Advances and Technical Standards in Neurosurgery 46
Series Editor: Concezio Di Rocco

Concezio Di Rocco *Editor*

Advances and Technical Standards in Neurosurgery

Volume 46

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This series, which has earned a reputation over the years and is considered a classic in the neurosurgical field, is now relaunched under the editorship of Professor Di Rocco, which relies on the collaboration of a renewed editorial board.

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Concezio Di Rocco
Editor

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Preface to the Series

Advances and Technical Standards in Neurosurgery (ATSN) represents the successful achievement of the wish of Jean Brihaye, Bernard Pertuised, Fritz Loew and Hugo Krayenbuhl to provide European neurosurgeons in training with a high level publication to accompany the teaching provided by the European postgraduate course. The project was conceived during the joint meeting of the German and Italian Neurosurgical Societies in Taormina in 1972, and the first volume was published in 1974. The English language was chosen to facilitate the international exchange of information and the circulation of scientific progress. Since then, the ATSN has hosted chapters by eminent European neurosurgeons and has become one of the most renowned educational tools on the continent for both young and experienced neurosurgeons. The successive editorial boards have maintained the ATSN's high scientific quality and ensured a good balance between contributions dealing with advances in neuroscience over the years and detailed descriptions of surgical techniques, as well as analyses of clinical experiences. Additional appeal has been added by the freedom granted by the Editor and Publisher in the length, style and organisation of the published chapters.

The current series aims to preserve the original spirit of the publication and its high-level didactic function, but intends to present itself not only as a historic European publication, but as a truly international forum for the most advanced clinical research and modern operating standards.

Hannover, Germany — Concezio Di Rocco

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Chapter 1
The World Health Organization Classification of Tumors of the Central Nervous System, Fifth Edition, 2021: A Critical Analysis

Douglas C. Miller

1.1 Introduction: Historical Perspectives

Since about the year 2000, the date of publication of the third edition of the World Health Organization (WHO) classification of primary central nervous system (CNS) tumors [1], the WHO classification has been regarded by the broad community of physicians, scientists, and others dealing with clinical or biological aspects of such tumors as a standard taxonomic framework. The book was produced by a WHO committee and issued through the International Agency for Research on Cancer (IARC). This acceptance of a common classification (pending episodic revision) facilitated further research, whether basic science, translational science, or clinical research, and allowed members of diverse medical specialties (neurosurgery, neurology, medical oncology, neuro-oncology, surgical pathology, neuropathology, radiology, neuroradiology, radiation oncology, and neuropsychology) to have a common language when discussing care of individual patients, constructing and running clinical trials, and seeking to improve care for patients with such tumors. This created a sense that the so-called blue books represented an essential resource for all such interactions regarding research and clinical aspects of these tumors.

This acceptance of the WHO classification was a significant change from prior years. To understand this, and then to understand how major changes in the WHO classification in the fourth edition [2], its revision [3] and now fifth editions [4] have impacted all of these fields, some background is necessary.

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It is generally accepted that the understanding of the nature of primary CNS tumors evolved as the specialty of surgical pathology matured in the latter years of the nineteenth century and the early years of the twentieth century. It is generally accepted that the ancestor of all modern classifications of these tumors was that published by Percival Bailey and Harvey Cushing, writing based on their experience with over 400 "gliomas" seen by them, and particularly by Cushing, at the Peter Bent Brigham Hospital and Harvard Medical School [5]. Their expressed aims were to produce a rational classification scheme to be used by surgical pathologists to classify CNS tumors, and thus to enable reliable prognostication for individual patients based on the types of tumors the patients were found to have when removed and examined pathologically. The idea was hardly original as prognostication based on pathological examination of other tumor types was already being done, but apparently Bailey and Cushing's work was the first to apply this framework to CNS tumors. By suggesting that individual tumor types reflected the normal brain cell types that had become transformed to neoplastic types, and basing their "catalogue" of normal cell types on the great body of work of Ramon y Cajal and his pupils of the "Spanish School of Neurohistology," they produced an organizing framework that dominated all subsequent classifications of CNS tumors and that continues to have influence even now with the fifth edition of the WHO classification.

Following the publication of the Bailey and Cushing work in book form (parts had been published earlier in journals, but as they stated themselves in the book, those parts were only a small portion of the total classification), various pathologists undertook additional studies of CNS tumor pathology and prognosis, using the best available methods of their times. Prior to the 1970s this meant, mostly, paraffin sections stained with hematoxylin and eosin (H&E), with other histochemical stains, and, importantly an array of metallic impregnations (gold sublimate, silver carbonate, various other silver methods, etc.) that were thought to provide specificity for particular CNS cell types, normal and neoplastic. These studies were largely carried out with sets of cases accumulated at single institutions. An exemplar of such studies were those coming from the Mayo Clinic, principally authored by James Kernohan. As the concept of relating prognosis to a system of histological grading of tumors had been originated at Mayo for other tumor types, Kernohan borrowed the idea and developed a grading system for gliomas, keeping (more or less) the individual tumor types proposed and described by Bailey and Cushing but applying grading criteria tied to ultimate clinical outcomes. This work was published at least in part in several journal articles prior to World War II, but saw far greater dissemination postwar in the first CNS tumor classification published as one of the "fascicles" put out by the Armed Forces Institute of Pathology (AFIP) [6].

At least in the USA, the AFIP fascicles were all highly influential, and Kernohan grading became widely accepted and almost universally applied by US pathologists and neuropathologists for diagnosis of CNS tumors. The notion was not as accepted in Europe; prewar and during the war's early years, the noted Belgian neuropathologist HJ Scherer, describing the pathological appearances of gliomas, was highly critical of the concept of grading a glioma from examination of only that portion of

the entire tumor that had been amenable to surgical resection [7], and Ringertz, while accepting the concept of grading, found that data from his cases fit into three grades, not the four suggested by Kernohan [8].

Other views were expressed in journals and books by many neuropathologists in the years after WW II up through the 1970s. One of the most influential of these was the text authored by Dorothy Russell and Lucien Rubinstein, which had perspectives from both the USA and the UK, and which went through several editions written solely by those two, and later (fifth edition) Rubinstein alone after Russell's death before evolving into a multiauthor, multi-editor text after Rubinstein also died [9–13]. For a time the views of these two had no significant rival, and Rubinstein was the author of the AFIP fascicle on CNS tumors that was the successor to Kernohan's [14]. The first of the WHO books on this topic, published in 1970 [15], had almost no text (just tables and illustrations) and had virtually no audience in the USA, and thus was no rival to the AFIP fascicle or the Russell and Rubinstein text. (It did have a blue cover, like all subsequent editions.)

This changed with the publication of a text on the surgical pathology of CNS tumors by two neuropathologists from Duke University Medical Center, Stephen Vogel and Peter Burger [16]. Theirs was an eminently readable, indeed often witty (for a medical text) book, covering all of the disorders which might be encountered as surgical samples from the nervous system, and which took fresh approaches within the broad framework of histogenetic classification as laid down by Bailey and Cushing. One major shift was that these authors went away from numerical grading of gliomas in favor of descriptive terms, hence "astrocytoma," "anaplastic astrocytoma," and "glioblastoma," and in so doing explicitly adopted a modified version of the three-grade system proposed by Ringertz and not the four-grade one described by Kernohan. While not pertinent to the intent of this chapter, it is worth recognizing that the influence of this book was such that as physicians and scientists working on neuro-oncological problems began to realize the importance of pooled data, forming the first multi-institutional cooperative groups, for gliomas the three-grade system was adopted as standard.

Up to the time of the publication of the first edition of Burger and Vogel's book, all of these books and the journal articles which preceded them in most instances were written solely by neuropathologists, and the primary audience was composed of pathologists. Others, notably neurosurgeons and various types of oncologists, needed to know what a diagnosis meant, to guide subsequent treatment and to inform patients of their prognosis, but the focus was on the pathological descriptions and how they then fit a classification scheme. Also, right up until the publications of the Rubinstein AFIP fascicle, the Burger and Vogel text, and a second edition of the WHO classification [17], the main means of examination described was H&E histology of paraffin sections, with a few histochemical stains. Metallic impregnations had largely fallen out of favor (often they were too difficult and too capricious) with the exception of those silver stains used for diagnosis of neurodegenerative disorders such as Alzheimer's disease, obviously not a topic of books about CNS tumors. The illustrations in these texts, therefore, were mostly half-tone photomicrographs. In the 1970s, one began to see a few color illustrations for

immunohistochemical stains (hereafter, for brevity, just "immunostains"), notably for glial fibrillary acidic protein (GFAP).

The introduction of an ever-growing library of commercially available antibodies for use in immunostains transformed the practice of diagnostic pathology and in particular neuropathology in the late 1970s and 1980s, and texts concerning classification of CNS tumors were thus increasingly turning to color illustrations of many immunostains in those years. (Producing useful half-tone photomicrographs of immunostains proved to be a difficult, often impossible task.) Thus, the first edition of Burger and Vogel's book lacked any index reference to GFAP, but the second edition, published in 1982 [18], had eight lines for that entry in its index (but no color illustrations). In 1982 the AFIP published a thin supplement to the Rubinstein-authored Second Series fascicle, including two pages of color plates illustrating GFAP immunostains in various entities [19]. (To those of us actively practicing diagnostic neuropathology then, this seemed to be behind the times.) Subsequent editions of the Russell and Rubinstein text (as a multiauthor, multi-editor book), of the Burger and Vogel book (with the addition of Bernd Scheithauer as a third author, and more voluminous but less readable text), and other texts all were increasingly replete with color illustrations chiefly for these many different immunostains against an ever-increasing range of antigens.

This change in how pathologists practiced was a great boon to diagnosis, allowing for more certainty in many cases in assigning cellular differentiation and thus presumed "lineage," for example. The once-controversial entity of primary CNS lymphoma, referred to in different authors' hands as "microglioma," "reticulum cell sarcoma," or "lymphoma," was firmly established as almost always a B-cell non-Hodgkin lymphoma by immunostains (for a review see Hochberg and Miller 1987 [20]). This created a conundrum for the WHO, however. Unlike the AFIP, or texts by individuals at major academic medical centers, the WHO had an explicit mission to publish information of benefit to physicians and their patients throughout the world, including those in nations without the sophisticated infrastructure to purchase reagents for, and produce, immunostains. Therefore, the second edition of the classification [17], while illustrating some GFAP immunostains, refrained from suggesting that immunostains were necessary to pathologically diagnose any CNS tumor as one of the entities listed in the classification. This was an editorial, and perhaps political decision, and not a scientific one.

The third edition of the classification [1] was informed by a considerable change in this policy suggested by a book [21] that was issued by the IARC press without the imprimatur of the WHO classification (although with WHO support) in 1997. This was pulled together by Paul Kleihues, a neuropathologist who became something of a godfather of IARC publishing for a time, together with Webster Cavenee, a physician-scientist whose career was devoted to unraveling molecular genetic alterations in tumors. This book, with its title incorporating "Pathology & Genetics," explicitly discussed the molecular genetic and chromosomal alterations then known to be associated with certain types of CNS tumors in the general framework (including the cover designs) of a histogenetic classification of those tumors. This relatively slim volume was packed with color illustrations of photomicrographs, many

of them immunostains, as well as including neuroimaging (computed tomography (CT) and, mostly, magnetic resonance imaging (MRI)), and also contained a wealth of information about the genetic alterations pertinent to each diagnostic category.

As noted, this greatly influenced the WHO's third edition of a CNS tumor classification, so much so the books shared a cover design, a text layout, and a style. This third edition classification blue book was essentially an update of Kleihues and Cavenee 1997, albeit now explicitly the official WHO classification volume, third edition. While providing updated and additional molecular genetic information about many if not most of the tumor types, it still was a pathology text, written in large part for pathologists to use in classifying individual tumors from patients, and then to share the language of the diagnosis with the treating physicians. Importantly, it still based the classification strictly on histopathology: the molecular genetic data supplied were to enlarge knowledge about the tumors and about their possible pathogenesis, but were not endorsed as diagnostic criteria. This remained true in the fourth edition [2] published in 2007. Multiple texts about CNS tumors, including the last editions of Russell and Rubinstein, Burger, Scheithauer, and Vogel, one I wrote [22], and others all incorporated as much of the latest information available as of the time of writing as was possible, but did not make changes in classification based solely on molecular information. Thus, as just one example a text might assert that most oligodendrogliomas had co-deletion of chromosome arms 1-p and 19q (see below), but they did not require those chromosomal changes to make the diagnosis.

However, the 2016 revision of the fourth edition, which for complicated WHO bureaucratic reasons was not called a new, fifth, edition, was radically different. The point of this historical introduction is to deal with this drastic change in policy, as in the 2016 revision some molecular genetic or chromosomal changes became essential to diagnosis, and the former worry about the inability to obtain, in some countries or places, sophisticated testing (which now went far beyond immunostains to include molecular cytogenetics, DNA and RNA sequencing, detection and characterization of fusion genes, and detection of the presence or absence of epigenetic changes such as methylation of DNA or alterations of DNA-binding proteins (histones)) was now made an essential part of many diagnoses.

This built upon a mounting pile of evidence that clearly went back into the early years of the twenty-first century. The prognostic and predictive importance for patients with diffuse gliomas as to whether there was methylation of the MGMT gene's promoter region, the prognostic importance of the presence or absence of a mutation in the IDH1 or IDH2 genes in diffuse gliomas, and the predictive and prognostic value of the presence of co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), which had been learned in various steps through The Cancer Genome Atlas and other large-scale studies, was no longer left to supplement a pathology diagnosis; they were now mandated by the revised fourth edition classification to be part of that diagnosis. There were other similar changes; notably the creation of separate diagnostic categories of medulloblastomas based on the driver mutational pathways (sonic hedgehog, SHH; wingless, WNT; and types/groups 3 and 4), and the further splitting of the SHH group

into favorable and unfavorable groups based on the absence or presence of an associated mutation in a TP53 gene.

These and others were major steps, changing diagnostic practice at least as fundamentally as immunostains did two decades earlier. They forced neuropathologists to find ways, either in their own laboratories or by sending specimens to reference laboratories, to obtain the requisite molecular data for accurate and precise diagnosis. Not unimportantly, they forced clinicians to put up with delays in obtaining final diagnostic reports, often for several weeks, as the neuropathologists waited for the molecular data to add to the histological and immunostain data to determine an "integrated diagnosis." They forced diagnostic laboratories to find the financial resources to obtain the necessary assays, in-house or at reference laboratories.

In the USA there was an additional effect of this change. For many years there has been a federal anti-fraud statute, known for its author as the "Stark Law," which was focused on self-referrals in other medical specialties. For pathologists, the Stark Law forbids ordering (and billing for) special assays and stains except for diagnostic requirements. Prior to the 2016 publication of the revised fourth edition of the WHO blue book, I could not order 1p/19q co-deletion assays, MGMT promoter methylation assays, or IDH1/IDH2 mutation assays, as these were deemed to be "prognostic" or "predictive" but not "diagnostic." Once defined by the WHO as essential components of an "Integrated Diagnosis," I and other US pathologists can order those where relevant and appropriate without asking for a clinician to place the order with us.

As much as the 2016 revision of the fourth edition of the WHO Classification changed the landscape, the fifth edition published in 2021 did more. A greater number of molecular data points were now required, and knowledge of these led to a major alteration in the entire formulation of the classification, which begins to deviate from the basic concept of a histological histogenetic classification to one based more on molecular genetic data than on conventional pathology. In the remainder of this chapter I will further examine those changes. In view of the nature of this analysis, I am not illustrating the various tumor types' histopathological features, as those are readily available elsewhere (including in the WHO book) and are not really central to this analysis of the classification.

1.2 General Changes: Constructing a Classification

To begin, the committee that put together the fifth edition was influenced to have the CNS volume conform more to the style of other volumes (dealing with neoplasms of other body sites) in the fifth edition of WHO classifications. Some of the changes are semantic, but still important in the larger context of CNS tumor taxonomy. One result of this is that tumors are now regarded as falling into distinct "types," and are no longer regarded or referred to as "entities." Types can have subtypes. This is key, for example, for meningiomas; all meningiomas are now part of a single type, with subtypes based on histological or molecular characteristics. (The WHO has not

divided meningiomas into separate types based on genetic changes, but this might be coming in a sixth edition.) Certain "entities" in the former classifications have ceased to be recognized; this happened in the revised fourth edition to the term "primitive neuroectodermal tumor" (see later), and without an explicit statement, this has happened in the fifth edition to pediatric oligodendrogliomas. Similarly there are essentially no mixed gliomas, or "oligoastrocytomas" anymore (although perhaps there should be, as the reader can discover later in this chapter). Other tumor types have been substantially moved from one taxonomic category to another, or categories have been merged that were formerly separate. The WHO has also declared certain more newly described types of tumors as "provisional types," meaning that more data will need to be seen before these can be reliably included in the classification.

An expressed motivation for some of the changes in tumor taxonomy was to simplify; for example, the early pages cite the revised fourth edition classification of 2016 as having 15 diffuse astrocytoma entities with IDH mutations, and the new 2021 classification has only 3 "types." This is more than a little disingenuous, as there are still grades that subdivide types; the degree of simplification is somewhat overstated.

Another major change has to do with types of data, or methods used to obtain data. All readers of this analysis will be at least somewhat familiar with DNA sequencing, which used to be laborious, nucleotide by nucleotide, as devised by Sanger. Next-generation sequencing (NGS) is faster (on the whole) and can evaluate hundreds of targeted genes or even whole genomes (whole exome or whole genome options are available) than Sanger sequencing, which is important for speed of diagnosis. A major relatively new addition to the methodological armamentarium is use of methylation array classifiers. This involves mapping methylation patterns throughout the tumor genome and using one or another informatics pipeline to assign tumors to particular categories based on identical or similar methylation array patterns. A few tumor types in the 2021 classification are only identified with certainty if methylation array assays are done, and the technique is also proving powerful for subtyping medulloblastomas.

Less fundamentally, but still a change, is that grades (for those types of tumors that are graded) are no longer expressed in Roman numerals; to avoid confusion and to match up with the practice used throughout all other WHO classification books, grades are given as Arabic numerals. Pathologists are also urged to express grades as "CNS WHO Grade n" to make clear the grading system that is being used, since a clinician might not know that a given number might have different significance in a classification scheme preferred by some pathologist instead of the WHO scheme.

Here I will interject that we who practice in the broad field of neuro-oncology should be careful about our terminology as it matters more than just as a matter of semantics. I will illustrate this by an example from before these updated WHO classifications, going back to the third edition (2007). At one time, "glioblastomas" were diagnosed in diffuse astrocytomas with necrosis, and the presence of vascular hyperplasia ("endothelial proliferation," "microvascular proliferation") was allowed

for the diagnosis of "anaplastic astrocytoma." In at least two large cooperative group studies published between 1983 and 1985, each from a collaborative group combining data from multiple major academic medical centers, the median survival for patients with glioblastomas (then WHO Grade IV) defined as requiring necrosis was on the order of 8 to at most 10 months, following maximal safe surgical resection (based on data from CT images as the best then available) followed by radiation therapy to about 5–6 Gray, with or without adjunctive chemotherapy with CCNU (lomustine). The median survival for patients similarly treated but with anaplastic astrocytomas (WHO Grade III) with vascular hyperplasia was close to 22 months. The third edition of the WHO classification adopted a position long advocated by neuropathologists at the University of California San Francisco, using vascular hyperplasia as a surrogate for necrosis in biopsies having no necrosis but with microvascular proliferation. I have not seen a critical analysis of what this did to survival data, other than mine, but let us be clear: it moved from Grade III to Grade IV some number of tumors that were already known to be associated with longer survival (because they were in the group originally classified as anaplastic astrocytomas, without necrosis), thereby making the survival for the entire group with glioblastomas better; and, by subtracting out of the anaplastic astrocytoma group patients whose tumors had vascular hyperplasia, the survival of that group was also increased. Anyone comparing published survival statistics in similar cohorts with the diagnosis made by the 2007 criteria against those of the earlier cohorts would think the treatment for glioblastoma and anaplastic astrocytoma had marginally improved, but what actually happened was just a shift of some patients from one category to another based on a more or less arbitrary decision. One must be careful in all changes in a taxonomy not to be confounded by apparent changes in survival or response to therapy that are actually only a result of a change in taxonomic rules.

One final sort of general terminological change was introduced in this fifth edition. Formerly the abbreviation "NOS" (not otherwise specified) carried a certain ambiguity. The WHO committee has eliminated the ambiguity: NOS means that the assays necessary to more precisely type a tumor or confirm a diagnosis were not done (e.g., in former times, one could make a diagnosis of "oligodendroglioma, NOS" if one could not or would not get 1p/19q co-deletion testing). Now there is also "NEC," for "not elsewhere classified," which recognizes that on rare occasions a tumor will be as fully investigated for mutations, fusion genes, chromosomal alterations, and even by methylation array classifiers and is found not to fit properly into any of the described tumors in the new classification.

The following sections will deal with changes in the classification of individual groups of tumors, or types of tumors. It is not the aim of this chapter to recapitulate all the information contained in the rather large book that is the fifth edition of the WHO. Nor, in my judgment, is it useful to heavily illustrate the chapter with histopathology images, given that these are widely available (including in the WHO text itself) and the focus for the audience of this chapter is what is new in the classification, not the histopathology.

1.3 Gliomas

The former distinctions between diffuse gliomas and more circumscribed gliomas are kept in the fifth edition, but the latter are no longer referred to as "special types" as they were formerly. More fundamentally, the new taxonomy recognizes a division of gliomas into adult-type and pediatric-type tumors, based on the epidemiology of the particular types in question. It is explicit that some pediatric-type gliomas will be found in adults, particularly younger adults, and that some children, especially older children or adolescents, may be found to have adult-type gliomas. Thus, there are separate broad categories for adult-type diffuse gliomas, pediatric diffuse gliomas (further divided into low- and high-grade groups), and circumscribed astrocytic gliomas. This is the first of several fundamental and important changes in the organization of the taxonomy of gliomas.

1.3.1 Adult-Type Diffuse Gliomas

1.3.1.1 IDH-Mutant Diffuse Gliomas

In the revised fourth edition, it was clear that tumors classified based largely on histopathological grounds as glioblastoma fell into two major groups, those with and those without mutations in IDH1 or, less commonly, IDH2. Some of these data are as old as The Cancer Genome Atlas, from the early years of this century, and they raised the seemingly paradoxical situation in which a patient with a "glioblastoma" with an IDH mutation could be expected, on a statistical basis, to live longer than a patient with a histological "anaplastic astrocytoma" which was IDH wild type. The WHO committee resolved to fix this anomaly, and they did so in a rather radical way: the diagnosis of "glioblastoma" can now be applied only to diffuse astrocytic gliomas which are IDH wild type (and lack certain other distinctive mutations; see later). Thus, a histological grade 4 (Arabic number) astrocytoma with necrosis and vascular hyperplasia that has an IDH mutation is not a glioblastoma, and so these are now classified as "Astrocytoma, IDH-mutant, CNS-WHO grade 4." An IDH wild-type counterpart is to be signed out as "Glioblastoma, IDH-wildtype, CNS WHO grade 4."

Among the IDH-mutant diffuse astrocytomas, then, there are low-grade (grade 2) tumors and intermediate-grade (grade 3, formerly but no longer "anaplastic astrocytoma") tumors. These tumors commonly share but are not required to have additional genetic alterations including mutations in TP53 and in ATRX. The latter gene when mutant is constitutively active in elongating telomeres and thus promoting cell survival and preventing cell senescence; tumors with an ATRX mutation almost always have unmutated TERT genes, as the usual TERT mutations are in the promoter and also result in constitutive repair and elongation of telomeres, and tumor cells gain no benefit from having both telomere-related mutations. The presence of

TP53 mutations is well known, and usually occurs in sporadic tumors, but these tumors are sometimes a feature of the Li-Fraumeni tumor predisposition syndrome, patients with which have germline TP53 mutations.

IDH-mutant astrocytomas generally lack mutations or chromosomal alterations characteristic of IDH wild-type glioblastoma, including EGFR amplification, coexisting gains of chromosome 7 and loss of chromosome 10, and PTEN mutations. Those IDH-mutant astrocytomas which have homozygous deletion of CDKN2A or CDKN2B (or, not infrequently, both as they are both on chromosome 9p) are associated with a shorter survival compared to that of patients with such tumors with those CDKN2 losses, and such tumors, by the new classification, are grade 4 even without necrosis or vascular hyperplasia.

The other of diffuse glioma which carries an IDH1 or IDH2 mutation is oligodendroglioma. It must be remembered that the definition of oligodendroglioma was made dependent on the presence of both an IDH mutation and co-deletion of chromosome arms 1p and 19q in the revised fourth edition of 2016; this is maintained in the 2021 edition. We are all used to this now, but this was quite a change when promulgated in 2016. It had the effect of converting 1p/19q codeletion from a prognostic and predictive factor (patients with "anaplastic oligodendrogliomas," histologically defined, did better on PCV chemotherapy than their counterparts with that diagnosis without co-deletion), and so a subset of tumors previously so diagnosed were now left to be put into other categories. Additionally, it was already well known in the 1990s that many if not all oligodendrogliomas exhibited some signs of neuronal differentiation, whether by electron microscopic examination showing synaptic and dense-core vesicles or by immunopositivity for a neuronal antigen such as synaptophysin. The dictate from the fourth edition, revised, was that such neuronal differentiation did not alter the diagnosis of "oligodendroglioma." Among other things this made the diagnosis of parenchymal or "extraventricular" neurocytoma very rare and rather nebulous (even more so than it was previously). Otherwise, unlike IDH-mutant astrocytomas, oligodendrogliomas typically have mutations in the promoter region of the TERT gene; this does not carry a negative prognostic import as such mutations do in other settings. Grading of oligodendrogliomas is somewhat problematic, as the tumors are described as occupying a continuous spectrum from lot to high grade. In general, necrosis, vascular hyperplasia, and high mitotic counts (or Ki67 labeling indices) suggest grade 3 instead of grade 2, and the WHO suggests without stating unequivocally that homozygous deletion of CDKN2A correlates with grade 3.

Grading of IDH-mutant astrocytomas that are either grade 2 or grade 3 remains without strict guidelines. Greater mitotic counts obviously push one toward grade 3, and the presence of even a single mitotic figure in a small stereotactic biopsy might be cause to grade such a tumor as grade 3.

Another change in the taxonomy from 2016 in this area is the disappearance of a tumor type "protoplasmic astrocytoma." The WHO committees have had a longstanding animus (I'm being frank) against the diagnosis of mixed glioma; in prior classifications the existence of tumors that appeared histologically mixed astrocytoma and oligodendroglioma was largely dismissed as genetically all one (ATRX

mutant, no co-deletion) or the other (TERT mutant, with co-deletion). The 2021 classification notes the unequivocal demonstration of rare cases with a "dual genotype," that is, an IDH-mutant diffuse glioma with one subpopulation of tumor cells having ATRX loss and TP53 mutation associated with an astrocytomatous appearance in tissue sections, and another with co-deletion and an oligodendrogliomatous histomorphology. It also notes a few cases described with IDH mutations, ATRX loss, TP53 mutation, and co-deletion of 1p and 19q. Thus, there probably are very rare "true" mixed gliomas. As elsewhere in the sections on IDH-mutant diffuse gliomas the 2021 classification text includes information on "cell of origin" being diverse, some IDH-mutant diffuse gliomas apparently arising from cerebral stem cells, some from neuronal precursors, some from oligodendrocyte precursors, and some from astrocytic precursors, this is hardly surprising.

1.3.1.2 IDH Wild-Type Diffuse Gliomas

There is not much changed for most tumors that lack an IDH1 or an IDH2 mutation and are histologically a diffuse astrocytic glioma with grade 4 histologic features, i.e., necrosis and vascular hyperplasia. It is established that many of these tumors commonly carry particular mutations, in ATRX or TERT, in EGFR, or in PTEN; smaller but significant numbers have mutations in NF1, RB1, or other cell cycle control genes that are oncogenes when mutant or deleted, or have amplification of EGFR. There are also common chromosomal abnormalities, such as the simultaneous gain of chromosome 7 with loss of chromosome 10 mentioned earlier. These molecular genetic or cytogenetic alterations are now prominent when a tumor is histologically low grade (grade 2), perhaps in a limited biopsy, but has some of these genetic markers otherwise associated with glioblastoma. The WHO now defines such tumors as "genetic glioblastomas" and recommends assigning a grade of 4 and a diagnosis of glioblastoma as the integrated diagnosis, even in the face of no histological feature of more than grade 2. Other genes which if mutant or partners in certain fusion genes carry a similar significance include FGFR1 and the three NTRK genes.

The 2021 classification retains a long section on histological patterns or variants of glioblastoma without making any of them "types" or "subtypes" that make it into the tabular listing of such tumors. Thus, one can still find gliosarcoma, giant cell glioblastoma, and small cell glioblastoma. Epithelioid glioblastoma is discussed and noted to have a histological relationship to pleiomorphic xanthoastrocytomas and to share with those tumors frequent alterations in BRAF pathway genes. Of particular note because there is a molecular association is the glioblastoma with a primitive neuronal component, MYCN amplified.

In summary, the WHO now views itself as having simplified these adult-type diffuse gliomas into only three "types": IDH-mutant astrocytoma, IDH wild-type glioblastoma, and oligodendroglioma. They acknowledge that one needs to grade the first type into one of three grades (2, 3, or 4), and probably the last type into one of two grades (2 or 3).

1.3.2 Pediatric-Type Diffuse Gliomas

These are less common than adult-type diffuse gliomas, but there are more "types." Among other things, I would note that this makes clinical trials for pediatric high-grade gliomas more difficult, either to conduct or to interpret given a necessarily heterogeneous population of tumor types in the included patients; also despite the taxonomy a fair number of some of these tumor types occur in adults who are likely excluded from pediatric CNS tumor clinical trials. The pediatric-type diffuse gliomas are further divided into low-grade and high-grade groups each with several types.

1.3.2.1 High Grade

The defined types include diffuse midline glioma, H3K27M-altered; diffuse hemispheric glioma, H3 G34-mutant; diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type; and infant-type hemispheric glioma. Here the first entity is well known and was established in the revised fourth edition, but the terminology has been changed from "H3K27M-mutant" to "H3K27M-altered" as not all examples are just mutated. The last entity is usually found to have alterations (including in some, fusion genes) of genes in receptor tyrosine kinase pathways, including ROS1, AlK, and Met, plus examples with NTRK fusion genes. These are all listed as subtypes of the infant-type.

The pediatric high-grade glioma, H3 and IDH wild type, is defined first by the lack of those genetic changes, and then the tumors may have one or another of multiple changes, each of which is not specific. These include TP53 mutations, PDGFRA mutations or amplification, NF1 mutations, or MYCN amplification. This tumor type is best definitively identified, according to the WHO classification, using methylation array classifiers. The details are not important here and are, obviously, available in the text of the new classification.

1.3.2.2 Pediatric Diffuse Low-Grade Gliomas

This group as a group is wholly new, essentially, although it includes tumor types that were previously known but placed elsewhere in the overall former taxonomy. Among those are angiocentric glioma, which no longer is thought to have a single characteristic genetic signature; something new called diffuse astrocytoma, MYB- or MYBL1-altered; another new entity, pleiomorphic low-grade neuroepithelial tumor of the young, usually abbreviated as PLNTY; and diffuse low-grade glioma, MAP-K pathway altered. Of interest in this group is that both PLNTY and low-grade glioma, MAP-K pathway altered may histologically have areas that resemble oligodendroglioma, and presumably these groups include all the tumors previously classified as pediatric oligodendrogliomas (known to have neither IDH mutations or 1p/19q co-deletion). There are no longer pediatric-type oligodendrogliomas in the taxonomy, unlike in 2016.

1.3.3 Circumscribed Astrocytic Gliomas

This group includes well-known and established tumor types such as pilocytic astrocytoma, pleiomorphic astrocytoma (PXA), chordoid glioma, and subependymal giant cell astrocytoma (SEGA). None of these are molecularly defined; indeed they have variable molecular changes depending in part on age at diagnosis and site. Many pilocytic astrocytomas are known to harbor mutations or other alterations (fusion genes) in BRAF, including the well-known BRAF V600E mutation that also characterizes most melanomas. Some pilocytic astrocytomas are described with FGFR1 mutations in hotspots known to be oncogenic. Of interest PXAs, gangliogliomas, and a less defined tumor type in the new classification, epithelioid glioblastoma, all may have BRAF alterations, and methylation array classifiers frequently lump these together as PXAs.

This is probably significant taxonomically if not clinically, and the point seems to have escaped the WHO committee. They are grouping PXA and SEGA into the "circumscribed astrocytic gliomas" when each of those tumor types is well described to have neuronal as well as glial differentiation (which would seem to make sense with the BRAF alterations). SEGAs are well known for their association with tuberous sclerosis complex as a tumor predisposition syndrome. Nobody is asking me but I would have put both of these in with the glioneuronal tumors.

Another tumor type in this group has a long but controversial history, namely, astroblastoma, which is now validated as a genuine tumor type with a distinctive genetic abnormality, alteration of MN-1. (Formerly this was a controversial "entity," but the controversy seems settled now that there is an identified distinctive molecular signature.)

Finally this group includes a tumor now being labeled as high-grade astrocytoma with piloid features. This diagnosis replaces a former category of anaplastic pilocytic astrocytoma, because the relationship to pilocytic tumors is not genetically demonstrable. It is not clear to me that these are truly "circumscribed" astrocytic tumors. Furthermore, there is no distinctive molecular abnormality that characterizes this tumor; the WHO fifth edition states that the diagnosis can only be made with certainty using a methylation array classifier. Some of these tumors are reported to have FGFR1 hotspot mutations. I will note here that in general these methylation array classifiers remain more of a research tool than a diagnostic one, although that is changing. They remain less available (and performance of them is not yet reimbursable) and sometimes give results so at variance with the histological appearance as to call into question their reliability. Nevertheless many centers are starting to use them, and one can anticipate that the use of these, and thus validation of them for most purposes, will increase.

One point to recognize here is that the 2021 classification puts "pilomyxoid astrocytoma" back into pilocytic astrocytoma, denying it status as a subtype, much less a type. This is solidly based on observations that these purportedly more aggressive mostly infant tumors, when recurrent, have assumed a more classical pilocytic histologic appearance; plus, there are no detectable molecular differences between them and ordinary pilocytic astrocytomas.

1.4 Neuronal and Glioneuronal Tumors

This is another broad category that has had new tumor types added to those classically defined. The classical tumors in this group are ganglioglioma (GG), desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA), dysembryoplastic neuroepithelial tumor (DNT, or sometimes DNET), papillary glioneuronal tumor (PGNT), rosette-forming glioneuronal tumor (RGNT), gangliocytoma, dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), central neurocytoma, cerebellar liponeurocytoma, and "extraventricular" neurocytoma. There are no significant changes associated with any of these diagnoses in the new classification, although as noted the diagnostic criteria for parenchymal neurocytoma are now fairly nebulous. I think it is worth wondering why the WHO committee retained the modifier "cerebellar" on the liponeurocytoma when such tumors have clearly been reported in other brain locations. While the names are embedded in the literature and likely can't be easily changed, I wish that "central" neurocytomas were renamed as intraventricular neurocytomas (since they are by definition intraventricular masses) and that "extraventricular neurocytomas" (an awkward name, calling it by what—or where—it is not) were called "parenchymal neurocytomas." The defining characteristics of parenchymal neurocytoma remain vague; many tumors previously called that are likely now oligodendrogliomas having IDH mutations and co-deletion of chromosome arms 1p and 19q, and I have seen others defined as astrocytomas because of the finding of ATRX mutations, despite the immunohistochemical evidence of neuronal differentiation.

Of importance there are some "new" entities. One of these is myxoid glioneuronal tumor, which has the disconcerting tendency to occupy the lateral ventricles attached to the septum pellucidum, and so clinically and radiographically mimics central neurocytoma. Another is multinodular and vacuolating glioneuronal tumor. The category of glioneuronal tumors also has one of what the WHO calls a "provisional entity," i.e., one that they are not sure will be proven to be a real tumor type: this is the diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters. Despite a similarity in name, this should not be confused with the diffuse leptomeningeal glioneuronal tumor, which used to be a provisional entity in the 2016 classification but is now well accepted as a tumor type in the 2021 classification. This tumor has the peculiar characteristics of having no IDH mutation, an oligodendroglioma-like histologic appearance, and 1p deletion (some with 1p/19q co-deletion). BRAF fusion genes are commonly found with these tumors, but indeed they characterize many of the glioneuronal tumors.

1.5 Ependymomas

There is not too much that is new with regard to ependymomas in the new classification. The 2016 revision already contained the information that genetically there were at least three molecularly different tumor subtypes in each of the three major

compartments (cerebral hemispheres, posterior fossa, and spinal cord, thus nine types total). The 2016 identification of RELA-fusion partnered cerebral ependymomas having a bad prognosis has been somewhat modified as the fusion partners are better identified and so that subtype is now two subtypes, supratentorial ependymoma, ZFTA fusion-positive and supratentorial ependymoma, YAP1 fusion-positive. To me it did not make a lot of sense that all of those supratentorial ependymomas with those fusion genes would be as aggressive as the 2016 revision of the fourth edition classification suggested, since I had worked with the late Fred Epstein and others to show that grade II (old classification) supratentorial ependymomas that were completely excised from children did not require adjunctive therapy in most instances. The update in the 2021 classification seems to validate that caution about the 2016 recommendation that these be regarded as highly aggressive tumors.

The aggressive clinical behavior of posterior fossa (PF) A ependymomas is affirmed in the current classification, particularly if there is loss of chromosome arm 1q. Such loss is rare in PFB ependymomas, which tend to occur in older patients (i.e., not children) and have a better prognosis. The distinction between them, it is emphasized, can be suggested by immunostains demonstrating loss of (PFA) or retention (PFB) of the trimethylation of the H3K27 locus. Alternatively these different types are identifiable by methylation array classifiers, where available. The 2021 classification describes, without much detail, five different molecularly defined subtypes of PFB ependymomas. In sum, with the separation of the RELA-fusion supratentorial type into two subtypes, and of PFB ependymomas into five subtypes, there are more subtypes now described than formerly.

1.6 Embryonal Tumors

This next large category contains multiple types that have been classically recognized, all the way back to Bailey and Cushing. The term "primitive neuroectodermal tumor," which was never popular with the WHO committee members over the years, has been wholly banished, and this category is called "embryonal tumors." In my view this is pure semantics; PNET would do as well to describe the group, although not as a unifying hypothesis as proposed in 1982 by Lucy Rorke (rather than go into what is essentially a dead issue, I will suggest interested readers read the relevant sections of my text [22]).

1.6.1 Medulloblastomas

Of course the largest category within this large group is medulloblastoma. The 2021 classification retains a dichotomy from the 2016 revision of the fourth edition, with three histologic subtypes (classic, anaplastic/large cell, and

desmoplastic/nodular, with a fourth, "with extensive nodularity," really fitting into the desmoplastic group), but also separating out molecular subtypes which have some but not complete correlation with the histological types. Thus, there are medulloblastoma driven by alterations in the sonic hedgehog (SHH) pathway, many of which are desmoplastic/nodular tumors found in very young (<3 years old) children. The SHH group is subdivided further into those with TP53 mutations and those that are TP53 wild type, the former having a much worse prognosis, whereas deaths from tumor among the latter are almost nonexistent. Another well-characterized group is driven by genetic alterations in the wingless (WNT) pathway; these also tend to do very well clinically, and are mostly classic medulloblastomas histologically. The group 3 and group 4 medulloblastomas are more aggressive; group 3 medulloblastomas commonly overexpress MYC, in some tumors due to MYC amplification and in others from upstream genetic alterations. Some of these tumors are histologically anaplastic/large cell, but the relationship is not dependable.

1.6.2 Non-medulloblastoma Embryonal Neoplasms

Other embryonal tumors include atypical teratoid/rhabdoid tumor, about which more is now known; there are now three recognized distinct molecular subtypes. The most common AT/RTs have biallelic SMARCB1 (INI-1) inactivation (usually germline deletion of one allele and somatic mutation of the other); rare examples have similar inactivation of SMARCA4 (BRG1). The three molecular variants, however, are described from expression profiles or from methylation array classifiers, and are AT/RT-SHH, AT/RT-TYR, and AT/RT-MYC.

The 2016 volume merged medulloepithelioma and embryonal tumor with abundant neuropil and true rosettes (ETANTR) into one tumor type, the embryonal tumor with multilayered rosettes (ETMR); the 2021 edition splits ETMR into two molecular subtypes, one with DICER mutations and the other with the previously described C19MC alteration.

The embryonal tumor category has one new provisional entity, cribriform neuroepithelial tumor, and two additional types: a CNS tumor with BCOR internal tandem duplications and CNS neuroblastoma, FOXR2 activated. The last named clearly just clarifies a prior diagnosis of cerebral neuroblastoma, and the scant comments about the BCOR-related tumor indicate that it might turn out to be a sarcoma instead of a neuroepithelial tumor. There is still a category for embryonal tumor NOS or NEC, meaning that genetic characterization was not done (NOS) or that the tumor was tested and does not fit any other category in the classification (NEC).

A peculiar omission from this section of the classification is pineoblastoma. It is lumped in with the other pineal parenchymal tumors, but pineoblastomas are clearly embryonal tumors, so its placement is, at least in my eyes, odd. It does not matter in the long run.

1.7 Pineal Tumors

Pineal tumors are next in the sequence of "chapters" in the WHO classification. There is not too much here that is new. Pineocytoma is not significantly differently described from prior classifications. The tumor called pineal parenchymal tumor of intermediate differentiation is retained as a tumor type, with notes that some examples have a recurring KBTBD4 in-frame insertion as a molecular change. The classification does not require such to make the diagnosis or suggest that all such tumors have that alteration.

The most changed tumor type here is pineoblastoma, in that four molecular subtypes have now been defined. These are pineoblastoma, miRNA processing altered 1, with DICER, DROSHA, or DGCR8 mutations (mostly found in children); pineoblastoma, miRNA processing altered 2, with DICER, DROSHA, or DGCR8 mutations (mostly found in older children and carrying a somewhat better prognosis); pineoblastoma, MYC/FOXR2 activated (found mostly in infants); and pineoblastoma, RB1 altered (found mostly in infants and resembling retinoblastoma).

The classification retains the previously recognized tumor papillary tumor of the pineal region, and adds a wholly new tumor type, desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant.

1.8 Peripheral Nerve Sheath Tumors

The next section of the fifth edition deals with peripheral nerve sheath tumors. For the purposes of this chapter, these can be largely skipped. Of note is the addition of a new tumor, atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP). This term more or less replaces the somewhat "unofficial" term of atypical neurofibroma. It is meant to be used only for patients with neurofibromatosis type 1 (NF-1), and describes a neurofibroma with a higher than typical mitotic rate and a greater degree of cellular "anaplasia," insufficient to justify a diagnosis of malignant peripheral nerve sheath tumor (MPNST). These are believed to be an intermediate stage in the development of MPNSTs from neurofibromas in NF1 patients. For reasons that are not clear to me at all, the committee included paraganglioma and gangliocytic paraganglioma of the cauda equina among the peripheral nerve sheath tumors.

1.9 Meningiomas

One organizational change for this section from prior classifications is that the committee regarded all meningiomas as now being a single type of tumor; all the other former "types" or "entities" are now regarded as subtypes. The revised

classification retains a grading system from 1 to 3, with grade 1 being the most common and benign, grade 3 being "anaplastic" and clearly malignant, and grade 2 being "atypical." A significant change is that subtypes formerly regarded as automatically meriting a grade 3 diagnosis (papillary meningioma; rhabdoid meningioma) now are graded the same way all other subtypes are, and if the individual tumor in question does not meet general criteria for grade 3 (high mitotic rate), or for grade 2 (mitotic rate over 4 mitotic figures per 10 high power (×10 X ×40) fields, brain invasion, some combination of necrosis, loss of architecture, prominent nucleoli, presence of small anaplastic cells), then those grades are not assigned. Of interest the chordoid meningioma and clear cell meningioma subtypes are still regarded as grade 2 without reference to these other histological features.

While molecular assays of meningiomas are still not often ordered at many centers, particularly if the tumor is a grade 1 meningioma, certain molecular findings are useful. Clear cell meningiomas frequently have mutations in SMARCE1. Mutations in BAP1 are associated with rhabdoid meningiomas and papillary meningiomas, and alterations of KLF4/TRAF7 are associated with secretory meningiomas. Most neuropathologists can make those histologic diagnoses without requiring molecular testing for confirmation.

However, certain genetic changes alter diagnosis significantly. TERT promoter mutations in meningiomas correlate with aggressive clinical behavior and are suggested to force a diagnosis as grade 3; similarly homozygous deletion of CDKN2A and CDKN2B should mean a grade of 3. While not mandating a change in grade, loss of trimethylation of the H3K27M locus is associated with a worse prognosis compared to meningiomas of comparable histologic appearance but no such loss. When to investigate a meningioma for these molecular alterations is not clear, and I think the WHO CNS committee is awaiting more data.

1.10 Mesenchymal Non-meningioma Neoplasms

The 2021 fifth edition covers a spectrum of mesenchymal tumors only some of which were previously included in former editions. Notable among the returning tumors is the dural solitary fibrous tumor. For this edition the committee dropped the cumbersome hybrid name "hemangiopericytoma/solitary fibrous tumor" of the prior fourth edition as revised. This section also includes among vascular tumors hemangioblastoma, as well as the well-characterized variety of vascular malformations and hemangiomas. Relatively new tumor types, for this classification, include intracranial Ewing's sarcoma, a primary intracranial sarcoma, DICER1-mutant, and a CIC-rearranged sarcoma. A provisional entity of intracranial mesenchymal tumor, FET-CREB fusion-positive, is described. Primary CNS rhabdomyosarcomas are also listed.

1.11 Bone and Cartilage Tumors

The classification includes a fairly standard group of tumors of chondro-osseous origin that may occur in the skull or spine. Among these are the well-known tumor types chordoma, chondrosarcoma, and mesenchymal chondrosarcoma. There are no major changes regarding these tumors.

1.12 Hematolymphoid Tumors

This section includes not only the standard primary CNS B cell lymphoma; it has separate categories for immunodeficiency-related CNS lymphoma, lymphomatoid granulomatosis (which I thought had been subsumed into other lymphoma types a long time ago, but which resurfaces here), intravascular large B cell lymphoma (which in my view is not really a CNS tumor although it causes infarcts and thus often presents in the CNS), and a category for "miscellaneous rare lymphomas of the CNS." The classification also recognizes as a separate tumor type low-grade MALT lymphoma of the dura, and for anaplastic large cell lymphoma, whether Alk-positive or Alk-negative. There is a category for primary T cell CNS lymphoma, which is quite rare, and for NK/T cell lymphoma. This broad category also includes the histiocytoses which may affect the CNS including Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, juvenile xanthogranuloma, and histiocytic sarcoma.

1.13 Sellar Tumors

This section covers craniopharyngiomas (both adamantinomatous and squamous papillary), pituitary adenomas, pituitary blastoma, and the once-separate tumor types pituicytoma, granular cell tumor of the infundibulum, and spindle cell oncocytoma. The last three tumor types share characteristics and are now regarded as different histologic patterns of a single tumor type. The section on pituitary adenomas highlights the now-common use of immunostains for lineage markers, and floats a proposal clearly stimulated by the endocrine pathology section of the WHO to change the name "pituitary adenoma" to "pituitary neuroendocrine tumor" or "PitNET." Personally I suspect there will be great resistance to that proposal.

1.14 CNS Germ Cell Tumors

The section on CNS germ cell tumors has little or no change, as far as I can tell. There are no new insights from molecular characterization, and the histopathology of the full array of germ cell neoplasia is well known.

1.15 Conclusion

The fifth edition of the WHO classification of CNS tumors has significant and important changes in the organization of the taxonomy, as well as many changes in diagnostic categories with the addition of a wealth of new information from molecular genetic, molecular cytogenetic, and epigenetic (methylation array classifiers) assays. There were some decisions made that I find questionable, but on the whole the increased knowledge about a plethora of primary CNS tumors is of considerable importance and should be studied not only by neuropathologists but also to some extent by neurosurgeons, neuro-oncologists, medical oncologists, radiation oncologists, and others who care for patients with CNS tumors.

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Chapter 2
Intracranial Tumors in the First Year of Life

José Francisco M. Salomão and Tatiana Protzenko

2.1 Introduction

The incidence of intracranial tumors diagnosed in children and adolescents, according to the Central Brain Tumor Registry of the United States (CBTRUS), is 6.14 per 100,000 [1]. Intracranial tumors are rarely diagnosed in the first year of life, and in this age group, they are the second most common type of pediatric cancer after leukemias, the leading cause of cancer death and the most common solid tumor in children [2, 3]. The incidence of intracranial tumors in the first year of life (TFYL) ranges from 1.9 to 18% in several pediatric brain tumor series [4–8].

TFYL present unique peculiarities that pose special difficulties in management, and the rate of malignancies may reach more than three-quarters of cases reported [9], while other authors inform a similar percentage of patients harboring benign tumors [10]. These tumors are often very large and accommodated inside the intracranial compartment due to the skull expansibility provided by open sutures, fontanels, and generous extracellular and CSF spaces that can lead to an expressive delay in diagnosis, not always established timely [11].

Most of these tumors are congenital, and, with higher-definition imaging, more antenatal cases have been recognized. As integrated diagnosis incorporates both morphologic and molecular features, more types and subtypes of tumors have been recognized in addition to those previously known [12–14]. It is also known that, in this age group, neoplasms differ from those seen in older children concerning

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location, histological features, behavior, and management, suggesting that one is dealing with a different disease than the one seen in late childhood [15].

Genetic syndromes that predispose to cancer, such as neurofibromatosis type 1, tuberous sclerosis, Li-Fraumeni, Gorlin, Aicardi, and Turcot are, in addition to radiation therapy, recognized risk factors for brain tumors [16–19]. The diagnosis of these lesions is difficult since their signs and symptoms can be common to several other clinical and neurological conditions but "no patient is too young to have a brain tumor included in the differential diagnosis of known or suspected central nervous system abnormality" [20].

2.2 Incidence, Demographics, and Definitions

According to Arnstein et al. [21], neonatal brain tumors were firstly reported by Holt in 1917. In 1951, these authors reviewed the literature and found 13 cases to which they added a personal one. These tumors were, by the time, deemed as exceptional and usually an autopsy finding [22, 23]. In 1980, when uterine ultrasound became available for routine examinations in pregnant women, their diagnosis increased [24, 25]. Later, computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were responsible for a three- to fourfold increase in the diagnosis of brain neoplasms in this age group [4, 7, 8]. TFYL account for 0.5–1.9% of all pediatric tumors [22, 26–29], and in most of the series, there is a slight prevalence of males [3, 8, 23, 28, 30–33].

The tumors, diagnosed before birth, are denominated fetal (Fig. 2.1) [18, 34]. The term perinatal, according to the WHO criteria, includes both the fetal and

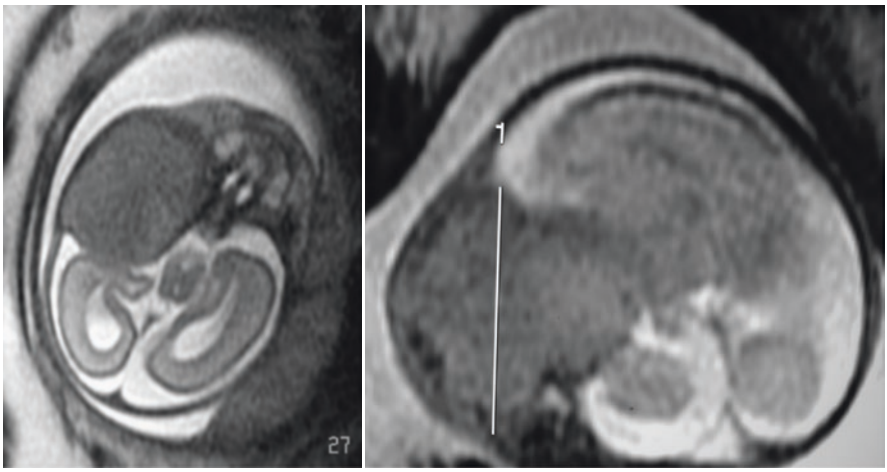

Fig. 2.1 Intrauterine US of a 26-week-old fetus showing a huge craniofacial tumor. There was a premature delivery with death shortly after birth. The histopathologic diagnosis was immature teratoma

neonatal periods limited to the first week of life, while the denomination neonatal comprises all tumors diagnosed in the first 60 days of life [34–36].

There are controversies regarding when to apply the label congenital to TFYL. Solitare and Krigman in 1964 [37] proposed that a tumor is said definitely congenital when symptomatic at birth, probably congenital when symptomatic during the first week of life, and possibly congenital if symptomatic within the first month of life, later extended to 2 months [21, 23]. Some authors consider congenital only tumors whose diagnosis is known up to the first week of life, while others extend the inclusion criteria from 6 months and even to 1 year or longer [19, 32, 38, 39], provided clinical manifestations were reported back to the first year of age [22].

Currently, prenatal and neonatal diagnosis has made it possible to recognize the "certainly congenital" group, while the others depend on additional criteria that include histopathological characteristics, immunohistochemistry, and genetical features, regardless of the patient's age, since some tumors might remain asymptomatic or oligosymptomatic for longer periods [9, 10, 22, 28, 38]. Despite this, only tumors manifested and treated during the first year of life are considered here.

2.3 Geographical and Racial/Ethnic Variations

In 1990, Oi et al. [40] surveyed Far East countries concerning TFYL and found that medulloblastoma and teratoma were more commonly diagnosed than astrocytoma. Specifically, in Japan, the incidence of germinoma, craniopharyngioma, and teratoma was higher than outside there [23, 40]. Retrospective studies conducted at Kolkata, India, and Lille, in France, showed that, among other dissimilarities, germ-cell tumors and HGG were the most common types at Kolkata, while at Lille, predominated LGG and CPC [41].

2.4 Clinical Presentation and Findings

Abortion, intrauterine deaths, stillbirths, polyhydramnios, and fetal hydrops are some events reported during pregnancy. Intrauterine intracranial tumors are often incidentally discovered at routine obstetrical workup, in cases of fetal distress or absence of fetal movements, in dystocia due to the cephalopelvic disproportion and/or exaggerated size of the fetal head, conditions in which Cesarian section can be justified [6, 21, 23, 28, 42–47].

After birth, the clinical picture may be nonspecific and slowly progressive. Due to the characteristics of the infantile skull, the growth of the tumor toward the CSF spaces, and the adaptability of the immature brain to compression, the diagnosis can be delayed or missed [5, 6, 10, 32]. Signs and symptoms vary according to the topography of the lesion and the stage of clinical evolution (Fig. 2.2). Consequently, some patients may experience sudden deterioration due to decompensation of

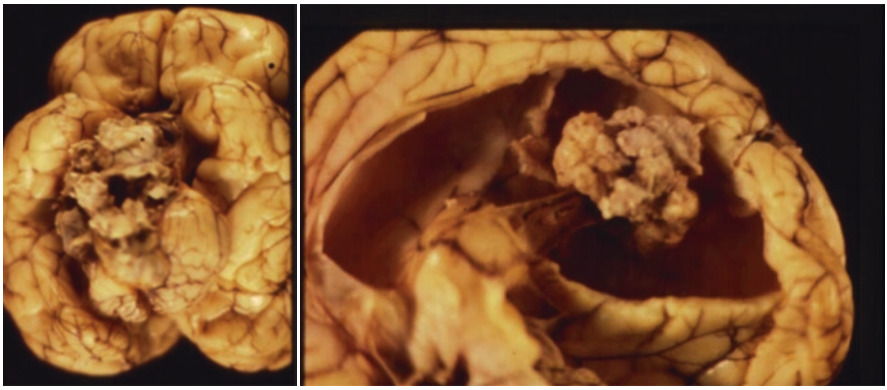

Fig. 2.2 Anatomopathological specimen of a neonate died shortly after birth. A voluminous posterior fossa medulloblastoma with deposit inside the lateral ventricle was found

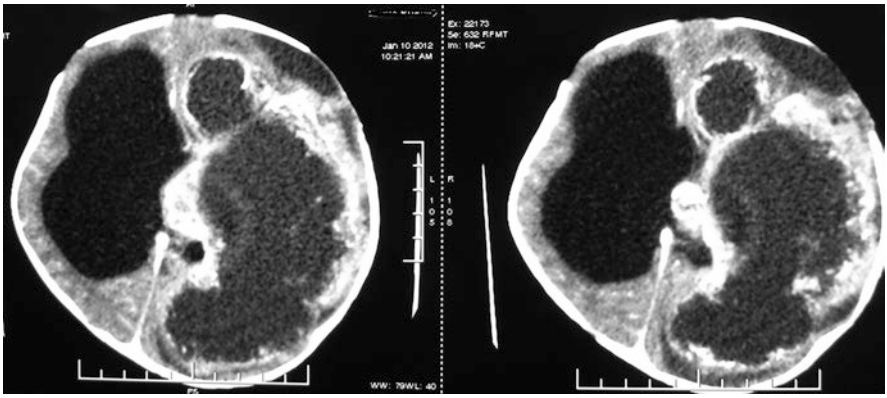

Fig. 2.3 MRI of a 5-month-old female with a massive non-medulloblastoma embryonal tumor of the left lateral ventricle

hydrocephalus, tumor enlargement, or intracranial hemorrhage leading to death [23, 42, 47, 48].

Vomiting and macrocrania are the most frequent findings at birth and can be seen in up to 80% of patients [6]. Intracranial hypertension parallels macrocrania, the second more common finding due to hydrocephalus and tumor volume [6, 23, 31, 38, 48]. Hydrocephalus usually affects children with posterior fossa and choroid plexus tumors [8, 18, 31, 46]. Bulging fontanel, diastasis of the sutures, vomiting, prominent scalp veins, stupor, upward gaze palsy, and developmental delay are described [19, 35, 42, 49]. TFYL are particularly large compared to other age groups in childhood and adolescence and can occupy much of the intracranial space, replacing intracranial content and extending to neighboring structures (Fig. 2.3) [31, 33, 35, 44, 50–52].

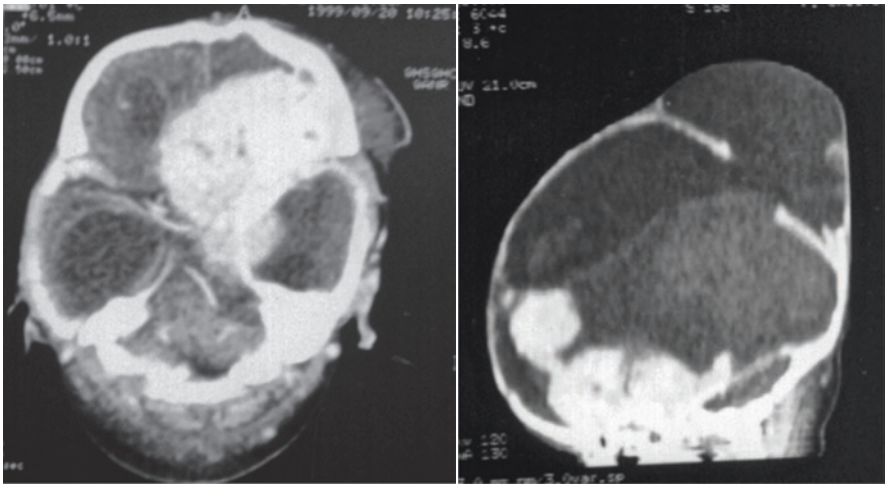

Fig. 2.4 CT scan: immature teratoma, neonate male with a brain tumor and encephalocele ruptured at time of delivery

Seizures are reported in 5–20% of patients [4, 6, 30, 31]. Focal motor deficit is rarely seen. Diencephalic syndrome, precocious puberty, or cerebellar fits occur in tumors at specific localization. Irritability, failure to thrive, poor sucking, torticollis, papilledema, optic atrophy, blindness, nystagmus, cranial nerves palsy and exophthalmos, stupor, and coma are observed in a variable number of patients [5, 10, 53]. Homolateral cranial bossing is sometimes noticed.

Bizarre presentations such as rupture of the skull and associated encephalocele are occasionally seen along the sutures or anterior fontanel (Fig. 2.4) [26, 49, 54, 55]. Associated congenital malformations were reported in some series [22, 26, 40].

2.5 Location

Two-thirds or more of the TFYL are supratentorial. Overall, irrespective of the location, more than half of the lesions are found in or near the midline [4, 7–9, 30–33, 46, 47, 56]. This preference can be explained because most neuroectodermal tumors in this age group arise from phylogenetically older structures of the CNS, such as the periventricular regions, brainstem, and cerebellum [57]. Some neoplasms occupied the supra- and infratentorial compartments (Fig. 2.5).

Some bilateral lesions of the lateral ventricles demand differential diagnosis with choroid plexus hypertrophy, requiring specific staining for the proliferation index [58, 59]. Low-grade astrocytoma and AT/RT are reported to be found at multiple primary sites [31]. Some tumors, mainly teratoma, may present with extracranial extension to the orbit, pharynx, and neck. This occurrence when associated with polyhydramnios may prompt prenatal detection [54, 55]. A rare congenital form of

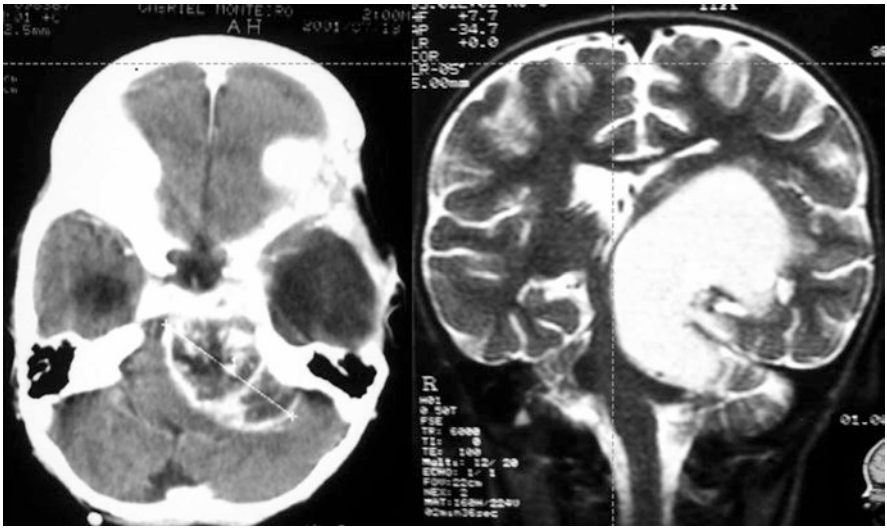

Fig. 2.5 CT scan and MRI of an 8-month-old male with a grade 3 astrocytoma occupying the supra and infratentorial compartments

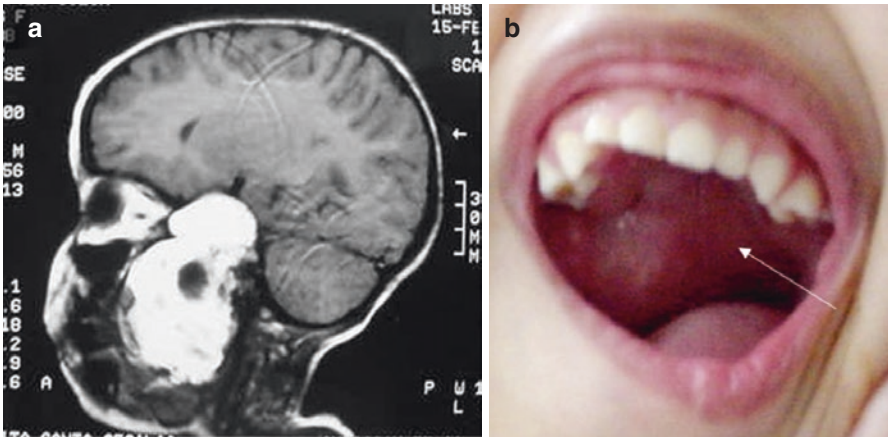

Fig. 2.6 Epignathus. In (**a**) MRI. In (**b**) oral teratoma (arrow) invading the cranial fossa media

orofacial teratoma (epignathus) may have intracranial continuity and even invade the brain (Fig. 2.6).

Metastatic tumors can be found along the CSF pathways, leptomeninges, or intracranially, at the diagnosis or during the follow-up (Fig. 2.7) [18, 22, 31, 33, 60]. The incidence of metastases can reach almost one-third of the patients [33]. Extracranial tumors have been rarely reported in associations with AT/RT [6].

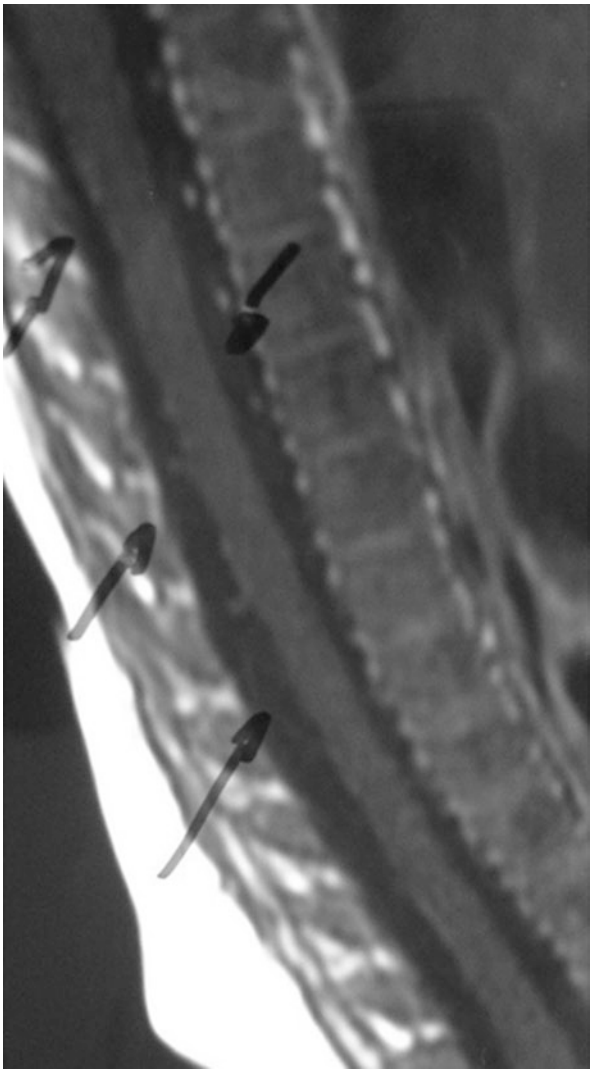

Fig. 2.7 Spinal MRI. Multiple spinal deposits (arrows) as a first clinical manifestation of a medulloblastoma

2.6 Prenatal Imaging and Management

Fetal ultrasonography (US) shows heterogenic images that are calcified in cases of teratomas. If a tumor or hydrocephalus is identified in preterm infants, the proposal is to wait, if possible, and then proceed with a C-section. Cephalocentesis is a choice to decrease intracranial pressure and allow safer delivery if hydrocephalus or a voluminous cyst are detected when gestational age is less than 34 weeks. Corticosteroids are a helpful option to accelerate fetal lung maturation [42]. Parents should be part of the decision-making process and informed about the risks of a premature delivery.

2.7 Postnatal Imaging

Cranial US is easy and safe to perform in newborns and infants who have an open fontanel. It should, whenever possible, be complemented with contrast and non-contrast computed tomography and/or MRI that provides multiplanar images. Computed tomography has the advantage of being faster and can be performed without anesthesia but exposes the newborn to ionizing radiation. In turn, MRI provides more details, and allows for various sequences that are useful in the characterization of tumors and surrounding structures but requires sedation or general anesthesia. Infant astrocytoma is hypointense on T1, hyperintense on T2, with contrast enhancement [61, 62]. Medulloblastoma is preferentially found in the midline or laterally in the posterior fossa. They are hypointense on T1, and isointense on T2, with cystic or necrotic areas. Contrast enhancement is usually seen within the solid portions. Diffusion restriction is observed in the solid portion [32, 61, 62]. In this age group, the most common site of choroid plexus tumors (CPTs) is the lateral ventricles. CPTs are papillary or lobulated, with or without cysts, often accompanied by hydrocephalus, generally isointense on T1 and hyperintense on T2, with strong contrast enhancement [58, 61]. MRI high signal on T2 is seen in cystic degeneration, necrosis, and vasogenic edema, with heterogeneous enhancement after contrast administration. AT/RT are seen in the supra- or infratentorial compartments. They are often necrotic, large, rapid-growing, heterogeneous, sometimes mineralized masses, with solid and cystic components with intralesional hemorrhage (Fig. 2.8) [60, 63, 64]. Teratomas are frequently very large and heterogeneous

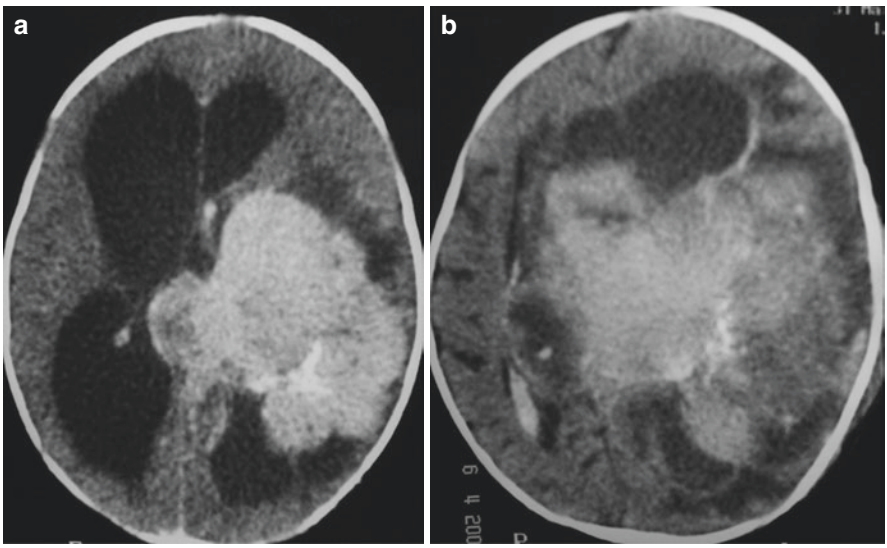

Fig. 2.8 CT Scan of a 4-month-old male with macrocrania and respiratory distress. A left ventricular tumor (**a**) that increased in volume after hemorrhage 5 days after admission (**b**). After a needle biopsy, the diagnostic was PNET

solid and cystic contrast-enhancing masses containing fat and calcifications [35]. Intratumoral or intraventricular hemorrhage and hydrocephalus are frequently seen [5, 35, 42].

2.8 Preoperative Care

Some patients are found in poor clinical conditions and need to be stabilized before intervention, since severe problems can turn even minimally invasive measures not feasible. As patients in this age group have difficulties in thermoregulation, hypothermia should be avoided by warming the environment and the child. Appropriate venous lines are necessary as volume replacement is very often required. Hydrocephalus is more a rule than an exception in this age group, and CSF drainage, temporarily or definitively, might be required to control intracranial pressure, although some infants will be shunt-free in the follow-up.

2.9 Classification and Histological Types

Brain tumor classification progressively evolved from purely histological to histochemical findings, then to immunohistochemical and ultrastructural features and, more recently, incorporated molecular and genomic similarities of subclasses that impacted the understanding and treatment of some lesions. Among other changes, adult and pediatric gliomas were separated, the nomenclature experienced some changes and novel types, and subtypes of neoplasms were introduced [65–67]. The need to combine different data types resulted into an integrated use of WHO Central Nervous System Classification (CNS5) where the report is featured at the top, followed by layers that display histological, molecular, and other key types of information [68]. An analysis of the last WHO classification of brain tumors is out of the scope of this review.

Histological types vary according to the series consulted. If only tumors diagnosed in the first 2 months of life are considered, teratomas appear as the most common fetal and neonatal brain tumor, representing about 30% of all TFYL [19, 35, 44, 51, 69, 70]. However, at the end of the first year of life, these are only 4.9% of the total [9, 21, 35, 37, 42]. In a following section, the most common types will be discussed.

2.10 Some General Considerations on Surgery of TFYL

Neurosurgery in this age group requires an experienced team that includes neuroanesthesiologist, neuropathologist, and intensive care personal and specialized tools according to the needs of the patient.

Pre- or postoperative external ventricular drainage or Ommaya reservoir may be required in about half of patients [8, 18]. According to the ISPN survey, 44% of infants required CSF shunting before or after treatment [30]. Endoscopic third ventriculostomy for treating hydrocephalus has a very high failure rate in this age group.

Positioning small children in sitting position can be very difficult and should be avoided in neonates and infants, whenever possible, due to the risk of air embolism and arterial hypotension. In addition, these patients are better accommodated in prone or lateral position, which allows for safer immobilization of the patient's head and is more comfortable for the surgeon. The anesthesiologist should check the positioning of the head and neck periodically. The head must not be below the atrial level, and the neck must not be inadvertently flexed to obstruct the orotracheal tube.

Bleeding of the skin and bone must be minimized. Excessive bleeding from the dura may originate from the persistence of the fetal dural venous pattern.

Since some tumors are very bulky, and often have very large draining veins requiring great manipulation, the craniotomy must be wide enough to avoid herniation of brain tissue and blood vessels along its edges minimizing edema and/or cerebral hemorrhage.

As the neonate and infant's blood volume is small, careful hemostasis is critical. The volume of many lesions such as CPT can be progressively reduced with meticulous bipolar coagulation turning possible to identify and occlude the feeders, minimizing bleeding. The progression of the resection can be estimated in real time with ultrasonography.

The rate of total removal varies in different series, ranging from less than 10% to more than 50% [10, 32]. Sometimes the excessive bleeding and the size of the tumor lead to staged removal and additional surgeries. In some tumors even biopsies are not possible due to the location of the tumor, the characteristics of the mass itself, or the clinical status of the patients. In selected cases, chemotherapy may be very useful preoperatively or when surgery is interrupted due to excessive bleeding.

2.11 Pediatric Low-Grade Gliomas (PLGG)

PLGG, as a whole, represent 30% of the tumors in this age group, being the more frequent neoplasm in childhood [5–7, 9, 31, 71]. PLGG are classified as WHO grade 1 or 2 due to morphologic features such as the absence of necrosis, mitoses, and vascular proliferation. PLGG comprise circumscribed and diffuse tumors. Pilocytic astrocytoma (PA) and subependymal giant cell astrocytoma (SEGA) are the two more frequent OMS grade 1 circumscribed gliomas. Different molecular changes and mutations in specific genes are present in circumscribed and diffuse low-grade tumors in which the mitogenic-activated protein kinase (RAS/MAPK) pathway is a necessary step in the development of these tumors (Table 2.1) [12, 73].

The OMS grade 2 pediatric low-grade diffuse gliomas (PLGDG) encompass four subtypes: diffuse astrocytoma, MYB—or MYBL1-altered; angiocentric glioma;

Table 2.1 Histologic diagnoses of PLGG and main molecular alterations, modified from Ryall et al. [72]

Histological diagnosis		Main molecular events (%)
Glial tumors	Pilocytic astrocytoma	KIAA1549-BRAF (70–80%)
		FGFR1-TACC1 (3–5%)
		FGFR1 SNV (3–5%)
		BRAF p.V600E (3–5%)
	Subependymal giant cell astrocytoma (SEGA)	TSC1/2 SNV (85–95%)
	Diffuse astrocytoma	BRAF p.V600E (20–40%)
		MYBL1 alteration (5–10%)
		KIAA1549-BRAF (5–10%
	Pleomorphic xanthoastrocytoma	BRAF p.V600E (80–90%)
	Oligodendroglioma	GFR1-TKD duplication (10–20%)
		FGFR1 SNV (10–20%)
		BRAF p.V600E (5–10%)
Mixed glioneuronal tumors	Ganglioglioma	BRAF p.V600E (40–50%) KIAA1549-BRAF (10–15%)
	Desmoplastic infantile astrocytoma and ganglioglioma (DIA/DIG)	BRAF pV600E/D (40–60%)
		FGFR1 SNV (5–10%)
		KIAA1549-BRAF (2–5%
	Dysembryoplastic neuroepithelial tumor (DNET)	FGFR1-TKD duplication (20–30%)
		FGFR1 SNV (20–30%)
		FGFR1-TACC1 (10–15%)
	Papillary glioneuronal tumor	SLC44A1-PRKCA (80–90%)
	Rosette-forming glioneuronal tumor	PIK3CA SNV (20–30%)
		KIAA1549-BRAF (20–30%) FGFR1 SNV (20–30%)
	Angiocentric glioma	MYB (80–90%)
	Chordoid glioma of the third ventricle	PRKCA SNV (80–90%)
	Polymorphous low-grade neuroepithelial tumor of the young PLNTY	BRAF p.V600E (30–40%) FGFR2/3 fusions (30–40%)
	Multinodular and vacuolating neuronal tumor (MVNT)	MAP2K1 SNV/indel (50–60%)
		BRAF p.V600E (5–10%)
		Other BRAF SNV (5–10%)

polymorphous low-grade neuroepithelial tumor of the young, and diffuse low-grade glioma, MAPK pathway-altered [12].

Optic pathway gliomas (OPG) are the most frequent low-grade gliomas in the first year of life [31, 48, 53] accounting for 20–61% of these tumors [74]. OPG can be sporadic or syndromic. In the second form, OPG is associated with neurofibromatosis type 1 (NF1), a known tumor predisposition syndrome, associated with different tumors of the nervous system. Syndromic forms are

different from the sporadic ones and affect the optic nerves unilaterally or bilaterally in 15–20% of the cases. They are usually asymptomatic, may have a slow, indolent course, and even disappear over time [75]. When symptomatic it may cause exophthalmos and loss of vision [4, 30, 76]. The NF1 gene codes for neurofibromin, and the loss of expression of both affects control of cell growth and proliferation in OPG [72, 77].

Pilomyxoid astrocytoma was not graded by the WHO and, in the first year of life, is frequently found in the chiasmatic-hypothalamic region [78]. According to some authors, PMA is a more aggressive variant of PA. Lundar et al. [48] call attention that three out of four optical pathway astrocytomas they found in the first 6 months of life were of the pilomyxoid variant, much more aggressive.

Sporadic pediatric OPG are prone to occur in infants and younger children in which visual complaints are rare [79]. More often they present with diencephalic syndrome (Russell syndrome) and precocious puberty. Nystagmus and hydrocephalus are seen when the tumor obstructs the CSF pathways toward the third ventricle or Sylvian aqueduct. These tumors can even extend toward the optic radiations and cortex, unilaterally or bilaterally (Fig. 2.9) [77, 80–82]. These tumors may have translocations or mutations of the BRAF gene, which may also promote tumor development in pleomorphic xanthoastrocytoma, ganglioglioma, and extracerebellar pilocytic astrocytoma [72, 83].

Patients with grade 1 and 2 astrocytomas surgically treated have the greatest possibility of cure, and in neonates and infants, chemotherapy must be strongly considered as a complementation to surgical treatment when total removal is not achieved [36, 74].

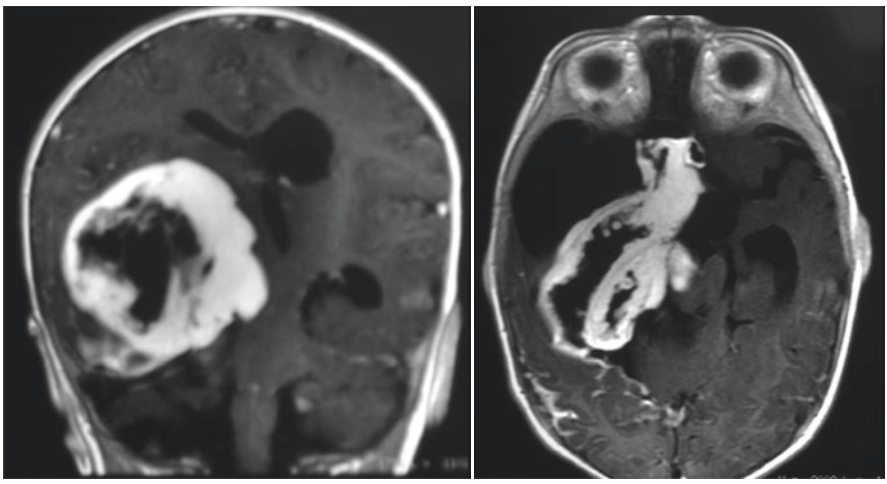

Fig. 2.9 MRI: Optic pathway tumor extending toward the optic radiations on the right. No surgical intervention was contemplated

2.12 Subependymal Giant Cell Astrocytomas (SEGAs)

Subependymal giant cells astrocytomas (SEGAs) are seen in tuberous sclerosis complex (TSC), an autosomal dominant disorder characterized by hamartomas in multiple organs. Cortical tubers, subependymal nodules, and SEGAs are detected mainly in the brain of children and adolescents. The tumor is rarely diagnosed in fetus, neonates, and during the first year of life, although stigmata may be seeing at birth [84]. SEGA arises close to the foramen of Monro that can be obstructed unilaterally or bilaterally. Although tumor resection may be done safely, their aggressive behavior in this age group and complications due to intracardiac rhabdomyomas may lead to a poor outcome [85]. SEGAs express diverse glial markers such as vimentin, and GFAP and neural stem cell markers. The use of everolimus, a mammalian target inhibitor of rapamycin (mTOR), has been considered a pharmacologic alternative to surgical resection [86].

2.13 Pediatric-Type Diffuse High-Grade Gliomas (PTDHGG)

This group includes high-grade glioma (HGG) WHO grade 3 and grade 4, both very rare in neonates and infants and classically supratentorial [65]. Pediatric GBMs are clinically and biologically heterogeneous, with distinct subtypes that correlate with outcomes [87]. A review of 101 astrocytomas collected in fetuses and neonates showed that half of the cases were grade 4, very large and accompanied by obstructive hydrocephalus, cystic degeneration, necrosis, edema, and hemorrhage [34]. The fetal and neonatal survival rate of these neoplasms is low, with a high percentage of babies born moribund [36]. However, some authors report a relatively favorable prognosis [88]. Malignant gliomas are highly vascular and have an accelerate growth due to hemorrhages, and there are frequent reports of surgery interruption in hemodynamically unstable patients to avoid intraoperative deaths, a not so rare occurrence [45, 89]. Occasionally, embolization has been tried, without practical results [90].

The current literature has withdrawn the GBM nomenclature related to pediatric tumors [68]. Now, considerations regarding histone mutations are very important, especially in diffuse midline gliomas. Approximately half of mutations in high-grade gliomas show involvement of the histone complex. Thus, high-grade tumors are divided into midline glioma H3K27-altered, diffuse hemispheric glioma H3G4-mutant, diffuse pediatric-type high-grade gliomas H3-wt and IDH-wt, and infant-type hemispheric glioma. Diffuse midline gliomas H3K27-altered are centered not only in the pons, thalamus, and spinal cord. They can be present in the third ventricle, hypothalamus, pineal region, and cerebellum [68].

2.14 Medulloblastoma (MB)

MB is the most common malignant brain tumor, accounting for 20% of intracranial tumors in childhood and 10–15% of the tumors in the first year of life [91–96]. MBs are biologically and clinically heterogeneous tumors and molecularly distinct from other embryonal neoplasms of the brain [13]. MB is associated with cancer predisposition syndromes especially the Gorlin syndrome, familial adenomatous polyposis (FAP), and more rarely Li-Fraumeni, Rubinstein-Taybi, and Fanconi anemia [97, 98].

Medulloblastomas were classically classified in four morphologic types: classic; desmoplastic/nodular (DMB); with extensive nodularity (MBEN); and large cell/anaplastic. In 2012, a consensus paper classified MB in four main molecular subgroups, WNT, SHH, group 3, and group 4, according to the signaling pathways involved in their pathogenesis [96]. The groups 3 and 4, not associated with cell signaling pathway abnormalities, are highly heterogeneous and with several molecular patterns [95, 96, 99]. The most common molecular subgroup in infants and children less than 3 year old is SHH [13, 100]. In 2021, MBs were stratified into four molecular subgroups with four and eight further subgroups for SHH and non-WNT/non-SHH MB, respectively [95]. Among the four SHH subgroups, SHH-1 and SHH-2 are related to MBs from young children and have a higher metastatic rate [93–95].

Both DMB and MBEN have a better outcome than other variants, with a lower incidence of metastasis and also a significant percentage of cure with associated chemotherapy and without radiotherapy (RT) [101].

2.15 Non-medulloblastoma Embryonal Tumors: Other CNS Embryonal Tumors (CET)

In the past, the denomination “primitive neuroectodermal tumors” (PNET) included all non-medulloblastoma embryonal neoplasms. This denomination is no longer used since 2016, when it was decided to name them non-medulloblastoma or other CNS embryonal tumors [13, 66, 87, 91]. CET account for 8.4–26.7% of all the TFYL [9, 35, 47]. These tumors have similarities with neuroblastomas and ependymoblastomas and are histologically denominated accordingly as tumors with multilayered rosettes (ETMR), abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL), and medulloepithelioma (MEPL) [102, 103]. These lesions are very aggressive and are occasionally seen in the first 12 months of age, in which RT is associated with a better outcome [104, 105].

Atypical teratoid/rhabdoid tumors (AT/RT): These tumors were in the past misdiagnosed as medulloblastoma or other aggressive tumors of the SNC due to clinical similarities and biological characteristics, being sometimes reported in association with malignant rhabdoid tumors of the kidney [106].

Although histologically like medulloblastoma, AT/RT is characterized by the presence of rhabdoid cells and by specific gene abnormality that include decrease or absence within the long arm of chromosome 22, the INI1 gene [107]. They account for 4.4% of all CNS tumors in children aged less than 5 years and for 40% of embryonal tumors in the first year of life, preferentially located in the posterior fossa and with tendency to early metastatic dissemination [60, 64]. MRI findings are not specific for conventional diagnosis and include patterns of restricted diffusion like medulloblastomas. Supratentorial tumors correlate with a better prognosis, attributed to neuronal differentiation, while infratentorial neoplasms are more aggressive. AT/RT is chemotherapy-sensitive, focal radiation therapy has been employed even in children less than 3 years, but the overall prognosis correlates only with the extent of removal and remains very poor [15, 91].

2.16 Choroid Plexus Tumors (CPTs)

Between 5 and 20% of TFYL arise from the choroid plexus. Half of them is found inside the lateral ventricles, and the rest is distributed among the third and, less frequently, the fourth ventricles [9, 53, 59]. CPTs are more frequently found in the first year of life, and macrocephaly with intracranial hypertension is common, since the tumor produces CSF. Regarding histopathology, according to WHO classification, choroid plexus papilloma (CPP) is graded 1; atypical choroid plexus papilloma (aCPP) is graded 2, and choroid plexus carcinoma (CPC) is graded 3. Somatic mutations in the TP53 tumor suppressor gene have been associated with poor prognosis in CPC. DNA methylation profiles (DNAm) showed significant differences between CPC, aCPP, and CPP, with novel subgroups making possible to distinguish more aggressive from more benign forms of CPTs [108, 109]. Bilateral tumors of the ventricles are rare, and differential diagnosis from choroid plexus hypertrophy may be difficult, requiring specific staining for the proliferation index [58, 59].

The surgical removal of choroid plexus tumors poses some difficulties: as they are richly vascularized and usually large, gaining access to the feeder vessels before debulking the tumor is fundamental [110]. This can be achieved with bipolar coagulation to gradually shrink the lesion, and then find and occlude the feeders (Fig. 2.10). Hydrocephalus due to CSF pathway obstruction and/or excessive production may require transient preoperative ventricular drainage or even postoperative shunting in case of persistent fluid collection. Bilateral tumors of the choroid plexus can be removed in the same or in different surgical sessions. Preoperative embolization reduces significantly intraoperative blood loss, increasing the chances of gross total resection [90]. Once totally resected, PPC and aPPC have a good prognosis. CPC invades the brain parenchyma and has a worst prognosis.

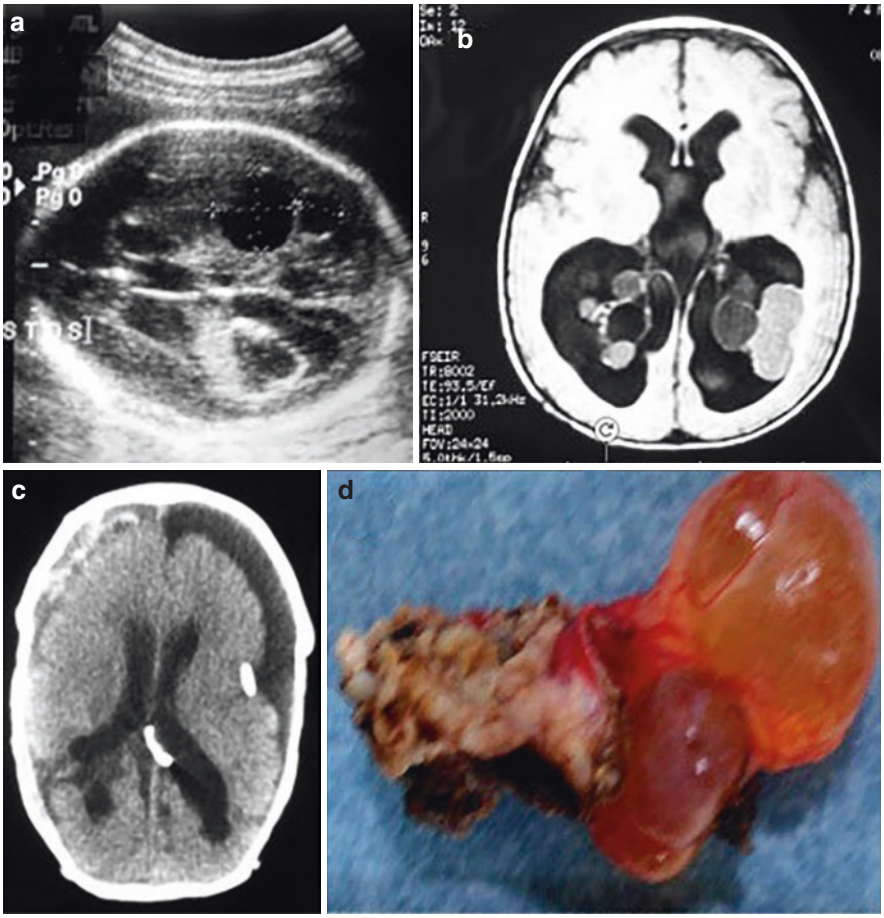

Fig. 2.10 Bilateral plexus papilloma in a 4-month-old female. The tumor had a cystic component that demanded differential diagnosis with choroid plexus cyst. In (**a**, **b**), trans-fontanel US and MRI, respectively. In (**c**, **d**), postoperative MRI and surgical specimen

2.17 Ependymomas

Ependymomas are among the three more common tumors in the first year of life and, in two-thirds of the cases, are infratentorial. Currently, ependymomas are classified according to the anatomical site, histopathological features, and molecular alterations [65, 73]. A recent molecular classification has distinguished nine subgroups of ependymal tumors that excluded tumors grade 1, due to their features [111]. Ependymomas can spread through CSF, and the disease staging includes CSF cytology and craniospinal magnetic resonance imaging.

Posterior fossa ependymomas (PFE) are divided into groups A and B. The pediatric-type (PFA) is quite distinct from adult-type (PFB), found mostly in

adolescents and young adults [112]. PFA are highly aggressive anaplastic ependymoma (WHO grade 3), showing a balanced genomic profile typical of infancy, suggesting that they are biologically distinct from those diagnosed in older children [112–114]. PFA patients have a lower median age than the others, ranging from 0.5 to 2.2 years [115]. Characteristically, they arise from the lateral recess of the fourth ventricle and tend to occupy the cerebellopontine angle, involving neural and vascular structures, which often preclude complete removal of lesions, resulting in cranial nerve deficits, which may be transient or not (Fig. 2.11).

Ependymomas grades 2 and 3 are unquestionably surgical lesions whose prognosis depends on the extension of removal and radiation therapy [114, 116]. A second-look surgery is advisable when an unrecognized residual tumor is left in place, and when findings on postoperative MRI point that gross total resection is feasible [117].

Infants with ependymomas have a very poor prognosis. PFA tumors invading the CP angle pose difficulties concerning total removal, and the residual tumor is associated with a high recurrence rate, and reoperation must be complemented by chemotherapy since radiation or reirradiation is questionable in infants [118]. The benefit of chemotherapy reflects only in a significantly higher rate of event-free survival in very young children [119].

The 10-year survival rates based on surgery and RT in children aged >1 year vary between 50% and 60% [120]. Tumor recurrence and mortality with 5-year progression-free and overall survival rates are about 44% and 65% [121].

Supratentorial ependymomas (STE) are mostly intraparenchymal and generally large, solid, or with a cystic component, frequently heterogeneous, iso- to hypodense

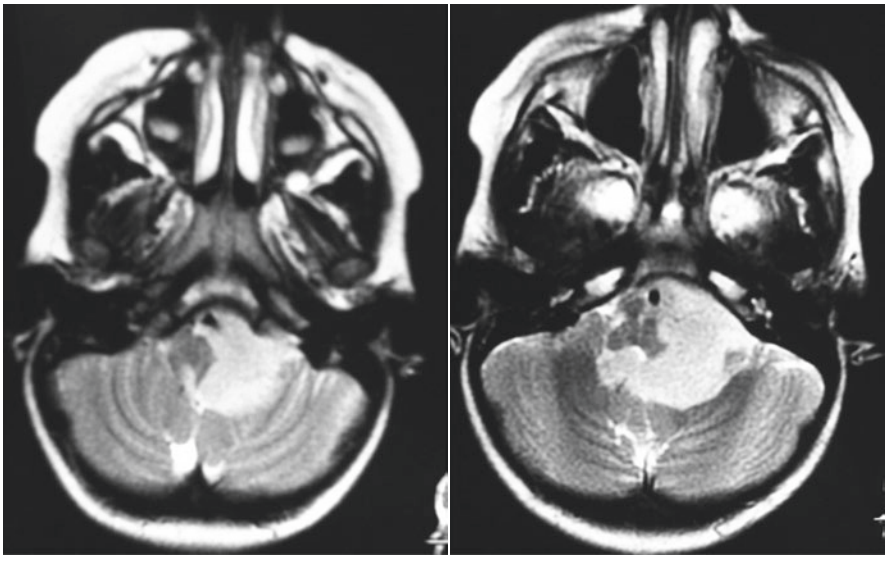

Fig. 2.11 Posterior fossa ependymoma (type A) occupying the fourth ventricle and growing toward the cerebellopontine angle, involving neural and vascular structures

in T1 and hyperintense to white matter in T2, with heterogeneous enhancement. As in infratentorial tumors, CSF dissemination may occur.

There are recognized nine supratentorial subgroups, each with distinct DNAm profile and associated genetic alterations. Two of these subgroups are much more common in children and contain genes RELA and YAP1 [111, 118]. The subgroups associated with RELA fusion are very aggressive and carry a worse prognosis, representing about 70% of the cases. Otherwise, the YAP1-MAMLD1 (Fig. 2.12) has an excellent prognosis [122, 123]. In 2021, Zschernack et al. [123] reported on a series of 18 pediatric non-RELA/non-YAP in which two main patterns were identified: RELA-like and tanycytic ependymomas that seem to represent different biological entities.

In infants and children aged 3 years or younger, the treatments adopted are maximum safe surgery and conventional chemotherapy. Radiation therapy is indicated in supratentorial tumors carrying RELA or YAP fusions and PFA ependymomas. According to Merchant et al. [124, 125], immediate postoperative conformal radiation therapy proved to be more beneficial than delayed the use of RT.

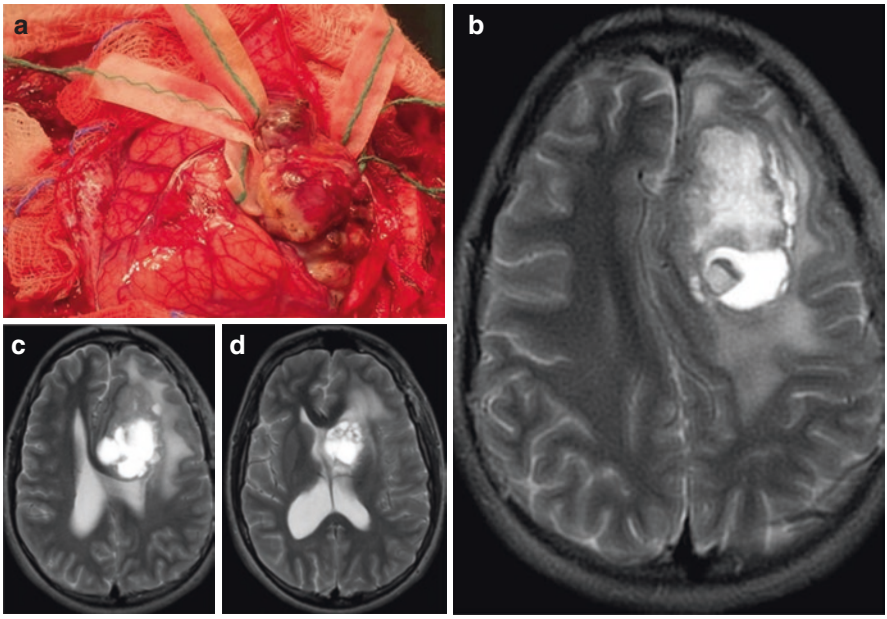

Fig. 2.12 Ependymoma of the left lateral ventricle (YAP fusion). Surgical removal (**a**) and MRI findings (**b**–**d**)

2.18 Teratomas

Germ-cell tumors (GCTs) are rare. The WHO classification system divides intracranial GCTs into germinomas and non-germinatous germ-cell tumors (NGGCT). Among the last, teratomas, mature and immature, predominate in the fetal and neonatal periods [42, 126, 127], declining progressively from 46% to around 5% at the end of the first year, when are surpassed by neuroepithelial tumors [4, 5, 9, 30, 33, 52, 57, 70]. Teratomas arise from multipotent cells, and the three embryologic layers are usually present. Teratomas are frequently diagnosed during the fetal period and are mainly responsible for intrauterine, perinatal, or neonatal deaths [26, 46, 69]. They are frequently voluminous (massive) and heterogeneous solid-cystic contrast-enhancing masses containing fat and calcifications [26, 35, 40, 44, 51, 55, 126]. Most teratomas are in the pineal region, followed by the suprasellar area, with the cerebral hemispheres being more extensively involved in the neonatal period [69, 126].

CSF and serum levels of α-fetoprotein (αFP) and β-human chorionic gonadotropin (β-HCG) help to diagnose tumors and evaluate remnants and recurrent lesions [128]. Survival is poor and rarely exceeds 12%, especially when they are of the massive type, immature, or with malignant transformation [36, 47].

2.19 Desmoplastic Infantile Ganglioglioma (DIG) and Astrocytoma (DIA)

These tumors are rare, usually attain large size, and are mostly hemispheric with mixed cystic and solid areas which show a strong contrast enhancement [129–131]. DIG and DIA are highly vascular and adherent to the dura mater. As a cleavage plan is often found and as they are benign, a favorable clinical course is expected, provided a total removal is achieved. The biological behavior among these neoplasms, chiefly when multiple, is uncertain, and some studies suggest that chemotherapy could play an important role in their management [132].

2.20 Operative Mortality (OP)

OP fluctuates according to the series and is usually related to blood loss and cardiovascular instability [4, 10] which in part reflect the indication criteria adopted to operate or not these patients. Operative mortality progressively decreased in three series of the same institution. In the oldest one (1984), it was 30% [27], declining to less than 10% in 1999 [71] and reaching 4.4% in 2018 [52]. Comparing the series,

the authors question their differences, arguing that discrepancies may be partly explained by the higher success rate of CPPs treated in the last series, due to technological and scientific progress.

2.21 Surgical Complications

Subdural collections are occasionally described and are related to the disproportion between content and continent after tumor removal. Subdural collections may be asymptomatic, resolving over time or requiring shunting diversion [4, 58]. Hydrocephalus may persist, requiring internal ventricular shunting in up to 60% of cases [38, 53, 110, 115]. Cranial nerve paralysis is reported especially in posterior fossa tumors reaching the CPA [115].

2.22 Outcome

Overall survival depends on histopathology and the quality and extent of the resection, the most important prognostic factor [5, 32, 33, 133].

In a survey on the series, the 5-year survival varied widely, ranging from 26% to 81% [10, 71, 133, 134]. Young et al. [10] reported a 5-year survival rate of 81% with a 5-year progression-free survival in 51%. In their series 12 out 13 patients remained alive by the end of the study. The 5-year survival rate in the group who underwent subtotal resection was 100%, and there was a predominance of low-grade tumors. In Jurkiewicz's series [32] the median survival time and progression-free survival were lower in posterior fossa tumors, in patients with benign tumors partially excised and in those that underwent only a biopsy. Regarding academic performance, approximately one-third of the surviving children can attend regular school. Most survivals have neurological, endocrine, psychological, intellectual, and behavioral disorders with a high impact on quality of life [10, 71, 133, 134].

Outcomes correlate also with tumor location. Malignant tumors are more often found in the infratentorial location where up to 60% of the tumors were graded as WHO III and IV [8, 135]. Other authors did not find relationship in mortality and morbidity between infra- and supratentorial tumors [5].

2.23 Adjuvant Therapy

RT in this age group is related to deleterious consequences and should be delayed as much as possible [45, 92, 130, 136, 137]. Due to RT toxicity, chemotherapy is an important option to reduce size and gain control of some tumor with an additional effect on vascularization either pre- or postoperatively (Fig. 2.13) [138]. However, surgical resection remains the mainstay of treatment of these tumors.

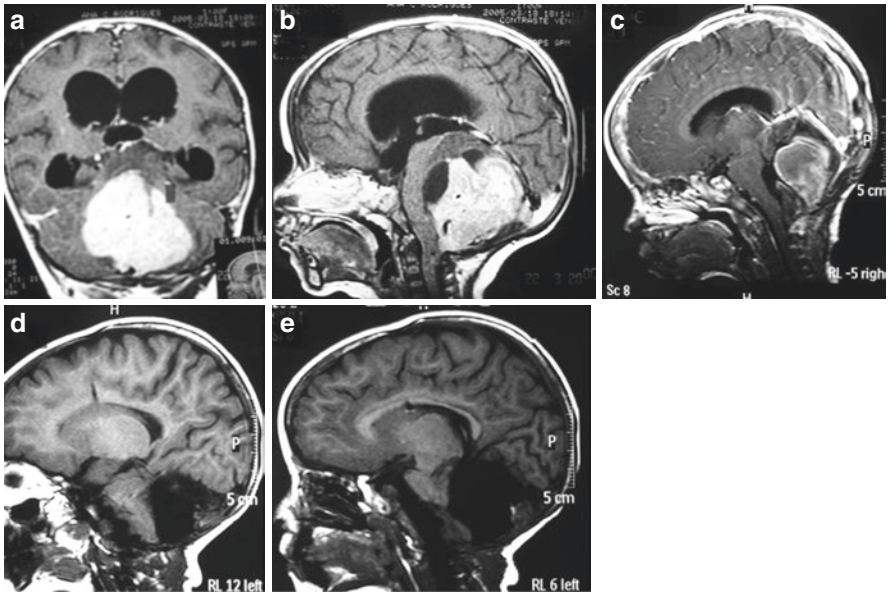

Fig. 2.13 MRI of a 5-month-old female with a posterior fossa ependymoma (**a**, **b**). The procedure was interrupted just after obtaining a sample for biopsy, due to profuse bleeding and hemodynamic instability. After chemotherapy, note decrease in the volume and vascularity of the lesion (**c**) allowing total removal of the mass lesion (**d**, **e**)

2.24 Conclusions

1. Pediatric low-grade gliomas are distinct from adult-type low-grade gliomas and comprise circumscribed and diffuse tumors classified as WHO grade I or II, based on molecular changes and genetic mutations.
2. The oncogenic pathway RAS/MAPK is most commonly involved in human cancers, and the BRAF mutation is commonly seen in pediatric low-grade glioma.
3. Optic pathway gliomas (OPG) are the most frequent low-grade gliomas in the first year of life and associated with neurofibromatosis type 1 (NF1), a known tumor predisposition syndrome.
4. High-grade gliomas are very rare in neonates and infants and are classically supratentorial, with distinct subtypes that correlate with outcomes.
5. Medulloblastoma is the most common malignant brain tumor, and accounts for 10–15% of the tumors in the first year of life, currently classified in four morphologic subgroups, according to the signaling pathways involved in their pathogenesis.
6. Medulloblastoma groups related to young children have a higher metastatic rate.
7. The tumor groups previously denominated PNET include all non-medulloblastoma embryonal neoplasms, are very aggressive, and are occasionally seen in the first 12 months of age.

8. AT/RT, formerly misdiagnosed as medulloblastoma, is related to specific gene abnormality and is chemotherapy-sensitive, and focal radiation therapy has been employed even in children less than 3 years.
9. Half of the choroid plexus tumors are found inside the lateral ventricles, are richly vascularized, and are usually large, and surgery is risky due to intraoperative blood loss.
10. Ependymoma in infants is distinct from adult-type: is highly aggressive, and occupies the CPA, involving neural and vascular structures, which often preclude complete removal of lesions.
11. Teratomas are frequently diagnosed during the fetal period and responsible for intrauterine, perinatal, or neonatal deaths, having a poor survival.
12. Operative mortality in TFYL is usually related to blood loss and cardiovascular instability.
13. Overall survival depends on histopathology and quality and extent of the surgical resection.
14. RT in this age group is rarely considered, chemotherapy is an important adjuvant therapy, but surgical resection remains the mainstay of treatment.

Compliance with Ethical Standards The authors declare no conflict of interest.

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Chapter 3
Supracerebellar Infratentorial Approach, Indications, and Technical Pitfalls

Alican Tahta and Nejat Akalan

3.1 Introduction

Any deep-seated lesion within the brain requires meticulous planning of the surgical approach. All intracranial approaches are designed and modified according to certain basic principles: shortest trajectory from the surface, enabling to use natural anatomical passages for minimal neural tissue interruption, providing gravitational or minimal retraction. The supracerebellar infratentorial approach (SCIT) was described in the early twentieth century originally for pineal tumors but never been popularized until the 1970s. Although it had been an ingenious attempt for that period, this approach was abandoned probably due to inadequate technical circumstances. Introduction of surgical microscope and advancing microsurgical techniques supported by diagnostics and anesthesiology improvements enabled this approach to be a common procedure in modern neurosurgical practice.

Supracerebellar infratentorial approach with its several modifications is a straightforward and safe alternative to reach posterior tentorial incisural space, mainly for pineal, mesencephalic, superior cerebellar hemisphere and vermis pathologies.

3.2 Historical Background

SCIT was first introduced by Krause in 1911, as reported by Brunner and Rorschach [1, 2]. Tandler and Ranzi mentioned the advantages of this surgical corridor [3, 4]. Stein utilized this approach in 1971 for accessing the pineal

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region [5]. SCIT paramedian route was first used by Yasargil to approach the superior cerebellar artery [6]. Evolution of surgical microscope and microsurgical technique has led various surgeons to promote this approach for the lesions of pineal region, upper brain stem, parahippocampal gyrus, and peduncles [7–9]. In 1990, the extreme lateral route was defined by Van den Bergh, and then various studies were carried out to reach the posterior midbrain via this route [8, 10–12].

3.3 Surgical Anatomy

Posterior incisural space, quadrigeminal plate, and ambient cistern can be reached with the SCIT approach, and the thalamus medial temporal lobe can be reached by opening of tentorium [13]. The pineal gland is located inferior to the splenium. The third ventricle is located anterior, and collicular plate is located inferior to the pineal gland. Pulvinars are located laterally. Posteriorly, the vein of Galen is located. This region where the pineal gland and the vein of Galen are located is called the posterior incisural space. There are neural tissues around the posterior incisural space (except its posterior). Its anterior wall is formed by the pineal gland, superior and inferior colliculi, lingula, and superior cerebellar peduncle. Habenular and posterior commissures provide the gland's attachment with the third ventricle. The roof of the posterior incisural space is formed by the splenium and the terminal part of the crura of fornices. The culmen of the vermis, central lobule, and quadrangular lobules are located on the floor of the posterior incisural space. The posterior incisural space extends inferiorly to the cerebellomesencephalic fissure. The pulvinar, crus of the fornix, dentate, and parahippocampal gyri are on the lateral wall.

The posterior cerebral artery crosses the crural and ambient cisterns, reaches the posterior incisural space, and gives off its terminal branches. The superior cerebellar artery passes under the trochlear nerve and over the trigeminal nerve and enters the cerebellomesencephalic fissure.

Internal cerebral veins, basal veins, the vein of Galen and their tributary veins pass through the posterior incisural space. The internal cerebral vein passes through the velum interpositum and enters the posterior incisural space, and then joins with the contralateral internal cerebral vein. Bilateral internal cerebral veins merge to form the vein of Galen. Anterior cerebral and deep sylvian veins combine to form the basal vein. Basal vein drains into the internal cerebral vein or vein of Galen. Pineal veins originate from habenular trigone and course superior or inferolaterally and drain into the internal cerebral vein or the vein of Galen. The vein of Galen drains into the straight sinus inferior to the splenium.

3.4 Preoperative Workup

Decision on a particular approach requires a thorough evaluation of the lesion: origin, size, texture, and vascular and neural relationships. For any lesion within the perimeter comprised by this approach, the first step is to define the origin. Magnetic resonance imaging (MRI) is the gold standard providing information on not only the origin but also the dimensions, extension, and histological structure of the lesion, which would help to decide on the most appropriate approach (Fig. 3.1).

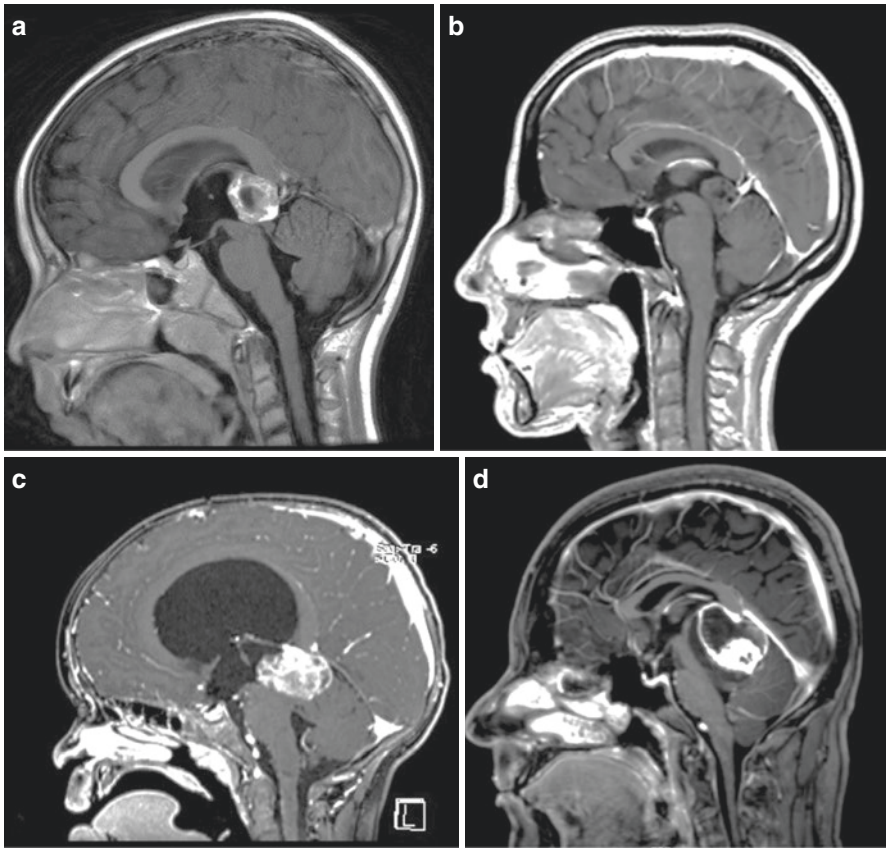

Fig. 3.1 Variety of pineal region tumors with different relationship to tentorial incisura with different tentorial angles. (**a**) Moderate-sized tumor located equally over and under the tentorial edge with a moderate tentorial angle. (**b**) Similarly sized tumor with the previous but located totally under tentorium perfectly suitable for an infratentorial approach despite a very high tentorial angle. (**c**) Larger, homogenously enhancing tumor intruding to the third ventricle but lying entirely under the tentorium facilitates an infratentorial approach. (**d**) Large, cystic tumor entirely infratentorial overhanging cerebellum rather than third ventricle in which SCIT approach would be the only choice

Standard MRI sequences, T2- and T1-weighted images with and without contrast (axial, sagittal, and coronal) should be supplemented by diffusion and MR angiography and venography. Besides the basic characteristics of the lesion, hydrocephalus, as a frequent feature, can readily be appreciated as a main determinant for timing surgery. Evaluation of the tentorial angle is important to appreciate the extent of neck flexion during positioning (Fig. 3.1). More neck flexion may be required in patients with steep tentorial angle. It may be more challenging in obese patients with short neck and steep tentorial angle because of inadequate flexion. SCIT approach requires information on the variations of venous structures. Dural venous sinuses should be examined in detail with MRI, MR angiography, or CT angiography before surgery. Transverse and sigmoid sinuses may show variations and craniotomy should be planned accordingly. The posterior incisural space has the most complex venous relationships in the cranium, because the internal cerebral and basal veins and many of their tributaries converge on the vein of Galen within this area [14]. Compared to its alternatives, infratentorial approach especially for pineal region tumors provides a direct encounter to the lesion without interfering the upward and laterally displaced deep venous system. Furthermore, relationship of deep venous structures with the tumor can only be appreciated following removal is the main disadvantage compared to supratentorial route. Deep venous structures may be displaced posteriorly in thalamic tumors, which may prevent the use of SCIT approach.

3.5 Indications

Superior part of the cerebellum and vermis, posterior incisural space, posterolateral part of the upper pons and mesencephalon, posterior third ventricle, parahippocampal gyrus, and pineal region can be reached via midline and off-midline variations of the SCIT approach. Germ cell tumors, pineoblastomas, astrocytomas, meningiomas in pineal region, tumors in posterior third ventricle, tentorial vascular malformations, mesencephalic cavernomas and pilocytic astrocytomas, aneurysms of superior cerebellar artery, petrous apex and tentorial meningiomas, astrocytomas, arteriovenous malformations, and cavernomas located in parahippocampal gyrus and posterior hippocampus are appropriate targets for SCIT.

3.6 Technique

3.6.1 Surgical Position

SCIT approach can be performed in the sitting or semi-sitting positions, prone or three-quarter prone positions depending on the personal preference of the surgeon [15, 16]. Semi-sitting position is ideal for SCIT approach according to our

experience. Widened surgical corridor without retraction by the help of both gravity and evacuation of cerebrospinal fluid even in untreated hydrocephalic patients can be achieved with semi-sitting position. In addition, low venous pressure along with gravity drainage of blood and cerebral spinal fluid from surgical field avoids continuous need for aspiration. On the anesthesiology side, sitting position facilitates direct access to the endotracheal tube, chest wall, and extremities with lower airway pressure requirement to expand the chest wall [17]. However, air embolism is a traditionally feared complication of sitting position. Although it had been introduced into clinical practice in 1913, due to the potential serious complications and malpractice liability claims, more than half of the neurosurgical centers have abandoned sitting position after the 1980s [18].

Implementation of invasive monitoring techniques along with precordial Doppler, transesophageal echocardiography, continuous end-tidal volume monitoring, and central venous line to the right heart can readily detect and reverse the detrimental effects of air embolism without abandoning the procedure. Nevertheless, patients with cardiac defects are highly susceptible to air embolism with catastrophic results. Therefore, preoperative Doppler ultrasonography (USG) is recommended to rule out the presence of cardiac right-left shunt. If the patient has a persistent foramen ovale, it is recommended to avoid sitting position.

Sitting position requires careful planning and begins with placing three-pin skull clamp after induction of anesthetics. Operating table is tilted gradually until the torso is 60–90° to horizontal. Patient's legs are elevated until the knees are at heart level, and compression stockings should be worn to avoid venous pooling. Compression should be avoided by placing pads under the articular joints. Neck flexion is carried out until the tentorial line is parallel to horizontal avoiding compression of internal jugular veins and kinking of the endotracheal tube (Fig. 3.2a). Surgeon's comfort will increase as the working angle becomes vertical. In addition, visualization of the pineal region and the posterior part of the third ventricle will be facilitated with forward tilt of the operating table.

3.6.2 Incision, Craniotomy, and Dural Opening

Vertical midline incision starting 2 cm above the inion and extending to the foramen magnum is preferred (Fig. 3.2b). The posterior arch of C1, spinous process and laminae of C2, and foramen magnum do not need to be exposed. Exposing above and below of superior nuchal line which corresponds to transverse sinus is enough.

Suboccipital craniotomy revealing the transverse sinuses and torcula is performed by using two burr-holes on transverse sinuses laterally (Fig. 3.2c, d). Air embolism should be prevented by applying bone wax to the bone edges. Wide exposure of transverse sinuses is important. Inferior edge of the transverse sinus should be mobilized superiorly to expose superior surface of the cerebellar hemispheres (Fig. 3.3a). This mobilization should not be done too tight due to the risk of transverse sinus thrombosis. Extending the craniotomy to the foramen magnum is not

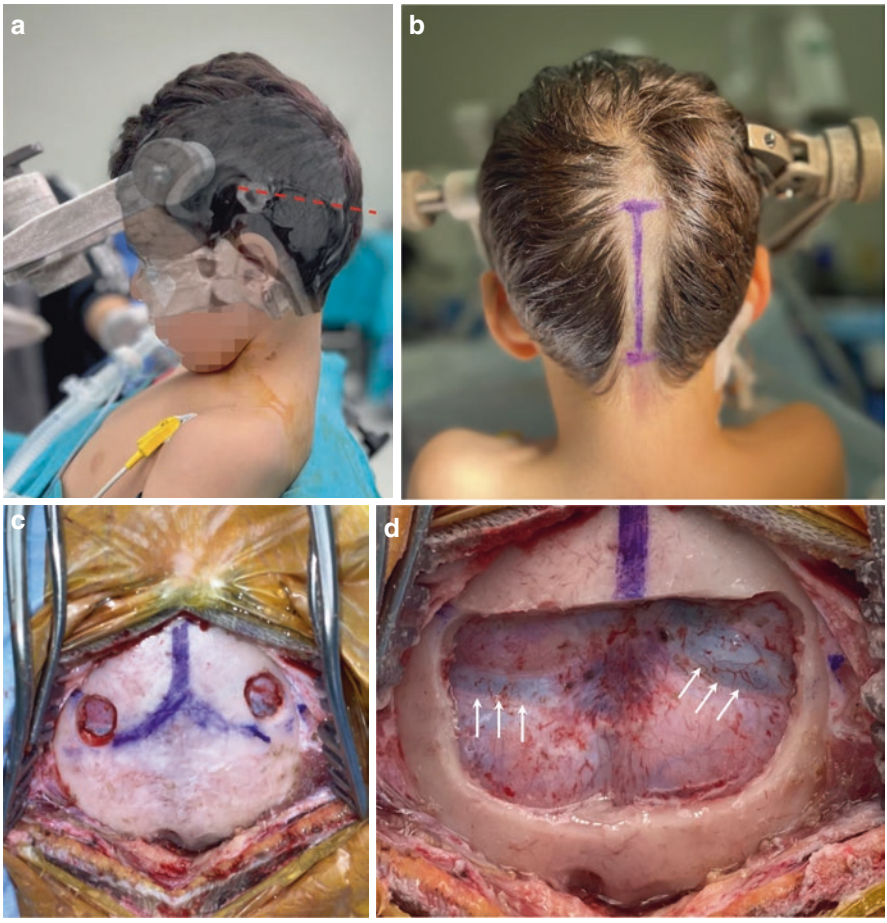

Fig. 3.2 (**a**) Neck flexion is carried out until the tentorial line becomes horizontal. It should be ensured that the internal jugular veins and the endotracheal tube are not compressed. (**b**) Vertical midline incision starting 2 cm above the inion and extending to the foramen magnum. (**c**) Two burr-holes are performed above transverse sinuses laterally. (**d**) Suboccipital craniotomy revealing the transverse sinuses and torcula is performed (arrows, left and right transverse sinus

required in routine cases. However, if hydrocephalus is detected in the preoperative period and CSF drainage is planned, the inferior edge of the craniotomy can be extended to the foramen magnum to provide CSF drainage from the cisterna magna without the need to use Keen's point for ventricular drainage.

The dura is opened curvilinear, with its base in the transverse sinuses, starting from the transverse-sigmoid sinus junction on both sides. It is necessary to lengthen the dural incision as close as possible to the junction in lateral sides. Care should be taken in terms of transverse sinus injury. Then, dura incisions starting from both sides are connected in the midline. Superficial part of the falx cerebelli should be secured with sutures to prevent bleeding and air embolism in case of encountering

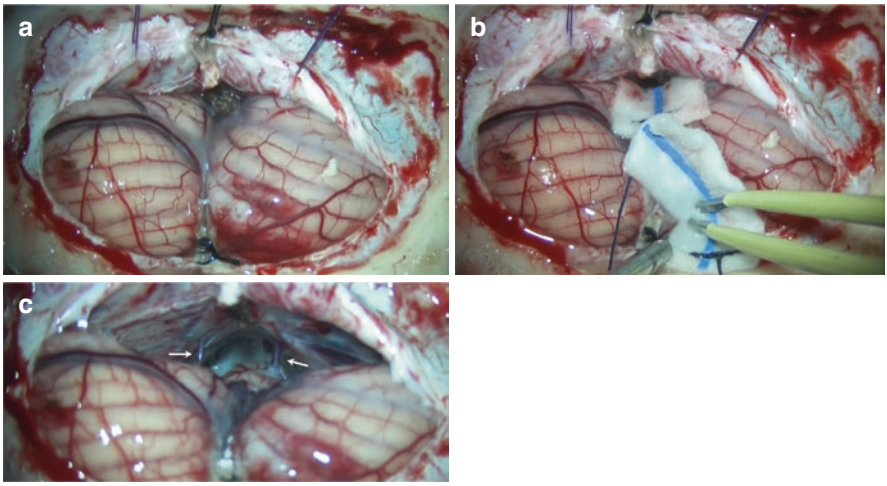

Fig. 3.3 (**a**) Inferior edge of the transverse sinus is mobilized superiorly via tack-up sutures to expose superior surface of the cerebellar hemispheres. Cerebellar tissue fills the dural opening due to hydrocephalus. (**b**) CSF drainage from the cisterna magna is performed. (**c**) Descending of cerebellar hemispheres and revealing of supracerebellar route after CSF drainage (arrows, bridging veins between the superior surface of the cerebellum and the tentorium are visualized bilaterally)

inferior occipital sinus, especially in pediatric cases. Superior retraction of dura flap can be achieved by sutures. Inferior edge of the dural flap acts as a support for the cerebellum and prevents the cerebellar hemispheres from sagging due to gravity. When CSF drainage from the cisterna magna is required, retracting of the inferior edge of the dura would be enough (Fig. 3.3b). After the dura is opened and retracted appropriately, the operating microscope should be brought to the operating field.

3.6.3 Microsurgical Procedure

The arachnoid bands extending from the surface of the cerebellum to the inferior of the transverse sinus are divided carefully under high magnification till reaching superior surface of the cerebellar hemispheres. Minor arachnoid bands between the cerebellum and tentorium, running superior to the cerebellar hemispheres and inferior to the transverse sinus, should also be divided. Bridging veins between the superior surface of the cerebellum and the tentorium will be visible as these bands are separated (Fig. 3.3c). However, some veins may interfere with surgical trajectory. It is recommended to preserve all the veins as much as possible, because it is difficult to predict whether a major venous infarction may occur after vein(s) interruption, due to the large venous variation in this region.

Nevertheless, if any vein at the surgical trajectory is anticipated to be lacerated due to stretching at the advanced stages of the surgery, it is recommended to coagulate and cut

at the beginning as venous tears during surgery can cause excessive bleeding and air embolism. Coagulation and cutting of the vein should be done close to the cerebellar surface. Thus, possible tentorial sinus thrombosis is prevented, and re-coagulation becomes easier in case of incomplete coagulation. Brain retractors can be used if adequate cerebellar relaxation and supracerebellar opening cannot be achieved after CSF aspiration and drainage. However, surgeon should avoid prolonged retraction. Retraction of the cerebellum can be avoided by taking advantage of the effect of gravity and low venous pressure if the sitting/semi-sitting position is preferred [19].

The arachnoid of the quadrigeminal region is usually thickened in existence of tumor. These thick arachnoid membranes must be intersected to open the cisternal space at the level of the cerebellar culmen. Arachnoid membranes should be opened by sharp dissection (Fig. 3.4a). This opening should be kept close to the vermis and cerebellar hemispheres to prevent damage to deep veins. Deep veins located anteriorly become visible as this arachnoid is dissected. Surgical corridor is created by pushing these veins to the right and left sides (Fig. 3.4b). Inferior part of the vein of Galen is exposed superiorly to this corridor. Precentral cerebellar vein (connecting vermis to the vein of Galen) can be visualized after deep veins are exposed (Fig. 3.4c). This vein may prevent surgical trajectory when approaching midline lesions from the SCIT midline route. Therefore, this vein may be needed to be sacrificed in the midline approach. Sacrificing this vein usually does not cause any significant clinical problems. However, some authors do not recommend coagulation of this vein [20]. The posterior wall of the tumor is reached after transection of this vein (Fig. 3.4d). Meanwhile, it should be noted that the trajectory is toward the vein of Galen.

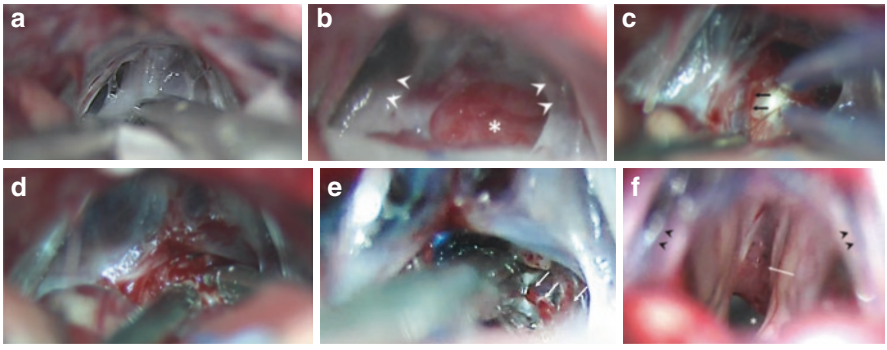

Fig. 3.4 (**a**) Arachnoid membranes of the quadrigeminal region are usually thickened in existence of tumor. Their opacity obscures the underlying anatomy and meticulous sharp dissection is mandatory to reach the target area. (**b**) Tumor is visualized after dissection of thick arachnoid membranes (asterisk). Bilateral internal cerebral veins can also be seen (arrowheads). (**c**) Precentral cerebellar vein (arrows) is visualized after deep veins are exposed. (**d**) Tumor debulking is achieved between deep cerebral veins. (**e**) Pineal arteries (white arrows) can be visualized lateral to tumor after tumor debulking. (**f**) Posterior third ventricle (asterisk) and choroid plexus on the roof of the third ventricle (white arrow) can be clearly visualized after removal of tumor (arrowheads: left and right internal cerebral veins)

The inferior part of the quadrigeminal plate may not be visualized despite retraction of the culmen. Meticulous arachnoidal dissection provides significant downward displacement of the superior vermis, so minimal retraction can be provided. In this way, the inferior part of the quadrigeminal plate can be easily visualized by bringing the operating microscope to the more craniocaudal direction. Superior retraction of the transverse sinuses with tack-up sutures provides larger surgical area, so bringing operating microscope to more craniocaudal direction can be achieved. These maneuvers are not necessary if the tumor is completely in the pineal region and visualization of the inferior tectal plate is not required.

The pineal arteries are usually located lateral to the tumor and anterior to its superior pole (Fig. 3.4e). Therefore, these arteries cannot be clearly visualized at the beginning of surgery. Likewise, the superior cerebellar artery and posterior cerebellar artery cannot be visualized as well. Sharp dissection, especially at the lateral borders of the tumor, prevents arterial injury and may help unveiling the relationship of the tumor with these arteries.

Removal of the tumor proceeds below the vein of Galen, internal cerebral veins, and basal vein of Rosenthal. Tumor dissection should continue from the inferior pole to the lateral margins. Caution should be exercised because the tumor may be associated with the collicular region in the inferior border. Tumor's relationship with the surrounding venous and arterial structures will be more clearly demonstrated as it is debulked. Ultrasonic aspirator can be used in hard-consistent tumors and in cases where cleavage cannot be found. Intracranial pressure will decrease with CSF drainage when the third ventricle is reached, which will facilitate tumor debulking (Fig. 3.4f). Dissecting the superior pole is easier when the tumor shrinks. Care should be taken in the pineal veins draining into the deep veins. These veins should be cut with microscissors after coagulation. Internal cerebral vein and the vein of Galen injuries can be encountered.

Bleeding cessation is expected when the tumor is totally removed. Residual lesion should be suspected if bleeding continues. Hemostasis can often be achieved by mechanical compression with the help of cottonoids. Any tumor remnant adherent to arteries and especially major venous structures has to be inevitably left behind as injury to neural and vascular structures in this region can cause severe morbidity.

3.6.4 Complications of the Approach

There are various complications associated with the SCIT approach. These can be grouped under three main headings as complications related to sitting/semi-sitting positions, complications related to posterior fossa surgery, and complications related to the approach itself.

Position-related complications include dural venous sinus injury and venous air embolism. Venous sinus injury may be seen during opening of burr-hole and craniotomy. If there is a venous sinus injury, the bone flap should be removed quickly, and the damaged part of the venous sinus should be repaired. Sometimes, despite

sinus injury, bleeding may not occur due to low venous pressure. In these cases, bleeding areas should be revealed by applying positive pressure, and hemostasis should be ensured. Bone edges should be covered with bone wax after the craniotomy is accomplished. Inferior occipital sinus bleeding is common in pediatric patients. Therefore, inferior occipital sinus should be completely closed with lock stitch while the dura is opened in the midline in pediatric patients.

Perioperative complications can be encountered due to working through a deep and narrow surgical corridor. There are bridging veins of various numbers and sizes with wide variation between the cerebellar hemispheres and the tentorium through surgical corridor. Precentral veins are found in the midline and hemispheric veins in the lateral. These veins can be coagulated if they interfere with the surgical corridor. However, there is possibility of life-threating venous infarction although it is rarely seen in reports in the literature. This infarction is usually due to disruption of the bridging veins between the superior surface of the cerebellar hemispheres and the tentorium. According to the literature review by Smrcka and Navratil, venous infarction was detected in 2 of 578 patients and the risk of venous cerebellar infarction was calculated as 0.345% [21]. Specific preoperative examination is not available to avoid this complication. Some authors report sacrificing a large bridging vein can be tolerated due to developed anastomosis. Sacrificing multiple small veins is reported to be less tolerated [22]. There is a correlation with the number of sacrificed veins and risk of complications [23]. Therefore, the possibility of complications can be reduced by sacrificing as few veins as possible during the operation. Also, the possibility of venous infarction can be reduced by minimizing cerebellar retraction with sufficient CSF drainage.

3.6.5 Midline vs. Off-Midline Routes

Distance between the inion and the transverse-sigmoid sinus junction was divided into three in previous studies [24]. The midline route was described as a surgical corridor below torcula in the midline, the paramedian route is the corridor along the junction of medial and intermediate thirds, the lateral route is the corridor along the junction of intermediate and lateral thirds, and the extreme lateral route is the corridor along the junction of transverse and sigmoid sinuses.

SCIT approach, midline route, was developed to reach tumors located in the pineal region and posterior third ventricle. Lateral and inferior visualization of the quadrigeminal plate is limited due to the angle of the tentorium and the obstructive apex of the culmen in this route. For this reason, SCIT off-midline routes (paramedian, lateral, and extreme lateral) have been developed to overcome this disadvantage of the midline route and at the same time use the advantages of the SCIT approach. Posterior incisural space can be accessed with more lateral angle, middle incisural space can be exposed, less bridging veins can be sacrificed along the surgical corridor, the slope of the culmen can be avoided, and the need for cerebellar retraction can be reduced with off-midline routes.

In the study conducted by Matsuo et al., the midline and three off-midline routes of the SCIT approach were compared [24]. According to this study, midline route is the shortest and direct corridor to the pineal gland. Off-midline routes are 5 mm deeper than the midline route. However, slope of the tentorial surface is steepest in midline route. The angle decreases as the approach shifts extreme lateral route. The slope of the tentorial surface in midline route was calculated as twice the angle in the extreme lateral route. Approach angle is the same in midline, paramedian, and lateral routes. However, it is slightly higher in extreme lateral route which allows for better manipulation of surgical instruments.

Surgical resections of vascular malformations located at the pontomesencephalic junction [25], thalamic and pontomesencephalic gliomas [16, 26], parahippocampal lesions [27, 28], and extra axial tumors in the petroclival region [29, 30] using off-midline routes have been described in previous studies.

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Chapter 4
The Cerebellar Mutism Syndrome: Risk Assessment, Prevention and Treatment

Jonathan Kjær Grønbæk, Ditte Boeg Thomsen, Karin Persson, René Mathiasen, and Marianne Juhler

4.1 Introduction

In childhood, brain tumours are the second most common cancers, and half of them are in or near the cerebellum. The primary treatment is surgery, sometimes more than one operation, which contributes to a high overall 5-year survival. However, approximately one out of four patients experiences a severe complication known as

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the cerebellar mutism syndrome (CMS). It is characterized by post-operative speech impairment (POSI), defined as speech capacity limited to a few words (reduced speech) or complete absence of speech (mutism), and emotional lability seen as inconsolable crying, incongruent emotions and poorly contained agitation. These are often accompanied by loss of muscle strength in one or both sides of the body and difficulties in movement coordination and swallowing.

CMS is thought to occur due to surgical injury to anatomical structures connecting the cerebellum and the brainstem, which harbour neural networks between the cerebellum and the cerebrum.

This chapter introduces the general principles of language acquisition and the role of the cerebellum in language followed by a section about the historical development of the terminology CMS. This introduction leads to exploration of the clinical risk factors for development of CMS considering them either modifiable or unmodifiable. We further report the historical development in incidence of CMS in relation to progress in pre-operative risk assessment and prevention strategies and discuss available and hypothetical options for intervention.

4.1.1 Language Acquisition

Language acquisition is the spontaneous process of learning to communicate with other people by perceiving and producing meaningful words and sentences. Language acquisition involves both higher-cognitive developmental processes (acquiring *language* as a symbolic system) and motor developmental processes (developing motor skills to produce fluent *speech*). While developments at the two levels are intertwined, especially in the first years of life, language and speech are underpinned by distinct neural networks [1], and each can be independently impaired [2].

Language During the second half of the first year of life, children develop skills to segment the continuous speech stream and recognize recurring word forms, depending among other skills on statistical learning [3]. At the same time, they begin to associate these auditory word forms with meanings, causing a shift in neural response to spoken language in the left frontal region [4]. Children begin to produce words themselves around their first birthday, and over the next few years, their word learning escalates: during the preschool years, they acquire many new words each day, and around age 5, their receptive and productive vocabularies contain thousands of words [2, 5]. Alongside increases in vocabulary breadth, speed of lexical access (word finding) increases over childhood and adolescence [6]. From around 18–20 months, children begin to combine words in two-word utterances, and over the next years, they develop grammatical competencies to comprehend and produce sentences of increasing length and structural complexity [5, 7]. During the third year of life, the first grammatical markers typically emerge (e.g. plural and past tense endings). There is wide variation in children's acquisition of words and gram-

mar, depending on characteristics of their target language, on the specific linguistic input they experience in their social environment and on their own sociocognitive and general cognitive abilities.

Speech Children's speech skills comprise skills of motor planning, execution and control. These skills develop to allow them to deliver words and sentences fluently at an appropriate speed with appropriate loudness, pitch and rhythm, with normal voice quality (not too breathy, strained, nasal or hoarse) and with clearly pronounced speech sounds and syllables in correct order, without pervasive repetitions, omissions or breakdowns. For pronunciation of speech sounds, studies show that motor-speech skills develop markedly from the third to the fourth year of life, where most children can articulate most speech sounds precisely [8]. Children's abilities to pronounce complex syllables with consonant clusters may continue to develop until around age 5 [9], with variation between languages. For other aspects of motor-speech skills, research into typical child development is still sparse, making assessment of deviations at different ages less certain.

4.1.2 The Cerebellar Role in Language and Speech

The cerebellar role in coordination of motor functions is well established [10], and a disorder of motor-speech control, ataxic dysarthria, is the communication disorder most often seen in cerebellar pathology in adults [11]. However, the cerebellum was also early on suggested to play a role in cognitive processing, affective regulation and linguistic functions. Dating back to 1831, Combette described impaired affection, cognition, speech and motor function in an 11-year-old girl with agenesis of the cerebellum [12]. Schmahmann and Sherman referred to this case in their characterization of the cerebellar cognitive affective syndrome, which is characterized by impaired executive function, spatial cognition, personality changes and linguistic difficulties including agrammatism, impaired naming and decreased verbal fluency [13].

Production of spoken words is a complex process considered to involve lexical selection, phonological encoding, phonetic planning and articulation [14]. One dominant psycholinguistic theory is that words as units of meaning are retrieved from a mental dictionary (lexical selection) and that their sound structure is retrieved from the mental lexicon and mapped into the rhythm of the word in context (phonological encoding), planned for motor processing of the individual syllables (phonetic planning) and implemented as a specific coordinated motor output of articulation [14]. The cerebellum may be involved at all levels. It should be noted that this model is based on adults and may be less accurate for children, as processes of spoken-word production are likely to change across development [15].

As for the level of articulation, the cerebellum, as the motor function coordinator, expectedly plays an important role in overt articulation where speech sounds are produced [11]. As for the level of phonetic planning, Ziegler et al. suggest that

studies of adults do not support cerebellar involvement [16], but children with cerebellar tumours may suffer from apraxia of speech, a disorder of motor-speech planning and programming, both before and after tumour resection [17, 18]. Whether this discrepancy reflects a decrease in cerebellar involvement in phonetic planning across development or sparse investigation of cerebellar involvement in adult phonetic planning is currently unclear. As for retrieval of words from the mental lexicon, studies using phonemic (sound-based) and semantic (meaning-based) fluency tasks suggest that the cerebellum is involved in higher-order linguistic processes of retrieving words as sound structures (level of phonological encoding) and as units of meaning (lexical selection) [16].

Beyond the domain of word production, a line of studies have demonstrated cerebellar involvement in higher-order language processes such as verbal working memory and grammatical processing, including both production and comprehension [16]. Based on a meta-analysis of neuroimaging studies examining cerebellar activation in neurotypical adults, Stoodley and Schmachmann proposed an internal functional topography of the cerebellum [19], with distinct areas supporting motor control including speech and higher-order processes including language. Language processing in the cerebellum has been shown to be cross linked with the contralateral cerebral hemisphere with language domains typically lateralized to the left side [20].

4.1.3 Cerebellar Mutism Syndrome

CMS is a complication of posterior fossa tumour resection with the vast majority reported in children. It is characterized by onset of mutism or severely reduced speech and emotional lability after the resection. Intriguingly, the resection is usually followed by a time period of a few days where the child remains able to speak. Hypotonia and ataxia are accompanying symptoms in most children. Brainstem dysfunction and cranial nerve deficits (CND), including dysphagia, are also common [21]. Speech usually returns within weeks to months of onset; however, it is often followed by long-lasting dysarthria and long-term neurocognitive sequelae affecting the quality of life in many patients [21–29].

As CMS is seen in 8–39% of patients, varying with different study designs and populations, it is both common and severe [30–36].

Even though CMS has been known as a complication for several decades, inconsistency in terminology and definition of the syndrome still exist. This reflects not only an academic debate but also the difficulty in assessment and scoring of this severe syndrome.

4.1.3.1 Terminology

In 1958 Daly and Love described *akinetic mutism* in a 14-year-old boy after tumour resection of an astrocytoma in the fourth ventricle:

> On command he would grasp his father's hand. Although he lay inert, infrequent movements of all extremities suggested that no paralysis existed. He responded to aspiration by coughing and gagging, but he did not speak or utter any sounds [37]

Some slow gradual improvement was seen 1 week post-operatively, though he remained mute for a month.

In their report they referred to a case from 1941 described by Cairn et al., who introduced the term *akinetic mutism* seen in a patient with an epidermoid cyst in the third ventricle [38].

In 1984 Wisoff and Epstein reported mutism as a component of a *pseudobulbar syndrome* in patients after resection of large midline vermian and fourth ventricular tumours. With a delayed onset, the patients developed supranuclear nerve palsies, mutism and emotional lability which resolved over several weeks [39].

The term *cerebellar muteness* was introduced in 1985 as a complication of bilateral surgical injury to the dentate nuclei of the cerebellum in children [23]. *Posterior fossa syndrome* was later introduced as a triad of symptoms including speech difficulty, irritability and nystagmus [40].

Cerebellar mutism syndrome has been used interchangeably with PFS, though a clearer consensus of the definition of CMS was reached by the Posterior Fossa Society:

> Post-operative pediatric CMS is characterized by delayed onset mutism/reduced speech and emotional lability after cerebellar or 4th ventricle tumor surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the cerebellar motor syndrome, cerebellar cognitive affective syndrome and brainstem dysfunction including long tract signs and cranial neuropathies. The mutism is always transient, but recovery from CMS may be prolonged. Speech and language may not return to normal, and other deficits of cognitive, affective and motor function often persist. [21]

Previous studies have used various definitions of the syndrome. A large prospective study investigated if 'symptoms of CMS were present after the initial tumor resection' in children with MB [30]. The survey of symptoms included mutism, ataxia, hypotonia and irritability measured in severity by the duration of the symptoms. Mutism was not obligatory for the patients to be considered having CMS as 6 out of 107 (6%) did not have mutism.

A study of PFS assessing children undergoing posterior fossa tumour resection 'to identify those children developing PFS' without further specification of the diagnostic criteria reported that 6 out of 41 patients (14%) had PFS without mutism, of whom 5 had reduced speech [31].

A recent study considered PFS as impaired post-operative verbalization in children undergoing posterior fossa tumour surgery. They introduced the subcategories PFS1 with 'complete absence of vocalization (mutism)' and PFS2 with 'paucity of

speech with inability to string 3-word sentences' [41]. This distinction was made to be able to differentiate between severities of speech impairment and to reflect a spectrum of post-operative speech in these children. This study argued that this definition is in accordance with the consensus definition by the Posterior Fossa Society and that it is supported by a recent expert survey of PFS in which all 32 responders considered PFS as continuous rather than dichotomous [42]. Most responders (16 out of 21, 76%) considered mutism to be one symptom pathognomonic for PFS.

4.1.3.2 Incidence

The incidence of CMS is clinically relevant when informing the patients and their parents about possible surgical complications. Historically, the incidence of CMS varies extensively between studies according to study populations and diagnostic criteria; however, the overall incidence is unchanged or even increased over the last few decades (Fig. 4.1).

Thus, despite considerable advances in imaging and surgical technology, CMS is still frequent more than 40 years after the first description of this surgical complication. This calls for improved risk assessment, prevention and treatment options.

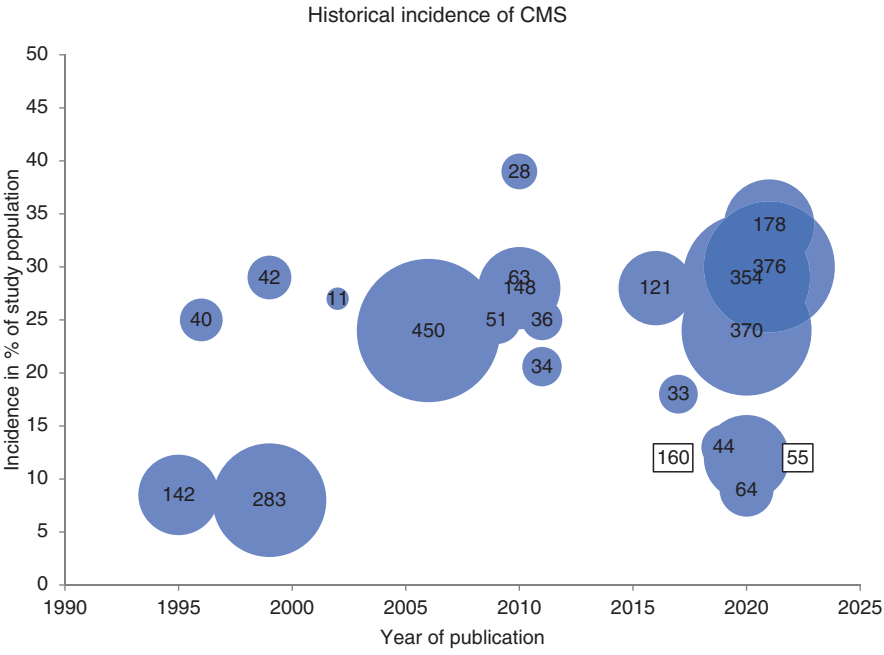

Fig. 4.1 Historical incidence of CMS as reported in studies since 1995 [17, 30–36, 41, 43–55]. The size of the bubbles indicates size of the study population

4.2 Risk Factors for the Cerebellar Mutism Syndrome

Since the first description of CMS, several studies have identified numerous risk factors for development of the syndrome. In this chapter, we divide the risk factors into unmodifiable (Table 4.1) and modifiable (Table 4.2) as we find this differentiation useful in addressing risk stratification (unmodifiable risk factors) and prevention (modifiable risk factors), respectively. In the tables, we considered a prospective design and large study population indicators for a high level of evidence, whereas case-control design and small study sample were considered indicators for a lower level of evidence.

Table 4.1 Unmodifiable risk factors for CMS

Risk factor	Direction of association[a]	Level of evidence[b]	Reference	*n*[c]
Lower age	–	+++	Robertson 2006 [30]	450
	↑	+++	Grønbæk 2021 [55]	426
	↑	+++	Khan 2021 [41]	178
	↑	+++	Toescu 2020 [54]	167
	↑	++	Korah 2010 [44]	63
	–	+	Law 2012 [56]	51
	–	+	McMillan 2009 [34]	51
	–	+	Catsman-Berrevoets 1999 [46]	42
	–	+	Wells 2010 [36]	28
Sex	–	+++	Robertson 2006 [30]	450
	–	+++	Grønbæk 2021 [55]	426
	–	+++	Khan 2021 [41]	178
	–	+	Catsman-Berrevoets 1999 [46]	42
	–	+	Wells 2010 [36]	28
Left-handedness	–	++	Grønbæk 2022 [57]	250
	↑	+	Law 2012 [56]	51
Low socioeconomic level	↑	+	Kupeli 2011 [43]	36
Pre-operative language impairment	↑	+	Di Rocco 2011 [17]	34
Tumour				
Medulloblastoma histology	↑	+++	Grønbæk 2021 [55]	426
	↑	++	Catsman-Berrevoets 2010 [31]	148
	↑	+	Doxey 1999 [33]	253
	↑	+	Law 2012 [56]	51
	↑	+	Catsman-Berrevoets 1999 [46]	42
	↑	+	Kupeli 2011 [43]	36
	↑	+	Di Rocco 2011 [17]	34
	↑	+	Kotil 2008 [58]	32
Atypical teratoid rhabdoid histology	↑	+++	Grønbæk 2021 [55]	426

(continued)

Table 4.1 (continued)

Risk factor	Direction of association[a]	Level of evidence[b]	Reference	n[c]
Brainstem infiltration or compression of the tumour	↑	+++	Robertson 2006 [30]	450
	↑	+	Doxey 1999 [33]	253
	↑	+	Pols 2017 [59]	71
	↑	+	Korah 2010 [44]	63
	↑	+	McMillan 2009 [34]	51
	↑	+	Wells 2010 [36]	28
Midline tumour location	–	+++	Robertson 2006 [30]	450
	↑	+++	Grønbæk 2021 [55]	426
	↑	++	Catsman-Berrevoets 2010 [31]	148
	↑	+	Korah 2010 [44]	63
	–	+	Law 2012 [56]	51
	↑	+	Catsman-Berrevoets 1999 [46]	42
	↑	+	Kupeli 2011 [43]	36
	↑	+	Kotil 2008 [58]	32
	↑	+	Wells 2010 [36]	28
Cerebellar hemispheric location	↓	+++	Robertson 2006 [30]	450
	↓	+++	Grønbæk 2021 [55]	426
Larger tumour volume	–	++	Catsman-Berrevoets 2010 [31]	148
	↑	++	Toescu 2020 [54]	167
	↑	+	Pols 2017 [59]	71
	↑	+	Law 2012 [56]	51
	–	+	McMillan 2009 [34]	51
	↑	+	Catsman-Berrevoets 1999 [46]	42
	–	+	Wells 2010 [36]	28

[a] ↑ = associated with a higher risk of CMS, – = no association, ↓ = associated with a lower risk
[b] Level of the statistical evidence based on study design and power. (+) indicates a vague design or no control group
[c] Number of patients in the study

4.2.1 Unmodifiable Risk Factors

Age Myelination begins prior to birth and the brain further matures until the mid-twenties [70]. In the early years of life, children begin developing their speech and language, and they generally pronounce all speech sounds of their language at the age of 7 years [9].

Recent large studies have found a higher risk of CMS associated with lower age of the patient [41, 54, 55]. This corroborates some earlier findings [44], contradicts others [30, 46, 56] and raises the question if younger age is an individual risk factor for CMS.

During the phase of development and establishment of new connections, the brain and its white matter tracts could be more susceptible to surgical injury, which might explain a higher risk of POSI in younger children compared with older

Table 4.2 Modifiable risk factors for CMS

Risk factor	Direction of association[a]	Level of evidence[b]	Reference	*n*[c]
Telovelar surgical approach	–	+++	Grønbæk 2021 [55]	426
	–	++	Toescu 2020 [54]	167
	↓	+	Cobourn 2020 [60]	65
	↓	(+)	Tomasello 2015 [61]	45
	↓	(+)	Atallah 2019 [51]	44
	↑	(+)	Zaheer and Wood 2010 [62]	20
	↓	(+)	El-Bahy 2005 [63]	16
Transvermian surgical approach	–	+++	Grønbæk 2021 [55]	426
	–	++	Toescu 2020 [54]	167
	↑	(+)	Cobourn 2020 [60]	65
Splitting of the vermis	↑	++	Catsman-Berrevoets 1999 [46]	42
	–	+	Pollack 1995 [35]	142
	↑	+	Grill 2004 [64]	76
	↑	+	Cobourn 2020 [60]	65
	↑	+	Kotil 2008 [58]	32
	–	+	Siffert 2000 [65]	16
	↑	(+)	Dailey 1995 [66]	110
Surgical expertise/high-volume centre	–	+++	Robertson 2006 [30]	450
	↓	+++	Khan 2021 [41]	178
Extent of resection	–	+++	Robertson 2006 [30]	450
	–	+++	Khan 2021 [41]	178
	–	++	Toescu 2020 [54]	167
	↑	++	Korah 2010 [44]	63
	–	+	Law 2012 [56]	51
	↑	(+)	Schepke 2020 [50]	160
Retraction	–	++	Grønbæk 2022 [67]	463
	↑	+	Cobourn 2020 [60]	65
Use of ultrasonic aspirator	–	++	Grønbæk 2022 [67]	463
	–	++	Toescu 2020 [54]	167
	↑	(+)	Cobourn 2020 [60]	65
	↑	(+)	Wells 2010 [36]	28
	↑	(+)	Avula 2015 [68]	–
Pre-operative hydrocephalus	–	+	Catsman-Berrevoets 1999 [46]	42
	–	+	Wells 2010 [36]	28
	↑	(+)	Pols 2017 [59]	71
	↑	+	Van Dongen 1994 [69]	15
Cerebrospinal fluid leak	–	+++	Robertson 2006 [30]	450
Meningitis	–	+++	Robertson 2006 [30]	450
	–	+	Wells 2010 [36]	28
Post-operative high body temperature	↑	+	Pols 2017 [59]	71

[a] ↑ = associated with a higher risk of CMS, – = no association, ↓ = associated with a lower risk
[b] Level of the statistical evidence based on study design and power. (+) indicates a vague design or no control group
[c] Number of patients in the study

children. Yet speech assessment in younger children is limited by immature speech development prior to surgery, and the incidence of clinical speech disturbances in children younger than 2–3 is more uncertain than in older children. Accordingly, the validity of the speech assessment in children below 3 years of age in the large multicentre Nordic/European CMS study could reasonably be questioned [55]. In addition, this age dependence could pertain to risk factors other than language maturation. Younger children are more likely to have high-grade tumours, particularly MB and ATRT, which were found to be associated with a higher incidence of CMS than other tumour types with preponderance in older children [55].

Sex No major studies of CMS have found a statistically significant risk of CMS associated with sex [30, 41, 55]. Language deficiency syndromes (autism spectrum disorders, mental retardation, learning disabilities) are more common among boys, and generally boys are more vulnerable to developmental disorders than girls. Even though the speech impairment seen in CMS is not fully understood regarding speech perception vs. speech production, patients having recovered their speech after CMS have described that their ability to mentally construct sentences was intact, yet impossible to express [71]. This might indicate that the CMS speech disturbance is different from the language disturbances where boys are overrepresented.

Handedness Damage to the DTCp connecting the right cerebellar hemisphere to the left cerebral hemisphere was suggested to be the underlying mechanism, when left-handedness was suggested as a risk factor for CMS [56].

Handedness has been suggested to be associated with speech and language functionality for about a century. Both stuttering and dyslexia are been reported to be more frequent in left-handed individuals. In the early twentieth century when left-handedness was discouraged, it was found that biological left-handers, who had repressed their hand preference, were more prone to stutter than biological right-handers [72]. It was suggested that the pathophysiology of stuttering implicates a dysfunctional SMA, and more recently, it was found that stuttering children were more likely to have disrupted cerebellar white matter in the afferent and efferent fibres in the cerebellar peduncles [73, 74]. This implies an overlay in anatomical structures involved in the pathophysiology of stuttering and POSI with the possibility that patients with stuttering are at higher risk of development of POSI. It could also be considered if stuttering could be an early symptom of a posterior fossa tumour.

Patients with stuttering share some similarities with patients with apraxia of speech [75]. A study found pre-operative apraxia of speech in all but one patient who subsequently developed CMS after the surgery, and it was suggested that pre-operative speech impairment was a risk factor for CMS [17]. Stuttering, apraxia of speech and CMS may share pathophysiological substrates; however, this has not been substantiated in a clinical trial [57].

Pre-operative Speech and Language Impairment Assessment of pre-operative speech and language is a prerequisite for evaluating the impact of tumour resection on post-operative speech and language, as the presence of the tumour itself is likely to affect speech and language before surgery. Pre-operative speech and language are

rarely investigated, but di Rocco and colleagues identified pre-operative impairment in both language (lexical naming, verbal fluency and utterance length) and speech (dysarthria, apraxia of speech) and found these pre-operative deficits to predict CMS [17, 76].

Tumour Location Midline tumour location, including the brainstem, the fourth ventricle and the vermis, is a strong risk factor for CMS [30, 31, 46, 55]. The brainstem harbours important neurological functions in the cranial nerve nuclei and the long tracts passing vertically past them. These structures can be affected by tumour compression and invasion, or by surgery aiming at gross-total resection of a tumour located near the brainstem. This adds to the burden of neurological symptoms seen in CMS, yet it does not explain the diminished language production. The fourth ventricle forms and circulates cerebrospinal fluid, and obstruction can cause hydrocephalus; however, the ventricle in itself does not harbour neurological function at surgical risk, but the walls and peduncles do. As damage to the SCP has been associated with CMS, it is likely that the risk of CMS seen with fourth ventricle and brainstem tumour location is due to damage to the SCP situated on the borders of the fourth ventricle, either from mass effect of the tumour or mediated by surgery [77–79].

Tumour resections of the posterior fossa in children are quite heterogenous surgical procedures in terms of age of the patients, tumour histology and location, surgical approach and applied surgical techniques and technologies, and these factors are individually co-associated. Tumour histology varies with patient age, tumour location is associated with tumour histology, and tumour location highly defines the preferred surgical approach [80–89]. For instance a lower risk of CMS is associated with a lateral cerebellar approach used for tumours located in the cerebellar hemispheres, which is also the location for tumour types (e.g. pilocytic astrocytoma) carrying a lower risk of CMS; conversely, a higher risk of CMS is associated with a vermian or telovelar approach to the midline, which is also the location for tumour types (e.g. MB) carrying a higher risk of CMS [55].

Tumour Histology The most common tumour histologies found in the posterior fossa in children are medulloblastoma (MB), pilocytic astrocytoma (PA) and ependymoma (EP). Among more rare tumours are atypical teratoid rhabdoid tumour (ATRT) and diverse other entities [90].

Both EP and especially PA are documented to carry a low risk of CMS [31, 33, 56], and MB is a well-established risk factor for CMS [31, 33, 46, 55], whereas ATRT was only recently shown to be a risk factor [55]. ATRT is quite rare, and in order to investigate this association, a large unselected population of childhood posterior fossa tumours was needed. Importantly, ATRT occurs in younger children, in whom the age-dependent risk of CMS is higher; however, correcting for the influence of age, ATRT was still shown to be individually associated with CMS.

Compared with PA, MB and ATRT are more infiltrative fast-expanding tumours. The increased risk of CMS with MB and ATRT indicates that there are other properties of the tumour than the location that is linked with the development of

POSI. Whereas the majority of PAs have well-defined anatomical borders, more than half of MBs produce an invasive growth pattern [50, 91]. If the intent of surgery of an invasive tumour is gross-total resection, it will involve resection in the border area of mixed CNS and tumour tissue. As such, an infiltrative growth pattern may be associated with surgical injury to tumour-adjacent anatomical structures such as the SCP, which could cause POSI. Similarly, tumour invasion of the brainstem has been shown to increase the risk of CMS, also underlining the importance of the relation between tumour and the surrounding structures [30, 33].

Invasive growth of the tumour can cause neurological symptoms, which would be expected to be present at diagnosis. A study with pre-operative neuropsychological evaluation reported a tendency towards tumour infiltration of the dentate nucleus in patients with pre-operative language impairment [17]. The patients with pre-operative language impairment were more likely to develop CMS after the surgery, which could indicate an additive effect of tumour invasion and surgical injury. However, compression or other effects caused by the tumour may also play a role, and these can be difficult to distinguish from tumour invasion.

Tumour Size As space is limited, a tumour in the posterior fossa will cause displacement and compression of the adjacent anatomical structures—the effect intensifying with a larger tumour size. A larger tumour size is associated with a higher risk of CMS [46, 54, 56]. This can both be related to effects caused pre-operatively by the compression by the tumour and to the relatively more complex surgery of a large tumour. The immediate surrounding anatomical structures are determined by the location of the tumour, but with increasing size the tumour will extend to other regions of the posterior fossa and more likely affect neighbouring anatomical structures crucial to development of CMS. With the general intent of complete resections, these structures are at risk of surgical injury during the tumour resection.

4.2.2 Modifiable Risk Factors

Surgical Approach Decades ago, incision of the cerebellar vermis was implied to inflict mutism in children undergoing posterior fossa tumour surgery, and it was suggested to avoid a transvermian surgical approach (Fig. 4.2) [66].

Since then, several studies pursued this idea by applying a telovelar surgical approach (Figs. 4.2 and 4.3), though it was mainly reported in smaller case series and their conclusions disagreed [62, 63, 93]. A recent study argued that their shift towards a strategy of less traumatic surgery, including a preference for the telovelar surgical approach and reduced retraction, had contributed to reducing the incidence of CMS over time [60]. Larger, more recent studies found no difference in risk of CMS between the transvermian surgical approach and the telovelar surgical approach, and it is now well established that the surgical approach is not a major risk factor for CMS [54, 55].

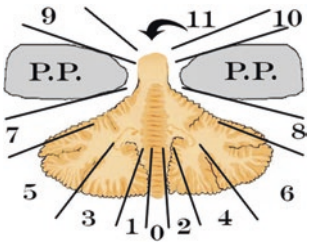

Fig. 4.2 A posterior view of the cerebellum. Surgical approaches to tumours of the posterior fossa. 0 = transvermian, 1–2 = telovelar, 3–6 = lateral cerebellar hemispheric, 7 and 8 = retrosigmoid, 9 and 10 = anterior, 11 = supracerebellar. (From Wibroe et al. 2017, with permission from the author [92])

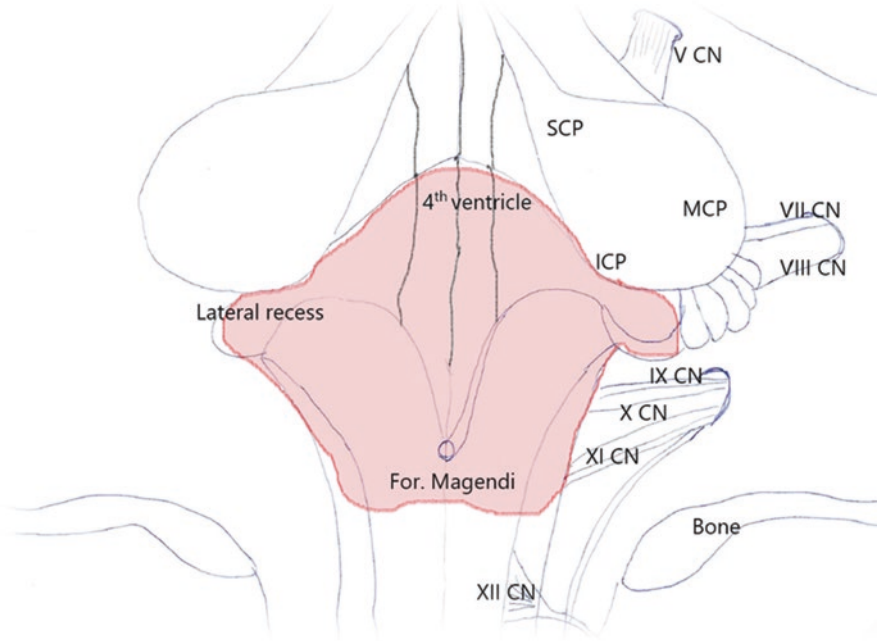

Fig. 4.3 Posterosuperior view of the posterior fossa, where the cerebellar hemispheres have been removed. The red area resembles the surgical area accessible through the cerebellomedullary fissure, which is dissected during the telovelar approach. *SCP*, *MCP*, *ICP* superior, middle and inferior cerebellar peduncles, *CN* cranial nerve, *For.* foramen. (Illustration by the author inspired by Toshio Matsushima [89])

Ultrasonic Aspirator and Retraction The heat generated by an ultrasonic aspirator during tumour resection has been suggested to increase the risk of CMS [68]. In theory, if the tumour bed is surrounded by anatomical structures crucial in the development of CMS, the risk of CMS can be increased by thermal injury to these structures. Changing the surgical strategy towards less abundant use of an ultrasonic

aspirator particularly at the tumour boundaries has been reported to decrease CMS incidence [36, 60]; however, studies investigating the association between CMS and the use of an ultrasonic aspirator have not validated this strategy [54, 67]. When assessing a possible association between CMS and use of an ultrasonic aspirator, it should be considered that there are settings to adjust the aspirator in regard to ablation size, and thus the use cannot necessarily be categorized binarily.

Similarly a decrease in use of retraction was implied to lower the CMS incidence [60], yet was not validated in a prospective setting [67]; however, it is also object for individual preference and adjustment.

How, where and how long both of these surgical techniques are applied can vary considerably from one surgical procedure to another, and their use can be influenced by anatomical features of the tumour which are by themselves CMS risk factors (e.g. tumour size).

Surgical Expertise Posterior fossa tumour surgery conducted by an accredited paediatric neurosurgeon as opposed to an adult surgeon seems to carry a lower risk of CMS, and centres in resource-limited countries may have a higher incidence compared with resourceful centres [41]. It is unclear whether surgical expertise defined by a high caseload decreases the risk [41, 55].

Cerebrospinal Fluid Leak and Meningitis Cerebrospinal fluid (CSF) leak and meningitis following the posterior fossa tumour removal can be considered modifiable as a careful waterproof closure in more layers may decrease risk of fluid leak and infection. Considering the delayed onset of CMS, these typical complications in the first post-operative days may be of interest in relation to risk of CMS; however, no association has been established [30, 36].

Management of Hydrocephalus Hydrocephalus is present in around 70% of patients with a tumour in the fourth ventricle at diagnosis due to tumour obstruction of the CSF flow through the fourth ventricle [54]. Hydrocephalus is treated either by tumour removal or by a prior hydrocephalus intervention (endoscopic third ventriculostomy, external ventricular drainage, ventriculo-peritoneal shunting). In emergency cases, where the patient's consciousness is affected by the increased intracranial pressure, primary hydrocephalus intervention allows for postponing tumour removal to carefully plan surgery.

There is conflicting evidence concerning pre-operative hydrocephalus and risk of CMS [36, 46, 59, 69]. The pressure on the cerebellum and the brainstem and connections between them may explain an association between pre-operative hydrocephalus and CMS. It could be proposed that pre-operative distress of the dentate nucleus and the cerebellar peduncles may contribute to these structures being more vulnerable to surgical damage during the tumour resection. However, hydrocephalus will typically be associated with a tumour located in the fourth ventricle [69], which in itself carries a high risk of CMS [46, 55].

Post-Operative Body Temperature and Infections It remains enigmatic that CMS occurs as late as 15 days after surgery [94], yet the delayed onset may indicate a second hit or a later exposure causing the impairment. A higher mean body tem-

perature in the first days after surgery has been suggested to increase the risk of CMS, where the raised temperature was not likely explained by infection [59]. Close monitoring of temperature in patients following posterior fossa tumour resection could identify patients with a high body temperature, which could be modified by cooling and possible decrease the risk of CMS.

Secondary Resection The risk of CMS in relation to secondary resection compared with the primary resection was recently investigated [95]. It was hypothesized that secondary resection should carry a higher risk of CMS compared with the primary surgery. This was based on the expectation that post-operative changes from the primary resection such as scar tissue could complicate the procedure and that residual tumour could be intentional due to risk of surgical injury to adjacent eloquent structures during the primary surgery. If secondary surgery was aiming at complete resection of a residual tumour, and the residual was left on intent, it would indicate further and more aggressive surgery to the same site. Contrary to the hypothesis, it was found that the risk of CMS was lower in secondary compared with primary tumour surgery, whereas the risk of CND was comparable [67].

Serial surgeries allowing recovery based on neuronal plasticity have been described as a successful strategy in removal of low-grade gliomas in eloquent cerebral regions [96]. Recently, a planned radical staged surgical approach to extensive ependymoma was reported with recovery between primary and secondary resections resulting in a good neurological outcome [97]. It is interesting that a lower risk of CMS but no difference in risk of CND was found in association with the secondary surgery compared with the primary surgery considering that the anatomy responsible for CN function is very well known, whereas the eloquent anatomy of CMS is less evident. The CN anatomy is situated mainly in the brainstem, whereas the CMS anatomy is thought to involve a complex neuronal connection between the cerebellum and the cerebrum [77, 78, 98]. As such, the effector organ for CN function is located closely to the surgical site, and if there is damage to these structures, there is no neuronal reserve to take over the function. Comparably, the structures involved in speech and language are located more remotely, and could therefore be more protected from damage, as there are more relay stations between the surgical site and the effector organ in the cerebrum.

Accordingly, a strategy of staged resections could theoretically be considered to reduce the risk of CMS, if functions could be taken over by more remote structures resulting in a protective effect against more radical surgery later in the same location.

4.3 Prevention and Treatment

4.3.1 Risk Assessment and Prevention Strategies

Different models for CMS risk assessment based on a pre-operative MRI scan have been suggested. A recently published model based on age and tumour location (Table 4.3) implies a high risk of CMS in the youngest patients with a tumour located in the midline [55].

Table 4.3 Absolute risk of speech impairment after tumour surgery in the posterior fossa in relation to patient age and tumour location. Data from Grønbæk et al. 2021, with permission from the author and the journal [55]

	Tumour location	
Patient age	Midline	Hemispheric
0–2 years	51%	11%
3–6 years	43%	7%
7–17 years	28%	9%

One of the first models suggested that the important risk factors were primary tumour location, tumour compression or invasion of the middle cerebellar peduncles, invasion of the dentate nucleus and age >12.4 years [99]. Interestingly, their finding of a higher age as CMS risk-increasing is contrary to the results of most larger studies [41, 54, 55]. A second model included a new parameter named the 'D-sag' indicating the distance over which the tumour compresses or invades the brainstem and the 'd-sag' measuring the level of compression and invasion (Fig. 4.4) [100].

A third study sought to validate the previous models in a separate cohort by adding further factors to previous models providing the Rotterdam model, which improved the prediction accuracy. The Rotterdam model includes radiological diagnosis, tumour location, d_{sag} and invasion of the brainstem, middle cerebellar peduncle and superior cerebellar peduncle as proposed for significant risk factors [101].

Altogether, these models offer a common strategy that can be useful in preoperative information to patients and parents about the expected risk of CMS, which in itself serves a reasonable purpose. However, as modifiable risk factors are scarcely identified, there are limited options to act on for risk reduction.

Currently, identified risk factors for CMS are useful for prediction, but these factors are inherent to patient and tumour characteristics and thus not affected by treatment options. Modifiable factors are related to planning and execution of treatment modalities (e.g. surgical approach and use of surgical instruments), but unfortunately these have no, little or questionable impact on the risk for CMS. Strategies to reduce the risk and/or the effect of CMS therefore require a shift of focus, which could be shifting unmodifiable risk factors towards modifiable:

- Patient age—earlier diagnosis: The ability to detect tumour at smallest possible size by CT, MRI and PET-CT/MR has improved significantly, and still new methods are tested, thereby reducing the impact of surgery-induced toxicity. Attention on symptoms of the tumour through national campaigns aimed at both the general population and health professionals is well documented to have an effect on early detection of brain tumour diagnosis in children [102].
- Tumour size: In the treatment of paediatric brain tumours, the paradigm is that surgical intervention is preceding other adjuvant treatment. Only a few studies have verified the reduction of tumour size with other treatment prior to tumour surgery. An approach with minimal surgical intervention, e.g. stereotactic biopsy

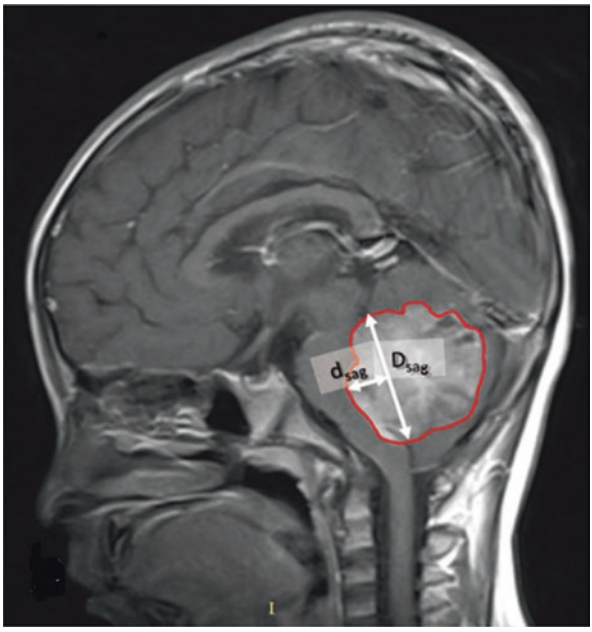

Fig. 4.4 Sagittal MRI of a posterior fossa tumour in a child indicating the measurement of d_{sag} and D_{sag}. (The figure is modified from Childs' Nervous System with permission from the editor [100])

or diagnosis by examination of liquid biopsy, including ctDNA in blood or CSF, could provide diagnostic information that is sufficient to initiate treatment with, for example, pre-operative chemotherapy or targeted treatment to obtain a tumour reduction, after which surgical intervention if continued necessary can be done with less risk of late sequelae such as CMS [103].

4.3.2 Aetiology

Through observations on the time course of CMS, we have identified four phases describing the development and prognosis of the syndrome, displayed in Fig. 4.5. In the following section, we address the different aetiological theories for the development of CMS and hypothesize about relevant preventive or treatment-related measures in relation to this model.

Disruption of the DTCp The leading theory about CMS aetiology involves the cerebellar dentate nuclei and their outflow tracts in the dentato-thalamo-cortical pathways (DTCp; Fig. 4.6) connecting the cerebellum to the cerebrum. The dentate nucleus in the cerebellum projects its fibres through the superior cerebellar peduncle (SCP) to the contralateral thalamic red nucleus. From there the pathway reaches the cerebral cortex including the supplementary motor area (SMA) through ascending thalamo-cortical tracts [104–107].

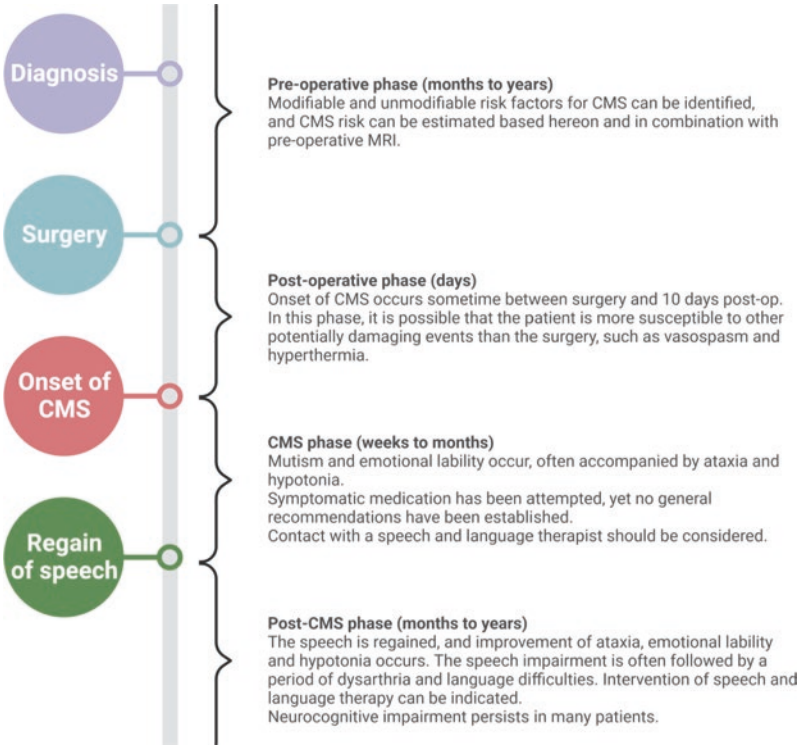

Fig. 4.5 The four phases surrounding the development and prognosis of CMS. (Created by Grønbæk JK adapted from 'Timeline (8 Segments, Vertical)', by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates)

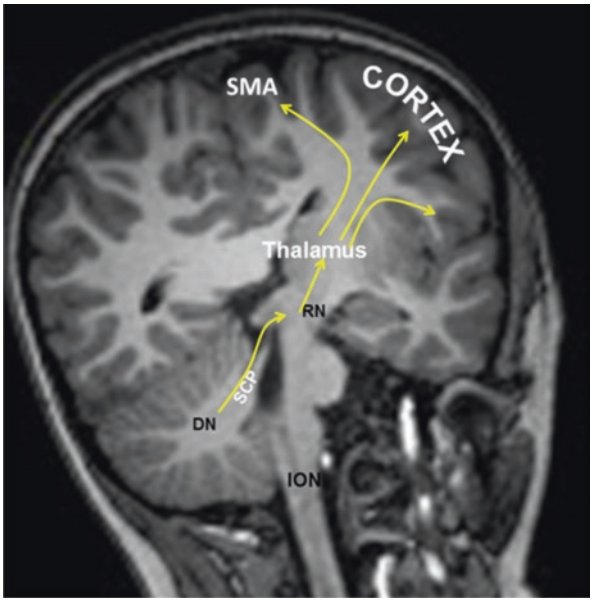

Fig. 4.6 Illustration of the dentato-thalamo-cortical pathway. *DN* nucleus dentatus, *RN* red nucleus, *SMA* supplementary motor area. (From Grønbæk et al. 2018 with permission from the author)

Disruption of the DTCp at the level of the SCP has been associated with CMS. This was shown in studies using diffusion tensor imaging measuring fractional anisotropy of water molecules to estimate axonal organization [77–79]. Neuronavigation based on pre-operative mapping of the anatomical structures may help in preventing disruption of the DTCp. Especially the proximal part of the SCP should be considered an area of interest [108]. Brain shifting during the craniotomy can impair the precision of the neuronavigation, but the use of intraoperative MRI may adjust for this (Table 4.4).

Hypoperfusion of cerebral areas has been implied as a consequence of surgical damage to the SCP [109]. This phenomenon has been labelled 'crossed cerebellocerebral diaschisis' describing the depression of activity of cerebral cortical areas as a result of disrupted cerebellar input [110].

Tumour resection in the SMA can be complicated by the SMA syndrome, which has striking similarities with CMS, as the patients experience transient mutism [111, 112]. These clinical similarities have given rise to a hypothesis of the possible pathophysiological involvement of SMA in CMS given the anatomical connectivity [92, 113]. This hypothesis is supported by a study detecting lower cerebral blood flow in pre-SMA and the SMA in children with CMS [114]. Overall, it seems that the SMA plays an important role in CMS, possibly due to an inactivation depending on absent stimuli from efferent tracts from the cerebellum and a neurotransmitter insufficiency. Hypothetically, external electrostimulation of the SMA could substitute the lack of neuronal input, and pharmacological substitution could adjust the lack of neurotransmitters (Table 4.4).

Vasospasm Another study suggested that post-operative vasospasm causing cerebellar ischemia could be the underlying pathophysiology for CMS, though it was not substantiated by functional imaging of the cerebellum [115]. Treatment with calcium antagonists could counteract vasospasm, even though this is highly hypothetical and the evidence in children is sparse (Table 4.4).

Hyperthermia Pols et al. (2017) found that a higher body temperature in the post-operative period was associated with development of CMS [59]. For other traumatic brain traumas, hyperthermia has been reported as a risk factor for later neurological deficits. This could suggest that the brain of a hyperthermic patient is under a higher level of stress, which may act as a further load on an already overloaded system. Continuous temperature measurement and cooling of the hyperthermic patient to normo-temperature might prevent this. In vitro and in vivo studies have linked gabapentin treatment and a decrease in the incidence and severity of hot flashes among predisposed individuals, which could give an opportunity for lowering the temperature, although knowledge about optimal peri- and post-operative core temperature in children at different ages is lacking.

Oedema and Tumour Pressure Brain oedema seen as a result of leakage of plasma into the parenchyma is frequently seen pre-, peri- and post-operatively, and most patients are treated liberally with corticosteroids. There are several biological mechanisms of brain oedema including vascular endothelial growth factor,

Table 4.4 Treatment forms and preventive measures relating to suggested risk factors for and aetiological aspects of CMS

Time phase	Risk factor	Aetiology	Symptom	Intervention/effect
Pre-operative	Unmodifiable			
	• Tumour location			Risk stratification
	• Tumour size			Risk stratification
	• Tumour type			Risk stratification
	• Patient age			Risk stratification
	Modifiable			
	• Tumour oedema			Corticosteroids
	• Hydrocephalus			Shunt/EVD
Peri-operative				
	Modifiable			
	• Retraction			Decrease retraction
	• Ultrasonic aspirator			Decrease use
		• Disruption of the DTCp		Neuronavigation and intraoperative MRI
		• Vasospasm		Calcium antagonists
Post-operative	Unmodifiable			
		• Hyperthermia		Cooling
		• Transmitter insufficiency		Transmitter substitution
	Modifiable			
		• Vasospasm		Calcium antagonist
CMS				
	Modifiable			
		• Absent neural stimulation of the SMA		External electrostimulation
Post-CMS			Speech and language impairment	Speech and language therapy

leukotriene C4 and probably metabolites from injured peritumoural tissue. The risk of POSI for patients treated with corticosteroids is only investigated in few studies and should be addressed. In the future other drugs such as selective VEGF inhibitors or corticotropin-releasing factor, an endogenous peptide for secretion and synthesis of corticosteroids, could be relevant at different timepoints peri- or post-operatively.

4.3.3 Speech, Language and Communicative Assessment and Intervention

In this section we will describe and discuss speech, language, and communicative impairments in children with tumours of the posterior fossa in the pre-operative phase, the CMS phase and the post-CMS phase. Within these phases we will also discuss assessments and interventions from a speech and language therapist perspective.

4.3.4 Pre-operative Phase

Pre-operative impairment is sparsely investigated, but both language and speech may be impaired, and impairment has been found to be associated with tumour involvement of the dentate nuclei and brainstem infiltration [17, 76]. Large-scale studies are needed to clarify whether specific types of pre-operative speech and language impairment predict CMS as well as different types of impairment in the post-CMS phase. Pre-operative prediction of outcomes would help prepare affected families and plan intervention. In the pre-operative phase, contact with a speech and language therapist should be initiated.

4.3.5 CMS Phase

To date, there are no established guidelines for speech and language assessment or intervention in the CMS phase when the child may be mute or have severely reduced speech production. However, in this phase, an introduction of any augmentative and alternative communication (AAC) must be considered, especially if the phase continues for months. Communication with AAC should not substitute attempts to elicit spoken language.

4.3.6 Post-CMS Phase

Speech In the post-CMS phase, persisting speech deficits often comprise ataxic dysarthria [116, 117], but symptoms differ from the cluster characteristic of adult ataxic dysarthria and are sometimes compatible with other dysarthrias [118, 119]. Speech problems have also been described as phonological disorders and apraxia of speech [17, 18]. Dysarthria and apraxia of speech share overlapping symptoms, making differential diagnosis challenging, and dynamic speech assessment (interactive process-oriented assessment where the examiner flexibly adapts new cues to the

child's responses and evaluates how the dynamic cues affect child performance) is needed to distinguish [120–122]. Differential diagnosis is important as these speech disorders require different therapy.

For dysarthria, there are currently no RCTs or quasi-experimental studies in efficacy of intervention for children and adolescents with brain injury [123], but there is preliminary evidence for positive effects of both perceptual and instrumental biofeedback treatments [124–126]. For acquired apraxia of speech, adult intervention studies have found positive effects of both an articulatory-kinematic approach and a rhythm/rate approach [127], but it is uncertain whether these approaches work for children.

Language In the post-CMS phase, difficulties in higher language functions (production and comprehension of words, morphology and syntax, including word finding) have been reported [18, 25, 128, 129]. Language assessments should target lexical, grammatical and discourse-level abilities in both comprehension and production including follow-up as the child recovers. All tests must be adapted to the child's age and native language.

No studies have investigated language intervention for children with CMS. For cognitive outcomes in general, indirect (family-supported) intervention has been shown to be superior to direct (clinician-delivered) intervention in children with acquired brain injuries [130]. For language intervention, most studies target children with developmental language impairment. For children with developmental language disorder, direct, clinician-delivered language intervention has been found to support both comprehension and production of both words and sentences and to be superior to indirect, nursery-based intervention [131]. Specifically for children with word-finding difficulties, there is evidence for positive effects of semantic intervention (targeting word meanings) [132, 133], and preliminary evidence for semantic and phonological intervention differentially supporting children with different types of word-finding difficulties [133].

Communication To the best of our knowledge, no studies have directly examined social communication in the post-CMS phase. Studies examining neurocognitive outcomes in the post-CMS phase have reported difficulties in attention, executive functions and reasoning [134, 135], and these general cognitive difficulties can be expected to result in cognitive communication difficulties, as found for adolescents with injury in other areas of the brain than the cerebellum [136]. If cognitive communication difficulties do arise, they may not be fully visible until the child is older and academic and social demands increase [137, 138]. To assess communication, a checklist or a questionnaire is preferable [138, 139], and a functional evaluation of performance in complex communication activities is recommended [136], preferably supplemented with neuropsychological assessment.

No intervention studies have targeted communication in children with CMS, but for children and adolescents with traumatic brain injury, there is support for interventions including collaboration with schools [140], helping the children's or

adolescents' network to understand and accommodate to the strengths and difficulties of the child and improving metacognitive strategies [141–143].

In conclusion, we suggest a multidisciplinary management where the speech and language therapist should be included in the pre-operative phase, in the CMS phase as well as in post-CMS phase with assessments and interventions of speech, language and communication. It is important to identify the risk of late effects, and plan for long-term follow-ups as difficulties in language and communication may become apparent later as the child develops.

To provide children with the best support in the post-CMS phase, there is a critical need for new studies. Currently, intervention for children in the post-CMS phase is based on intervention studies from other populations, as intervention studies for children with CMS are lacking for all levels of communication (speech, language, social communication). For social communication in this group of children, there is further a profound lack of basic knowledge. From clinical experience, we know that children do experience problems with social communication in the post-CMS phase, but as of yet, no studies have investigated their character and prevalence. Finally, new studies examining predictive relations between pre-operative impairment and impairment in the CMS and post-CMS phases will help speech and language therapists plan relevant intervention and prepare affected families for expected outcomes.

4.3.7 Summary and Conclusion

Over the last decades, the attention on CMS as a complication to posterior fossa tumour surgery in children has intensified. Many studies have set out to identify risk factors, aetiological aspects and treatment measures of the syndrome, yet the incidence of CMS remains unchanged (Fig. 4.1). There is quite large agreement within unmodifiable risk factors, as to which patients may be at the highest risk of developing CMS, yet there is not consistency in regard to preventive measures such as a preferred surgical approach or a less radical surgical tactic when nearing important anatomical structures. Overall, we are currently able to identify patients at risk, but we are unable to do much to prevent it from occurring.

There are theories of the effect of a second hit following the tumour resection, but occurring before the onset of CMS, such as hyperthermia and vasospasm, yet these remain untested hypotheses.

Once CMS sets in, several symptomatic pharmacological treatments have been suggested, but only in smaller case series and not in randomized controlled trials, and it is not clear whether the treatment or time itself had a helpful effect.

At some point within weeks to months, most patients regain their ability to speak after a phase with mutism or severely reduced speech; however, many patients continue to have speech and language deficits [55, 116–118]. At this point, anti-cancer treatment with chemotherapy and radiotherapy may be of focus more than the

prognosis of CMS; however, many patients continue to have speech problems for months and years to come, and they are at high risk of other neurocognitive sequelae as well.

Without reliable measures to prevent or treat the syndrome, we may look towards improving the prognosis of speech and neurocognitive functioning in these patients. As speech and language impairment is the cardinal symptom and late effect of CMS, the effect of intense and early-onset speech and language therapy as a standard of care in these patients should be investigated in relation to its effect on regaining speech capacity.

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Chapter 5
Trigeminal Schwannoma Surgery: Challenges in Preserving Facial Sensation

Ken Matsushima and Michihiro Kohno

Abbreviations

ABR	Auditory brainstem response
ASL	Arterial spin labeling
CT	Computed tomography
MEP	Motor evoked potentials
MRI	Magnetic resonance imaging
NF2	Neurofibromatosis type 2
SEP	Somatosensory evoked potentials
SWI	Susceptibility-weighted imaging

5.1 Introduction

Schwannomas, such as vestibular schwannomas, are one of the most common tumors in the cerebellopontine angle, where multiple cranial nerves are densely encased [1, 2]. Advances in various diagnostic and treatment modalities, including radiological imaging, neuromonitoring, skull base techniques, and radiosurgical

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procedures, have substantially improved the treatment of schwannomas, and at the present, the surgical aim of this benign tumor is long-term tumor control by maximum tumor resection while avoiding permanent neurological damage. Among the various cranial nerves, the function of the tumor-originating nerve, such as hearing function in vestibular schwannoma or pharyngolaryngeal function in jugular foramen schwannoma, is the most challenging to preserve during schwannoma treatment [3–8]. In the treatment of trigeminal schwannoma, the most common non-vestibular schwannoma, this must be the facial sensation. However, in many previous reports in the literature, facial sensation has not been focused on or investigated adequately. Thus, we reviewed our surgical experience of more than 50 trigeminal schwannoma patients, particularly focusing on their facial sensation.

5.2 Patient Populations and Tumor Characteristics

During a 19-year period between 2003 and 2021, we performed 52 operations on 51 consecutive patients with trigeminal schwannoma. The patients comprised 30 men and 21 women, with a mean age of 43.9 years (range: 13–80 years). Five patients were diagnosed as having neurofibromatosis type 2 (NF2) [9, 10]. Tumor location was classified based on the MPE classification [11]; type P (posterior fossa) in 11 tumors (21%), type MP (middle and posterior fossae) in 29 tumors (56%), type M (middle fossa) in 6 tumors (12%), type ME (middle fossa and extracranial space) in 3 tumors (6%), and type MPE (posterior and middle fossae with extracranial extension) in 3 tumors (6%). Thirty-five tumors (67%) had a dumbbell shape, and extended into multiple fossae. All extracranial extensions were through the foramen ovale, and orbital extension was not identified in our series. Contrast-enhanced heavily T2-weighted (constructive interference in steady state [CISS]) imaging was routinely performed to analyze the association of the tumor with neighboring neurovascular structures (Fig. 5.1b). Arterial spin labeling (ASL) MRI was utilized to predict the vascularity of the tumor [12, 13]. When a tumor mimics a meningioma, presence of intratumoral spotty signal voids on susceptibility-weighted imaging (SWI) was useful to distinguish a schwannoma from a meningioma (Fig. 5.2b) [14, 15]. The average tumor size was 34.1 mm (range: 12–56 mm). Four patients had received previous treatment, including two with prior surgery, one with radiosurgery, and one with both surgery and radiosurgery. Some of the patients involved in this cohort have been introduced in our previous reports [16–19].

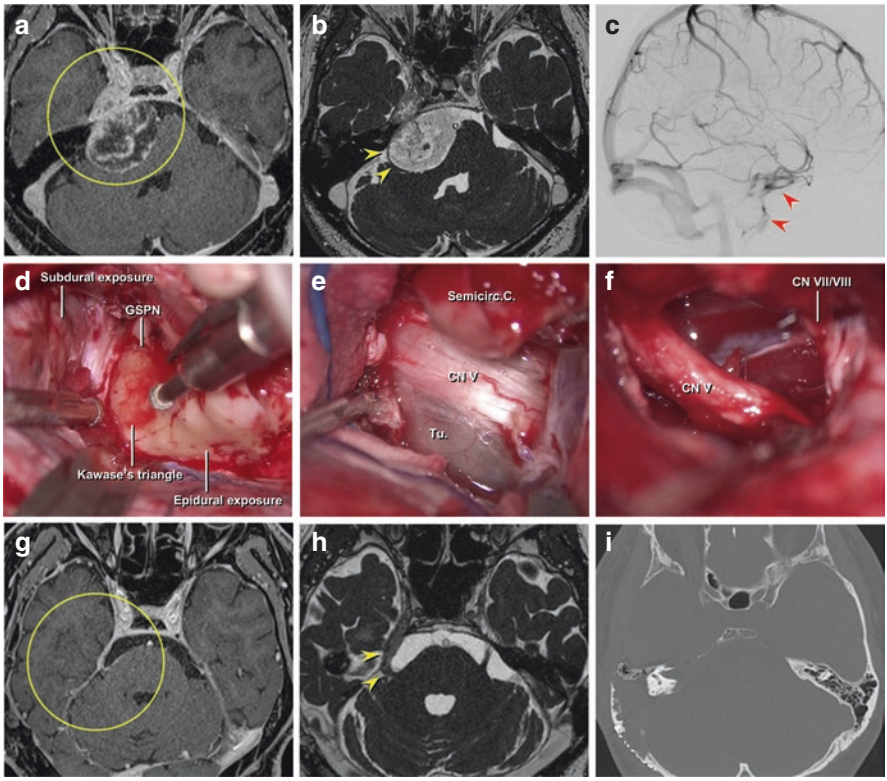

Fig. 5.1 A 52-year-old man with trigeminal schwannoma (type MP) treated via the modified combined transpetrosal approach experienced improvement of preoperative facial hypesthesia. (**a**) Preoperative contrast T1-weighted MRI displaying a right trigeminal schwannoma extending into the posterior fossa and Meckel's cave (yellow circle). (**b**) The intact trigeminal fibers (yellow arrowheads) were displaced lateral to the tumor in contrast-enhanced heavily T2-weighted (CISS) imaging. (**c**) The sphenobasal vein (red arrowheads) to the pterygoid plexus through the foramen ovale was identified as the main drainage route of the superficial middle cerebral vein on right internal carotid angiography (lateral projection). (**d**) To preserve the sphenobasal vein, the ventral temporal lobe was retracted subdurally, and the dorsal middle fossa was exposed epidurally to expose Kawase's triangle. (**e**) The intact trigeminal fibers were displaced laterally, as expected on preoperative CISS imaging. (**f**) Near-total tumor resection was achieved while preserving most intact trigeminal fibers. (**g**) Contrast T1-weighted MRI at the 4-year follow-up displayed no residual tumor or regrowth of the tumor (yellow circle). (**h**) Contrast CISS image at the follow-up confirmed preserved trigeminal fibers (yellow arrowheads). The patient's preoperative facial hypesthesia was improved postoperatively (from V1/V2/V3: 9/5/5 preoperatively to 9/10/10 postoperatively) without any other neurological deficit. (**i**) Postoperative CT scan displaying the extent of osseous drilling around the semicircular canals. *CN* cranial nerve, *GSPN* greater superficial petrosal nerve, *Semicirc. C.* semicircular canals, *Tu.* tumor

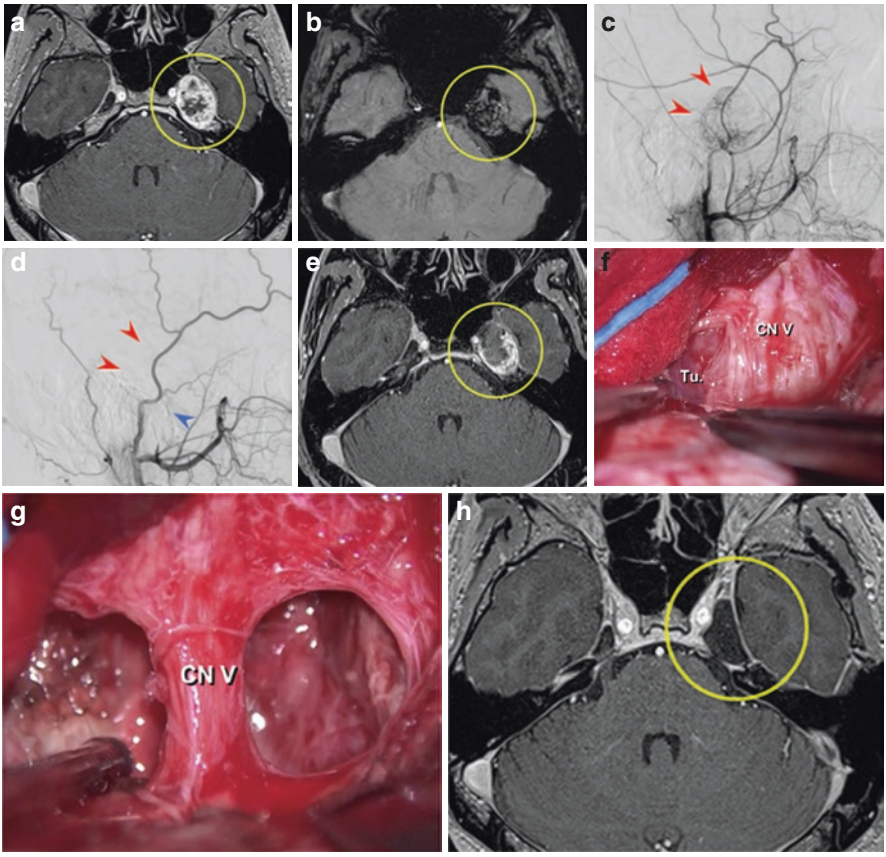

Fig. 5.2 A 36-year-old man with trigeminal schwannoma (type M) treated via the anterior transpetrosal approach with preoperative embolization. (**a**) Preoperative contrast T1-weighted MRI displayed a left trigeminal schwannoma around Meckel's cave (yellow circle). (**b**) Intratumoral spotty signal voids on susceptibility-weighted imaging (SWI) were typical findings of schwannoma (yellow circle). (**c**) External carotid angiography (lateral projection) displayed tumor stains fed by the middle meningeal artery (red arrowheads). (**d**) The feeding artery was occluded using embosphere particles and coil embolization (blue arrowhead) with the careful provocative testing. The tumor stain disappeared (red arrowheads) on postembolization external carotid angiography (lateral projection). (**e**) Postembolization MRI displayed a decrease of enhancement inside the tumor (yellow circle), suggesting successful devascularization of the tumor. (**f**) After interdural dissection of V3 through the middle fossa approach, the tumor was exposed behind the intact V3 fibers. (**g**) The tumor was completely resected while preserving most intact trigeminal fibers. (**h**) Contrast T1-weighted MRI at the 2-year follow-up displayed no residual or regrowth of the tumor (yellow circle). *CN* cranial nerve, *Tu.* tumor

5.3 Surgical Results

Tumor removal was attempted via the middle fossa or by the anterior transpetrosal approach in 41 patients (79%; Case 2; Fig. 5.2). In three patients with extracranial extension, the middle skull base lateral to the foramen ovale was drilled out to access the infratemporal fossa, after conventional middle fossa exposure [18]. In three patients with NF2, the retrosigmoid, retrolabyrinthine, or translabyrinthine approach was used additionally to resect other tumors in one-stage surgery [9, 10]. The retrosigmoid approach was selected for ten type P tumors (19%), and the combined transpetrosal approach was required for one patient (2%) with a large type MP tumor (Case 1; Fig. 5.1). In the middle fossa or anterior transpetrosal approach, modified dural management (combination of subdural and extradural exposures) was used to prevent sacrificing the sphenobasal or sphenopetrosal sinus/vein, when developed venous structures were present (Case 1; Fig. 5.1c, d) [20, 21]. Preoperative embolization successfully reduced tumor vascularity without any neurological deficits in one patient with a hypervascular tumor (Case 2; Fig. 5.2c–e). Surgery was performed under neuromonitoring, including ABR, SEP, MEP, and electromyograms of the extraocular, masseter, and facial muscles. On average, 98.3% (range: 90–100%) tumor removal was achieved without any postoperative mortality or severe morbidity. Complete tumor removal was achieved in 23 surgeries (44%), and less than 95% removal was achieved only in 3 surgeries (6%). During surgery, we attempted to preserve intact trigeminal fibers as much as possible, and the entire trigeminal nerve was sacrificed in only six patients (12%). Although tentoriotomy was routinely needed in the anterior transpetrosal approach for the resection of meningiomas or other tumors, in this trigeminal schwannoma surgery, the small-sized posterior fossa tumor compartment was often completely resected without tentoriotomy, as we previously introduced in our video [18].

5.4 Preoperative and Postoperative Facial Sensation

Facial sensory impairment was assessed on a scale of 0–10 in each of the three divisions of the trigeminal nerve (V1, ophthalmic nerve; V2, maxillary nerve; and V3, mandibular nerve), by comparison to the healthy side [17, 19]. Score 10 was defined as no difference with the healthy side, and score 0 was defined as complete loss of the facial sensation. As perioperative transitions in facial sensation sometimes demonstrated different tendencies at each division even in a single patient, both patient-based outcomes (average of the three divisions in each patient) and division-based outcomes of facial sensation were evaluated.

Preoperative facial hypesthesia was investigated in 48 patients without any treatment history, in order to investigate the natural history of the disease without any bias of previous treatments (Table 5.1). Among the 48 patients who had no treatment history, 27 patients (56%) had facial hypesthesia. On average, preoperative

Table 5.1 Preoperative facial sensation with trigeminal schwannoma without treatment history

Tumor type	Preop. hypesthesia	Patient-based evaluation (average of three divisions in each patient)	Division-based evaluation		
			V1	V2	V3
Total (n = 48)	27 (56%)	8.4 (0.3–10)	8.3 (0–10)	8.5 (0–10)	8.5 (1–10)
Type P (n = 9)	2 (22%)	9.9 (9.0–10)	10 (10–10)	9.6 (7–10)	10 (10–10)
Type MP (n = 28)	17 (61%)	7.9 (0.3–10)	7.6 (0–10)	8.0 (0–10)	7.9 (1–10)
Type M (n = 6)	4 (67%)	9.0 (7.0–10)	9.2 (8–10)	9.2 (8–10)	8.7 (5–10)
Type ME (n = 2)	1 (50%)	7.2 (4.3–10)	5.0 (0–10)	7.5 (5–10)	9.0 (8–10)
Type MPE (n = 3)	3 (100%)	8.8 (8.7–9.0)	9.0 (8–10)	8.3 (8–9)	9.0 (8–10)

facial sensation was 8.4 (average of 3 divisions; range: 0.3–10), compared with the healthy side. Sex, age, surgical side, and tumor size did not have statistically significant effects on preoperative hypesthesia. Regarding tumor location, the average preoperative facial sensation was the most favorable in patients with a type P tumor (9.9 on average) and the least favorable in those with a type ME tumor (7.2 on average). Analysis of each division separately demonstrated that preoperative facial sensation was 8.3 (range, 0–10) at the V1 division, 8.5 (range, 0–10) at V2, and 8.5 (range, 1–10) at V3.

Postoperative facial sensation was evaluated in 50 of the 52 surgeries for which follow-up data for more than 1 year was available. An increase or decrease of more than 1 point on the 10-point scale was defined as an improvement or worsening, respectively, of facial sensation. The average postoperative facial sensation of the patients was 5.1 (range, 0–10), which was −2.8 (range, −10 to 4.7) from the preoperative measurement (Table 5.2). Among the 31 patients with preoperative facial hypesthesia, 8 patients (26%) experienced improvement of facial sensation, 10 (32%) had persisting symptoms, and 13 (42%) had worsened symptoms. Among the remaining 19 patients without preoperative facial hypesthesia, facial sensation in all the divisions was completely preserved in only 1 patient, and some degree of newly developed hypesthesia in at least 1 division was identified in 18 patients (36%). Sex, age, surgical side, tumor size, and tumor resection rate did not have statistically significant effects on postoperative facial sensation. Regarding tumor location, the average postoperative change in facial sensation was most favorable in type ME tumors (+0.9), and the least favorable in type P tumors (−5.5). Complete facial sensory loss in all trigeminal divisions (V1–3) occurred in 2 patients (4%; 1 with a type MP tumor and 1 with a type P tumor), and the remaining 48 patients (96%) maintained a certain degree of facial sensation.

In the division-based investigation, the average postoperative facial sensation was 4.7 (range, 0–10; −3.1 from the preoperative score) at the V1 division, 4.7 (range, 0–10; −3.2 from the preoperative score) at V2, and 5.9 (range, 0–10; −2.2

Table 5.2 Patient-based outcomes (average of three divisions in each patient) of facial hypesthesia after trigeminal schwannoma surgery

Tumor type	Facial hypesthesia						
	Score transition (preop. to postop.)	Preop.	Postop.				
			Among pts. with preop. hypesthesia			Among all pts.	
			Improved	Persisted	Worsened	Newly developed	Lost (V1/V2/V3: 0/0/0)
Total (n = 50)	7.9–5.1	31 (62%)	8 (26%)	10 (32%)	13 (42%)	18 (36%)	2 (4%)
Type P (n = 11)	8.7–3.2	4 (36%)	1 (25%)	1 (25%)	2 (50%)	7 (64%)	1 (9%)
Type MP (n = 28)	7.6–5.2	18 (64%)	6 (33%)	5 (28%)	7 (39%)	10 (36%)	1 (4%)
Type M (n = 5)	8.8–6.2	4 (80%)	0 (0%)	1 (25%)	3 (75%)	1 (20%)	0 (0%)
Type ME (n = 3)	6.4–7.3	2 (67%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)
Type MPE (n = 3)	8.8–7.4	3 (100%)	0 (0%)	2 (67%)	1 (33%)	0 (0%)	0 (0%)

Postop. postoperative, *Preop.* preoperative, *Pts.* patients

Table 5.3 Division-based outcomes of facial hypesthesia in trigeminal schwannoma surgery

Division	Facial hypesthesia						
	Score transition (preop. to postop.)	Preop.	Postop.				
			Among pts. with preop. hypesthesia			Among all pts.	
			Improved	Persisted	Worsened	Newly developed	Lost (score 0)
Total (n = 150)	7.9–5.1	78 (52%)	32 (41%)	27 (35%)	19 (24%)	63 (42%)	26 (17%)
V1 (n = 50)	7.8–4.7	27 (54%)	10 (37%)	9 (33%)	8 (30%)	19 (38%)	14 (28%)
V2 (n = 50)	7.9–4.7	28 (56%)	9 (32%)	10 (36%)	9 (32%)	20 (40%)	10 (20%)
V3 (n = 50)	8.1–5.9	23 (46%)	13 (57%)	8 (35%)	2 (9%)	24 (48%)	2 (4%)

Postop. postoperative, *Preop.* preoperative, *Pts.* patients

from the preoperative score) at V3 (Table 5.3). Preoperative facial hypesthesia at the V3 division improved most frequently (57%) and worsened least frequently (9%). New development of facial hypesthesia also most frequently occurred at the V3 division (48%), in which facial sensation was most frequently intact before surgery. Facial sensory loss (score 0) was experienced in 14 patients (28%) at the V1

division, 10 (20%) at V2, and 2 (4%) at V3. Among a total of 150 divisions in 50 patients, preoperative facial hypesthesia was identified in 78 divisions (52%), and improved in 32 divisions (41%) and worsened in 19 divisions (24%). Facial sensation was lost in 26 divisions (17%), and a certain degree of facial sensation was preserved in the remaining 124 divisions (83%).

Six patients (12%) experienced facial pain before surgery, which disappeared postoperatively in all patients without medical treatment.

5.5 Illustrative Case 1

A 52-year-old man presented with left facial hypesthesia. MRI displayed a dumbbell-shaped tumor extending into the right posterior fossa with brainstem compression and deviation of the fourth ventricle (Fig. 5.1a, b). The intact trigeminal fibers were displaced lateral to the tumor on preoperative CISS imaging (Fig. 5.1b). The sphenobasal vein to the pterygoid plexus through the foramen ovale was the main drainage route of the superficial middle cerebral vein (Fig. 5.1c). The combined transpetrosal approach was selected to achieve safe and maximum tumor resection. Instead of standard epidural exposure with middle fossa dural elevation, Kawase's triangle was exposed by subdural retraction of the ventral temporal lobe and epidural exposure of the dorsal middle fossa while preserving the sphenobasal vein (Fig. 5.1d). The tumor was 97% resected while preserving most of the intact trigeminal fibers (Fig. 5.1e, f). The patient's preoperative facial hypesthesia (V1/V2/V3: 9/5/5) improved postoperatively (9/10/10) without any other neurological deficits. At the most recent follow-up examination 4 years after the operation, the patient had no other neurological deficits or signs of recurrence (Fig. 5.1g, h).

5.6 Illustrative Case 2

A 36-year-old man presented with slight left facial numbness. MRI displayed a tumor around the left Meckel's cave with intratumoral spotty signal voids on SWI (Fig. 5.2a, b). This trigeminal schwannoma was highly vascularized by the middle meningeal artery, so feeder occlusion was performed using Embosphere particles and coil embolization 5 days prior to the surgery (Fig. 5.2c, d). A decrease of the enhancement inside the tumor on MRI suggested successful devascularization of the tumor (Fig. 5.2e). The sphenobasal or sphenopetrosal vein/sinus was not developed in this case. After the middle fossa exposure and interdural dissection of V3 from the foramen ovale, the tumor was exposed behind the intact V3 fibers (Fig. 5.2f). Between the bands of intact V3 fibers, the tumor, which originated from some V3 fibers, was completely resected, while preserving most of the intact V3 fibers (Fig. 5.2g). The patient newly developed slight facial hypesthesia (V1/V2/V3: from 10/10/10 preoperatively to 10/8/8 postoperatively), although his facial

numbness disappeared without any other neurological deficits after the surgery. At the most recent follow-up examination 2 years after the operation, the patient had no other neurological deficits or signs of recurrence (Fig. 5.2h).

5.7 Discussion

The effects of trigeminal schwannoma treatment on facial sensation have not been investigated in detail to date, as previous studies have focused on more crucial symptoms, such as mortality, limb weakness, and facial nerve palsy. The difficulty in objectively and quantitatively evaluating facial sensation may also be a reason for the lack of studies focusing on this symptom. However, treatments for trigeminal schwannoma have substantially improved in the previous few decades, and it has become possible to avoid most critical complications, as shown in many recent reports [22–30]. Similarly, there were no mortalities with more than 95% preservation of good facial and hearing functions, among our patients with sporadic trigeminal schwannomas. Similar to hearing preservation in vestibular schwannoma treatment, we believe that we should now aim to preserve facial sensation in trigeminal schwannoma treatment.

In our experience, tumors limited to the posterior fossa (type P) tended to most infrequently affect facial sensation before surgery, whereas they were the most difficult tumor type to preserve facial sensation during surgery. To the best of our knowledge, a recent report by Jeong et al. [25] is the only study to date that has investigated postoperative trigeminal nerve outcomes based on tumor location. They also found that preoperative hypesthesia most frequently worsened postoperatively in posterior fossa tumors, and discussed that preganglionic nerve injury was more critical in trigeminal dysfunction than postganglionic damage. In our division-based investigation, we found that the V3 region was most favorable before and after surgery, with the most frequent improvement and the least frequent functional loss, although many tumors originated from V3 fibers.

Some recent studies performed analyses of facial sensation before and after surgery or radiosurgery using relatively large cohorts (Table 5.4) [22, 24–26, 28, 29]. Briefly, surgery improved preoperative facial hypesthesia in 11–28%, and worsened it in 3–23% of patients. Radiosurgery improved hypesthesia in 42–69%, and worsened it in 6–18% of patients. On the other hand, surgery improved preoperative facial pain in 82–100% of patients, whereas radiosurgery improved it in 46–90%. Our experience shows the same tendency as these previous surgical reports, with more frequent worsening of and newly development of hypesthesia. These results may suggest that surgery can have the advantage of resolving preoperative facial pain, whereas radiosurgery can be more favorable for improving preoperative facial hypesthesia in small tumors. However, there are several problems in comparing the results of surgery and radiosurgery, or even comparing reports on the same treatment method. First, owing to difficulties in the objective and quantitative evaluation of facial sensation, assessment methods may be different among the studies. Second,

Table 5.4 Review of recent literatures on facial sensation outcomes in surgery and radiosurgery for trigeminal schwannoma

Authors (year)	*N*	Tumor size	Previous treatment history	Facial hypesthesia					Facial pain				
					Postop.					Postop.			
					Among pts. with preop. hypesthesia			Among all pts.		Among pts. with preop. pain			Among all pts.
				Preop.	Improved	Persisted	Worsened	Newly developed	Preop.	Improved	Persisted	Worsened	Newly developed
Surgery													
Wanibuchi et al. (2011) [29]	105	NA	14%	66%	16%	72%	12%	8%	23%	92%	8%	0%	2%
Chen et al. (2014) [22]	55	4.6 cm	NA	65%	28%	69%	3%	0%	20%	100%	0%	0%	0%
Jeong et al. (2014) [25]	49	4.0 cm	NA	71%	11%	66%	23%	20%	22%	82%	0%	18%	8%
Our cases (2022)	50	3.4 cm	8%	62%	26%	32%	42%	36%	12%	100%	0%	0%	0%
Radiosurgery													
Hasegawa et al. (2013) [24]	53	6.0 cm^3	36%	81%	46%	NA	18%		30%	75%	NA	12%	
Sun et al. (2013) [28]	52	7.2 cm^3	39%	56%	69%	NA	NA	0%	19%	90%	NA	NA	2%
Niranjan et al. (2021) [26]	50	3.4 cm^3	34%	66%	42%	52%	6%	2%	26%	46%	46%	8%	0%

NA. not available, *Postop.* postoperative, *Preop*. preoperative, *Pts.* patients

most studies did not assess each trigeminal division (V1–3) separately. In our experience, perioperative facial sensation in each division sometimes demonstrates significantly different tendencies even in a single patient. Therefore, differences in assessment methods or evaluated division can remarkably change the outcomes. In fact, in our series, "improved cases" are only 10% of the patients when defined as complete improvement in all the divisions to score 10, but becomes 23% when defined as improvement in all divisions by at least 1 score or preservation of score 10, becomes 29% when defined as an improvement in at least 1 division to score 10, and 61% when defined as an improvement in at least 1 division by at least 1 point. Third, differences in tumor size and previous treatment history between surgical and radiosurgical reports cannot be ignored. Therefore, to clarify the outcomes of facial sensation in trigeminal schwannoma treatment and to accomplish its more rigid preservation, standardized perioperative assessment methods and further clinical studies are required.

5.8 Conclusions

We reviewed the treatment effects of trigeminal schwannoma, particularly focusing on facial sensation, and introduced our detailed MRI investigation and operative techniques. In our experience with 50 surgical patients, although facial sensation was postoperatively decreased on average by 2.8 points on a scale of 0–10, postoperative facial sensation remained in 96% of all patients and in 83% of all trigeminal divisions. Facial pain was relieved in all patients. Facial sensation was most difficult to preserve in posterior fossa tumors (type P), and the V3 region demonstrated most favorable results both before and after surgery, with the most frequent improvement and the least frequent functional loss. Standardized assessment methods of perioperative facial sensation may be required to clarify the current outcomes in surgical and radiosurgical treatments, and to achieve more effective preservation of facial sensation.

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Declarations None

Ethics Approval This study was approved by the ethics committee of Tokyo Medical University (study approval no.: T2022-0026).

Consent to Participate The patients and their parents gave consent for the use of their information and images for research purposes.

Conflict of Interest The authors declare no competing interests in association with this study.

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Chapter 6
Evolution of Making Clinical Predictions in Neurosurgery

Hendrik-Jan Mijderwijk

6.1 Evolution of Making Clinical Predictions

Making predictions regarding a patient's outcome is a vital part in the daily clinical practice of every single physician including neurosurgeons. During conversations with patients and their significant others (e.g., parents, surrogates, and social network), questions about the chances of the patient are common. Patients including their significant others and the physician need an accurate prediction assessment of the anticipated outcome so that informed decision-making, enabling adequate future planning, becomes better feasible [1]. Clinical predictions made by physicians can be based on solely their intuition or informed by scientific material such as studies reporting on population risks, risk factors, and recently clinical prediction models (Fig. 6.1) [2].

6.1.1 Intuition

Although there is value in the "gut feeling" of surgeons in predicting postoperative outcome, the predictions are likely to be overestimated and underestimated pending on the outcome of interest [3, 4]. The more experienced the physicians are, the higher the accuracy of their predictions, although the intensity of the

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Fig. 6.1 Four ways to predict a patient's outcome. To make predictions for individual patients in clinical practice, physicians may use their intuition (*top*), population risks (*bottom*), risk factors or prognostic factors (*left*), and clinical prediction models (*right*)

physician-patient relationship is likely to modify the accuracy of the prediction [5]. Over the last decades, making clinical predictions based on physicians' intuition has been shown to be flawed. For example, reports from 1972 and 2000 show that predicting the length of survival in terminally ill patients by physicians is substantially overestimated by physicians [5, 6]. In 1992, a report showed that 56% of the predictions made by an experienced neurosurgeon were correct in predicting the 1-year outcome for severely head-injured patients [7]. More recently, in 2012 and 2017, it has been reported that making clinical predictions for neurovascular patients based on the intuition of neuro-physicians is also imperfect [8, 9]. Even the brains of the smartest neurosurgeons cannot consider all single potential variables of an individual patient that interfere with the outcome of the patient. Scientific material may help to improve predictions.

6.1.2 Publications Reporting Population Risks

Neurosurgeons may extrapolate data extracted from studies reporting risks at population level. For example, results from the Childhood Cancer Survivor Study among 1311 long-term survivors of medulloblastoma patients show that 15-year cumulative incidence rate of all-cause late mortality has dropped from 23.2% to 12.8% due to modern multimodal treatment [10]. This reduction was mainly a result of the risk reduction for death due to medulloblastoma recurrence, which dropped from 17.7% to 9.6% [10]. Such population risks are a valuable starting point for informing patients and their significant others about their disease and anticipating events. Even if such overall risk estimates are precise, it is still not clear whether a specific patient is the one who will die or will live. In daily clinical practice, we do not treat a population; we treat individuals. To estimate the risk an individual patient, relevant patient characteristics such as age, comorbidities, functional capacity, and other risk profiles need to be considered.

6.1.3 Publications Reporting on Risk Factors

Publication reporting on risk factors (or prognostic factors) generally uses relative effect measures to quantify the strength of the association with the outcome. For example, recently, a large study (n = 1457) assessed risk factors for developing subdural hematoma and hygromas (SDH) after insertion of a shunt in patients suffering from idiopathic normal pressure hydrocephalus [11]. The study showed that—among others—male sex was associated with a doubling of the odds (OR 2.084, 95%CI 1.421–3.058) of the outcome (i.e., development of SDH). Note that a doubling of the odds does not mean a doubling of risk. Only when the baseline risk of an outcome is low (≤10%), the odds ratio approximates the relative risk [12]. For instance, if the risk of developing SDH for females is 2%, then men would have a risk of 4% of developing SDH. If the risk of developing SDH equals 5% for females, then the risk of developing SDH for mean is 10%. Thus, a different baseline risk may lead to different risk estimations for a patient. Applying risk factors or prognostic factors from the literature to individual patients in clinical practice should be done taken into account the relevant baseline risk.

6.1.4 Publications Reporting on Clinical Prediction Models

Neurosurgeons may also make use of clinical prediction models to arrive at a prediction with a high accuracy. These models simultaneously combine a set of predictor variables to predict the likelihood of disease (diagnosis) or a future event (prognosis) in a patient [13]. The risk predictions derived from these models have

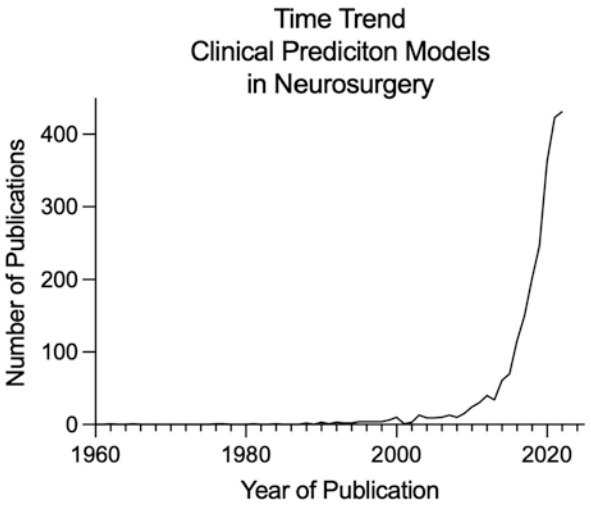

Fig. 6.2 Time trend of the number of articles reporting on clinical predictions models in the field of neurosurgery. The following previously published [13] systematic PubMed search was updated at 04.10.2022: (Prognostic-index* OR Prognostic-rule* OR Prognostic-model* OR prediction-index* OR prediction-rule* OR prediction-model* OR predictive-index* OR predictive-rule* OR predictive-model*) AND (Neurosurgery[mh] OR Neurosurgical Procedures[mh] OR Neurosurg* OR Neurological-surg*)

great potential in guiding neurosurgeons in their everyday decision-making with or for their individual patients. These data-driven tools have shown to outperform predictions made by neuro-physicians and other clinicians [14–16]. Nowadays, clinical prediction models are increasingly published in neurosurgery [13, 17]. An updated PubMed search confirms this ongoing time trend (Fig. 6.2). Clinical prediction models should be deployed appropriately, and their strengths and weaknesses should be known to neurosurgeons [1]. Hereafter, a synopsis of three important phases of a clinically useful prediction model is provided [14, 18].

6.2 Clinical Prediction Models

6.2.1 Phase 1: Development and Internal Validation

The development of a robust clinical prediction model requires several steps, including—but not limited to—selection of predictors, obtaining an adequate effective sample size, and handling of missing data [13]. Although the use of machine learning is popular, prediction models are commonly generated using traditional multivariable regression techniques on data from preferably cohort studies [13]. It is preferred to select the predictors prior to the start of the statistical analyses based on profound review of the literature and knowledge from clinical experts. Selecting

predictors based on data-driven strategies such as automated stepwise selection procedures and univariate analysis is not recommended in small datasets because these selection methods are prone to overfitting [19]. An overfitted prediction model shows promising results on the data used for its development but will perform poorly when applied to other patient data.

Another way to prevent the risk of an overfitted model is to ensure an adequate effective sample size. This means that the number of patients with the outcome of interest is large enough. Rules of thumb have suggested a minimum of ten events per predictor (EPV). Thus, if 5 predictor variables are considered, then at least 50 patients with the outcome of interest are needed and at least 50 patients without the outcome; the minimal total sample size includes then 100 patients [17]. Recently, more refined calculations for the minimum required sample size are suggested to build more robust prediction models [20–22]. The obtained EPV is a minimum and larger sample sizes are preferred, provided that the data quality is adequate.

To retain an adequate sample size, it is important to deal adequately with incomplete datasets [23]. Removing patients with missing data to perform a *complete case analysis* may induce bias because the missingness is likely not completely at random, and may affect the EPV negatively, jeopardizing reliable modeling. Multiple imputation has been commonly recommended to replace the missing data [24].

The developed prediction model should always be subjected to an internal validation procedure to correct for overfitting [24]. Internal validation is imperative before a model can be published. Bootstrap resampling and cross-validation are recommended techniques for internal validation [24, 25].

6.2.2 Phase 2: External Validation

External validation addresses the generalizability of the model in a different set of patients not used for the generation of the model [26]. This step is necessary before a model can be applied in clinical practice [27]. Traditionally, an external validation study requires at least 100 patients with the outcome of interest and 100 patients without the outcome, although modern sample size calculations are recommended [28]. Validation techniques gauge the quality of the model, which is commonly evaluated with measures for calibration and discrimination [29].

Discrimination tells us how well the model can differentiate between patients with the outcome and patients without the outcome. Discrimination is quantified by the concordance statistic (*c*-statistic), ranging from 0.50 (no discriminative ability) to 1.00 (perfect discrimination) [13].

Calibration assessment is needed to get an impression of the agreement between the observed outcomes and the predictions made by the model. For example, if the model predicts a 25% 1-year survival probability, the observed frequency of survival should be circa 25 out of 100 patients with such prediction. A calibration plot is very useful to address the magnitude and possible miscalibration of the model [24]. However, often a calibration plot is not included in articles reporting on

clinical prediction models. For example, external validation studies evaluating the performance of the (modified) Canadian Preoperative Prediction Rule for Hydrocephalus in children with posterior fossa tumors all report on discrimination but did not include a calibration plot [30]. It is important to stretch the usefulness of such a plot, because calibration has been labeled as the Achilles heel of prediction [31].

It is likely that model performance drops at external validation. It is then wise to consider updating techniques instead of concluding that the model failed at external validation [30, 32]. A wide range of updating techniques are available to adjust the model to the new circumstances [33, 34].

6.2.3 Phase 3: Impact Analysis and Implementation

The effectiveness of an externally validated prediction model in daily clinical practice should be ideally evaluated in impact studies [35, 36]. Such studies require a comparative study design to evaluate the benefit of using the prediction model compared to not using the prediction model in terms of clinical effectiveness (e.g., improvement of patient outcome) and cost-effectiveness of care [37]. Impact studies are recommended, but underrepresented in the literature. If the prediction model should be used for decision-making, an intermediate approach to assess the clinical impact can be a decision curve analysis (DCA) [29, 38]. A DCA provides a graphical summary showing the net benefit of using the model compared to default strategies of treating all patients or treating no patients. The prediction model has shown clinical effectiveness if the net benefit is higher than the default strategies. Didactic papers have been published, highlighting appropriate interpretation and usage of this analysis [39–41].

Ultimately, the indicator variable for a successful clinical prediction model is the wide adoption of the model by end users. Important factors include—but are not limited to—the support of leading neurosurgeons, the user's trust in the model, the complexity of the model, and ease of use of the model at "the bedside" [18]. Of particular interest is the presentation format of the prediction model. A user-friendly format will foster implementation of the prediction model in clinical practice and should be chosen with care [42]. Possible formats include score charts, nomograms, and web applications among others. Many prediction models have been transformed or simplified into a score chart to facilitate clinical use [43–46]. It should be known that every simplification of prediction model leads to some loss of predictive accuracy due to rounding of regression coefficients and categorization of continuous predictor variables [42, 47]. The Colloid Cyst Risk Score is an example of a point score system to identify symptomatic lesions and make risk stratification of obstructive hydrocephalus feasible [46, 48, 49]. A nomogram is a graphical (not a simplification) presentation of a prediction model. When a nomogram is presented, it is important to provide directions for use for the end users [47]. An advantage of a web application is that the prediction model does not need to be simplified to create a

user-friendly format [42]. The equation of the prediction model is hidden behind the user interface—see https://www.evidencio.com/models/show/2384 for an example. To enable future validation attempts, apart from the chosen format, presentation of the full model equation is imperative [42].

6.3 Clinical Example I: Predicting Rupture in Arachnoid Cysts

Arachnoid cysts are common with prevalence estimates up to 2.6% in the population [50]. Most arachnoid cysts are found incidentally and are asymptomatic. The reported risk of rupture ranges from 2.3% to 6% [51, 52]. For some neurosurgeons, the risk of rupture justifies a prophylactic surgery [53]. In 2010, Di Rocco addresses the question if the risk of rupture justifies a prophylactic surgery in an asymptomatic patient [54]. Likely, not all patients should undergo a surgical intervention. A patient tailored estimate of the risk of rupture will help the (shared) decision-making process whether to operate the child or not, especially considering the known complications and costs of a surgical intervention [55]. Currently, a clinical prediction model for rupture risk has not been published, and only risk factors for rupture have been published. Larger arachnoid cyst size and recent head trauma are labeled as risk factors for arachnoid cyst rupture [52]. However, these data do not provide an individual patient estimate of the risk of a rupture. Predicting rupture risk for patients with intracranial cysts is therefore still based on intuition in combination with results from population-based studies and studies reporting on risk factors. In line with Di Rocco, Maher recently advocates a high threshold for surgical treatment but urges for more research regarding the indications for arachnoid cyst surgery [56].

6.4 Clinical Example II: Predicting Rebleeding After Aneurysmal Subarachnoid Hemorrhage

A rebleed after aneurysmal subarachnoid hemorrhage (aSAH) should be prevented. Guidelines recommend treatment as early as possible, but within 72 h [57–59]. To guide future clinical decision-making, recently, the ARISE prediction models were developed to estimate the individual risk of aneurysmal re-rupture prior to aneurysm closure [60]. Details from the model development phase and internal validation approach, provided in the article, are as follows:

- Selection of predictors: The predictor variables were selected based on profound review of the literature and knowledge from experts. A total of eight predictor variables (with a total of ten parameters) were included: age, gender, arterial

hypertension, WFNS grade, Fisher grade, aneurysm size, CSF diversion, and aneurysm irregularity.
- Sample size: 2075 patients from 5 multinational datasets were included. Two hundred sixty-nine patients suffered from rebleeding prior to aneurysm closure. According to traditional sample size recommendations, the EPV was adequate.
- Missing data: For seven predictor variables, the missing data proportion ranged from 0% to 4%. As irregularity data was completely missing for one center, the total missing data for this predictor was 65%. The missing data were imputed with the multiple imputation technique. To address the missing data in the irregularity variable, a sensitivity analysis was also performed, which showed similar model results.
- Internal validation: The bootstrapping procedure with 1000 samples was used. The *c*-statistic was at least 0.77 showing promising discrimination by the model.

The ARISE models have shown promise in the prediction of re-rupture after aSAH. Furthermore, the DCA shows the potential clinical impact the models may have. However, at least for now, by lack of external validation studies, the ARISE models should not be used in clinical practice despite the robust data analysis.

6.5 Clinical Example III: Predicting Survival in Glioblastoma Patients

Since the 2016 WHO classification, predicting survival in *IDH* wild-type glioblastoma patients needed an update to provide reliable predictions [61]. Therefore, recently, an updated prediction model for survival in these glioblastoma patients was developed and externally validated [61].

Some details according to the above-described phases are depicted below.

Model Development Based on literature review and subject matter knowledge from experts, the following predictors were identified: patient characteristics (patient age, gender, and Karnofsky Performance Status), surgical results in terms of extent of resection (gross-total resection (GTR), non-GTR, and biopsy), glioblastoma biology (MGMT promoter methylation status), and adjuvant treatment strategies (Stupp, non-Stupp, and no therapy). Patient data from three university hospitals from the Netherlands and Germany were used to obtain a reasonable patient set. The sample size was large enough according to the traditional rules of thumb and according to modern advanced sample size calculations. Missing data was assumed to be missing at random, and multiple imputation was used to impute the missing entries.

Model Validation To assess the external validity of the model, an internal-external cross-validation procedure by country was used [62]. The calibration plots showed some miscalibration of predicting long-term survival, especially beyond the first year of survival. The *c*-statistic of the final model was 0.73 (95% CI 0.71–0.75).

Impact Analysis and Implementation The full model equation is provided in the report to enable future independent validation and updating attempts. The prediction model was further presented in nomograms to enable ease use of the model. In addition, the model was launched online at the Evidencio platform: https://www.evidencio.com/models/show/2384. This web application can also be downloaded as an app for a tablet or smartphone. Consequently, the model is readily available to provide support for physicians in almost every clinical context. Next to the user-friendly interface, the possibility to provide relevant model information in the available disclaimer, and the quality check by Evidencio before the model is released, enhances user's trust and implementation in daily clinical practice. For example, in the disclaimer it is noted that the model gives a probability estimate of 1-year survival and that the model should not be used for treatment decisions. Due to lack of a comparative design in the used datasets, confounding by indication should be taken into account when deploying the prediction model. In more detail, it is likely that patients with a good condition will get standard glioblastoma therapy. However, patients with a poor general condition at presentation have a greater probability to receive modified (adjuvant) therapy or even no adjuvant therapy. This glioblastoma survival model is suited to inform patients and their significant others in clinical practice to clarify the anticipated 1-year survival, given that a particular treatment has been chosen [61].

6.6 Discussion

The evolution of making clinical predictions in neurosurgery has shown a shift toward the use of clinical prediction models (Fig. 6.2). They aim to assist (not replace) neurosurgeons with their prediction of a patient's outcome [18]. If these models are properly used, two advantages will follow. In the first place, they will help to make a more accurate prediction of a patient's outcome. Well-validated prediction models are generally exposed to large patient numbers, while the experience from a neurosurgeon is based on a relatively small number of patients. It is recommended that "a good physician should no more refuse use them than a good driver should refuse to use his car's headlights at night" [1].

In the second place, clinical prediction models aim to make informed decision-making better feasible [18]. Nowadays, it is of utmost importance for patients and their significant others that the predictions made by physicians are adequately communicated and how these predictions are derived [63]. Furthermore, patients and their significant others want to be informed about the uncertainty associated with the prediction [64, 65]. The International Patient Decision Aid Standards recommend to present probabilities in decision aids tools [66]. However, physicians may be reluctant to communicate risk estimates derived from a clinical prediction model in daily clinical practice. A study among neurosurgeons and other physicians in the United States involved in the care of patients suffering from traumatic brain injury investigated the use of the well-validated International Mission for Prognosis and

Analysis of Clinical Trials (IMPACT) model in clinical practice [67]. The IMPACT model aims to predict the patient's functional outcome after 6 months [43, 68]. The results from the semi-structured interviews revealed that many physicians preferred to avoid communicating the prediction estimates derived from such models because of the fear of misleading families [67]. Stein et al. reported that the resistance of following clinical prediction models in the neurosurgical community is partly due to a lack of familiarity and skepticism [69]. Therefore, educating end users is an important element of the implementation of prediction model in clinical practice [69]. Several didactic articles addressing the development and application of clinical prediction models have been published previously to make the neurosurgeon more familiar with these tools [13, 17, 19, 41, 69, 70].

When neurosurgeons communicate their predictions with their patients to assist in the decision-making process, they also need to take the concerns and anxiety of patients and their significant others into account [71]. When new medical situations are faced, patients themselves make predictions on the impact the anticipated future outcomes may have. Affective forecasting research has described that patients likely make inaccurate predictions of their future well-being and underestimate their potential to adapt to new medical situations [72]. This can be nicely illustrated. Neurosurgeons are often consulted to perform a decompressive hemicraniectomy (DHC) in patients suffering from ischemic stroke. One study reported that the majority of the general population would reject a DHC if a future ischemic stroke would occur, even if only a moderate impairment is expected [73]. In contrast, patients who underwent a DHC for ischemic stroke all reported to have chosen a DHC again, even if a major drawback was experienced [74].

Another issue to consider is misfearing: "the human tendency to fear instinctively rather than factually" [75]. As Rosenbaum describes, humans are more worried about dramatic things such as terrorist attacks than things that are more likely to kill them, such as a stroke [75]. When clinical prediction models are used for decision-making with the patient and/or their significant others (i.e., shared decision-making), neurosurgeons should also take these psychological effects into account as clinical prediction models do not address such phenomena.

It is of utmost importance that the patient we are making predictions for resembles the patients used for model development and validation [76]. To make appropriate use of clinical prediction models feasible, adequate reporting according to the TRIPOD guidelines is incumbent to identify study bias [47, 77, 78]. For example, selection bias may emerge when missing data is inappropriately dealt with [79]. Other biases such as misclassification and confounding should be evaluated. It is known that within prediction studies, misinterpretation of causality of predictor effects is common [80]. Therefore, in addition to the clarification in the published article, the authors of the prediction model presented in *Clinical example III* have addressed causality of predictor effects in the disclaimer at the Evidencio platform to ensure safe use of the prediction model. The knowledge and vigilance of end users like neurosurgeons is crucial to recognize bias.

It is not needed to develop or use a clinical prediction model for every single clinical decision. A prediction model will not change the decision to evacuate a

significant epidural hematoma in a child. However, clinical prediction models have the potential to play a prominent role in supporting decision-making when there is equipoise regarding the optimal treatment [76]. As demonstrated in *Clinical example I*, there is currently equipoise in treatment of arachnoid cysts [56]. A clinical prediction model identifying patients at high risk of arachnoid cyst rupture will likely help the shared decision-making process between the neurosurgeon and the patient whether to surgically intervene or not.

An adequate patient sample size to ensure reliable modeling can be hard to achieve. It is wise to initiate a collaboration between clinical centra including their research groups. As shown in the articles illustrated in *Clinical examples II and III*, combining several datasets provide analyses that increase the robustness of the results. Furthermore, such collective efforts will likely focus on the development of one single well-validated model that has impact on the patient outcome of interest. The participation of multiple centra will also foster the implementation of the developed model in clinical practice [18]. Ultimately, inclusion of a well-validated clinical prediction model in clinical practice guidelines is likely needed for a wide adoption of the model in the neurosurgical community.

In conclusion, the use of clinical prediction models for making predictions for a patient's outcome plays an increasingly prominent role in medicine and neurosurgery and is nowadays commonplace in neurosurgical research. To properly use these models and to communicate them adequately with patients and their significant others, neurosurgeons should become familiar with them [69]. Education in methodology and statistics tailored to the neurosurgeon will likely foster the use of clinical prediction models. To retain as clinically useful as possible, prediction models should be regularly evaluated with updated data. Prediction models should assist the neurosurgeon and not replace his or her clinical acumen.

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Chapter 7
Evolving Concepts of Craniovertebral and Spinal Instability

Atul Goel, Ravikiran Vutha, and Abhidha Shah

7.1 Introduction

"Mobility" defines life. Mobility and stability are essential elements of life. Human beings are additionally "burdened" by their life long-standing posture. The major bulk of human muscles is located on the extensor compartment of the spinal column or on its "back" and caters to movements that facilitate sitting, standing, and running. On the other hand, only relatively "few" strands of muscles are located in the flexor or anterior compartment of the spinal column, flexion movement being essentially of passive nature. The activity of all major extensor muscles is focused on the facetal articulation of the spine that forms the point of fulcrum of all movements. "Essentially" activity of no major muscle group is focused on the disc or the odontoid process, or in other words the disc or the odontoid process does not form a fulcrum point of movements. Our articles have discussed the role of the disc and the odontoid process in human movements [1]. We philosophized that both disc and odontoid process are like opera conductors who regulates all music without holding any instrument in his hands. Whilst muscles are the brawn, disc (and odontoid process) is the brain of all movements. Weakness of muscles related to their disuse,

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abuse, or injury forms the basis of all spinal instability. Instability is the primary process or the nodal point of pathogenesis of majority of the known craniovertebral junction "anomalies" and a number of spinal ailments that include the so-called "degenerative" spinal disease and deformities. In situations with chronic instability, a number of structural musculoskeletal and neural alterations are a part of Nature's protective or adaptive endeavors. These alterations are secondary, naturally protective, and potentially reversible following treatment that involves spinal segmental stabilization. Understanding the fact that these secondary alterations point towards the unstable spine can rationalize and direct the treatment.

7.2 Craniovertebral Junction

Craniovertebral junction has a supremely designed architecture that caters to the most mobile and most stable region of the body in addition to providing safety to the most critical neural and vascular structures that transit in the region. Mobility and stability are the hallmarks of craniovertebral junction. Occipitoatlantal joint is the most stable joint, and atlantoaxial joint is the most mobile joint of the body. Whilst atlantoaxial joint is the most mobile joint, it is potentially most susceptible to instability. Our four-decade-long experience in the field suggests that it may not be erroneous to state that atlantoaxial instability is possibly the most frequent, most neglected and misunderstood and undertreated clinical entity in our subject. "Compression" of the neural structures by the odontoid process is the most feared issue in the subject of medicine in general and in craniovertebral junction in particular. In general, craniovertebral junction instability is synonymous with atlantoaxial instability, and craniovertebral junction stabilization is synonymous with atlantoaxial stabilization. Inclusion of the occipital bone in the fixation construct is unnecessary, adds to the possibilities of complications, and results in suboptimal fixation. Occipitoatlantal instability is extremely rare clinical entity and is encountered in high-speed vehicular injury and also rarely in syndromic multisegmental spinal instability.

7.3 Atlantoaxial Articulation

The atlas and axis vertebral bones are specially designed [2]. The spinous process of axis is largest, transverse processes of atlas are longest, and facets of the atlas and axis are the strongest of the entire spine. The articular surface of the atlantoaxial joint is flat and round, like no other joint in the body. It caters to circumferential movements of the region. Occipitoatlantal articulation has a cup-and-saucer configuration and facilitates attachment for strong and thick ligaments all along its edges.

7.4 Atlantoaxial Dislocation or Instability

Incompetence of the muscles and ligaments at the fulcrum point of facets of atlas and axis at the atlantoaxial facetal articulation results in atlantoaxial instability. The atlantoaxial instability can be anteroposterior wherein the atlantodental interval abnormally increases and there can be dural and neural compression opposite the tip of the odontoid tip. Atlantoaxial instability is diagnosed on dynamic images with the head in flexion and in extension. The atlantodental interval of more than 3 mm in adults and 5 mm in pediatric age group is generally considered to be indicative of atlantoaxial instability. This parameter to diagnose instability is the most frequently used and is probably the only validated parameter to identify instability [3, 4].

Atlantoaxial instability can be **mobile and reducible** (Fig. 7.1) when atlantodental interval returns to normal on head extension and **partially or completely fixed or irreducible** (Fig. 7.2) when atlantodental interval does not change or only partially reduces on head extension [5].

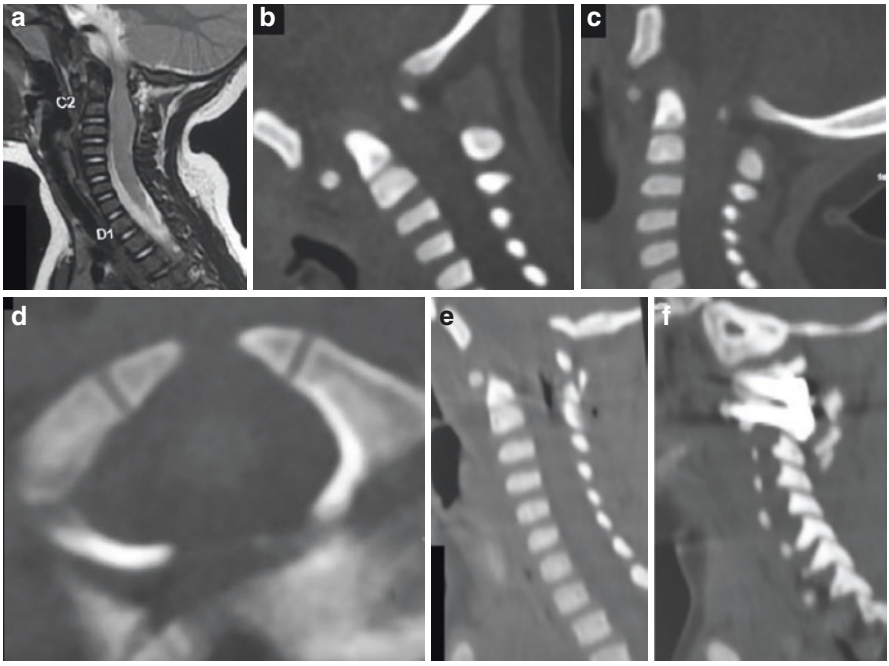

Fig. 7.1 Images showing mobile atlantoaxial instability in a 3-year-old male patient. (**a**): T2-weighted magnetic resonance image showing atlantoaxial dislocation and cord compression opposite the odontoid process. (**b**) Computed tomographic (CT) scan with the head in flexion shows atlantoaxial dislocation. (**c**) CT scan with the head in extension position showing incomplete reduction of the dislocation. (**d**) Axial cut of CT scan showing bifid anterior and posterior arches of atlas. (**e**) Postoperative CT scan showing atlantoaxial fixation in reduced position. (**f**) Image showing the implants in the facets of atlas and axis

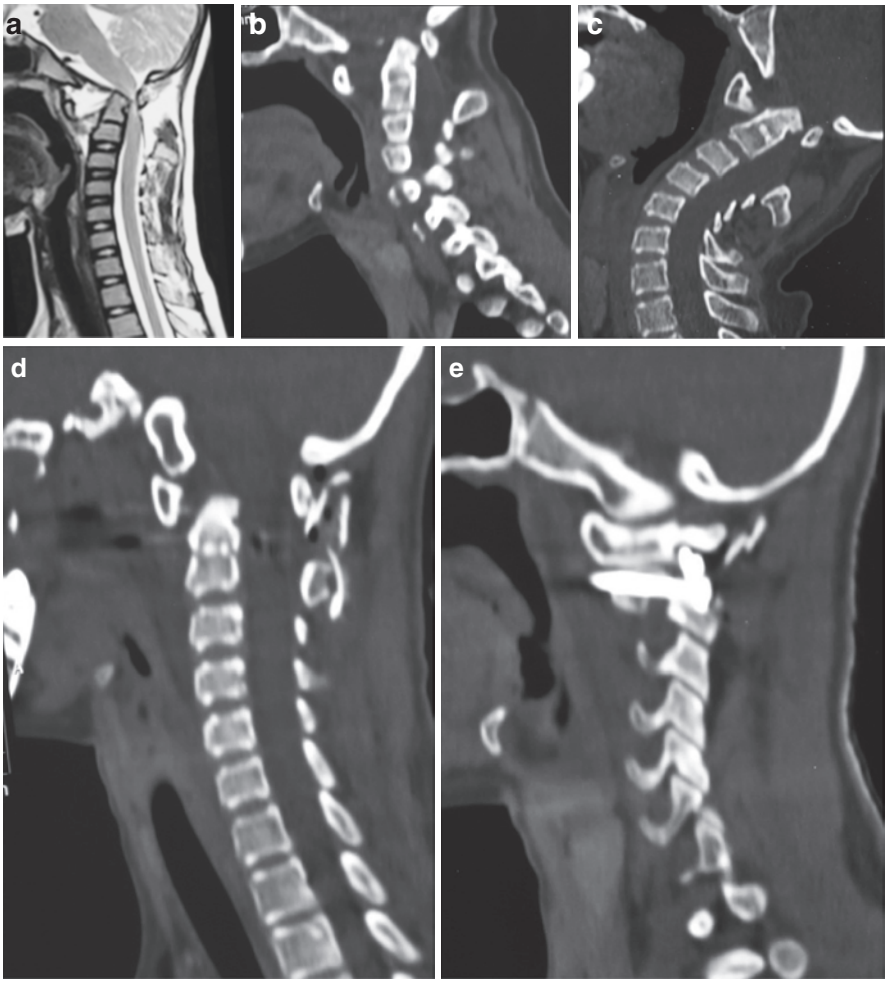

Fig. 7.2 Images of an 18-year-old male patient showing "irreducible" atlantoaxial dislocation. (**a**) T2-weighted MRI showing atlantoaxial dislocation and cord compression by the odontoid process. (**b**) CT scan with the head in flexed position showing severe atlantoaxial dislocation. (**c**) CT scan with the head in extension position does not show any reduction in atlantoaxial dislocation. (**d**) Postoperative CT scan showing realignment of the craniovertebral junction and the atlantoaxial fusion. (**e**) Postoperative image through the facets showing lateral mass plate and screw fixation

In the year 2009, we identified **vertical** atlantoaxial instability (Fig. 7.3) wherein the odontoid process moves up and down in the form of a piston on dynamic imaging that involves flexion and extension of the head [6]. There is no abnormal alteration in the atlantodental interval during these movements.

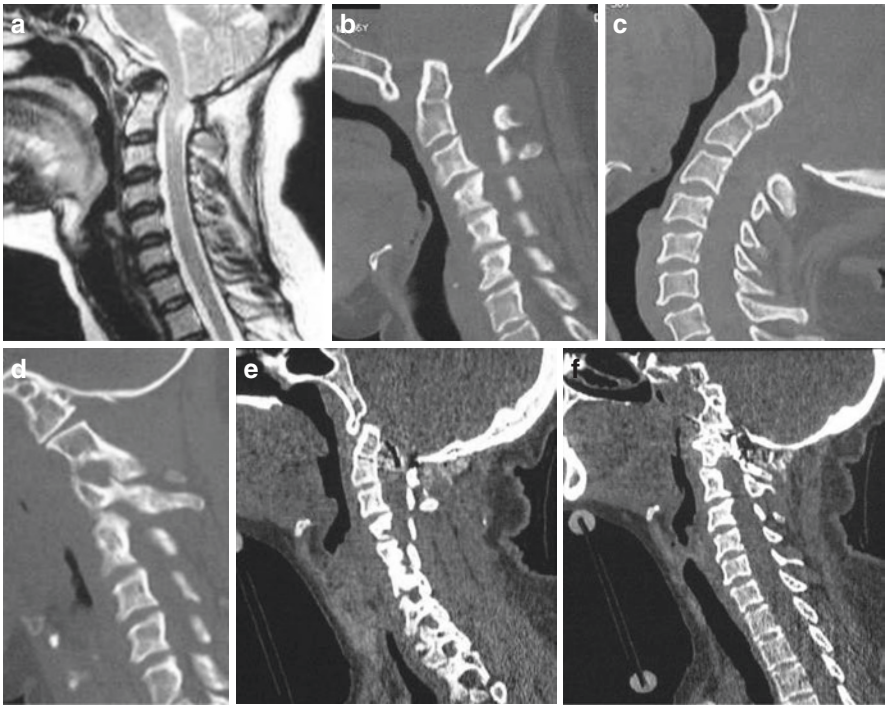

Fig. 7.3 Images of a 23-year-old male patient showing mobile atlantoaxial dislocation in a case with basilar invagination. (**a**) T2-weighted MRI image showing basilar invagination, assimilation of atlas, Chiari formation, and cord compression. (**b**) CT scan with the head in flexed position showing basilar invagination in the form of vertical or superior migration of the odontoid. (**c**) CT scan with the head in extension showing reduction of the dislocation. (**d**) CT scan cut through the facets showing assimilation of atlas and no significant malalignment. (**e**) Postoperative CT scan showing realignment of the craniovertebral junction. (**f**) Postoperative image through the facets showing lateral mass plate and screw fixation

In fracture of the ring of atlas related to trauma, destruction related to tumor or infection like tuberculosis or presence of bifid atlas, the facets of atlas are dislocated laterally in relationship to the facet of axis. Such dislocation is termed as **lateral** atlantoaxial dislocation [7, 8].

Rotatory dislocation is when there is an element of rotation in the facets of atlas and axis with the facet of atlas positioned anterior to the facet of axis on one side and posterior to the facet of axis on the other [9] (Fig. 7.4). A number of types of rotatory dislocation have been discussed in the literature.

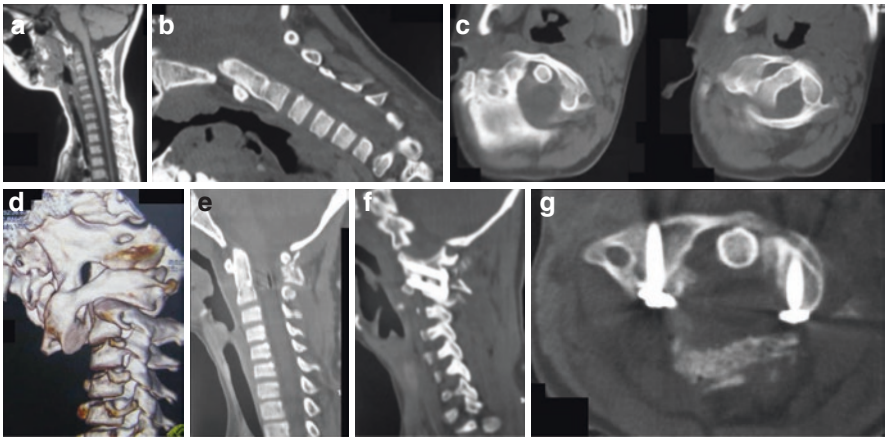

Fig. 7.4 Images a 12-year-old female patient showing rotatory atlantoaxial dislocation. (**a**) T1-weighted MRI showing abnormal tilt of the odontoid process with no change in atlantodental interval. (**b**) Sagittal cut of CT showing abnormal alignment of the odontoid process with no change in atlantodental interval. (**c**) Axial view of the CT scan showing rotatory dislocation. (**d**) 3D reconstructed view of CT showing the rotatory dislocation. (**e**) Postoperative CT scan showing reduction of the tilt of odontoid process. (**f**) Sagittal image of the CT scan showing fixation of the facets of atlas and axis in reduced position. (**g**) Axial CT scan showing screws passing through the facets of atlas. Reduction of the dislocation can be observed

7.5 "Fixed" or "Irreducible" Atlantoaxial Instability

Till about three decades ago, the surgical treatment of mobile and reducible atlantoaxial instability was fixation or stabilization; the treatment of fixed or irreducible atlantoaxial instability was decompression, by resection of the compressing odontoid process by the transoral surgical route and foramen magnum decompression from the posterior surgical route. In the year 2005 for the first time in the literature, we identified that the so-called fixed or irreducible atlantoaxial dislocation is "never" fixed or irreducible, but it is always mobile and pathologically hypermobile and can be reduced by atlantoaxial facetal manipulation and distraction [5] (Fig. 7.2). This concept is now established, and majority of surgeons dealing with craniovertebral junction attempt craniovertebral junction realignment and stabilization in such cases, rather than resorting to decompression by bone resection.

7.6 Central or Axial Atlantoaxial Instability (CAAD)

In the year 2014, we classified atlantoaxial instability on the basis of alignment of the facets of atlas and axis on lateral profile imaging with the head in neutral position [10]. **Type 1** atlantoaxial facetal instability is when the facet of atlas is dislocated anterior to the facet of axis. Atlantodental interval is increased in such

dislocation, and there may be dural and neural compression. **Type 2** atlantoaxial facetal instability is when the facet of atlas is dislocated posterior to the facet of axis. **Type 2 rotatory** atlantoaxial facetal instability is when the facet of atlas is dislocated posterior to the facet of axis on one side and is normally aligned on the contralateral side. **Type 3** atlantoaxial instability is when the facet of atlas and axis are in alignment. Instability in such cases is diagnosed on the basis of telltale radiological and clinical evidences and is confirmed by direct manipulation of bones during surgery. In both type 2 and type 3, there may not be any abnormal alteration of atlantodental interval or any evidence of dural or neural compression by the odontoid process. Such instability is labeled as central or axial atlantoaxial instability (CAAD) [11–13]. Whilst type 1 atlantoaxial instability is usually relatively acute in onset and symptoms are pronounced, CAAD is usually of chronic or long-standing nature, and the symptoms are relatively subtle and relentlessly progressive.

7.7 Acute and Chronic Atlantoaxial Instability

Acute atlantoaxial dislocation is more often related to trauma or injury. Symptoms related to acute atlantoaxial instability are pronounced and sudden and can be disabling and less frequently even fatal. Moderate to severe pain in the nape of the neck, neck stiffness and muscle spasm, and varying range of neurological symptoms and deficits in the limbs are more often the presenting symptoms. On the other hand, atlantoaxial instability can be of chronic or long-standing nature [14, 15]. The duration of instability can be of months or years. Chronic instability is usually of type 2 or 3 atlantoaxial facetal instability or of CAAD. In such potential or manifest instability, there are several and wide-ranging musculoskeletal and neural alterations that appear to be anomalies and "pathological" or compressive but have a protective role and are potentially reversible following atlantoaxial stabilization. These secondary musculoskeletal alterations include the "complex" of basilar invagination. Skeletal alterations include platybasia, Klippel-Feil abnormality, bifid anterior and posterior arch of atlas, bifid posterior elements of C2, os odontoideum, assimilation of atlas, and C2–3 fusion. Neural alterations include Chiari 1 formation, syringomyelia, syringobulbia, external syringomyelia, and external syringobulbia. Our earlier article discuss that in the presence of chronic atlantoaxial instability, there can be short head, short neck, and short spine. Whilst short neck is associated with low hairline and torticollis, short spine can be associated with dorsal kyphoscoliosis. Atlantoaxial instability is indicated when all these naturally protective and secondary alterations are present either discretely or in cohort. More importantly, they suggest the need for atlantoaxial stabilization. All the secondary alterations are potentially reversible following atlantoaxial fixation. Any kind of direct surgical manipulation to any of the abovementioned secondary alterations can only have negative clinical consequences.

7.8 Basilar Invagination

A number of radiological parameters have been described that determine basilar invagination. Amongst these, Chamberlain's line, McGregor's line, and Wackenheim clival line are amongst the more popularly deployed. For several decades, basilar invagination was considered to be associated with "fixed" atlantoaxial instability, and "decompression" of the craniovertebral junction was the accepted form of surgical treatment.

Our understanding of basilar invagination has evolved in three stages. These are briefly discussed.

Stage 1: In the year 1998, we divided basilar invagination into two groups [16]. Group 1 basilar invagination was when the odontoid process migrated into the foramen magnum, and Group 2 was when there was Chiari 1 malformation or tonsillar herniation. As basilar invagination was considered to be a fixed anomaly, decompression was identified to be the treatment. For Group 1 transoral decompression and for Group 2 foramen magnum decompression was considered to be the ideal form of treatment. Role of stabilization was not entirely clear at this time and was considered only because resection of bones from transoral route or by foramen magnum decompression was identified to have potential destabilizing effects in the long run. During this phase of evolution, it was observed that for Chiari malformation and for syringomyelia, there might not be any role for opening the dura after the surgical procedure of foramen magnum decompression [16].

Stage 2: In the year 2004, we divided basilar invagination into two groups [17]. Group A was when odontoid process migrated into the foramen magnum resulting in an increase in atlantodental or clivodental interval (Fig. 7.5). Group B was when there was no alteration in the atlantodental interval (Fig. 7.6). Whilst instability was identified in Group A, Group B basilar invagination was still considered to be a "fixed" anomaly. We identified similarities between lumbar spondylolisthesis and C1 over C2 facetal listhesis that results in Group A basilar invagination [18]. Similarities between the treatment protocol of lumbar spondylolisthesis and basilar invagination were accordingly identified. For Group A, atlantoaxial stabilization and attempts towards craniovertebral junction realignment were advocated, and for Group B, foramen magnum decompression was considered to be the treatment. Distraction of facets of atlas and axis and reduction-stabilization of atlantoaxial articulation introduced a novel concept and a new format of treatment of Group A basilar invagination. The concept that basilar invagination can be reduced and that transoral decompression can be avoided radically changed the treatment of this clinical entity. During the years, the authors have treated several cases of basilar invagination Group A with only stabilization and without any form of decompression.

Stage 3: In the year 2012, it was observed that "chronic" atlantoaxial instability forms the point of pathogenesis of Group B basilar invagination [19]. More often, such patients have central or axial atlantoaxial instability (CAAD). Secondary musculoskeletal and neural alterations are more profound in such cases. Atlantoaxial

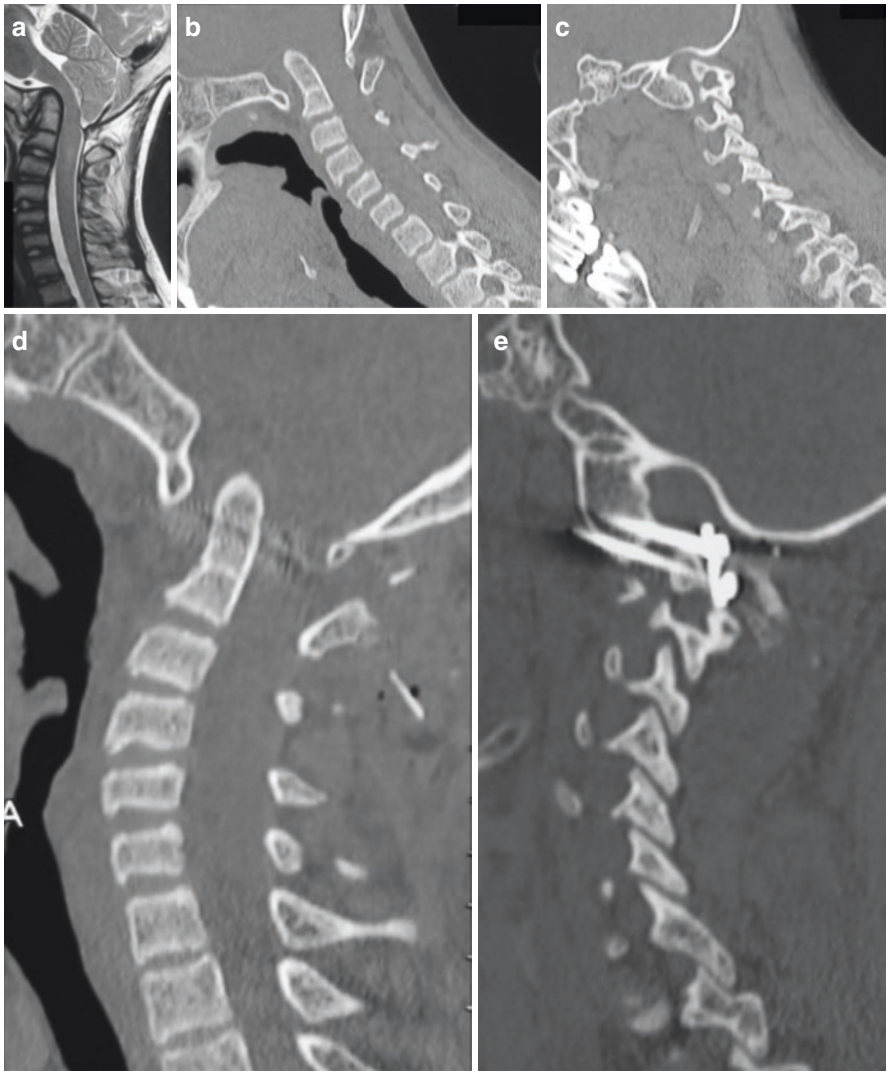

Fig. 7.5 Images of a 30-year-old female patient showing with Group A basilar invagination and Chiari formation. (**a**) T2-weighted MRI showing Group A basilar invagination and Chiari formation and indentation of the brainstem by the odontoid process. (**b**) CT scan with the head in flexion showing the basilar invagination. (**c**) CT scan with the cut passing through the facets showing type 1 atlantoaxial dislocation. (**d**) Postoperative CT scan showing the craniovertebral junction realignment. (**e**) Postoperative image with sagittal cut passing through the facets showing the metal construct

stabilization forms the basis of surgical treatment [20, 21]. Any form of decompression can have negative clinical implications. The author is convinced that foramen magnum decompression in such cases can soon become a historical operation.

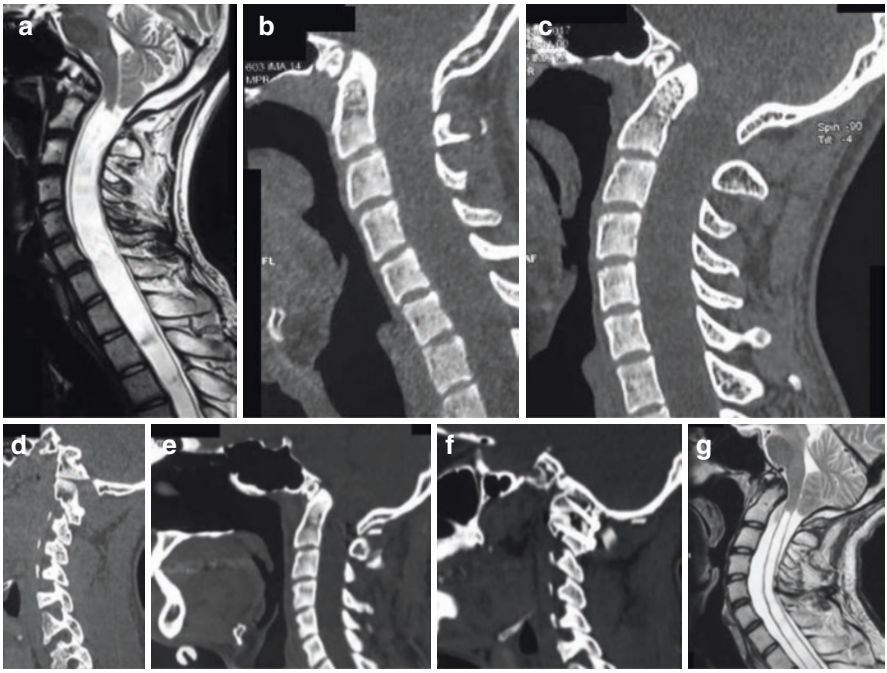

Fig. 7.6 Images of a 23-year-old male patient having Group B basilar invagination. (**a**) T2-weighted MRI showing basilar invagination, Chiari formation, and syringomyelia. (**b**) CT scan with the head in flexed position showing basilar invagination. Assimilation of atlas is seen. (**c**) CT scan with the head in extended position shows so significant alteration in craniovertebral junction bone alignment. (**d**) CT scan cut through the facets showing that the facets of atlas and axis are in alignment. (**e**) Postoperative image. (**f**) Postoperative image with the cut passing through the facets showing the metal implant. (**g**) Delayed postoperative MRI showing reduction in the size of the syrinx

Essentially, the treatment strategy of all types of basilar invagination has changed in the last few years from only decompression to only fixation. Basilar invagination is now identified to be a secondary and protective outcome of chronic atlantoaxial instability, and atlantoaxial stabilization is considered to be the treatment.

7.9 Craniovertebral Junction Alterations

Platybasia, Klippel-Feil alteration, assimilation of atlas, C2–3 fusion, bifid arches of atlas, os odontoideum, and several other so-called pathological clinical entities are secondary to atlantoaxial instability, are naturally protective, and are potentially

reversible following atlantoaxial stabilization [22–28]. Chiari formation, syringomyelia, and basilar invagination are a common clinical triad [29]. When they are present discretely or in cohort or when they are present in association with one or more of other musculoskeletal alteration are indicative of presence of atlantoaxial instability and are suggestive of the need for surgery that involves atlantoaxial stabilization.

7.10 Chiari Formation and Syringomyelia

Chiari formation and syringomyelia are relatively common clinical entities. They are associated with relentlessly progressive clinical symptoms. The symptoms range from neck pain, pain in shoulders and hands, and weakness in the hands that progresses eventually to weakness of all four limbs, sensory dysfunction, breathing disturbances, sleep apnea, and several such symptoms that can eventually lead to crippling neurological deficits. Chronic atlantoaxial instability is the nodal point of pathogenesis. The understanding that Chiari formation is associated with atlantoaxial instability and atlantoaxial stabilization is the treatment has a potential to radically alter the generally followed surgical treatment of foramen magnum decompression (Fig. 7.7) [23, 24, 30–33]. Presence of Chiari, syringomyelia, basilar invagination, and any of the other listed secondary alteration either in a cohort or discretely indicate presence of atlantoaxial instability and suggest the need for atlantoaxial stabilization. Any kind of decompression that involves bone or soft tissue resection in the presence of unstable atlantoaxial articulation can only have negative implications. Dramatic clinical recovery from all symptoms was observed that started on awakening from anesthesia. We identified recovery of motor evoked potential during surgery at the moment when spinal stabilization is completed [34].

We introduced the terms “external” syringomyelia and “external” syringobulbia when “excessive” or more than usual amount of CSF is present around the spinal cord or brainstem [35–37]. Such CSF alteration is Nature’s protective formation and indicates presence of atlantoaxial instability.

Short neck, short head, and short spine are secondary “protective” consequences of chronic atlantoaxial instability [38]. Whilst short neck can be associated with torticollis, short spine can be associated with dorsal kyphoscoliosis [39]. Presence of such spinal alterations is protective, is indicative of chronic atlantoaxial instability, and is potentially reversible following atlantoaxial stabilization.

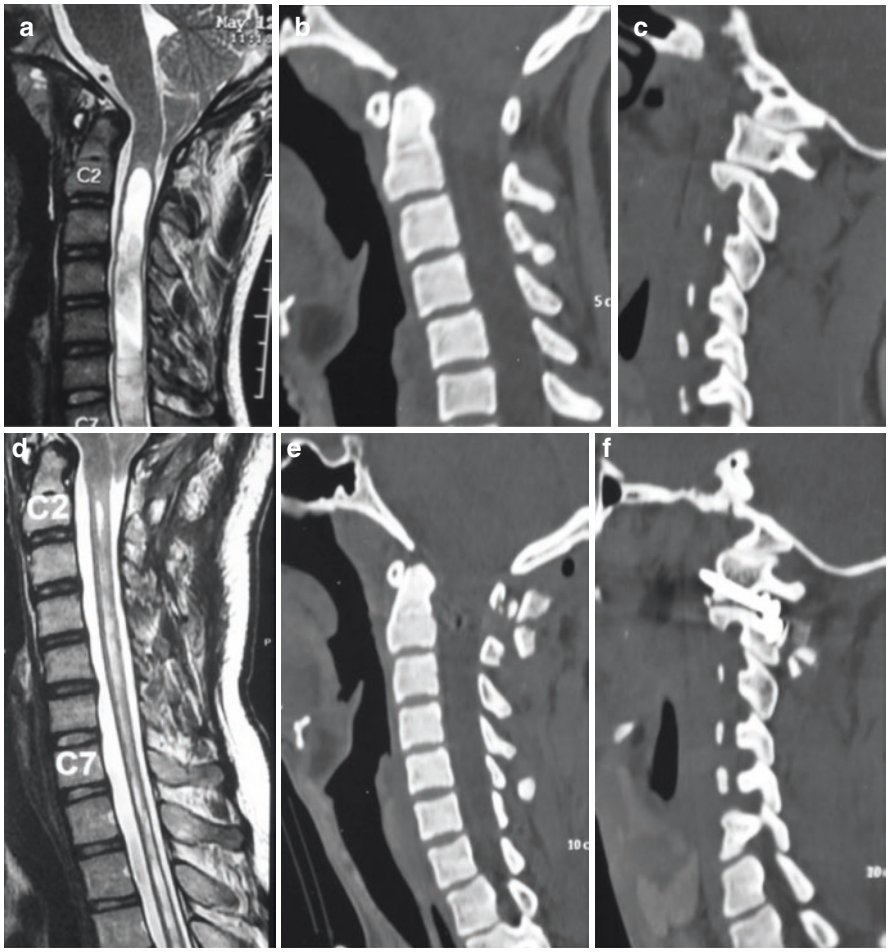

Fig. 7.7 Images of a 19-year-old male patient having Chiari formation and syringomyelia without any significant bone alteration at the craniovertebral junction. (**a**) T2-weighted sagittal MRI showing Chiari formation and syringomyelia. (**b**) CT scan showing no craniovertebral junction bone anomaly. (**c**) CT scan with the cut passing through the facets showing type 2 facetal instability. (**d**) Postoperative T2-weighted MRI showing resolution of the Chiari formation and syringomyelia. (**e**) Postoperative CT image showing no bony decompression. (**f**) Postoperative CT scan showing the implants

7.11 Vertical Spinal Instability

Standing position makes humans unique. This position entails lifelong stress on the extensor muscles located on the "back" of spine. Weakness of these muscles due to disuse, abuse, or injury leads to listhesis of the facets and telescoping of the spinal segments. This retrolisthesis may not be identified on plain or dynamic imaging. Our articles on the subject identify listhesis of the facets as the nodal point of genesis of spinal degeneration [40–46].

7.12 Spinal Degeneration

A number of clinical and radiological features characterize spondylotic disease. Disc space reduction, osteophyte formation, ligamentum flavum hypertrophy, and eventual reduction of spinal and root canal dimension result in symptoms of radiculopathy or myelopathy. Facetal retrolisthesis is included in the gamut of degenerative changes and is considered to be a secondary phenomenon to primary disc space reduction. For several decades degenerative spondylosis has been defined as secondary processes that result from primary disc degeneration, reduction of its water content, and disc space reduction.

Era of computer-based imaging: Advances in the MRI and CT scan technology now provide a clear image of the consequence of spinal degeneration. Compression and deformation of the neural structures by bulging or herniated disc, osteophytes, and thickened ligaments are clearly visualized. Effect on the spinal cord is demonstrated by signal alterations. As cord compression has been considered to be the primary squeal of spinal degeneration, decompression of the spinal cord by anterior decompressive measures like corpectomy and discoidectomy and posterior decompressive measures like laminectomy and laminoplasty have been the prime focus of surgical treatment. The aim of decompression is to provide space for the spinal cord so that the "intruders" could be accommodated and tolerated. Osteophytes and hypertrophy of the ligamentum flavum and other intervertebral ligaments are considered to be the prime factors that result in cord compression and its related ill effects. The more modern treatment focuses on the disc, osteophytes, and thickened ligaments, and the surgical procedure aims to resect these "pathological" entities and provide space for spinal cord and nerve roots.

Issue of spinal instability: The concept that disc degeneration or disc space reduction is not the primary issue in spondylotic spinal disease has a potential to influence or revolutionize the treatment strategies. The issue of instability has never been incorporated as the primary and nodal point of pathogenesis of spondylotic process. The need of treatment by stabilization is generally considered because the surgical treatment by anterior or posterior decompression is likely to have a secondary destabilizing effect on the spine. Considering this possibility, currently decompression-fixation has been the preferred twin operations. Specialized distractor-spacer-fixator placed in the intervertebral space after wide removal of the disc partakes in the process of decompression and provides a background for arthrodesis. Posterior interlaminar and interspinous process spacers have also been popular options.

More recently, some authors prefer to introduce artificial disc with the aim of retaining the movements of the intervertebral joint after wide and appropriate decompression. The possible issue with movement preserving surgery over fusion-fixation option is currently a debated issue.

Goel's concept of pathogenesis of degenerative spine: In the year 2010, Goel introduced an alternative concept regarding the pathogenesis of degenerative spondylotic disease. This concept hypothesized that spinal instability is the

primary pathogenetic issue in the initiation, development, and progression of degenerative spinal disease [41, 42]. Instability is related to and a direct consequence of the weakness of the muscles of the nape of the neck and back. The weakness of the muscles can be due to injury, misuse, or disuse and lack of their proper care by appropriate and full use. The weakness of the muscles is also related to standing human position that lays long-term stress. **Vertical spinal instability** and facetal overriding or listhesis are manifestations of weakness or incompetence of the paraspinal muscles [40]. Even modern images do not show clearly the abnormalities of alignment or instability of the facet joint on dynamic imaging. Due to oblique profile of the facets in the cervical and dorsal spine and a more vertical orientation in the lumbar spine, the dislocation is not horizontal but vertical or oblique when observed from a profile view.

Goel speculated that the primary or the initiation point of spinal degeneration is the facet joint [40–42]. This is the nodal point of initiation and progression of the "spondylotic" disease process. Facetal instability is of vertical nature and results in facetal overriding or listhesis. The facetal instability is manifested by reduction in the intervertebral spaces and buckling of the ligaments. This concept is in marked variation of the earlier hypothesis that suggested disc space reduction is the primary issue and rest of the consequences being secondary. From reduction of the anterior intervertebral space, the concept now places focus on the overriding of the posterolaterally placed facets. The generally identified primary issues in spinal degeneration of disc space reduction, osteophyte formation, ligamentum flavum buckling, and reduction in the spinal canal and neural foramina are secondary and probably protective issues related to primary spinal instability [47–49]. The emphasis on instability as the primary issue has the potential of changing the focus of treatment from decompression to stabilization. The symptom of claudication pain related to lumbar canal stenosis also appears to be secondary to weak back muscles that give way or get fatigued after a period of walking [50]. It seems that the muscles not only play a role in the movements of the spine but also participate in distraction of the intervertebral segments.

Disc herniation appears to be secondary to or can be a cause of focal spinal instability. Instability is the defining issue, and stabilization of the affected spinal segment is the treatment (Figs. 7.8, 7.9, and 7.10). Our studies identify disc herniation to be a protective natural issue, and the related pain or radiculopathy assists in avoiding excessive local movements in the face of focal spinal instability [51–55].

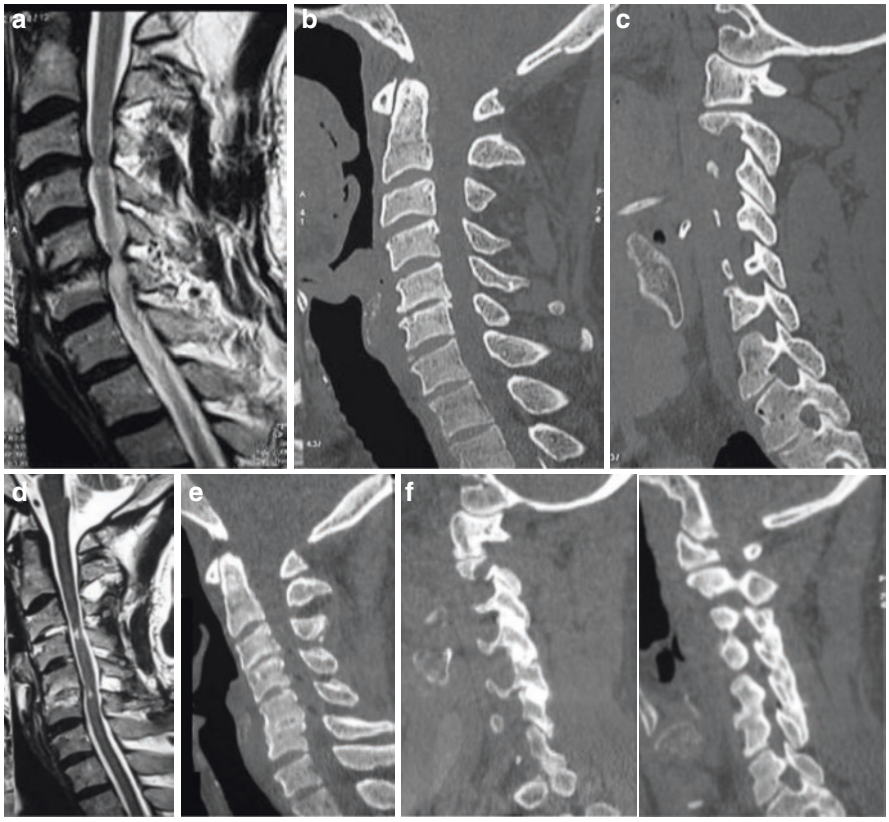

Fig. 7.8 Images of a 48-year-old male patient showing fixation using facet spacers. (**a**) T2-weighted MRI showing evidence of significant spondylotic disease with cord compression opposite C3–4 and 5–6 disc spaces. (**b**) CT scan showing degenerative changes in the spine. (**c**) Sagittal section depicting the facets. (**d**) Postoperative MRI showing reduction in the extent of cord compression. Resorption of the osteophytes and reduction in the buckling of posterior longitudinal ligament and ligamentum flavum at the levels treated can be seen. (**e**) CT scan showing distraction and increase in the intervertebral and interspinous process spaces. (**f**) Sagittal section through the facets showing the spacers with the C3–4, 4–5, and 5–6 facet joints with evidence of arthrodesis

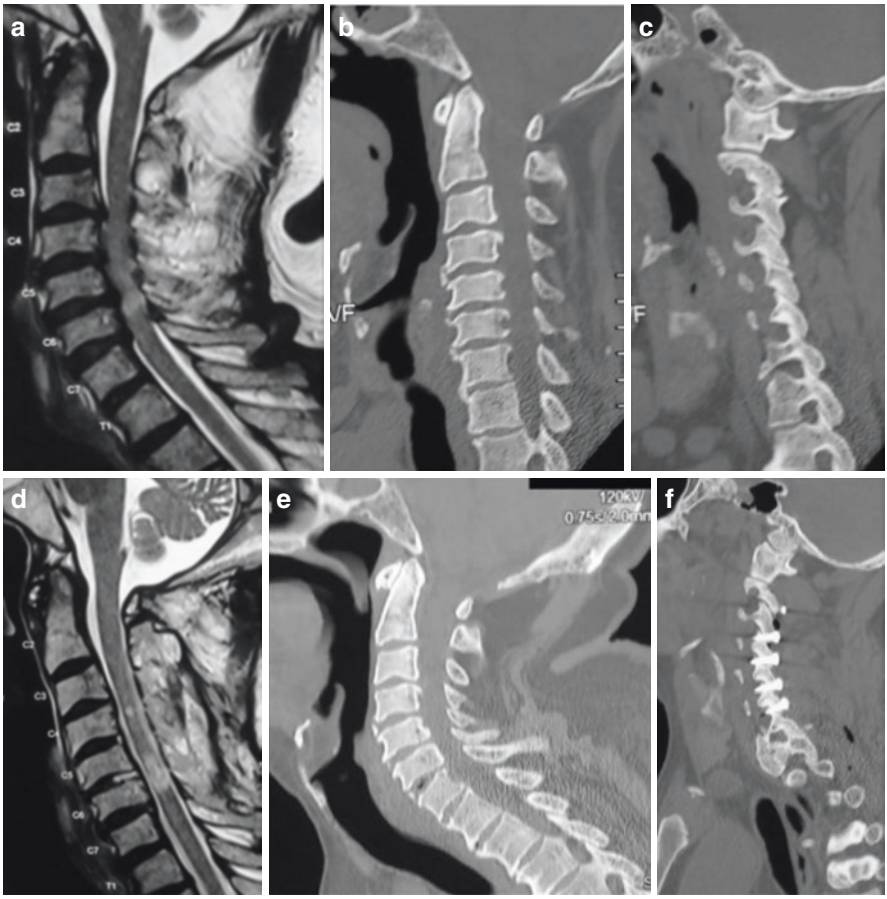

Fig. 7.9 Images a 65-year-old male patient showing fixation using transarticular facet fixation. (**a**) T2-weighted MRI showing evidence of significant multi-level spondylotic disease with cord compression. (**b**) CT scan showing degenerative changes in the spine. (**c**) Sagittal section showing the facets. (**d**) Postoperative MRI showing reduction in the extent of cord compression. (**e**) Postoperative CT showing no bone decompression. (**f**) Sagittal section through the facets showing C2–7 transarticular screw fixation

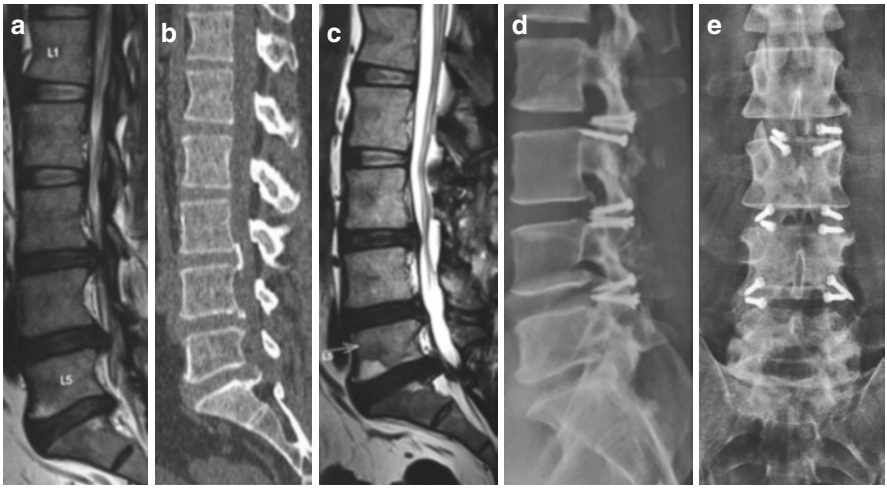

Fig. 7.10 Images showing lumbar transarticular screw fixation. (**a**) T2-weighted MRI showing degenerative changes in the lumbar spine. (**b**) CT scan of the lumbar spine. (**c**) Postoperative MRI (3 months after surgery) showing reversal of the degenerative changes. (**d**) Lateral X-ray showing the double insurance transarticular screw fixation. (**e**) Anteroposterior view of radiograph showing the fixation

7.13 Facet Distraction-Stabilization-Arthrodesis Surgery

Facet distraction and arthrodesis as treatment of single- or multiple-level cervical radiculopathy and myelopathy and lumbar spine degeneration added a new dimension to the treatment and to the understanding of the process of spinal degeneration [43, 44]. Introduction of intra-articular inter-facetal spacers reversed or had the potential of reversal of the entire spectrum of degenerative processes in the spine (Fig. 7.8). Distraction of the facets resulted in an immediate increase of dimensions of spinal canal and neural foramen and also increased the intervertebral distances that included an increase in the intervertebral height. Distraction resulted in stretch to the buckled ligamentum flavum and circumferential intervertebral ligaments that included the posterior longitudinal ligament. There is a potential of regression of osteophytes and restoration of disc fluid volume following facetal distraction. The fact that there is a reversal or potential of reversal of all known pathogenetic factors described in degenerative spinal disease following a single act of facet distraction points towards the site of initiation of the process of degeneration.

The technique of facet distraction involves opening of the joint, denuding of the articular cartilage, introduction of bone chips within the articular cavity, and impaction of the Goel facet spacer. The adjoining posterior surfaces of the laminae of the spine are widely decorticated, and bone graft harvested from the spinous processes or from the iliac crest is placed in the region and forms an additional ground for bone fusion and arthrodesis.

7.14 Only Fixation as Method of Treatment

As we mature further in the understanding of spinal degeneration, we realize that spinal stabilization alone without distraction can be a rational form of treatment [45, 46]. Identification of the unstable spinal segments and their stabilization can form the surgical treatment for single- or multiple-level radiculopathy or myelopathy. This understanding is based on realization that more than neural deformation or compression, it is repeated microtrauma or injury to the spinal cord related to instability that is the cause of symptoms of radiculopathy and myelopathy [48]. Long-term deformation or compression of the neural structures is well tolerated. This fact can be observed in cases with benign spinal tumors and syringomyelia that develop over long periods, and the reduction in cord girth is surprisingly well tolerated by the patient [37]. We resorted to transfacetal or transarticular Camille's technique of screw insertion in the affected spinal segments and identified this as a more effective, safe, and rather simple surgical procedure [56, 57] (Fig. 7.9). Insertion of the screw into the strongest part of the spinal segment provides for firm stabilization of the region with possibility of "zero" movement and a ground for solid arthrodesis. Real-time identification of unstable joints by direct inspection and their stabilization even in the absence of their radiological demonstration can lead to effective treatment of spinal instability. Identification of the level of unstable segment is done by clinical and radiological guides but is finally confirmed by direct visual observation of the facets and by manual manipulation of bones of the region.

7.15 Association of Atlantoaxial Instability in Cervical Spinal Degeneration

Cervical spondylosis is usually considered to involve only the lower cervical vertebral levels and less commonly upper cervical levels. Atlantoaxial joint degeneration is seldom associated with cervical spondylosis. Whilst the special atlantoaxial joint structure facilitates performance of circumferential movements, it also makes it more susceptible to instability. It seems that the instability of the atlantoaxial joint may even be the primary site of degeneration that may be manifested radiologically at the subaxial spinal levels. Instability of the atlantoaxial joint can be identified by direct observation by manual handling of the bones during surgery or can be evaluated by radiological demonstration of facetal malalignment on lateral profile imaging in neutral spinal position.

In chronic degenerative changes, atlantoaxial instability is more often of central or axial type (CAAD). Atlantoaxial instability is more often associated in cases with multisegmental cervical spondylotic disease and particularly when the myelopathy is "severe" [58–61]. Ignoring atlantoaxial instability whilst treating subaxial spinal

degeneration can be a major cause of failure of treatment or can be associated with a poor surgical outcome. A modified form of atlantoaxial fixation involves sectioning of the muscles attached to the C2-spinous process and C2–3 transarticular fixation [62]. The technique allows rotatory movements executed by the muscles attached to the transverse process of the atlas and fixates anteroposterior movements, particularly those that involve the odontoid process.

The treatment of acute and chronic, single- or multiple-level spinal spondylotic disease presenting with radiculopathy and/or myelopathy is thus focused on stabilization of the affected spinal segments. The spinal bones are used for arthrodesis of segments, and their removal for "decompression" in the presence of spinal instability can only have negative consequences. All the so-called pathological "compressive" entities are secondary, naturally protective, and reversible after spinal stabilization surgery. Disc herniation, or prolapse, can regress and resorb, osteophytes can reverse, ligamentum flavum bulge can disappear, disc space height can recover, and there is a potential for bone fusions to un-fuse.

It does seem that a ground has been laid for relegating surgery of spinal canal and foraminal decompression by laminectomy or laminoplasty and corpectomy-discoidectomy into realm of history [63]. The validity and need for osteophyte resection, removal of disc, resection of ligamentum flavum, and enlarging the spinal canal dimensions by laminectomy/laminoplasty/corpectomy that forms the current basis of surgical treatment of degenerative spine can be questioned. Surgical processes that enhance the fixation and arthrodesis should be appropriately adopted in the treatment. It is important to identify the levels that need stabilization, and atlantoaxial joint should not be ignored when treatment is planned and executed. It must be realized that the spinal levels that appear to be affected on radiological imaging may not be the only segments that are actually unstable. Manual physical and visual analysis of stability of the bones of the region on the basis of clinical and radiological guides can have a major impact on guiding the surgeon on the number of spinal levels that need fixation. The concept that there can be instability without any radiological demonstration can expand the scope of surgery.

Ossification of posterior longitudinal ligament (OPLL) and cervical myelopathy: Our studies have identified that like osteophyte formation, OPLL is a manifestation of unstable spinal segment [64–67]. Instability of the spinal segment initiates the process of abnormal ossification. Atlantoaxial instability is frequently associated with subaxial spinal instability in cases with OPLL. The pathogenesis of both spinal degeneration and of OPLL is related to subtle and long-standing spinal instability.

The pathogenesis of **Hirayama disease** has been under discussion. Compression of neural structures by unusually formed dural band has generally been identified to be the causative issue. Our studies have identified multisegmental cervical spinal instability that generally includes CAAD to be the point of pathogenesis of Hirayama disease. Spinal stabilization rather than spinal decompression appears to be a rational form of surgical treatment [68].

7.16 Conclusions

Essentially, our studies identify the validity of spinal stabilization and futility of any form of spinal decompression in cases with radiculopathy and myelopathy for single- or multi-level spinal degeneration. Muscle weakness-related instability of the spinal segments is the cause of spinal degeneration, and correct identification of unstable spinal segments and their strong stabilization form the basis of surgical treatment.

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Chapter 8
Chiari Malformation Type 1 in Adults

Athanasios Zisakis, Rosa Sun, Joshua Pepper, and Georgios Tsermoulas

8.1 Introduction

The term Chiari malformation refers to a heterogeneous group of anatomical abnormalities at the craniovertebral junction that involve abnormal protrusion of cerebellar tonsils through the foramen magnum. A number of types have been described and Chiari malformation type 1 (CM1) is the most commonly encountered form. It usually manifests clinically in early adult life, although cases may present in childhood or later life. It is sometimes associated with syringomyelia and/or syringobulbia.

The four types of Chiari malformation in the original classification by Hans Chiari share different pathophysiology and natural history [1]:

– Chiari malformation type 1 is characterized by underdevelopment of the posterior cranial fossa with normal development of the hindbrain. It is defined as cerebellar tonsillar decent of ≥5 mm below the McRae (basion-opisthion) line [2]. Cerebellar tonsillar ectopia of 3–5 mm associated with syringomyelia or peg-like tonsils is also considered pathological by some experts.

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– Chiari malformation type 2 is a congenital disorder due to prenatal CSF hypotension secondary to spina bifida. Its severity varies and many patients undergo ventriculoperitoneal shunting in childhood.
– Chiari malformation type 3 and type 4 are extremely rare. Type 3 is associated with encephalocele and type 4 with hypoplastic or aplastic brain without herniation through the foramen magnum. They are both severe disorders with fatal complications in infancy.

More recently, two more types have been proposed [3]:

– Chiari malformation type 1.5 refers to tonsillar herniation associated with brainstem kinking and skeletal abnormalities of the craniocervical junction (Klippel-Feil anomaly, atlanto-occipital fusion, basilar invagination, retroversion of the odontoid process).
– Chiari malformation type 0 refers to idiopathic syringomyelia with minimal or no herniation of the cerebellar tonsils.

8.2 Historical Perspective

Hans Chiari's meticulous autopsy and dissection work has led to this condition being everlastingly linked with his name [1]. However, this abnormality was possibly described first in the seventeenth century, and in 1881, a decade before Chiari's publication, Theodor Langhans described the cerebellar tonsils herniating like "pyramidal tumor" in the craniocervical junction associated with a cervical syrinx [4, 5]. The first patient Chiari described was an autopsy specimen of a 17-year-old girl who died from typhus and had "elongation of the tonsils" projecting into the spinal canal together with hydrocephalus [1].

There are reports of surgery for the treatment of patients with Chiari malformation in the first half of the twentieth century, with mostly poor outcomes. In 1950, Gardner and Goodall published their series of patients with Chiari malformation and syringomyelia operated at the Cleveland clinic [6]. Symptomatic improvement occurred in most of these patients, and this represented the earliest published successful treatment for hindbrain hernia in the western literature, which led to a revolution in the management of this condition.

8.3 Epidemiology

It is estimated that the overall prevalence of CM1 is approximately 1% [7–9]. It changes with age, and in adults it is more prevalent in the third and fourth decades of life. This may be related to the change in the normal position of the cerebellar tonsils in different age groups. In young children, the tonsils lie just above the foramen magnum and slowly descend to early adulthood where its mean position lies just below this level and then progressively rises again so it is firmly within the posterior fossa after the fourth decade [10].

CM1 is more common in women, with a reported female to male ratio of 3 to 1 [2, 11, 12]. It is associated with syringomyelia in approximately 25–70% of cases [8, 9, 13, 14]. It is sometimes associated with other abnormalities of the craniocervical junction such as Klippel-Feil syndrome, platybasia, hypermobility syndromes, spondyloepiphyseal dysplasia, basilar invagination, odontoid retroflexion, as well as few other rarer conditions [8, 9, 15].

8.4 Clinical Presentation

CM1 is asymptomatic in the majority of cases. It has been estimated that in about 14–32% of cases, the condition is diagnosed coincidentally [8, 16]. In symptomatic adults, the onset of the symptoms usually occurs in late 20s or early 30s [2]. Headache is by far the most common symptom. The typical headache is the so-called pressure dissociation headache induced by Valsalva maneuvers, like coughing, sneezing, laughing, and straining, and it is encountered in just under 80% of cases [12] (Fig. 8.1). The phenotype of the headache is paroxysmal with varying

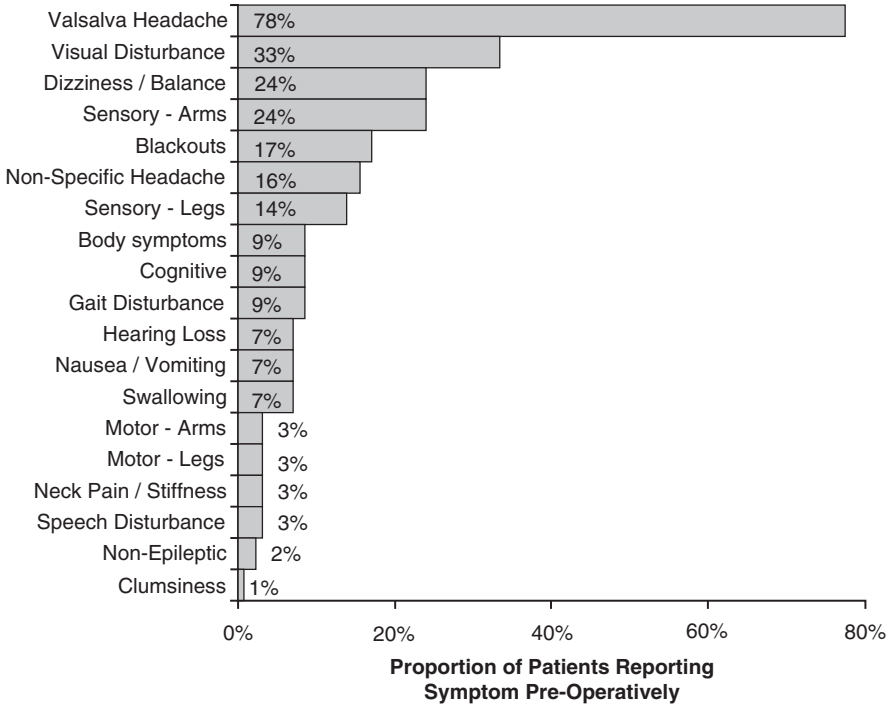

Fig. 8.1 Preoperative symptoms from 129 surgically treated patients with Chiari malformation type 1. (Fom Pepper J, Elhabal A, Tsermoulas G, Flint G. Symptom outcome after craniovertebral decompression for Chiari type 1 malformation without syringomyelia. Acta Neurochir (Wien). 2021 Jan;163(1):239-244, published under CCBY 4.0)

intensity and duration, commonly located in the occipital, suboccipital, or upper cervical region. The headache pathogenesis is related to the valve mechanism created by the herniated cerebellar tonsils, which occupy the volume normally taken up by the cisterna magna. In doing so they create a one-way valve that impedes the normal to-and-fro movement of the cerebrospinal fluid (CSF) across the craniocervical junction. In a normal state of anatomy, the CSF within the posterior fossa and the spinal theca is a continuous column, and it is subject, during normal daily activity, to two main energy sources: the first is comprised of cardiac systolic impulses, which are regular and of low energy; the second is brought on by normal, everyday Valsalva maneuvers that induce surges of CSF flow from the spinal theca into the head. These surges are normally followed by free flow of CSF back into the spine via the cisterna magna, but in CM1, the herniated cerebellar tonsils impede return of craniospinal flow [17]. A volume of spinal CSF is temporarily trapped within the head, briefly raising the intracranial pressure, sufficient to generate intense headache, which abates when the extra volume of "injected" fluid is gradually dissipated [18].

Visual disturbances are common in symptomatic patients and are often nonspecific. They include retro-orbital pain, flashing lights or floaters, blurred vision, photophobia, diplopia, transient vision loss, and peripheral visual loss [12]. Nystagmus is the most frequent eye movement deficit in this condition and often the only positive neurological finding on examination [19]. Horizontal or vertical nystagmus is present in up to 45% of cases [20]. In particular, downbeat nystagmus and oscillopsia are salient features, probably due to brainstem compression from the herniated tonsils, and often improve after surgery [21, 22]. The basis of other, nonspecific visual symptoms such as blurriness is not well established [23].

Approximately, one half of patients without associated syringomyelia report nonspecific sensory symptoms involving the upper limbs, trunk, or lower limbs [12]. These include paresthesia and numbness of no particular dermatomal distribution. The disturbance is due to compression of the ascending fasciculus cuneatus and fasciculus gracilis, or their respective nuclei within the cervicomedullary junction. Dizziness and balance problems affect between 25% and 60% of patients [2, 12]. These feelings of subjective imbalance may be due to subtle compression of cerebellar or vestibular nuclei and their white matter connectivity by the descended tonsils, and just over half of patients with imbalance will improve after surgery.

Loss of consciousness is a rare presentation in CM1, but not an uncommon component of the overall symptom profile [12]. Patients report blackouts and episodes of collapse, not associated with aura or other seizure markers, which last for a short period of time, from seconds to few minutes. Occasionally, they are induced by a Valsalva-like maneuver or by an episode of physical exertion. The underlying pathophysiology is not entirely clear, and proposed mechanisms include compression of the medulla or the vertebral artery, transient impairment of the ascending reticular activating system, hypoperfusion secondary to postural orthostatic tachycardia syndrome, and profound bradycardia [24–28].

There is a variety of other symptoms that patients with CM1 often report and include tinnitus, hearing loss, swallowing difficulty, trigeminal pain, sleep disturbances, and clumsiness [2, 12, 29, 30]. Some of these symptoms may be due to altered CSF dynamics resulting in traction on the lower cranial nerves and medullary compression, but they are nonspecific, and their link to the underlying condition remains unclear. From the neuropsychological perspective, the general cognitive functioning is preserved, but affective functioning is often impaired, manifested as anxiety and depression of varying severity [31].

The presence of syringomyelia and/or syringobulbia in patients with CM1 usually dominates the clinical picture. The degree of brainstem and spinal cord dysfunction varies and may not be related to the extent of the syrinx cavity on radiological imaging. The symptoms usually develop slowly over time, and in some cases they are exacerbated or triggered by Valsalva maneuvers. The typical symptoms are muscle weakness and wasting, loss of pain and temperature sensation, and neuropathic pain. The characteristic sensory deficit over the shoulders and back is described as a "cape-like" distribution. Affected individuals may also describe stiffness secondary to spasticity and reduced coordination secondary to ataxia, which may affect dexterity and gait. Severe cases of syringomyelia can result in paralysis. Associated syringobulbia causes cranial nerve dysfunction, which manifests with dysphagia, dysarthria, oscillopsia, and loss of pain and temperature sensation in the face.

8.5 Natural History

The knowledge of the natural history of CM1 is imperative to inform decision-making when counseling patients about surgical intervention versus expectant management. However, the natural history is not well established, mainly because of the lack of long-term longitudinal data and the disagreement about universal diagnostic and treatment criteria [32]. A literature review on the natural history for adults with CM1 managed nonoperatively reported that most patients either improve or remain clinically unchanged and approximately 11–25% deteriorates over time [33]. In general, the course of mild symptomatic and asymptomatic adults is benign, and a nonsurgical approach is reasonable, irrespective of the degree of tonsillar descent or even the presence of syringomyelia. A consensus opinion of multiple international experts utilizing the Delphi approach agreed with expectant management in cases of incidental CM1 without syringomyelia, but there was less consensus on numerous other management strategies [34]. However, there is no high-class evidence to guide management; the adoption of a universal diagnosis along with the study of the natural history and treatment effect of surgery with a prospective trial will enhance understanding of the condition and improve decision-making [35].

8.6 Pathophysiology

The pathophysiology of CM1 is rather complex, and some patients may develop syringomyelia as a result of crowding of the foramen magnum [36]. It is considered multifactorial that results from a heterogeneous group of ontogenetic errors and pathological mechanisms [37]. To date, there is no single theory that is universally accepted. A congenital etiology seems to exist but often without a clear genetic background. Most cases occur sporadically, but familial transmission has been described both by autosomal recessive and autosomal dominant inheritance with incomplete penetrance [2, 38]. CM1 must be differentiated from tonsillar descent secondary to a CSF pressure gradient across the craniocervical junction, caused by intracranial hypertension or hypotension, and this section presents the various theories behind the pathophysiology of this enigmatic condition.

8.6.1 Small Posterior Cranial Fossa

Posterior cranial fossa overcrowding is the predominant theory and refers to the underdevelopment of the posterior cranial fossa with a normally developed hindbrain resulting in herniation of the cerebellar tonsils [39]. This theory was supported by studies on morphometric analyses of the posterior cranial fossa, which showed reduced volume in CM1 patients compared to controls [40, 41]. Upward herniation through the tentorial incisura and/or downward herniation through the foramen magnum may lead to hydrocephalus, which sometimes coexists with CM1. It has been estimated that the posterior fossa brain in adults with CM1 occupies 83% of the total posterior fossa space, versus 79% in healthy individuals [42, 43]. Further evidence for the mismatch between brain and skull volume is provided by the "occipital dysplasia theory" that proposed a development defect of the occipital bone leading to a small volume of the posterior cranial fossa [44].

8.6.2 Tethered Spinal Cord

It has been suggested that CM1 can occur due to a tight filum terminale essentially pulling down on the spinal cord [45]. An association between CM1 and tethered spinal cord has been described in a subset of patients with normal size of the posterior cranial fossa [46]. The pathogenesis is attributed to downward traction on the cervicomedullary junction that results in stretching of neuronal elements and lowering of the cerebellar tonsils. The diagnosis of tethered cord is based on radiographic evidence of a short, thick, or fatty filum terminale and low-lying conus with its tip positioned at or below the lower endplate of L2 [47]. Occult tethering has been proposed as a pathophysiological mechanism in patients with CM1 without

low-lying conus and filum terminale sectioning proposed as an effective procedure. However, the evidence regarding the efficacy of this operation is mixed and merits more rigorous scientific examination [46, 48, 49].

8.6.3 Other Theories

Instability of the atlantoaxial and/or atlanto-occipital joints has been proposed as the underlying cause in the development of CM1 [50, 51]. The cerebellar tonsillar herniation is deemed to represent a protective response to the joint instability [50]. This theory is based on radiographic evidence of smaller occipital condyles and shallow facets of the atlas and morphometric analysis of the craniocervical junction ligaments that demonstrate defects in the transverse and alar ligaments [51]. The coexistence of hypermobile Ehlers-Danlos syndrome and CM1 is presented as supporting evidence to the joint instability theory and is used to justify instrumented fixation for the management of this condition [52]. However, this theory is contentious and subject of ongoing scientific debate [53, 54].

Physical trauma and exertion have been implicated in the onset of symptoms to a subset of CM1 patients [2]. A survey found that the most common triggering events were related to injury secondary to car accidents (16%), falls (11%), direct head trauma (10%), and sports (5%) [55]. Pregnancy (13% of female respondents) and physical exertion (9%) were also cited to the survey. However, the tonsillar herniation probably predated the trauma and physical stress, and there is no sufficient understanding of the underlying pathophysiological process that triggered the onset of symptoms in a pre-existing condition [36].

8.6.4 Syringomyelia: The Filling Mechanism

The filling mechanism of the syrinx remains elusive, and a number of theories have been proposed. A fundamental principle is that the net inflow of fluid into the cavity exceeds the net outflow, due to either increased inflow or reduced outflow. The composition of syrinx fluid is similar to the CSF, which supports a hydrodynamic mechanism of the syrinx formation, but other theories propose formation of the syrinx by interstitial fluid. Aquaporins may also be partly responsible for the transport of fluid within the cavity, and it is possible that changes in aquaporin expression enhance movement of fluid within the syrinx or alternatively prevent fluid from moving out [56].

The hydrodynamic theory was first proposed by Gardner who suggested that obstruction of the CSF outflow from the fourth ventricle diverts the CSF pulse waves during systole into the central canal inferiorly resulting in syringomyelia and superiorly to the aqueduct of Sylvius, resulting in hydrocephalus [57]. During diastole the obex closes, thus preventing escape of the CSF from the syrinx. His hypothesis

was called the "water-hammer theory," which was later modified by Williams who suggested that the obstruction was dynamic from the descended tonsils, rather than fixed [58]. According to this theory, CSF is forced from the spinal to the cranial compartment during Valsalva maneuvers, but after relaxation, the tonsils act as a valve and prevent fluid return to the spinal compartment, which is in turned forced to the central canal through the obex. These theories have led to the adoption of the surgical technique that included a suboccipital craniotomy with plugging of the obex to prevent inflow of CSF from the fourth ventricle to the syrinx. They are now considered obsolete as they do not explain the vast majority of syrinxes [56].

The most widely accepted theory nowadays has been proposed by Oldfield who suggested a transmedullary filling mechanism [42]. In contrast to previous hypotheses, the flow is trans-parenchymal from the spinal subarachnoid space through perivascular spaces, rather than from the fourth ventricle. Oldfield proposed that the cerebellar tonsils act as "pistons," which transmit high-energy pulsatile waves during cardiac systole to the spinal subarachnoid space, leading to influx of CSF within the spinal cord. Subsequent studies that modeled the pulsatile properties of the spinal subarachnoid space and arterial blood flow within the spinal cord demonstrated that a phase difference between the CSF and arterial pressure waves leads in the formation of a dynamic unidirectional valve within the perivascular spaces that drives CSF within the cord substance [59]. Much work remains to be done to provide sufficient understanding of the precise mechanism and the role of aquaporins, blood-spinal cord barrier disruption and fluid perturbations in the formation and expansion of syrinxes.

8.7 Clinical and Radiological Investigations

The decision about management of patients with CM1 depends on neurological symptoms and signs and investigations that aim to link the underlying condition with the clinical picture. This is particularly important because often the symptoms are nonspecific and in many patients the condition is incidental, given that its prevalence is around 1% [7–9]. In addition, the level of tonsillar descent is not strictly predictive of clinical symptoms [60]. The approach to patients with CM1 should be multidisciplinary and involve neurosurgeons, neurologists, radiologists, ophthalmologists, psychologists, and clinical nurse specialists. The first step in this approach is a clinical assessment to ascertain whether the condition is symptomatic and the impact on patient's well-being and quality of life.

8.7.1 Phenotyping of Symptoms

The typical "Chiari headache" is the prevalent complaint in symptomatic patients with CM1. Based on the current International Classification of Headache Disorders, this headache is, usually occipital or suboccipital, of short duration (less than 5 min),

Table 8.1 Diagnostic criteria for headache attributed to CM1 based on the International Classification of Headache Disorders third edition by the International Headache Society

A. Headache fulfilling criterion C
B. Chiari malformation type I has been demonstrated
C. Evidence of causation demonstrated by at least two of the following:
1. Either or both of the following:
• Headache has developed in temporal relation to the CM1 or led to its discovery
• Headache has resolved within 3 months after successful treatment of the CM1
2. Headache has one or more of the following three characteristics:
• Precipitated by cough or other Valsalva-like maneuver
• Occipital or suboccipital location
• Lasting <5 min
3. Headache is associated with other symptoms and/or clinical signs of brainstem, cerebellar, lower cranial nerve and/or cervical spinal cord dysfunction
D. Not better accounted for by another ICHD-3 diagnosis

CM1 Chiari malformation type 1, *ICHD-3* International Classification of Headache Disorders 3rd edition

is provoked by cough or other Valsalva-like maneuvers, and remits after successful treatment (Table 8.1) [61]. It is important to differentiate the headache phenotype, given that a large proportion of patients with CM1 present with a primary headache. There is a significant overlap with other headache syndromes, most often migraines, and there are also reports of associations with cluster headaches [34, 62, 63]. Interestingly, headaches secondary to CM1 are often descriptively similar to primary cough headache in patients without hindbrain hernia on imaging, with the exception that sometimes the latter last only for seconds.

The importance of seeking the opinion of a headache specialist in phenotyping the symptoms in patients with CM1 cannot be overstated. CSF pressure dissociation headaches respond well to decompressive surgery, whereas atypical headaches do not, and headache syndromes such as migraines typically respond well to medical management [64]. It is possible that patients have more than one contributing factor to their symptoms and appropriate phenotyping will inform decision-making, especially when the offer of a major surgery aims to address a benign condition that is unlikely to lead to neurological injury if left untreated. In addition, surgery may result in post-decompression occipital neuralgias or chronic post-craniotomy headaches, and therefore preoperative assessment and counseling is paramount in managing patients' expectations [65, 66].

Many of the other symptoms in patients with CM1 without syringomyelia are nonspecific and require detailed investigations to establish their relevance. There may be an overlap with disorders that cause chronic widespread pain, fatigue, multiple somatic and psychiatric symptoms, and cognitive disturbance. Disorders like demyelinating disease, vascular disorders, fibromyalgia, and idiopathic intracranial hypertension may mimic CM1, and the presence of such disorders should be considered in the diagnostic evaluation. Of note, idiopathic intracranial hypertension is associated with high incidence of tonsillar decent and carries many similarities with CM1 [67]. A high index of suspicion is required in women of childbearing age with

the phenotypical body habitus, given the high complication rate of decompressive surgery in the presence or raised intracranial pressure.

8.7.2 Radiological Imaging

As CM1 is not uncommon, the majority of cases are initially reported incidentally in patients undergoing brain imaging, for a wide variety of indications. The midsagittal view demonstrates tonsillar descent below the foramen magnum, and the axial view shows a crowded foramen magnum with decreased CSF spaces around the brainstem.

8.7.3 Magnetic Resonance Imaging (MRI)

MRI is the gold standard investigative modality for CM1. The degree of tonsillar descent is measured at the midsagittal plane as the perpendicular vertical distance of tonsillar tip to the McRae line. The cutoff value of ≥5 mm is considered pathological, and the cerebellar tonsils usually appear elongated and "peg-like," as opposed to blunt and more rounded in the general population (Fig. 8.2) [68]. MRI scans also reveal abnormalities of the craniocervical junction that may be associated with

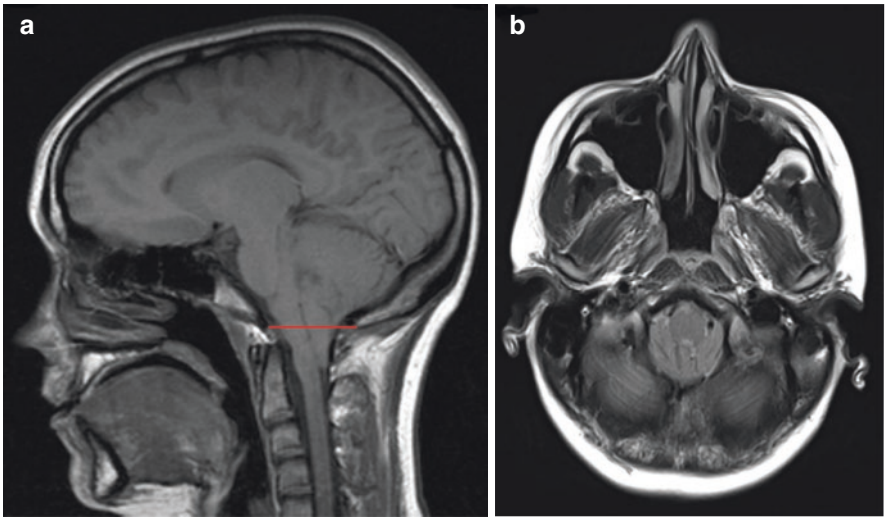

Fig. 8.2 MRI scan of a 24-year-old patient with typical cough headaches. (**a**) Sagittal T1 sequence shows the cerebellar tonsils 18 mm below the McRae line (red) and appears "peg-like." (**b**) Axial T2 sequence shows crowding at the level of the foramen magnum with reduced cerebrospinal fluid in the cisterna magna and perimedullary cisterns

CM1, the most common being platybasia, basilar invagination, and a retroflexed odontoid. A volumetric analysis of the posterior cranial fossa size is helpful in differentiating tonsillar decent due to CM1 versus a secondary cause [69]. It is also important to search for features of raised intracranial pressure, because in these case the tonsillar decent is not due to CM1 from underdevelopment of the posterior cranial fossa and the management is different. These include hydrocephalus, increased perioptic CSF spaces, tortuous optic nerves, flattened optic nerve head, and empty or partially empty sella turcica (Fig. 8.3).

Phase-contrast cine-mode MRI is used to examine CSF flow dynamics in patients with CM1. It demonstrates abnormal pulsations of tonsils and intermittent obstruction to CSF flow in association with Valsalva-induced headaches. The typical findings are downward displacement during cardiac systole and lack of diastolic upward flow of CSF [70]. There is a positive correlation between the degree of tonsillar descent and the impedance to CSF flow across the craniocervical junction [71]. This imaging modality is useful to differentiate clinical or radiological equivocal cases. Decompressive surgery improves CSF flow dynamics, and the absence of preoperative CSF flow abnormality in phase-contrast cine-mode MRI is associated with poor postoperative improvement [72]. Its use, however, is not widely adopted in clinical practice.

Imaging of the entire neuraxis with MRI of the whole spine is recommended in patients with CM1 in order to exclude associated conditions like syringomyelia and tethered cord, even in the absence of symptoms of spinal cord dysfunction. Incidental syrinxes at the cervical or thoracic level will require surveillance. The

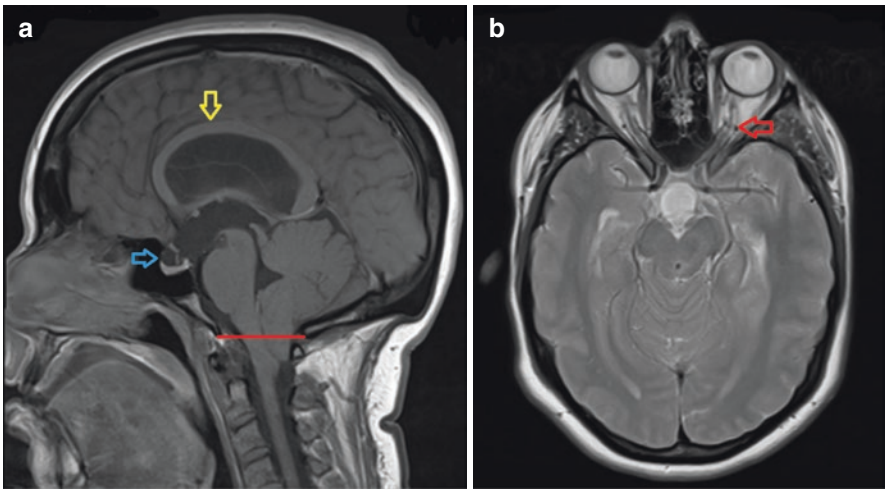

Fig. 8.3 A MRI scan of a 33-year-old patient with headache and blurred vision due to mild papilledema. (**a**) Sagittal T1 sequence shows arching of the corpus callosum (yellow arrow) due to hydrocephalus, partially empty sella (blue arrow), and tonsils 12 mm below the foramen magnum (red line). (**b**) Axial T2 sequence shows dilated optic nerve sheaths with redundant retrobulbar segment. The appearances are suggestive of chronically raised intracranial pressure

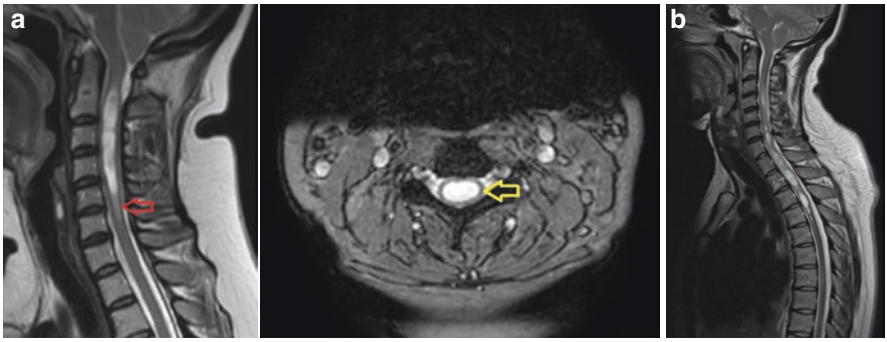

Fig. 8.4 Two cases of syringomyelia related to Chiari 1 malformation. (**a**) Sagittal (1) T2 sequence of a 45-year-old patient with arm weakness. The syrinx extends from C2 to C5 and the pre-syrinx edema (red arrow) suggests that the cavity may expand. The axial cut (2) at the level of C3 shows that the syrinx occupies most of the spinal canal and expands the spinal cord (yellow arrow) symmetrically. (**b**) Sagittal T2 sequence of a 39-year-old patient with burning pain in the arms and ataxia shows a multi-compartmental cervicothoracic syrinx

MRI demonstrates the extent of the syrinx, which usually starts at the upper cervical cord. Syrinx cavity above the foramen magnum constitutes syringobulbia. The typical appearance of a syrinx is a cavity within the cord parenchyma, which is oriented either centrally or eccentrically on cross-sectional imaging; it is hypointense on T1 and hyperintense on T2, although there may be hypointense regions within the cavity representing flow or pulsation artifact. It may be a single cavity of various lengths and can even affect the whole cord (holosyrinx), or it may have multiple septations, or may be formed by separate components with intervening normal-looking cord parenchyma (Fig. 8.4). T2 hypo-intensity adjacent to the syringomyelia cavity constitutes pre-syrinx edema and is a positive predictor of expansion of the cavity [73].

Syringomyelia refers to a pathological condition and should be differentiated from a persistent central canal. Such slit-like cavities are lined by ependymal cells and represent remnants of the embryonal central canal. They are asymptomatic, unlikely to change in size and should be considered an incidental finding. The term hydromyelia is sometimes used interchangeably with dilated central canal and even syringomyelia. It refers to pathological enlargement of the central canal, and therefore, in contrast to syringomyelia, it has ependymal lining. The clinical relevance is debatable, and most experts do not distinguish between the two pathologies.

Positional MRI allows imaging of the craniocervical junction with patients in upright or weight-bearing positions and can be combined with imaging in dynamic positions, such as flexion, extension, and rotation. Some experts advocate that it can detect better abnormalities of the craniocervical junction compared to traditional recumbent MRI and that MRI in the upright position is more sensitive in diagnosing cerebellar tonsillar ectopia in symptomatic patients [74]. MRI with the neck in

dynamic positions has also been used to assess the stability of the joints of the craniocervical junction, but there is not agreement on what should be interpreted as pathological instability and what constitutes hypermobility, especially in the context of hypermobility syndromes [54].

8.7.3.1 Computed Tomography (CT) and X-ray

CM1 is sometimes associated with instability of the joints of the craniocervical junction. Skeletal abnormalities like assimilation of C1 vertebra, basilar invagination, and Klippel-Feil syndrome raise the degree of suspicion of a coexisting connective tissue disorder that affects the atlanto-occipital and atlantoaxial joints. The concern is weakening of the craniocervical junction with decompression surgery, and it is common practice in some centers to obtain dynamic imaging. Evaluation of the joints is performed with either X-ray or CT in neutral and/or dynamic positions, which depict the bony anatomy more accurately. Atlanto-dens interval of more than 3 mm and translation of the tip of the odontoid of more than 4 mm from the basion are indicative of instability [75].

8.7.3.2 Intracranial Pressure Monitoring

Mean ICP in patients with CM1, irrespective of the presence of symptoms, is within normal range [76, 77]. It is recommended that the diagnostic workup of patients with CM1 should include an assessment on ICP, because tonsillar decent may be secondary to CSF pressure gradient and both intracranial hypertension and hypotension may mimic CM1 clinically and radiologically.

Intracranial pressure can be assessed indirectly with fundoscopy or neuro-ophthalmic examination. Optical coherence tomography is widely used to detect papilledema. However, the optic discs may be normal in about 5–15% patients with elevated ICP, or drusen may be misinterpreted for papilledema [78]. In some centers routine intracranial pressure monitoring is performed to exclude hydrodynamic abnormality prior to decompression surgery. Lumbar puncture has been traditionally avoided in the context of CM1 to measure ICP, but it is not considered an absolute contraindication if CSF analysis is required, in suspected subarachnoid hemorrhage or meningitis, for example [79]. In the presence of tonsillar decent, lumbar puncture is not a reliable method for assessing ICP, as it may provide an underestimate due to the craniospinal CSF pressure dissociation.

It has been suggested that pulsatile ICP is raised in a group of symptomatic patients with CM1, which by deduction represents reduced compliance [77]. In these cases, CSF diversion with a ventriculoperitoneal shunt has been recommended as first-line management, and therefore ICP monitoring has been advocated for all patients with CM1, but this practice is not widely accepted.

8.8 Management

The management of CM1 is variable and sometimes controversial. The main controversies exist around the indications for surgery and the type of surgical procedure [80]. The lack of high-quality evidence on best treatment strategy and lack of consensus on reporting outcomes have resulted in wide variations in practice. There are no universally accepted guidelines nor consensus on management [81]. The presence of syringomyelia renders the decision to offer surgery relatively straightforward, but in the absence of spinal cord dysfunction, there is an ongoing debate on the selection of the best surgical candidates and the best surgical approach. One of the main challenges in decision-making is establishing a link between symptoms and the underlying condition. Nonetheless, in the majority of cases, the natural history of CM1 is benign, and development of neurological deficits is a rare occurrence [8]. The natural history in patients with syringomyelia is less benign and more variable, but progression of symptoms is usually gradual.

Adults with incidental and asymptomatic CM1 do not require treatment. A period of clinical and/or radiological monitoring and review on an as-required basis are both considered appropriate management options [82]. Asymptomatic patients with syringomyelia are usually monitored as well, but some surgeons may offer treatment based on radiological features. The management of patients with mild or fluctuating symptoms again varies; a period of observation is not unreasonable, but the approach should be individualized, and engagement of patients in decision-making is crucial. The main concern of a nonoperative approach is that neurological deficits from spinal cord dysfunction may not recover, even following successful surgery with collapse of the syrinx. Therefore, vigilance from doctors and patients is essential in identifying early symptoms and signs of disease progression and prevent irreversible cord damage.

8.8.1 Medical Management

Headache is the cardinal symptom of CM1 and CSF pressure dissociation headache may coexist with types of primary headache, more often migraine. Symptomatic treatment, ideally within a Headache Service, should be the first-line management. Beneficial lifestyle changes include optimization of sleep pattern, weight management in patient with high body mass index, and regulation of caffeine and alcohol intake [83]. Physiotherapy can also help with many of the symptoms caused by CM1. It can address pain and muscle spasms, and vestibular rehabilitation may improve balance and gait problems. There is also anecdotal evidence that acupuncture and massage therapy may alleviate symptoms in a small group of patients.

Analgesic medication for treatment and prevention of migraines will benefit patients with a mixed phenotype and may determine which symptoms are related to CM1 and likely to benefit from surgery. A wide range of analgesics may also

improve Chiari-related headache, like paracetamol, ibuprofen, amitriptyline, topiramate, and gabapentin. Acetazolamide is a diuretic that has shown some benefit [84]. It is commonly used in idiopathic intracranial hypertension, and the treatment response may represent a misinterpretation of the tonsillar ectopia as being due to CM1 [67]. Local anaesthetic occipital nerve blocks should also be considered in patients with occipital headache, because occipital neuralgia can sometimes be indistinguishable from pain caused by CM1 [85].

Surgical management is a significant undertaking, and the general agreement is that it should only be considered in cases that conservative treatment fails to control symptoms associated with negative impact on quality of life. Patient education is important, and social media may provide misleading information by linking the condition to a high rate of neurological disability or even reduced life expectancy. Patient support group exist in many countries and provide useful information and advice to patients and their families. They help in understanding the diagnosis, the therapeutic options, and what to expect during the hospital experience. In the United Kingdom, the Ann Conroy Trust (www.annconroytrust.org/) is a charity that assists people living CM1 and related conditions, and promotes education and research.

8.8.2 Surgical Management

Surgery is reserved for patients with significant symptoms and preoperative counseling is important in managing patient expectations, because in the vast majority surgery is optional rather than imperative, as CM1 only rarely leads to neurological deficits. The symptom that most often responds to surgery is the pressure dissociation headache, which constitutes the main indication, but in a small group of patients, surgery may not improve or may even exacerbate the headache. In patients with syringomyelia, the presence or the degree of spinal cord dysfunction is the determining factor in decision-making. Motor weakness is a strong indication for surgical treatment in order to improve power and dexterity or at least halt progression of paresis. Sensory symptoms and deficits, especially if they are progressive, are also indications for surgery, but tend to respond less compared to motor symptoms.

8.8.2.1 Decompressions Surgery

The main surgical treatment for CM1 is foramen magnum decompression, which is also known as posterior fossa decompression or craniovertebral decompression. The surgical objective is to unblock the subarachnoid channels across the craniocervical junction and improve the flow of CSF that is impeded by the impacted tonsils. A number of surgical techniques with a varying degree of dissection have been described which include a bony-only decompression leaving the dura intact, extra-arachnoidal decompression with opening of the dura, opening the arachnoid with/

without resection and/or reduction of the cerebellar tonsils and dissection of arachnoid adhesions [34, 81, 86]. Intraoperative ultrasonography is sometimes used to determine the extent of decompression necessary to achieve adequate CSF flow [87]. Bony decompression is the only common step of all techniques and entails removal of the occipital squama below the inferior nuchal line and laterally to the level of the equator of the foramen magnum.

Duroplasty is another contentious point that divides surgical opinions. In the dura-open technique, the dural edges are hitched at the edges of the surgical field to allow a formation of a pseudomeningocele that will serve as an artificial cisterna magna. Figure 8.5 demonstrates one method of dura opening. The closed-dura technique entails either primary closure or the use of a dural graft for augmentation duroplasty. A systematic review has not shown superiority of one technique over the other in terms of clinical improvement but suggested a higher complications rate with the duroplasty technique [88]. However, the majority of studies were retrospective case series, and to date there is no randomized clinical trial on surgical technique for CM1.

A single-stage decompression and instrumented fixation of the craniocervical junction are recommended in the presence of joint instability, diagnosed during

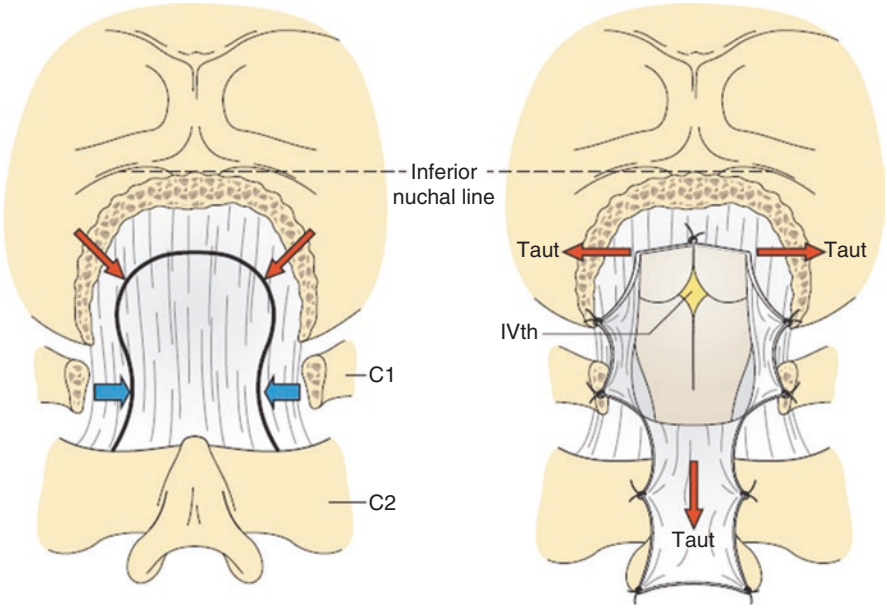

Fig. 8.5 Decompression without duroplasty. The dura is opened as an inverted "U" flap, which is sewn down, taut, over the C2 spinous process. The dural edges are hitched on the surrounding tissues, and the cerebellar tonsils are reduced with bipolar coagulation. The newly created artificial cisterna magna communicates freely with the fourth ventricle superiorly, the basal cisterns laterally, and the spinal subarachnoid space inferiorly. (From Marks, S., Flint, G. (2014). Medicolegal Aspects. In: Flint, G., Rusbridge, C. (eds) Syringomyelia. Springer, Berlin, Heidelberg, with permission)

preoperative radiological assessment. Occipito-cervical and atlantoaxial fixation have been described in patients with CM1, and the extent of the construct depends on the affected joints. Basilar invagination, retroflexed odontoid, and platybasia raise the suspicion of instability, which would require occipito-cervical fixation. Bulbar dysfunction due to compression from the odontoid may require odontoidectomy. Delayed instability following decompression surgery is rare and should be suspected if new neck pain or neurological deficits develop, in which case revision surgery with stabilization should be considered.

The surgical outcomes following decompression surgery are measured by the degree of symptomatic improvement and complication rate, but the quality of reported outcomes in literature is mixed. A major limitation is the lack of an agreed method in reporting outcomes, and the Chicago Chiari Outcome Scale has been proposed as a disease-specific standard outcome measure to compare the results of different studies against each other [89]. In general, it is estimated that following decompression surgery, headaches improve in approximately four out of five of patients, but the rate of improvement of other symptoms is less [22, 90–92]. The treatment effect of surgery in case of syringomyelia is more objectively reported in studies, as both motor and sensory symptoms can be quantitatively assessment. The magnitude and extent of neurological improvement is larger if the duration of symptoms is shorter. In other words, early decompression surgery is associated with better spinal cord recovery [93]. Radiological improvement is demonstrated as collapse of the syrinx on spinal imaging and is observed in about four out of five cases [94]. Sometimes however, changes in the size of the syrinx may take several months despite early clinical recovery (Fig. 8.6).

Early complications of decompression surgery include aseptic meningitis, postoperative CSF leak, and symptomatic pseudomeningocele. They are often related to the surgical technique. In duroplasty, complication rates for autografts and nonautologous grafts are similar, but some nonautologous grafts result in higher rates of

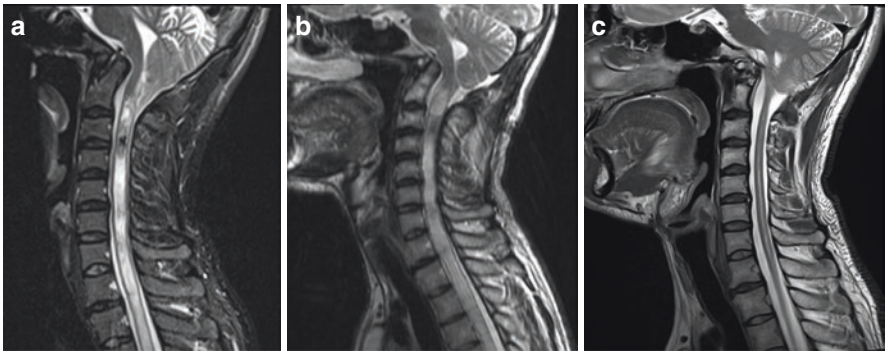

Fig. 8.6 Timeframe of radiological resolution of the syrinx on a 35-year-old patient who presented with tetraparesis that resolved following decompression surgery. (**a**) Preoperative sagittal T2 sequence shows the cervical part of the holosyrinx and tonsillar decent to the C2 level. (**b**) Sagittal T2 sequence 8 months after surgery shows persistent syringomyelia. The tetraparesis had resolved at that stage. (**c**) Sagittal T2 sequence 21 months after surgery shows collapse of the syrinx

meningitis [95]. Development of hydrocephalus is rare. An uncommon delayed complication is formation of dense arachnoid scaring at the surgical side which results in failure of the decompression with recurrence of symptoms. Revision decompression surgery provides headache relief in about two thirds of cases. Recurrent syringomyelia is a positive predictive factor of response to revision surgery [90].

8.8.2.2 CSF Diversion

The traditional management of patient with CM1 and hydrocephalus is CSF diversion, usually with a ventriculoperitoneal shunt. Endoscopic third ventriculostomy is more common in the pediatric population, but it has also been beneficial in adults with CM1 [96]. The presence of obstruction at the level of the aqueduct or fourth ventricular outflow increases the success rate of endoscopic third ventriculostomy. In a group of patients with normal mean ICP and increased pulsatile pressure, ventriculoperitoneal shunting is considered a good alternative to decompression surgery as a means of improving intracranial compliance [77]. In these cases, CSF shunting has been recommended as first-line management, and therefore ICP monitoring has been advocated for all patients with CM1. However, CSF shunting is not considered a good treatment strategy for long-term relief of headache, and as shunts come with their own complications and drawbacks, the practice is not widely accepted [97].

8.8.2.3 Other Surgical Techniques

Spinal cord untethering with sectioning of the filum terminale has been suggested as the surgical technique of choice in selected patients with low-lying conus [46]. It has a more favorable risk profile compared to decompression surgery, and it is believed to address the underlying pathophysiological mechanism in patient with a normal-size posterior cranial fossa. However, sectioning of the filum for "occult tethering" is controversial. Another controversial technique is instrument fixation of joints of the craniocervical junction without decompression, which has been proposed as another treatment that addresses the cause of the disease [50]. Direct shunting of the syringomyelia cavity is effective in selected cases, especially as a secondary procedure. The choice between syringopleural, syringoperitoneal, and syringothecal shunt is a matter of the individual surgeon's preference [98].

8.9 Special Considerations

8.9.1 Pregnancy

CM1 is frequently diagnosed in women of childbearing age, and these women and their doctors may justifiably develop concerns about pregnancy, labor, and delivery. Especially when it comes to childbirth, the second stage of labor, with the repetitive

bearing down that the mother has to do, constitutes arguably the most pronounced form of Valsalva-like maneuver. The concern is that physical straining would cause the mother to experience severe headaches and worsen the tonsillar decent, which may lead to detrimental consequences. The presence of syringomyelia further complicates this position as the rise in the intraspinal pressure may also lead to neurological deterioration.

In the past, Caesarean section was recommended, as this will avoid the mother needing to bear down and potentially suffer as a result. However, there is little in the way of clinical evidence and virtually no research to guide the management of pregnant women with these conditions [99]. Review of the literature lacks reasonable justification for management of the majority of such patients outside the normal obstetric lines [100]. Anecdotal and unpublished cases of neurological deterioration during vaginal delivery should not inform guidelines.

Management decisions should be made by an interdisciplinary group of clinicians. There is no uniform recommendation with respect to a particular mode of delivery, but most experts agree that normal vaginal delivery, or at least a trial thereof, is not contraindicated in asymptomatic people. The threshold to convert to Caesarian section should be lower in those with pressure dissociation headaches. Epidural anesthesia can be administered, and in cases of inadvertent dural puncture, an epidural blood patch should be considered. Spinal anesthesia is not contraindicated either, and again an epidural blood patch should be considered if the patient develops low-pressure symptoms. If there is syringomyelia, large cavities may dictate the need for Caesarean section, but many smaller cavities, especially those without associated spinal cord dysfunction, may not present any hazard during a normal birth. If general anesthesia is required, excessive or prolonged neck extension during endotracheal intubation should be avoided [101]. Neither the CM1 nor any associated syringomyelia poses any direct detrimental risks upon the developing fetus or the condition of the neonate.

Genetic factors play a role in the development of these conditions, which occasionally run in families. However, inheritance is rare and should not cause women to avoid becoming pregnant. Even if a child were to inherit the same anatomical abnormality as one of its parents, it is by no means inevitable that the Chiari malformation will become symptomatic.

8.9.2 Sports

Despite the lack of evidence to support a significant risk of catastrophic or severe neurological injury secondary to CM1 with or without syringomyelia during athletic activities, there is currently no consensus on the safety of sport participation. It is certainly the case that people with these conditions can experience deterioration in their symptoms after physical straining, although this is not a common event. The literature suggests that the risk of neurological injury related to CM1 during sport is low [102]. Expert opinion is divided and ranges from no specific precautions to

avoidance of all strenuous exercise. In general, advice should be individualized, and it is reasonable to assume that people with asymptomatic conditions that do not develop symptoms during sports are not at risk and should not restrict their lifestyle. On the other hand, contact sport or activities that predispose to head or whiplash injuries should be avoided, especially in symptomatic patients or those with large syrinxes. Such advice is based on common-sense reasoning and application of current understanding of the physiological disturbances that accompany CM1 and syringomyelia. These restrictions may be revisited following successful surgery.

8.9.3 Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of rare inherited conditions that affect connective tissue. EDS type 3 or hypermobility type is caused by defects in collagen; the laxity of the joints at the craniocervical junction may be a pathogenic factor for chronic neck pain and headache [103]. Currently there are no genetic markers and the diagnosis is based purely on clinical grounds. CM1 has been reported to be a comorbid condition to hypermobile EDS, and their coexistence poses certain challenges in the management of these patients. Mild symptoms may improve spontaneously or respond to conservative treatment. In case of more severe symptoms, the main challenge is differentiating the contribution of the two pathologies and whether surgical intervention is appropriate. Some surgeons suggest that craniocervical fixation can significantly improve not only the classic Valsalva-related headaches but also many of the additional, disabling symptoms associated with EDS. This treatment is not, however, widely accepted, and indeed the term "instability," used in relation to the cervical spine and craniocervical junction, in patients with hypermobility, is arguably inappropriate [54]. Craniocervical fixation should be considered during decompression surgery in patients with significant symptoms attributed to CM1, because of the high risk of destabilizing a hypermobile craniocervical junction.

Compliance with Ethical Standards The authors report no conflict of interest.

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Chapter 9
Controversies in the Treatment of Arachnoid Cysts with Special Emphasis on Temporal Arachnoid Cysts

Aurelia Peraud and Rebecca Ibel

9.1 Introduction

Intracranial cysts are a common reason for pediatric neurosurgical consultations. Arachnoid cysts (ACs) account for the majority of intracranial cystic lesions followed by posttraumatic/porencephalic or neoplastic cysts.

The first medical cases of intracranial ACs were described by Richard Bright in 1831 [1]. In 1955 Richard G. Robinson, a neurosurgeon from New Zealand, reported of temporal ACs found in patients with temporal bone protrusion, which he believed develop due to temporal agenesis. It was Starkman in 1958 who finally confirmed the hypothesis of Bright that these cysts develop in a duplication of the arachnoid membranes [2].

ACs are found in all age groups but most often (75%) occur in children. This is also reflected by the incidence of 2.6% in children and 1.4% in adults [3, 4]. There is a male-to-female preponderance ranging from 2:1 to 5:1 [3, 5]. ACs can occur in different locations, most frequently in the middle cranial fossa. An accepted classification for temporal ACs is according to Galassi, which distinguish three types depending on the cyst size [2].

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9.2 Etiology

The exact etiology is not clear. ACs are assumed to arise during embryological development within duplicates of the arachnoid membrane or are the result of ischemic, traumatic, or infectious insults. The latter hypothesis is no longer supported [1, 2]. A more recent viewpoint for middle cranial fossa/temporal ACs is that it was a failure of the frontal and temporal embryonic meningeal merging, resulting in a duplication within the sylvian fissure [6].

Three different pathological mechanisms are discussed with regard to AC expansion.

One theory assumes an active fluid section from cells of the cyst membrane [7, 8]. Helland et al. could show that the activity of the Na-K-2Cl cotransporter is higher in the membrane of ACs than in normal arachnoid. The corresponding gene NKCC1 encoding for the transporter is upregulated [8]. Another theory describes a unidirectional flow through a vessel-associated slit valve mechanism [9]. The last theory discusses a fluid influx via an oncotic pressure gradient [10].

Some syndromes have been associated with ACs, and these syndromes include Aicardi syndrome, mucopolysaccharidosis, acrocallosal syndrome, Marfan syndrome, a missense mutation (c.2576C>T) in the arginine-glutamic acid dipeptide repeats gene (RERE), and Chudley-McCullough syndrome [11–26].

9.3 Location

Although ACs occur throughout the neuroaxis, nearly half are found in the middle cranial fossa [5, 27]. Other common locations include the posterior fossa, the suprasellar region, and occasionally within the ventricles and over the convexity or between the hemispheres [3]. Common reported side preference for unilateral ACs is the left side, without clear explanations for this phenomenon [6, 27]. Temporal cysts are divided into three types according to the classification of Galassi [28]. Galassi type I cysts are small and are purely located in the middle cranial fossa, thereby compressing the temporal pole to a varying extent. Galassi type II cysts are larger and extent toward the sylvian fissure and expose the insula. Galassi type III cysts are large, ovaloid, or round shaped, and lead to a compression of frontal and parietal lobes. The ventricles and midline structures are displaced to the opposite side.

Another classification exists for suprasellar ACs [29], who represents 9–21% of intracranial ACs. SAC-1 cysts extend upward and can block foramen of Monro, thereby leading to ventricular enlargement. SAC-2 cysts on the other side have a prepontine extension and expand the interpeduncular cistern. Finally, SAC-3 cysts are asymmetric and show lateral extensions not seldomly associated with macrocephaly.

Very rarely ACs can also develop within the ventricles [30, 31]. Most ACs are constant in size and small, but they can also increase in size especially in the very young [3].

9.4 Symptoms

Most ACs are incidental findings on imaging done for other reasons, such as trauma, seizure, hydrocephalus, suspected stroke, hemiparesis, nausea/vomiting, dizziness, cranial nerve dysfunctions, tinnitus, vertigo, developmental delay/regression, behavior concerns, visual symptoms, and headaches [32]. Fortunately, ACs in the most common locations such as the middle cranial fossa and the retrocerebellar region rarely cause symptoms. Nevertheless, many patients with a history of headaches are referred to a pediatric neurosurgeon when an AC was found. It can be a challenge to decide whether the headaches are related to the cyst or whether these are of a different etiology (migraine, sinusitis, problems with visual acuity, drugs, etc.). In most cases the AC is not related with headaches, but if they are very large or increase in size over time, they can be a cause of headaches or seizures [33, 34]. A thorough workup together with an experienced pediatric neurologist is of immense value to evaluate the type of headaches and to advocate conservative treatment options. Only clearly localized pain at the area of the AC or headaches with an underlying hydrocephalus caused by the AC can be considered related to the AC. Most patients, especially teenagers, tend to have tension headaches or migraine, often with family background [35]. Temporal ACs present not seldomly along with a subdural hygroma or hematoma with or without prior head trauma [12].

Cysts in less common locations are more likely to cause symptoms, and they present most likely either due to mass effect or due to rupture [36–39]. Irrespective of whether the cyst ruptures spontaneously or after a (minor) head trauma, this can be accompanied by a subdural hygroma or hematoma [38–40].

Very rarely ACs cause significant neurological symptoms such as cranial nerve deficits (visual loss, third nerve palsy, trigeminal neuropathy, hemifacial spasm, hearing loss, facial palsy, vagal nerve pals, double vision), hydrocephalus, or ataxia. Clearly, the symptoms are related to the cyst location, e.g., a suprasellar AC can compress the optic chiasm or the optic nerve (Fig. 9.2), thereby leading to bitemporal hemianopia or visual deficits as well as hypothalamic symptoms. Or an AC covering the convexity is able to provoke symptoms due to the compression of the underlying cortex, e.g., homonymous hemianopia or optic seizures in a cyst affecting the occipital cortex [41–43]. Another very rare symptom resulting from ACs is the bobble-head doll syndrome, a rhythmic anterior-posterior head movement related to expansive lesions in the third ventricular region involving the tectum and the cerebellum [44–52]. Also, neuropsychiatric disorders are described in the context of ACs most common in frontal or temporal location. These include depression, anxiety, and hyperactivity syndromes [53, 54]. There are more and more reports on the relationship between temporal ACs, especially on the left side, and learning as well as language deficits in the diagnosis of attention deficit hyperactivity disorder (ADHD) [53, 55–60]. On the other side, Maher just recently questioned the relationship of temporal ACs and cognitive dysfunction as well as learning disabilities. He speculates that children with learning problems and concerned parents undergo more often diagnostic imaging and neurosurgical consultation [61].

9.5 Diagnostics

Radiological imaging not only plays an important role for diagnostic purposes but also serves for presurgical planning and follow-up controls. Due to the broad use of computer tomography (CT) and magnetic resonance imaging (MRI) as well as ultrasound, the frequency of diagnosed ACs increased [4, 62].

In general, ACs exhibit an MR signal comparable to cerebrospinal fluid. A displacement of surrounding structures can also be seen. MR has a higher soft tissue contrast than CT and provides additional information by the use of distinct sequences. The two most common sequences are T1- and T2-weighted. T2-weighted images have an increasing signal intensity with increasing water content. In contrast, in T1-weighted images, ACs appear hypointense and if present hemorrhages can be highlighted. Furthermore, MR sequences can be sensitive to flow, thereby allowing to evaluate for sufficient drainage after fenestration postoperatively [63, 64]. The wall of ACs is sometimes difficult to discern, because it is very thin and can be best visualized on thin CISS 3D sequences (Fig. 9.1). On CT, ACs are hypodense structures, which are well circumscribed. CT has the disadvantage of radiation exposure, especially in the pediatric population, has a lower soft tissue contrast than MR, and should be reserved for emergencies, when an acute hemorrhage is suspected. Nevertheless, it is widely used because it is easily accessible and cheaper than MR. A local thinning of adjacent skull bone, detected on CT bone windows, supports the finding of an AC [28, 65].

On differential diagnosis other cystic intracranial lesions must be considered. These are, for example, colloid cysts, ependymal cysts, choroid plexus cysts, or cystic tumors [66, 67]. A retrocerebellar fluid collection in the posterior fossa can

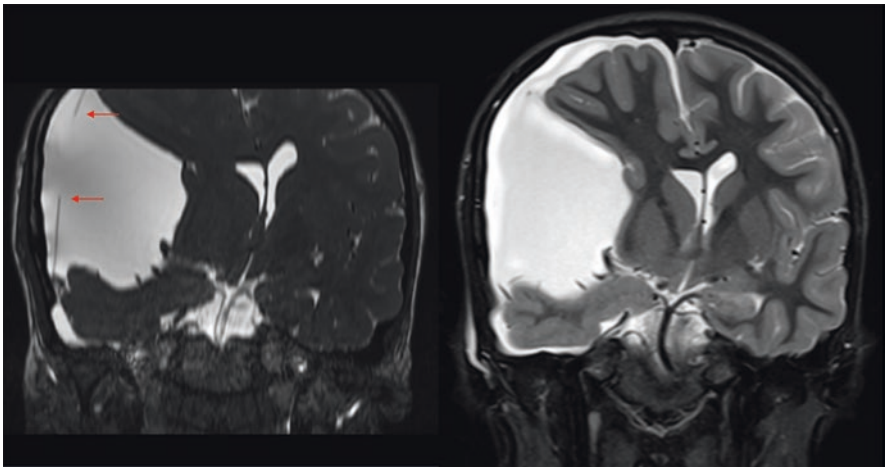

Fig. 9.1 Coronal view of a Galassi type III AC on CISS (left) and T2 (right)-weighted MR images. The cyst membrane has ruptured with concomitant subdural hygroma. The fine cyst wall with the site of rupture (arrow) can only be seen on CISS sequences

either represent a mega cisterna magna, a Dandy-Walker malformation, or an AC. If there is no compression of the cerebellum and free communication with the surrounding subarachnoid space, it represents rather a mega cisterna magna than a midline AC. In case of Dandy-Walker malformation, hypoplasia of the cerebellar vermis is evident. Definite diagnosis can be performed with MR or CT cisternography. Epidermoid tumors are located in the suprasellar cistern or in the cerebellopontine angle. For differential diagnosis diffusion-weighted MR sequences can distinguish between both entities. Epidermoid tumors show a very high signal due to diffusion restriction [67]. A porencephalic cyst is a cystic lesion within the brain parenchyma and has the same signal on MR as ACs; the differentiation can be made mainly due to the location. Intraventricular cystic lesions can also be colloid cysts, subependymal cysts, and choroid plexus cysts. A neurenteric cyst is a rare differential diagnosis. It is often associated with vertebral body malformations and involves a cystic lesion anterior to the neural axis [68]. Furthermore, there exist tumors in the subarachnoid space, for example, meningiomas, schwannomas, or metastases. Usually, the differentiation to ACs is clear. Also some infectious lesions can be cystic and may appear similar to ACs [69].

Sometimes ACs are even detected intrauterine by prenatal ultrasound or intrauterine MR images [70, 71]. On ultrasound, ACs are often detected on routine midtrimester sonography as hypoechoic masses without color Doppler signal. Most ACs do not grow during pregnancy, but there are reports on prenatally detected and progressively growing suprasellar ACs [70, 72–75]. In addition, optic nerve sheath diameter measurements can help to identify ACs that are symptomatic and cause increased intracranial pressure [76] (see also the optic nerve sheath on Fig. 9.3).

9.6 Basic Research

An interesting aspect in temporal ACs is that these cysts are the only ones that are associated with a bleeding risk. The reason for this selective bleeding risk is not well understood. Lee at al. undertook a study with a finite element model analysis and compared models for sylvian, suprasellar, and posterior fossa cysts as well as for cyst shape (round versus ovaloid). They measured the shear force between dura and outer cyst wall. In the final regression analysis, only the presence of an AC was associated with an increased shear force on impact and thereby with an increased bleeding risk. Neither location nor shape of the AC was correlated with shear forces at least in this theoretical model [77]. However, cyst size seems to matter with regard to the likelihood that an AC requires surgery. In a study by Ali and coworkers, the only prognostic factor whether an AC was treated conservatively or surgically in multivariate analysis was the size of the cyst (>68 cm^3) and age [78]. A case-controlled study by Cress et al. even proofed that larger cysts have a significantly higher risk for rupture and hemorrhage [36].

The study of Berle et al. on differentially detected cyst proteins in comparison with proteins in the CSF of the same patient does support the hypothesis that

arachnoid membranes shed proteins into its cystic cavity and contradicts the hypothesis of an oncotic pressure or valve mechanism responsible for AC development and growth [7].

9.7 Treatment: Indications

The indication for surgery in the presence of an AC is sometimes difficult to make. Hardly any other pathology provoked more discussion even among experienced pediatric neurosurgeons on whether and how to treat than ACs [79–83]. There are even reports in the literature indicating that ACs can spontaneously disappear [84–86]. Symptomatic ACs associated with focal neurological deficits, localized seizures, or hydrocephalus present a clear indication for surgery. Those cysts that exhibit a progression over time and those causing disfiguring bulging of the overlying frontal or temporal bone or the orbit are also surgical candidates. The correlation of headaches with the ACs is often debatable, but if the headaches are localized at the cyst side or associated with marked hydrocephalus, the correlation cannot be neglected [41]. Kershenovich and colleagues have conducted a preoperative trial with acetazolamide to detect those patients who would profit from surgery [87]. Di Rocco et al. have proposed ICP monitoring for sylvian ACs [88]. They found that ICP was almost always increased in Galassi type III ACs and was supportive to distinguish those ACs that require surgical intervention. Seizures if localized and in the context of the cyst location can be considered an indication for AC surgery [41]. Typically, the cysts are hemispheric in location and compress the underlying cortex (Fig. 9.2). Other seizure types, especially when they are not localized on EEG recordings, are of questionable correlation with the presence of the AC. The prophylactic indication of AC surgery has been discussed in very large cysts to prevent hemorrhage, which derives form vessels within the cyst wall. So far there is not enough evidence or data available regarding the natural course of very large cysts and the avert risk of hemorrhage. Only in the case-controlled study by Cress et al. cyst size and recent head trauma were significant risk factors for cyst rupture and hemorrhage [36] (Figs. 9.3 and 9.4). In contrast, severe headaches resulting from the rupture of a typically temporal AC with associated subdural hygroma or even hematoma represent a clear indication for surgery. Not seldomly patients suffer from symptoms of highly increased intracranial pressure [89, 90]. However, there exists also a contradictory report of Maher et al. which showed comparable good results after conservative treatment [90, 91].

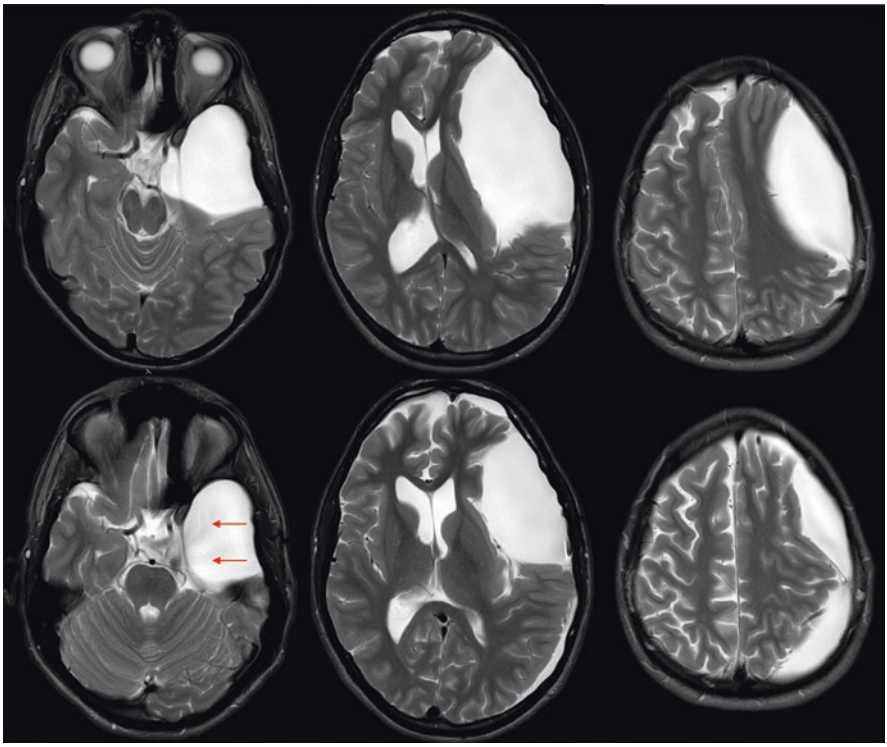

Fig. 9.2 Axial T2-weighted MR images pre- (upper row) and post-op (lower row) of a Galassi type III AC, which displaces the optic nerve and chiasm to the right side. After microsurgical fenestration of the AC, a flow void through the fenestration can be detected (arrows), and the medial cyst wall is no longer herniating over the tentorial edge. The gyri of the frontal and parietal lobes are no longer compressed, but a subdural fluid collection can be seen

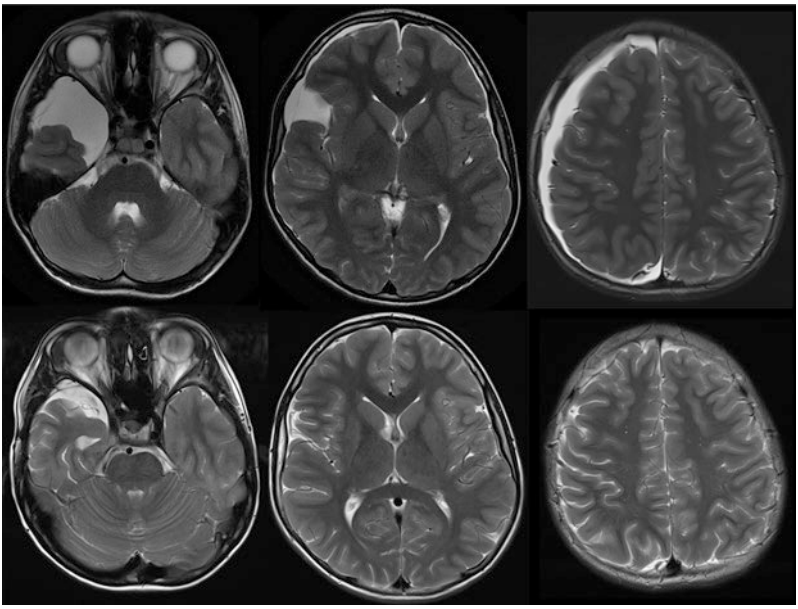

Fig. 9.3 Axial T2-weighted MR images of a Galassi type II AC of a 12-year-old boy after spontaneous rupture with subdural hygroma formation (upper row). Notably, the cyst almost disappeared after microsurgical fenestration to the basal cisterns, and the subdural collection subsided (lower row)

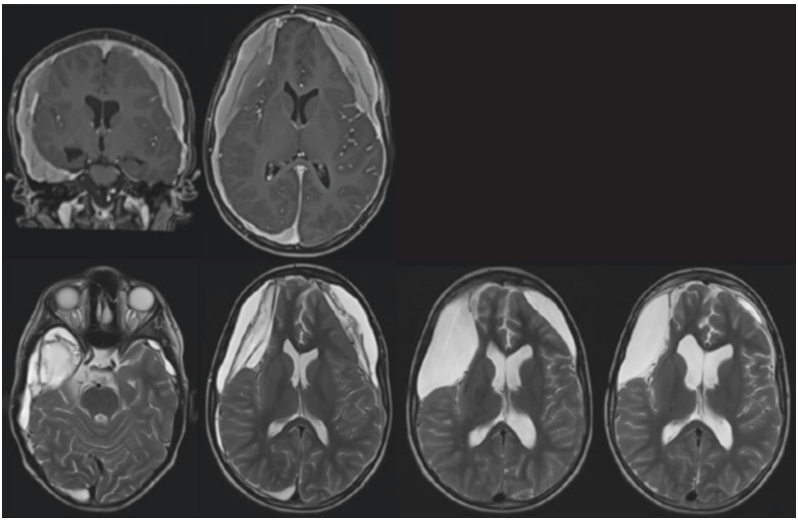

Fig. 9.4 The T1-weighted MR images in axial and coronal view show bilateral subdural chronic hematoma in a 9-year-old boy who experiences repetitive minor head trauma (upper row). Obviously, the right temporal AC ruptured and caused chronic bleeding into the subdural space over both hemispheres. After simultaneous irrigation and drainage of the subdural hematomas as well as fenestration of the AC, subdural hygromas became smaller over a period of 12 months (lower row)

9.8 Treatment Options

Conservative management may be an option for selected cases, especially when symptoms are mild and there is only minimal mass effect of the cyst or the concurrent subdural hygroma. Li et al. reported of a boy with headaches during physical activity, and he was diagnosed with a large middle cranial fossa AC and bilateral subdural hematomas which resolved over a period of several weeks [92]. Maher et al. presented eight children with temporal AC and subdural hygroma, and only one of them required surgery with comparable good outcomes [90]. Nevertheless, the mainstay of treatment in symptomatic ACs remains surgery. Irrespective of the mode of surgical intervention, the goal is to achieve cyst decompression and to establish communication between the normal and the pathological CSF/cyst spaces. In general, the surgical treatment of symptomatic pediatric ACs seems to be effective according to a literature review performed by Carbone et al. [32]. It improves patient's outcome with up to 90% in middle cranial fossa cysts [32, 93, 94]. Postoperative cyst volume does not correlate with patient's outcome [93–95].

The main surgical options are microscopic cyst fenestration and resection, endoscopic fenestration, cyst shunting, and cystoperitoneal shunt. The latter is mainly reserved for cyst recurrences despite sufficient fenestration. The surgical technique chosen is generally determined by the surgeon's preference, experience, and cyst location. Tamburrini et al. undertook an interesting study on the surgical preference among pediatric neurosurgeons, and at least at this time, 66.6% favored microsurgical resection [96]. In general, craniotomy with cyst wall resection/marsupialization is favored in cysts of the convexity, where drainage into normal CSF pathways is not possible [32] or in posterior fossa cysts. Fenestration of ACs is feasible either by a minicraniotomy under microsurgical means or by endoscopy. Still, there is no class I evidence regarding the optimal treatment of intracranial ACs in children [41, 89]. The success rate and the risk of postoperative hygroma formation or cyst recurrence seem to be comparable between microsurgical and endoscopic fenestration of temporal ACs [97]. There are reports that favor microsurgical fenestration via a keyhole approach, thereby combining the advantages of both methods [82, 98]. The risks and benefits of conservative and surgical options have to be carefully weighed on an individual patient basis [41, 91].

9.8.1 Microsurgical AC Fenestration

The option for bimanual cyst manipulation has the benefit to control bleeding from vessels of the cyst wall. It also offers the possibility to carefully excise the frequently multilayered and firm medial cyst wall in temporal ACs toward the basal cisterns, and to preserve the integrity of internal carotid artery, perforating arteries, and optic as well as oculomotor nerve [97, 99]. This can be done even with a minicraniotomy of less than 2 cm in diameter. Integration of neuronavigation is

nowadays routine [100, 101]. By this route several fenestrations can be safely performed (optico-carotid window, between carotid artery and oculomotor nerve). If there is no interface of the temporal AC with the basal cisterns, microsurgery offers the possibility to create a communication with the sylvian fissure [101]. To avoid subdural fluid collection, care should be taken to open the outer cyst wall only under the dural incision and to seam the cyst wall to the dura [100]. The success rate in clinical remission was considered highest after microsurgical fenestration by several authors [79, 102–104].

9.8.2 Endoscopic AC Fenestration

The minimally invasive approach via an endoscopic cyst fenestration is clearly indicated in suprasellar, quadrigeminal plate or intraventricular ACs [99, 105–107]. The implementation of neuronavigation is also possible, but requires invasive fixation of the head, which might not be possible in small children. Endoscopy is also favored by many pediatric neurosurgeons for middle cranial fossa ACs [101, 104, 108–111]. The number of stomata obviously matters with regard to cyst recurrence in temporal ACs, and multiple openings should be performed [108, 112]. Disadvantages of the endoscopic approach might be more difficulties to control bleeding, less depth perception due to bidimensional view, and higher risk of inadvertent injury to vascular of neural structures in the basal cisterns [79, 82, 97]. Whether the risk of postoperative subdural fluid collections is less than after microsurgical fenestration is inconsistent in the current literature with no definite conclusion [79, 100, 113, 114]. Oertel et al. reported on the endoscopic treatment of 66 ACs in different locations and concluded that temporal ACs were the most difficult to treat with the lowest clinical success rate (81%), the highest recurrence (19%), and the highest complication rate (24%) [115, 116]. As for the other locations, ventriculocystostomy and ventriculocystocisternostomy yielded the highest overall success rate of 100% [115].

9.8.3 Shunt Procedures

Regardless of AC location, the highest rate of cyst volume reduction can be achieved with shunt implantation [78]. The presence of an AC even with an associated hygroma or hematoma does not implicate disturbed CSF circulation. Therefore, drainage of the cyst by a cystoperitoneal shunt may cause overdrainage symptoms and permanent shunt dependency in the long run with repeated surgeries for shunt failure [100, 117]. This shunt dependency is related to younger age, large cysts, and low-pressure valves [117, 118]. Overdrainage may also lead to intracranial hemorrhage and distortion of brain anatomy in case of near obliteration.

Internal shunt catheter implantation (cysto-ventricular shunts) by stereotactic means was successfully performed for different kinds of intracranial cyst by Lenski et al. [119].

Gong et al. published a meta-analysis on 11 articles comparing intracranial versus extracranial shunt placement in the treatment of intracranial ACs [120]. There was no significant difference in improvement of symptoms or epilepsy, reduction of cyst size, occurrence of hematoma, or CSF leak as well as recurrence rate. However, the risk for intracranial infection was higher in the group of patients with extracranial drainage of the AC.

9.9 Complications

Irrespective of whether or not an ACs has been treated conservatively or surgically, significant complications can be encountered. Numerous reports stated spontaneous rupture of ACs mainly in the middle cranial fossa [36, 121, 122] (Figs. 9.1 and 9.3). This can be accompanied by subdural hygroma or hematoma formation [38, 40, 89] (Fig. 9.4). Prior minor head trauma is not always evident [89, 123]. But even after surgical fenestration, subdural effusion, sometimes requiring additional surgical interventions, can occur [79, 100, 113, 114] (Fig.9.2). Overall, the complication rate of surgical treatment of ACs is high with 5–7% [95]. The complication rate with postoperative subdural hygroma formation in temporal ACs was similar in microsurgical and endoscopic procedures [113]. The risk is higher in younger children (up to 44%) [80, 108, 113]. Marnat et al. even suggested embolization of middle meningeal artery in case of subdural hematoma development [124]. Other reported vascular complications include cerebral vasospasm after endoscopy [125] and hemorrhagic infarction after microsurgical fenestration [126]. Additional rare complications are oculomotor palsy, epilepsy, and CSF leakage as well as infections [113, 127].

9.10 Outcome

The surgical outcome of clearly symptomatic ACs is good in general [100]. Headaches as presenting symptom improve if they were clearly related to the cyst or the subdural effusion caused by the cyst. However, some may experience new headaches after surgery when a subdural hygroma is emerging. In most cases these subdural hygromas do reside with time and limited physical exercise [35].

A thorough neuropsychological testing and cognitive evaluation for mainly temporal ACs revealed that patients had overall lower mean values in all tests and did significantly improve in neurocognitive tests after surgery [128–130]. In a series of 25 patients with temporal ACs, Schertz and coworkers found a trend that only a minority of children with Galassi type II or III cysts show abnormal neurodevelopment when compared to their siblings [131]. Therefore, they suggested that neurocognitive testing should be included in preoperative evaluation.

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Chapter 10
Subdural Hematomas in Adults and Children

Sinan Sağıroğlu and Mehmet Turgut

10.1 Introduction

Subdural hematoma (SDH) is one of the most common phenomena a neurosurgeon encounters. Since ancient times, trephination has been performed to relieve the sick of their symptoms. While craniotomy is still the modality of choice for SDH, the search for a better solution is a never-ending endeavor. Acute (aSDH) and chronic (cSDH) forms of the hematoma have different pathophysiology; hence, different treatment approaches are required. Craniotomy or craniectomy may be the required intervention for aSDH. For cSDH, twist-drill craniostomy (TDC), burr-hole craniostomy (BHC), and middle meningeal artery (MMA) embolization are various medical treatment options developed and researched to better manage the disease and reduce the cost of medical expenses. Here we present current treatment options for SDH.

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10.2 Surgical Management of Subdural Hematoma in Adult Population

An aSDH develops after a traumatic brain injury with an incidence of 31% [1]. About 69.8–74.3% of these patients are initially treated conservatively [1, 2]. Of these patients, 6.5–11% required delayed surgery primarily due to the progression of the aSDH, and raised intracranial pressure (ICP) [1, 2]. While the decision for surgery remains controversial and varies from one center to another, Brain Trauma Foundation guidelines are still used today [1]. The guideline states that an aSDH thickness >10 mm or >5 mm midline shift should be surgically evacuated regardless of GCS score. A patient with GCS <9 without the abovementioned criteria should be evaluated for surgery if the GCS score drops by 2 or more points during hospitalization or if there is an asymmetric dilated pupil or ICP of >20 mmHg [3].

A cSDH is usually a disease of the elderly with an incidence of 1.72–20.6 per 100,000 which increases with age [4, 5]. There is consensus that large hematoma size, midline shift of more than 5 mm (Fig. 10.1), the disappearance of the basal cisterns, and a neurologic deficit are indications for surgery [6]. Contrary to aSDH, cSDH is a process that develops over time and may be silent for some time before the onset of the symptoms [4].

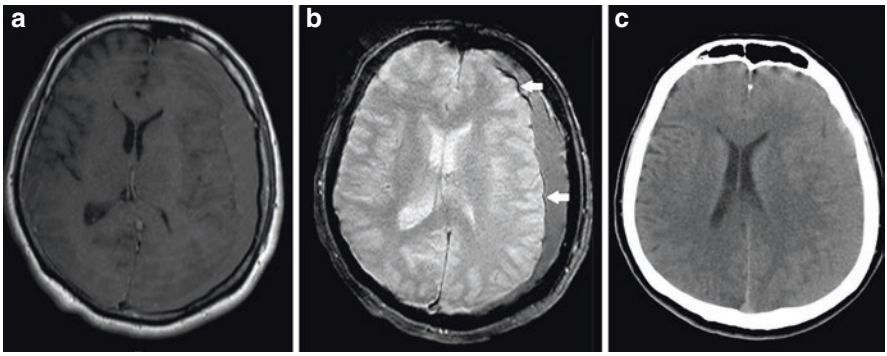

Fig. 10.1 T1-weighted (**a**), T2*-GRE (**b**), and CT (**c**) images of a homogenous iso-dense cSDH with acute components on the frontal pole of the hematoma. Large hematoma volume and midline shift support surgical intervention. Hemosiderin staining is shown along the inner membrane of cSDH on T2*-GRE (white arrows)

10.2.1 Craniotomy, Minicraniotomy, and Endoscope-Assisted Surgery

A craniotomy is the main surgical treatment for aSDH. Surgery is useful for thick clot removal, possibly localizing and managing the source of the bleed and, if necessary, converting to craniectomy to relieve potential raised ICP, since most of the aSDH are a result of trauma. Bleeding is due to ruptured bridging veins or cortical arteries [7]. The craniotomy must encompass the acute hematoma borders as much as possible. The surgeon should avoid the superior sagittal sinus, and expose inferiorly to near the base of the temporal fossa including the greater wing of the sphenoid bone. A large 12 × 15 cm frontotemporoparietal craniectomy is recommended for severe traumatic brain injury [8]. The dura is incised in a starlike fashion. The hematoma is removed using a combination of suction, irrigation, and forceps with careful traction. Irrigation is a powerful tool for hematoma removal. After hematoma evacuation, careful inspection of the surface of the brain may reveal the bleeding origin. Bleeding is controlled with bipolar electrocautery or, preferably, with an absorbable hemostatic agent. A subdural soft drain may be placed if the irrigation fluid is not clear and the origin of the bleeding site cannot be visualized. The dura is sutured closed in a watertight fashion, and dural tenting sutures are placed circumferentially to prevent developing an epidural hematoma. The bone flap is replaced with plates and screws. Subgaleal drain placement and standard closure techniques are followed.

Minicraniotomy with endoscope-assisted surgery is another recent technique developed for treating the elderly since conventional surgery for both aSDH and cSDH can have an unfavorable outcome [9]. The rationale for this approach is the removal of the hematoma and identifying the source of the bleeding under local anesthesia in a patient with a high risk for general anesthesia or a major surgical intervention.

The standard craniotomy procedure is performed over the thickest part of the hematoma, with a 2–5 cm diameter craniotomy. A recent cadaveric study on craniotomy locations of the minicraniotomy for the endoscopic operations found a 3-cm-diameter craniotomy over the most convex point of the parietal bone between the superior temporal line and the mid-pupillary line provides for optimal reach with a rigid endoscope. Yet the authors state that a minimum of a 6 mm subdural space is needed to avoid cortical damage [10]. A flexible endoscope may provide a better view compared to a rigid endoscope, but this has little meaning if the other tools cannot reach to evacuate the hematoma [9]. The dura is incised in a starlike fashion, and hematoma removal using suction, irrigation, and forceps is ensued. Then, the endoscope is used to visualize and remove as much as possible of the rest of the hematoma with the same techniques. The source of the bleed is controlled with bipolar electrocautery if possible. Endoscope-assisted aSDH removal is an alternative technique that may be beneficial in select patients [9].

Craniotomy or endoscope-assisted minicraniotomy is reserved for patients with extensive membrane formations, calcified hematomas (Fig. 10.2), or recurrent

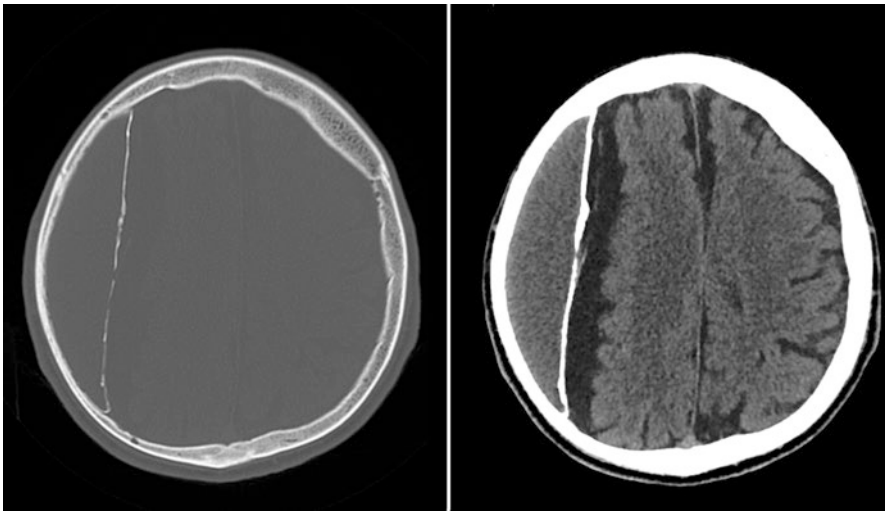

Fig. 10.2 CT image of a calcified/ossified cSDH, which requires craniotomy if the patient is symptomatic

bleeding [6, 11, 12]. Some studies report increased mortality or poor outcome for older patients with surgery [11, 13, 14]. Hence, the inclination toward minimal intervention has resulted in the development of safe and alternative techniques for cSDH treatment.

10.2.2 Burr-Hole and Twist-Drill Craniostomies

A burr-hole is described as a 10–30 mm craniostomy of the skull [15]. The hole must be drilled over the thickest part of the hematoma, typically in the parietal bone, slightly above the superior temporal line. A second burr-hole is preferable for large hematomas, usually in the frontal bone. The patient must be positioned so the frontal hole should be the highest point of the head. After the holes are prepared, bony bleeding must be waxed, and the dura is coagulated with bipolar cautery. In large hematomas and typically patients with a high Markwalder Grading Score (MGS), intracranial pressure (ICP) may be so high that a liquid hematoma may expel itself. The surgeon must avoid a sudden pressure drop and rapid expansion of the brain to avoid axonal injury. The dura and outer membranes are incised starting from the frontal hole; dark purple-red hematoma and the typical "engine oil" appearing fluid are evacuated. Irrigation of the hematoma with a soft catheter may be beneficial due to lower recurrence rates, without significant evidence [16]. Thorough irrigation is preferred without intradural cannulation in our center due to the reduced risk of the drain clogging with a clot and increased risk of parenchymal injury from blind insertion of the catheter. External membrane and dural leaflets are cauterized to

avoid recurrence. The parietal hole is closed first with a mesh or gel foam, and the galea and skin are sutured. The subdural space is filled with saline, and a subdural or subgaleal drain is placed before the galea and skin closure. Drainage after hematoma evacuation is recommended and reduces the recurrence of cSDH by 60% [6, 16]. A subperiosteal drain is as effective as a subdural drain and has a potentially lower complication rate [6]. The order of closure of the holes and their filling with saline is meant to reduce air entrapment which may prevent brain re-expansion.

Twist-drill craniostomy is described as a quick and bedside intervention performed under local anesthesia. Under local anesthesia, approximately a 1 cm incision over the thickest part of the hematoma and drilling of the bone with a 45° angle to the surface of the bone are performed. The dura and the outer membrane are perforated, and the subdural cannula is inserted, which is connected to a reservoir for passive drainage [17]. Later modifications of the technique abandon intradural cannulation and instead place a hollow screw, YL-1 needle, or a subdural evacuating port system (SEPS) through the hole. This approach lowered the complication rates of the procedure and was deemed successful as first-line treatment as it is minimally invasive, requires no general anesthesia, and does not require occupying the operating room. TDC has a similar success and recurrence rate as BHC, with approximately half the complication rate of BHC [18].

Both BHC and TDC are effective in CSDH evacuation. The advantages of BHC are direct visualization and possible intervention of multiple membranes of the hematomas with subacute components or septations, which may occlude the TDC drain and result in unsuccessful hematoma resorption. Some studies report BHC to have a lower recurrence rate, yet some have found no significant difference [6, 19]. TDC on the other hand is easy to perform, suitable for patients with a high risk for general anesthesia and those with shorter hospitalization time [18, 20].

10.3 Embolization of Middle Meningeal Artery for Chronic Subdural Hematoma

It is hypothesized that the external membrane of cSDH is the reason for maintaining and expansion of the hematoma [21]. Recent studies propose eliminating the arterial supply of the tissue by embolizing MMA which might halt hematoma expansion and facilitate resolution [21]. MMA embolization significantly reduces the recurrence of cSDH compared to serial neuroimaging or surgical intervention [22].

Under local anesthesia, after femoral or radial arterial catheterization, a catheter is placed in the proximal external carotid artery. Selective angiography reveals the internal maxillary artery and MMA. A microcatheter is advanced into the MMA with a guidewire. Anastomoses of MMA branches with the ophthalmic artery and inferolateral trunk and anatomical variations of the artery must be kept in mind before the administration of the embolizing agent [23]. Branches supplying the dura are selectively cannulated and embolized with liquid or particle embolic agents (Fig. 10.3).

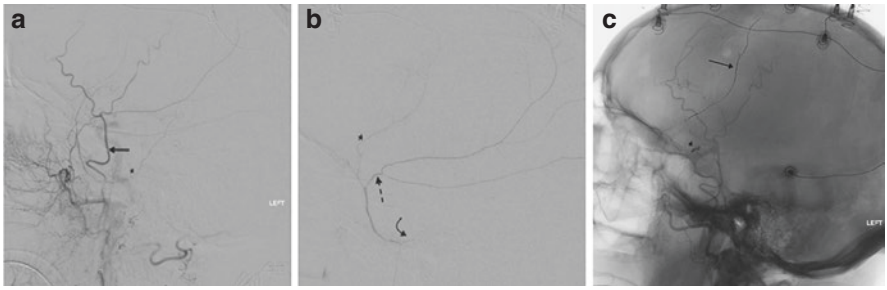

Fig. 10.3 Angiography demonstrating terminal branches of the left external carotid artery (**a**). MMA (asterisk) and superficial temporal artery (black arrow) are shown. Superselective angiography demonstrates the frontal (asterisk), parietal (dotted arrow), and petrosal branch (curved arrow) of MMA (**b**). The occluded frontal branch of MMA with a liquid embolic agent (arrow) and coil embolization of the parietal branch (asterisk) (**c**) [24]

While the technique is reserved for asymptomatic patients, since neurologic deterioration requires surgical intervention, MMA embolization is a promising treatment option. Several studies have found MMA embolization significantly reduces the recurrence rates of BHC and may be a viable first-line intervention for patients with asymptomatic cSDH and several medical comorbidities [6, 21, 22].

10.4 Medical Management of Chronic Subdural Hematoma

While surgical intervention is the primary approach to cSHD, in some patients surgery might not be a viable option due to comorbidities such as severe cardiac or pulmonary diseases. Surgical mortality and morbidity of patients with cSDH, which are typically in the elderly population, also support the initiative for nonsurgical treatment options. Patients with high surgical risk, with minor symptoms, and with an MGS score of 0–1 and those that refuse surgery are candidates for medical treatment [6]. Regardless of whether surgery is performed or not, recent studies recommend medical treatment to reduce recurrence [25]. Several medical alternatives have been established for the treatment of CSDH.

10.4.1 Dexamethasone

Neomembrane formation and leakage of blood or blood products from the neocapillaries of the membrane are the prominent theories for cSDH formation and maintenance [26]. Dexamethasone (DXM) may be beneficial in the resolution of

hematoma by inhibition of the immune response ergo and maturation of neomembrane [27, 28]. A recent meta-analysis states that DXM is the best medication to prevent the recurrence of cSDH [25]. However, an overall increase in mortality with DXM even with low doses might negate the potential benefits [28]. Recent studies recommend the use of DEX in low doses and for short duration [25, 28].

10.4.2 Atorvastatin

Atorvastatin (ATO), an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, has recently been established to reduce hematoma volume in cSDH through anti-inflammatory effects [28]. Recent meta-analyses support the effectiveness of low-dose ATO both as a first-line treatment and to improve the effectiveness of the surgery [25]. ATO is associated with good recovery [28]. DEX has a synergistic effect with ATO where both drug levels increase in the hematoma and increase the anti-inflammatory effects through macrophage regulation [29].

10.4.3 Tranexamic Acid

Tranexamic acid (TXA) is a synthetic plasmin inhibitor that inhibits fibrin-plasminogen bonding [30]. TXA is found to be the second most effective single treatment after DEX in preventing cSDH recurrence and also the second best treatment in reducing hematoma volume after ATO [25, 28]. TXA has been shown to increase the incidence of epilepsy in a dose-relative manner indicating cautious use is advised [31].

10.4.4 Goreisan

Goreisan (GRS) is an inhibitor of aquaporin-4 found on the outer membrane of the cSDH. Goreisan is theorized to prevent fluid inflow into the cSDH resulting in the resolution of the hematoma [32]. However, some recent studies found little to no effect in preventing the recurrence of SDH [25, 30]. Harada et al. [33] found Goreisan to be effective in homogenous iso-dense type cSDH (Fig. 10.4), and less effective in other types of the disease.

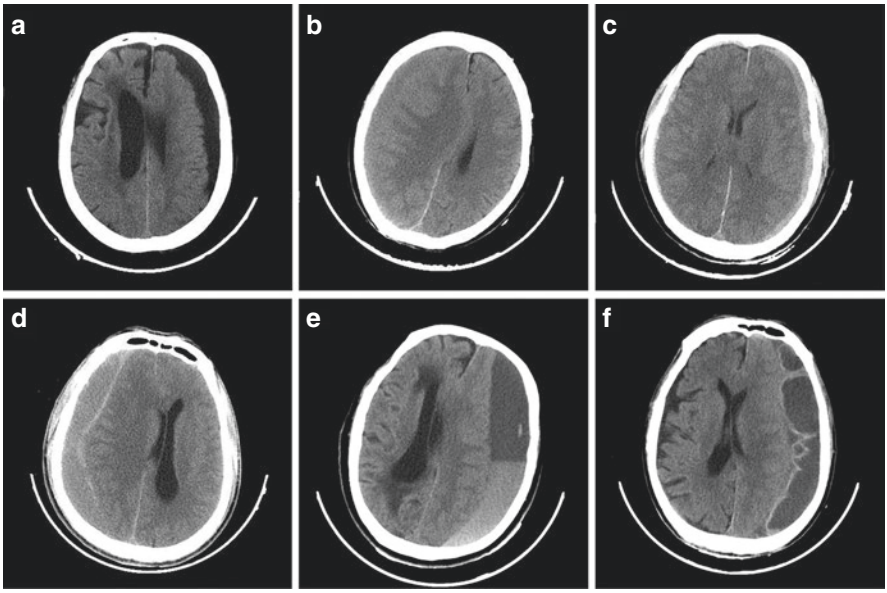

Fig. 10.4 Nakaguchi classification of cSDH. Homogenous hypo-dense (**a**), homogenous iso-dense (**b**), homogenous hyperdense (**c**), laminar (**d**), separated (**e**), trabecular (**f**) [34, 35]

10.5 Surgical Management of Subdural Hematoma in Pediatric Population

An aSDH is almost always associated with non-accidental traumatic injury in children [36, 37]. Other causes are trauma, surgical complications, fetal SDH, traumatic birth, aneurysm, arachnoid cyst, hematological diseases causing coagulopathy, glutaric aciduria, galactosemia, and hypernatremia [37]. Severe trauma may require conventional craniotomy/craniectomy and hematoma evacuation. If craniectomy is performed, future cranioplasty may be required due to physiologic growth of the skull and possible resorption of the bone flap [38].

If cSDH is seen in an infant, subdural tapping may be a viable option if the anterior fontanel is patent. The tapping point is the crossing of the mid-pupillary line and coronal suture of the anterior fontanel. The catheter is inserted approximately 1 cm posterior to the point and advanced subcutaneously and then turned 90° perpendicular to the skull. This subcutaneous advancement prevents cerebrospinal fluid leakage after tapping. Sudden decompression must be avoided.

External subdural drainage is an effective way to treat infantile cSDH [39]. External drainage is an effective way for cSDH treatment but increases the risk of infection, and catheter obstruction may complicate the treatment [39]. Another common technique is the placement of subdural shunts for hygromas and cSDH [40, 41]. Subdural to intraperitoneal or subdural to subgaleal shunts without a valve have been reported with success [40, 41]. While subdural shunts are reported to

have lower recurrence rates than other procedures, a second surgery is almost always necessary for complications such as obstruction or infection or removal of the shunt after resolution of the hematoma [40, 41]. Hyperdense hemorrhage on computed tomography (CT) suggests that blood products may cause shunt occlusion in the future, and alternative methods could be considered [42].

Multiple membranes on imaging may require BHC or minicraniotomy. The technique is similar to that described above. The use of drainage has been reported with mixed results, and BHC seems to have a higher recurrence rate in contrast to adults [43, 44]. Minicraniotomy may be a better option in the pediatric population with a relatively lower recurrence rate, therefore fewer surgical interventions [44]. Creating a subgaleal pouch without using drainage may be a viable modification for lower recurrence rates in infants [45].

Low-dose dexamethasone and atorvastatin-combined treatment has been shown to resolve post-BDH recurrence in pediatric patients [46]. MMA embolization was also successfully demonstrated to be effective in treating recurred hematoma after BHC in an 18-month-old patient [47].

10.6 Conclusion

There are extensive research and ample meta-analyses regarding SDH in adult and geriatric patients in the literature. Optimal surgical intervention must be decided on a case-by-case basis. Considerations must be made on multiple factors such as the etiology of the hematoma, age, comorbidities of the patient, and CT findings. The optimal approach is still debatable, and recent advancements in the field have created a stir in the community. Thanks to recent advances in the TDC technique, it appears to have a similar success and recurrence rate to BHC. MMA embolization or therapeutic medical options such as low-dose dexamethasone and atorvastatin in combination may preclude surgical intervention in select patients or can be used to improve surgical success rates.

The pediatric population and infants have different characteristics and success rates for the same procedures compared to adults. Hence, different approaches are often used. Unfortunately, reports in this area are scarce, and the quality of evidence is far lower than that found in adults. Further research in the field is necessary for the development of standardized surgical guidelines.

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Chapter 11
Trapped Fourth Ventricle: Pathophysiology, History and Treatment Strategies

Pasquale Gallo and Fardad T. Afshari

11.1 Introduction

11.1.1 Definition

The trapped fourth ventricle (TFV) is a rare anatomo-pathological entity characterised by a remarkable dilatation of the IV ventricle resulting from the progressive accumulation of cerebrospinal fluid (CSF) produced from choroid plexus following the occlusion of the IV ventricle main outlets (foramen of Magendie, Luschka foramina and Sylvius aqueduct).

The clinical picture is often similar to that of an expansive posterior fossa lesion with headaches, nausea, vomiting, ataxia, diplopia, weakness and progressive drowsiness, although, sometimes, the diagnosis is an incidental finding during a routine radiological follow-up [1].

11.1.2 Physiopathology of the Trapped Fourth Ventricle

There are several causative mechanisms that can contribute to the isolation of the IV ventricle such as haemorrhage (intraventricular and/or subarachnoid), infections (bacterial, fungal, parasites), inflammatory processes (e.g. sarcoidosis), congenital anomalies (e.g. arachnoid cysts) and tumours (e.g. meningeal carcinomatosis).

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Nonetheless, this entity is mostly observed in paediatric patients shunted in their infancy for the treatment of a post-infective or post-haemorrhagic hydrocephalus who have undergone several shunt revisions [2].

The incidence of TFV, according to the literature, ranges between 2.4% and 3% of the paediatric population with shunt for hydrocephalus [3, 4] and represents nearly 17% of the cases of complex hydrocephalus [5].

In 1921, Dandy described his experience with nine cases of hydrocephalus with a huge dilatation of the IV ventricle due to the obstruction of the foramina of Luschka and Magendie and concluded that this peculiar form of hydrocephalus should be considered congenital or the result of an inflammatory process [6].

In 1968, McLaurin and Ford proposed a new clinical entity, "the post-operative Dandy-Walker syndrome" caused by adhesions following posterior fossa surgery leading to obstruction of the IV ventricle outlets without evidence of aqueductal stenosis [7].

In 1969, Raimondi and colleagues described the first cases of TFV post-shunting in patients with congenital atresia of the foramina of Magendie and Luschka, defining this entity "encisted IV ventricle" [8]. According to their observations, the aqueduct remained patent for a relatively long period of time, finally obliterating and causing the definitive isolation of the IV ventricle. Since their report, the TFV has been listed amongst the possible complications related to the treatment of hydrocephalus with shunts.

Similarly, in the pre-computer tomography (CT) era, also Folz and Shurleff reached the same conclusion acknowledging that a communicating hydrocephalus (particularly post-infective or post-haemorrhagic) which had caused an inflammatory reaction of the outlets of the IV ventricle could be converted in a triventricular one following the aqueductal stenosis induced by the shunt [9].

Although in the last 40 years a relatively high number of cases of TFV have been published in the literature, the mechanism of secondary aqueduct obstruction has not been completely clarified.

Raimondi et al. speculated that this phenomenon was the result of a pressure gradient created between the supra- and infratentorial compartments. The increase of the pressure in the posterior fossa, compressing and displacing the superior cerebellar structures toward the top, would result in the aqueduct occlusion. They noticed that reducing the pressure in the infratentorial compartment will cause a reopening of the aqueduct, resolving the TFV.

The same observation was made, nearly 15 years later, by Oi and Matsumoto [10, 11] which classified this type of aqueduct occlusion as "reversible" or "functional" (because they were able to resolve it after the transient insertion of an Ommaya reservoir in the IV ventricle), to distinguish it from the "irreversible" one caused by the inflammatory reaction following infection, haemorrhage or posterior fossa surgery (resolvable only with the insertion of a shunt into the IV ventricle or a direct approach to the posterior fossa to re-establish the CSF pathways).

Other authors later referred to this condition as "double-compartment hydrocephalus", "isolated fourth ventricle" and "trapped fourth ventricle" [2, 12–15].

Recently the above two classic pathological mechanisms of the secondary closure of the Sylvian aqueduct (functional and irreversible) have been criticised by some authors in light of their neuroendoscopic evidence [16–18].

Segan et al., for example, have not found intraoperatively in any of their TFV cases a collapse or stenosis of the aqueduct walls despite the clear presence of a supratentorial hyperdrainage with slit ventricles [18]. According to them, chronic treatment with shunt is not the major cause of the isolation of the IV ventricle, but instead, the formation of intraventricular membranes, a very common phenomenon in the post-inflammatory hydrocephalus, is the key driving force.

More studies are needed on the functional reversible obstruction of the aqueduct to improve our understanding of this pathological condition.

11.1.3 Surgical Treatment Strategies for the TFV

There have been several surgical strategies proposed by neurosurgeons to treat the TFV ranging from the direct approach to the posterior fossa through a craniotomy and fenestration of the membranous tissue obstructing the CSF flow, with or without stenting of the Sylvius aqueduct [19–21], to shunting of the IV ventricle (direct or stereotactic) [22, 23].

However, these techniques are associated with a high rate of morbidity and have transformed the TFV in one of the most complex neurosurgical conditions to manage [24, 25].

In the last 25 years, thanks to the advances of the neuroendoscopic techniques [26], an increasing number of publications have appeared in the literature on the endoscopic treatment of TFV with aqueductoplasty with or without stenting [27–43]. The endoscopic approach is feasible through a supratentorial transventricular route [27–33, 35, 39–43], or through a suboccipital one (transcerebellar or trans-Magendie), and it is considered nowadays the gold standard in the treatment of this condition [34, 36–38].

However, before discussing in detail, the endoscopic techniques, it is imperative to review the historical steps and pioneers that allow us today to manage this challenging condition in a more effective and minimally invasive way.

11.2 History of the Intubation of the Sylvius Aqueduct

In 1920 Dandy published the first two cases of aqueductoplasty and stenting in the treatment of triventricular hydrocephalus due to short aqueductal stenosis [44].

After positioning the patient prone, a large suboccipital craniotomy was performed exposing both cerebellar hemispheres, then the dura opened, and the vermis elevated with a spatula in order to provide access to the IV ventricle through the foramen of Magendie. To obtain a better view of the superior third of the IV

ventricle and the aqueduct's aditus, the inferior vermis was incised and kept open using a nasal speculum. Subsequently, a small probe was introduced into the aqueduct and forced till the III ventricle, overcoming the obstruction, and CSF was seen flowing again through the aqueduct. The manoeuvre was repeated with probes of bigger diameter, and finally a rubber catheter, perforated in several points but in the part occupying the aqueduct, was placed into the aqueduct and left in situ for 2–3 weeks to prevent re-occlusion. The inferior part of the rubber catheter was tied and anchored to the dura at the level of the foramen magnum to avoid dislodgement of the catheter (Fig. 11.1).

The main reason to leave the stent only temporarily was based on Dandy's hypothesis that aqueductal stenosis was an event secondary to a foetal insult which created an injury to the epithelial layer of the aqueduct walls triggering a natural attempt of cicatrisation from the subependymal glial tissues. When this reaction was excessive, it would cause a severe stenosis of the aqueduct's lumen. In Dandy's view, leaving the rubber catheter in place for a short period of time allowed, on one hand, the formation of the epithelial layer around the catheter, thus reducing the secondary aqueduct obstruction, and, on the other hand, prevented a possible foreign body reaction. Only the second patient, 1 year old, survived with a long-term control of his hydrocephalus, whilst the other patient, 5 years old, died 7 weeks following the procedure from pneumonia.

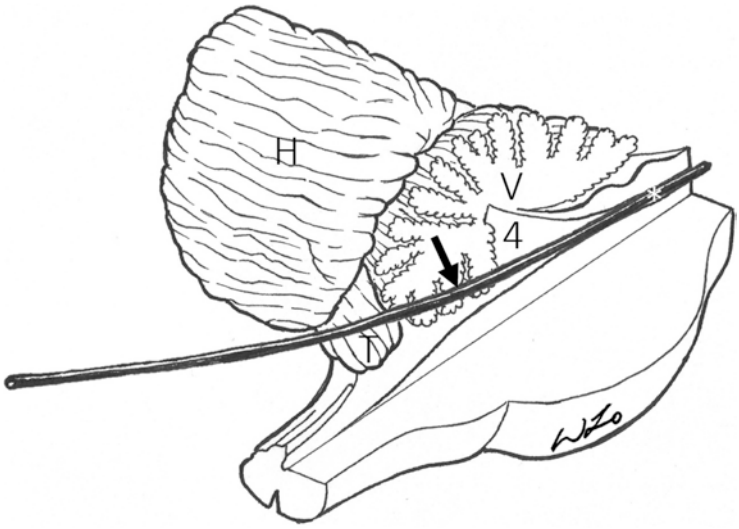

Fig. 11.1 Artistic illustration showing in the sagittal view the suboccipital approach according to Dandy to perform the stenting of the aqueduct. The roof of the fourth ventricle has been opened and the lower part of the vermis split (V). With the aid of the nasal speculum, the upper terminus of the fourth ventricle is exposed (black arrow). The floor of the fourth ventricle (4) was illuminated by the small lamp. A graduated probe (*) was inserted through the aqueduct into the third ventricle. H, cerebellar hemisphere; T, tonsil; 4, IV ventricle; *, probe; V, cerebellar vermis

The author's arguments to propose this procedure, despite the extremely high operative risks at the time, remain in principle valid today: direct treatment of the cause of the hydrocephalus, recanalisation of the aqueduct, possibility to treat through the same approach an obstruction to any of the IV ventricles outlets.

Nonetheless, for several reasons, not least the advent of the shunts, this approach was rarely used by Dandy's contemporaries and by his successors and became an unfamiliar procedure for most of the neurosurgeons for over half century.

Following a thorough historical review of the post-Dandy literature, we were able to identify some sporadic courageous attempts to reintroduce this technique.

In 1923 John Fraser and Norman Dott published their surgical experience in the treatment of the obstructive and communicating hydrocephalus. The technique utilised in the obstructive hydrocephalus—that they defined "ventricular" and divided in four grades according to the area of the aqueduct obstructed—is the same of Dandy, with the only difference that they did not leave any stent into the aqueduct but were content with the aqueductoplasty alone. Out of ten cases operated on, their operative mortality was 50%. In three cases they managed to halt the progression of the hydrocephalus, and only two cases were reported as truly successful [45].

Twenty years later, Leksell, who worked in the neurosurgical department directed by Prof Olivecrona, introduced an innovation to the Dandy's technique, utilising a tantalum spiral as stent. At a median follow-up of 18 months, he reported a 50% success rate amongst adult patients with hydrocephalus from aqueductal stenosis and a 33% operative mortality; results were poorer in the paediatric population below 1 year of age [46]. This technique was successfully utilised, in the same neurosurgical unit, by Norlen in the treatment of two patients with tumoural aqueductal stenosis [47].

In the following 40 years, due to the introduction and diffusion of shunts in the treatment of hydrocephalus and its complications, including TFV, only five articles were published on the intubation of the aqueduct.

Greenwood and Hickey in 1956 published eight cases of aqueductal stenosis of different aetiology (tumoural, congenital and malformative) obtaining a clinical success in six cases [48].

In 1966, in the *Journal of Neurosurgery*, two articles were published on the intubation of the aqueduct in the treatment of obstructive hydrocephalus. The first is the Elvidge's series of ten cases with a 20% mortality and a long-term resolution of hydrocephalus without sequela in the 8-surviving patient [49].

The other experience is that of Turnbull and Drake. They describe the clinical outcome in four patients with membranous obstruction of the aqueduct treated with direct approach and perforation of the membrane. Three patients obtained a full resolution of the preoperative symptomatology, whilst one died for an intraoperative complication (excessive retraction on the tectum). In two patients a plastic stent was left in place because the opening obtained after the membrane perforation was considered too narrow. In their article the authors concluded that this technique, despite the risks due mainly to the approach to the IV ventricle, was the preferred option over the Torkildsen technique for cases with short aqueductal stenosis [50].

In 1973, Crosby publishes his personal series on the intubation of the Sylvius aqueduct in children with non-tumoural stenosis. Out of the 30 cases reported, 23 were younger than 1 year of age, 12 had a myelomeningocele, and 9 had a Chiari malformation. All patients underwent initially a ventriculo-atrial shunt to treat their hydrocephalus and then followed up till the first episode of shunt malfunction. At that point, the shunt was revised and the intubation of the aqueduct performed as definite treatment of the hydrocephalus. Crosby stresses in his article the importance of having a working shunt before performing the intubation of the aqueduct.

The operative technique, with the patient in prone position, entailed a suboccipital craniotomy with vermis retraction till the aqueduct was clearly visualised and the stenosis confirmed; then, the aqueduct was cannulated with ureteral probes of growing diameter leaving a 2.5 cm Silastic tube in place at the end of the procedure. Patients with signs and symptoms of hydrocephalus resolved and with a non-functioning shunt (judged on the basis of the manual depression of the shunt reservoir only) were considered successful because "shunt independents".

The overall mortality of this series was 30% with an intraoperative mortality of 13%. Amongst the transient complications observed within 48 h, there were dysconjugate gaze, tachycardia, tachypnoea, moderate hyperthermia and arterial pressure instability; in two cases the stent migrated toward the supratentorial ventricular system; therefore, a modification to the distal cranial end of the stent was practised avoiding this phenomenon. Twenty-one out of 30 patients survived and 12 had a non-working shunt; thus, 63%, according to the author, was "shunt independent" [51].

The most important experience of the aqueduct intubation, at least from a numerical point of view, remains that of Claude Lapras from Lyon which was published in 4 different articles, from 1975 till 1980 including a total of 77 patients operated on.

Lapras introduced also several modifications to the technique initially described by Dandy. The patient was always placed in the sitting position, and the choroid plexus of the IV ventricle fully coagulated to facilitate the access to the ventricle. The vermis was elevated with a single retractor to expose the superior third of the IV ventricle and the aditus of the aqueduct which was eventually cannulated directly with a special catheter with soft mobile double wings to avoid stent migration designed by Lapras and produced by Codman (Fig. 11.2a–e). Fourteen patients out of 77 were below 1 year of age. In 36 cases the intubation was practised as first line of treatment, whilst the remaining patients had previously undergone shunt insertion. The mortality of this series was 8.2%. Three deaths happened in the immediate post-operative period, and only one was directly correlated to the technical procedure (a brainstem haemorrhage). The remaining three deaths occurred more than 1 year following the procedure and were ascribed to a failure in the control of the hydrocephalus.

In nearly 60% of the patients, a control of the symptomatology was obtained (33% in children below 1 year of age and 65.4% older than 1 year of age). Amongst the post-operative complications, the author reported 1 case of hypotonia and ataxia; 3 cases of post-operative seizures; 4 cases of stent migration (all before the introduction of the double-wing stent); 5 cases of Parinaud, completely resolved in 3

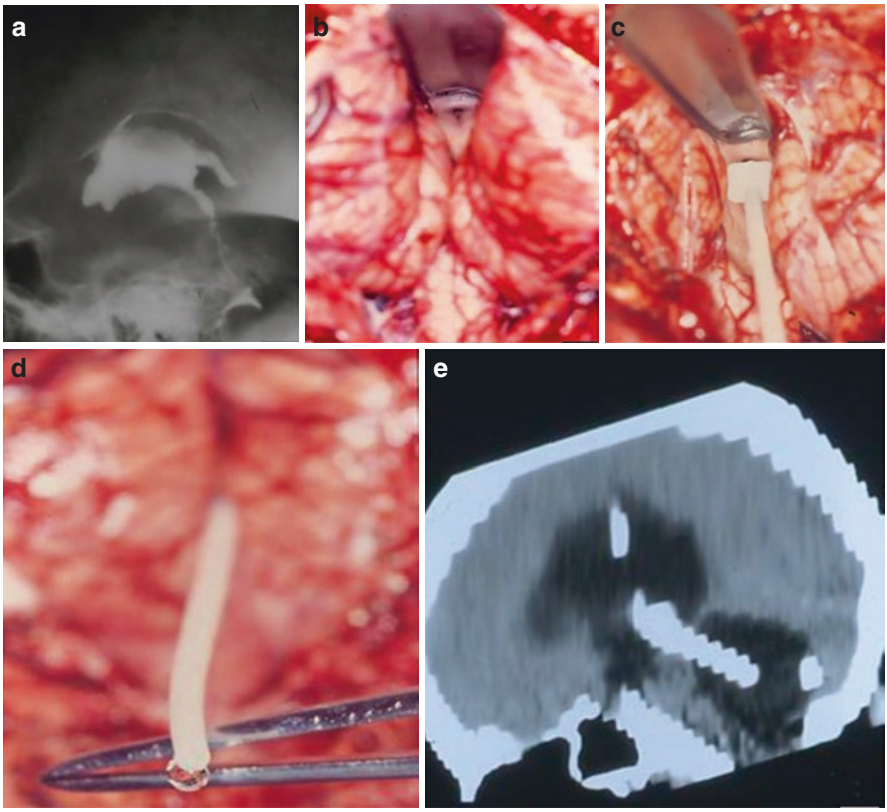

Fig. 11.2 (**a**–**e**) Surgical technique of the intubation of the Sylvius aqueduct according to Lapras. (**a**) ventriculography showing a stenosis at the level of the aqueduct; (**b**, **c**) intraoperative phases of the intubation of the aqueduct with a double-wing stent catheter; (**d**) test of the successful stenting with CSF coming from the third ventricle; (**e**) post-operative CT scan sagittal view showing the position of the stent. (Gentle concession of Dott Carmine Mottolese, Neurochirurgie, Lyon)

patients; and 12 cases of pseudomeningocoele complicated in 2 patients by a CSF leak [52–54].

The last experience to mention in chronological order is the stereotactic recanalisation of the Sylvian aqueduct of Backlund and colleagues from Karolinska Hospital in patients with obstructive hydrocephalus caused by a short aqueductal stenosis.

Their technique entailed the use of a Teflon radiopaque probe into the aqueduct through a stereotactic approach to cannulate the aqueduct in a minimally invasive way. The procedure was performed, in selected cases, also under local anaesthesia. Four out of seven patients treated with this method showed a good post-operative control of their hydrocephalus; two patients required additional procedure to reposition the stent; in three patients, instead, a shunt was necessary to treat the hydrocephalus. They reported no mortality in the 13 procedures performed and only 1 transient post-operative Parinaud [55].

11.3 Endoscopic Routes to the IV Ventricle

In general, there are three possible endoscopic ways to access the IV ventricle [16]. The first one is the classic (and the longest) supratentorial route through the foramen of Monro, the third ventricle and the aqueduct; the second is a lateral transcisternal way through the foramen of Luschka; the third possibility is the suboccipital route through the cisterna magna, via trans-Magendie or transcerebellar parenchyma.

11.3.1 The Supratentorial Trans-Aqueductal Route

Reaching the supratentorial system with a rigid endoscope is nowadays a routine neurosurgical procedure in the treatment of the obstructive hydrocephalus [28]. However, to intubate the aqueduct through this procedure, it requires some modifications of the standard approach. The patient is positioned supine, and a burr hole is usually performed on the right side of the midline anterior to the coronal suture. This distance mostly depends on how the surgeon is planning to approach the aqueduct. If a rigid scope is used, then the burr hole is usually performed more anterior compared to a standard ETV in order to reach an ideal alignment with the foramen of Monro and the aqueduct which allows a safe stenting of the aqueduct. If a flexible endoscope is used instead, the burr hole can be done in the classic coronal-pre-coronal area. The disadvantage of the flexible scope is that stenting the aqueduct maybe difficult or unfeasible, and only an aqueductoplasty can be performed.

A peel-away is used to cannulate the horn of the lateral ventricle, and endoscope is inserted through the peel away. After an exploration of the ventricular anatomy, a ventricular catheter, previously adapted to be used as a stent (adding some holes in addition to the existing ones to the portion of the catheter remaining into the supratentorial ventricular system), is advanced parallel to the scope through the same peel-away into the lateral ventricle and through the Monro into the third ventricle till the level of the aqueductal aditus where the obstruction of the Sylvius' aqueduct is fenestrated directly with the catheter. Alternatively, if the supraventricular size is large enough, another burr hole can be performed posteriorly or anteriorly to the other and the catheter advanced through a different approach. It is not recommended, in the authors' experience, in cases where the aqueduct' walls are not massively dilated, to perform an aqueductoplasty enlarging a Fogarty balloon into the aqueduct as this is the most common cause of postoperative ophthalmoplegia. Neuronavigation is extremely useful to plan the trajectory and be confident of the aqueductal aditus in the presence of post-haemorrhagic veils or membranes. Once the aqueductal stenting has been performed, the ventricular catheter is connected to a subcutaneous Ommaya reservoir which is left in place.

11.3.2 The Trans-Cisternal Lateral Route Through the Foramen of Luschka

This approach does not have a real clinical indication in the daily practice and particularly in the treatment of the trapped fourth ventricle, but it could sometimes be a useful endoscope-assisted adjunct to assess the quality and radicality of a microsurgical lesion resection, or to fenestrate an arachnoid cyst in the pontine-cerebellar angle.

Following a standard retro-sigmoid approach, the endoscope is introduced into the cerebellar pontine angle. The arachnoid of the basal cisterns is widely fenestrated and the tool advanced along the posterior margin of the vestibulo-cochlear nerve till reaching the choroid plexus which leads to the Luschka. At this point the IV ventricle can be explored paying attention to the vascular web found at this level, formed mainly by the AICA rami and the veins of the lateral portion of the IV ventricle.

11.3.3 The Suboccipital Route Trans-Foramen of Magendie

This endoscopic approach to the IV ventricle is mainly used in cases of trapped fourth ventricle with a slit supratentorial ventricular system and/or a working supratentorial shunt. The patient can be positioned in a prone Concord (Fig. 11.3a–d) or sitting position (Fig. 11.4a–f) according to the team's preference and experience.

A straight midline 4 cm skin incision is made at the level of the craniocervical junction. Following soft tissue and muscle dissection, the foramen magnum and the C1 posterior arch are exposed. A minimal amount of occipital bone is upcut, and if needed, to achieve the right angle and orientation for the stenting, also part of the middle C1 posterior arch is resected. The posterior atlanto-occipital membrane is dissected and a small dural incision (just enough for the endoscope to pass through) performed, possibly without tearing the arachnoid. The dura is suspended on each side and the arachnoid dissected and opened under endoscopic guidance. Then, the endoscope is advanced into the cisterna magna and through the Magendie into the IV ventricle. The first inferior IV ventricular floor structures encountered are the obex and calamus scriptorius, then the striae medullaris and the facial colliculi.

Keeping the sulcus medianus as reference for the midline, we reach the inferior part of the aqueduct of Sylvius. Often, in patients with trapped IV ventricle with previous intraventricular haemorrhage or infection, this area is covered by a tiny veil or membrane, and it can be challenging to identify the exact location of the aqueductal aditus and the orientation for the stenting without the help of neuronavigation. Therefore, a stealth stiletto is introduced into the catheter, and utilised directly to perform the stenting of the aqueduct. As in the supratentorial approach, if this is a standard ventricular catheter, additional holes are performed for the portion remaining into the IV ventricle, and the distal end is either connected to a

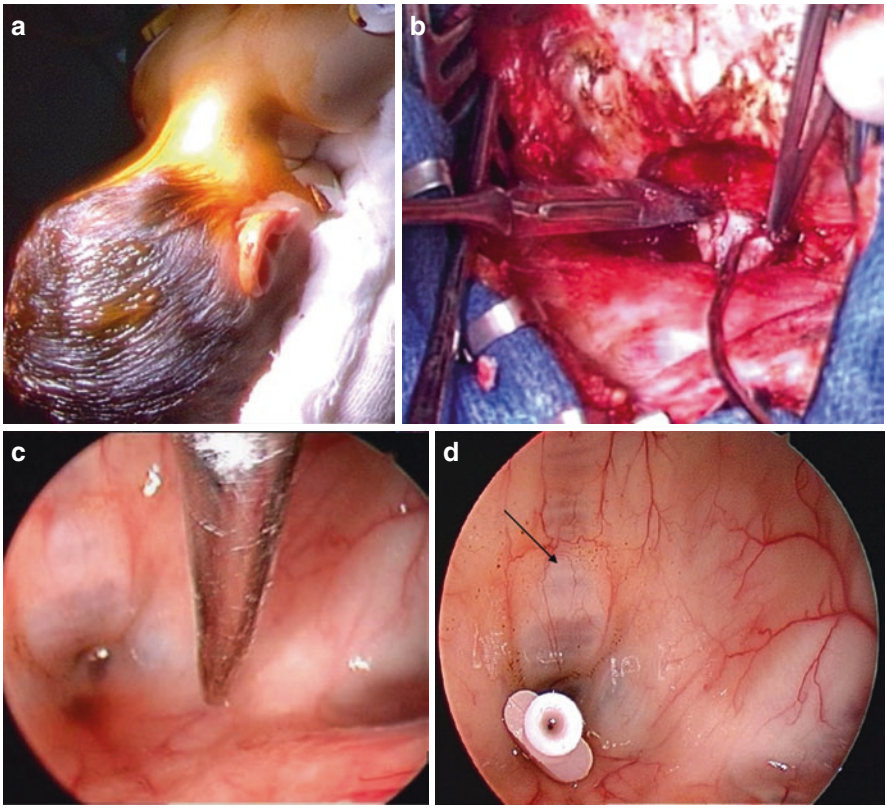

Fig. 11.3 (**a**–**d**) Surgical steps of the cannulation of the Sylvius aqueduct by using a double-wing Lapras stent in prone position. (**a**) patient positioned prone, the amount of neck flexion needed to align the Sylvius aqueduct and the foramen magnum is identified by reviewing carefully the inclination of the aqueduct on the MRI; (**b**) a small amount of bone is removed from the suboccipital bone and the atlanto-occipital membrane is opened and partially removed exposing the underlying dura; (**c**) endoscope inserted through a minimal dura opening; after aspirating the CSF, we can identify the principal landmarks inside the fourth ventricle (the lateral recess with its choroid plexus and the structures of the fourth ventricle floor); the endoscope is moved toward the caudal end of the aqueduct, and a Lapras tube with double wings is pushed forward, keeping in mind the orientation of the aqueduct, until the superior wing reaches the third ventricle; (**d**) the inferior wing of the tube remains into the fourth ventricle and the distal end cut; the arrows show the stigmata of the previous intraventricular haemorrhage on the superior medullary velum. (Reprint from Gallo, P., Szathmari, A., Simon, E., Ricci-Franchi, A. C., Rousselle, C., Hermier, M., & Mottolese, C. (2012). The endoscopic trans-fourth ventricle aqueductoplasty and stent placement for the treatment of trapped fourth ventricle: long-term results in a series of 18 consecutive patients. *Neurology India*, *60*(3), 271–277)

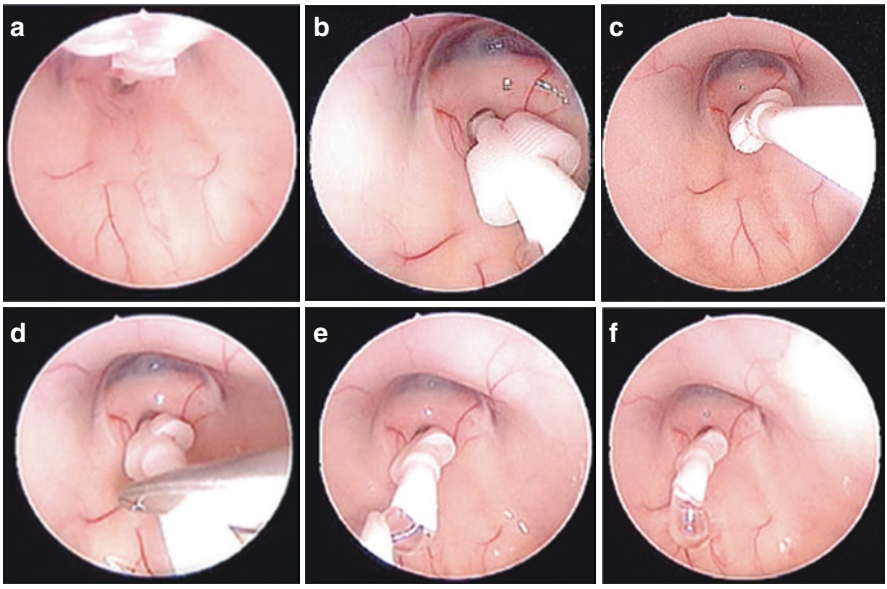

Fig. 11.4 (**a**–**f**) Endoscopic view of the intubation of the aqueduct with the patient in sitting position. (**a**–**c**) After we have identified the principal landmarks inside the ventricle, the endoscope is moved toward the caudal end of the aqueduct, and a Lapras tube with double wings (Codman) is pushed through the aqueductal stenosis, keeping in mind the orientation of the aqueduct, until the superior wing reaches the third ventricle; (**d**) the inferior wing of the tube remains into the fourth ventricle and the distal end of the catheter is cut; (**e**, **f**) the right position and the functioning of the catheter are tested by gently irrigating a Ringer solution inside the distal end of the tube and observing the dripping of the fluid into the fourth ventricle. (Reprint from Gallo, P., Szathmari, A., Simon, E., Ricci-Franchi, A. C., Rousselle, C., Hermier, M., & Mottolese, C. (2012). The endoscopic trans-fourth ventricle aqueductoplasty and stent placement for the treatment of trapped fourth ventricle: long-term results in a series of 18 consecutive patients. *Neurology India*, *60*(3), 271–277)

subcutaneous Ommaya or tied with a suture and stitched to the dura to prevent migration. If a Lapras's double-wing catheter is utilised instead, one wing is pushed through the aqueductal stenosis into the third ventricle, and the other wing remains into the IV ventricle. After the catheter has been tested and found functional, its distal portion is cut 1 or 2 cm below the caudal wings (Fig. 11.4a–f).

11.4 An Algorithm for the Treatment of the Trapped Fourth Ventricle

The management of TFV is a topic of controversy. Both conservative and surgical management strategies for TFV have been reported in the literature with some advocating conservative management in asymptomatic cases [56] versus surgical

intervention in all cases in other series [57]. This difference in the threshold for surgery is likely explained by how this entity is defined by different groups. Some authors consider TFV as complete isolation of fourth ventricle, and therefore by definition such patients tend to always clinically deteriorate or radiologically demonstrate evidence trapped large fourth ventricle and brainstem distortion ultimately leading to surgical intervention. Others consider increase in size of fourth ventricle disproportionate to supratentorial component as trapped fourth ventricle which may include a mixed cohort of patients with complete or incomplete communication to CSF cisterns or third ventricle. A proportion of such mixed cohort of patients may have stable large fourth ventricular size due to some residual outflow and may be asymptomatic.

What is commonly agreed amongst different studies is that symptomatic clinical deterioration and radiological progression on interval imaging with increase in the size of trapped fourth ventricle and brainstem displacement are clear indications for surgical intervention. Magnetic resonance imaging (MRI) is the gold standard mode imaging. This should include sagittal T2 with CISS sequences to further delineate aqueduct patency and degree and length of aqueductal obstruction which has significant impact on the management strategies. What is less agreed is the surgical strategy used in the treatment of TFV. Management is dictated by anatomy of ventricular system and aqueduct, primary cause of trapped fourth ventricle, presence of supratentorial hydrocephalus, presence of supratentorial shunt and expertise and resources available.

The management of TFV can be broadly divided to those targeting the fourth ventricle directly (such as fourth ventricular shunting or microscopic fenestration) or those aiming at equalising supratentorial and infratentorial pressures by re-establishing aqueduct connection between the third and fourth ventricles using aqueductoplasty with or without stent. Depending on the size of the lateral ventricles, supratentorial versus infratentorial approaches can be considered. If lateral ventricles are large, aqueductoplasty or stent insertion can be attempted endoscopically from supratentorial approach. On the other hand, if ventricles are small or slit-like, infratentorial approaches can be utilised to create a patent aqueduct. A simple algorithm for decision-making in the management of trapped fourth ventricle is depicted in Fig. 11.5.

Literature available on success and failure rates of different approaches is unreliable and heterogenous preventing meaningful direct comparison amongst studies. Thanks to the advances in endoscopic skills and equipment, endoscopic approaches and stent placement are gaining more momentum and are increasingly being utilised with good outcomes and considered nowadays the gold standard in the treatment of this condition [57]. Complications following management of TFV are common. These are particularly reported in fourth ventricular shunting procedures which has been the most common technique utilised in the management of TFV historically till the advent of neuroendoscopy [24]. Reported complications for treatments include shunt migration and blockage and need for frequent revisions

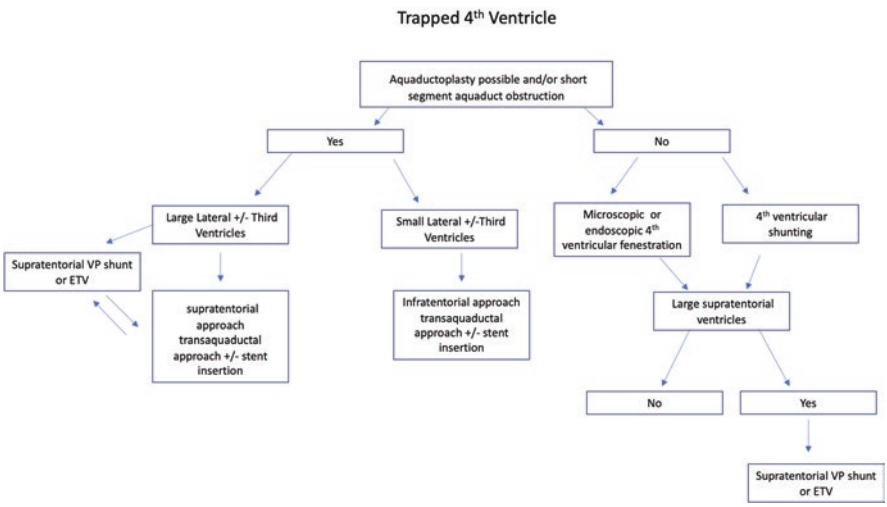

Fig. 11.5 Basic algorithm in management of trapped fourth ventricle

which is the main cause of morbidity. Other more serious complications reported in management of TFV include fourth ventricular floor injuries, cranial nerve palsies and ophthalmoplegia (transient and permanent) [24, 56–58]. Studies with long-term follow-up of patients with TFV are limited. Although reoperation and revision rates remain high in most studies, reports with longest follow-up reveal a better prognosis following endoscopic approaches and stenting [55, 56, 59].

11.5 Conclusions

Trapped fourth ventricle is an entity defined by isolation of fourth ventricle leading to progressive dilatation and ultimate brainstem displacement and neurological deterioration. Regular clinical and imaging assessment is recommended to allow timely intervention. Endoscopic approaches via supratentorial or infratentorial routes for aqueductoplasty with stenting have become the mainstay treatment strategies in managing this challenging condition. Direct microscopic fenestration of the fourth ventricle or shunting options are reserved for cases where endoscopic approaches to aqueductoplasty are not feasible due to anatomical considerations. With further advances in endoscopic techniques, the management of this condition is likely to become less invasive and ultimately lead to increased safety.

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Chapter 12
Role of Endoscopy in Treatment of Complex Hydrocephalus in Children

Nasser M. F. El-Ghandour

12.1 Introduction

Complex hydrocephalus is any form of hydrocephalus which cannot be treated with a single neurosurgical intervention. It arises from intraventricular membranes resulting in isolated single or multiple compartments. Different names had been used for this disease in the literature like loculated or compartmentalized or septated hydrocephalus. Complex hydrocephalus is considered to be a serious problem in pediatric neurosurgery [1, 2]. Surgical treatment is required; however, the exact surgical procedure remains controversial. Traditionally, it has been treated by shunts, usually multiple shunt tubes, and usually requiring multiple revisions [3, 4].

Cyst aspiration using stereotaxy has been advocated by some neurosurgeons as one of the surgical options [4, 5]. Communicating these compartments through craniotomy has been advocated by others using either transcortical approach [6] or transcallosal approach [7]. Endoscopic cyst fenestration has been used recently in treating these patients, as a simple procedure that communicates the isolated compartments together and communicates it with the ventricular system as well. The endoscopic procedure can be done through the same burr hole which has been used for placement of the ventricular catheter. Neuroendoscopy can eliminate the necessity for inserting ventriculoperitoneal shunting [1].

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12.2 Historical Background

For decades, microsurgery was considered to be the primary method of treatment of complicated hydrocephalus. In 1972, a case of multilocular hydrocephalus was converted to a single cavity through small corticectomy using the microsurgery; a shunt tube was implanted to treat the hydrocephalus [8].

In 1982, the first successful endoscopic procedure was performed using the bronchoscope in a patient with ventricular cyst [9]. In 1986, an intraventricular cyst was operated through a flexible endoscope and fenestrated using argon laser [10]. In 1992, among a series of seven patients, the same procedure had been used successfully in five of them [11].

In 1991, ventricular cyst fenestration was performed using saline torch [12, 13]. In 1993, six patients with multilocular hydrocephalus were treated by fenestration using the transcallosal approach; shunt revision rate was reduced significantly after operation [7]. In 1995, the first study from the USA including 34 patients with complex hydrocephalus operated using the endoscopic procedure was published [14]. In 2003, the second study from Poland with 47 patients suffering from complex hydrocephalus operated by endoscopy was published [15]. These two studies included both types of complicated hydrocephalus, the unilocular and multilocular types.

In 2008, the third study from Egypt was published, including 24 children with multilocular hydrocephalus operated by endoscopic fenestration. This was the first study specific for the endoscopic treatment of the multiloculated type of complex hydrocephalus, and it was the largest series at such time. The results were promising with eliminating the need for shunts or simplifying complex shunts, and postoperative shunt revision rate was reduced significantly. These results were comparable to those reported by using microsurgery; nevertheless, the endoscopic procedure has an important privilege of being minimally invasive [1].

12.3 Classification

Complex hydrocephalus is divided into two types. The presence of a single intraventricular cyst is referred to as uniloculated hydrocephalus. The presence of many compartments or cysts separated by membranes is referred to as multiloculated hydrocephalus. Any of these two types can be further classified to be either supratentorial or infratentorial. Uniloculated hydrocephalus is usually congenital in origin with normal subarachnoid space, whereas multiloculated hydrocephalus is usually post-inflammatory or postinfectious with scarred subarachnoid spaces. Both types of complex hydrocephalus are considered to be divergent, because they have different pathogenesis, prognosis, and outcome of surgery; for this reason, they should be studied separately [1].

Another classification of complex hydrocephalus has been proposed which depends on anatomical complexity and cerebrospinal fluid absorption. Simple

uniloculated hydrocephalus occurs if there is a single compartment and normal absorption. Complex uniloculated hydrocephalus occurs if there is single compartment and cerebrospinal fluid absorption is abnormal. Simple multiloculated hydrocephalus occurs if there are multiple compartments, absorption is normal, and there is no anatomical distortion. Physiologically complex multiloculated hydrocephalus occurs if there are multiple compartments, absorption is abnormal, and complicating factors are existing. Complex multiloculated hydrocephalus occurs if there are multiple compartments, absorption is normal, and there are no complicating factors, but anatomical distortion exists [16]. Nevertheless, this classification is difficult to apply clinically, because it mainly depends on disturbed cerebrospinal fluid absorption which is considered to be a diagnosis of exclusion [17].

12.4 Incidence

Complicated hydrocephalus usually occurs in the pediatric age group especially neonates, with almost equal incidence among males and females. The incidence of complex hydrocephalus has not been reported in most of the studies; however, concerning neonatal meningitis, which is one of the most important causes, its incidence ranges from 0.37% to 2.24%. The incidence of hydrocephalus occurring as a consequence of neonatal meningitis has been reported to be 31% [18, 19]. Ventriculitis is a usual consequence of bacterial meningitis; it was reported to be up to 92% of cases at postmortem and up to 100% of cases clinically. Post-meningitic hydrocephalus usually occurs due to problem in the absorption of cerebrospinal fluid occurring at the level of the subarachnoid space [18].

The hydrocephalus resulting from neonatal meningitis is uncommon, and the specific subgroup of multiloculated hydrocephalus is rare. The scarcity of this patient population in the literature is one of the main challenges facing neurosurgeons when trying to study multiloculated hydrocephalus. Another challenge researchers face when discussing any type of complex hydrocephalus is the ambiguous nomenclature used to classify this disease; different terms have been used to describe these patients [20].

12.5 Pathogenesis

The pathogenesis of complicated hydrocephalus is still unknown; it might be due to inflammatory reaction or intraventricular gliosis following ventriculitis, mainly due to Gram-negative enteric organisms [19]. The common factor between meningitis, shunt infection, and intraventricular hemorrhage is the ventriculitis. It seems that ventriculitis whether chemical or infectious in origin will probably encourage subependymal glial tissue proliferation leading to the formation of exudates and debris which results in the development of multiple septations inside the ventricular system.

These membranes not only distort the ventricles, but it also interferes with cerebrospinal fluid flow resulting in its accumulation inside the isolated compartments with progressive hydrocephalus [7]. Grossly, the ventricular system is transformed into multiple compartments isolated by multiple membranes which are varying in thickness, and they are usually transparent in early cases. Microscopically, the membranes consist of polymorphonuclear cells with fibroglial elements [3].

It has been speculated that the physical trauma of shunt implantation can also potentially initiate the progression of hydrocephalus; direct trauma to the ependyma sustained during catheter insertion may stimulate loculations through the formation of fibroglial septa [21, 22]. After they are imbedded, the ventricular catheters become a nidus for bacteria that stimulates additional compartmentalization [14]. Accordingly, intraoperative proper depth perception and estimating length of the ventricular catheter correctly are very important as a prophylaxis against inducing any trauma to the ependyma during the shunting procedure. Moreover, overdrainage of cerebrospinal fluid through the ventricular catheter can isolate the ventricular compartments, cause morphological changes in cerebrospinal fluid pathways, and alter its dynamics [23]. For this reason, ventriculoperitoneal shunting is not recommended to be used as a treatment option in patients with multiloculated hydrocephalus [1].

It has been reported that in any infection-related condition, the debris of any surgical intervention will promote hydrocephalus. Precipitation of proteins originating from any surgical wound inside the ventricular system will create arachnoid granulations which hinders absorption of cerebrospinal fluid significantly [24]. The intraventricular precipitation of proteins may act as a chemical irritant, which may probably result in denudation and glial proliferation with the formation of intraventricular septations and isolation of compartments. This means that any type of intracranial surgical interference in these patients carries the risk of perpetuating hydrocephalic symptoms [21].

12.6 Predisposing Causes

12.6.1 Uniloculated Hydrocephalus

Many synonyms have been used to describe this type of complex hydrocephalus such as unilateral hydrocephalus or trapped lateral ventricle. It occurs if the lateral ventricle becomes isolated due to obstruction of one of the two foramina of Monro by noncolloid neuroepithelial cysts (choroid plexus, ependymal or arachnoid cysts). Although arachnoid cysts are usually located extradurally, they rarely occur inside the ventricular system [25].

In shunted myelodysplastic children treated by low-pressure shunt implanted in contralateral ventricle, the ipsilateral ventricle continues to over drain, whereas the contralateral ventricle becomes dilated resulting in uniloculated hydrocephalus.

These patients usually remain without symptoms requiring no treatment. Nevertheless, if symptomatic dilatation of the lateral ventricle opposite to the shunt progresses, the shunt valve pressure must be upgraded or a shunt catheter is implanted in the contralateral ventricle [26]. Occlusion of the foramen of Monro may be due to reactive and inflammatory changes induced by shunt tubes, infection, hemorrhage, and the formation of scar tissue inside the ventricular system resulting in an isolated lateral ventricle [25].

Obstruction of the Sylvian aqueduct and outlets of the fourth ventricle leads to isolated fourth ventricle; it sometimes occurs if patients with post-meningitic or posthemorrhagic hydrocephalus have been treated by shunting. It results in accumulation of cerebrospinal fluid, with ballooning of the fourth ventricle which exerts pressure over the cerebellar parenchyma and brain stem. The presence of lateral ventricular shunt worsens the condition; it decreases supratentorial pressure and decreases the pressure needed in order to maintain the aqueduct of Sylvius open, leading to aqueduct collapse. Accordingly, decompression of the ventricular system occurs, whereas the fourth ventricle remains ballooned.

Several treatment options had been used in treatment of the trapped fourth ventricle such as ventriculoperitoneal shunting from the fourth ventricle, microsurgical fenestration of the fourth ventricle outlets, and microsurgical canalization of the aqueduct. With the introduction of endoscopy in neurosurgery, the treatment of isolated fourth ventricle becomes feasible through endoscopic third ventriculostomy in addition to reconstructing the aqueduct of Sylvius, a procedure called aqueductoplasty. Some authors advocated implanting a stent during this reconstruction [27].

Among a series of 31 children suffering from unilocular hydrocephalus operated by endoscopy, the most common cause was noncolloid neuroepithelial cysts (54.8%), followed by neonatal meningitis and intraventricular gliosis (35.5%), and ventriculitis (9.7%) [28]. In a series including 21 cases of unilocular hydrocephalus, the commonest cause was noncolloid neuroepithelial cysts (71%), followed by choroid plexus cysts (14%), postoperative gliosis (10%), and meningitis (5%) [14].

12.6.2 Multiloculated Hydrocephalus

When the ventricles become encysted following meningitis or intraventricular hemorrhage, the condition is called multiloculated hydrocephalus. This condition can be referred to as polycystic or compartmentalized hydrocephalus [3, 29]. Many predisposing causes have been reported to be responsible such as congenital anomalies, low-birth infants, prematurity, and perinatal problems [18]. Among a series of 24 children with multilocular hydrocephalus, neonatal meningitis was the commonest cause, followed by intraventricular hemorrhage, intraventricular gliosis, and neuroepithelial cysts [1]. Among a series of 13 patients suffering from multilocular hydrocephalus, commonest causes were intraventricular hemorrhage and multiple neuroepithelial cysts (each 31%), followed by meningitis (23%) and intraventricular gliosis (15%) [14].

12.7 Clinical Picture

Infants and neonates will present by macrocephaly, whereas older children present by symptoms of intracranial hypertension. Other symptoms include epilepsy, ataxia, hemiparesis, and delayed milestones. Children with multilocular hydrocephalus are difficult to treat; they are often suffering from mental deterioration. In a series of 33 children with multilocular hydrocephalus, 87.9% were severely impaired or almost vegetative [6].

In a series including 34 patients with complicated hydrocephalus, symptoms were headache (41.2%), followed by developmental delay (32.4%), macrocephaly (17.6%), seizures (14.7%), gait ataxia (5.9%), and progressive hemiparesis (5.9%) [14]. In a series of 24 pediatric patients with multilocular hydrocephalus, macrocephaly was present in all patients, whereas the incidence of developmental delay was 75%, epilepsy 16.7%, and hemiparesis 8.3% [1].

12.8 Diagnostic Studies

12.8.1 Ultrasound

Ultrasound is considered to be a reliable modality in making the diagnosis if the fontanel is open. It demonstrates the cyst walls revealing the presence of multiple compartments that has occurred. It is non-radiating, noninvasive, it gives a multiplanar view and sedation is not required. It has the disadvantage of being operator-dependent, and it was not considered to be a definitive preoperative diagnostic method [30]. However, with advancement of technology, ultrasound proved to be a valuable method in detecting the septations and compartmentalization, and in making the diagnosis [31].

12.8.2 Computed Tomography Scan

Non-contrast CT scan can be used for screening of patients, and it might reveal disproportionate hydrocephalus. Nevertheless, it is usually difficult to recognize cyst walls properly because the membranes are usually transparent and the cysts are hypodense, the same like the ventricular density. Usually, CT scan shows multiple septations which are transversely oriented; they have varying thickness and heterogeneous distribution, making the ventricular contour irregular.

In the early stage of the disease, the septations are usually not visible; later on, the pattern of progressive loculations and disproportionate hydrocephalus could be easily seen. The normal ventricular architecture becomes invisible, resulting in

large single or multiple isolated compartments. In advanced stage, the anatomy is muffled, and it becomes impossible to identify the ventricles or the normal anatomical features [7].

12.8.3 Magnetic Resonance Imaging

Magnetic resonance imaging is the ideal method in establishing the diagnosis. Gadolinium is very important in order to be able to recognize the septations. Multiplanar MRI is more accurate than CT scan in showing the membranes. The increased protein content of these cysts allows them to be differentiated from the ventricular system due to the difference in density as compared to cerebrospinal fluid. It can also delineate the pathology such as a neuroepithelial cyst. Magnetic resonance imaging is a simple and reliable method to identify obstructive membranes in patients with multiloculated hydrocephalus. It is capable of providing detailed pictures in three different planes (axial, coronal, sagittal), and delineating cyst walls; however, its ability to evaluate cerebrospinal flow and detect whether or not there is communication between the different loculations is still suboptimal [32].

12.8.4 Contrast CT Ventriculography

Contrast CT ventriculography is considered to be the definitive diagnosis that demonstrates if the cysts are communicating or noncommunicating with the ventricular system, and it defines margins of the cyst walls. Metrizamide (1–2 mL) is injected inside an external ventricular drain or into the proximal catheter of the shunt system, using a 22-gauge spinal needle. The patient's head is rotated back and front so that the contrast material will be adequately dispersed inside the ventricular cavity, in order to show any compartmentalization. Another CT scan is performed after injecting the contrast material by 30–60 min.

Contrast CT ventriculography provides definitive confirmation of communication or noncommunication of the cysts, which is important to plan the surgical procedure which will be adopted, and it allows direct visualization of the ventricular loculations. Nevertheless, it requires multiple punctures of multiple cysts in order to determine if communication exists in patients with multiloculated hydrocephalus. This diagnostic modality can be used postoperatively in order to confirm successful endoscopic fenestration. Sample of cerebrospinal fluid can be also withdrawn; if it shows high protein content, this can be used as an indicator for noncommunication [7].

12.9 Surgical Management

Medical treatment may be required before any surgical interference should be undergone, for patients who give history of ventriculitis or prematurity. The aims of surgery are to control hydrocephalus, reduce shunt revision rate, avoid inserting new shunts, simplify complex shunts, and decrease operative complications. Complex shunts mean the presence of multiple nonfunctioning shunts, and simplification of complex shunts means that all multiple shunts are replaced with a single shunt (only one reservoir, one proximal tube, and one distal tube).

12.9.1 Ventricular Shunting

The main obstacle in multiloculated hydrocephalus is the presence of loculations inside the ventricular system which interferes with drainage of cerebrospinal fluid, making the shunting procedure non-successful. Accordingly, placement of multiple shunt systems is required to drain the compartmentalized ventricular system [33].

Using repeated procedures and multiple hardware will be associated with higher risk of malfunction. Implanting shunts in these patients with complex hydrocephalus results in shunt malfunction and sometimes ventriculitis which adds to the complexity of the disease, and is associated with high incidence of morbidity and mortality. In one study the mortality rate was 54%, with the surviving patients severely compromised [19]. Consequently, it will be much better to avoid this method of treatment as much as possible [6]. Implanting proximal tube with multiple perforations has been advocated; however, it was not considered to be a successful method [19].

12.9.2 Stereotactic Procedure

Traditionally stereotactic procedures had been used in the treatment of patients with intraventricular cysts, with the advantage of its operative simplicity and low complication rate. Nevertheless, the lack of success in treating some patients had been reported; an intraventricular cyst may resist puncture either due to tough wall or because it moves away from the puncturing needle and after several attempts the procedure fails [4]. An important disadvantage of this procedure is that it is done without any visual control; it is considered to be a blind procedure [34]. Stereotactic procedures have not been popularized, simply because it is associated with high recurrence rate (up to 80%), mainly because of its inability to create a large fenestration [5].

12.9.3 Microsurgical Treatment

There are few articles in the literature describing microsurgical treatment of these children, and they include a small number of patients. Good results were documented using the transcallosal technique [7], and the transcortical technique [6]. Neurosurgeons using microsurgery claim that proper hemostasis can be easily accomplished since the procedure is performed under direct vision. Moreover, microsurgery allows using both hands which allows better control of the surgical instruments, like regular suction and bipolar cautery, with the feasibility of applying hemostatic material, an advantage which is not available during the endoscopic procedures. The surgical microscope allows proper visualization of multiple membranes and loculations under high magnification [6]. Moreover, microsurgery allows a stereoscopic view with better depth perception during deep membrane dissection [35].

However, the microsurgical procedures are not without risk. Transcallosal surgery can result in many complications like venous infarction (due to coagulating bridging veins), sagittal sinus thrombosis, and injuring the pericallosal arteries or the fornix resulting in cognitive changes [36]. If the cortical mantle is thinned, subdural collection may occur following the transcortical surgery, and it may be associated with seizures [11, 12].

12.9.4 Endoscopic Treatment

The high incidence of failure rate of shunting and the significant morbidity associated with the microsurgical technique pushed many surgeons to try to find another method of treatment. If the strategy of treatment depends mainly on performing multiple fenestrations in the walls of these cysts in order to communicate these compartments with the ventricular system, the endoscope as a minimally invasive procedure will be considered the proper choice in the treatment of these patients. After endoscopy, patients recover on the ward, and they can be discharged on the first postoperative day; in contrast, after microsurgical surgery patients routinely stay in the intensive care unit for an overnight [14].

12.9.4.1 Endoscopic Tools

Flexible endoscopic lenses have been recommended by many neurosurgeons because of its steerability which offers better manipulation [14]. Nevertheless, it needs much experience, and I think its main job in multilocular hydrocephalus is to perform aqueduct reconstruction in patients suffering from isolated fourth ventricle. I prefer using rigid endoscopic lenses, due to optimal light projection and excellent optics which offer better endoscopic views. The drawback of lower flexibility of

rigid endoscopes can be overcome by properly choosing the burr hole placement location and by enlarging edge of the burr hole in order to provide more flexibility in moving the endoscope in different directions [1].

12.9.4.2 Endoscopic Trajectory

Each case is unique; proper preoperative planning is an important prerequisite for successful outcome. The trajectory is planned depending on many factors such as cysts' location, site of old implanted shunt catheters, and the necessity of implanting new catheter. Anteriorly located cysts are attacked through a Kocher burr hole, whereas posteriorly located or temporally located cysts are approached through an occipital/posterior parietal route. Edge of the burr hole is beveled laterally in order to allow the endoscopic lens to reach the opposite side, and the approach is planned to perforate as many cysts as possible, and this can be performed guided by preoperative multiplanar MRI. Usually, it is not possible to puncture all the cysts during initial procedure, and it is usual to have multiple procedures in the management of these patients.

The peel-away sheath with the stylet inside is introduced inside the ventricle trying to avoid the escape of significant amount of cerebrospinal fluid. After pulling the stylet, the endoscopic lens is then inserted (2-mm-diameter rigid lens, straightforward, wide-angle, zero degree, with 3 mm working channel and angled eye piece). In advanced cases with complex cysts, this operation can be performed through multiple burr holes (multiportal technique), in order to allow better localization and a greater number of cysts to be perforated. However, I prefer working through a single burr hole; in most of the patients, I noticed that the multiple burr hole technique is usually associated with the presence of intraventricular air postoperatively which hinders the recovery of these patients significantly [1].

12.9.4.3 Cyst Localization

Ultrasonography is beneficial both in localization and in providing a live intraoperative feedback and anatomical orientation. It is also valuable in providing depth perception of the surgical field and in detecting the presence of any solid structures inside these loculations, as well as any brain shift occurring during the endoscopic procedure.

Nevertheless, the use of ultrasound during operation requires creating a window in the skull vault, and it has the disadvantages of operative dependability and crowding of the surgical room [25]. Moreover, the presence of open fontanel is essential, which makes this method of localization only valid in infants and neonates. However, with advancement of technology, the development of high-frequency, small-footprint probes makes the use of ultrasound feasible in older children, which can possibly be used through thinner areas of bone, like the temporal bone [31].

There is no doubt that neuronavigation or frameless stereotaxy has optimized safety and accuracy of the endoscopic fenestration, and it might be helpful in overcoming the problem of distorted anatomy. Nevertheless, in young children, the skull cannot be fixed by pin holder. Important to mention that the head must remain in a stable position after markers have been registered; significant errors might happen and this requires to repeat the process of registration. Pinless frameless stereotactic systems have been used by many neurosurgeons in infants and proved to be successful; nevertheless, errors can still occur due to brain shift. It is worth noting that the frameless stereotactic system in contrast to intraoperative ultrasound is not real time and cannot provide live feedback during surgery. Accordingly, both systems might be used simultaneously in order to get benefit of the advantages of both of them [25].

There is paucity of information in the literature about the role of neuronavigation in treating patients with multilocular hydrocephalus. Among a group of pediatric patients with multilocular hydrocephalus who were operated by the endoscopic procedure assisted by navigation, the fenestration procedure was successfully performed in all patients. The authors did not encounter significant problems with brain shift. This observation was attributed to the small size of majority of the cysts and to the continuous irrigation which has been used throughout the procedure in order to maintain the existing anatomy and dimensions of the penetrated cysts and the ventricles [37].

It has been suggested to use intraoperative magnetic resonance imaging as useful navigation tool in conjunction with endoscopy; this makes anatomical orientation easier after brain shift and cerebrospinal fluid drainage. It can also provide an intraoperative updated information about the septations which are not yet fenestrated, which increases the chance of fenestration of a greater number of loculations [38].

12.9.4.4 Operative Findings

Usually, it is impossible to see the normal features of the ventricular system because the anatomy is severely muffled. Differentiating cyst wall from ependyma is very important; the cyst wall is mobile with cerebrospinal fluid pulsations; and the wall thickness is variable (translucent in early cases). Previous intraventricular hemorrhage might give yellow discoloration to ependyma in many patients, and glial tufts are frequently present. It was also noticed that all patients with complicated hydrocephalus who presented at late stage are suffering from more anatomical disruption and their septations are thicker than other cases. Accordingly, long delay before surgical intervention is usually associated with bad prognosis [1].

12.9.4.5 Endoscopic Cyst Fenestration

Cyst fenestration can be done by using different methods such as bipolar electrode, flexible fiberscope, saline torch, and argon or YAG laser. An avascular portion of the cyst wall is chosen as an ideal area for perforation in order to avoid any bleeding. A

very wide fenestration has been recommended [1], because there is high risk of postoperative reclosure of small-sized openings due to the inflammatory nature of the disease and because of the low-pressure differential existing across the cyst walls (Figs. 12.1 and 12.2). Enlarging the fenestration is performed using either Fogarty balloon catheter, forceps, or scissors [1, 22].

Devascularizing the cyst wall might be performed by coagulating its blood supply in order to avoid recurrence. Pulsed irrigation using lactated Ringer is prophylactic against thermal injury and ventricular collapse. If any bleeding occurs intraoperatively, it is usually controlled by using irrigation and/or coagulation. It is possible to make assessment about successful fenestration by watching saline jet bubbles moving during surgery within the created fenestrations. The intraoperative contrast-enhanced ultrasound ventriculography, using an aerated saline flush technique, can be used to confirm successful endoscopic cyst fenestration [31].

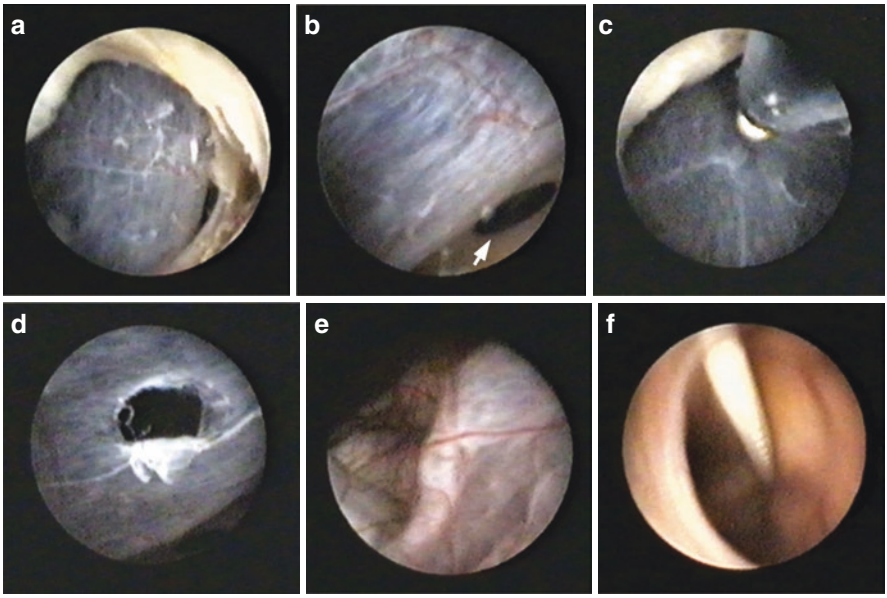

Fig. 12.1 Intraoperative photographs. (**a**) The cyst wall before fenestration looks bluish in color. (**b**) The cyst is not adherent to the ependyma. Arrow indicates the FOM obstructed by the cyst. (**c**) Bipolar electrode coagulates the cyst wall and makes an initial perforation. (**d**) The resulting endoscopic ventriculocystostomy. (**e**) The cyst is collapsed at the end of the procedure with opening of the FOM and restoration of the CSF pathways. (**f**) After performing the ECF and removing the old malfunctioning ventricular catheter, a new one is placed in the optimal position under direct visualization in order to drain both the cyst and the ventricular system. (Reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2013)

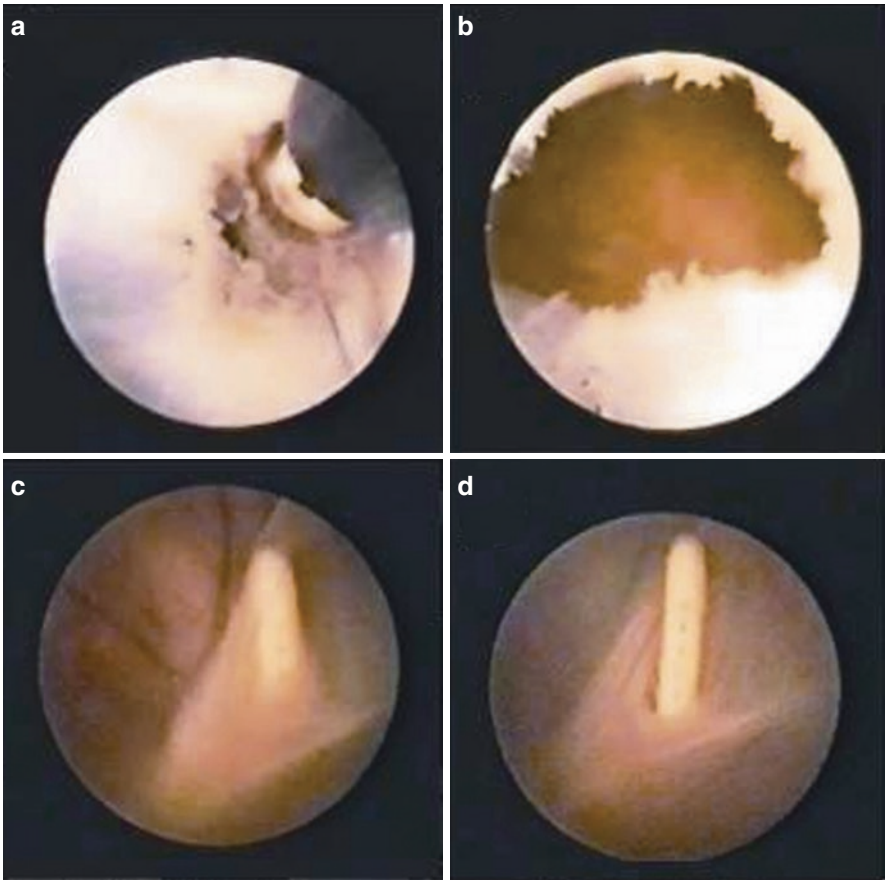

Fig. 12.2 Intraoperative photographs. (**a**) Showing bipolar electrode coagulating the cyst wall and making initial perforation. (**b**) Very wide fenestration is done in order to avoid reclosure. Note yellow discoloration due to previous intraventricular hemorrhage. (**c**) Pre-existing ventricular catheter is seen obstructed by adherent membranes. (**d**) Tip of the catheter after being dissected so that it can be withdrawn safely without risking intraventricular hemorrhage. (Reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2008)

12.9.4.6 Septum Pellucidotomy

It can be used in treating unilateral hydrocephalus, eliminating the need of implanting two shunts, and sometimes completely avoiding shunts. Identifying the septum pellucidum intraoperatively in a patient with bilateral hydrocephalus is easily accomplished; nevertheless, in patients with unilateral hydrocephalus, it is usually difficult to recognize the septum pellucidum intraoperatively without using neuronavigation.

It is advised to locate the burr hole more laterally than the standard location (5–6 cm from midline). Rigid endoscopic lens is introduced through the small

lateral ventricle directed to the septum pellucidum. Reaching the septum pellucidum by introducing the endoscopic lens via the dilated ventricle is a risky procedure, simply because the opposite ventricle is non-dilated and penetrating lateral wall of the contralateral ventricle is a high possibility. It is better to avoid any delay between introducing the endoscopic lens inside the lateral ventricle and perforating the septum pellucidum because cerebrospinal fluid can be lost resulting in an error due to brain shift.

It is well-known that the septum pellucidum consists of an avascular tissue, and the procedure of septostomy can be usually done safely; however, it is important to be careful not to injure the fornix or corpus callosum. Anatomically, always keep in mind that the ideal area of septum pellucidum for fenestration is usually located above and in front of the Monro foramen, simply because this is the thinnest part. Using cautery or laser is extremely helpful in performing the septum pellucidotomy procedure; it offers a good opportunity to perform a wide fenestration. Blood vessels should never be seen during this procedure; if they are encountered or if there is significant hemorrhage, this might be an indicator that the endoscope is passing in a wrong trajectory, going inside or at a higher level than the corpus callosum [39].

12.9.4.7 Endoscopic Third Ventriculostomy

Performing endoscopic third ventriculostomy in patients with multiloculated hydrocephalus is technically very difficult if not impossible, because of the significant anatomical changes induced by the disease in the ventricular system, and the third ventricle could not be easily recognized. It has been reported that the role of endoscopy is limited to fenestration, and most of the patients especially infants will still need shunting to treat the hydrocephalus due to immaturity of the subarachnoid cerebrospinal fluid dynamics. Moreover, the pathophysiological mechanism that are initially responsible about creation of the septations are responsible about the deficient absorptive capacity of the subarachnoid space, due to scarring of arachnoid granulations [39]. However, this procedure has been done successfully, and it succeeded to eliminate the need for shunting in some studies [1].

12.9.4.8 Aqueductoplasty

This procedure can be used in the treatment of premature neonates with trapped fourth ventricle. In these patients, the fourth ventricle can be fenestrated and connected with the occipital horn or with the lateral ventricular trigone. Aqueductoplasty might be a suitable procedure if the trapped fourth ventricle is confined within the posterior fossa.

The flexible endoscope is used in treating these patients; it is inserted via a Kocher burr hole to the third ventricle through the lateral ventricle. The Sylvian aqueduct is recognized, then the membrane covering the orifice is perforated using angioplasty balloon catheter, and it is dilated by inflating the balloon. It is important

to observe the flow of cerebrospinal fluid through the dilated canal indicating success of the procedure. A small tube can be implanted in the aqueduct to ensure its patency.

This procedure is not without risks; complications include stent dislodgment and/or migration, and possibility of injuring the tegmentum of the midbrain (ventrally) or the tectal plate (dorsally), with consequent postoperative dysconjugate eye movements, which usually resolves with time [27, 39, 40].

12.9.4.9 Endoscopic Shunt Retrieval

Ventricular catheters adherent to the choroid plexus or embedded in scar tissue can be more safely removed under endoscopic visualization without risking intraventricular hemorrhage. YAG laser can be used to dislodge the catheter from the embedded scar tissue by cutting along the interface of the scar and the tube. Irrigation should be discontinued when you start firing the laser because it causes movement of the cyst wall and the choroid plexus. Working through fluid medium by using irrigation is important in order to decrease the risk of thermal damage to surrounding brain structures. If the embedded ventricular catheter was implanted initially through an occipital approach, an anterior coronal approach is recommended so that laser can be directed in a line perpendicular to the shunt tube [14].

Concerning pre-existing nonfunctioning shunts with previously implanted shunts through occipital or posterior parietal burr holes, I recommend performing another burr hole 2–3 cm above the old burr hole; the endoscope can then be introduced parallel to the proximal catheter with slight inclination toward the catheter tip. Extreme difficulty has been encountered in retrieving a pre-implanted proximal catheter in 33% of patients with multilocular hydrocephalus. Bipolar diathermy probe was used to dissect the tip of the catheter from adherent membranes; it was then dislodged and pulled safely without causing intraventricular hemorrhage. In conclusion, retained pre-existing nonfunctioning proximal catheters in patients with multilocular hydrocephalus could not be retrieved safely without using the endoscopic procedure [1].

12.9.4.10 New Shunt Placement

Most neurosurgeons recommend using external ventricular drainage routinely after the endoscopic procedure and postpone new shunt placement to another session [25]. Personally, I don't use external ventricular drainage in these patients except if there is intraoperative bleeding. External drainage can result in collapse of the cyst, and it can initiate postoperative reclosure of fenestrations because it interferes with pressure gradients. If new shunt implantation is required, I prefer to implant it at the same sitting of endoscopic procedure and not at a later date [1].

When old proximal catheter is retrieved, a new shunt tube is placed in the proper location guided by endoscopy. Both procedures, shunt removal and shunt

implantation, are performed at the same sitting with the endoscopic procedure. Nevertheless, if there is any sort of intraoperative bleeding, it will be much better to perform external ventricular drainage and to delay shunt implantation, in order to avoid shunt malfunction due to the presence of bloody cerebrospinal fluid [1].

New shunt placement can be performed endoscopically using different methods; the proximal tube can be loaded to the endoscope with the tip exposed for better visualization. The tube is then inserted inside the ventricular system via a proper trajectory; the direction of proximal shunt tube should be monitored continuously using the endoscope in order to confirm proper positioning. If the position is inappropriate, the catheter is pulled out and the trajectory is corrected.

Another technique, which has been used by many neurosurgeons, is performed by using a rod lens endoscope system; a special peel-away shunt catheter is introduced inside the ventricle, and endoscopic lens is then inserted. In such way, the proper catheter location is confirmed and the length of the proximal tube can be properly estimated. The endoscope is then withdrawn, and the catheter is implanted inside the ventricular system, with the desired estimated length. The peel-away catheter is withdrawn, whereas the proximal tube is gently held with a non-toothed forceps, implanting the proximal catheter in the correct position [41]. With the new advancement in technology, new ventricular shunt catheters can be also placed in the proper position guided by ultrasound [31].

12.9.4.11 Repeated Endoscopic Procedure

In a study including a group of children suffering from multilocular hydrocephalus which were operated by endoscopy, the incidence of repeated endoscopic procedure was 33% (mean follow-up of 30 months). At the second operation, unpunctured cysts were detected in 21% and reclosure was detected in 12.5%. An important observation was reported; children in whom shunts were placed prior to fenestration showed a 7.5 risk of having repeated endoscopic procedure more than children in whom fenestration was performed prior to shunting [1].

In another study including a group of patients suffering from unilocular hydrocephalus which were operated by endoscopy, the incidence of repeated endoscopic procedure was 48.4% (mean follow-up of 4.3 years). At the second operation, the fenestration was found to be closed in all patients, and a repeated endoscopic fenestration was done in all of them. An important observation was reported; children in whom shunts were placed prior to fenestration showed a 7.4 risk of having repeated endoscopic procedure more than children in whom fenestration was performed prior to shunting [28].

While another factor might be contributing, which is the severity of the disease in the first group (children in whom shunts were placed prior to fenestration), which might explain the increased incidence of repeated endoscopic procedures, however, such assumption is not considered to be valid, because the difference in incidence of recurrence between both groups was highly significant. The incidence of 13% repeat rate encountered when endoscopic fenestration was done prior to shunt

insertion is comparable to the 16% incidence detected in a group treated by microsurgery [7]. It is recommended that parents of the children suffering from complex hydrocephalus should be aware of the possibility of repeat operations, and the importance of monitoring these children both clinically and radiologically [37].

The considerable difference between the high incidence of repeated endoscopic procedure in patients operated by shunting prior to endoscopic fenestration versus patients on whom endoscopic fenestration was done prior to shunt operation (highly significant, $p < 0.001$) makes an evident conclusion that establishing an early diagnosis and offering an early treatment are very important in order to obtain the best results in the management of these children. The better surgical outcome encountered in the second group (children in whom fenestration was performed prior to shunting), might be attributed to the thinner ventricular membranes, technically easier perforation, less vascularity, and less possibility of re-closure [1].

When shunt systems are handicapped or nonfunctioning due to the presence of high degree of compartmentalization, the aim of the endoscopic procedure is to restore communication between the different compartments so that a single ventricular shunt tube will drain all the ventricular cysts. However, it is usual that patients with multiloculated hydrocephalus require multiple endoscopic procedures, simply because the disease has often not yet reached its final stage when the patient presented to clinical consultation and so postoperative recurrence or reclosure is expected in most of these patients [1].

12.10 Complications

There are few articles available in the literature reporting the morbidity associated with endoscopy if used in treating patients with complicated hydrocephalus. Major complications of the endoscopic procedure include ventriculitis, intraoperative bleeding, injury to brain structures, and leakage of cerebrospinal fluid. Ventriculitis and intraventricular bleeding might induce new septa formation. Proper preoperative planning and trying to establish an intraoperative anatomical orientation are paramount, it increases safety of the procedure, and it reduces the risk of occurrence of postoperative complications. Anatomical disorientation can be overcome to a big extent by using intraoperative ultrasound and/or navigation [25].

It has been claimed that the possibility to control intraoperative bleeding during endoscopy is suboptimal, and this can lead to significant postoperative morbidity [7]. Nevertheless, I didn't encounter any serious bleeding during the management of these patients using endoscopy. Among a group of children suffering from multilocular hydrocephalus operated using the endoscopic procedure, intraoperative bleeding occurred in 8% of patients. The bleeding was minimal; it stopped spontaneously in a few minutes by the help of irrigation without using coagulation; the endoscopic procedure was successfully completed in all patients without postoperative deficits or seizures [1]. Nevertheless, it has been advocated that intraoperative bleeding during endoscopic fenestration is considered to be one of the important

factors predicting bad outcome, simply because it increases the risk of postoperative reclosure and recurrence [28, 42].

There were no mortalities and complications were minimal; leakage of cerebrospinal fluid was encountered in 8%, and it stopped conservatively within a few days [1]. Although the mortality rates have decreased over years due to the advancement of equipment and technology, the quality of life in many of these patients is still poor. It has been reported that 10% of these patients have minor learning disabilities and the majority present with serious cognitive deficits [22].

12.11 Outcome and Prognosis

Although many studies address the surgical outcome of treating these patients among the short-term follow-up, studies evaluating the quality of life among the long-term follow-up are lacking. Many factors have an impact on the surgical outcome, mainly the surgical procedure adopted and the type of complicated hydrocephalus. The ventricular complexity and the treatment history both play an important role in determining the success of treatment [20]. The outcome can be assessed in many ways including improvement of hydrocephalus, eliminating the need for shunts, reducing shunt revision rate, and simplifying complex shunt systems. Unilocular hydrocephalus is easier to treat by endoscopy, and it is associated with better outcome than multilocular hydrocephalus. In one study, 84% of patients with unilocular hydrocephalus who underwent endoscopic fenestration remained shunt-free, or they didn't require new shunt implantation [25].

In a study including a group of patients with multilocular hydrocephalus operated by the endoscopic procedure, hydrocephalus improved in 75% of patients; significant decrease in cyst size and/or ventricular size with restoration of normal ventricular architecture was detected in postoperative imaging (Figs. 12.3, 12.4, and 12.5). The need for shunt placement was avoided in 12.5% of patients; in these patients endoscopic third ventriculostomy was successfully performed [1].

In a subgroup of children with nonfunctioning pre-implanted shunts, endoscopy reduced shunt revision rate from 2.7/year prior to endoscopic fenestration (mean observation 12.3 months) to 0.25/year following the endoscopic fenestration (mean follow-up of 32.2 months) (highly significant, $p < 0.001$) (Table 12.1). Simplification of complex shunts was achieved in 100% of patients [28].

In spite of the improvement of surgical techniques and equipment over time, the prognosis of patients with multilocular hydrocephalus is still poor. One of the most important reasons is that the pathophysiological mechanisms that caused septations are responsible for deficiency of absorption capacity due to scarring of arachnoid

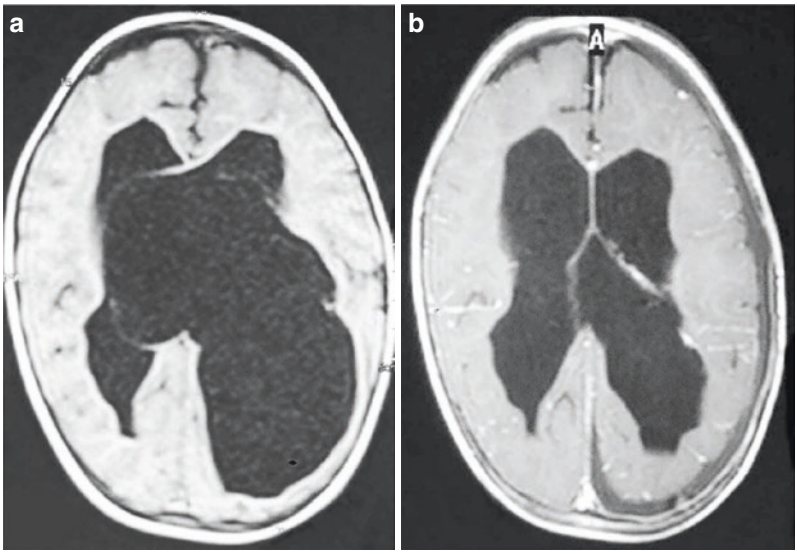

Fig. 12.3 (**a**, **b**) Axial T1-weighted MR imaging. (**a**) Preoperative image showing huge intraventricular neuroepithelial cyst obstructing both foramina of Monro resulting in hydrocephalus. (**b**) Postoperative image performed 3 months after ECF showing significant reduction in both cyst and ventricular size with restoration of ventricular architecture. (Reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2013)

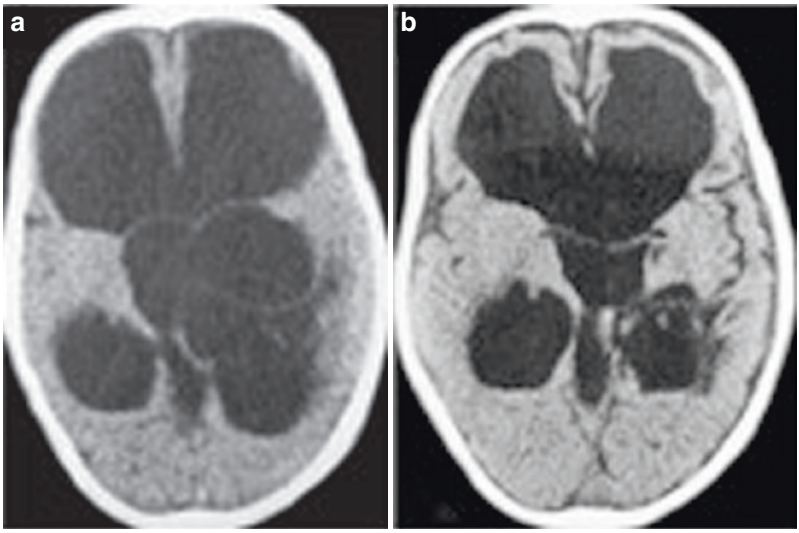

Fig. 12.4 (**a**) Preoperative CT scan axial view of a 1.5-year-old female patient with multiloculated hydrocephalus (**b**) postoperative CT scan performed 3 months after surgery showing improvement of hydrocephalus, increase in cerebral mantle, opening of subarachnoid space, and restoration of ventricular architecture. This patient has been operated through a biportal technique (left coronal + left occipital burr holes). (Reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2008)

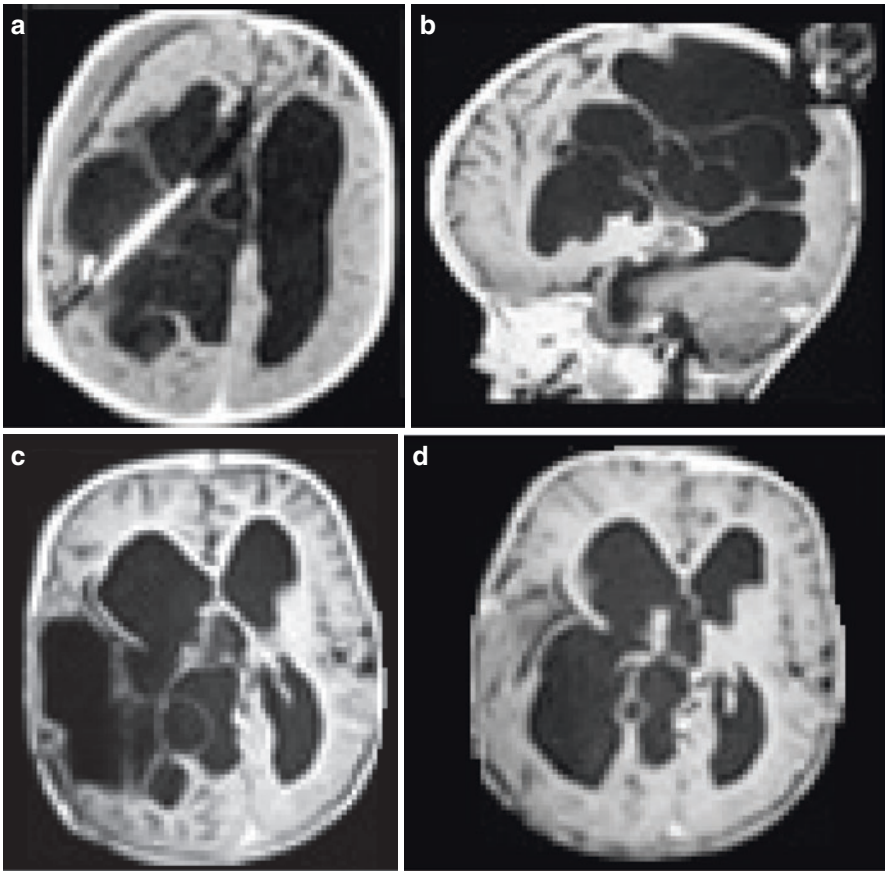

Fig. 12.5 (**a**, **b**) Preoperative axial MR imaging of a 7-month-old male patient with multiloculated hydrocephalus due to intrauterine toxoplasmosis infection. (**c**) Axial MR imaging performed 3 months after surgery showing improvement of hydrocephalus. (**d**) Axial MR imaging performed 1 year after surgery showing improvement of hydrocephalus increase in cerebral mantle, and restoration of ventricular architecture. (Reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2008)

Table 12.1 Age, observation period in months (mos), and shunt revision rates before and after endoscopic cyst fenestration (ECF), in nine patients with uniloculated hydrocephalus presented with pre-existing shunts (reprinted with permission from J Neurosurg Pediatr, El-Ghandour 2013)

		Observation period (mos)		No. of revisions		No. of revisions/ year	
Case No.	Age at ECF (mos)	Pre-ECF	Post-ECF	Pre-ECF	Post-ECF	Pre-ECF	Post-ECF
1	9	6	36	2	0	4	0
2	15	8	32	2	1	3	0.38
3	49	15	25	2	1	1.6	0.48
4	7	3	24	1	0	4	0
5	30	13	36	3	1	2.76	0.33
6	10	5	42	1	0	2.4	0
7	58	12	18	2	1	2	0.66
8	35	10	30	2	1	2.4	0.4
9	13	6	48	1	0	2	0
Mean	25.1	8.66	32.33	1.77	0.55	2.68	0.25
S.D.	18.8	4.06	9.35	0.66	0.52	0.85	0.25
Median	15	8	32	2	1	2.4	0.33

granulations. Consequently, most of these patients after performing endoscopic cyst fenestration still need implanting a ventriculoperitoneal shunt [1, 20].

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Chapter 13
Apert Syndrome: Selection Rationale for Midface Advancement Technique

Cassio Eduardo Raposo-Amaral, Enrico Ghizoni, and Cesar Augusto Raposo-Amaral

13.1 Introduction

Apert syndrome is characterized by a wide spectrum of clinical features including premature fusion of the cranial and facial sutures (craniofaciosynostosis) and complex syndactyly of the upper and lower limbs [1]. Apert patients always present abnormally retruded maxillary morphology, varying degrees of exophthalmos due to shallow orbits (exorbitism), and significant multilevel airway obstruction [2]. Additionally, Apert patients frequently present elevated intracranial pressure due to craniosynostosis [3].

Based on a myriad of clinical features, comprehensive Apert syndrome management should begin at early infancy in a multidisciplinary setting. The paramount surgical goals in Apert syndrome treatment are (1) alleviation of elevated intracranial pressure, (2) protection of the ocular globe, (3) improvement of airway status, (4) reduction of facial morphologic disproportions without prejudicing maximum cognitive development, (5) achieving full use of upper and lower limbs, (6) providing five-digit hand function and dexterity [4–6], and (7) improving facial and limb aesthetics [7] (**Reference 4, Level of Evidence: Therapeutic, IV**).

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Although decisions as to the specific type of midface advancement to be performed and the technique selected could have major impacts on all of the aforementioned craniofacial-related goals, one of our primary objectives is to ensure that by the time our Apert syndrome patients reach 8 years of age, they no longer present any clinical or radiological signs of elevated intracranial pressure. In order to achieve this specific objective, we perform posterior vault distraction osteogenesis and/or fronto-orbital advancement at early infancy [7–9].

Assuming that elevated intracranial pressure has already been effectively treated at early infancy, the decision on the type of midface advancement to be performed to address excessive ocular globe protrusion and airway obstruction (both of which may significantly vary in Apert syndrome patients) should be based on the individual facial morphologic characteristics of each Apert patient.

Taylor and Bartlett described four specific surgical techniques for midface advancement, and addressed the potential costs and benefits of each procedure [1].

This article will review and discuss the six midface advancement surgical techniques that are currently in use at our hospital to treat Apert syndrome patients. In addition, this article will also address the patient selection criteria rationale for each of these six surgical techniques, which depends upon the most common craniofacial characteristics presented by each Apert patient. As per Hopper, the decision as to which type of midface advancement technique to be used needs to be tailored to the specific facial dysmorphology presented by the individual patient [10–12].

13.2 Midface Advancement

Of the six types of midface advancement with distraction osteogenesis performed on Apert syndrome patients, four of these procedures are subcranial, and two are transcranial. Distraction protocol is based on a 5–7-day latency period followed by an activation period, during which the midface is advanced at a rate of 1 mm per day. After the activation period is concluded, there is an 8-week consolidation period.

These six surgical techniques are identified below.

Subcranial (1) Traditional Le Fort III, (2) low Le Fort III, (3) Le Fort II with zygomatic repositioning, and (4) zygomatic rotation with maxillary expansion

Transcranial (5) Monobloc frontofacial advancement and (6) facial bipartition monobloc

The following craniofacial features presented by Apert syndrome patients can be effectively addressed with midface advancement [2, 13].

Craniofacial and soft tissue characteristics:

1. Turribrachycephaly with forehead retrusion, mild to severe forehead asymmetry and supraorbital grooves.

2. Shallow orbits resulting in mild to severe ocular globe protrusion (also known as exorbitism).
3. Hypertelorism and vertical orbital dystopias due to rotation of the orbits.
4. Maxillary hypoplasia (vertically deficient) and retrusion, and an inverted "V" maxilla, defined as an abnormal maxilla in an abnormal position [14].
5. Anterior open bite (characterized by counterclockwise rotation of the occlusal plane) and lateral crossbite.
6. A short nasal dorsum ("parrot beak") nose.
7. Overly wide face.
8. Downslanting of the palpebral fissure, characterized by lateral canthi that are located lower than the medial canthi (also known as reverse canthal tilt). This is a common characteristic of the syndromic Apert face.

13.3 Grading System

A grading system that stratifies the effect of each procedure on the different types of facial features as major, moderate, and mild is shown in Table 13.1, and described below (Table 13.1) (Supplemental Digit Content 13.1).

Table 13.1 Table displaying the effect of each midface advancement technique on the most prevalent clinical features of Apert syndrome patients

Facial characteristics	Le Fort III	Low Le Fort III	Le Fort II + ZR	ZR + ME	MB	FB + MB
Severe reverse canthal tilting	–	++	+++	–	–	+++
Hypertelorism	–	–	–	–	–	+++
Vertical orbital dystopia	–	–	–	–	–	+++
Exorbitism[a]	++	+	++	+	+++	+++
Nasal lengthening	+++	+++	+++	–	+	+
Divergent strabismus	–	–	–	–	–	++
Inverted "V" maxilla	–	–	–	+++	–	+++
Midface lengthening[b]	++	+++	+++	+	++	++

Table based on the most prevalent clinical features found in Apert syndrome patients to be addressed with midface advancement. Procedures described: FB + MB = facial bipartition monobloc, MB = monobloc frontofacial advancement, Le Fort III = traditional Le Fort III, Le Fort II + ZR = Le Fort II with zygomatic repositioning, ZR + ME = zygomatic rotation with maxillary expansion. Grading system varying from + to +++ (mild, moderate, major)

[a] Exorbitism correction depends upon the magnitude of sagittal orbital advancement and not solely on the type of osteotomy. Most Apert syndrome patients present mild to moderate exorbitism. Osteotomies involving the entire orbital cone have a greater impact on improving orbital volume

[b] Midface lengthening is defined as the ability to bring the central midface forward

13.3.1 Subcranial Techniques

13.3.1.1 Traditional Le Fort III

The first reported use of the midface advancement procedure in a syndromic craniosynostosis patient was by Gillies in 1950 [15], but as Gillies neither followed Le Fort III osteotomy lines nor used bone grafts and rigid fixation, exorbitism correction was limited [16]. Subsequently in 1967, Paul Tessier in Rome described a midface advancement technique that combined step osteotomies on the frontal nasal and malar regions, sagittal splitting of the lateral orbital wall, and generous bone grafts on the osteotomy sites along the frontal glabellar region, along the medial orbital walls posterior to the lachrymal crests, orbital floor, lateral orbital wall, zygoma, maxillary tuberosity, and pterygoid processes [17–19]. This surgical procedure later became known as the Le Fort III Tessier I osteotomy [16].

The Le Fort III osteotomy represents the most common subcranial procedure utilized to treat patients with syndromic craniosynostosis. The Le Fort III osteotomy advances the nasal bone; medial, inferior, and lateral orbits; and the zygomatic body and maxilla. As this procedure does not also advance the forehead, turribrachycephaly characterized by forehead retrusion may become even more pronounced postoperatively, but can be effectively addressed with a subsequent procedure.

The osteotomy per se has less impact on the configuration of lateral and medial canthi, as both ligaments are merely brought forward simultaneously with no differential movement. As the Le Fort III has a major effect on nasal lengthening, this procedure should not be used in treating the rare subgroup of Apert syndrome patients who already present a long nose. As Le Fort III osteotomies do not involve the entire orbital cone, there is a moderate effect on exorbitism correction. Similarly, as Le Fort III does not enable differential forward movement, it has a moderate effect on midface lengthening. Depending on the surgeon's preference, either internal or external halo distractor devices can be utilized with the Le Fort III procedure (Figs. 13.1 and 13.2a, b).

13.3.1.2 Low Le Fort III

The low Le Fort III (or modified Le Fort III) has been successfully used at our hospital to treat Apert syndrome patients who have mild ocular globe protrusion combined with severe retrusion of the central midface, and moderate to severe downslanting of the palpebral fissure, without evidence of hypertelorism.

The osteotomy does not include the lateral orbital wall, as the lateral osteotomy is made in the zygomatic body instead. Thus, while the medial canthi are brought forward and downward, the lateral canthi remain in place, still attached to the bone, and can be suspended with lateral canthopexy if needed. The low Le Fort III is more

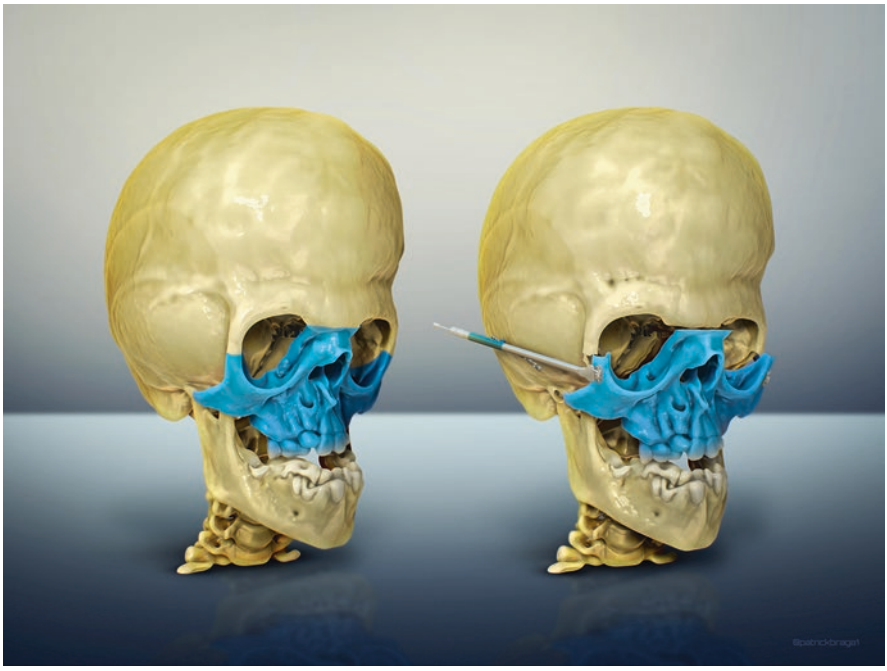

Fig. 13.1 Artistic drawings showing the osteotomy lines of traditional Le Fort III advancement

effective than the traditional Le Fort III in reducing the reverse canthal tilting. Due to the configuration of the low Le Fort III osteotomy, use of an external halo device postoperatively is mandatory. Our postoperative low Le Fort III preference is to use a palatal acrylic splint accompanied by an orthodontic headgear bow that is affixed with wires in the maxilla, which enables appropriate distribution of force of the external halo device during traction, counterclockwise rotation of the maxilla, and pivoting rotation at the nasoglabellar angle in order to reduce the impact of the midface advancement on nasal lengthening. A similar modified osteotomy was described by Fearon, and was utilized to prevent distortion of the upper eyelid caused by forward movement of the lateral orbits [20].

A transconjunctival incision with lateral canthotomy does not require coronal incision, and offers direct access to the zygoma, facilitating oblique lateral osteotomy of the zygoma, and direct visualization of the orbital floor, which creates adequate space for safe access to the medial orbital wall. The superior region of the medial orbital wall is osteotomized via a 3 mm upper eyelid incision using a small osteotome. The low Le Fort III has a major effect on nasal lengthening and midface lengthening, a moderate effect on severe reverse canthal tilting correction, and a mild effect on exorbitism correction (Figs. 13.3 and 13.4a, b).

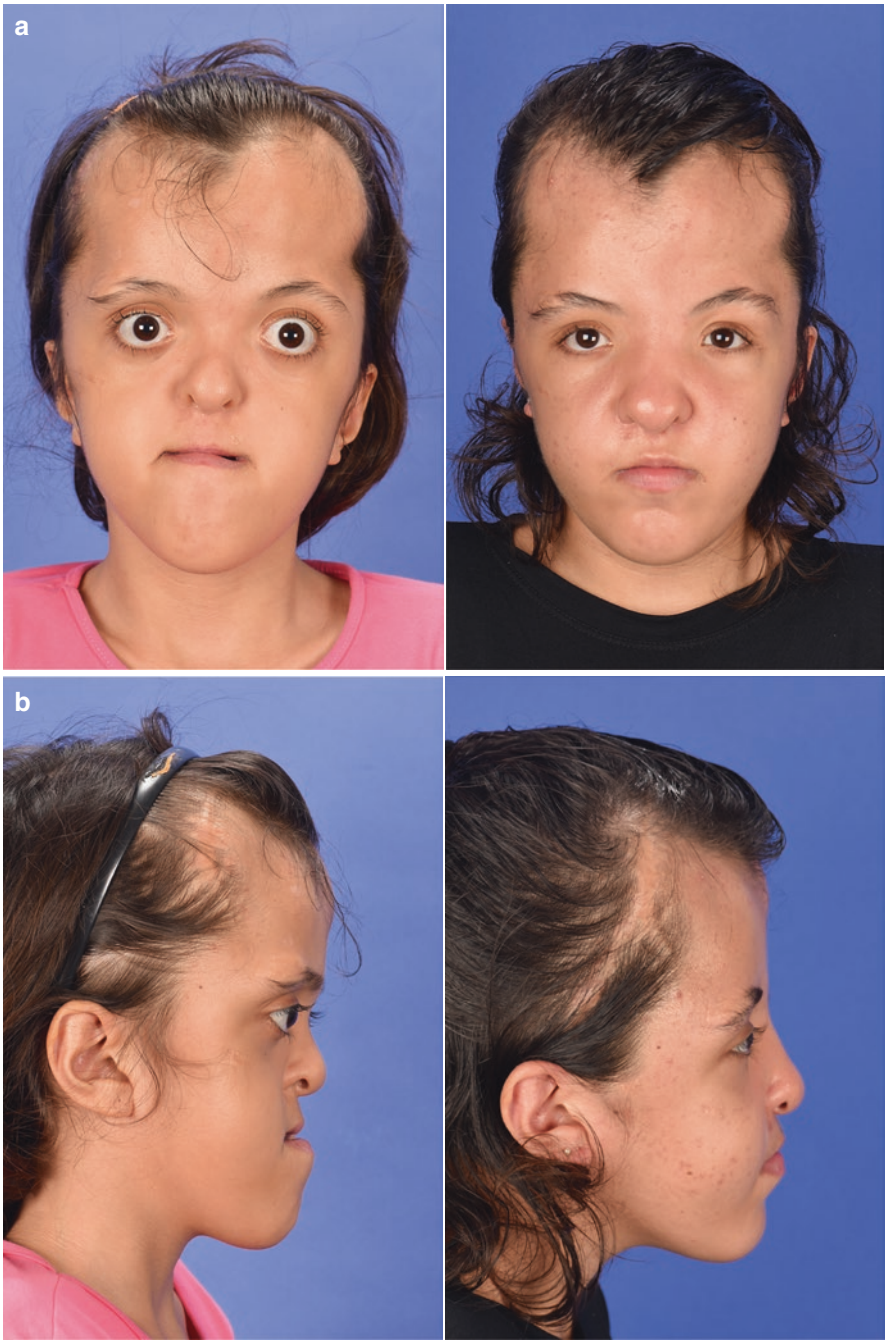

Fig. 13.2 (**a**) (*Left*) Preoperative frontal photograph of a 12-year-old Apert patient who underwent a traditional Le Fort III advancement. (*Right*) Postoperative frontal photograph of the same patient. (**b**) (*Left*) Preoperative lateral photograph of a 12-year-old Apert patient who underwent the traditional Le Fort III advancement. (*Right*) Postoperative photograph of the same patient

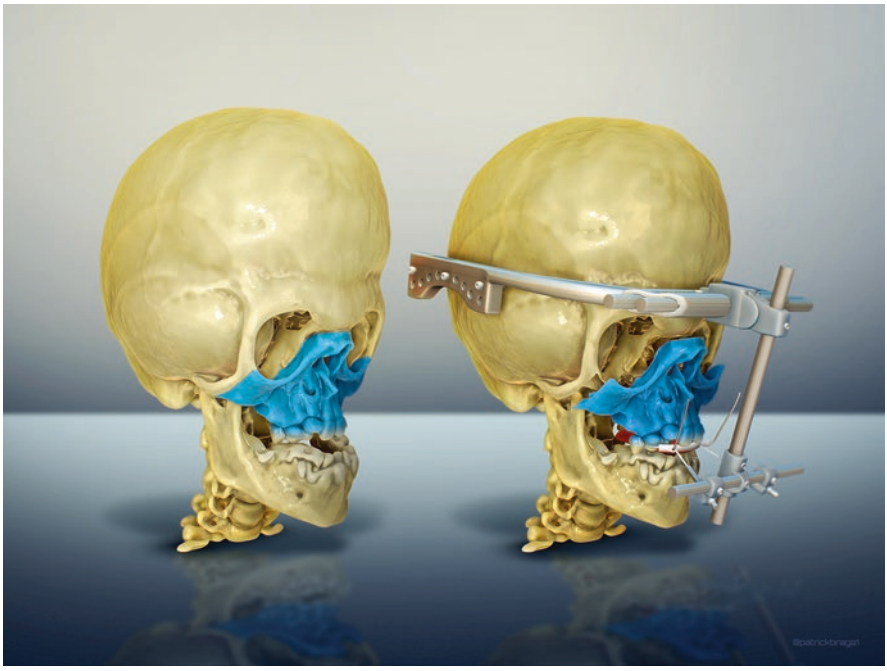

Fig. 13.3 Artistic drawings showing the osteotomy lines of the low Le Fort III advancement

13.3.1.3 Le Fort II with Zygomatic Repositioning

The Le Fort II with zygomatic repositioning was first described and popularized by Hopper [21] (**Reference 20, Level of Evidence: Therapeutic, III**), and involves differential movement of the central midface which is brought forward independently of the lateral orbits and zygomas, enabling both sagittal and vertical correction without orbital distortion [22–24]. The lateral orbits and zygomas are then advanced and affixed with plates and screws, while the central face is pulled forward via the external halo distractors, which enables maximum lengthening of the face. Similar to the low Le Fort III, the lateral canthi remain attached to the lateral orbit (which is suspended in this particular technique), while the medial canthi of the eyelids are brought forward with the Le Fort II segment, which then addresses the reverse canthal tilting. Hopper and collaborators advocate the use of a customized forehead implant for frontal recontouring simultaneous to the procedure [22].

Custom forehead implants have been successfully applied during subcranial procedures without any implant-related complications [25]. The benefits of providing simultaneous harmonious forehead convexity may outweigh the necessity of keeping patients intubated for an additional 48 h, to prevent air leakage from the nasopharynx to the forehead, and potential implant contamination. However, our surgical team prefers to extubate all patients, and addresses the forehead during a subsequent procedure.

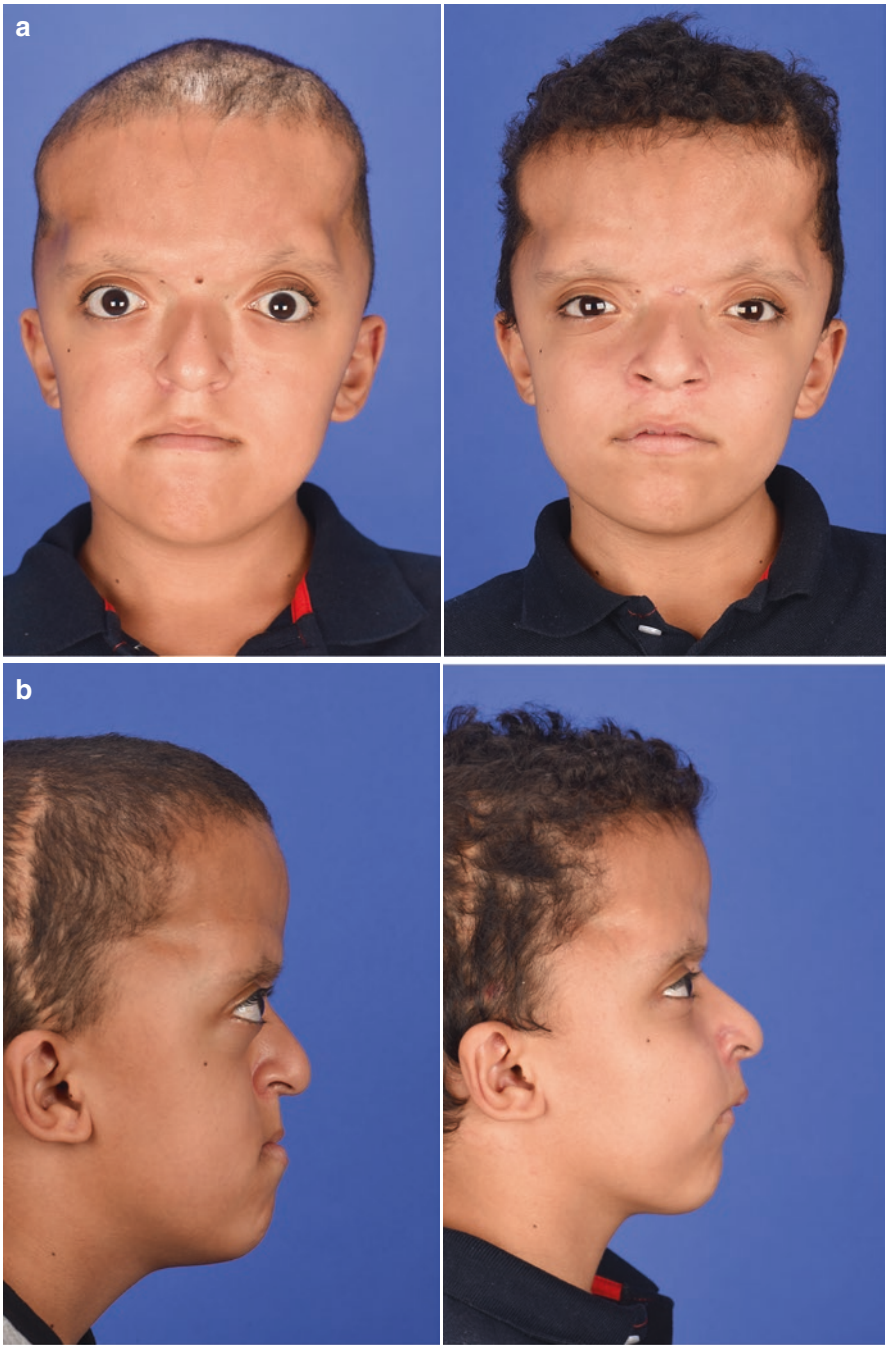

Fig. 13.4 (**a**) (*Left*) Preoperative frontal photograph of an 8-year-old Apert patient who underwent the low Le Fort III advancement. (*Right*) Postoperative frontal photograph of the same patient. (**b**) (*Left*) Preoperative lateral photograph of an 8-year-old Apert patient who underwent the low Le Fort III advancement. (*Right*) Postoperative photograph of the same patient

The Le Fort II with zygomatic repositioning has a significant role in Apert syndrome treatment, as the majority of Apert patients do not present severe ocular globe protrusion, as is frequently found in patients with severe cases of Crouzon and Pfeiffer syndromes.

The use of an external halo device following this specific procedure is mandatory due to the configuration of the osteotomy, which provides counterclockwise midface rotation. As this specific procedure is the most effective technique utilized in lengthening the Apert face, it may also cause a significant discrepancy between the maxilla and mandible, thereby requiring further mandibular advancement.

A recent study has shown that the critical region causing airway obstruction in Apert syndrome patients is the hypopharynx [26]. This finding appears to correlate with those Apert syndrome patients who have associated micrognathia (as shown in Figs. 13.5 and 13.6). These patients are ideal candidates for coordinated midface-mandibular distraction. The Le Fort II with zygomatic repositioning has a major effect on severe reverse canthal tilting correction, nasal lengthening, and midface lengthening, and a moderate effect on exorbitism correction (Figs. 13.5 and 13.6a, b).

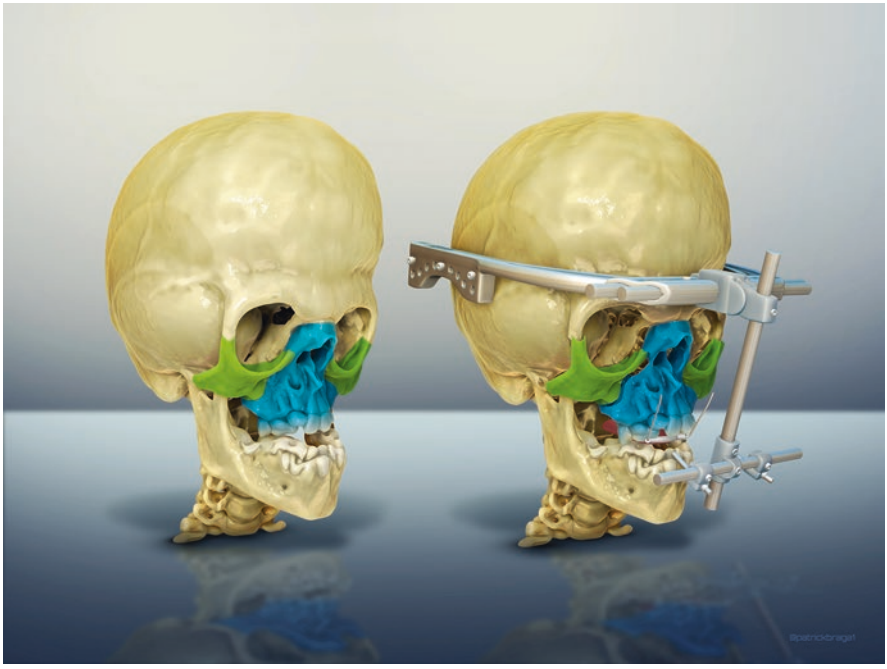

Fig. 13.5 Artistic drawings showing the osteotomy lines of the Le Fort II with zygomatic repositioning

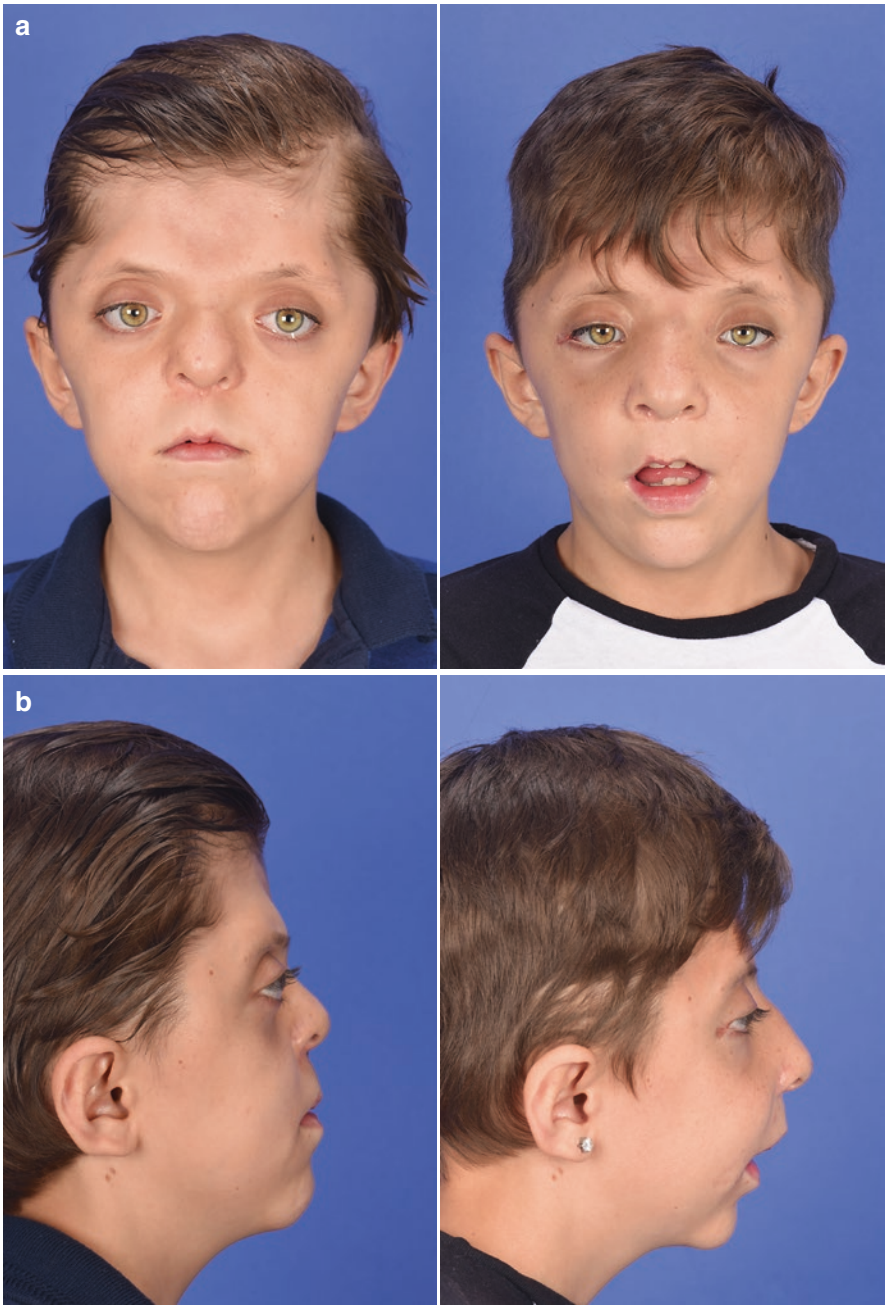

Fig. 13.6 (**a**) (*Left*) Preoperative frontal photograph of an 8-year-old Apert patient who underwent the Le Fort II with zygomatic repositioning. (*Right*) Postoperative frontal photograph of the same patient. (**b**) (*Left*) Preoperative lateral photograph of an 8-year-old Apert patient who underwent the Le Fort II with zygomatic repositioning. (*Right*) Postoperative photograph of the same patient

13.3.1.4 Zygomatic Rotation with Maxillary Expansion

Zygomatic rotation with maxillary expansion is a particular procedure that has not yet been specifically described in the literature for treatment of Apert syndrome patients. The osteotomy begins inside the pyriform aperture along the orbital floor, excluding the medial orbital wall, but includes the lateral orbit and zygomatic body. The inverted "V" maxilla is addressed by osteotomy of the palate, which extends along the anterior nasal spine, and divides the anterior maxilla into two halves. Additional transconjunctival incisions enable ample access for osteotomies of the orbital floor, zygoma, and lateral orbital wall.

As this specific procedure does not include the nasal bone, it is a particularly effective technique in treating the rare subgroup of Apert syndrome patients who have a long nasal dorsum, accompanied by mild ocular globe protrusion, a relatively mild (or none) discrepancy between the medial and lateral canthi, and mild or no clinical evidence of obstructive sleep apnea. The postoperative use of both an external halo distractor device and a palatal acrylic splint to stabilize the osteotomized maxilla, which provides a distraction vector and prevents misalignment, is mandatory. Zygomatic rotation with maxillary expansion has a major effect on inverted "V" maxilla correction, and a mild effect on exorbitism correction and midface lengthening (Figs. 13.7 and 13.8a, b).

13.3.2 Transcranial Techniques

13.3.2.1 Monobloc Frontofacial Advancement

In 1971, Tessier pioneered midface advancement using a fronto-orbital bar and frontal bone in segmental upper osteotomies [18]. The seminal principles described by Tessier served as the basis for creation of the monobloc frontofacial advancement technique by Ortiz-Monasterio, which mobilizes the craniofacial region in single bloc [16]. Ortiz-Monasterio asserted that a simultaneous mobilization of the roof, floor, medial, and lateral orbital walls with the anterior cranial base along with the zygomatic arch and pterygomaxillary suture would produce a more anatomic correction and natural appearance, and also stressed the necessity of performing the procedure in such a way that would provide a moderate degree of overcorrection. The length of the nose is preserved or slightly augmented, and relationship between the medial and lateral canthi does not change with the monobloc osteotomy. Monobloc frontofacial advancement has a major effect on exorbitism correction, a moderate effect on midface lengthening, and a mild effect on nasal lengthening (Figs. 13.9 and 13.10a, b).

Fig. 13.7 Artistic drawings showing the osteotomy lines of the zygomatic rotation with maxillary expansion

13.3.2.2 Facial Bipartition Monobloc

Facial bipartition monobloc using internal distraction devices was first described by the UCLA group in 2008 [27]. The Great Ormond Street Hospital (GOSH) group described a similar technique using an external halo device, and popularized the procedure with sequential studies [28–30] (**Reference 29, Level of Evidence: Therapeutic, III**).

In the facial bipartition monobloc procedure, medialization of the hemi-halves of the face, previously referred to as facial bipartition by Van der Muelen [31], is combined with monobloc advancement in a single bloc, in order to provide rotation to the orbits.

After completion of the monobloc osteotomies, a V-shaped osteotomy is marked and performed from the upper medial orbital border toward the nasal bone. If the patient also presents vertical orbital dystopia, this factor should be taken into account during the medialization maneuver in order to compensate for the vertical discrepancy between the orbits. The hemi-halves of the face are brought together and affixed with plates and screws.

Facial bipartition monobloc has a major effect on severe reverse canthal tilting correction, hypertelorism, vertical orbital dystopia, exorbitism, and inverted "V"

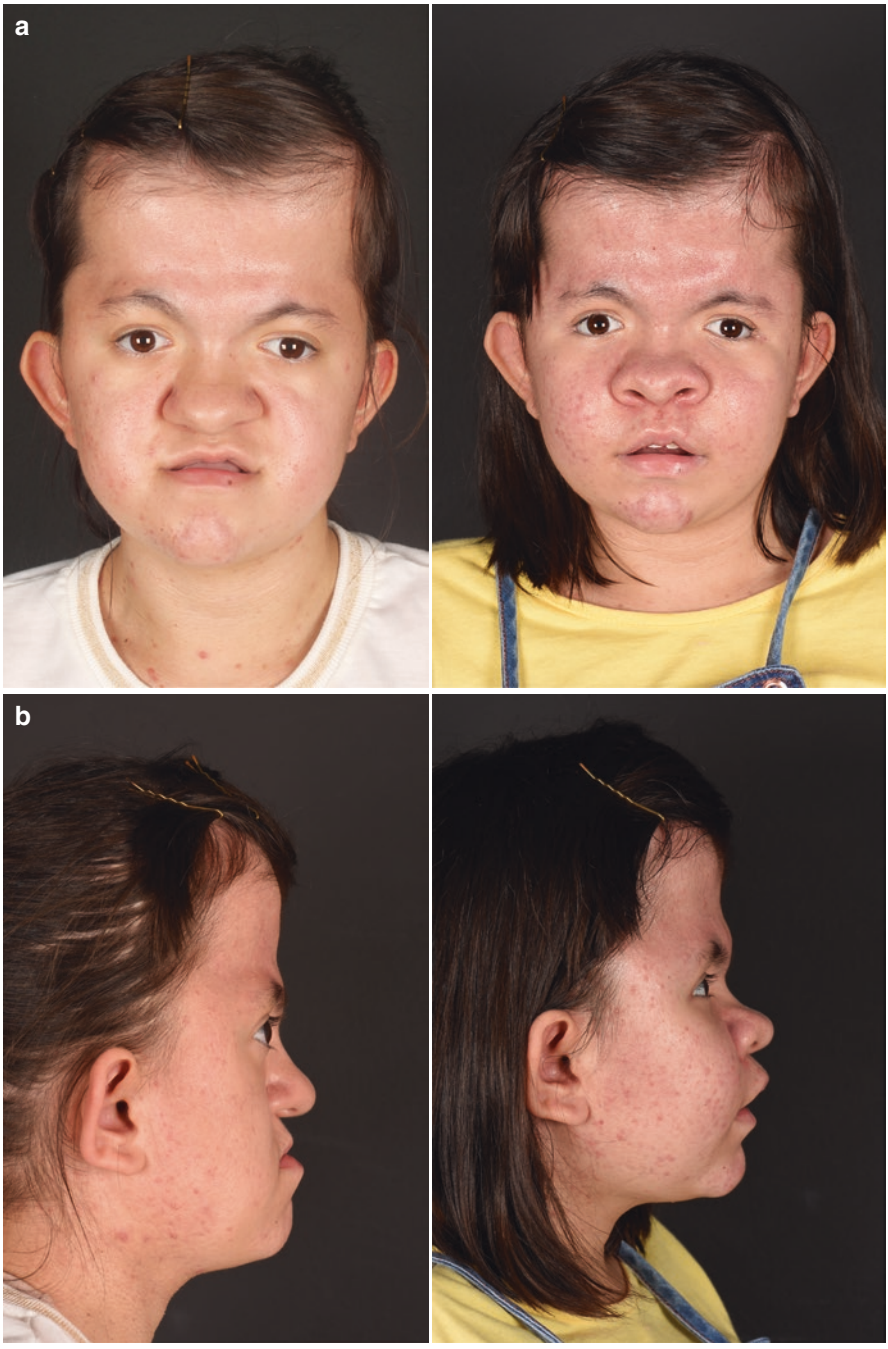

Fig. 13.8 (**a**) (*Left*) Preoperative frontal photograph of an 11-year-old Apert patient who underwent the zygomatic rotation with maxillary expansion. (*Right*) Postoperative frontal photograph of the same patient. (**b**) (*Left*) Preoperative lateral photograph of an 11-year-old Apert patient who underwent the zygomatic rotation with maxillary expansion. (*Right*) Postoperative photograph of the same patient

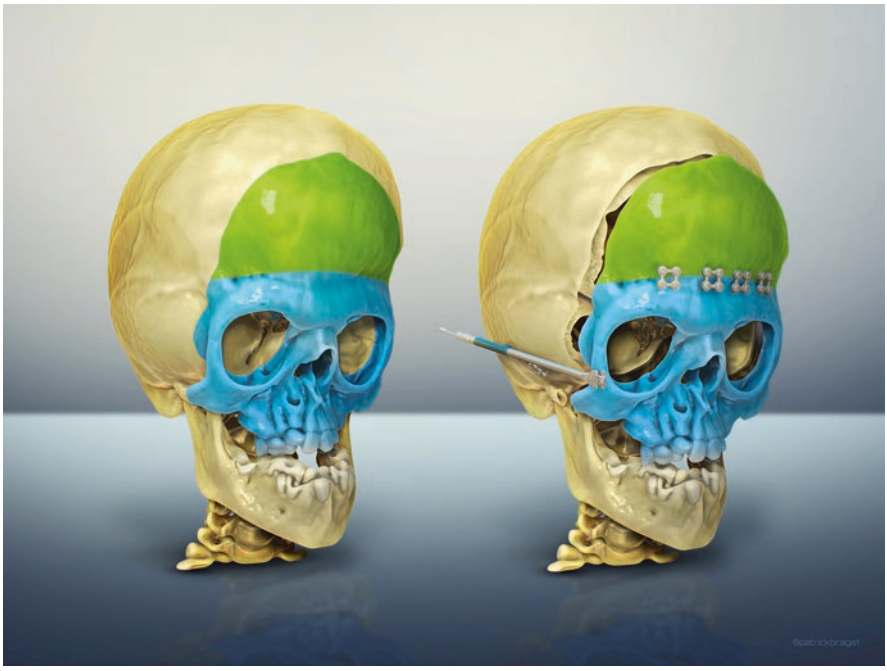

Fig. 13.9 Artistic drawings showing the osteotomy lines of the monobloc advancement

maxilla correction, a moderate effect on midface lengthening and divergent strabismus correction, and a mild effect on nasal lengthening [32, 33].

As recently pointed out by the GOSH group, spontaneous dental compensation resulting in amelioration of the frontal incisor diastema occurs without prejudicing posterior expansion at the molar region during the facial bipartition monobloc follow-up period [34]. Transverse posterior maxillary relapse and spontaneous dental compensation were observed in our group of Apert syndrome patients who underwent facial bipartition monobloc [33], and our patients who underwent the zygomatic rotation and maxillary expansion procedure. Therefore, we defer performance of orthodontic treatments until at least 6 months following facial bipartition monobloc and zygomatic rotation and maxillary expansion (Figs. 13.11 and 13.12a, b).

13.3.3 Management of the Lateral Canthi for Each Technique

Monobloc frontofacial advancement, traditional Le Fort III, and zygomatic rotation and maxillary expansion are techniques that do not provide differential movement between the lateral and medial orbits (and its insertion of the canthi); thus, the lateral canthus will need to be stripped and resuspended. As the lateral orbit is kept in

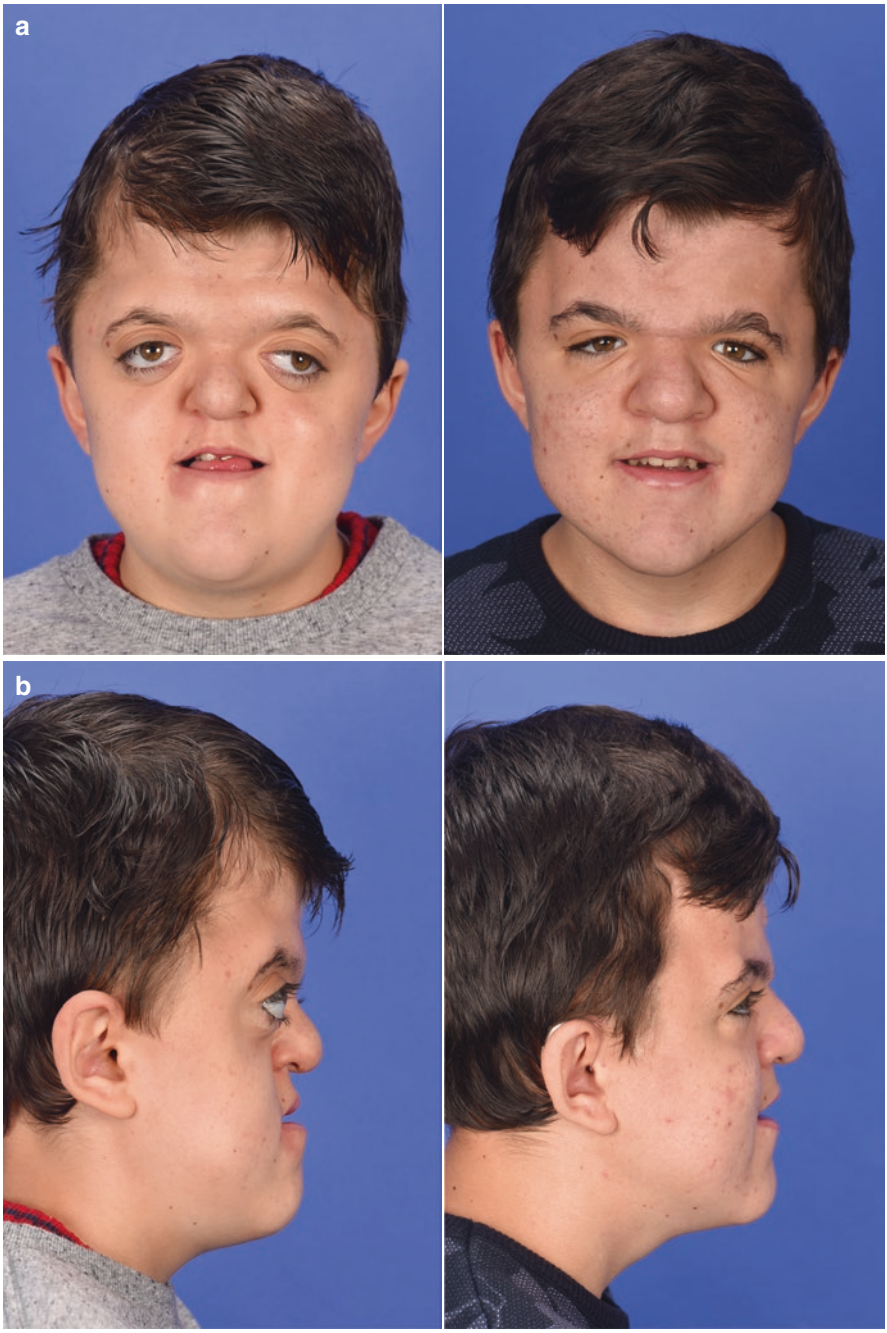

Fig. 13.10 (**a**) (*Left*) Preoperative frontal photograph of an 11-year-old Apert patient who underwent the monobloc advancement. (*Right*) Postoperative frontal photograph of the same patient. (**b**) (*Left*) Preoperative lateral photograph of an 11-year-old Apert patient who underwent the monobloc advancement. (*Right*) Postoperative photograph of the same patient

Fig. 13.11 Artistic drawings showing the osteotomy lines of the facial bipartition monobloc advancement

place, but the medial orbit and the medial canthi are brought downward in a low Le Fort III, the lateral canthus only needs to be resuspended, and not stripped.

Two midface advancement techniques that do provide differential movement between the lateral and medial orbits (and insertion of the canthi) are the facial bipartition monobloc and the Le Fort II with zygomatic repositioning, and they have a major effect on severe reverse canthal tilting correction. The lateral canthi do not need to be stripped, and resuspension can be performed as needed. These two procedures play a major role in destigmatizing the Apert syndrome face.

13.3.4 Occlusion Management

Anterior open bite is expected to occur in patients who undergo counterclockwise midface rotation, and is managed with dental elastics and orthodontia. The inverted "V" maxilla posterior crossbite in patients who do not undergo simultaneous procedures that expand the maxilla will require subsequent transverse expansion utilizing orthodontic devices.

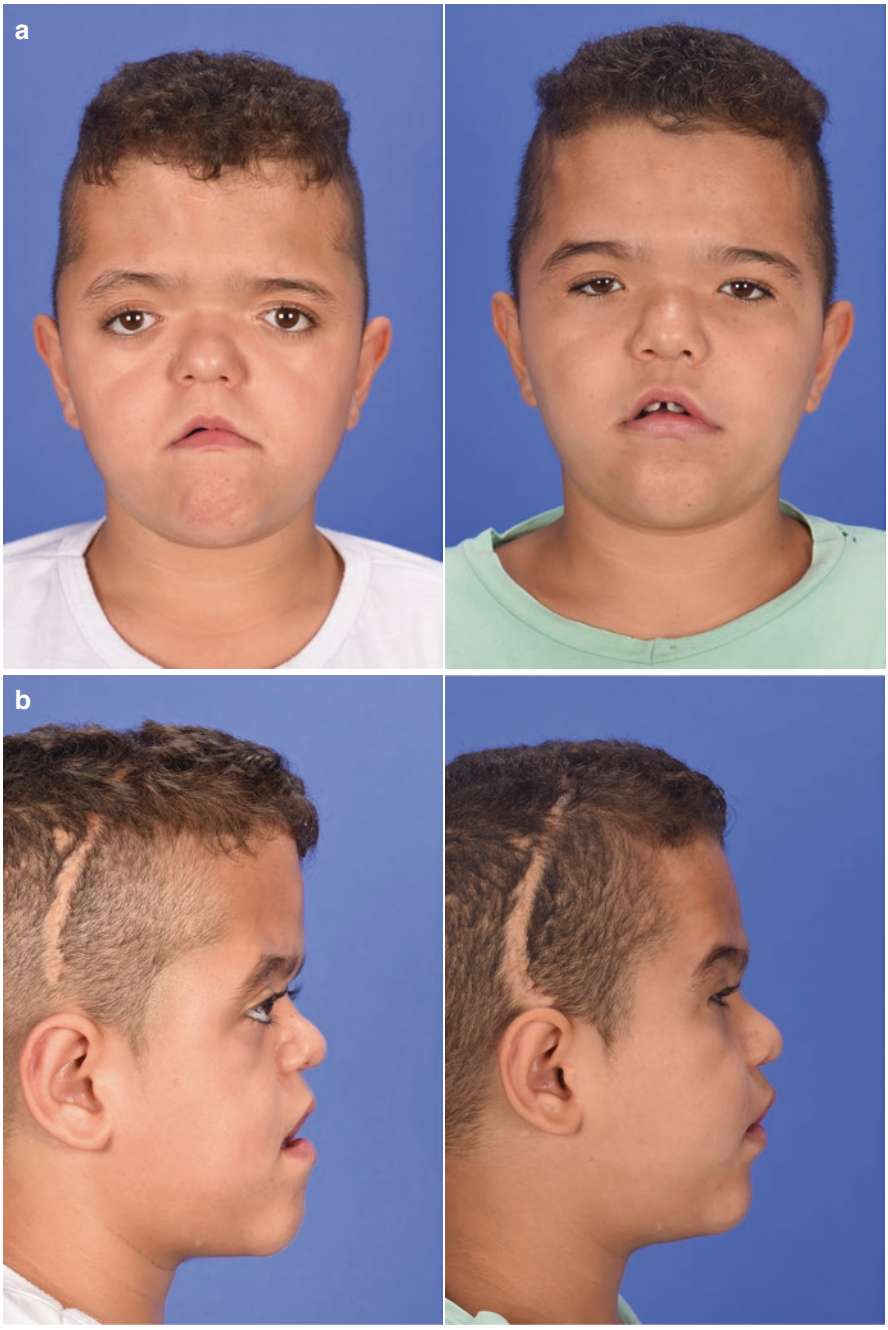

Fig. 13.12 (**a**) (*Left*) Preoperative frontal photograph of an 8-year-old Apert patient who underwent the facial bipartition monobloc advancement. (*Right*) Postoperative frontal photograph of the same patient. (**b**) *(Left)* Preoperative lateral photograph of an 8-year-old Apert patient who underwent the facial bipartition monobloc advancement. (*Right*) Postoperative photograph of the same patient

13.3.5 Distractor Types, Vectors, and Endpoints

The use of both internal and external distractor devices has been compared with similar outcomes, but with different dynamics [35]. The differences between using internal and external distractors, which involve issues related to differential vector control and patient comfort, have been previously discussed by other authors [20, 36–38] (**Reference 36, Level of Evidence: Therapeutic, V**). As levels of neurocognitive function may greatly vary in Apert syndrome patients [8, 39], patients with significant neurocognitive delays may not tolerate external distractor devices for extended periods postoperatively; thus, craniofacial plastic surgeons should be adept with both types of devices, and understand the type of movement provided by each device (counterclockwise rotation for external devices versus clockwise rotation for internal devices).

The distraction endpoints are defined by the positions of the orbital rim and the ocular globe. Patients with skeletal immaturity are left with mild enophthalmos, but adult patients are not overcorrected. Resultant occlusal distortion can be addressed with orthognathic surgery once the patient's facial growth has been completed.

13.3.6 Final Considerations

Apert syndrome frequently results in numerous types of airway obstruction that may be worsened by central apnea and Chiari malformation [40, 41].

The largest airway volume expansion following Le Fort III and other osteotomies utilized in midface advancement is at the nasopharyngeal level, and correlates with the magnitude of anteroposterior advancement achieved [42–44]. Central midface advancement and differential movement seem to play critical roles in the resolution of obstructive sleep apnea [45]. Therefore, techniques that provide segmental osteotomies such as Le Fort II with zygomatic repositioning [43], and facial bipartition monobloc (by adding transverse expansion to the osteotomies), may result in additional benefits to Apert syndrome patients [26]. Counterclockwise maxillary rotation following subcranial advancement, accompanied by larger advancement, will contribute to greater airway expansion [43].

Apert syndrome is predictive for increased blood loss during major craniofacial procedures [25, 46], which may contribute to increased overall surgical complications.

Descriptions of complication rates for transcranial and subcranial midface advancement significantly vary according to craniofacial groups [47, 48] (**Reference 47, Level of Evidence: Therapeutic, V**).

Serious complications for transcranial procedures can reach 59%, with a mortality rate of 4.5% [49]. While neurosurgical complications are more likely to occur during transcranial procedures, similar complications have been described for subcranial procedures [47]. Even in the most experienced hands, mortality has been

described for both subcranial procedures [50] and transcranial procedures [51]. Our complication rates for transcranial and subcranial procedures have been reported in the literature [52, 53]. Severe neurosurgical complications such as persistent cerebrospinal fluid leakage in 26% of patients, accompanying meningitis in 8.7% of patients, and seizures in 30.4% of patients were solely found in those of our patients who underwent transcranial procedures. Our preference is to refrain from performing midface advancement until the Apert patient is at least 8 years old, by which time the majority of craniofacial skeletal growth has already occurred, consistent with published data on long-term follow-up that shows sufficient bony midface stability and a lower relapse rate [53–56] (**Reference 52, Level of Evidence: Therapeutic, IV**, **Reference 56, Level of Evidence: Therapeutic, IV**).

The degree of a patient's facial asymmetry due to underlying bony irregularities in the forehead, and the performance of specific subcranial procedures, may also necessitate the performance of additional procedures to improve forehead contour. Patients with Apert syndrome will most likely require future orthognathic surgery, rhinoplasty, and/or final touch ups on the face, regardless of which specific subcranial and transcranial procedures are initially performed as part of a comprehensive treatment protocol.

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