Brain Tumors, Intraocular and Orbital Tumors

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In children, brain and spinal cord tumors account for approximately 25 % of all cancer (40–50 % of all pediatric solid tumors). Overall, they are second only to the leukemias in frequency [1, 2]. There have been reports of an increasing incidence of both adult and pediatric brain tumors which may, in part, be due to "detection bias" although some epidemiology groups suggest that the increases are real [3]. The annual incidence is approximately 2–5 cases per 100,000 (1 in 2500 children aged 0–16), which translates to approximately 300–400 new cases being diagnosed in the UK per year [4].

A wide variety of tumor types ranging from the highly malignant to the histologically benign is seen in the pediatric age range. However, prognosis depends not only on histological type but also on the location of the tumor with some low grade tumors (for example, craniopharyngiomas and hypothalamic gliomas) frequently resulting in severe morbidity or sometimes death. Although it is widely taught that infratentorial tumors are more common than supratentorial in the pediatric age group, it can be clearly seen from Table 25.1 that this ratio varies with age. Overall, there seems to be a slight preference for central nervous system (CNS) tumors in males – in particular in some of the more common tumor types – primitive neuroectodermal tumors (PNET), craniopharyngioma, brain stem glioma, ependymoma, and germ cell tumors arising in the pineal region [5] – the most striking sex preference being seen in relatively rare pituitary adenomas with a 7:1 male:female ratio [5].

For the majority of pediatric brain tumors no specific etiological agent or event can be found. Known risk factors include genetic syndromes (such as Neurofibromatosis I and II, basal cell naevus, tuberous sclerosis, Gorlin, Turcott, Li-Fraumeni, and von Hippel-Lindau), which account for 5 % of cases [6], and radiation exposure. Although there has been concern over exposure to low-level electromagnetic radiation (power lines) and from mobile phones, this association remains controversial [7].

The care of children with CNS tumors has probably changed more in the last 25 years than any other pediatric surgical group. This is due to changes at every stage of patient care:

1. Improvement in diagnostic techniques – computerized tomography (CT) in the 1970s, magnetic resonance imaging (MRI) in the 1980s, and functional imaging in the 1990s – with the ability to map eloquent cortex preoperatively (motor/sensory/visual/speech and memory). In addition, MR spectoroscopy can non-invasively shed light on the possible diagnosis of tumours.
2. Developments in neuroanesthesia (including intra and perioperative monitoring – including the use of "awake procedures" in those old enough to tolerate them). With the patient awake it is possible to map areas of eloquent cortex as well as to undertake sub-cortical mapping of white matter tracts.
3. Advances in surgery (including use of the operating microscope, the ultrasonic aspirator, stereotaxy, endoscopy, intraoperative functional mapping - including motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPS); – which allow for safer resection particularly of spinal cord and basal ganglia tumours).
4. Developments in adjuvant therapy (including both chemotherapy and radiotherapy, the use of multicenter trials, the recognition of the detrimental effects of radiotherapy on the developing CNS, the use of fractionated

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Table 25.1 Site of tumor by age

Age	% Infratentorial
0–6 months	27
6–12 months	53
12–24 months	74
2–16 years	42

From Greenberg [14], with permission

radiotherapy and stereotactic radiosurgery) and more recently the greater availability of Proton therapy;
5. Improvements in supportive services (physiotherapy; occupational and speech therapy; social, psychological, and educational support; palliative care).

From the surgical perspective, the result has been that a tissue diagnosis can virtually always be achieved regardless of the site and aggressive surgical removal of tumors can usually be attempted. Technology now available aims to use the detail of neuroimaging to help direct the surgeon during the operation. This "neuronavigation" relies on the surgeon registering the patient's head, which is then tracked by infrared cameras. Surgical instruments, fitted with light-emitting diodes, are also tracked as they come into the line of sight of the cameras. The workstation on which the preoperative imaging studies are held will then display where the instrument is within the head and its relationship to the tumor or target. The main drawback of neuronavigation is the fact that the information used is preoperative rather than real time. Intraoperative MRI units (where the patient's head is held within a small MRI magnet or where the operative layout includes a scanner within the operating theatre into which the patient is intermittently placed) are now available but it is yet to be shown that they are cost effective.

Another area of change in the last two decades has been the widespread use of immunohistochemical techniques to further classify poorly differentiated tumors. The World Health Organization (WHO) published a consensus document in 1979, updated in 1993 and again in 2000, giving a standardized reporting system. More recently, it has become clear that in the future CNS tumors may be classified by their molecular genetic profile. Molecular genetics is already important in helping to diagnose rhabdoid tumors/ATRTs (deletions or mutations of the gene hSNF5/INI1) [8], and is of prognostic and therapeutic value in the management of patients with oligodendrogliomas (1p/19q deletion being associated with prolonged survival and chemosensitivity in adults) [9].

Despite these advances, epidemiological data from the UK Childhood Cancer Research Group shows the overall 5 and 10-year survival rates to be approximately 55 % and 50 %, respectively, and there has been little change in the past 10 years. This is in contrast to the substantial rise in survival rates seen over this period in children with leukemia and non-CNS tumors [10]. This and the recent reporting of improved survival statistics on selected tumor subtypes (e.g., medulloblastoma) have emphasized the need for further collaborative studies. In particular it is hoped that the development of biologically directed therapies and the application of functional imaging to increase the safety and extent of surgical excision will result in significant improvements in outcome. In the last few years, trials in adults have shown significant improvements in survival duration in patients with malignant gliomas (using concomitant Temozolomide [11] or intratumoral chemotherapy [12]) and these results have been the first significant improvement in the management of these patients in the last 40 years. Phase III trials of a number of new agents (including gene therapy) are underway in adult patients – although methods of delivery (for example, convection-enhanced delivery) still need further refinement.

Phakomatoses

The phakomatoses (or neurocutaneous syndromes) are a group of conditions in which cutaneous stigmata are associated with CNS abnormalities or tumors. Although considered relatively rare, up to 10 % of all pediatric astrocytomas are associated with neurocutaneous syndromes [13]. Recognition of these syndromes is important as it may alter the indication and goals of surgery. Likewise, an understanding of the natural history and genetics of the disease is essential for dealing with both patient and family.

Neurofibromatoses

This group comprises by far and away the most common type of phakomatosis and the patients fall broadly into two subtypes – neurofibromatosis types 1 and 2 (NF1 and NF2). Previously, NF1 was known as von Recklinghausen's disease and this, with an incidence of approximately 1/3000 births, is responsible for more than 90 % of cases of neurofibromatosis. It shows an autosomal dominant inheritance with almost 100 % penetrance, but up to 50 % of cases represent spontaneous somatic mutations [14] with the gene responsible being located on chromosome 17. Optic pathway tumors are the most common type of tumor seen in NF1 but other low-grade gliomas and meningiomas are also seen. The incidence of CNS tumors is approximately 10 % [14–16].

Similarly, NF2 is also an autosomal dominant condition with the gene probably being on chromosome 22 [14]. The pathological signature of NF2 is the presence of bilateral acoustic neuromas. Although both NF1 and NF2 may be associated with multiple intradural spinal tumors, these are more common in NF2 than in NF1. Other non-CNS tumors also have

an increased frequency in NF2 (including neuroblastoma, sarcoma, leukemia, Wilms' tumor, and ganglioglioma) [14].

The subcutaneous neurofibroma are usually sessile in children but increase in size and in number with puberty and pregnancy and often become pedunculated. These tumors can undergo malignant degeneration in 2–29 % of patients (but usually during adult life) [17]. Congenital neurofibromas are often of the plexiform type with a propensity for the periorbital region where they may be progressive and very vascular. A further orbital problem is the characteristic dysplastic lesion seen in NF1 with sphenoid dysplasia leading to pulsatile exophthalmos, and indeed this may be the presenting sign of NF1 in an infant or young child [15].

Other skeletal lesions include congenital bowing of long bones and pseudoarthrosis, vertebral scalloping and scoliosis. Visual problems as a result of an anterior visual pathway tumor may be the first manifestation of NF1 in a young child and may be quite marked by the time medical attention is sought. As a general rule, tumors affecting the optic nerve tend to present at a slightly older age (early 20s) while chiasmatic tumors most often present in the first decade of life often in association with endocrine disturbance and hydrocephalus [18]. In contrast, the defining characteristic of NF2 is the presence of bilateral acoustic tumors, which usually present in adolescence [14, 16].

Another fundamental difference between NF1 and NF2 is the apparent disorganization of the CNS and the presence of hamartomas, heterotopias and low-grade neoplasms in NF1. Macrocephaly may be seen in three-quarters of patients with NF1 [19] and approximately one-third of NF1 patients are intellectually impaired, probably reflecting this widespread intrinsic cerebral disorganization. In addition, MRI scans frequently show areas of abnormal signal intensity but these remain of unknown significance. In contrast, the brains of patients with NF2 do not show this marked disorganization and cognitive function is usually normal.

Tuberous Sclerosis

Tuberous sclerosis (TS), also known as Bourneville's disease, is inherited as an autosomal dominant trait, although many cases are sporadic [16, 20, 21]. The prevalence is approximately 1/10,000 [20] and the disease usually declares itself in childhood with epilepsy and mental retardation. Non-CNS manifestations include "ash leaf spots," facial angiofibromas ("adenoma sebaceum"), café-au-lait spots, shagreen patches (subependymal fibrosis), subungual fibromas, retinal hamartomas, honeycomb lungs, angiomyolipomas of the kidneys, and cardiac rhabdomyomas. In the CNS there are multiple benign hamartomatous lesions which occur in the lining of the lateral and third ventricles (subependymal nodules) and cortical nodules ("tubers").

The characteristic brain tumor in TS is the subependymal giant cell astrocytomat (SEGA), which is believed to arise from subependymal nodules and nearly always occurs at the Foramen of Monro (Fig. 25.1a, b). The sites of these tumors frequently result in obstructive hydrocephalus, which is the usual cause of presentation. The reported incidence of SEGAs ranges from 7 to 23 % [22]. Pathologically, these are usually low grade giant cell astrocytomas which are benign and therefore the aim of surgery is to establish free communication of the cerebrospinal fluid (CSF) pathways rather than necessarily a total resection, which may be difficult to achieve. Surgery may also be considered for intractable epilepsy if it can be shown that one of the tubers or an abnormal area of brain around the tuber is acting as a focus. More recently the use of Everolimus, a drug which inhibits the mammalian target of rapamycin (a protein regulated by gene products involved in the tuberous sclerosis complex) has been used with some success. However, the role of this targeted drug in TS is not yet defined for treatment of either the epilepsy related to the tubers or for the treatment of an associated SEGA. For the latter, it may well be that Everlimus is useful in decreasing the size and vascularity of the SEGA prior to surgical intervention.

Von Hippel-Lindau Disease

This syndrome consists of CNS hemangioblastomas (usually cerebellar but may be spinal and occasionally supratentorial), in association with angiomatosis retinae, cysts/tumors in various organs and polycythemia [16]. This disease usually presents in adulthood and has an autosomal dominant trait with variable penetrance and a positive family history is only seen in approximately 20 % of cases. The diagnosis is made by the presence of two or more separate characteristic lesions or a single lesion with a positive family history. The most common associated lesions are pheochromocytomas and renal cysts/tumors (renal cell carcinoma being present in approximately 30 % of patients) [16]. Adenomas are also seen in the pancreas, liver, spleen, lung, epididymis and ovaries. The CNS tumors may be multiple and on imaging are usually cystic with a strongly enhancing mural nodule. At surgery, the tumors are highly vascular but usually well demarcated.

Posterior Fossa Tumors

Tumors in this region fall into two distinct groups those arising from the cerebellar hemispheres or the fourth ventricle, and those arising from the brain stem itself. These two distinct groups have different clinical presentations and surgical goals and will therefore be discussed separately.

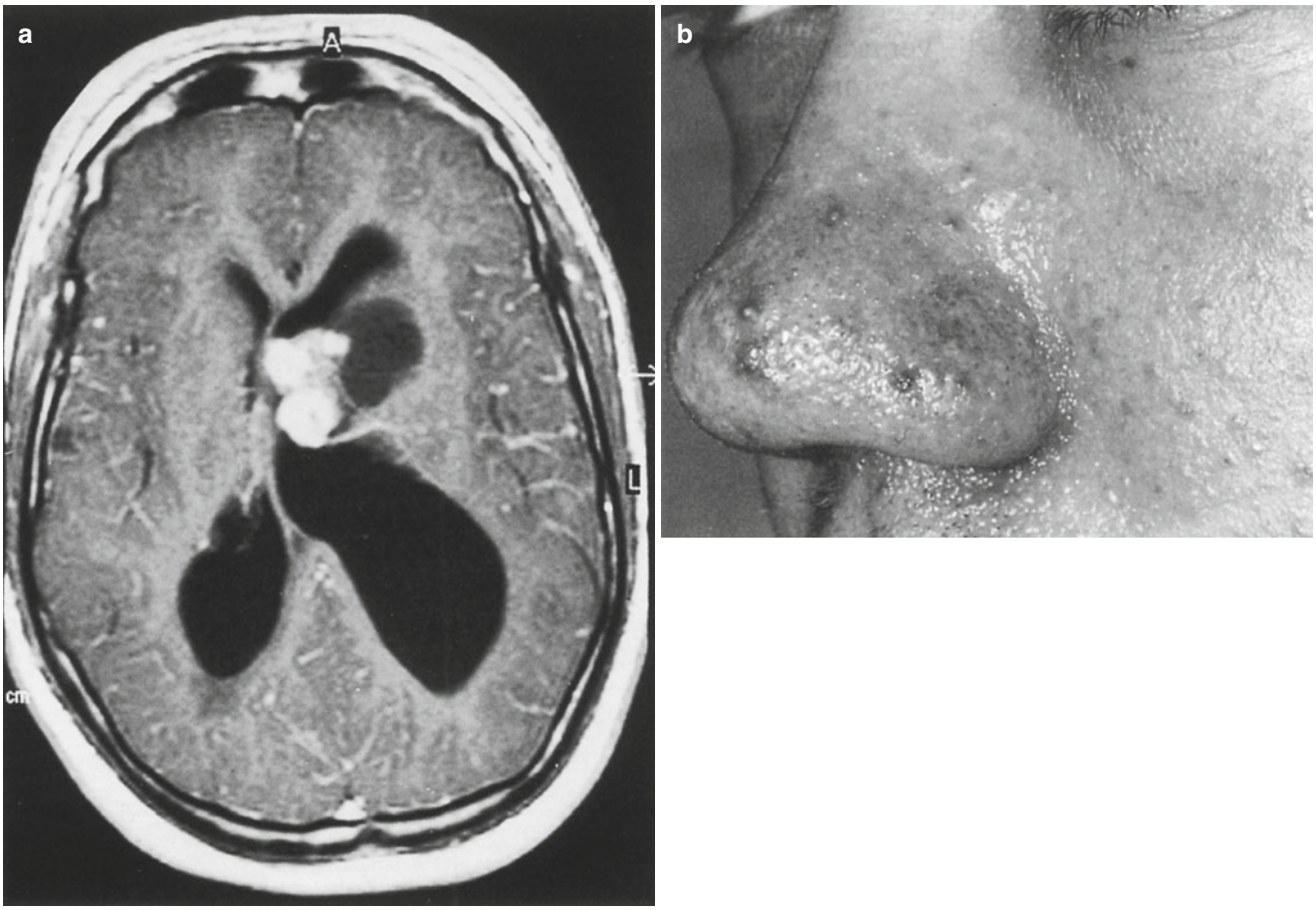

Fig. 25.1 (**a**) Axial T1-weighted MRI with gadolinium showing a giant cell astrocytoma at the Foramen of Monro in an adolescent patient with tuberous sclerosis. (**b**) The classical facial angiofibromas (adenoma sebaceum) of tuberous sclerosis

"Cerebellar" Tumors

Within this group of tumors are included cerebellar astrocytomas, medulloblastomas, and ependymomas. Cranial nerve tumors (for example, acoustic neuromas or 5th nerve tumors) will not be discussed due to their relative rarity in children.

As a group, these tumors usually present once they are large enough to cause hydrocephalus by blocking off the outflow of the fourth ventricle. The duration of symptoms rather than type of symptoms correlate with tumor type. Young children, in whom the sutures have not fused, may present with macrocrania, vomiting, and irritability. In older children headache, classically in the morning, and nausea and vomiting are the usual symptoms. It is not infrequent for patients to have been investigated for gastrointestinal problems prior to having a head scan which shows a tumor. If the cerebellar tonsils have been impacted into the foramen magnum, there may be neck pain or head tilt or even opisthotonus. Clinical examination may reveal papilloedema, a 6th nerve palsy (a false localizing sign due to the hydrocephalus) and by the time patient presents there is normally a degree of ataxia and past pointing. If the hydrocephalus is left untreated, the patient will eventually become comatosed.

From a surgical management point of view, there are two main problems: treatment of the hydrocephalus and surgical removal of the tumor. Although historically there was a vogue to insert ventriculoperitoneal shunts into all these patients prior to tumor removal, with the widespread availability of CT and MR scanning these children have tended to present earlier and the usual practice today is to commence dexamethasone and perform early surgery. If required, an external ventricular drain may be inserted either prior to surgery or at the time of surgery. Alternatively, it is possible to treat the obstructive hydrocephalus (either pre or post-tumour removal) by means of an endoscopic third ventriculostomy (ETV). This procedure basically creates an internal diversion of the CSF in order to bypass the obstruction – by making a hole in the floor of the III ventricle. In the setting of a patient over 1 year of age with obstructive hydrocephalus, the success rate for an ETV is of the order of 70–80 %. Each tumor type will now be dealt with individually.

Cerebellar Astrocytomas

Cerebellar astrocytomas are virtually always of the low-grade (pilocytic) type in children. This tumor type makes up approximately one-third of childhood posterior fossa tumors [23] with patients being slightly older than those with the malignant posterior fossa tumors. Grossly, these tumors are found to lie either in the cerebellar hemisphere or may involve the midline (vermis). They are either cystic (70 %) with a mural nodule or a solid mass (22 %) with multiple cystic areas [24]. Although well demarcated, areas where it may be difficult to obtain a complete removal include extension through the cerebellar peduncles into the brain stem (brain stem invasion being reported in 8 % of cases) [24] or when tumor is found high in the tentorial notch towards the vein of Galen. The microscopic features of these tumors are characteristic with a biphasic pattern of dense and compact areas with elongated (pilocytic cells) that alternate with loose areas containing stellate astrocytes and microcysts [24]. The cells may contain intracytoplasmic eosinophilic inclusions termed Rosenthal bodies. Vascular proliferation may be seen in cerebellar astrocytomas and unlike other gliomas, this does not indicate a more aggressive behavior of the tumor. Calcification may also be seen in these tumors.

On CT scan, hydrocephalus is often present and in the posterior fossa the classical finding is of a cystic tumor with an enhancing nodule. The tumor is iso or hypodense on noncontrasted scans. Occasionally, the cyst wall itself enhances and looks thickened and in these cases, surgical excision of the wall is indicated as it will consist of tumor. However, if the cyst wall does not enhance, then at the time of surgery a thin cyst consisting of gliotic tissue rather than tumor is found. The solid type of tumors can be difficult to differentiate from ependymomas or medulloblastomas. The differential diagnosis of the cystic astrocytoma is with a cystic hemangioblastoma – but the latter are exceptionally rare in the pediatric age group. Today, MRI scanning is usually also obtained as this helps with surgical planning. Cerebellar astrocytomas are usually isoor hypointense on T1-weighted images and hyperintense on T2-weighted images. Additionally, the MRI will often show on the sagittal plane that the tonsils have herniated through the foramen magnum (Fig. 25.2).

The goal of surgery in these patients is total removal of tumor as this is an important prognostic factor. Additionally, if total surgical excision has been performed then no further adjuvant therapy, specifically radiation, is needed [25]. Garcia et al. reviewed 80 children with cerebellar astrocytoma and the recurrence rate was 2.5 % for patients with total removal and 3.5 % for patients who had a subtotal removal. Interestingly, radiation did not affect the outcome of patients who had a subtotal excision [25]. Nonetheless, subtotal resection is compatible with long-term survival [26, 27]. From the Garcia study, the 5-, 10-, and 25-year disease-free survival rates were 92 %, 88 %, and 88 % respectively.

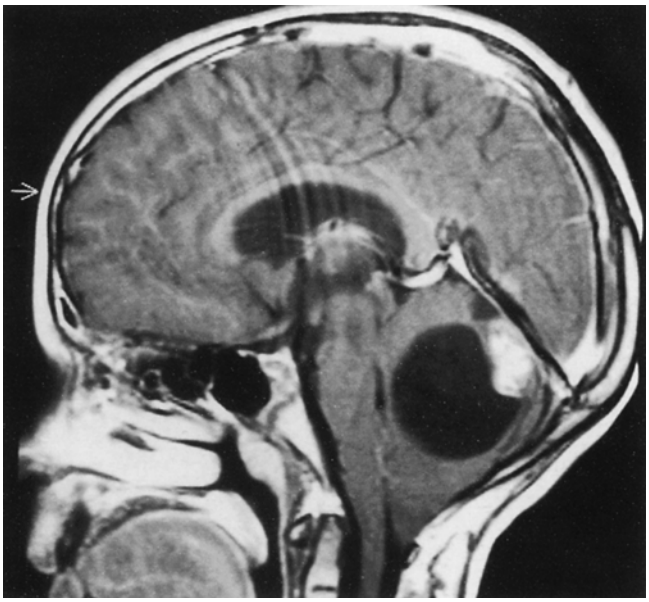

Fig. 25.2 Sagittal T1-weighted MRI with gadolinium showing a large posterior fossa cyst with an enhancing nodule characteristic of a pilocystic astrocytoma. Note that the cerebellar tonsils have herniated through the foramen magnum

There are, however, case reports of recurrence after 36 years [28] and occasionally, malignant change is seen in the recurrence. For these reasons these patients require long-term follow-up, with intermittent scanning. Nonsurgical treatment includes radiation or chemotherapy and is only recommended when there is a recurrence and further surgical excision is not feasible, and/or if the recurrent tumor has a malignant histology [29].

Medulloblastoma

Medulloblastomas were first described in 1925 by Bailey and Cushing, who suggested that these tumors were derived from a primitive pluripotent cell called the medulloblast. This putative cell has never been found but the name has now become entrenched in the neurosurgical literature. More recently, it has been recognized that the medulloblastoma should be classified under the heading of Primative Neuroectodermal Tumor (PNET). Medulloblastoma is the most common malignant CNS tumor in childhood comprising 15–20 % of childhood brain tumors [30] and make up approximately one-third of all posterior fossa tumors in childhood. The peak incidence is between the ages of 3 and 8 years – being slightly younger than the pilocytic astrocytoma age range. However, these tumors may occur in the infancy and are occasionally seen in adults.

Medulloblastomas are most commonly found in the region of the fourth ventricle arising within the vermis. The tumors are reddish in color, friable and frequently vascular. A “desmoplastic” variant has been described which is char-

acterized as being firm and well demarcated but this tends to occur in older children and adults. Recent evidence suggests that this subtype carries a better prognosis compared to classical medulloblastomas [31]. In contrast, large-cell medulloblastoma has been recognized as a distinct subtype which is associated with a poor prognosis [32].

A characteristic of medulloblastoma is the ability to spread via the CSF pathways into the spinal ("drop metastases") or cerebral subarachnoid spaces or within the ventricles. Such dissemination maybe diffuse or nodular and it is reported that 20–30 % of patients with medulloblastoma have seeded within the craniospinal axis at the time of diagnosis [30]. Extraneural metastases are seen in 5 % of patients [2] and this rate of extraneural deposition does not appear to be altered by the use of a (millipore) filter in association with a ventriculoperitoneal shunt.

Histologically, the classic medulloblastoma is composed of densely packed small cells with hyperchromatic nuclei and very little cytoplasm. There are frequent mitoses and rosettes of the Homer-Wright type are seen in about 20 % of cases. Over the last decade cytogenetic and molecular studies have shown that isolated 17p loss and elevated expression of erbB2 and c-myc are associated with a poor prognosis [33].

On CT scanning, medulloblastoma appears as a well-marginated, homogeneously hyperdense mass arising from the vermis and filling the fourth ventricle. The mass typically enhances with contrast and calcification is seen in approximately 15 % of cases [30]. Mild to moderate edema is common around the tumor and hydrocephalus is present in 95 % of patients [30]. The investigation of choice in all posterior fossa lesions is MRI as it gives far better definition and resolution. The tumors are usually hypodense on T1-weighted images and on T2-weighted images but enhancement is still the rule after gadolinium has been injected (Fig. 25.3a, b); MRI is also superior in picking up subarachnoid seeding and spinal metastases.

The aim of surgery is gross total resection but in approximately one-third of cases a medulloblastoma infiltrates the dorsal brain stem and this precludes total removal [34]. These tumors usually require a long incision in the vermis and this may result in transient truncal ataxia and dysconjugate gaze, which usually resolves over a couple of weeks. In patients in whom the tumor has involved the cerebellar peduncle, there may be long-standing ipsilateral dysmetria. Occasionally, patients will suffer with cerebellar mutism, which is poorly understood but tends to resolve over a matter of weeks.

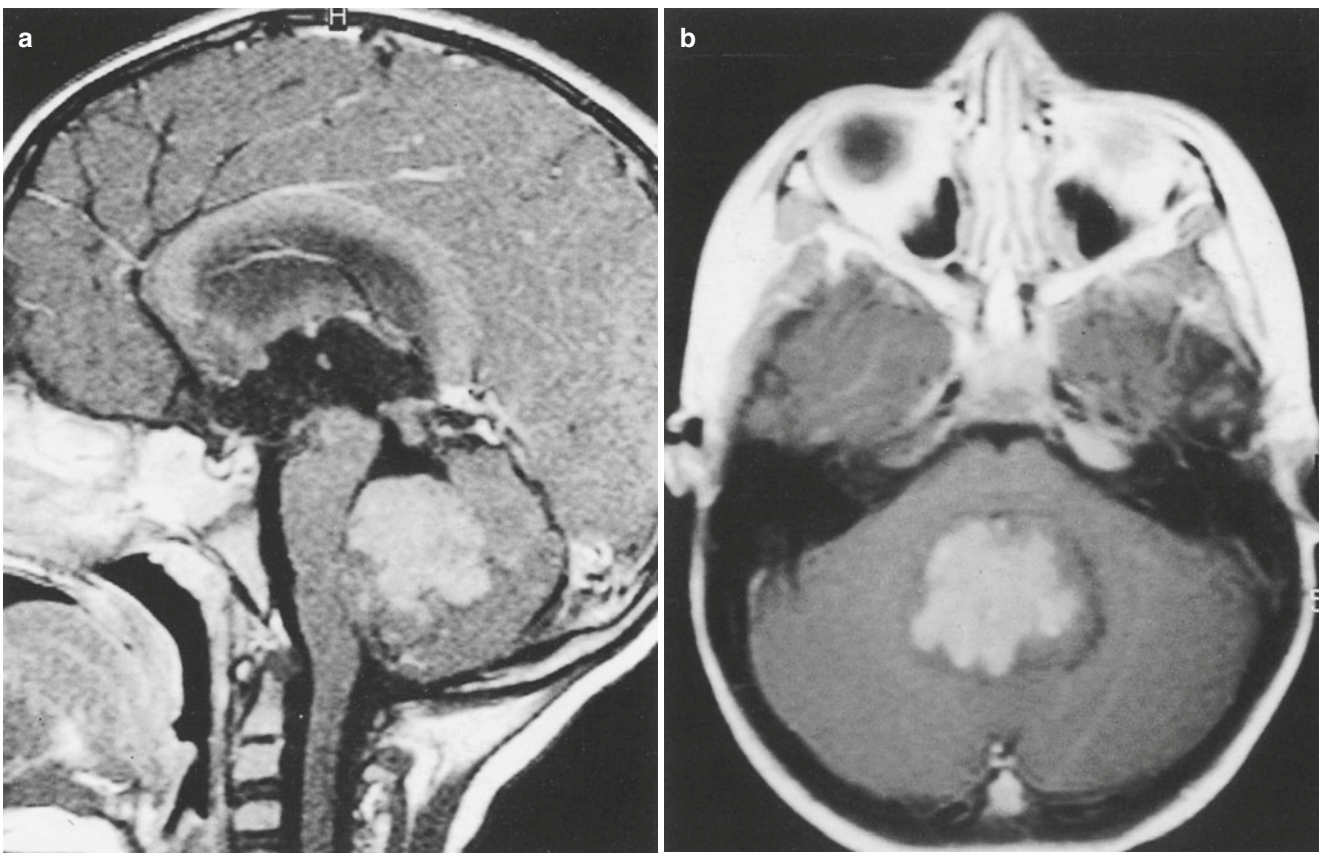

Fig. 25.3 (**a**) Sagittal and (**b**) axial T1-weighted MRI with gadolinium showing a large posterior fossa tumor in the fourth ventricle with variable uptake of contrast. Histologically verified as a medulloblastoma

Prognostic Factors

1. Extent of Surgical Resection. Differing definitions and surgical impressions have made this area fraught when trying to undertake comparative studies. It is now generally accepted that a gross total resection is one at which the surgeon feels there is no tumor left and an early CT or MRI examination with and without contrast fails to show any tumor deposit. A subtotal resection is one in which a small amount of tumor is known to have been left by the surgeon or if a postoperative scan shows a small lump of enhancing tissue in the operative bed (<1.5 cm^2). Using these strict criteria, there does not appear to be a significant difference in outcome between the two groups [30]. In comparison, patients with a partial excision (>1.5 cm^2) or a biopsy alone fare far worse [30].
2. Size/Dissemination. The Chang staging system has been widely employed for many years and characterizes medulloblastoma by tumor size (T stage T1 to T4) and the presence or absence of metastases (M0 to M4). More recently, it has become apparent that preoperative tumor size per se is of no predictive value [30]. However, the presence or absence of dissemination at the time of diagnosis is the most significant factor in predicting the survival of patients with medulloblastoma. It is therefore essential to arrange a preoperative staging spinal MRI. Furthermore, in order to detect M1 disease (malignant cells identified in the CSF) an LP for cytology should be carried out 10–14 days after the posterior fossa surgery.
3. Age. Probably for multifactorial reasons, younger children fare less well than older children with medulloblastoma (Table 25.1). Younger children are more likely to have disseminated disease at the time of diagnosis and younger patients are less likely to receive aggressive treatment due to the adverse effects of radiotherapy.
4. Histology and Molecular Genetics
   Using these three main criteria (gross total/subtotal versus partial/biopsy; <3 years of age versus >3 years of age; no dissemination versus dissemination) patients with medulloblastoma have been subdivided into "average risk" and "high risk" by the American Children's Oncology Group (COG). It can be estimated that for the poorest group, overall survival is approximately 36 % at 5 years with standard postoperative craniospinal axis irradiation, versus 60–80 % for children without adverse risk factors [30, 35].

Adjuvant Therapy. It is quite clear from the literature that medulloblastomas are highly radiosensitive. However, follow-up studies have shown that radio therapy at a young age may have a devastating effect on final neuro and cognitive development. These cognitive sequelae are dependent on age at treatment and dose and field of irradiation given [30, 36]. Thus although the "standard" dose of radiation given to patients with medulloblastoma is 5500 cGy with a dose of 3600 cGy to the neuraxis [30, 37], it is obvious that these dosages are unacceptable to the immature brain and therefore trials have been undertaken using chemotherapeutic agents to see if it is possible to withhold radiation either temporarily or permanently in very young children [38]. In children older than 3 years the addition of chemotherapy to the standard treatment of surgery and radiotherapy has a resulted in improved survival, even in association with reduced radiotherapy dose to the craniospinal axis [35]. Further clinical trials looking at both survival and quality of survival, while employing lower doses of radiotherapy, are underway. Other areas of research interest include the use of hyperfractionated radiation and of stereotactic radiosurgery for small deposits/recurrences [39].

Endocrine dysfunction is another common problem after radiotherapy [40] with hypothyroidism and growth failure being the most common deficiencies. While the use of growth hormone is beneficial, the final height attained is significantly less than the midparental height [41]. Cushingoid appearance associated with the use of steroids is another common problem during treatment.

Medulloblastoma is clearly a chemosensitive tumor, as demonstrated in numerous phase I and II studies carried out at disease relapse [42, 43]. Chemotherapy has also been used as an adjuvant in medulloblastoma therapy for many years. Studies of chemotherapy given after surgery and before radiotherapy ("sandwich chemotherapy") have shown a survival advantage of 14 % at 5 years in patients who received chemotherapy [44]. Standard therapy is, however, to give chemotherapy after completion of radiotherapy as described by Roger Packer and survival is now more than 80 % at 5 years [35]. For various reasons – ranging from earlier diagnosis, to better anesthetic and surgical technique and the use of adjuvant therapy – medulloblastomas are one of the few CNS tumors in which there has been a significant improvement in 5-year survival over the last 20–30 years. At present, 5-year survival rates in the range of 70–80 % are to be expected [30, 35, 45].

Ependymoma

Ependymomas are rare tumors accounting for 6–12 % of brain tumors in childhood (30–35 new cases per year in the UK) [46]. Although they may be found throughout the CNS in children, 70 % of ependymomas occur in the posterior fossa [47]. Half of these tumors present in pre-school children and the posterior fossa tumors occupy the fourth ventricle and extend through the outlets of the fourth ventricle into the cerebellar pontine angles and down over the cervical medullary junction. On CT, the ependymoma is usually

either isoor hyperdense and may show calcification. Enhancement after contrast is variable. Often MRI with its better definition shows more clearly the spread of the tumor over the cervical canal or out of the Foraminae of Luschka (Fig. 25.4). In the preoperative work-up, it is important that a spinal MRI is performed to look for spinal drop deposits.

Histologically, ependymomas are composed of well differentiated cells which are often arranged around blood vessels forming perivascular rosettes. These tumors vary from being well differentiated through to having anaplastic features with high cellularity, pleomorphism, necrosis, and high mitotic activity. However, the significance of the histological changes is yet to be verified as there is only a tendency towards worse prognosis with increasing anaplasia [48]. Until recently, reviews in the literature included the highly malignant ependymoblastoma in the anaplastic group and this adversely skewed the survival curve for these children. The ependymoblastoma is now considered to be an embryonal tumor (a variant of the PNET) [49].

With the ependymoblastoma removed from the heading of anaplastic ependymoma, the survival curves are not dramatically different from those showing more low-grade histological features.

Fig. 25.4 Sagittal T1-weighted MRI with gadolinium showing a large enhancing posterior fossa tumor which has involved the herniated cerebellar tonsils

At the time of surgery, approximately 10–25 % of posterior fossa ependymomas are found to be invading the floor of the fourth ventricle [47, 50]. As with medulloblastomas, the aim of surgery is maximum possible resection without causing neurological deficit. However, due to the frequent extension to the cerebellar pontine (CP) angle, there is a higher incidence of lower cranial nerve palsies after resection. Due to this combination of brain stem invasion and CP angle involvement, the rate of complete resection is relatively low. Recent single institution retrospective studies have emphasized the importance of obtaining gross total removal with 10-year survival rates of over 70 % in patients with radiological confirmation of gross surgical removal [51, 52]. This is to be compared with the 30 % 5-year survival rate usually quoted for this disease [53]. A multivariate analysis of prognostic factors identified complete resection as the most favorable prognostic factor [54]. This importance of complete resection has led to the concept of second look surgery, after treatment with chemotherapy, to allow removal of any residual tumor.

Postoperatively, patients should be imaged within 48 h looking for residual tumor. In the absence of dissemination, radiotherapy is given (5400 cGy to the tumor bed), with spinal radiation only being given to those patients with proven deposits. Results from trials using hyperfractionated and conformal radiotherapy are awaited. In an attempt to avoid radiotherapy in young children various chemotherapeutic trials have been undertaken. There is now evidence that some children can have long-term remission with chemotherapy alone [55] although some children still suffer late recurrences. The approach is still worthwhile in this situation as the chemotherapy can result in very significant delays in the requirement for radiotherapy [56].

Brain Stem Tumors

It is only really since the advent of CT and perhaps even more importantly MRI that the true heterogeneity of this group of tumors has been understood. The classification used here is that based on Abbott et al. [56] and it has allowed for a rational approach to this diverse group of tumors. This has meant that some patients are not subject to any surgical procedures while others are treated aggressively as the underlying tumor may well be benign. The clinical presentation is also somewhat variable and will be discussed with each tumor type.

Diffuse Pontine Glioma

Unfortunately, this is the majority of brain stem tumors (comprising 60–70 % of the New York series) [57]. It was this tumor group with its dismal prognosis that all patients were assumed to have prior to the advent of modern imaging.

The patients present with a short history of ataxia and multiple cranial nerve dysfunction. An MRI scan demonstrates an expanded pons which is hypointense on T1 images (Fig. 25.5a, b). However, the extent of tumor involvement is best appreciated on T2 imaging with the tumor having a hyperintense signal. Enhancement is variable and hydrocephalus is not usually apparent. No treatment has been shown to be effective, with a median survival of 9 months [58]. Radiation has been shown to have a palliative effect and to increase the duration of survival. To date, chemotherapy trials have also failed to demonstrate efficacy but more aggressive regimens and biological "new agents" are currently being evaluated. With the classical MRI picture and clinical history, it is generally agreed that submitting these children to a biopsy is not warranted for diagnosis, although biopsy to obtain tissue for biological studies may be necessary if newer molecular treatments are being considered.

Focal Tumors

These tumors may arise anywhere within the brain stem and may even be partially exophytic into the CSF spaces. These patients usually have histories going back many months or years, and focal neurological signs. The solid portion of these tumors typically enhances with gadolinium. In the presence of progressive symptoms, surgical debulking of these tumors is a feasible option as the histology is usually of a low-grade astrocytoma. Radiotherapy is not indicated and it is feasible to re-operate on these focal tumors to achieve a complete resection. A subset of these focal tumors is the tectal gliomas, which not infrequently will have been initially "misdiagnosed" as a congenital aqueduct stenosis. These tectal gliomas will frequently show calcification on CT scans [59]. These tumors would seem to have a very benign course and can usually be watched with serial imaging (Fig. 25.6).

Exophytic Tumors

These tumors arise from the subependymal glial tissue and fungate into the fourth ventricle [57] with more than 90 % of the tumor residing within the ventricular system. The clinical history is long but because of the potential to cause hydrocephalus, patients with these tumors may present with raised intracranial pressure. Additionally, the site of the tumor may result in intractable vomiting, "failure to thrive" [60], ataxia, and nystagmus. On imaging alone, it can be difficult to differentiate these tumors from medulloblastomas or astrocytomas of the vermis. However, in general, these tumors tend to be isointense and tend to enhance with gadolinium on MRI (Fig. 25.7). The aim of surgery is to shave the tumor flush with the surrounding floor of the fourth ventricle but not to advance ventral to this plain. These tumors are usually

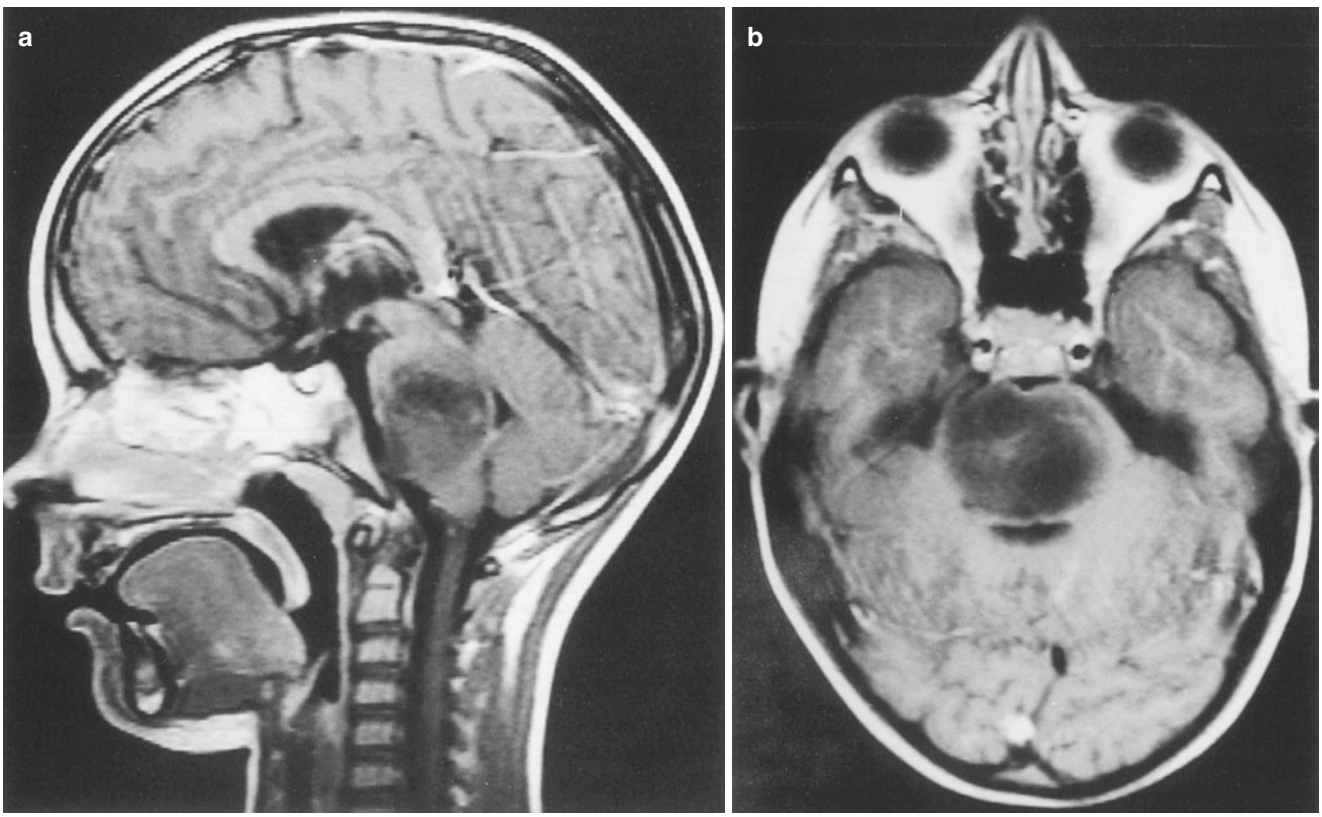

Fig. 25.5 (**a**) Sagittal and (**b**) axial T1-weighted MRI with gadolinium showing massive expansion of the pons by a poorly enhancing tumor – characteristic of a diffuse pontine glioma

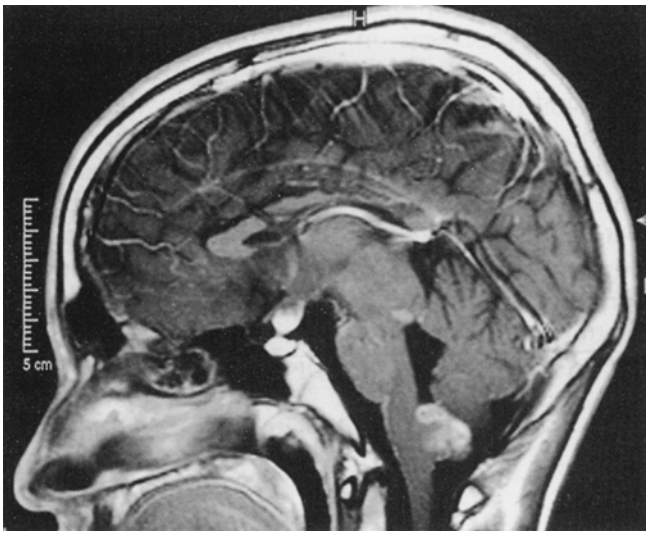

Fig. 25.6 Sagittal T1-weighted MRI with gadolinium showing an exophytic enhancing tumor arising off the medulla. Note also, the tectal plate tumor (with a small area of enhancement) and the enhancing hypothalamic tumor. This 12-year-old boy had presented with hydrocephalus 5 years earlier and on the basis of the CT scan performed at that time, the diagnosis of hydrocephalus secondary to aqueduct stenosis was made. Although asymptomatic, further imaging of the spine revealed another tumor (Fig. 25.9)

Fig. 25.7 Axial T1-weighted MRI with gadolinium showing a large partially cystic, enhancing tumor involving the parenchyma and with extension into the lateral ventricle. The associated edema is characteristic of a malignant tumor

benign and surgery followed by surveillance with repeat MRI is required. At the time of tumor recurrence, probably the best form of further therapy is repeat operation.

Cervicomedullary Tumor

These glial tumors involve the upper cervical cord/ medulla. In effect, they should be treated like spinal cord tumors, the main difference being that as they have "run out of spinal cord" at the level of the decussating white matter tract, they exophytically grow into the cisterna magna [61]. These patients present with long-standing neck pain and gradually develop myelopathy and sensory dysesthesias. These patients also often exhibit torticollis.

Imaging relies on MRI scanning and this shows an enlarged upper cervical cord with distortion of the medulla, usually with an exophytic component going into the cisterna magna. Enhancement with gadolinium is variable. In general, these tumors are low-grade gliomas although very occasionally malignant spinal cord tumors may mimic these findings.

Again, the aim of surgery is to remove as much tumor as possible without damaging normal neural tissues. The cervical tumor is interparenchymal and this requires a midline myelotomy. The exophytic component of the tumor is dealt with in the normal fashion being wary of vascular damage to the posterior inferior cerebellar artery vessels. Some groups find intraoperative electrophysiological monitoring helpful with this group of patients [57]. Postoperatively, these patients are at risk of respiratory failure and problems with protecting their airway and may require tracheostomy and feeding gastrostomies [57].

Supratentorial Tumors

These tumors usually present clinically with focal neurological signs (e.g., hemiparesis, visual disturbance); or with mass effect either directly due to tumor size or as a result of obstructive hydrocephalus; or with seizures. Supratentorial tumors are a heterogenous group and approximately one-third of these neoplasms involve the cerebral hemisphere [48, 62]. The most common tumor is the low-grade astrocytoma (WHO grade 2), which is composed of fibrillary or protoplasmic neoplastic astrocytes. Other low-grade tumors in this location include juvenile pilocytic astrocytomas (similar to cerebellar astrocytomas), oligodendroglioma, ependymoma, mixed glioma, dysembryoplastic neuroepithelial tumor, and ganglioglioma [48]. During the first 2 years of life, supratentorial tumors are more common than infratentorial and most of these are malignant neoplasms – usually PNETs, choroid plexus carcinomas, or teratomas [48, 63]. Overall, in children, approximately 20 % of supratentorial tumors are malignant neoplasms, the most common being

the malignant glioma. A brief run through the more common hemispheric tumors will be given prior to discussion of other supratentorial tumor types.

Cerebral Hemispheric Tumors

Astrocytomas

This group of tumors comprises one-third of hemisphere neoplasms and shows equal sex distribution with a peak incidence between the ages of 8 and 12 [64, 65]; 10–20 % of these tumors will be juvenile pilocystic astrocytomas (having identical histological makeup as those found in the posterior fossa). Malignant gliomas make up a further 20–30 % and overall, tumor cysts are found in approximately 40 % of children with supratentorial astrocytomas [48]. In adult patients distinct genetic signatures have been found for some glioma tumour types – and these mutations can have some bearing on prognosis. The best characterized of these is the 1p19q co-deletion seen classically in oligodendrogliomas and which confers an improved survival and sensitivity to both chemotherapy and radiotherapy. In high grade gliomas methylation of the gene encoding the repair protein DNA methyltransferase (MGMT) has been shown to correlate with response to Temazolamide. In grade II gliomas (rare in children) TP53 and IDH1 mutations are considered genetic hallmarks in adult patients and when present in GBM specimens implies that the tumour is a "secondary" GBM and has up-graded from a grade II or III tumour. Unfortunately, most of these genetic alterations are commonly not seen in paediatric gliomas – which strengthens the argument that these tumours in children are biologically and clinically different to those seen in adults. One "marker" that is seen in adult and paediatric tumours is the BRAF oncogene – which can be useful in confirming the diagnosis of pilocytic tumours.

Once again, it has been shown that gross total/subtotal (>90 %) resection confers survival advantage over partial resection/biopsy in both low-grade and highgrade tumors [48]. In spite of the benign histology in the low-grade group, only 60–70 % of children will be long-term survivors [48]. This probably reflects the fact that in most series all supratentorial low-grade gliomas are grouped together – including those involving deep vital structure like the hypothalamus and basal ganglia. Nonetheless, the aim of surgery should be to remove as much of the tumor as is safely feasible. The use of radiation postoperatively in these patients with low-grade gliomas is an area of contention. When gross total excision has been accomplished it would seem reasonable to follow these patients with serial imaging. In those patients with partial debulking or biopsy only due to the site of the lesion and in whom clinical progression is occurring, then radiotherapy is indicated. Chemotherapy, using vincristine and carboplatin, is effective and is now used routinely in younger children (less than 8 years of age) and in children with NF1 in whom the use of radiotherapy is to be avoided [66] (Fig. 25.8a–d).

With regard to the malignant tumors, there is clear benefit of adjuvant irradiation and it has been shown that doses of 5400–6000 cGy appear to offer longer survival time than does that under 5000 cGy [67]. Additionally, postirradiation chemotherapy has been shown to significantly increase survival in children with malignant astrocytomas [68] with an increased 5-year survival from 13 % in those patients receiving irradiation only to 43 % in those also receiving a nitrosourea-based regimen. The alkylating agent Temozolomide has been investigated in both adults and children with high-grade glioma but while its use during and following radiotherapy has been shown to increase duration of survival when compared with radiotherapy alone in adults, no such advantage has been shown in children [69–71]. Further trials of new agents are under way at present.

Ependymoma

These tumors make up approximately 10 % of all CNS tumors in childhood, and approximately 30 % are located supratentorially [48]. Over half of ependymomas occur before 2 years of age [48]. Although the posterior fossa ependymoma is located in relation to the fourth ventricle, the supratentorial ones often lie within the parenchyma and are thought to arise from ectopic rests of ependymal cells adjacent to the ventricles. Histologically, supratentorial ependymomas are identical to those found in the posterior fossa (see above). Likewise, the aims of surgery are similar to those of the posterior fossa ependymomas. Imaging of the spine is required to exclude drop metastases. Overall, 5-year disease free survival is better than for the infratentorial tumors and ranges between 40 and 60 % [51, 72, 73], with children with gross total resection faring better and giving recent survival rates of up to 85 %. The use and indications for adjuvant therapy are the same as for infratentorial ependymomas.

Oligodendrogliomas and Oligoastrocytomas

While pure oligodendrogliomas are rare tumors in the pediatric age group (2–3 % of hemispheric tumors) [48], up to 30 % of supratentorial gliomas consist of a mixed population of astrocytes and oligodendrocytes – giving them the term "mixed glioma" or "oligoastrocytoma" [48, 64]. Peak incidence is between 6 and 12 years and there is a strong male predominance [48, 74]. These tumors are usually located in the frontal lobe. Histologically, oligoastrocytomas consist of more than 25 % astrocytes whereas the oligodendrocytomas are uniform monotonous sheets of cells with perinuclear clear zones or halos producing a "fried egg" appearance [48]. Both tumor types are histologically graded in a similar fashion to astrocytomas. There has been great variation in the incidence of this diagnosis in series of patients with glioma, raising the possibility of international differences in the diagnostic criteria.

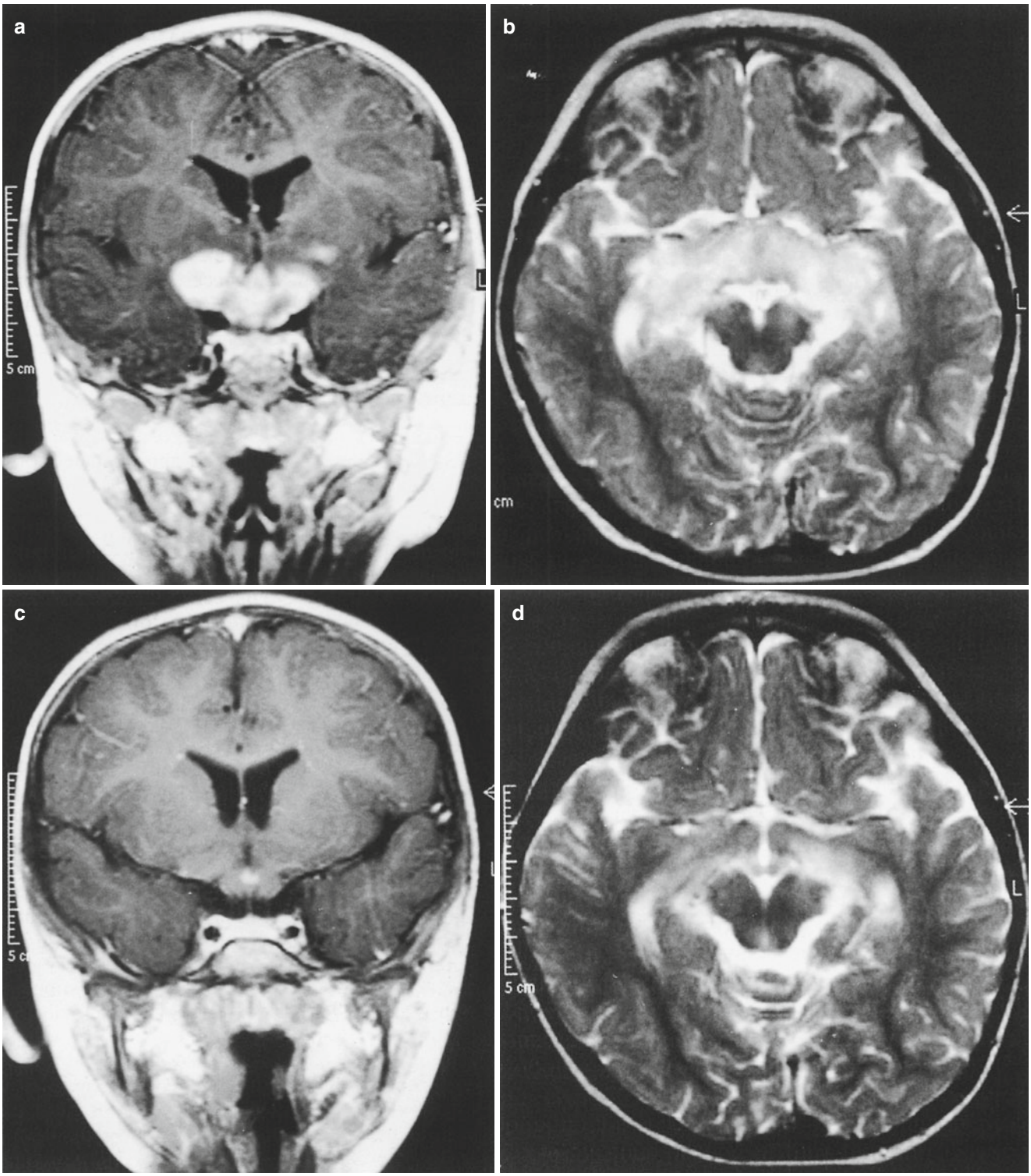

Fig. 25.8 (**a**) Coronal T1-weighted MRI with gadolinium taken at the level of the hypothalamus and third ventricle showing an extensive enhancing tumor – histologically confirmed to be a pilocytic astrocytoma and at surgery found to involve the optic chiasm. (**b**) Axial T2-weighted MRI showing extension of the tumor along the optic radiation. (**c**, **d**) Are comparable MRI scans from the same 2-year-old patient after chemotherapy with the low grade "Baby Brain" protocol – there being a dramatic reduction in tumor bulk

However, recent advances in our understanding of the cytogenetic changes associated with oligodendrogliomas may help rationalize the diagnostic process. In particular, these tumors often show 1p/19q loss and usually do not show p53 mutations. The 1p/19q loss confers survival advantage and sensitivity to chemo-therapy [9]. On CT scan, calcifica-

tion may be present and there is patchy contrast enhancement with both CT and MRI. Tumor cysts are frequent. The aim of surgery is radical resection and the role of irradiation in these tumors is controversial but probably improves survival in subtotally resected anaplastic tumors. The 5-year survival for pure oligodendrogliomas ranges from 75 to 85 % [74, 75]. Malignant mixed tumors fare poorly with similar survival curves to the malignant gliomas.

Ganglioglioma

These tumors are also mixed tumors consisting of neoplastic ganglion cells and astrocytes and make up approximately 5 % of pediatric brain tumors [48]. Histological grading is based on the astrocytic component of the tumor with regard to features of anaplasia. These tumors have a predilection for the medial temporal lobe and usually present with poorly controlled seizure disorders. Males are more commonly affected and the tumors can occur throughout childhood. Use of MRI demonstrates a well-demarcated cystic temporal lobe mass with no edema.

These are indolent tumors but with often devastating social consequences due to the poorly controlled epilepsy. The aim of surgery is therefore to make the diagnosis, but also to relieve epilepsy. In patients with intractable epilepsy, it is therefore important preoperatively to fully assess the origin of the epileptic focus to confirm that this correlates with the MRI lesion. Longterm survival is seen in 75–90 % of patients following radical surgery [75, 76], and radiotherapy is not given in patients who have undergone gross total resection. The role of radiotherapy in patients with a subtotal resection is not yet determined.

Primitive Neuroectodermal Tumors (PNET)

These tumors are identical histologically to the infratentorial medulloblastomas. Imaging studies usually demonstrate large, relatively well-demarcated lesions with mixed enhancement patterns and areas of cysts and calcification and possibly hemorrhage [48] (Fig. 25.7). The aim of surgery is to remove as much tumor as possible and preoperatively; these patients require MRI of the spinal axis. Treatment is similar to that for infratentorial medulloblastomas, but the overall prognosis is poor with less than 30 % surviving 5 years [32]. Treatment is particularly difficult in young children due to the long-term cognitive consequences of radiotherapy to the supratentorial area.

Meningiomas

Although these tumors make up approximately 15 % of adult series, they only constitute approximately 2–3 % in pediatric series [77]. They are more common in females and in adolescence and may be associated with neurofibromatosis. A far higher percentage of pediatric meningiomas are intraventricular (25 %) than in the adult population [48]. As with adult meningiomas, the aim of surgery is total removal including adjacent dura, and long-term survival is expected although recurrence may occur. Occasionally, meningiomas are malignant and may metastasize.

Cerebral Metastases

Although common in adults, these tumors only make up approximately 5 % of pediatric brain tumors [48] with the most common primary tumors being sarcomas. Patients usually have pulmonary metastases by the time they present with CNS involvement and the prognosis is poor with survival being measured in months. Providing the lesion(s) are small (<3 cm) one treatment option for this group of patients is radiosurgery (stereotactically focused high dose single shot radiotherapy).

Midline Tumors

Germ Cell Tumors

Intracranial germ cell tumors (GCTs) account for 30 % of all GCTs and are histologically identical to extracranial GCTs. Table 25.2 shows the histological classification used for GCTs, which tend to occur in midline sites (suprasellar or pineal), although occasionally they may arise within a ventricle, or within the hemisphere [48]. The management of this group of tumors is covered under section "Pineal region tumors".

Optic Nerve/Chiasm and Hypothalamic Gliomas

Tumors occurring on the optic pathways make up approximately 5 % of all pediatric brain tumors [78] and 75 % of these present in the first decade of life. Histologically, these tumors are usually low-grade pilocytic astrocytomas, which very rarely undergo malignant transformation. The tumors may be solid or cystic and are usually fusiform. They may arise primarily in the optic nerve and go on to involve the chiasm or, conversely, they may arise initially in the chiasm and spread to the optic nerves or into the hypothalamus [18]. "Skip" lesions may also be seen along the optic pathways – especially in patients with neurofibromatosis. The symptoms and signs of optic nerve gliomas are dependent upon their

Table 25.2 Histological classification of intracranial germ cell tumors

Germinoma
Embryonal carcinoma
Yolk sac tumor (endodermal tumor) Choriocarcinoma
Teratoma
Immature teratoma
Mature teratoma
Teratoma with malignant change
Mixed germ cell tumor

anatomical location. The main presenting features are visual failure, squint, proptosis, endocrine dysfunction, and hydrocephalus. Overall, these tumors are associated with good long-term survival but this can be accompanied by slow progressive visual deterioration [18].

The treatment of these tumors remains controversial as their natural history is highly unpredictable – with some tumors progressing despite aggressive treatment while others remain indolent indefinitely [18, 78]. Up to one-third of patients with optic nerve gliomas have neurofibromatosis (NF1) and further evidence for this phakomatosis should be sought at presentation. In general, tumors in patients with NFI behave in a more indolent manner.

Patients with tumors within the orbit or on the intracranial optic nerve tend to present at a slightly later age (6 years) than those with chiasmatic tumors (2–4 years) [18, 78, 79]. Unfortunately, these posteriorly located tumors, which often involve the hypothalamus at presentation, are the most common form of optic nerve glioma making up some 60 % [80]. These patients may present with hydrocephalus and/or visual problems and/or pituitary dysfunction and/or hypothalamic dysfunction. The latter classically leading to the diencephalic syndrome (emaciation, pallor, and hyperactivity) seen in up to 20 % of patients under 3 years of age [79]. Other symptoms of hypothalamic involvement include diabetes insipidus, anorexia, obesity, and precocious puberty. These tumors also show markedly varying capacity for progression with some remaining indolent while others rapidly increase in size [81].

The imaging investigation of choice is MRI, which usually shows a hypointense tumor on T1-weighted images with enhancement after gadolinium (Fig. 25.8a–c). On T2, high intensity signal may be seen extending to the lateral geniculate bodies, although whether this represents tumor extension or optic tract edema has not yet been determined [79]. Visual evoked responses may be of assistance in monitoring visual function but are of limited value in screening [78].

Management of these tumors remains controversial but in general, patients with reasonable and/or static visual acuity only require surveillance with regular ophthalmic assessment and imaging. Surgery is reserved for problematic proptosis and tumors which are located within the optic nerve but without evidence of spread towards the optic chiasm. Tumors involving the chiasm/hypothalamus may require debulking if there is evidence of tumor progression or if the tumour is causing hydrocephalus – such surgery aims to debulk the mass but leave tumour near the hypothalamus and chiasm. Additionally, histological verification may be important in order to exclude other causes for a suprasellar mass and in particular ascertain if the tumour is a standard pilocytic glioma or the more aggressive pilomyxoid tumour. Frequently CSF diversion is required for the treatment of hydrocephalus in patients with posteriorly located tumors (and occasionally this may be complicated by the formation of problematic ascites).

The role of adjuvant therapy in the treatment of optic pathway tumors also remains controversial and is limited to patients with clinical and radiographic evidence of progression. The young age of many of the patients considerably limits the use of radiotherapy; nonetheless, Jenkin et al. [79] have shown that for posterior tumors, irradiation is effective with a 75 % 10 year relapse-free survival. Side-effects of irradiation therapy not only include those previously discussed (cognitive impairment, endocrine dysfunction, and secondary malignancy) but also an increased risk of developing Moyamoya phenomenon (cerebral ischemia secondary to spontaneous occlusion of the internal carotid arteries) especially in the setting of NF1 [82]. Of the chemotherapeutic agents available, the nitrosourea-based cytotoxic regimens have been shown to result in symptomatic improvement or stabilization [83]. More recently, carboplatin and vincristine has been reported to be effective in arresting growth in progressive optic gliomas and this is now considered standard treatment for patients with NF1 and young children (less than 8 years) [84] (Fig. 25.8).

Craniopharyngiomas

These tumors make up between 5 and 10 % of pediatric brain tumors and approximately 15 % of all supratentorial tumors [85] and thus are the most common nonglial tumors of childhood. Although 50 % of these tumors occur in adults, the peak incidence for the remainder is between the ages of 5 and 10 years [86].

The origin of these unusual tumors has caused much debate over the years but it is generally accepted that they arise from squamous cell rests of an incompletely involuted hypophyseal–pharyngeal duct [87]. Tumors are usually located in the suprasellar region and expand into the hypothalamus and third ventricle. In addition, they grow into the sella and down between the clivus and the brain stem. Approximately one-third of these tumors are purely cystic, while a quarter are purely solid and the remainder mixed – thus overall nearly three-quarters of the tumors are at least partially cystic [87]. The fluid in these cysts is like "engine oil" and contains variable amounts of protein with suspended cholesterol crystals. Calcification is seen in almost all childhood craniopharyngiomas [86]. Histologically, craniopharyngiomas are composed of epithelial cells and form two distinctive variants – the adamantinous and the squamous papillary type. The adamantinous type are mainly found in childhood and tend to be cystic tumors, with calcification seen on imaging, and which are prone to recur and have a worse overall outcome. The squamous papillary type are usually seen in adults and are generally solid, noncalcified lesions.

Although craniopharyngiomas do not invade neural tissue, they cause an extensive glial reaction – especially around the small finger-like tumor projections which occur within the hypothalamus. Additionally, they frequently are strongly

adherent to major arteries and cranial nerves at the base of the brain – in particular the optic chiasm and tracts, the pituitary stalk, and the arteries of the Circle of Willis. It is this unfortunate combination of benign histology and predisposition to form cysts and dense "adhesions" to vital structures that make these tumors such a surgical challenge.

Clinically, these children usually present with signs of raised intracranial pressure secondary to hydrocephalus. Additionally, disturbances of the hypothalamic–pituitary axis may be noted resulting in short stature, diabetes insipidus, obesity, and delayed or precocious puberty. Children of this age may well not complain of visual problems but on presentation over half of them have evidence of visual disturbance (poor acuity, field defect, diplopia or nystagmus) [85]. Plain x-rays show calcification in 85 % [86] and may also show an enlarged sella. Calcification is also shown by CT scans and the degree of cystic/solid makeup of the tumor and any associated hydrocephalus (Fig. 25.9a, b). Enhancement is intensive but mixed, and coronal scanning may help identify intrasellar extension; MRI is superior to CT for displaying general configuration of the tumor and its relationship to surrounding structures.

The treatment of craniopharyngiomas remains controversial, some proponents advocating aggressive total removal in all children [85, 88], while others consider surgery for craniopharyngiomas as merely palliative and believe that subtotal or partial resection followed by radiation therapy should be the rule [86, 89]. Certainly, if at surgery the hypothalamus is involved, a more conservative approach is warranted to avoid hypothalamic morbidity – as represented by the short, obese, somnolent child. It is becoming more widely accepted that survival and progression-free survival after conservative surgery and radiotherapy are as good as those seen after radical surgery and that there is a lower morbidity associated with the former treatment. However, radiotherapy has its own problems – occasional failure to prevent progression, calcification of the basal ganglia, radiation necrosis (especially of the optic apparatus). Although alternative treatments have been tried (e.g., intracystic injection of radioactive isotopes or bleomycin) these have not been widely adopted [85, 90]. Radiosurgery (single treatment high-dose focused radiotherapy) may have a role in treating small solid tumor remnants situated away from the chiasm [85].

Pineal Region Tumors

While making up less than 1 % of most adult series [91], pineal tumors are responsible for some 3–8 % of childhood brain tumors [92]. Tables 25.2 and 25.3 show the wide vari-

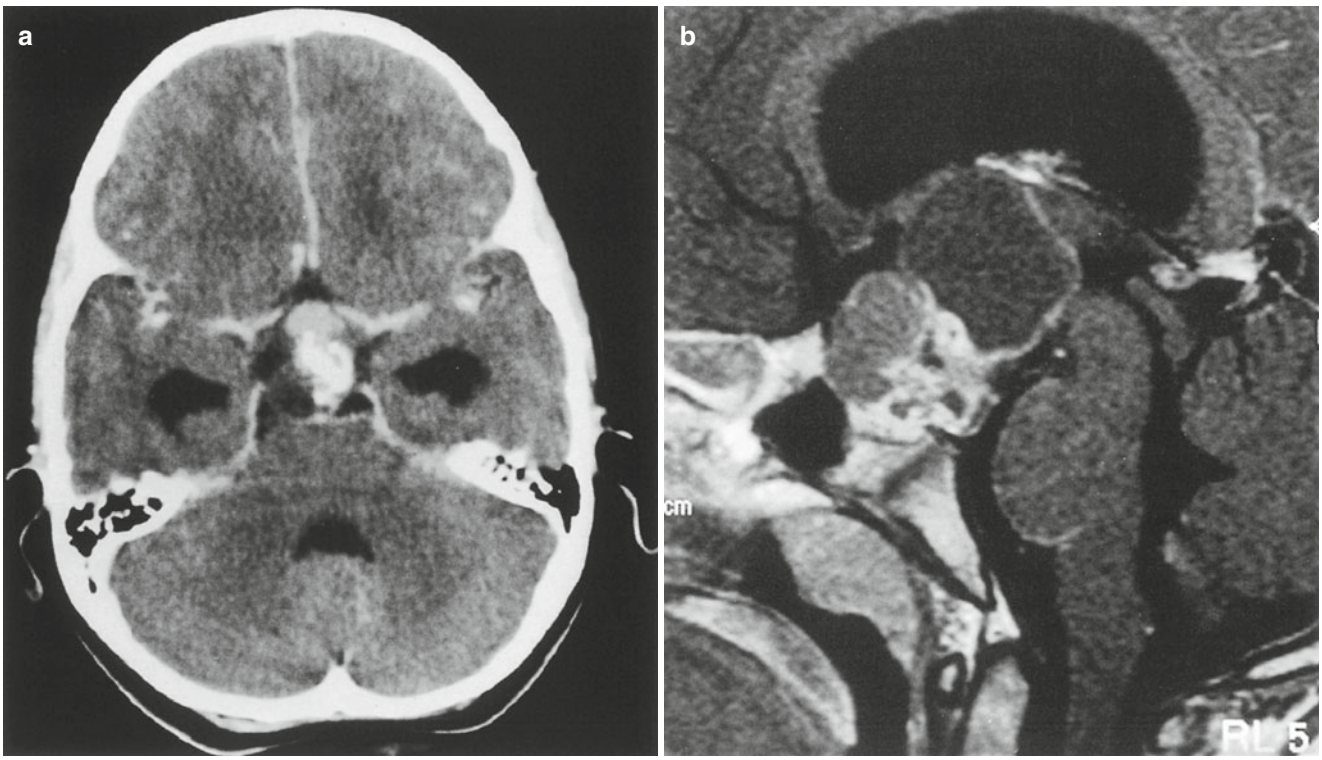

Fig. 25.9 (**a**) Axial CT with contrast showing a partially cystic and partially calcified craniopharyngioma. Note the relationship to the vessels of the Circle of Willis. (**b**) Sagittal T1 weighted MRI shows the extension of the same tumor into the sella turcica, just over the clivus and with a cystic component pushing into the hypothalamus

Table 25.3 Histological variation of tumors found in the pineal region

Tumors of germ cell origin
(see Table 25.2)
Tumors of pineal parenchyma
Pineocytoma
Pineoblastoma
Mixed
Tumors of supportive or adjacent tissues
Gliomas
Ganglioglioma
Meningioma
Non-neoplastic cysts
Pineal cyst
Arachnoid cysts
Vascular lesions
Vein of Galen aneurysm
Arteriovenous malformations
Cavernoma

ety of tumors that may be found at this location; however, between half and three-quarters of all tumors are either germinomas or of astrocytic origin [91]. Historically, surgical morbidity and mortality rates were high and the standard treatment was shunt insertion for the hydrocephalus and "blind" irradiation of the tumor [93–95]. Improvement in surgical instrumentation and the use of various surgical approaches have resulted in a far more favorable experience in recent years with acceptable mortality rates (0–2 %) [91].

Clinically, these children usually present with headache and may have dorsal midbrain syndrome (Parinaud's) consisting of poor upward gaze and difficulty with accommodation. Males are up to four times more likely to develop pineal tumors than females and the average age of presentation is 13 years [91]. Germinomas are particularly prevalent in Japanese adolescent males. Although CT and MRI are useful in delineating the tumor they are not diagnostic (Fig. 25.10). Tumor markers [alpha-fetoprotein (AFP), beta human chorionic gonadatrophin (HCG), and placental alkaline phosphatase (PLAP)] may be raised in both CSF and serum. Preoperative sampling of the CSF is required and at the same time cytology can be undertaken. Raised PLAP is classically seen with germinoma, AFP with yolk sac tumors, and raised HCG with choriocarcinoma.

Due to the wide variability in tumor type – not all of which are radiosensitive – it is now generally accepted that tissue diagnosis is required prior to treatment, the only caveat to this being "secretory tumors" which are positive for AFP or HCG. These markers are only positive in malignant germ cell tumors and many trial protocols would recommend upfront chemotherapy with surgery being reserved for postadjuvant residual tumor. Concern has been raised in the literature on the reliability of histological diagnosis from small specimens obtained by stereotactic biopsy [91] – especially as 15 % of tumors are of mixed histology [96]. Additionally, the site of pineal tumors with their proximity to the deep venous system has resulted in a higher rate of hemorrhage and morbidity with biopsies in this region than in other areas of the brain. For these reasons, open surgical approaches have gained popularity. However, recent reports of stereotactic biopsy in the management of pineal tumors [97] have shown good diagnostic rates and low morbidity and mortality.

Fig. 25.10 Sagittal T1-weighted MRI showing a pineal tumor compressing the tectal plate. The histology was pineoblastoma

The use of endoscopy in neurosurgery (originally reported in 1923) has increased dramatically over the last two decades, and it is now common practice to treat the hydrocephalus associated with pineal tumors by performing an endoscopic third ventriculostomy (making a small hole through the floor of the third ventricle into the interpeduncular cistern thus bypassing the obstruction at the level of the aqueduct). At the same time, CSF may be obtained for cytology and tumor markers and it may be possible to perform a biopsy of the tumor during the same procedure.

From a surgical perspective, patients with evidence of subependymal seeding or spinal drop metastases require a biopsy (either stereotactic or endoscopic) to obtain a diagnosis. Patients with substantially elevated tumor markers do not require histological confirmation prior to starting treatment. For all other patients, either a biopsy (endoscopic or stereotactic) or an open surgical approach with intraoperative fro-

zen section is required. When the histology is benign, attempt at total removal is undertaken; if the histology is reported as a germinoma, no more than a biopsy is performed; while in those children with malignant pineal region tumors an attempt is made to remove as much tumor as possible.

Postoperative adjuvant therapy is obviously tailored to tumor type with no further treatment being required for benign lesions while radiation and chemotherapy may be required for malignant tumors. The 5-year survival for germinomas treated with radiotherapy is over 90 % and therefore many groups recommend radiotherapy alone [91, 96]. Studies are underway to see if it possible to reduce the volume and dose of radiation in patients with germinomas while preserving high cure rates. Secreting tumors have a far poorer prognosis with radiotherapy alone and therefore the use of adjuvant chemotherapy (in particular using etoposide and platinum agents) is now advocated. CSF markers can be used for tumor surveillance and to assess treatment in this group.

Intraventricular Tumors

As a group, these tumors do not usually present until they have reached sufficient size to obstruct the ventricular system resulting in hydrocephalus. Choroid plexus papillomas may also cause hydrocephalus by overproduction of CSF, although the most likely cause for the hydrocephalus is due to raised protein and cellular debris blocking off CSF absorption. Apart from choroid plexus tumors, the other relatively common tumor types are colloid cysts and the subependymal giant cell astrocytoma. The latter is dealt with under the phakomatoses.

Choroid Plexus Tumors

These relatively rare tumors are histologically divided into choroid plexus papillomas (benign) (Fig. 25.11a) and choroid plexus carcinoma (malignant) (Fig. 25.11b). The latter show focal invasion and dedifferentiation of cells with marked nuclear pleomorphism [98]. Carcinomas tend to be larger at diagnosis than papillomas and they disseminate along CSF pathways. Both appear as reddish/gray frondular tumors which are highly vascular. For this reason, they enhance brightly on MRI and CT. In children, they tend to occur in the lateral ventricle [98] while the fourth ventricle is the more typical site in adults [99].

Choroid plexus tumors usually occur in children under 2 years of age in whom there is a small circulating blood volume. This, in combination with the fact that the vascular supply is usually found deep and medial to the tumor, makes these tumors a significant surgical challenge. Complete surgical resection is curative for the papilloma-type and the only long-term survivals

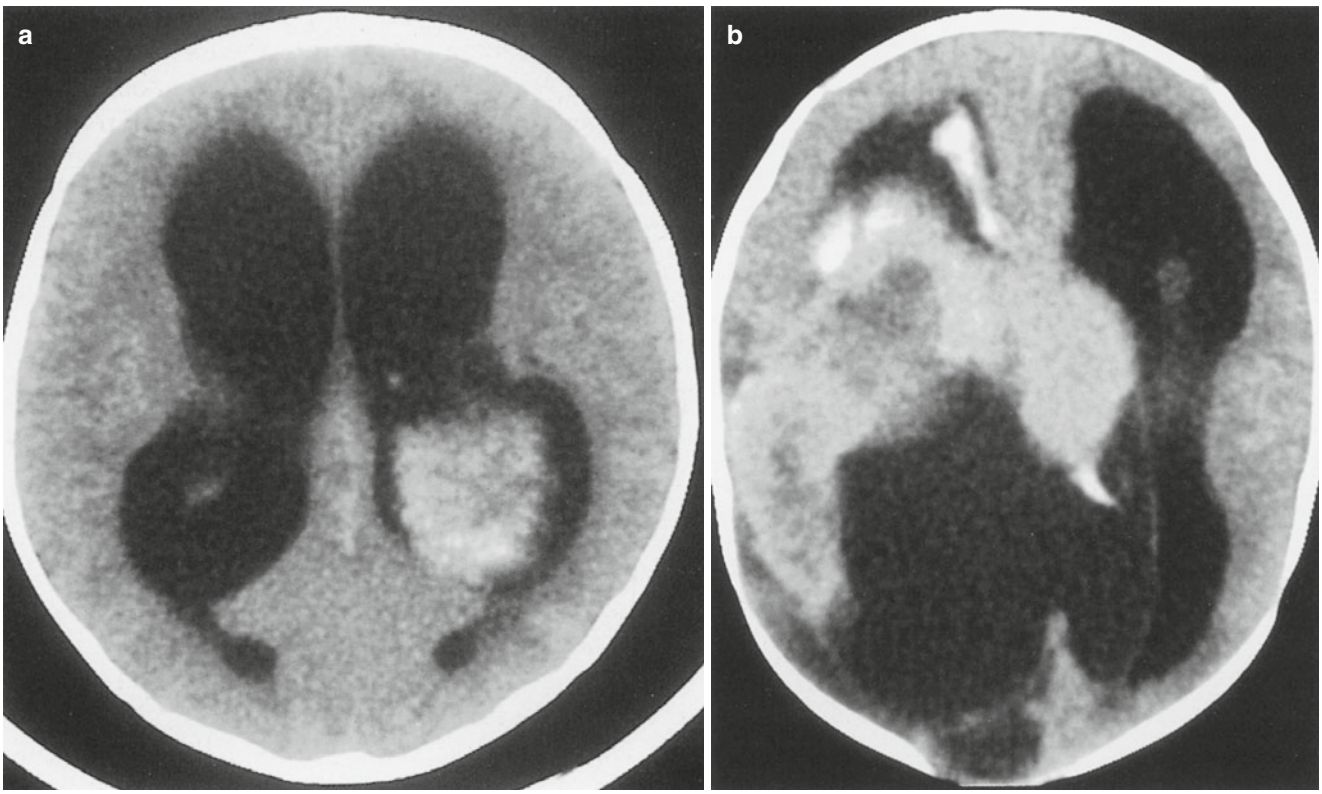

Fig. 25.11 (**a**) CT scan showing benign choroid plexus papilloma. (**b**) CT scan showing choroid plexus carcinoma

reported in the carcinoma-type have occurred after gross total resection and irradiation [100]. The role of presurgical chemotherapy to help devascularize these tumors has been raised by the Toronto group [101] and there are anecdotal reports of success in treating infants with multiagent chemotherapy and of trying to embolise the tumour pre-operatively.

Colloid Cysts

These tumors are rare in childhood but are still occasionally responsible for cases of sudden death. Colloid cysts are benign neuroepithelial cysts whose contents vary from gelatinous to firm in consistency. They are located in the anterior aspect of the third ventricle and may obstruct both Foramen of Munro. It is this site which makes them potentially lethal with their ability to suddenly cause hydrocephalus. Clinically, most patients do not present with acute deterioration or drop attacks but with symptoms of raised intracranial pressure. Various surgical approaches (open via a craniotomy, endoscopic, and stereotactic aspiration) have been advocated for the treatment of these lesions. The role of surgery in truly asymptomatic patients (without hydrocephalus) remains undetermined.

Tumors of the Skull

These "lumps" usually come to light incidentally after minor trauma and 75–90 % [102, 103] are benign with the most common being epidermoid or dermoid tumors and with Langerhans' Cell Histiocytosis being the next largest group.

Dermoid and Epidermoid Tumors of the Skull

Between them, these tumors probably make up less than 1 % of all pediatric brain/skull tumors. Dermoids are usually found around the orbits, around the anterior fontanel and along cranial sutures [103]. These tumors are cysts with stratified keratinizing squamous epithelium forming a capsule of epidermoid and additional dermoid appendages such as hair follicles and sebaceous glands including the walls of dermoids. The tumor usually presents as a painless swelling while those arising around the orbit may present with exophthalmos. Plain x-rays show a rounded erosion of the bone with sclerotic margin while CT scanning shows a lesion which is hypodense. Surgical excision is the treatment of choice.

Fibrous Dysplasia

In this condition, normal bone is replaced by fibrous tissue (fibroblasts and collagen fiber bundles) and the lesion probably represents a developmental defect of mesenchymal tissue [102]. Although occurring in the first few decades of life, lesions are most active during periods of bone growth and during puberty. In nearly 75 % of cases only one bone is involved (the cranium being involved in 10–27 % of cases) (monostotic form) while in the cases where more than one bone is involved (polyostotic) the cranium is involved in over 50 % of cases [102]. If associated with café au lait spots and endocrine dysfunction, the polyostotic form is termed Albright's syndrome. Plain x-ray appearance depends on the amount of bone within the lesion and ranges from radiolucent through to ground-glass or ossified and sclerotic. Growth of the tumor can lead to facial disfigurement or compression of cranial nerves exiting the foramina. Although surgery can be curative, the bones involved often preclude this. These lesions can undergo malignant degeneration to sarcomas (estimated risk of less than 0.5 %) but after radiation, this risk may increase up to 44 % [102].

Langerhans' Cell Histiocytosis (Histiocytosis X)

This refers to a range of proliferative diseases affecting the reticuloendothelial system which results in the formation of tumor-like lesions. The disease spectrum varies from Letterer-Siwe disease in which there is diffuse systemic involvement and which is progressive and often fatal, through an intermediate stage (HandSchüller-Christian disease) in which there is cranial involvement, exophthalmos, and diabetes insipidus; through to eosinophilic granuloma in which solitary lesions are found. The common histological feature is Langerhans' cell histiocytes. In all the conditions, calvarial lesions are the most common and these lesions are usually painful. On plain x-rays they appear punched-out without sclerosis (Fig. 25.12a, b). Diagnosis is obtained at the time of excisional biopsy with curettage. If confirmed, further evaluation (hematological, liver function, chest x-ray and skeletal survey) should be undertaken to determine the extent of active disease. No further treatment is required for single lesions but multiple lesions can be treated with low-dose radiation (300–1000 rads); however, multifocal and multisystem disease requires chemotherapy. After surgical excision of a solitary lesion, continuous followup is necessary as up to one-third of patients can later develop a new lesion after several years [102].

Hemangioma

Pathologically, these are cavernous hemangiomas growing within the diploe and forming a predominantly lytic lesion on plain x-rays. They have the classic sunburst appearance due to radiating bony spicules. Incision and curettage is usually curative.

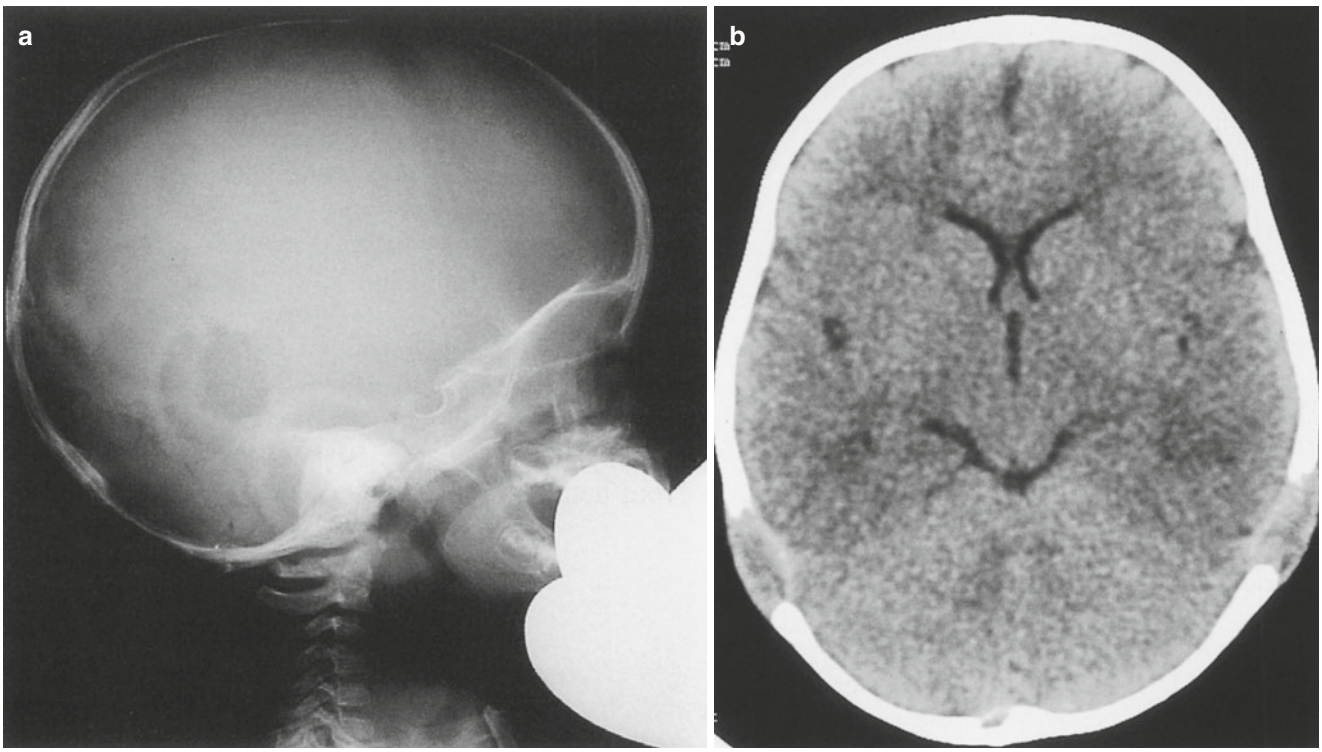

Fig. 25.12 (**a**) Plain x-ray of skull showing punched out lesion of histocytosis on both sides. (**b**) CT scan of the same patient

Osteoma

These are rare, benign, firm, nontender masses which are dense and well demarcated on plain x-ray. If required they can be easily removed.

Aneurysmal Bone Cyst

Although usually a disease of long bones and spine, approximately 5 % occur in the calvarium where they may appear lytic or calcified depending on their age on x-ray. Surgical excision is recommended to prevent hemorrhage after incidental trauma.

Chordomas

These tumors rarely present in childhood but when found in the pediatric population, they are usually located at the skull base involving the clivus and present with lower cranial nerve dysfunction. Metastases to the lung are more frequent in pediatric than in adult patients with chordomas [104]. The investigation of choice to display the tumor extent is MRI. The site makes surgical access difficult but removal has been achieved via far lateral, transoral and more recently endoscopic approaches. Long-term survival for children treated with surgery and radiotherapy approaches 50 % [102]. Proton therapy is thought to be more effective than standard radiation for these tumors.

Malignant Primary and Secondary Tumors

Neuroblastoma, because of its relative frequency, is often seen to metastasize to facial bones and the skull. All forms of sarcoma may be located in the cranium although it is rare for the skull bones to be the primary site.

Spinal Cord Tumors

Spinal cord tumors are divided into extradural and intradural – the latter being further subdivided into those which are intramedullary (meaning within the parenchyma of the spinal cord) and those that are extramedullary. Table 25.4 shows the types of tumor that may present with spinal cord compression (including extradural compression). Most series include all spinal tumors together and also include developmental anomalies – thus making the true incidence of any type difficult to ascertain. Di Lorenzo et al. [104] found a ratio of intracranial to intraspinal tumors of 6.7–1 (making spinal canal tumors some 12–15 % of all nervous system tumors). Nearly 70 % of these were extramedullary and over 40 % of

Table 25.4 Types of tumors causing spinal cord compression

Intradural
Congenital
Dermoid/epidermoid
Teratoma
Extramedullary
Meningioma
Nerve sheath tumors (schwannoma and neurofibroma)
Intramedullary
Primary (glioma, ependymoma, hemangioblastoma)
Metastatic (neural "drop" metastases)
Extradural
Direct Spread
Neural crest tumors (e.g., neuroblastoma)
Soft tissue tumors (e.g., sarcomas)
Bony tumors (benign and malignant)
Metastic

them were extradural. Causes of extradural cord compression include neuroblastomas (Fig. 25.13a–c), tumors of the bony spine and other metastasizing malignancies and these will be discussed in other chapters in this book.

Extramedullary Spinal Tumors

The presenting features depend on the pathology and the age of the child. Delay in diagnosis is the rule rather than the exception. The most common symptom is of pain and motor weakness and in young children the latter may result in regression of ambulatory skills. Sphincter disturbance may also be noticed by delay or regression – although often these symptoms are mistaken as behavioral. Progressive spinal deformity is another method of presentation. Although plain x-rays show abnormalities are present in 50–60 % of extramedullary lesions, the investigation of choice today is MRI.

Epidermoid and Dermoid Tumors

These lesions are generally believed to result from invagination of skin elements during development. However, occasionally, they may arise after multiple lumbar punctures [106]. Histologically, they are similar to their intracranial counterparts. Dermoids are more common in children and both are usually found in the lumbar region often in association with a cutaneous abnormality – hairy patch, port wine, nevus, or dermal sinus. The latter may present with a history of recurrent bouts of meningitis. On MRI scanning, dermoids have the intensity of fat (Fig. 25.14). Complete removal is advocated otherwise recurrence is likely.

Teratoma

These tumors either occur within the spinal canal (usually in the lumbar region) or in the sacrococcygeal area. The latter will not be discussed further here. A third of these tumors arise in children less than 5 years of age [107] and the tumors may be cystic or solid and are usually found in the thoracic or lumbar regions.

Use of MRI shows multiple tissue signals and surgical excision is the treatment of choice with failure of complete removal resulting in recurrence.

Meningioma

Most present in adolescence and usually occur in the thoracic region. Approximately 20 % of cases are associated with NF1 [107] and surgical excision is aimed for with good long-term results but with possibly higher rates of recurrence than that seen in adults [107].

Nerve Sheath Tumors

Schwannomas are composed of Schwann's cells while neurofibromas are a mixture of Schwann's cells and fibroblasts but with an abundance of collagen fibers. These tumors tend to present around puberty and approximately 25 % of them are associated with von Recklinghausen's disease (NF1) [107]. Varying amounts of the tumor may be in the spinal canal with dumb-bell shaped tumors being seen in 20 % of cases. Very occasionally malignant change can occur within them. The investigation of choice is MRI and treatment consists of total removal when feasible.

Hemangioblastoma

Hemangioblastomas may occur as part of von HippelLindau disease and approximately 50 % of spinal hemangioblastomas occur in conjunction with this syndrome. In general, although hemangioblastoma is rare in children, the spinal lesions are more common than cranial [107]. These tumors may be multiple. Treatment is surgical removal.

Metastatic Disease

Extraneural. Involvement of the central nervous system with leukemia is common and may be present at initial diagnosis in up to 30 % of patients with acute myelogenous leukemia (AML) [108]. Without prophylactic treatment, patients with acute lymphocytic leukemia (ALL) will develop CNS disease in 50–80 % of patients [107] but prophylactic treatment reduces this risk to 2–10 %. Leukemia of the CNS presents as either parenchymal or meningeal disease or both and the dural involvement may reach sufficient proportion to produce a mass lesion either within the cranium or within the spinal canal. Hemorrhage can occur from these lesions and infiltration of nerve roots or the spinal cord itself may occur. Diagnosis may be made by CSF cytology and MRI may show meningeal enhancement or masses. Treatment is a combination of radiation and chemotherapy.

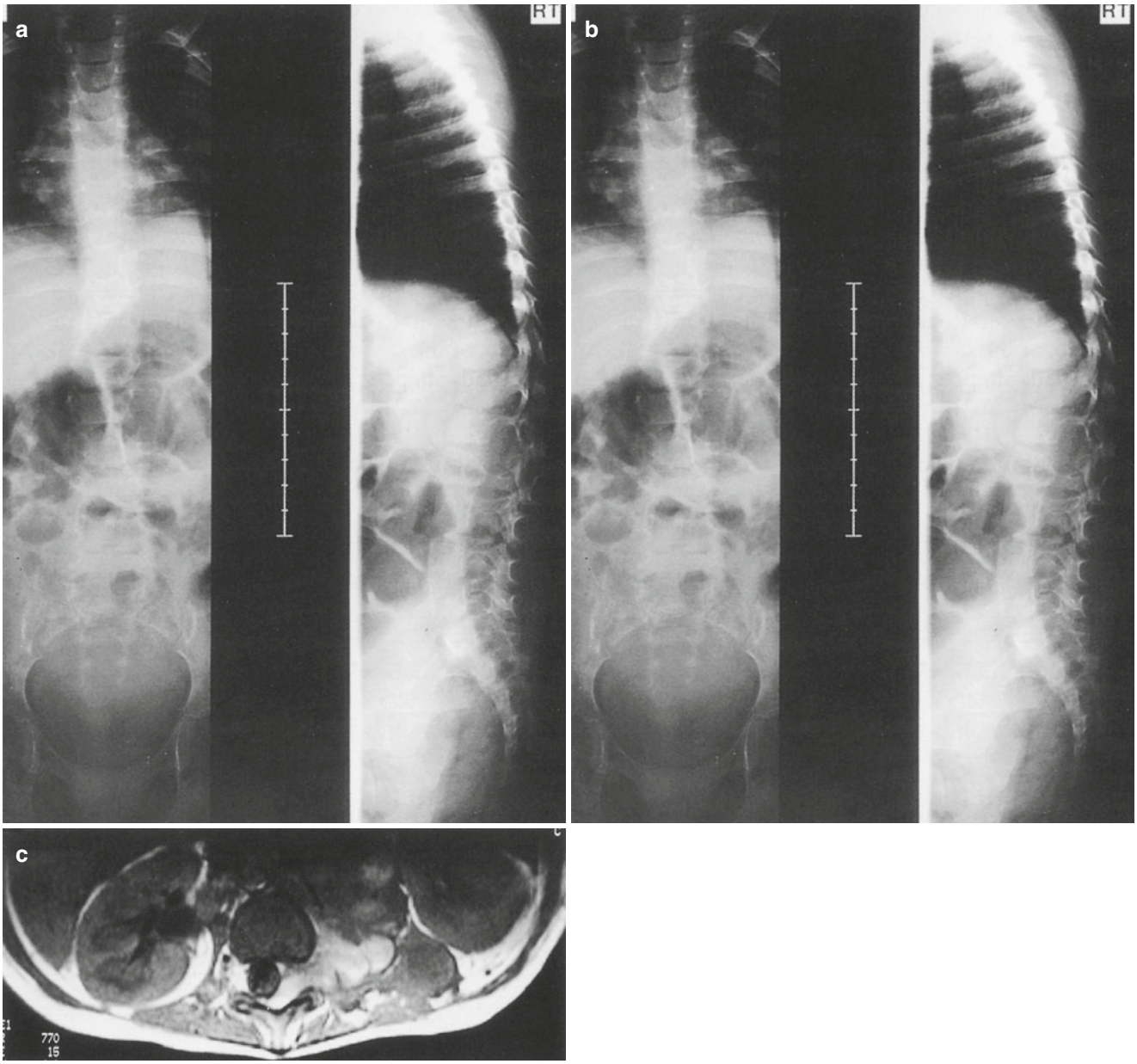

Fig. 25.13 (**a**) Plain anteroposterior and lateral x-rays of a paraplegic 3-year old child showing gross dilation of the nerve root exit foramina. (**b**) Axial and (**c**) sagittal abdominal MRI with gadolinium from the same patient, showing a large enhancing suprarenal mass entering the spinal canal via the left lumbar nerve root foramen. Histologically, this proved to be a ganglioneuroblastoma

Lymphoma can involve the CNS in either primary or secondary fashion. The primary lesions are non-Hodgkins lymphomas and are usually seen in immunocompromised patients [acquired immunodeficiency syndrome (AIDS) or transplant patients], classically being located in the periventricular regions of the cerebral hemispheres. Secondary deposits from both Hodgkin's and non-Hodgkin's lymphomas are seen and are usually extradural – often in the spinal canal. Although generally a medical disease, surgical intervention may be required for acute cord compression not relieved by treatment with chemotherapy.

Neural Origins. The most common causes of drop metastases are PNETs (including the medulloblastomas), anaplastic astrocytomas, ependymomas, and germ cell tumors. Drop metastases are usually seen in the lumbar region. Treatment is generally nonsurgical unless there is a solitary lesion producing acute neurological compression.

Intramedullary Tumors

These relatively uncommon tumors account for only 6 % of central nervous system tumors of childhood [109] and usually occur in adolescence. In the past, these tumors were usually biopsied and given radiotherapy but over the last two

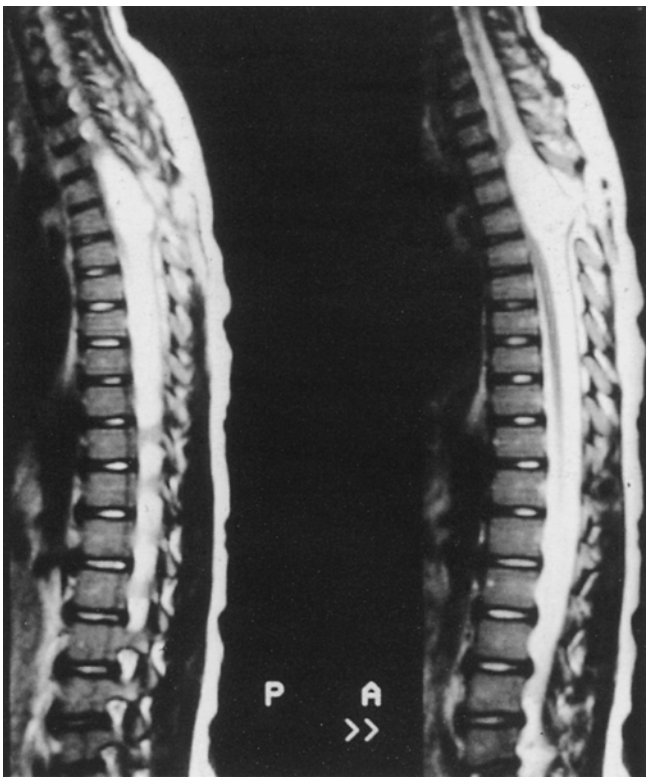

Fig. 25.14 Sagittal T2-weighted MRI of the spine showing a large dermoid (giving the same signal as fat) with marked compression of the spinal cord

Fig. 25.15 Sagittal T1-weighted MRI of the spine with gadolinium, showing an enhancing tumor arising from the conus

decades, it has become apparent that most of these tumors in children should be treated aggressively surgically.

In the pediatric age range, astrocytomas make up approximately 60 % of the tumors and ependymomas make up less than 30 % (compared with over 50 % in adults) [109]. Within the pediatric population there is also a predilection for the tumors to occur in the cervical region (nearly 50 % versus only 30 % in the adult series) [109]. Interestingly, over 10 % of patients at presentation will have associated hydrocephalus (the cause of which is still debated) [109].

The imaging of these tumors has been revolutionized by MRI, which has shown them to fall into two types – (a) holocord astrocytomas (these in effect are similar to the cystic variety of cerebral astrocytomas with a small solid component associated with a large rostral and caudal cyst which may extend the whole length of the spinal cord), and (b) focal tumors (Fig. 25.15). With the holocord type of tumor, surgery is restricted to removing the solid component and subsequent follow-up studies will show the rostral and caudal cysts to gradually disappear. Likewise, gross total excision of the focal tumor should be undertaken. For both low-grade astrocytomas and ependymomas, no further adjuvant therapy is required. It should also be noted that the success of surgery is directly related to the preoperative neurological status and therefore an expectant policy while a child gradually deteriorates is not in the long-term interest of the patient. Follow-up is required for these patients and if there is recurrence; further surgery is the first line of treatment.

Surveillance is also required to detect delayed spinal deformity which is more likely to occur the higher up the spinal column the tumor is located. The cause of this deformity (kyphosis or scoliosis) is not clear but probably represents a combination of structural damage (laminectomy) and neuromuscular imbalance. Laminoplasty (the re-insertion and holding down of the laminae in their original position after surgery) is now routinely employed (Fig. 25.16) although there is no evidence to date that this decreases the risk of spinal deformity.

Occasionally, the astrocytomas are malignant (usually with a shorter history) and in these cases radical resection is not indicated as not only is the morbidity associated with aggressive surgery far higher, but also there has been no improvement shown in survival after radical surgery. In this group of patients, total neuroaxis radiation is required but the outlook is dismal.

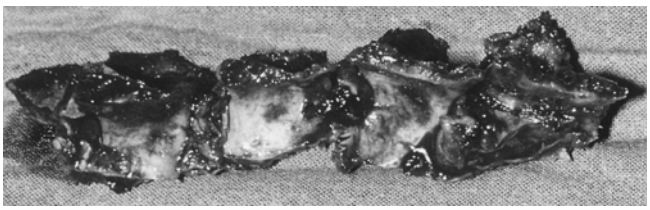

Fig. 25.16 Operative photograph showing four laminae removed en bloc (laminoplasty) which were replaced at the end of the procedure

Intraocular Tumors

Retinoblastoma

Retinoblastoma is the commonest ocular tumor of childhood, affecting one in 20,000 live births worldwide [110], with no racial or gender predilection.

It results from loss of the Rb tumour suppressor gene (Ch13q14). In the genetic (germ-line or heritable) form, every cell is missing one copy of the Rb gene. In the somatic (non heritable) type, a single developing retinal cell loses one copy of the Rb gene during retinal development. This is why genetic cases often have multiple tumours in one or both eyes, and can develop cancers elsewhere, while somatic cases are unilateral and unifocal [111].

Inheritance Patterns

Over 90 % of cases are sporadic. 40 % of all cases are bilateral. Over 90 % of children carrying the Rb gene defect will develop retinoblastoma [111].

Clinical Presentation

Bilateral cases often present early with poor vision, and nystagmus. Unilateral cases usually present later, at 2–3 years, with leukocoria and squint, or with glaucoma, iris heterochromia, phthisis bulbi, orbital inflammation and hyphaema.

Late presentation with proptosis or orbital mass carries a very poor prognosis (Fig. 25.17).

The tumour can spread along the optic nerve, or through the choroid to brain, bones, lungs and abdominal solid organs.

Digital flash photography can highlight the white reflex in some cases, and lead to earlier detection (Fig. 25.18).

The diagnosis of retinoblastoma is essentially clinical, supported by imaging in some cases. Diagnostic biopsy is contra-indicated because of the risk of extra-ocular spread.

The typical findings are one or more round white retinal masses (Fig. 25.19). A characteristic feature is calcification within the tumour on ophthalmoscopy or ultrasonography [16].

Fig. 25.17 Advanced stage retinoblastoma in a child from third world country

Fig. 25.18 Retinoblastoma presenting with leukocoria of the eye

The diagnosis can be confirmed histologically if the eye is enucleated, with characteristic Flexner–Wintersteiner rosettes, Homer Wright rosettes, and fleurettes (Fig. 25.20).

Genetic Testing

Mutation testing: can be performed on blood, and tumour tissue if available (from the enucleated eye). This helps identify germ line cases and consequently determine risk to the fellow eye and to unaffected relatives.

Differential Diagnosis

Coat's disease, Persistent fetal vasculature (PFV), Retinal dysplasia, congenital retinal infection (e.g., toxocariasis),

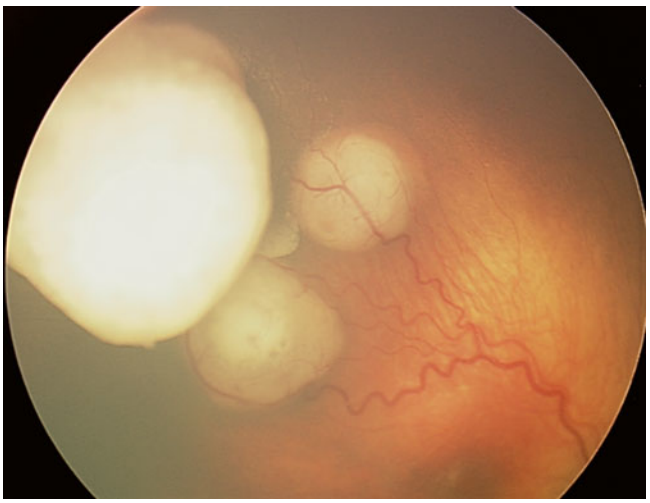

Fig. 25.19 Multiple white retinoblastoma tumours (Retcam photo)

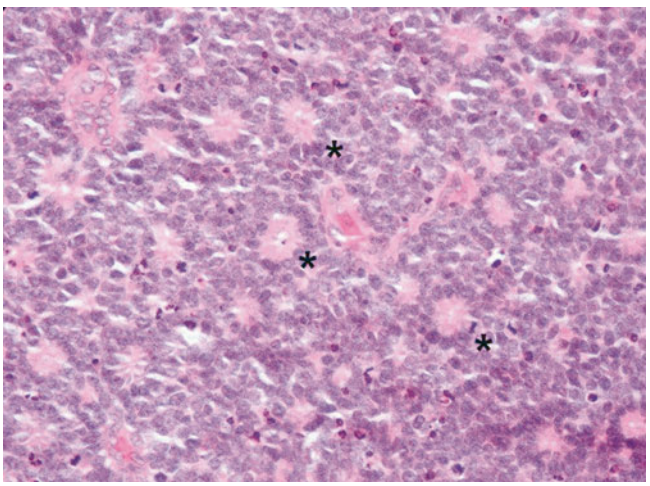

Fig. 25.20 Typical Retinoblastoma with Flexner Wintersteiner rosettes (*asterisks*)

congenital cataracts and glaucoma are all differential diagnoses that can be distinguished on clinical examination [112] (see Table 25.5).

Table 25.5 Table showing a differential diagnostic list of intraocular tumours

Primary ocular disease
Coats disease
Persistent hyperplastic primary
vitreous
Cataract
Coloboma
Retinopathy of prematurity
Myelinated retinal nerve fibers
Osseous choristoma
Infections
Toxoplasmosis Toxocariasis CMV retinitis
Metastatic endophthalmitis
Systemic disorders
Tuberous sclerosis
Norrie's disease
Incontinentia pigmenti
Leukemia
Metastatic malignancies
Other primary ocular tumors
Retinal astrocytomas
Medulloepithelioma
Glioneuroma
Hemangiomas
Retinal pigment hamartomas

Treatment

Retinoblastoma has evolved from a deadly childhood cancer to a largely curable cancer within the past 40 years. Current treatment strategies aim to salvage the eye and provide the best visual outcome possible. This requires significant multidisciplinary input and should be coordinated by a specialised centre.

The various modalities of treatment are:

Chemotherapy: Its main role is to shrink the tumours to a size where laser treatment can be effective (chemoreduction). It is also very effective against vitreous and subretinal disease, and for extraocular involvement and metastases [113].

Chemotherapy can be delivered by 4 routes-Systemic-Common regimens include carboplatin, etoposide, and vincristine (JOE or CEV chemotherapy). There are significant short and long term side effects of chemotherapy, including hearing loss with carboplatin, and nephrotoxicity.

Typically, this involves 4–6 cycles at 3 weekly intervals.

Peri-ocular- subtenon injections of Carboplatin or Topotecan

Intra-arterial- a newer technique involving trans-femoral canulation of the ophthalmic artery to deliver drugs such as Melphalan and Topotecan into the ocular circulation. Generally used as second line treatment for residual/recurrent disease.

Intra-vitreal- direct injection of chemotherapeutic agents into a disease free quadrant of the vitreous after anterior chamber aspiration to soften the eye. This is a new technique which holds promise for vitreous disease which can be difficult to eradicate. Although long term experience is lacking, the initial results are encouraging in selected cases [114].

Laser treatment- suitable for primary treatment of smaller tumours, or larger tumours after (chemoreduction). Laser treatment is however not effective for vitreous seeds.

Laser is delivered through dilated pupils using the indirect ophthalmoscope or microscope. The two common laser

wavelengths are 532 nM green light and 810 nM infrared light (Large spot infrared thermotherapy).

Cryotherapy: trans-scleral delivery results in temperatures of −60 to −80 °C, and is suitable for larger, peripheral tumours.

Radiotherapy: Once the mainstay of treatment, external beam radiotherapy (EBRT, teletherapy) is now reserved for diffuse disease in the only remaining eye, or recurrent disease not responsive to all other forms of treatment. There are significant risks including secondary malignancies in germ line cases, cataracts, dry eyes, soft tissue and bony atrophy.

Plaque brachytherapy involves high dose of radiation to a localized area without the risks of EBRT. It is highly effective against localized vitreous disease and for elevated tumours.

Enucleation: is the treatment of choice for advanced unioocular disease or very advanced eye of bilateral cases.

The eye is sent for histology, and mutation studies. A porous or non porous spherical orbital implant of appropriate size is used depending on the age of the child.

A prosthetic shell painted to match the other eye is fitted in due course for cosmesis.

Treatment Principles

A combination of treatment modalities helps minimize adverse effects.

Examination under anaesthesia (EUA) at decreasing frequency as the child grows older is important for early detection of recurrent or new tumours, with examinations without anaesthesia for older children.

During active treatment, chemotherapy is given over 4–6 cycles at 3–4 weekly intervals, with EUAs before each cycle to monitor response and apply local treatment (laser or cryotherapy). Local treatment may be continued at further EUAs until all tumours are inactive.

Supportive Treatment

Prosthesis fitting for enucleated eyes, psychological support for children and families, protective eye wear for the better/remaining eye during contact sport, long term oncological surveillance especially for germ line cases, and genetic/lifestyle health counseling are all important.

Early Diagnosis- The Role of Imaging and Tissue Sampling

If there is a family history of retinoblastoma there are several options to prevent retinoblastoma or enable early detection

(i) Pre-implantation genetic diagnosis (PIGD) involves screening embryos at the blastocyst stage. Unaffected embryos are selectively implanted ensuring the foetus is born free of the retinoblastoma mutation. Additionally, there is no risk of second cancers, and no risk to future generations. The obvious disadvantage of this technique is the need for in-vitro fertilization (IVF).

(ii) Chorion villous sampling (CVS) or amniocentesis for prenatal RB mutation testing.

(iii) Prenatal ultrasound- in the last few weeks of pregnancy. There is no consensus on the subject of early induction of labour to enable early treatment.

(iv) Cord blood testing for the Rb mutation.

(v) Free fetal DNA testing. This exciting new technique involves testing free (extracellular) fetal DNA which is known to cross the placental barrier. In cases where the mother is healthy and the father is the mutation carrier, maternal blood is tested using DNA amplification. If the mutation is found in maternal blood, one can deduce that it has come from the fetus which must be carrying the mutation. This can then be confirmed at birth with cord blood testing.

Screening for Retinoblastoma

If the mutation for the index case is known, blood testing can be offered to relatives. If the relative is mutation positive or if the mutation is not known for the index case, and risk cannot be excluded, screening exams are offered to enable early detection and treatment.

Screening is not needed if the relative does not carry the mutation.

Prognosis

Most untreated tumours proceed to local invasion and metastasis to cause death within 2 years. Occasionally however, the tumour may spontaneously stop growing to form a retinoma, or necrose to cause phthisis bulbi (shrunken globe).

Most small/medium tumours can be successfully treated while preserving useful vision, and globe salvage is possible in many larger tumours The survival rate varies between as low as 30 % in some developing countries to 95 % in the developed world. Poor prognostic factors include optic nerve involvement and extra-ocular spread.

Recurrence

Recurrence can develop within the eye in previously treated tumours, and regular follow-up examinations are essential. Delayed recurrence in the orbit or distant metastases can occur several years after the initial presentation [33].

Risk of Second Cancers and the Role of Long Term Surveillance

Patients with germ-line mutations are at increased risk of developing secondary malignancies such as pinealblastoma

(trilateral retinoblastoma) osteogenic or soft tissue sarcomas, melanoma and bladder cancer with cumulative risk between 20 and 48 % over 50 years in various studies [115]. This risk is increased with radiation exposure [37]. Patient education and health awareness play a key role in minimising delay in diagnosis and treatment of second malignancies in these patients.

Research Directions

It is likely future research will be directed towards targeted molecular therapy to individualize treatment, exploring biologic treatment eg anti angiogenic agents, growth factors and gene therapy to prevent tumour formation.

Medulloepithelioma

Medulloepithelioma is a rare tumor which arises from undifferentiated nonpigmented ciliary epithelium (though there are isolated reports of pigmented medulloepitheliomas in children). A report in 1988 detailed only 16 medulloepitheliomas recorded at the Institute of Ophthalmology in London over a 25-year period [113]. They can be locally invasive with malignant features and orbital invasion, but distant metastases are uncommon.

They most commonly present between 2 and 4 years of age as a pink-colored mass arising from the iris or ciliary body appearing in the anterior chamber of the eye. Secondary changes such as cataract with reduced vision or iris rubeosis and glaucoma may also be presenting features. Histopathological examination has shown that rubeosis iridis is the most common clinicopathological feature.

More than half of all medulloepitheliomas are classified as benign [115] while the remainder shows cytological features which may resemble neuroblastoma cells, features of embryonal sarcoma, or astrocytoma cells. When histopathology is difficult, because of poor differentiation, diagnosis may be facilitated by the use of immunohistochemistry to identify the neuro-epithelial origin of the tumor [116].

For some tumors local resection with an iridocyclectomy can be curative. Detailed ultrasonographic examination will serve to indicate the extent of the tumor and is a valuable aid in assessing the feasibility of local resection [117].

Successful conservative treatment with local Iodine 125 brachytherapy has also been described [118], but, in most instances, enucleation of the affected eye is necessary. If examination of the enucleated eye shows evidence of extrascleral extension than surgery needs to be followed by postoperative orbital radiotherapy. Rarely, if there is evidence of orbital recurrence, then orbital exenteration may be required.

Malignant Melanoma of the Iris and Choroid

Malignant melanoma of the choroid is the most common primary ocular tumor but rarely affects children. In a series of 3706 consecutive ocular melanomas, only 40 affected individuals were less than 20 years of age and 78 % were between 15 and 20 [119, 125]. Nonetheless, there are isolated reports of very early onset uveal melanoma [120, 126], and it must be considered in the differential diagnosis of retinoblastoma.

Diagnosis is established by identifying the characteristic ultrasonography findings of high internal reflectivity, and fluorescein angiography shows mottled fluorescence in the early phases.

Treatment depends on the size and location of the melanoma, but options include local resection, plaque brachytherapy, transpupillary thermotherapy with the diode laser or, most commonly, enucleation of the affected eye.

Juvenile Xanthogranuloma (JXG)

JXG is a benign inflammatory lesion of the iris and ciliary body containing histiocytes, lymphocytes, and Touton giant cells. Clinically JXG may take the form of a discrete nodule or a diffuse thickened yellow plaque on the iris, and is often associated with an ipsilateral, yellow papular skin lesion. JXG is a notorious cause of spontaneous hyphema (bleeding into the anterior chamber of the eye) in children, and if it shows that tendency, treatment with topical or subconjunctival steroids may be necessary.

Occasionally the uveal tract may become diffusely involved in Letterer-Siwe disease, a systemic histiocytic disorder.

Intraocular Vascular Tumors

Vascular intraocular tumors may appear in isolation or as part of a neurocutaneous syndrome (see section "Phakomatoses").

Choroidal Osteoma

Choroidal osteoma is usually unilateral, and consists of a well-circumscribed, yellow/orange placoid lesion. They show genuine bone formation with osteoblasts, osteocytes, and osteoclasts all present. The bone is laid down in trabeculae and there are intertrabecular marrow spaces.

They require no treatment and are easily identified with CT imaging which shows discrete shield-shaped plaque of calcification in the choroid. It should be considered with differential diagnosis for calcified unilateral retinoblastoma.

Myogenic and Neurogenic Tumors

Myogenic tumors, both leiomyomas and rhabdomyosarcomas, are extremely rare in an intraocular location.

Neurogenic tumors are also extremely rare in this location in childhood. The exceptions are those neurogenic tumors associated with the phakomatoses.

The phakomatoses are a group of disorders in which skin, eye, and central nervous system are involved. Included in this group of disorders are:

- Neurofibromatosis type 1 and 2
- Tuberous sclerosis
- Von Hippell-Lindau syndrome
- Sturge-Weber syndrome
- Klippel-Trenaunay-Weber syndrome
- Wyburn-Mason syndrome

Neurofibromatosis type 1 is a common neurocutaneous condition with an autosomal dominant pattern of inheritance. NF1 has a birth incidence of 1 in 2500 to 1 in 3000; the diagnosis is based on clinical assessment and two or more of the features listed in Table 25.6 are required [121]. The causative mutation occurs on the long arm of chromosome 17 at the q11.2 site and results in underproduction of the tumor suppressor protein neurofibrin [122].

Clinicians should be aware that some individuals with mosaic/segmental NF1 present with six or more café au lait patches and skin fold freckling; however, the skin manifestations are in a restricted segment of the body.

Lisch nodules, a highly characteristic pigmented hamartoma are found in 90–95 % of children by the age of 3 years. Histologically they are a variant of neurofibroma and are of value in establishing the diagnosis but need no intervention.

Plexiform neurofibromas, on the other hand, cause significant morbidity because they are diffuse, grow along the length of a nerve, and may involve multiple nerve branches and plexi. The lesions can be nodular, and multiple discrete tumors may develop on nerve trunks. Plexiform neurofibromas infiltrate surrounding soft tissue and bony hypertrophy is evident in some instances.

Table 25.6 Diagnostic criteria for neurofibromatosis 1

6 or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
Axillary or groin freckling
Optic pathway glioma
2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/ pseudarthrosis)
First degree relative with NF1

Facial plexiform neurofibromas causing disfigurement appear during the first 3 years of life and commonly affect the orbits and eyelids. Removal of benign plexiform neurofibromas is difficult due to encroachment of the tumor on surrounding structures and its inherent vascular nature. Life-threatening hemorrhage can occur and expert advice from experienced soft tissue tumor or plastic surgeons is essential before removal. A number of agents (including farnesyl transferase inhibitors, antiangiogenesis drugs, and fibroblast inhibitors) are being used in clinical trials to assess their therapeutic effect on growth of plexiform neurofibromas.

There is an 8–13 % lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST) in NF1, but predominantly in individuals aged 20–35 years. These cancers usually but not invariably, arise in pre-existing plexiform neurofibromas.

Optic pathway gliomas (OPG) are grade 1 pilocytic astrocytomas and are found principally in the optic pathways, brainstem, and cerebellum. They occur in about 15 % of children with NF1, are often asymptomatic and more indolent than their counterparts in the general population. However, some tumors produce impaired visual acuity, abnormal color vision, visual field loss, squint, pupillary abnormalities, optic atrophy, proptosis, and hypothalamic dysfunction. The risk of symptomatic OPG is greatest in children under 7 years and older individuals rarely develop tumors that require medical intervention [123]. If the integrity of the chiasm is threatened by an optic nerve glioma it is necessary to consider reducing the tumor volume with chemotherapy. Occasionally surgery is warranted to deal with severe proptosis with corneal exposure, or to debulk extensive chiasmal gliomas. Radiotherapy is not advocated in young children because of potential second malignancy [130].

Neurofibromatosis Type 2 (NF2) is an autosomal dominant neurocutaneous disease that is clinically and genetically distinct from NF1 and occurs in approximately 1 in 25,000 individuals. It is caused by inactivating mutations on chromosome 22q11.2 and is characterized by bilateral vestibular schwannomas. Affected individuals also develop schwannomas on other cranial, spinal, peripheral, and cutaneous nerves. Café au lait patches are less numerous than in NF1 and the skin lesions are predominantly schwannomas. Slit lamp examination reveals juvenile subcapsular lens opacities in the majority of patients and multiple retinal astrocytomas are much more likely than in NF1 (Figs. 25.21 and 25.22).

Children with Tuberous Sclerosis (TS) show a combination of cutaneous angiofibromas, retinal astrocytic hamartomas, and CNS hamartomas causing developmental delay and epilepsy. The ocular lesions require no treatment and will only cause visual disturbance if they are located at the

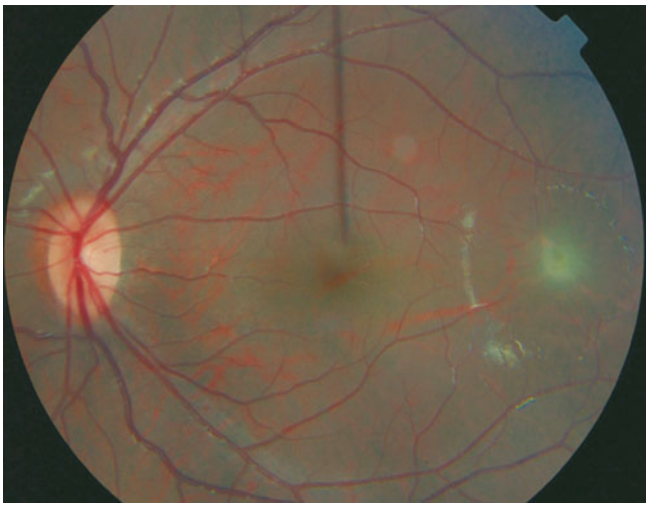

Fig. 25.21 Multiple retinal astrocytomas in neurofibromatosis

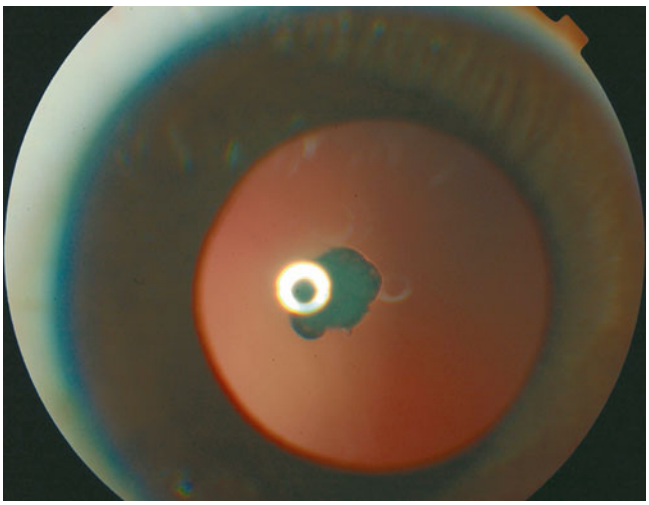

Fig. 25.22 Juvenile subcapsular lens opacities in neurofibromatosis

macula. However, the ophthalmologist may well be the first clinician to recognize the condition, and needs to ensure that a detailed assessment is undertaken, because of the association with renal and cardiac pathology (Fig. 25.23).

Von Hippel-Lindau syndrome is characterized by the formation of retinal capillary angiomas and cerebellar angiomas or hemangioblastomas. The retinal lesion may cause exudation, and since this exudation tends to accumulate at the macula area, it is associated with significant visual loss. In extreme cases the accumulated exudate leads to a retinal detachment, so that treatment at an early stage is desirable.

The aim of treatment is to encourage absorption of the exudate. For lesions between the equator of the globe and the ora serrata, cryotherapy to the base of the hemangioma is most appropriate, using a triple freeze thaw technique. For more posteriorly located tumors isolation with argon laser photocoagulation with later sealing of the feeder vessels is the preferred approach.

The major ophthalmic complication of Sturge-Weber syndrome is glaucoma with up to 30 % of affected children developing glaucoma. The diffuse choroidal hemangioma, which some affected children show, does not require surgical intervention in the vast majority of cases. If it is associated with sight-threatening retinal exudation, then laser photocoagulation, to promote absorption of the exudate, may be attempted.

Orbital Tumors

Orbital tumors in childhood may be benign or malignant; they may be derived from any of the structures within the orbit or they may metastasize to the orbit from a distant site. Table 25.7 reflects the nature and origin of the tumors and is a useful template for this discussion.

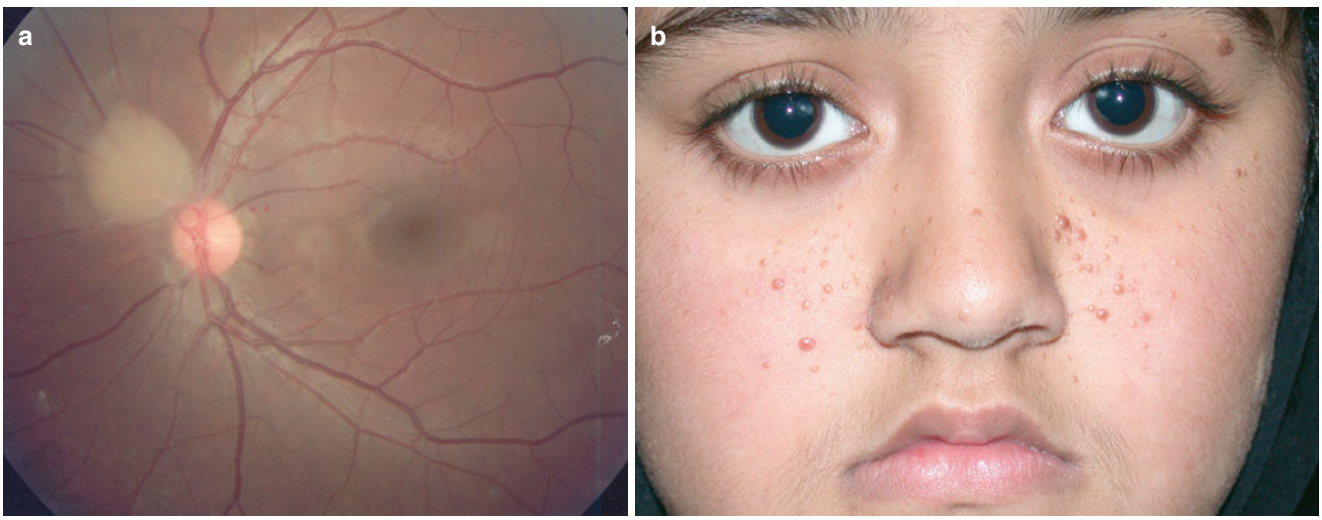

Fig. 25.23 (**a**) Retinal astrocytoma and (**b**) adenoma sebaceum in a child with tuberous sclerosis

Table 25.7 Classification of orbital tumors

Primary benign: Derived from orbital structures
Primary malignant
Secondary benign: Arising from adjacent structures
Secondary malignant
Orbital cysts
Metastatic
Associated with systemic disease

Diagnosis

Regardless of their nature, most orbital tumors present with proptosis and limitation of ocular rotations. Pain and inflammation are more variable symptoms and other signs will depend on the tissue of origin. For example, profound visual loss, pupillary abnormality and optic nerve swelling or atrophy are the hallmarks of optic nerve gliomas but are rarely seen with rhabdomyosarcoma.

Primary Benign Orbital Tumors

Neural
- Optic nerve glioma
- Optic nerve meningioma
- Neurofibroma
- Schwannoma

Vascular
- Capillary hemangioma
- Lymphangioma
- Varix
- AV malformation

Adipose and muscular
- Lipoma
- Myofibroma

Fibrous
- Fibroma
- Fibromyxoma
- Fibrous tissue dysplasia

Osseous and cartilaginous
- Osteoma
- Juvenile ossifying fibroma
- Aneurysmal bone cyst

Optic Nerve Glioma

Optic nerve glioma is the commonest intrinsic tumor of the optic nerve. It typically presents around the age of 5 years with loss of vision, painless axial proptosis, and limited ocular movements. Girls are more commonly affected than boys and up to 50 % of affected children have NF1 [127].

It is a benign, slow growing, low-grade pilocytic astrocytoma and carries a better prognosis when it is associated with NF1 [128]. Occasionally, particularly in younger children, optic nerve glioma shows more aggressive local expansion and these typically are the children likely to need surgical intervention.

The diagnosis is established by imaging which shows a tubular or fusiform swelling of the optic nerve, and characteristic "kinking" of the affected nerve. MRI will show the extent of the tumor, whether there is intracranial extension and any evidence of chiasmal involvement. Visual field testing (in children who are sufficiently cooperative) will identify any involvement of fibers derived from the contralateral optic nerve.

Management consists of observation, including serial visual fields, if the cosmesis is good and there is no threat to the chiasm. Poor vision with severe proptosis, or threatened chiasmal involvement are indication for either chemotherapy (usually with vincristine and carboplatin) or globe sparing optic nerve excision [129, 131]. This surgery can be performed through a lateral orbitotomy if only the orbital portion needs removal, but a craniofacial exposure permits more complete excision of the nerve including the intracranial prechiasmatic portion (Fig. 25.24).

Optic Nerve Meningioma

Optic nerve meningioma is a rare tumor in infants and children. The mean age of presentation is 10 years. It occurs more commonly in males with an increasing incidence with age. The orbit is one of the most common locations. Presentation is of chronic progressive visual loss with mild proptosis associated with diplopia, headache, and ptosis. The tumor is histologically benign but the clinical course tends to be more aggressive in children than in adults. There can be hereditary predisposition and on genetic testing there can be a deletion of part of chromosome 22.

Primary Orbital Cysts

- Dermoid
- Sebaceous
- Hematic
- Hydatid
- Lacrimal duct cyst (Dacryops)
- Microphthalmos with cyst

Fig. 25.24 (**a–c**) Sequence of clinical photos after intralesional injection of triamcinolone and dexamethasone

Malignant Orbital Tumors

Primary Orbital Malignancy
- Rhabdomyosarcoma
- Lacrimal gland adenoid cystic carcinoma
- Sarcoma
- Teratoma

Metastatic orbital malignancy
- Neuroblastoma
- Ewing's sarcoma
- Wilm's tumor

Orbital involvement in systemic malignancy
- Lymphoma
- Leukemia
- Histiocytosis
- Plasmacytosis

Primary Benign Orbital Tumors

- Sinus mucocoele
- Encephalocoele
- Meningocoele

Other Causes of Proptosis in Childhood

Lymphoid
- Benign reactive lymphoid hyperplasia

Histiocytic
- Eosinophilic granuloma

Lacrimal
- Ectopic lacrimal gland
- Lacrimal gland inflammation

Inflammation
- Orbital Pseudotumor
- Orbital myositis
- Wegners
- Sarcoid
- Tuberculosis (Table 25.8)

Table 25.8 Other causes of proptosis in childhood

Lymphoid
Benign reactive lymphoid hyperplasia
Histiocytic
Eosinophilic granuloma
Lacrimal
Ectopic lacrimal gland
Lacrimal gland inflammation
Inflammation
Orbital pseudotumor Orbital myositis Wegners
Sarcoid
Tuberculosis

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