Medulloblastoma-PNET, Craniopharyngioma Adult Tumors of Pediatric Origin

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10.1 Epidemiology

According to the new WHO classification, embryonal tumors comprise medulloblastomas, primitive neuroectodermal tumors (PNET), medulloepitheliomas, ependymoblastomas, and neuroblastomas. We include here also craniopharyngiomas.

A detailed description of medulloblastomas, PNETs, craniopharyngiomas, and ependymomas is given in the pediatric chapter. We will focus in the following on specific features that characterize adult tumors of these entities. Neuroblastomas are rarely found in neuro-oncological patients except when they metastasize in the central nervous system (CNS).

Medulloblastomas derive from primitive neuroectodermal precursor cells, are primarily pediatric tumors, and occur in 80% below the age of 15 years (median age 5–9 years) [24]. They represent 15–25% of all childhood brain tumors, but only 1% of adult intracranial neoplasms [13]. There is a certain male preponderance. Several reports found adult tumors more often located lateral in the hemisphere, whereas pediatric medulloblastomas are more frequent in the midline [24]. Consecutively, the desmoplastic medulloblastoma variant, which is found more often in the lateral distribution, occurs in a higher percentage in adults (35–73%), while the classical variant prevails in children (70–85%) [24]. Another very rare variant, found only in adults, is the lipomatous medulloblastoma with a favorable prognosis. Only 15 cases have been reported so far in the literature [7].

Rare variants of embryonal tumors are the medulloepithelioma, the ependymoblastoma, and the cerebral neuroblastoma. Medulloepitheliomas occur predominantly during the first 5 years of age in the cerebral hemispheres.

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Craniopharyngiomas arise in 40% after the age of 16 years and have a second peak incidence between 50 and 60 years of age.

10.2 Symptoms and Clinical Signs

The leading symptoms in approximately 90% of patients with medulloblastomas are headaches (due to occlusive hydrocephalus), followed by nausea and vomiting in about 75%, and ataxia in 67% [18].

In contrast, craniopharyngiomas become clinically evident through symptoms deriving from disturbance of the pituitary gland, the hypothalamus, or the brain stem, including adjacent cranial nerves. Hormonal dysfunction occurs in up to 60%, with hypogonadism in adults and growth retardation in children. Diabetes insipidus is present in 15–30%. Visual disturbances with reduced visual acuity or visual field defects are very common in 50–75%, followed by headaches in 57% [23].

10.3 Diagnostics

10.3.1 Medulloblastoma

In general, medulloblastomas appear as ill-defined, hyperdense lesions in the posterior fossa on CT images, with no consistent contrast enhancement. The MR characteristics, however, can be rather variable in children and particularly in adults. Most adult medulloblastomas are located in the cerebellar hemisphere, whereas the pediatric tumors are found in the vast majority in the vermis/midline. Medulloblastomas appear as low or isointense signal on T1-weighted and isointense signal on T2-weighted images. Cystic or necrotic areas are particularly visible on T2-weighted images (Fig. 10.1). Contrast enhancement is extremely variable from none to intense. A detailed analysis by Malheiros et al. [17,18] showed no distinction between different histological medulloblastoma types (classic versus desmoplastic) by MRI.

10.3.2 Craniopharyngioma

Characteristic features of craniopharyngiomas, which may have intra- as well as suprasellar extension, are calcifications, erosion of the clinoid processes and the dorsum sellae on CT scans, cyst formation (hyperintense on T2-weighted MR images), and strong contrast enhancement in hypointense tumor parts on T1-weighted MR images (Fig. 10.2) [21].

10.4 Staging and Classification

10.4.1 Medulloblastoma

Medulloblastoma is an invasive, malignant, neuroectodermal embryonal tumor, corresponding to WHO grade IV. Classic and desmoplastic medulloblastomas are the most common histological variants. The classic variant is composed of densely packed cells with highly hyperchromatic nuclei and scanty cytoplasm, whereas the desmoplastic variant is characterized by the presence of reticulin-free nodules (“pale islands”) with reduced cellularity surrounded by highly proliferative cells that produce a dense intercellular reticulin fiber network [13]. The lipomatous variant is very rare and only present in adults with a uniquely favorable prognosis. Apart from the typical blue, small-cell tumor features, this variant is dominated by multiple lipid vacuoles and adipocytes. On the molecular basis, several developmentally regulated genes have been detected that are involved in the pathogenesis of medulloblastomas. The sonic hedgehog signaling pathway directs the embryonic development of external granular cells of the cerebellum and is disrupted in medulloblastomas [26]. A panel of upregulated genes and overexpressed proteins in medulloblastoma, including Unc33-like protein (ULIP), SOX4, Neuronatin, BARHL1, nuclear matrix protein NRP/B, and the homebox gene OTX2, as well as a reduced expression of the HIC-1 gene, have been identified [31, 33].

Medulloepitheliomas characteristically exhibit tube-like epithelial formations comparable to the neural tube.

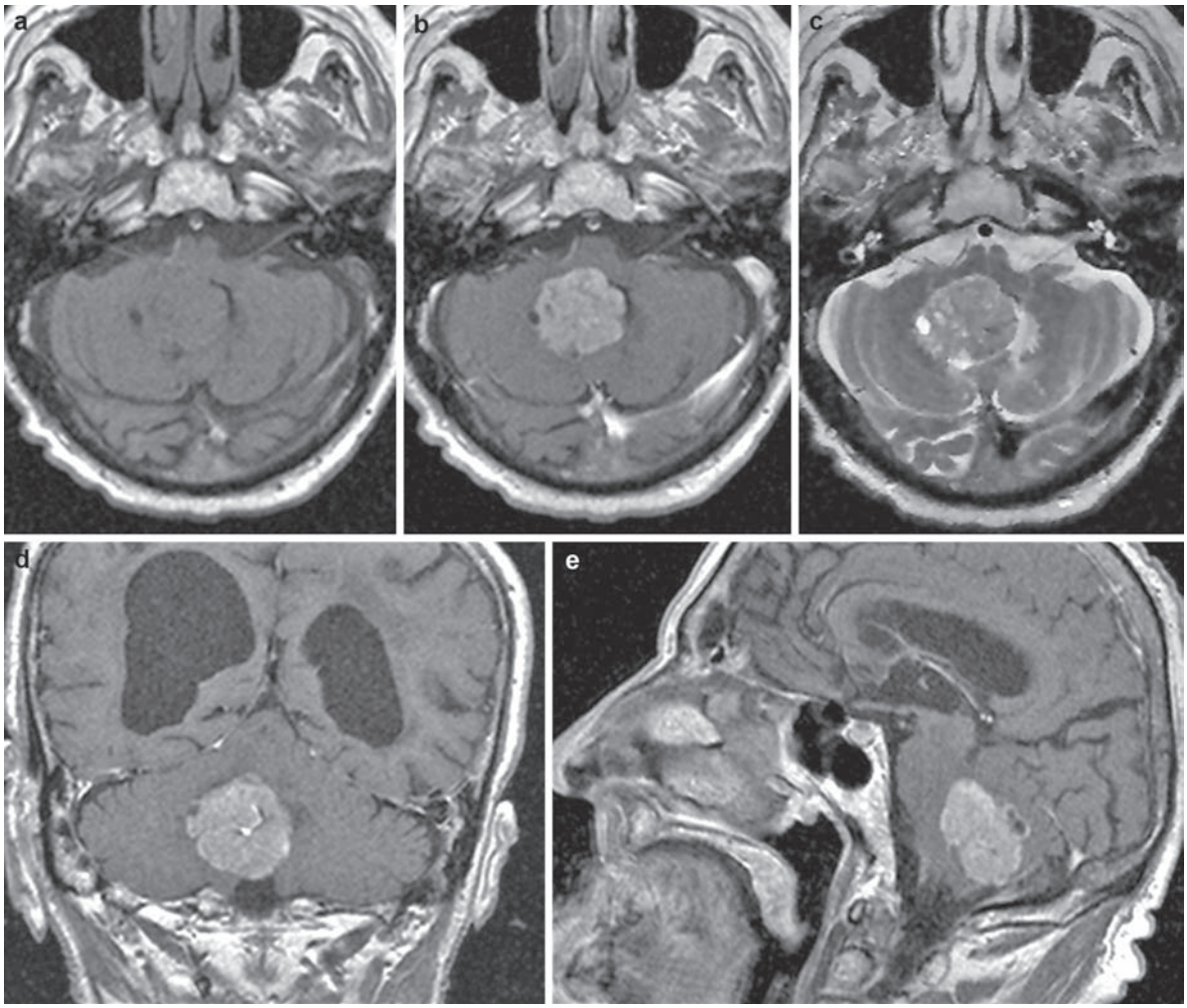

Fig. 10.1 (**a**–**e**) Medulloblastoma of an 81-year-old male patient. Axial T1-weighted image demonstrates an isointense lesion in the fourth ventricle (**a**) with some cystic areas (**c**). Axial (**b**), coronal (**d**), and sagittal (**e**) images show inhomogeneous contrast enhancement

10.4.2 Craniopharyngioma

This tumor derives from epithelial cell remnants of the former Rathke cleft, which later forms the pars intermedia of the anterior pituitary lobe. An adamantinomatous and a papillary type are discerned, without any known difference in the prognosis of both variants.

10.5 Treatment

10.5.1 Medulloblastoma

Medulloblastomas in adults are very rare, and the sole available data are derived from small retrospective series collected over long periods, during which

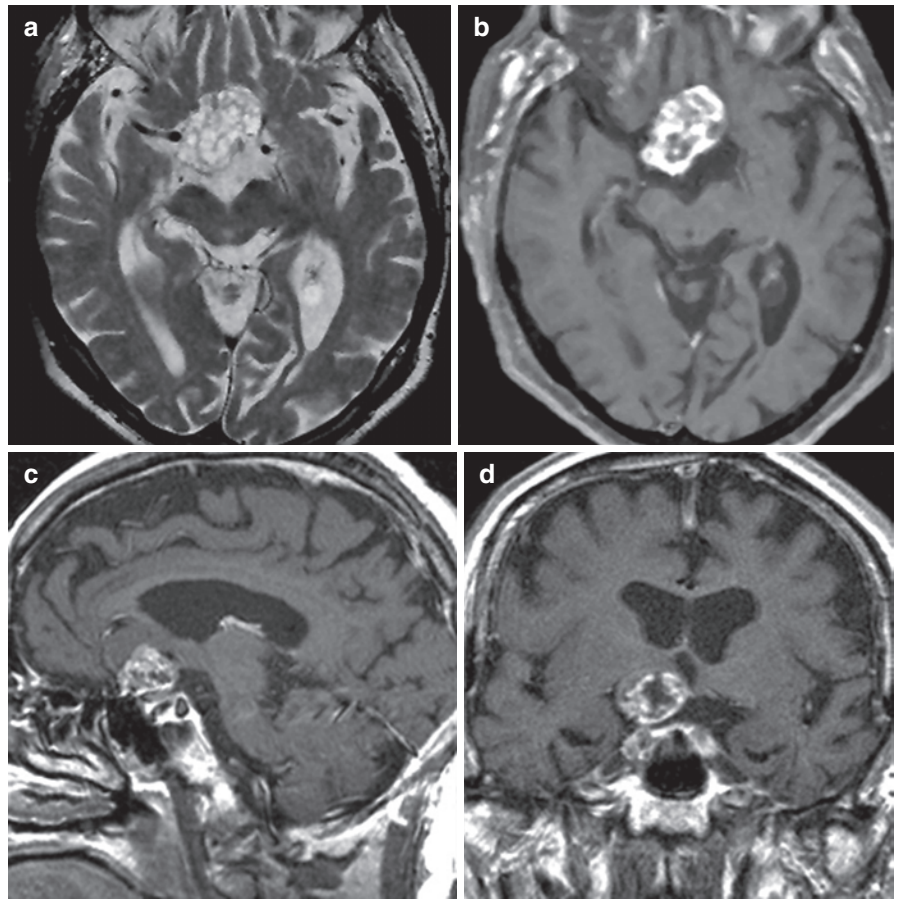

Fig. 10.2 (**a**–**d**) Craniopharyngioma of an 82-year-old male patient. Cystic tumor with suprasellar extension on T2-weighted MR image (**a**) and strong but irregular gadolinium uptake (**b, c, d**)

morbidity and mortality in neurosurgical procedures have drastically changed, radiotherapeutic techniques have improved, and treatment strategies including different chemotherapeutic protocols have been optimized. Brandes et al. [4] performed the first prospective study and included 36 patients over the age of 18 years.

Surgical resection of the lesion still remains the first-line treatment in medulloblastoma patients. According to Brandes et al., low-risk patients with no residual disease should receive craniospinal radiation of 36 Gy and a boost to the posterior fossa of about 18 Gy. High-risk patients with residual or metastatic disease should receive additional chemotherapy with cisplatin, etoposide, and cyclophosphamide [4]. Preradiotherapy chemotherapy did not affect the final outcome or result in tumor progression as postulated in children, although some authors recommend a few chemotherapeutic cycles prior to radiotherapy [18]. However, chemotherapy-related toxicity seemed to be higher and median survival time shorter than in the pediatric patient group [9]. In patients with recurrent medulloblastomas, high-dose chemotherapy with autologous stem-cell transplantation seemed to be effective [34].

10.5.2 Craniopharyngioma

Gross total resection, in most cases through a transcranial approach (solely intrasellar tumors can be resected by a transsphenoidal route), should be the primary goal [32]. Although the mainstay of treatment is still the attempt to radically remove a craniopharyngioma at the initial surgical procedure, removal of the dorsoapical parts of the tumor capsule, especially in patients of older age, can lead to severe neuropsychological deficits and hypothalamic syndromes. Thus, in these patients a more conservative approach is preferable [11]. In case of a cystic tumor or recurrent cysts, stereotactic catheter placement

for cyst aspiration is another option [3, 22, 25, 27]. Radiotherapy either as conventionally fractionated radiotherapy or radiosurgery is recommended by some authors for recurrent non-operable tumors [6, 8, 16, 20, 29].

10.6 Prognosis/Quality of Life/ Follow-Up/Specific Problems and Measures

10.6.1 Medulloblastoma

In general, the prognosis of medulloblastomas has significantly improved over the last decade because of new achievements in chemotherapeutic and radiotherapeutic regimens. The overall 5-year survival ranges between 65% and 84% [1, 15, 18], while the progression-free survival at 5 years is 51–74% [1, 5, 15, 2]. The prognosis in adults compares favorably with that in children, mostly due to the benefit of adjuvant radiotherapy [1, 15, 18, 19]. According to the study of Sarkar et al., the survival benefit in adults does not seem to be related to the histological variant (classical versus desmoplastic medulloblastoma variant), but rather to age [24]. The one exception, the lipomatous medulloblastoma variant, which occurs in adults only, has a uniquely favorable prognosis, even with incomplete resection or multicentric appearance [7].

10.6.2 Craniopharyngioma

Van Effenterre et al. retrospectively analyzed the outcome in 122 adult and pediatric craniopharyngiomas [28]. The functional results in both groups were excellent in 85%, good in 9%, and fair in 5% (usually due to ophthalmologic deficits), provided treatment was started at an early stage. The 5- and 10-year survival rates were 92% and 85%, respectively. Disturbances of the water-electrolyte system due to affection of the pituitary stalk with subsequent diabetes insipidus are common. However, this can be treated effectively today with ADH substitution as nasal spray or tablets. One can conclude that radical resection leads to good outcome in terms of survival, full recovery, and quality of life for both adults and children [12].

10.7 Future Perspectives

With the refinement of molecular diagnostics, an increasing number of genetic and epigenetic alterations in medulloblastomas and ependymomas have been found [10, 14, 26, 30, 33]. Spinal ependymomas are clinically and genetically distinct from their intracranial counterpart. They have a more favorable prognosis than intracranial ependymomas of the respective WHO grade. Allelic loss on chromosome 22q was detected in anaplastic intracranial ependymomas in children and in a subset of adult intraspinal tumors [10]. Detailed analysis suggested that there may be two distinct genes on chromosome 22q involved in ependymoma pathogenesis [14]. Another putative tumor suppressor gene HIC-1 residues on chromosome 17p, which was found to be hypermethylated significantly more often in intracranial tumors and in tumors of younger patients [30]. Knowledge of different molecular genetic factors that may influence the prognosis can be of importance for the clinical evaluation and treatment decisions in the future.

Stereotactic radiosurgery is becoming an interesting treatment option for craniopharyngiomas after incomplete resection or recurrent tumors in delicate locations such as the cavernous sinus.

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