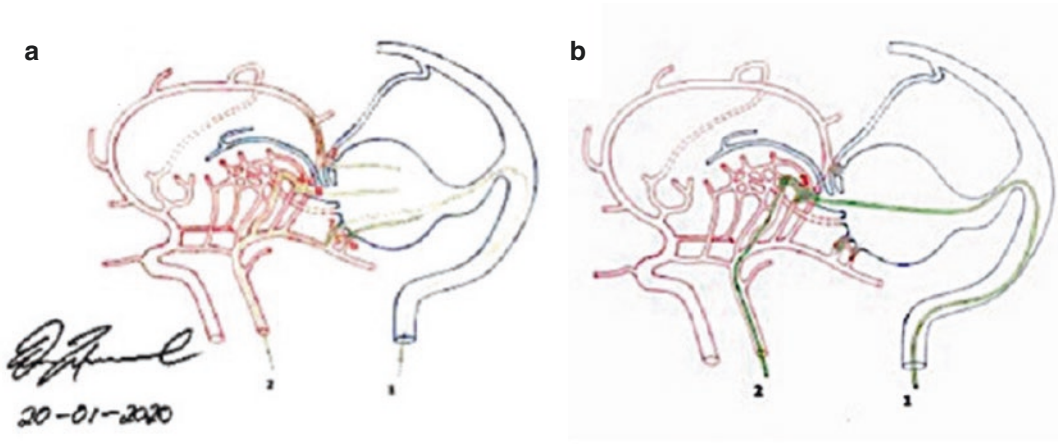

Fig. 23.5 First step of endovascular therapy: Occlusion of the major arteriovenous fistulae with the goal of hemodynamic and neurological stabilization (see also Figs. 23.3, 23.4, and 23.6). (**a**) Combined transvenous (1) and transarterial (2) occlusion of four major arteriovenous fistulae (3, 4, 5, and 6) with kissing microcatheters (7) applying coils; Note 1: 3 Occlusion of a high-flow arteriovenous fistula between the posterior pericallosal artery and the MPV (Lasjaunias type II-like VGAM with single-hole arteriovenous fistula); 4: Occlusion of a high-flow central arteriovenous fistula (choroido-thalamic collateral network of the Lasjaunias type I-like VGAM); 5 and 6: Occlusion of two high-flow arteriovenous fistulae of the VGAM (Lasjaunias type II-like VGAM connected with second minor Lasjaunias type II-like VGAM); Note 2: Because the retrograde catheterization through the arteriovenous fistula into the target high-flow arterial feeder via the transvenous route can be extremely challenging, refined neurointerventional techniques are under development; Note 3: Due to the high-flow arteriovenous fistulae, different coil systems (3, 4, 5, and 6) are used; and Note 4: The central coils positioned via the transvenous route (4) do not cover the junction of the internal cerebral vein and the dilated MPV. (**b**) Combined transvenous (1) and transarterial (2) occlusion of a high-flow central arteriovenous fistula (choroido-thalamic collateral network of the Lasjaunias type I-like VGAM) with kissing microcatheters (3) applying Onyx; Note 1: Because of the high-flow and the liver failure–induced coagulation disorder, coils alone may not be effective for occlusion, and therefore Onyx with high viscosity is additionally used; Note 2: Onyx embolization, displayed in green, via the transarterial route (posterior thalamoperforating artery) and via the transvenous route; and Note 3: The combination of coils (serving for flow reduction and as a tight scaffold) and Onyx (to obtain final occlusion of the major arteriovenous fistulae) is designated as the "ferroconcrete" concept

via the transvenous route does not comprise the occlusion of the dilated venous collector after technically infeasible transarterial embolization [58, 62]. Occlusion of the dilated venous collector should be regarded as exceptionally dangerous, as discussed in different articles [33, 62, 63]. Likely, preexisting physiological communications between the dilated venous collector and the deep cerebral veins (e.g., internal cerebral vein) are responsible for the occurrence of venous hypertension, hemorrhage, and infarction after embolization-induced occlusion of the dilated venous collector [2, 14, 15, 51]. Today, combined embolization via the transvenous and transarterial route with kissing microcatheters is our standard approach and is performed in >70% of patients.

23.2.3.4 Dedicated Materials for Endovascular Therapy

Standard vascular access is obtained after ultrasound-guided puncture of the femoral artery and contralateral or ipsilateral femoral vein with positioning of 3 F sheaths (IVA3F; BALT, Montmorency, France) in patients <2 years or 4 F sheaths (RADIOFOCUS INTRODUCER II; Terumo, Tokyo, Japan) in older patients. Under fluoroscopy guidance, the arterial feeders of the VGAM are catheterized with a 1.5 F microcatheter (Marathon Flow Directed Micro Catheter; Medronic, Minneapolis, USA) and a 0.007″ microwire (HYBRID WIRE; BALT, Montmorency, France), with or without the use of a 4 F guiding catheter (PERFORMA Vertebral; Merit Medical, South Jordan, USA). For trans-

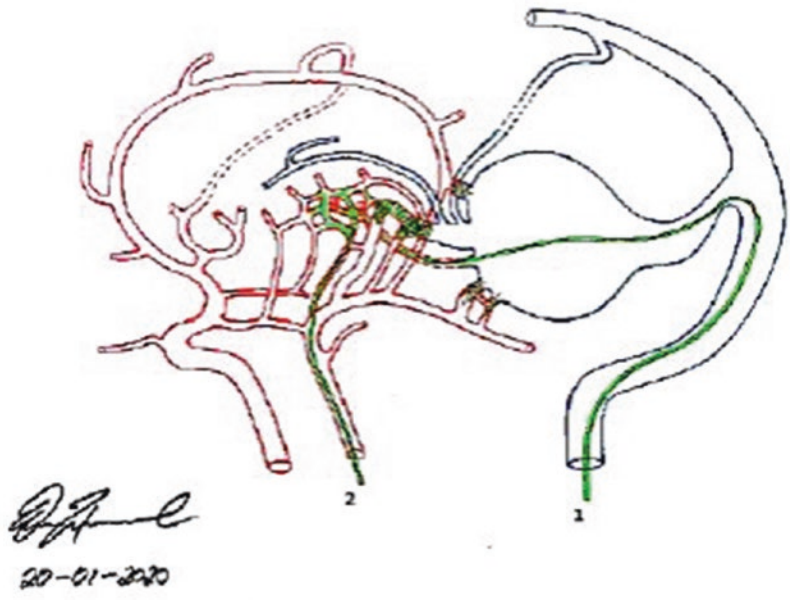

Fig. 23.6 Second step of endovascular therapy: Occlusion of the initially occult small plexiform arteriovenous fistulae (choroido-thalamic collateral network) with the goal of neurological stabilization (see also Figs. 23.3, 23.4, and 23.5). Note 1: Combined transvenous (1) and transarterial (2) occlusion of the small plexiform arteriovenous fistulae (choroido-thalamic collateral network) with kissing microcatheters (3) applying Onyx; Note 2: Because the small calibers of the collateral network adjacent to the in the first step of endovascular therapy occluded major arteriovenous fistulae cannot be catheterized superselectively, Onyx with low viscosities (4), displayed in green, is the embolic material of choice; Note 3: Via the transvenous route, Onyx encircles the microcatheter tip in the first step, and, secondarily, Onyx can be distributed in a retrograde fashion into the collateral network and its different arterial feeders; Note 4: Via the transarterial route, Onyx is distributed along the shortest route and along the largest pressure drop; and Note 5: After the second step of endovascular therapy, which can be performed as a repeat procedure and even in combination with embolization techniques, complete or almost complete VGAM occlusion can be achieved, resulting in normal or near-normal neurological development

venous catheterization, a 1.7 F microcatheter with two different radiopaque distal markers (Echelon: 10 Micro Catheter; Medtronic, Minneapolis, USA) and a 0.014″ microwire (Portal; Phenox, Bochum, Germany) are used. Diagnostic angiographies are performed with as few iodinated contrast material (240 mg iodine per mL) as possible injected via 1 mL standard syringes. Different embolic materials are applied for the ultra-selective embolization of the arteriovenous fistulae of the VGAM. For the embolization via the transarterial and transvenous route, coil systems such as a detachable 0.010″ microcoil (Electro Detach Coils; e.g., Ed Coil ES ExtraSoft or Ed Coil ∞ Soft; KANEKA, Osaka, Japan) or 0.0108–0.0115″ bare platinum coils (e.g., Axium Prime 3D Extra Soft and Axium Prime Helix Soft; Medtronic, Minneapolis, USA) are combined [37]. Onyx (Onyx 34, Onyx 20, or Onyx 18; Medtronic, Minneapolis, USA) is used via the transarterial and/or the transvenous route to optimize the occlusive effect of coils, which is essential in the setting of liver failure–induced coagulation disorder [43]. For follow-up diagnostic angiography, either a 2.7 F microcatheter (Progreat; Terumo, Tokyo, Japan) or a 4 F catheter (PERFORMA Vertebral; Merit Medical, South Jordan, USA) is used. The last remark in this paragraph is dedicated to the materials produced by other manufacturers, which could also be used for the endovascular therapy of VGAMs.

23.2.3.5 Radiation Exposure and Image Quality

Radiation exposure is a big issue in complex and repeat neurointerventional procedures, and especially if neonates, infants, and children need to be treated. Simulation and standardized training, prospective treatment plans, and high-end angiography units are mandatory to keep the radiation exposure as low as possible [37, 45, 48, 50, 51]. Pre-interventional and post-interventional Doppler ultrasound and high-resolution MRI imaging help to outline the treatment plan with the goal of optimal timing, reduced procedure times, and overall reduction of the number of endovascular therapies [40–43, 45, 48, 51]. A standard low-dose preset includes an individually collimated 22 cm field of view, 7.5 pulses/second during pulsed fluoroscopy and three images/second during digital subtraction angiography. In cooperation with the manufacturer, refined image acquisition and processing algorithms such as copper filtering (resulting in radiation hardening) and digital image filtering (resulting in noise filtering) are implemented in our two active biplane angiography units (Siemens Artis Q with PURE [and formerly Siemens Axiom Artis BA]; Siemens Healthineers, Erlangen, Germany). Currently, our setting allows a reduction of the radiation exposure of approximately 50% compared with usual angiography units. Besides that, it is evident that the thorough realization of all measures of radiation protection (e.g., ALARA principles and thyroid lead protection) reduce markedly the radiation exposure in both patients and operators [37].

23.2.3.6 Treatment Control and Aftercare

Elective and semi-elective endovascular therapies are followed by 1 day of routine monitoring in the intensive care unit. Routine discharge follows after clinical reassessment, EEG and transfontanellar Doppler ultrasound within another 10 days. Successful endovascular shunt reduction in VGAMs can be confirmed by normal or near-normal cranial Doppler RI signals [48]. Computed tomography (CT) or MRI imaging in the periprocedural period is necessary only in the case of complications or unexpected clinical events. As described earlier, repeat endovascular therapy is needed in the majority of patients, and it is performed after repeat ultrasound and MRI for dedicated treatment planning. For example, 2D time-of-flight MR venograms help to visualize the different changes of the venous drainage after endovascular therapy, which can impact on the embolization technique of a pending endovascular therapy [51]. The timing of re-referral and/or endovascular therapy depends on the severity of the illness, and it varies from repeat endovascular therapy within days or weeks in the emergency setting to staged endovascular therapy within months or even years in the elective setting. Six months after the last endovascular therapy with occlusion of the VGAM, follow-up MRI and diagnostic angiography are performed to verify complete occlusion of the VGAM. As part of the interdisciplinary and multimodal management, endovascular therapy is accompanied by regular clinical visits, EEG, and neurocognitive testing.

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Part VI

Cysts and Cyst-Like Lesions of the Pineal Region

24 Pineal Epidermoid and Dermoid Cysts of the Pineal Region

Najia El Abbadi and Fahd Derkaoui Hassani

24.1 Introduction

Epidermoid and dermoid cysts are rare and benign lesions with a slow development course. These cysts represent about 0.2–1% of intracranial lesions [1]. Their growth is known to be silent for many years. The pineal region is exceptionally subject to such kind of tumors. Epidermoid cyst represents 1.5–2.0% of the pineal region's tumors [2].

24.2 History

Cushing was the first to report the pineal localization of the epidermoid cyst in 1928 [3]. Subsequently, many authors reported on few cases of pineal epidermoid cysts [3]. Until 1974, nine cases were reported in the literature [4]. In 1999, 11 cases were analyzed by Mackay et al. [5]. Since this date, many other papers have been published dealing essentially with surgical treatment. Up to now, 92 cases of pineal epidermoid cyst were cited in the literature (Table 24.1).

Table 24.1 Reported cases on the literature of pineal epidermoid cysts since 1928

Author	Year	Number of cases
Cushing [3]	1928	1
Van Gehuchten et al. [3]	1940	1
Daum et al. [3]	1950	1
Fasiani et al. [3]	1955	1
Smaltino et al. [24]	1968	1
Schiavi et Gemolotto [25]	1968	1
Kirsch et Stears [26]	1970	1
Sambasivan et Nayar [4]	1974	1
McDonnel [27]	1977	1
Ventureyra et al. [28]	1981	1
Yamanouchi et al. [29]	1985	1
Braga et al. [30]	1987	1
Wang et al. [31]	1989	1
Maeda et al. [32]	1990	1
Kasai et al. [33]	1990	1
Kitchen et al. [23]	1992	1
Balderrama et al. [34]	1995	1
Kitayama et al. [35]	1996	1
Chandy et al. [19]	1998	11
Ziyal et al. [36]	1998	1
Mackay et al. [5]	1999	1
Konovalov et al. [15]	1999	6
Tosaka et al. [37]	2001	1
Koziarski et al. [38]	2003	1
Marwin et al. [39]	2003	1
Fischer et al. [40]	2004	1
Kurosaki et al. [41]	2005	1
Parwani et al. [42]	2005	3
Kumar et al. [43]	2006	2
Desai et al. [44]	2006	24

(continued)

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Table 24.1 (continued)

Author	Year	Number of cases
Pagni et al. [6]	2007	1
Roy et al. [45]	2008	1
Laleva et al. [16]	2009	4
Sajko et al. [46]	2009	1
Jimenez et al. [47]	2010	1
Meguro et al. [48]	2010	1
Jia et al. [21]	2011	2
Uschold et al. [49]	2011	1
Mao et al. [50]	2012	1
Senapati et al. [51]	2012	1
Oliveira et al. [52]	2013	1
Kontoangelos et al. [14]	2013	1
Walker et al. [53]	2014	1
Derkaoui et al. [54]	2014	1
Keraliya et al. [12]	2014	1
Toktas et al. [22]	2016	1
Jiang et al. [13]	2018	1

24.3 Pathology and Pathogenesis

24.3.1 Epidermoid Cyst

Epidermoid cysts arise from rests of ectodermal cells misplaced during the division of the neuroectodermal and cutaneous ectoderm during the third or fourth week of intrauterine development [5]. It is usually known to be a tumor with lateral development rather than a medial lesion as dermoid cyst.

Three main hypotheses can explain the occurrence of an epidermoid cyst [6]. The first one is about the aberrant closure of the dorsal neural tube, considered as the starter point of the development of the epidermoid cyst [7]. Ectopic ectodermal cells rests from the dorsal midline is the origin of the epithelial cells rests. The cutaneous lineage of the imprisoned ectoblast may be the growth origin of intracerebral epidermoid cyst in the late stage in embryogenesis after reaching the epidermal differentiation [7]. The second hypothesis is trauma and iatrogenic origin of the cyst [6]. The third one is the differentiation of multipotent residual cells. These cells will switch into squamous elements.

A pearly aspect characterizes the epidermoids. The histological examination describes a capsule of stratified squamous epithelium containing desquamated epithelial cells, keratin, and cholesterol [5].

24.3.2 Dermoid Cyst

Like for epidermoid cyst, the trapped ectoblast is the origin of the development of the dermoid cyst [7]. Arising between the third and fifth week of embryogenic life, the dermoid cyst is lined by stratified squamous epithelial cells [1]. The inner surface is covered by papillary projections to which the skin appendages may be restricted. The yellow color of the dermoid cyst is due to the presence of secretions of sebaceous glands and the desquamated epithelium mixed to the probable presence of hairs or teeth in addition to glands. The accumulation of products of gland's secretion, fat, oil, and desquamation of epithelial cells within their capsule is responsible for the dermoid cyst growth [1].

24.3.2.1 Natural History of Epidermoid and Dermoid Cysts

Epidermoid and dermoid cysts are known to be slow-growing tumors. Some complications related to these pathological entities could be seen during their natural evolution.

Malignant Transformation of Epidermoid Cyst

Malignant transformation of dermoid and epidermoid cysts is a very rare presentation. It is a well-documented situation where the cyst becomes a secondary cancer, such as squamous cell carcinoma [6]. Ernst was the first to describe this phenomenon in 1912 [8]. Garcia et al. [9] defined the malignant transformation to a primary squamous cell carcinoma as follows: "the tumor should be restricted to the intracranial intradural compartment without invasion of/or extension beyond the dura and cranial orifices, connection with the middle ear, air sinuses, or sella turcica, and with no evidence of a nasopharyngeal tumor" [8].

This transformation could be secondary to a previous surgical resection or can even be preex-

istent and discovered during the first surgical removal [6]. Kwon et al. reported literature review of 62 cases of primary intracranial squamous cell carcinoma, complicating an epidermoid cyst in 56 cases and dermoid cyst in only 4 cases [8]. Only two cases with pineal location were reported in the literature [2, 6]. A classification of the malignant transformation of intracranial epithelial cysts was established by Hamlat et al. [10], sharing this transformation into five types. The type 1 is initial malignant transformation of an epidermoid cyst. The type 2 corresponds to the malignant transformation from a remnant epidermoid cyst. The type 3 corresponds to malignant transformation from other benign cysts. The type 4 corresponds to malignant transformation with leptomeningeal carcinomatosis. The type 5 corresponds to other malignancies arising from benign cysts. Leptomeningeal carcinomatosis is related to a poor prognosis that can be improved by adding radiotherapy to removal surgery [10].

Rupture of Pineal Dermoid Cyst

Rupture of pineal dermoid cyst is a rare phenomenon [1]. It may occur on a subarachnoid space and in the ventricles. Rare cases were reported in the literature of a spontaneous rupture with a nonfatal outcome [1].

El-Bahy et al. have reported a literature review of 51 cases of ruptured dermoid cyst [1]. This rupture may be spontaneous, following a closed head injury, or dissemination of oily materials perioperatively. The physiopathology of this rupture can be explained by the fast enlargement of cyst during the hormonal changes, leading to the cyst rupture. Another explanation was given by Lunardi and Missori [11], supposing the hammer-like action secondary to brain pulsations and even the occurrence of rupture as a result of movements of head. All these triggers will cause fissure and leakage of the content of the cyst into the subarachnoid spaces or ventricles. As a consequence, the presence of fat in these spaces can cause many complications, such as aseptic meningitis, hydrocephalus, vasospasm, and cerebral ischemia [1].

24.4 Clinical Presentation

This condition can affect patients of all ages. Known to be a benign congenital cyst with a slow-growing potential, symptoms appear at 20–40 years of age [12]. The pineal location of these cysts can be responsible for a clinical presentation that is often characterized by headache, nausea, vomiting, and blurring of vision due to compression of aqueduct of Sylvius, resulting in obstructive hydrocephalus [12]. Clinical examination can reveal papilledema, diplopia, and Parinaud's syndrome due to the compression of the tectal plate. Hemiparesis and cerebellar signs can also be noticed [5]. Psychiatric symptoms such as schizophrenia [13] and depression [14] could be related also to a pineal epidermoid cyst, which suggest that brain imaging may be substantial in psychiatric symptoms.

24.5 Imaging

Epidermoid cyst is known to be often located in the cerebellopontine angle (CPA), whereas dermoid cyst prefers midline localization [15]. The pineal localization is a very rare presentation of these cysts.

24.5.1 Epidermoid Cyst

Intracranial epidermoid cysts can be developed in one of these three locations: cisternal, intracerebral, and intraventricular [7]. The most common locations of epidermoid cysts are the cerebellopontine angle (CPA) and Sylvian fissure [2]. Epidermoid cyst represents 7% of CPA tumors. Pineal epidermoid cyst is an exceptional location, which is developed in the quadrigeminal cistern in the pineal region. It represents 0.2–1% of all intracranial tumors [5, 16].

The computed tomography (CT) scan shows a cyst lesion. The density is similar to cerebrospinal fluid. Sometimes it is higher. We can appreciate a lesion of the quadrigeminal cistern, sometimes causing hydrocephalus without a con-

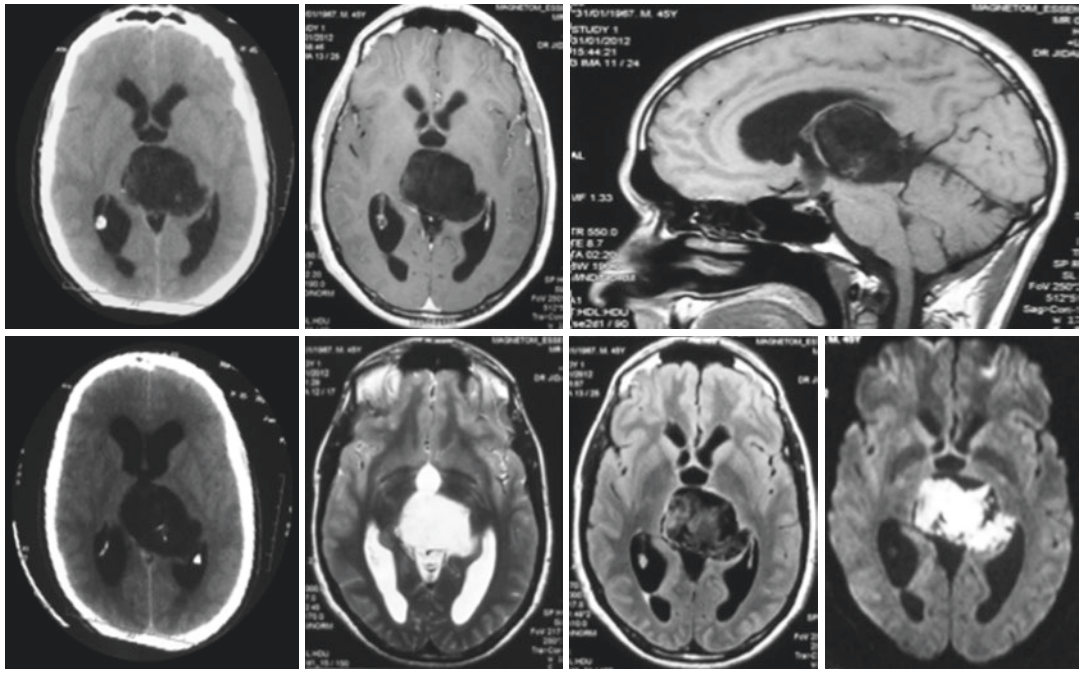

Fig. 24.1 Preoperative imaging of a pineal epidermoid cyst. A 45-year-old patient presented with a history of 18 months of headache and visual loss. The clinical examination revealed right hemiparesis and right facial hypoesthesia. CT scan showed hypodense lesion of the pineal region. On MRI, this lesion was hypointense T1-weighted with no contrast enhancement, hyperintense T2-weighted with bright on diffusion-weighted images

trast enhancement. A variable imaging appearance is due to the difference in cholesterol and protein content, and the presence of hemorrhage. On magnetic resonance imaging (MRI), epidermoid cyst is hypointense on T1-weighted images with no contrast enhancement and hyperintense lobulated on T2-weighted and fluid-attenuated inversion recovery (FLAIR)-weighted images [12, 15]. The diffusion-weighted images (DWIs) allow to make a difference between an epidermoid cyst and an arachnoid cyst [5]. Epidermoids are bright on DWI in comparison to other cystic lesions [17] (Fig. 24.1).

24.5.2 Dermoid Cyst

The presence of fat will influence the appearance of this cyst. On CT scan, dermoid cyst appears usually with an hypodensity located on midline. MRI will show an hyperintense lesion on T1-weighted images and a heterogenous signal on T2-weighted images [18].

24.6 Management

The main point of the surgical treatment is a radical excision of the epidermoid cyst with its capsule. However, it is a real challenge because of this localization. Some authors prefer to intentionally leave in situ fragments of the adherent capsule to the deep veins of this region to avoid any risk. Konovalov et al. [15] report that total removal was possible in only 50% of the presented cases of its series. Two approaches were described by Yasargil [15] in the surgical management of pineal epidermoids—the infratentorial supracerebellar approach and the occipital-transtentorial approach. The latter is preferred to directly attack the lesion with a significant supratentorial component [15, 19]. The

infratentorial approach allows to reach the tumor before the veins come into view [15]. Reid and Clark [20] preferred to use occipital transtentorial approach to deal with pineal region tumors. Other approaches are used, including the interhemispheric transcallosal approach [21], the transventricular approach [19], and the combined supra/infratentorial transsinus approach [5].

The ventriculoperitoneal shunt could be used in some cases of hydrocephalus with intracranial hypertension [19, 22]. A therapeutic stereotactic aspiration is also proposed for the treatment of epidermoid cyst. Kitchen et al. [23] reported one case with ventriculoperitoneal shunt and stereotactic aspiration. This technique remains with many disadvantages. First, the aspiration does not take off the capsule, which represents a high risk of recurrence, spontaneous rupture of the cyst, an aseptic meningitis, and malignant transformation of the epidermoid cyst. The direct surgical approach seems to be more helpful for these patients.

Mackay [5] analyzed 12 reported cases of pineal epidermoid cysts since 1968. The outcome was good in 10 of the 12 cases. Two cases had an aseptic meningitis. One death was recorded. The patient had presented a hemiparesis and cerebellar signs. He underwent a partial resection through an interhemispheric transcallosal approach for a large process of the pineal and thalamic region. He had only one ventriculoperitoneal shunt for hydrocephalus 6 months after the first surgery due to the progression of the lesion [5].

24.7 Conclusion

Pineal location of epidermoid and dermoid cysts is a very rare entity. Direct surgery with total removal is the ideal treatment. Even if it is not always possible because of the characteristics of these tumors and the pineal region, surgical removal remains the first choice. In addition to the surgical complications of pineal region approaches, some special complications should be underlined for these cysts, especially aseptic meningitis, malignant transformation, and rupture of the dermoid cyst.

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Pineal Cysts

25

Adrian Bălașa and Rareș Chinezu

25.1 Introduction

Pineal cysts (PCs) are better and more often detected with the evolution and wide expansion of magnetic resonance imaging (MRI) machines [1, 2]. Patients present with nonspecific symptoms, with a significant part of them being purely asymptomatic [1, 3]. The natural history of PCs is not yet fully understood, and controversies exist regarding the most appropriate management [1].

25.2 Prevalence and Incidence

The prevalence is between 1% and 4.8% in the general population [2]. Young adults and pediatric patients have the highest prevalence [2], with a pediatric peak incidence of PCs at 10–14 years of age [4], and afterwards prevalence decreasing with age [5]. Several studies have also shown that an overall female predominance exists in pediatric as well as in adult populations [2, 6, 7]. Probably, the rate of prevalence is much higher, as autopsy studies have shown the existence of PCs in 25–40% of all cases [8, 9].

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25.3 Imaging Aspects

Computed Tomography (CT): Some cases are discovered fortuitously with a CT scan, frequently performed for head trauma. On the CT imaging, PCs have a round-shaped aspect and hypodense contents [1]. In some of the cases (30%), hyperdense contents or walls, represented by either hemorrhagic contents or cystic calcifications, can be visible [1, 10].

MRI: MRI is the gold standard in the imaging of the pineal region [1], and even if there are inherent differences between examinations because of different machines, protocols, or modalities used [11], there are some imaging aspects that most of the PCs share. They are round or ovoid, smooth edged, and well-circumscribed lesions, which are better visible on sagittal scans, with contents of the cyst usually homogeneous and isointense to cerebrospinal fluid (CSF). PCs can present as irregular nodular enhancement on MRI images, which is secondary to surrounding venous structures, combined with a displaced pineal gland [1, 11, 12] (Fig. 25.1a, b).

The existence of internal septations may be difficult to assess on routine MRI studies [11], but when high-resolution studies are performed, such as three-dimensional (3D) fast imaging employing steady-state acquisition (FIESTA) or brain volume imaging (BRAVO), a large proportion of cysts can be found to have one or multiple internal septations [11, 13].

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Non-peripheral contrast enhancement of a PC is considered atypical and is correlated in one study with a 70% malignancy rate [14]. Unfortunately, there is no 100% clear way to differentiate pineal cysts from other malignancies that originate in this area, such as pineocytomas, pineoblastomas, germinomas, or mature teratomas [12].

25.4 Natural History

The natural history of PCs is still unknown, with literature data suggesting that around 80% are stable for at least 3 years after diagnosis and some even longer [1, 2, 15] (Fig. 25.2a, b). Some

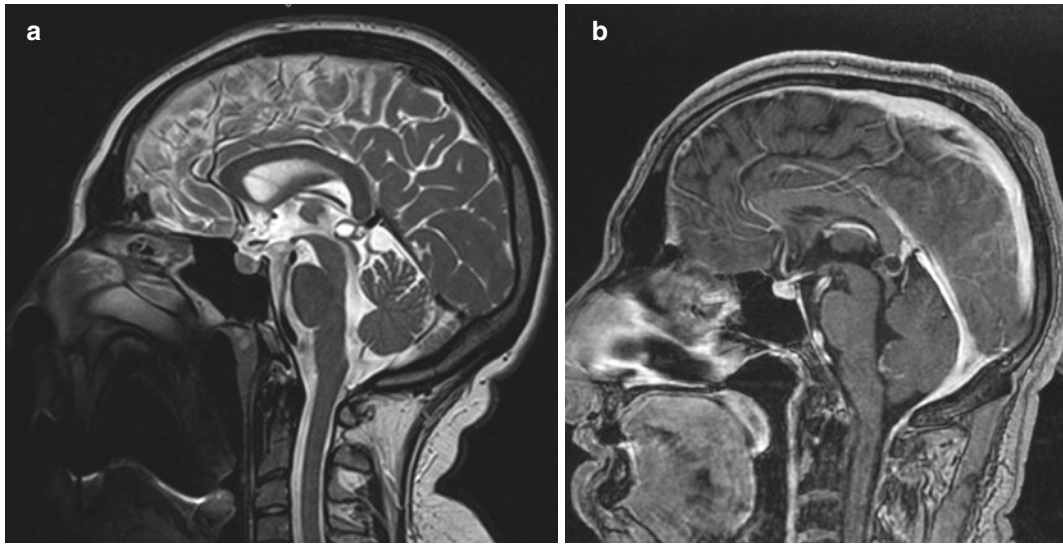

Fig. 25.1 (**a**, **b**) Sagittal T2 and T1+ contrast MRI sequences of a 23-year-old female performed for menses disturbance. Fortuitous discovery of a PC in an asymptomatic patient with no signs of hydrocephalus or visible postcontrast enhancement

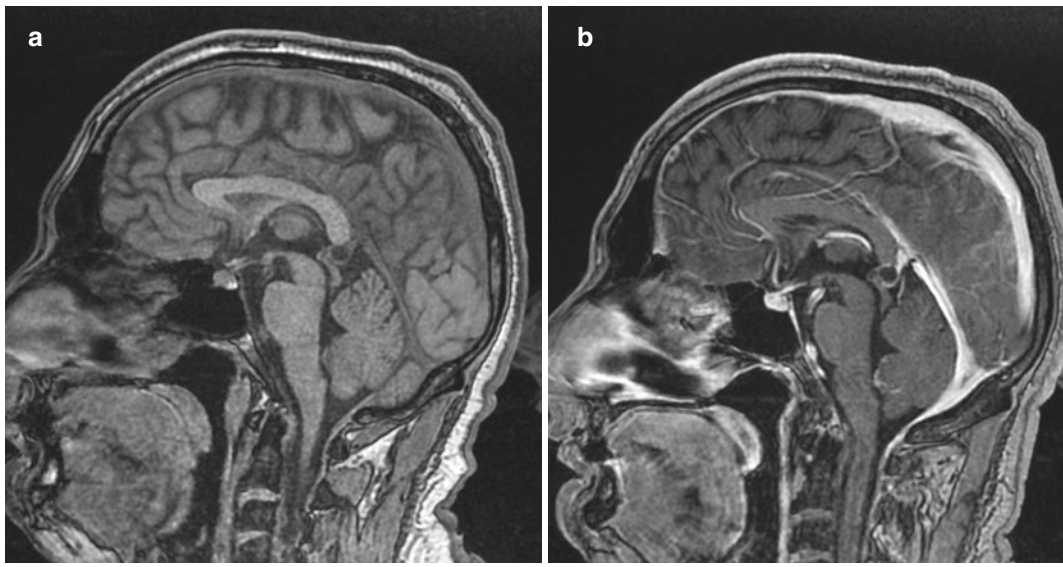

Fig. 25.2 (**a**, **b**) Sagittal T1 and T1+ contrast MRI sequences in a 30-year-old male with nonspecific headache. The cyst presents a peripheral contrast enhancement that is stable in size at 1-year follow-up (**b**).

cysts can even undergo a decrease in size, even to the point of complete involution [15]. A small proportion of pineal cysts can show an enlargement. The mechanisms behind this are poorly understood and are thought to be related to hemorrhage in the pineal cyst [16], the coalescence of smaller cysts [17], or hormonal influences, which can at least, in part, also justify the higher prevalence seen in females [5, 17, 18].

25.5 Clinical Features

The relation between size and symptoms: A few reports have tried to link the size of cysts to neurological signs and symptoms. Diameters larger than 1–1.5 cm appear to correlate more often with symptoms [8, 17, 19]. Nevertheless, other authors have described multiple cases of asymptomatic patients with cysts larger than 1 cm [2, 12, 15]. Up to this point, the size is not considered as a surgery indication in asymptomatic cases [1].

Nonspecific symptoms: Headache is a common symptom affecting half of the adult population [20], therefore it is not uncommon to have patients presenting both PCs and headaches. However, it is difficult to corelate one to each other in the absence of obstructive hydrocephalus [21]. There is data suggesting that melatonin dysfunction can be linked to headaches [22, 23] and it is important to look for other clinical symptoms related to melatonin secretion dysfunction, such as insomnia, delayed sleep phase syndrome, and desynchronosis in patients presenting with PCs [21].

Other non-specific symptoms that can be related to PCs are vertigo, nausea, fatigue, diplopia, tremor, seizures, and paresthesia [3], but thorough examinations should be performed before linking these symptoms to the presence of a PC (Fig. 25.3a, b).

Mass effect and typical neurological signs: Rarely, pineal cysts can grow large enough to cause compression on neighboring anatomical structures with associated typical textbook neurological signs: the quadrigeminal plate–oculomotor disturbances, Parinaud's syndrome, pupillary abnormalities, nystagmus retractorius, Sylvius aqueduct–obstructive triventricular hydrocephalus, Galen venous complex–intracranial hypertension, cerebellum–gait disturbances, ataxia, coordination anomalies, and the fornix–memory disturbances [1].

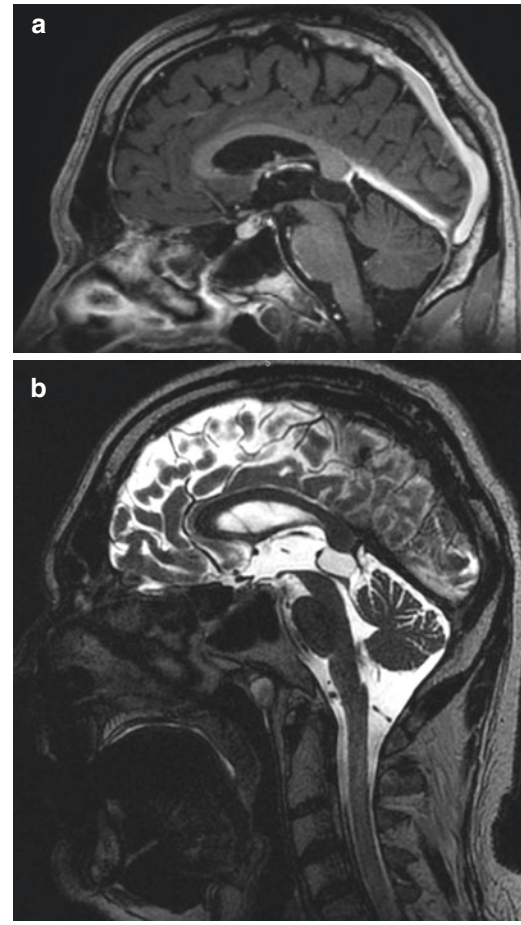

Fig. 25.3 (**a**, **b**) Sagittal T1+ contrast and T2 MRI sequences in a 54-year-old male who presented with morning generalized headache and diplopia. Imaging shows a PC with a diameter of about 2 cm, with the slight distortion of the Sylvius aqueduct. Nevertheless, a thorough neurological examination diagnosed the patient with myasthenia gravis with complete remission of symptoms following medical treatment.

25.6 Role of Surgery

Rationale for surgical treatment: The stable size of PC on long-term follow-up has convinced most authors to recommend that asymptomatic PC should not be surgically treated [1]. Surgery is recommended for symptomatic cases, presenting with clear neurological signs of compression and/or obstructive hydrocephalus [3].

Surgical treatment of cases with nontypical symptoms is controversial, with a recent study showing that venous congestion due to PC can lead to modified MRI biomarkers suggestive of a central venous hypertension syndrome [24]. The same authors report very good results, albeit in a small cohort, following PC removal in these nontypical symptom patients, but the exact mechanism by which these results are achieved is not clear [25].

25.6.1 Surgery Type

Microsurgery: Complete resection of the PC leads to far better results than just cyst fenestration [25]; this can be achieved either by supracerebellar infratentorial (SCIT) or by occipital transtentorial (OTT) approach. Unilateral SCIT in sitting position provides a natural corridor, and with surgical protection of the dominant transverse sinus and sparing of some cerebellar bridging veins, the risk of common complications such as diplopia and venous infarction of the cerebellum can be reduced [3]. The largest cohort for PC operated via sitting SCIT approach reported no postoperative complications [26]. OTT approaches the lesion from above, requires slight retraction on the occipital, and can lead to higher rates of postoperative complications, most common being transient hemianopsia, in 16.1–79% of cases [3] (Fig. 25.4a, b).

Shunting: In the absence of hydrocephalus, a recent study shows poor results with shunting, and the authors do not recommend the use of this surgical technique [25].

Other surgical techniques: Endoscopic fenestration or stereotaxic biopsy can only allow for cyst fenestration, and even if these procedures seem safe without significant complications, there are no clear reports of long-term results [3].

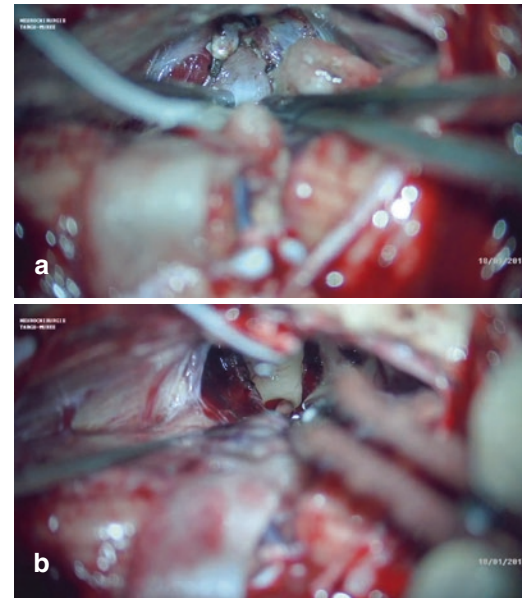

Fig. 25.4 (**a**) Intraoperative aspect showing the operating corridor via an SCIT approach and the thick whitish posterior wall of a pineal cyst. (**b**) Intraoperative aspect after complete removal of the cyst, with the opening of the third ventricle and visible Sylvius aqueduct

25.7 Conclusions

Pineal cysts are still a controversial pathology. Asymptomatic cysts should be monitored regardless of size. Complete resection of the lesions via supracerebellar infratentorial approach seems to provide the best results, even in cases with nonspecific symptoms, but due to limited data in the literature, surgical indications should still be limited and only placed after a thorough evaluation.

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Part VII

Miscellanea

Management Algorithm in Pineal Lesions

26

Claudiu Matei and Alin Borha

26.1 Introduction

The pineal region is, for the neurological surgeon, one of the most complex parts in the brain because of several reasons: it has deep intracranial location, it contains essential venous structures, and the pineal gland is a circumventricular organ; without blood-brain barrier (hematogenous metastatic dissemination), the different cell types in the pineal region can give rise to a wide variety of tumor processes.

Pineal region tumors represent 2.5–8.5% of all pediatric intracranial tumors and 1% of all cerebral tumors in adults. In Asian adult population, the incidence is five times higher. Pineal tumors are classified as germinal tumors, primary specific pineal tumors, and nonspecific pineal tumors [1, 2]. Primary neuronal tumors, arising intrinsically within the pineal gland, are referred to as pineal parenchymal tumors (PPTs). The World Health Organization (WHO) Classification of Tumors of the Central Nervous System from 2016 categorizes PPT as pineocytomas (grade I), pineal parenchymal tumors of intermediate differentiation (PPTID, grade II or grade III), or pineoblastomas (grade IV) [3]. Germ cell tumors (GCTs) are divided into germinomatous germ cell tumors (GGCTs) and non-germinomatous germ cell tumors (NGGCTs) [4]. The latter include teratoma (mature and immature), embryonal carcinoma, endodermal sinus tumors, choriocarcinoma, and mixed tumors. (Table 26.1) [2]. A new and rare entity, pineal papillary (PTPR), was introduced into the WHO classification of central nervous system (CNS) tumors in 2007. The PTPR is a tumor derived from specialized ependymal cells of the subcommissural organ [3, 5].

Table 26.1 Pineal region lesions

Germ cell tumors (60–70%) (GCT)
– Germinoma,
– Embryonal carcinoma, endodermal sinus tumor,
– Choricarcinoma, mature teratoma, immature teratoma, and,
– Mixed tumor.
Pineal gland cell tumors (25%)
– Pynealocitoma,
– Parenchymal tumors of intermediate differentiation (PPTID),
– Pinealoblastoma.
Tumors of glial origin
– Astrocytoma, oligodendroglioma, ependymoma,
– Glial cyst (pineal cyst).
Tumors of arachnoidian origin
– Meningioma and arachnoidian cyst .
Metastases
– Pineal papillary tumors.
– Other tumors: Dermoid and epidermoids.
– Vascular lesions: Vein of Galen aneurysm, cavernoma, and arteriovenous malformation (AVM).

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26.2 Diagnosis of Pineal Lesions

Patients with pineal tumors need to have a rigorous workup in order to establish the best plan for management. This evaluation should include the following:

- **MRI of the head** (T1, T2, gadolinium images in axial, coronal, and sagittal planes, fluid-attenuated inversion recovery [FLAIR], diffusion-weighted MR imaging [DWI], and susceptibility weighted imaging (SWI)); a very detailed MRI examination is crucial in order to obtain the best pineal tumor evaluation; size of the lesion, borders, vascularity, homogeneity, invasion, relationships with surrounding neural and vascular structures, and gadolinium enhancement create a tumor pattern specific to certain lesions [4, 6]. Computer tomography (CT) of the head is recommended in cases with MRI contraindication.
- **MRI of the entire spinal axis**, for drop metastases evaluation.
- **Tumor markers** in serum and CSF.
  - Most of the tumors located in the pineal region are germ cell tumors (GCTs), comprising 50–75%, which could produce tumor markers, detectable in blood and CSF. Alpha-fetoprotein (AFP) and human chorionic gonadotropin (βhCG), lactate dehydrogenase and placental alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA), human placental lactogen, cytokeratin, octamer-binding transcription factor 4 (Oct-4), and c-kit (CD117) are specific proteins secreted by germ cell tumors. These markers are useful in the diagnosis, estimation of prognosis, evaluation of the responsiveness to treatment, monitoring, and detecting recurrences [7]. In routine practice, essential AFP, βhCG, and PLAP are usually used. In case of positive markers, an oncological treatment can be proposed without need of surgical biopsy [8].
- **Cytologic examination of the cerebrospinal fluid**
  - In the pineal tumors, the cerebrospinal fluid cytologic studies could detect malignant cells or elevated proteins. CSF cytology could be positive in the presence of malignant tumors that spread along the neuraxis (germinomas, pinealoblastoma, glioblastomas). The CSF cytology is positive, particularly in tumors located or spread in the ventricular system or subarachnoidian space. CSF cytology in brain tumors is a very debatable topic and has a sensitivity of 60% in detecting malignant cells [2, 9].
- **Pituitary function examination**: This is performed when concomitant sellar tumors are detected or endocrine abnormalities are suspected.
- **Ophthalmological examination**: Exam of visual fields in the context of concomitant sellar tumor [2].
- **Cerebral Angiography:**
- **Pathological diagnosis.**
  - The main diagnosis in neurooncology is pathological exam. To obtain tissue for diagnosis in pineal region tumors, surgeons could perform open surgery, stereotactical biopsy, endoscopic transventricular, computer-assisted cisternal endoscopic approach [1, 6].

26.3 Management of Pineal Tumors

The clinical presentation of pineal lesions is usually an intracranial hypertension syndrome, produced by an obstructive hydrocephalus (72–80%) and visual disturbances [8].

The first step in the management of the lesion is the treatment of the hydrocephalus, usually by third endoscopic ventriculostomy, or less usually by a ventriculoperitoneal shunt [10]. Some authors recommend surgical biopsy during the same procedure (third ventriculostomy), which would need a second endoscopic trajectory (excepting large lesions involving the anterior third of the third ventricle). In a second time, depending on the marker results and biopsy findings, the surgical approach of the tumor must be discussed (Fig. 26.1).

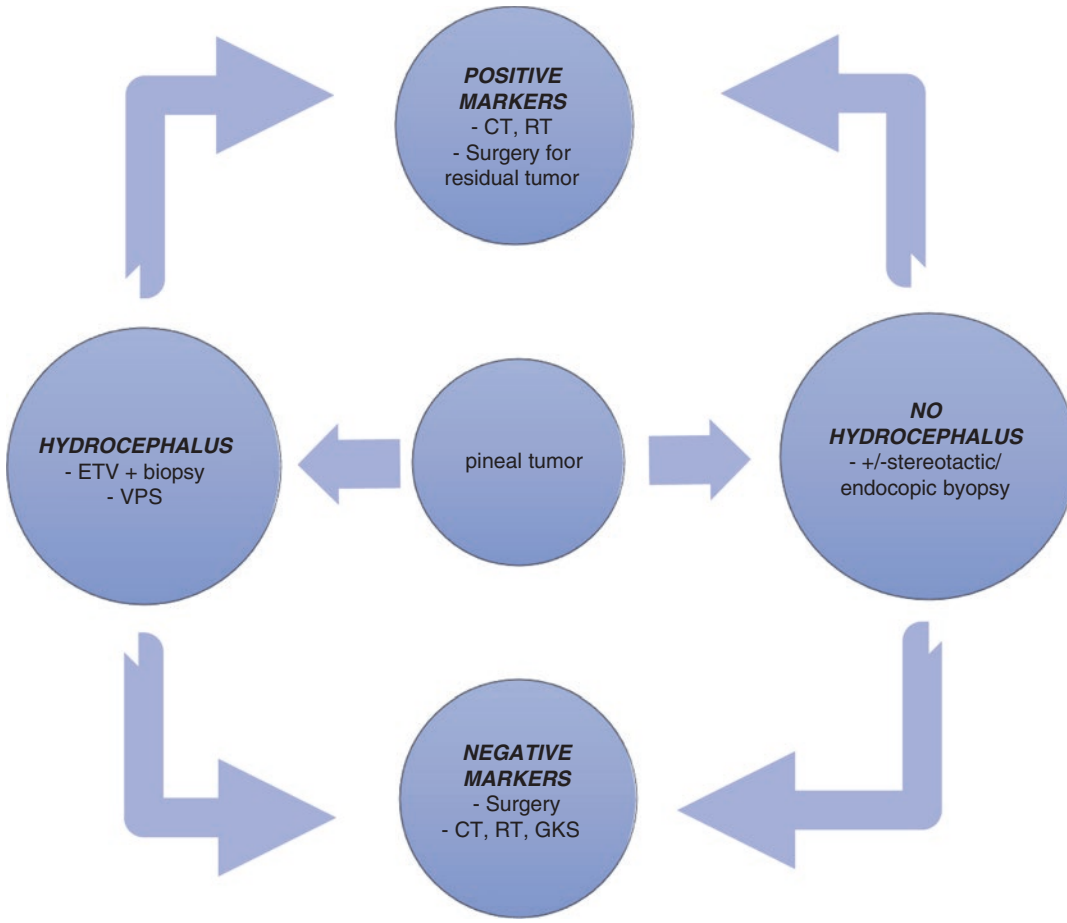

Fig. 26.1 A simplified management algorithm of pineal tumors (*ETV*, endoscopic third ventriculostomy; *VPS*, ventriculoperitoneal shunt; *CT*, chemotherapy; *RT*, radiation therapy; *GKS*, Gamma Knife surgery)

Making a biopsy from a pineal lesion is controversial and is also a matter of surgeon's experience. The biopsy has the advantage of obtaining a tissue confirmation; nowadays with the new stereotactic techniques, the morbidity is low, but the risk of false-negative results exists because of small specimens. Moreover, biopsied tissues generally do not reveal the heterogeneity of the tumor, and in many cases the correct pathological diagnosis could be missed. Nevertheless, the current consensus is to have tissue diagnosis [1, 6, 11, 12].

According to the current trends of key-hole endoscopic neurosurgery, the pineal tumor biopsy or even tumor removal could be performed by an endoscopic approach (computer-assisted cisternal endoscopic approach) through a classic third ventriculostomy or a supracerebellar infratentorial route. Endoscopic biopsy seems to be safer than stereotactic biopsy because it offers the possibility to visualize and to avoid the vascular elements.

There also exists a management algorithm developed by Japanese clinicians based on the radiotherapy response, due to the high incidence of radiosensitive pineal tumors in the Japanese population, which proposed a radiotherapy test without biopsy [6]. This is perhaps the most important controversy in the management of pineal lesions. In recent years, the trend has been to obtain confirmation tissue in all of the cases, due to advances in stereotactic techniques, microsurgery, and endoscopy, thus avoiding side effects of radiotherapy.

Positive tumor markers in serum and CSF: These are usually encountered in germ cell tumors, either in GCT (βhCG, PLAP) or in NGGCT, such as immature teratoma (AFP), choriocarcinoma (βhCG), and embryonal carcinoma (βhCG, AFP, CEA). There are controversies regarding patients with pineal masses and positive tumor markers; in these cases, histological confirmation is not necessary, according to many studies, because it is obvious that the patients have a malignant germ cell tumor, and the initial management consisted of neoadjuvant therapy [6, 7, 10]. In cases with residual tumor, after radiation therapy and/or chemotherapy, a mixed tumor is suspected, with benign components (e.g., mature teratoma), and surgical resection is the curative attempt [6, 10].

Germinomatous germ cell tumors, with negative tumor markers: After pathological confirmation, these could be cured by radiation therapy in more than 90% of the cases. In order to reduce the radiation dose, especially in younger children, the association of chemotherapy is recommended [6, 10].

Germinomatous germ cell tumors with positive tumor markers: These tumors tend to have a worse prognosis than those with negative tumor markers. Germinomas are highly radiosensitive tumors and a single dose of 1600 cGy could eradicate the tumor. The irradiation doses for germinomas are usually 5000 cGy (range 3000–5500 cGy) [6, 13]. In order to increase local control rate, the field of radiation should include tumor site along with third and lateral ventricles, and sellar and pineal regions. The recurrences have been cited to be 10% for germinomas, and they would be due to inadequate irradiation field and mixed tumors. In the presence of documented craniospinal seeding, the need of the irradiation of the spine is obvious; therefore protocols that recommend "prophylactic" spinal irradiation exist. Tumor markers are discharged directly in the CSF, and their levels here are not correlated with serum levels in pineal germinomas [6, 7, 13]. Germinomas with syncytiotrophoblastic giant cells comprise 13% of all germinomas and are positive for βhCG; these tumors have a higher recurrence rate because of lower response to radiation therapy. Gamma Knife surgery (GKS) has some advantages: low morbidity, less hospitalization, single-fraction radiation, good local control of the disease, and immediate chemotherapy administration. GKS is a useful tool in radiosensitive pineal tumors and can be associated with chemotherapy and/or conventional wide-field radiation therapy [11].

In the cases **of mature teratoma,** surgical resection may be curative, and there is no need for further adjuvant therapy when the tumor is completely removed. The Brain Tumor Registry of Japan reported a median survival rate of 81% at 5 years [6]. The malignant transformation of teratoma is an entity that includes mixed tumors: teratoma with adenocarcinoma or sarcoma; these tumors have a worse prognosis despite the associated high chemotherapy and radiotherapy doses, with a survival rate of 18% at 5 years [14].

Immature teratoma: These are nongerminomatous GCT and contain elements from all three germ layers: ectoderm, mesoderm, and endoderm [2, 6]. Diagnosis is based on imaging, serum and CSF tumor markers, and pathological appearance. Management of children with immature teratoma includes surgery and chemotherapy; radiotherapy is part of the therapeutic armamentarium of children older than 3 years of age [15]. A case illustration is a newborn girl, admitted to the Department of Neurosurgery with an intracranial hypertension syndrome. The imaging studies showed a giant pineal tumor, with solid and cystic components, extended in the medial part of the right hemisphere, with a heterogeneous gadolinium enhancement. Serum AFP had very high levels. The patient underwent surgery, and we removed a giant well-defined tumor that included hair, bone, cartilage, and teeth; the tumor contained intratumoral hemorrhages and small cystic components. Pathological examination revealed immature teratoma. Postoperatively, the patient was treated with adjuvant chemotherapy [15]. The patient is now in very good condition, and serial follow-up MRI shows no tumor recurrence (Fig. 26.2).

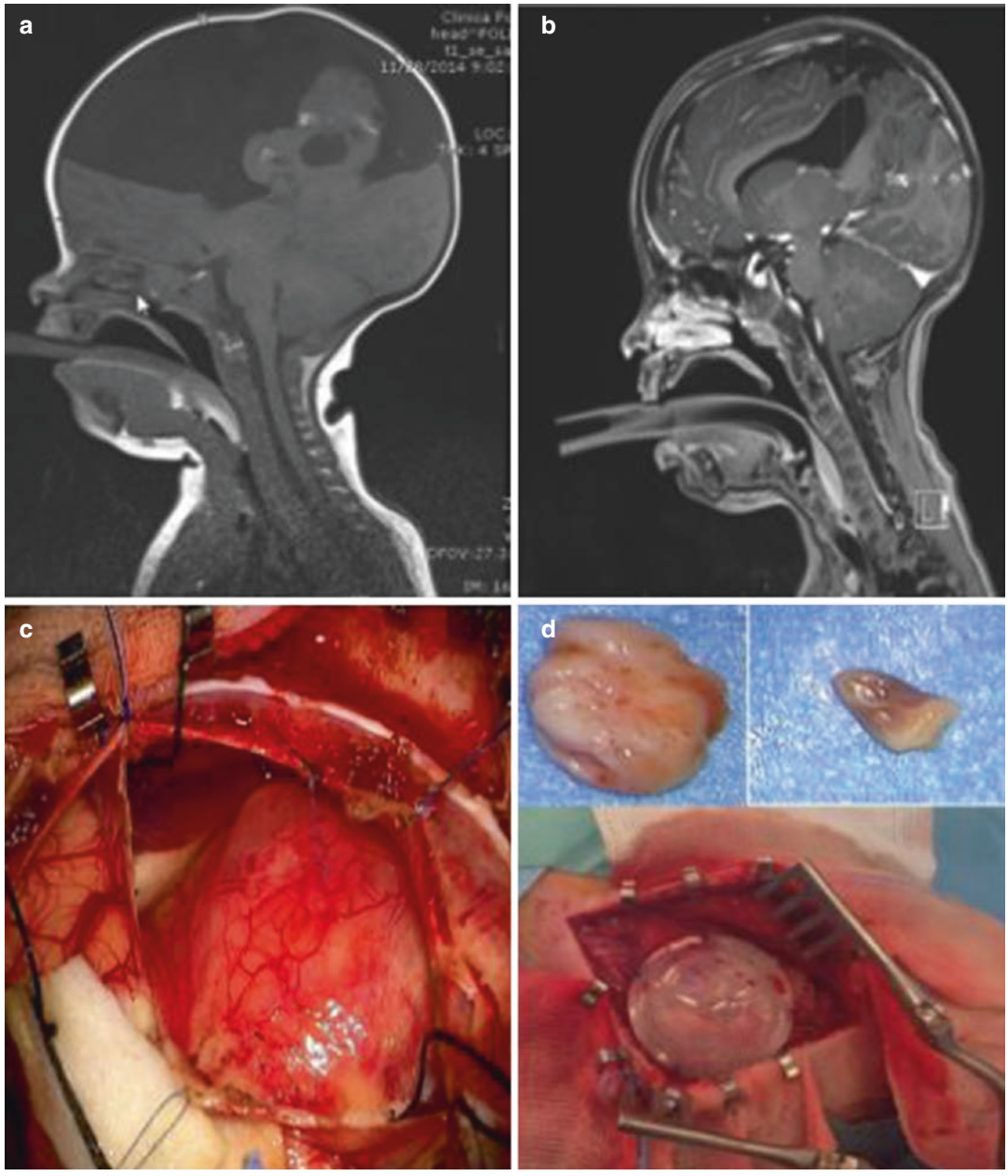

Fig. 26.2 Immature teratoma in a newborn. (**a**) Preoperative T1-weighted MRI with contrast, demonstrating a mass in the pineal region, extended into the medial aspect of the right hemisphere; (**b**) postoperative T1-weighted MRI with contrast, showing gross total resection of the tumor; (**c**) intraoperative aspect, through a right parieto-occipital transcystic approach; (**d**) intraoperative aspects and giant well-defined tumor that included hair, bone, cartilage, teeth; the tumor contained intratumoral hemorrhages and cystic components; postoperatively, we let in place an Ommaya reservoir useful to control intracranial pressure and to check CSF markers

Choriocarcinoma, embryonal carcinoma, and yolk sac tumor are non germinomatous germ cell tumors (NGGCT): More aggressive than GCT and, in many of the cases, are part of mixed tumors and tend to develop metastases along to spinal axis [6, 16]. Treatment usually is multimodal, consisting of surgery, adjuvant radiotherapy, or chemotherapy.

Primary pineal neuronal tumors: These arising intrinsically within the pineal gland are referred to as pineal parenchymal tumors (PPTs). The treatment of these tumors consists in safe resection, after the eventual treatment of the hydrocephalus, as a first step. The World Health Organization (WHO) Classification of Tumors of the Central Nervous System categorizes PPT as pineocytomas (grade I), pineal parenchymal tumors of intermediate differentiation (PPTID, grade II or grade III), or pineoblastomas (grade IV) [3]. Despite their common origin and the importance of surgical resection, the epidemiology and treatment of PPTs are diverse. Classically, pineoblastomas are found in pediatric patients, whereas pineocytomas and PPTIDs typically occur later in life. Pineocytomas have a favorable prognosis, with 5-year survival approaching 90% following gross total resection (GTR) [3, 6, 13].

Pineoblastomas: These have a high rate of recurrence and a propensity for neuraxial spread, and they are often managed with adjuvant craniospinal irradiation (CSI) and multiagent chemotherapy. Maximal safe surgical resection followed by craniospinal irradiation (CSI) and chemotherapy are used as standard therapy for older children with progression-free survival (PFS) rates of 60–70% for nonmetastatic patients. The prognosis of young patients with pineoblastoma treated with "infant-type chemotherapy" without radiotherapy is very poor. Mynarek analyzed the data of 135 children with pinealoblastoma: favorable prognostic factors were age ≥ 4 years and administration of radiotherapy. Metastatic disease, but not postoperative residual tumor, was associated with unfavorable prognosis. In 57 patients <4 years old, 5-year PFS/overall survival (OS) rates were 11% and 12%, respectively; in 78 patients aged ≥4 years, PFS/OS were 72% and 73%, respectively, for patients without metastases, and 50% and 55%, respectively, with metastases [3].

Papillary tumors: The pineal papillary tumors are a rare entity thought to arise from the specialized ependymal cells of the subcommissural organ, which is supported by the tumor's location, immunohistochemical staining profile, and ultrastructural features. Histologically, PTPRs are characterized by certain shared features, including loose papillary and dense cellular areas exhibiting pseudorosettes, true rosettes, variable necrosis, and sometimes vacuolated cytoplasm. They need maximal safe resection as initial step in management [5].

In the 31 cases reported by Fèvre-Montange et al. [5], 7 gross-total resections were achieved in 21, and 15 patients received radiotherapy after resection of the primary tumor. These authors reported estimates for 5-year overall survival and progression-free survival as 73% and 27%, respectively. Several studies have reported differing combinations of surgery, chemotherapy, and radiation; radiotherapy is often necessary due to the high risk of local recurrence [5].

Astrocytoma: Astrocytomas of the pineal region are usually low-grade lesions, developed from astrocytic elements of the pineal gland, quadrigeminal plate, or from posterior thalamus. An alternative is ventricular diversion associated with open surgery with tumor removal, stereotactic biopsy and radiation therapy, clinical and imaging observation (progressive disease only in 25% of the cases), and radiosurgery [6].

Pineal cyst: Pineal cysts are benign lesions with a prevalence of 1–10% [17]. The pathogenesis is not clear; one hypothesis is that they might be tumor-like cystic lesions surrounded by normal pineal tissue or glial tissue.

The gold standard diagnosis is MRI. Usually on MRI the normal pineal gland has the aspect of a solid nodule of tissue in only about 52% of cases, and its appearance can be more crescent-like (26%) or ring-like (22%), a change believed to be a cystic transformation with no pathological significance, provided its largest diameter is less than or equal to 5 mm (Lacroix 2011) [1, 17, 18].

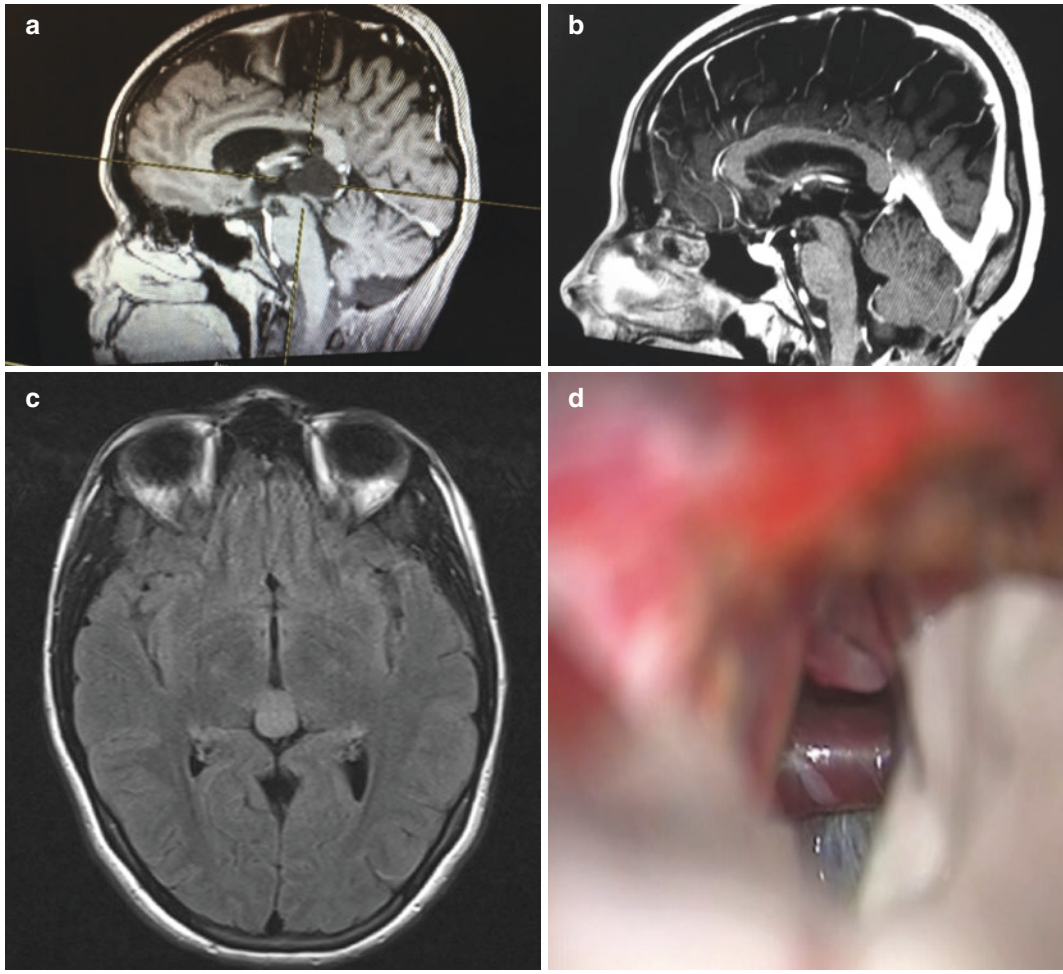

Fig. 26.3 Pineal cyst. (**a**) preoperative T1-weighted MRI, postcontrast sagittal view, reveals a pineal cyst; (**b**) postoperative T1-weighted MRI, postcontrast sagittal view, shows resolution of the cyst; (**c**) preoperative FLAIR MRI imaging sequence, showing a pineal cyst managed by marsupialization, using an interhemispheric approach; and (**d**) intraoperative view

Cysts have usually the same signal in T1 (or slightly elevated), T2 sequences as CSF, and are hyperintense on FLAIR sequences; also there can be a small wall enhancement on the delayed MRI contrast injection (Fig. 26.3).

Clinical pictures of pineal cysts fall into two categories, with and without hydrocephalus. Symptoms in cases with hydrocephalus are usually intracranial hypertension and visual disturbances. In cases without ventriculomegaly or hydrocephalus, symptoms are nonspecific, including headache, nausea and vomiting, dizziness, visual disturbances, and sleep disturbances. Usually cysts with a diameter superior to 1 cm are usually considered to be in relation with the symptomatology [12, 19].

In one of the largest series of pineal cysts without hydrocephalus, in 110 patients, the most common symptoms were headaches (62.7%) or vertigo (14.6%). During the follow-up, 5% of cysts increased in size, 6% decreased, and the others remained stable during a mean 3.74 years follow-up. Nineteen percent of patients were operated with good clinical results [19, 20].

26.3.1 Controversial Issues

Management of pineal cyst remains controversial. The majority of authors agree that surgery is reserved to symptomatic pineal cysts. In cases associated with hydrocephalus, there is agreement to treat hydrocephalus first. Asymptomatic cysts need a clinical and radiological follow-up.

It is a debate to recommend surgery in cases with chronic headaches without any other neurological signs. After ruling out other causes, pineal cyst without hydrocephalus can be managed by surgery. Some authors consider that the size of the cyst needs to be taken into consideration, in order to propose a surgery. Literature describes open surgical approach by interhemispheric transtentorial approach, infratentorial supracerebellar approach, stereotactic or endoscopic approaches. Usually fenestration or marsupialization of the cyst can be enough, with good clinical results. Other authors recommend complete surgical resection.

From a pathological point of view, pineal cysts contain Rosenthal fibers and fibrillary astrocytes. Their immunohistochemical pattern includes glial fibrillary protein staining and protein S100 pattern. Typically, markers beta human chorionic gonadotropin (beta-hCG) and AFP are not positive in pineal cysts and are not routinely performed. However, in the opinion of some authors, melatonin can be elevated in pinealocytoma and can be a marker to distinguish pineal cysts from tumoral lesions [21].

26.4 Pineal Epidermoid Cyst

The epidermoid cyst is a rare lesion that derives from ectopic inclusion of epithelial cells during closure of the neural tube between the third and fifth week of fetal development. The pineal localization is a very rare form of this intracranial lesion representing 0.2–6% of all pineal tumors [5, 22]. Dermoid cysts are even more rare, being 10–20% as frequent as epidermoids in the intradural compartment [22, 23].

Cushing was the first to report the pineal localization of the epidermoid cyst in 1928. Most common symptoms are headaches and ataxia [22, 24]. Imaging diagnosis is usually made using MRI. T1-, T2-, and proton density–weighted MR imaging show an irregularly shaped lesion with slightly greater intensity than the CSF, with a marbled or irregular inner pattern on T1-weighted images, and no enhancement by contrast medium. Sequences such as fluid-attenuated inversion recovery (FLAIR) and steady-state free precession and diffusion-weighted MR imaging (DWI) provide high contrast and can distinguish between epidermoid tumors and CSF [5, 25, 26].

Epidermoid and dermoid cysts are known to be slow-growing tumors. Some rare complications related to these pathological entities such as rupture or malignant transformation could be seen during their natural evolution [23, 25].

Treatment in symptomatic cases is surgical, usually by a supracerebellar or interhemispheric transtentorial approach. The goal of surgery is a maximal safe total resection, the capsule of the lesion having important adherences could be preserved and left in place.

26.5 Vascular Lesions of the Pineal Region

Vascular pathology of the pineal region is represented by the vein of Galen aneurysmal malformation, arteriovenous malformation (AVM), and cavernomas. These lesions are rarely located in pineal region and represent a real challenge for diagnosis and treatment.

26.5.1 Vein of Galen Aneurysmal Malformation

Vein of Galen aneurysmal malformation (VGAM) is a rare congenital cerebrovascular disorder, with an incidence reported to 30% from all vascular malformations in the pediatric age population and 1% in the adults [27]. VGAM represents direct arteriovenous fistulas with aneurysmal dilatation of the vein of Galen. There are few classification systems (Litvak, Lasjaunias, Yasargil, Motazavi), all of which take into consideration arterial feed-

ers, number of arteriovenous fistulas, and clinical features (heart failure, hydrocephalus) [27, 28]. The clinical presentation depends on the patients' age: in neonates, congestive heart failure is the main clinical aspect; in infants, it is hydrocephalus and macrocephaly; and in older children and adults, developmental delay, hydrocephalus, or headaches [28].

The management algorithm includes endovascular treatment, radiosurgery, and surgery. The main treatment is transarterial embolization, but time of treatment and patient selection are important features. Except in the emergency situations, it is recommended to perform endovascular therapy after 5 months of age [1, 27, 28]. Transvenous embolization is advisable when the arterial route is not available or in cases with failures of the transarterial embolization. Surgery could play a role in selected patients, with residual feeders after endovascular embolization. Radiosurgery could be an option in selected cases, as complementary treatment after embolization. Associated hydrocephalus is resolved usually after embolization of the malformation; ETV is useful in some of the cases and for ventriculoperitoneal there is consensus, which entails the risk of bleeding, aggravation of venous congestion, and brain edema, producing white matter calcifications and subependymal atrophy [27].

26.5.2 Pineal Arteriovenous Malformation

It is important to differentiate pineal AVMs that drain into the great vein of Galen from the malformations of this vein [27, 29]. In pineal AVM, nidus may be located intra- or extra-axially, in cisterns (quadrigeminal or posterior callosal cistern) or velum interpositum. The feeders come from the vertebrobasilar system or tectal arteries, such as the meningohypophyseal trunk, or the pericallosal or posterior choroidal arteries and the drainage is in the straight sinus via enlarged tectal and superior cerebellar veins, or within the basal vein of Rosenthal and the vein of Galen [29, 30]. The most common presentation is acute with hemorrhagic stroke. Diagnostic studies include CT, MRI, and digital subtraction angiography (DSA).

The AVMs' management is multimodal, including surgery, stereotactic radiosurgery, and endovascular therapy. For AVMs, surgical resection remains the definitive treatment, which can immediately and permanently remove the malformation, reducing the future risk of bleeding. The most used approach is supracerebellar infratentorial, but the occipital or parietooccipital interhemispheric may also be considered for certain cases. Endovascular treatment is indicated as a curative attempt for small or inoperable AVMs; endovascular embolization can be used preoperatively in order to reduce intraoperative hemorrhage [29, 31]. Endovascular treatment may be followed in some cases by stereotactic radiosurgery. Stereotactic radiosurgery has the advantage of being easy to do and the disadvantage of having a long obliteration time (5–6 years), which predisposes the patient further to the risk of hemorrhage [27, 32].

26.5.3 Cavernomas

Cavernous malformations or cavernoma are angiographically occult vascular malformations, which may occur anywhere in the central nervous system. Cavernoma located in the pineal region is a rare disease, accounting for 1% of all cavernomas and pose imaging diagnostic problems sometimes [33].

Management is decided according to the clinical aspects. Asymptomatic lesions are treated conservatively, through clinical and imaging follow-up for 2–3 years to rule out subclinical bleedings; further imaging studies are performed, individualized for each case [1, 33]. For symptomatic cavernomas, surgery is the curative therapy. Radiosurgery is controversial, according to the vast majority of the studies.

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27 Conclusions

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1. Described since more than 2500 years ago, the pineal gland has drawn considerable interest, even its mystic aura being palpable in the present times. Despite this, only a century has passed since the first successful surgical procedure performed on a pineal region tumor.
2. Playing a complex and as-of-yet incompletely elucidated role, the pineal gland is encompassed by highly functional structures that define the pineal region as a whole, rendering access to the pathology in this area rather difficult.
3. Within a reduced volume, but at a crossroads of extremely important neurological circuits, lesions arising inside the pineal region generate an intricate clinical presentation, dominated by headache, visual and hearing deficits, seizures, as well as endocrine and psychiatric disturbances.
4. Most often presenting as neurosurgical emergencies, initial diagnosis is performed through a computed tomography (CT) scan. Magnetic resonance imaging (MRI) scans should complete imaging diagnosis, yet there are only suggestive signs for certain pathologies, none of which are pathognomonic.
5. The etiological diagnosis is recommended for pineal region tumors in order to establish proper therapeutic management and avoid any unnecessary surgical interventions. To that purpose, tumor markers should be routinely determined, especially from the cerebrospinal fluid (CSF), being aware that marker negativity does not exclude the presence of a certain lesion.
6. Therapy is most often a multidisciplinary effort, surgeons having the primordial role in treating hydrocephalus, decompressing the region, and establishing the pathological diagnosis. Benign lesions may also be cured through complete resection.
7. Up to now, endoscopic third ventriculostomy (ETV) represents the easiest, fastest, and most efficient way of resolving obstructive hydrocephalus, also offering the possibility of a biopsy for certain tumors. Ventriculoperitoneal shunt (VPS) is reserved only for persistent symptomatic hydrocephalus.
8. Two major surgical routes are currently in use for pineal region tumor resection: the supracerebellar infratentorial (SCIT) approach and the occipital transtentorial (OTT) approach. Selecting the optimal route depends not only on a well-defined series of imaging findings but also on the experience and preference of the surgeon.
9. It is generally accepted that the SCIT approach is performed easier with the patient in a semi-sitting position.

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10. Endoscopy-assisted techniques may facilitate surgical resection, regardless of the selected approach.
11. Since many of the pineal region tumors are radiosensitive, radiosurgery and other means of focal radiotherapy are an accepted treatment method that may even be curative.
12. Chemotherapy as adjuvant therapy plays a well-defined role in decreasing radiation dose (in germinomas) or when associated with surgery and radiotherapy (non-germinomatous tumors, pineal cell tumors, high-grade gliomas). The most commonly used chemotherapy regimens are combinations of platinum agents with etoposide and ifosfamide in germ cell tumors; temozolomide, platinum, and etoposide or vincristine combinations in pineal cell tumors, and temozolomide in glial cell tumors.
13. Germinomas should not be treated surgically since these lesions may disappear after radiotherapy, with or without adjuvant chemotherapy. The issue is when tumor markers are negative and therapy mandates a biopsy. With the exception of the mature teratoma, all other non-germinomatous tumors are treated by a multidisciplinary neurooncological team.
14. Excepting the pineocytoma, where complete surgical resection may be curative, all other pineal cell tumors demand a combination of surgery (survivability depending on the grade of resection), chemotherapy (less efficient than in germinomas), and radiotherapy.
15. Regarding gliomas, a proper surgical treatment could offer the cure for low-grade lesions, whereas it should offer an improvement of the quality of life and, in the near future, conditions for a personalized adjuvant therapy for malignant tumors.
16. Meningiomas of the falcotentorial region are extremely rare, with complete surgical removal (preferably through a route dictated by the displacement of the venous complex) being the main goal. In the event that only subtotal resection can be achieved, both clinical and imaging follow-up and reintervention in significant recurrence are valid options; alternatively, radiosurgery for the remnant can also be taken into consideration.
17. A direct surgical approach of a small pineal region arteriovenous malformations (AVMs) is a valuable option in experienced hands, as is for symptomatic cavernous malformations (CMs) in this area. AVM radiosurgery is effective and often recommended as to avoid a high risk surgical intervention, whereas its effectiveness was not yet demonstrated for CMs, compared with the natural history. Endovascular embolization remains the only valid solution for vein of Galen aneurysms.
18. Cerebral metastases in the pineal region are extremely rare (estimated at 0.3% of all cerebral metastases) and should be treated in a multidisciplinary team of neurosurgeons, radiotherapists, and oncologists.
19. Epidermoid and dermoid cysts are a rare occurrence in this region, surgical evacuation being the mainstay form of treatment. As is the case for posterior fossa dermoids and epidermoids, complete resection of the capsule is limited by the adherences with the venous structures, in which case it should not be attempted.
20. The pineal gland cyst has an uncertain etiology, an unpredictable natural course, and an unspecific clinical presentation. As such, it is often difficult to establish a proper management strategy, clinical and imaging observation being the recommended solution. The persistence of symptoms tied to the pineal region may sometimes justify surgery, the SCIT approach having the most favorable results.
21. Given the anatomical and functional complexity of this region, the scarcity of pathologies in the general and neurosurgical practices alike, and the difficulty of surgical approaches, pineal region lesions should be treated in centers with sufficient experience.