Brain Tumors Relevant to Clinical Neuro-Ophthalmology

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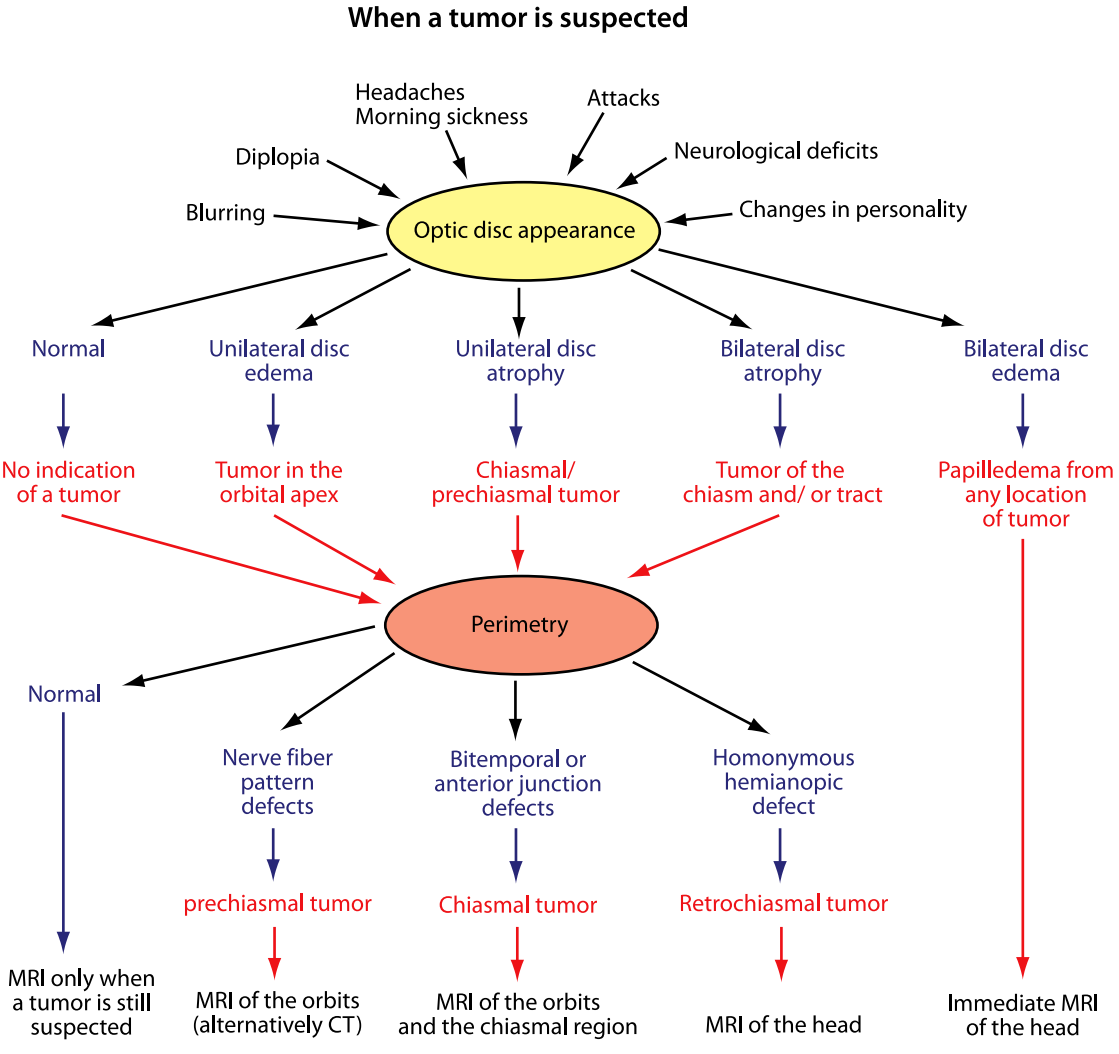
The ophthalmologist should keep in mind that the differential diagnosis always includes the chance that a brain tumor might be at fault. It is not at all unusual for these potentially life-threatening diseases to present with purely ophthalmologic symptoms.



Classification and Significance of Solitary Brain Tumors

Definition

Brain tumors as a group are meant to include all intracranial masses that arise from the brain parenchyma or other structures within the intracranial space.

The classification of brain tumors derives from the tissues of their developmental origins and is divided into neuroepithelial, mesodermal, and ectodermal tumors, as well as developmental malformations and metastases.

The importance of individual tumor types stems from their relative frequency. Included among neuroepithelial tumors (■ Table 12.1), glioblastomas, oligodendrogliomas, astrocytomas, pilocytic astrocytomas, and neurinomas are the most common. The mesodermal tumors encountered most frequently are the meningiomas, and the most common ectodermal tumors are pituitary adenomas. A fourth group, not belonging to the tridermic tumors, are developmental malformations, such as craniopharyngiomas and germinomas, and a fifth group is included for classification of intracranial metastases.

Table 12.1. Brain tumors of neuroepithelial origin

Glioblastomas
Oligodendrogliomas
Astrocytomas
Pilocytic astrocytomas
Neurinomas
Ependymomas
Medulloblastomas
Rarely: Choroid plexus papillomas, pinealomas, gangliocytomas

Pearl

Fifteen to 20% of all brain tumors are located in the region of the chiasma, and of these 50% are pituitary adenomas, 25% are craniopharyngiomas, 10% meningiomas, and 5% gliomas.

Symptoms of Brain Tumors

Pearl

Half of all patients with brain tumors have ophthalmic signs and/or symptoms.

The position of tumors in the intracranial space determines their associated, focal signs, and symptoms. Often, however, it is not the focal disturbance that catches attention, but the distant effects of tumors (such as obstruction to the flow of cerebrospinal fluid) that determine the patient's earliest symptoms. The historical time course of symptoms gives the examiner clues to the tumor's rate of growth. The patient's age makes certain tumor types more likely than others (■ Table 12.2). Therefore, a pituitary adenoma in a child is rare, but a craniopharyngioma as the source of a pediatric chiasmal syndrome is far more likely.

Table 12.2. Brain tumors, by life stages

Children, adolescents	Cerebellum and brain stem: medulloblastomas, pilocytic astrocytomas, ependymomas Chiasmal region: optic nerve gliomas, craniopharyngiomas
Middle-aged	Meningiomas, astrocytomas, oligodendrogliomas, pituitary adenomas, neurinomas
Elderly	Glioblastomas, metastases

Typical Signs and Symptoms of Brain Tumors

Typical signs and symptoms of a brain tumor include headache, neurological deficits, psychic changes (the patient and his/her relatives are usually unaware of these changes or misjudge them as trivial, especially when they have developed gradually) epileptic attacks, and visual symptoms (■ Table 12.3).

Table 12.3. Typical ophthalmologic signs and symptoms of brain tumors

Loss of vision
Optic disc changes (optic atrophy, papilledema)
Motility disorders (third, fourth and sixth cranial nerves)
Exophthalmos
Visual field defects
Loss of color vision (desaturation)
Loss of somatic sensation (fifth cranial nerve)

Note

An epileptic attack occurring in a patient past the age of 20 years with no prior history of epilepsy should raise the suspicion of a tumor.

Brain tumors that cause visual symptoms usually do so by compressing portions of the anterior afferent (pregeniculate) visual pathway. In the ophthalmic evaluation of such patients, the examination of even subtle changes in the visual field is of paramount importance (see Chap. 4). Such changes also give guidance when studying potential effects of brain tumors on the postgeniculate visual pathways (the optic radiations).

Examination Methods to be Used When a Brain Tumor is Suspected

If the abovementioned signs and symptoms raise the suspicion of a brain tumor, the following tests of visual function are particularly important:

- The visual acuities of both eyes with the best possible optical correction
- Testing for a relative afferent pupillary defect
- Careful perimetry of both eyes (pay particular attention to sign of an anterior junction syndrome; see Chaps. 3 and 4)
- Examination of ocular motility
- Fundus examination with particular attention to the optic discs, comparing one side to the other

Pearl

Additional tests during the examination should include visually evoked potentials, exophthalmometry, the testing of corneal touch sensitivity, and olfactory sensation.

Imaging by CT or MRI is mandatory, with the method of choice being the MRI. If the tumor is thought to invade, adhere to, or erode through bony structures, a CT scan can be added. The CT is also helpful when the tumor is associated with the formation of calcific deposits, as is typical for optic nerve sheath meningiomas (and pediatric retinoblastomas).

Metastasis of Brain Tumors

An intracerebral metastasis of a brain tumor is significantly more frequent than an extracerebral spread. Its tendency to spread is favored by elevated intracranial pressure, and it tends to seed areas where the flow of cerebral spinal fluid (CSF) is slow. Medulloblastomas and pineal tumors are particularly likely to behave this way. Typical are the so-called drop metastases within the spinal canal.

Pearl

Extracerebral metastases of brain tumors are very uncommon.

Metastasis is known to increase in likelihood following operative procedures (at the site of the sentinel tumor) and is most frequent among medulloblastomas, ependymomas, glioblastomas, and occurs much less commonly among meningiomas. Frequent sites for extracranial metastatic spread of brain tumors include the tissues of bone, lung, and lymph node.

Tumors of the Pregeniculate Afferent Visual Pathway

Tumors arising from the tissues of the pregeniculate afferent pathway can be classified as:

- Tumors arising from a component cell type of the optic nerve
- Tumors that develop from the sheaths of the optic nerve
- Tumors that arise from the tissues of surrounding structures
- Tumors due to the infiltration of malignant cells inside the optic nerve sheaths, or between the ganglion cell axons themselves

The clinical signs and symptoms of tumors affecting the optic nerves, the chiasm, and the optic tracts differ significantly from one another, depending on which of these segments they have damaged.

Signs and Symptoms of Tumors in the Pregeniculate Afferent Visual Pathway

Compression Syndromes

The development of a compression syndrome of the pregeniculate visual pathway should always suggest the possibility of an intracranial tumor, no matter which segment of the path is involved (nerve, chiasm, tract) or at what rate it has developed (acute, subacute, or slowly progressive).

Compression syndromes damage the afferent path by the mass effect of the pressure they exert on the involved segment. This can be caused by neoplasms, hemorrhages or obstruction to CSF flow (e.g., aqueductal stenosis), and causes ischemic damage to the ganglion cell axons. An

acute compression syndrome is characterized by a dramatic fall in visual acuity, acute development of defects in the visual fields (e.g., acute bitemporal hemianopia), afferent or efferent disturbances of pupillary function, and acute cranial nerve palsies.

Typical for chronic compression syndrome, on the contrary, are insidiously developing and frequently unnoticed loss of acuity, loss of color perception (red/green desaturation), a relative afferent pupillary defect, exophthalmos, cranial neuropathies, and visual field defects.

Signs and Symptoms of Tumors in the Prechiasmal Segment of the Afferent Visual Pathway

Tumors of the prechiasmal segment of the afferent visual pathway are typically unilateral (and for that reason often unnoticed), cause a fluctuating acuity deficit from day to day, and have a slow rate of progression. Monocular visual deficits that vary with the direction of gaze are frequently a sign of a retrobulbar mass, such as a hemangioma or an optic nerve sheath meningioma. Frequently an associated loss of color saturation, especially for red colors, also escapes the patient's notice. (Reds acquire a faded-orange or brown color.) Classically, monocular visual field defects develop, with features that vary according to the location of the compression. Early signs and symptoms often include mild unilateral proptosis, a change in eyelid position, and/or a restriction of ocular movements. Pain is very uncommon. There is commonly a relative afferent pupillary defect on the affected side, often combined with a varying degree of optic disc atrophy. Obstruction of normal axoplasmic flow by mass compression of the optic nerve fibers commonly causes a unilateral form of optic disc swelling, as can also happen with direct neoplastic infiltration of the optic disc. A chronic, slowly progressive compression (typical for optic nerve sheath meningiomas) causes the formation of optociliary shunts (■ Fig. 12.1) that provide an escape path for retinal venous blood that cannot exit through the compressed central retinal vein, allowing it to enter the choroidal vessels and exit the eye via the vortex veins. Large, rapidly growing infiltrating neoplasms with spread into the surrounding structures can cause diplopia by mechanical displacing or directly infiltrating the extraocular muscles. Such processes also cause an exophthalmos effected by axial proptosis of the globe, driven by a growing retrobulbar mass. Compression of the ocular wall can cause folds of the retina and choroid to appear (■ Fig. 12.2).

Fig. 12.1. **a** Development of optociliary shunt vessels on the optic disc, caused by optic nerve sheath meningioma. Initial findings. **b** Development of optociliary shunt vessels on the optic disc. Four years had elapsed between the time **a** and **b** were taken

Signs and Symptoms of Tumors Affecting the Chiasmal Region of the Afferent Visual Pathway

The pathognomonic signs of chiasmal disease include bilateral, usually bitemporal, visual field defects that respect the vertical meridian (see Chaps. 3 and 4). The bitemporal character of the visual loss and typical course of isopters with sharply defined discontinuities at the midline are easily detected with kinetic perimetry in the central 30° of the field, but discrete defects are more accurately demonstrable by automated static perimetry.

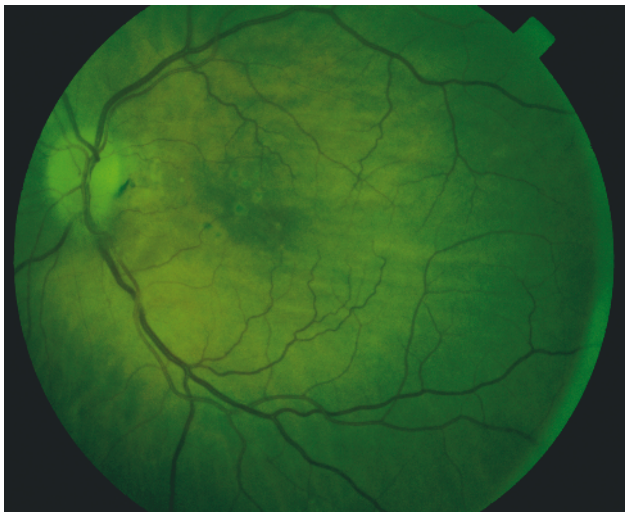


Fig. 12.2. Compression of the posterior pole with choroidal and retinal folds, caused by an optic nerve sheath meningioma

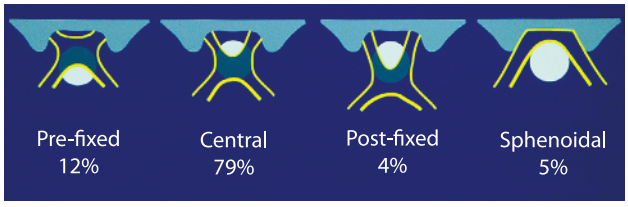


Fig. 12.3. Positional relationships between the chiasm and the pituitary gland, underlying the variations in visual field defects caused by chiasmal compression

Table 12.4. Space-occupying diseases in the sellar and suprasellar region

	Pituitary adenomas
Tumors thought to arise from sequestered groups of undifferentiated cells	*Craniopharyngiomas* Epidermoid cysts Chordomas
Germ cell tumors	Germinomas Teratomas Dysgerminomas Ectopic pinealomas
Other tumors	*Meningiomas* *Optic nerve gliomas* Astrocytomas
Metastases	Breast carcinomas Bronchogenic carcinomas Renal cell carcinomas

Pearl

Tumors that arise from positions inferior to the chiasm, such as those arising from the pituitary gland, initially produce deficits with a bitemporal component in the superior quadrants, close to the midline. Other tumors, like the craniopharyngiomas that approach the chiasm from above, are more likely to cause early bitemporal deficits that first appear in the lower quadrants (see Chaps. 3 and 4).

More important for the nature of early visual field defect, however, is the positional relationship between the chiasm and the diaphragma sellae. This varies significantly from one person to the next (■ Fig. 12.3). Compression of the chiasm by masses approaching from the anterior aspect are more likely to cause monocular or highly asymmetric visual field loss, while tumors that compress the posterior aspect of the chiasm are more likely to cause homonymous patterns of loss by damaging the optic tract(s). Tumor types are summarized in ■ Table 12.4 (particularly frequent types are in italics).

The extent of visual field loss at the time of diagnosis varies from (1) minimal deficits that the patient has not yet noticed to (2) complete bilateral loss of the temporal hemifields to (3) catastrophic, binocular loss of all light perception. The latter presentation is seen when necrosis of and subsequent hemorrhage into a rapidly growing pituitary adenoma results in pituitary apoplexy, an abrupt enlargement of the tumor that causes intense headache and acute, severe compression of the chiasm from below. Rapid surgical decompression of the chiasm by evacuating the mass often allows for substantial recovery of the acutely lost vision. Bilateral loss of the temporal hemifields causes a loss of depth perception, with a completely blind area beyond the object of regard and loss of fusional vergence control (due to loss of all binocular areas of visual field). The loss of motor control of ocular alignment due to the loss of all binocular areas of the visual field results in sensory disturbances that include absolute blind areas between separated nasal hemifields (in patients with antecedent esodeviations), diplopia with overlapping nasal hemifields (antecedent exodeviations), or splitting and relative vertical displacement of image halves in those with vertical heterophorias (the so-called hemifield slide phenomenon described in Chaps. 2 and 15). Acuity is not necessarily reduced but will more likely to appear the longer the process lasts and the deeper the visual field loss grows. Even in the early stages of chiasmal progression, the acuities of both eyes may be reduced. Compression of the chiasm is usually blunt, with large masses with smooth surfaces, and damage is done to both crossing and uncrossed axons within the

chiasm. This explains the loss of acuity in chiasmal disease and retention of normal acuity in patients with complete, retrogeniculate, homonymous hemianopias.

Optic atrophy may or may not be seen at the time of presentation, but is usually affecting both eyes (one exception: anterior junction syndrome, discussed in Chap. 3), a sign that the chiasmal damage is part of a long-standing disease process.

! Note

The extent of optic atrophy does not correlate with the extent of acuity loss. Even bilateral optic atrophy does not always rule out a possible recovery of both Snellen acuity and visual field. However, disc pallor does suggest that the recoverability of optic nerve and chiasmal function after surgical decompression is limited.

Development of papilledema caused by chiasmal/perichiasmal disease is very uncommon but does occur when the mass compresses and obstructs the foramina of Monro. This can happen when a large mass compresses and invades the third ventricle from below. Suprasellar masses like the craniopharyngiomas (particularly in children) are more likely to cause papilledema before the atrophy sets in. Combined appearances of both edema and atrophy in the optic discs are a good indication that both acute and chronic disease processes are at play.

When a tumor is suspected in the chiasmal region, it helps to inquire about nonvisual symptoms that suggest damage to the hypophysis, e.g., diabetes insipidus via compression of the supraoptic and paraventricular nuclei of the diencephalon (■ Fig. 12.4). This alters the level of antidiuretic hormone (ADH), causing excretion of dilute urine in large volumes, and a persistent thirst with a marked increase in water consumption. Diabetes insipidus is particularly common in patients with craniopharyngiomas, gliomas of the hypothalamus, and germinomas. Disturbances of pituitary function because of compression of the adenohypophysis are common and are more likely to be encountered in women than in men. A slowly developing insufficiency of the anterior lobe of the pituitary gland is usually associated with a drop in gonadotropic hormones, causing amenorrhea in women of childbearing age. This is often a presentation of chiasmal disease, although it is often first discovered by endocrinologists. A comparable hormonal syndrome occurs in men, with a loss of libido and erectile function, which is frequently assumed nonpathological. The tumors in men are on average larger than are those in women. This holds true for prolactinomas, which in women cause a galactorrhea and amenorrhea, and which in men usually cause a primary loss of libido and erectile function.

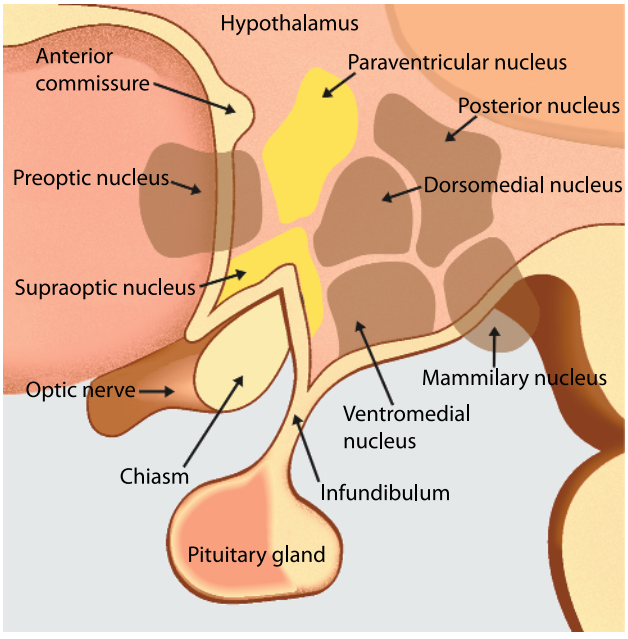


Fig. 12.4. Diagrammatic view of the hypothalamic nuclei located superior to the chiasm (the supraoptic nucleus and the paraventricular nucleus), which are the first to be compressed by expanding tumors arising in the midline from beneath the chiasm (modified after Netter)

! Note

Disease processes in the diencephalon are also marked by abnormally low growth rates and behavioral disorders, and when delayed growth in children is paired with optic atrophy, a tumor in the chiasmal region should be suspected.

When a tumor enlarges eccentrically to one side, it can invade the cavernous sinus, with corresponding clinical signs and symptoms (chiefly multiple cranial nerve palsies; see Chap. 10).

Signs and Symptoms of Tumors Affecting the Optic Tracts

Chiefly, the sign of a tumor compressing the optic tract is a poorly congruous, homonymous visual field loss (see Chap. 4) with a relative afferent pupillary defect (RAPD) in the eye that has lost its temporal hemifield, i.e., contralateral to the side of the damaged tract, with asymmetrical optic atrophy (see Chap. 8, ■ Fig. 8.23 and Chap. 19, ■ Fig. 19.6).

In addition, this presentation is frequently associated with focal signs and symptoms of neurological disease. Depending on the locus and extent of damage to structures near the optic tract, these focal problems often precede the correct diagnosis of an intracranial tumor and should indicate to the physician that a closer evaluation is needed.

Specific Signs and Symptoms of Brain Tumors Relevant to Clinical Neuro-Ophthalmology

Optic Nerve Gliomas (Pilocytic Astrocytomas)

Three groups of optic nerve gliomas are differentiated according to their distributions:

1. Confined to the optic nerve on one side.
2. Damaging the chiasm (a more frequent situation than the monocular form). Twenty-five percent of optic nerve gliomas have already reached the chiasm by the time of their discovery.
3. Involving the hypothalamus and the region of the third ventricle. Thirty percent of these patients have hydrocephalus.

Optic nerve gliomas are uncommon. Only 1 to 2% of all gliomas are found in the optic nerve. However, optic nerve gliomas represent 2 to 5% of all brain tumors in children. Among children and adolescents the glioma is a common tumor of the pregeniculate pathway and is especially frequent (6.6 to 20%) in patients with neurofibrosis type I (located on chromosome 17q11.2). Children under 6 years of age are at the greatest risk of developing symptomatic optic nerve gliomas. Lisch nodules of the iris are an important diagnostic clue (see Chap. 19). There is a significant gender difference, with girls and women more often affected than are boys and men.

Signs and Symptoms of Optic Nerve Gliomas

A common presentation includes exophthalmos with strabismus of the affected eye, associated with a loss of visual acuity, visual field defects, optic atrophy, and a relative afferent pupillary defect. Not infrequently, an acquired nystagmus is the first clinical sign. The most common sign is optic atrophy on the affected side, and bilateral involvement is not uncommon. The mass grows slowly and advanced stages of enlargement are commonly associated with diencephalic disorders, including diabetes insipidus, adiposity, delayed sexual maturation, and somnolence.

Treatment of Optic Nerve Gliomas

Treatment of these tumors is controversial. For those tumors that are confined to the intraorbital course of the optic nerve with complete loss of vision in the affected eye, options include surgical extirpation of the tumor (resection of the involved segment of the nerve), radiation therapy, and observation. The latter choice might be appropriate in the absence of pain with no significant disfigurement. For young children of less than 5 years of age who have demonstrable progression of chiasmal tumors the use of radiotherapy is to be avoided, since they have higher risks of associated morbidities, especially malignancies occurring later in the tissues exposed to the radiation. In these cases, chemotherapy is now preferred. Gliomas that are found in the hypothalamus seem to have a more favorable course following radiotherapy, rather than being simply observed. The differences are not great, however, and some still advocate conservative observation, particularly if serial MRI scanning shows stability of the tumor's size.

Pearl

A phase of initially rapid growth, followed by years of stable size, is typical for optic nerve gliomas.

Pituitary Tumors

Pituitary tumors are most frequently prolactinomas (35%), less commonly somatotropin-secreting tumors (25%), and even less commonly adrenocorticotrophic hormone (ACTH)-producing tumors (5%). Sporadically, tumors that produce thyroid-stimulating hormone (TSH) or gonadotrophins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) are seen. In some cases, a pituitary adenoma causes overproduction of several hormones.

Pearl

About two thirds of all pituitary tumors have some degree of endocrine-secreting activity, while the remaining third are said to be silent.

Middle-aged adults are most frequently affected by pituitary tumors (about 12 to 15% of all intracranial neoplasms), while children are seldom found to have primary pituitary adenomas. Both sexes are equally represented.

Pearl

Only 30% of patients presenting with pituitary tumors complain of visual problems. The tumor must rise more than 1 cm above the diaphragma sellae before causing a clinically detectable loss of visual field and/or acuity. Commonly, this is a hormonally inactive tumor that due to the absence of endocrine signs or symptoms has been very inconspicuous.

Pituitary microadenomas are those with a diameter of 10 mm or less. The threshold for radiological detection of a microadenoma is 3 mm or less. A macroadenoma is spoken of, when the tumor's diameter amounts to more than 10 mm.

Fig. 12.5. Pituitary apoplexy. The level boundary within the tumor corresponds to the superior margin of the hemorrhage (*arrow*)

Signs and Symptoms of Pituitary Tumors

The most common ophthalmological sign of a pituitary adenoma is the bitemporal loss of visual field (see Chaps. 3 and 4). Fundus findings are at most (and often subtly) optic disc pallor. A loss of visual acuity is not always present (see above). Disturbances of motility involving dysfunction of the trochlear or abducens nerves are found in only about 10% of patients. With very large, eccentrically growing tumors, there is occasionally damage to the first two branches of the trigeminal nerve.

Pituitary Apoplexy

see also Cases TES 1.1

Occasionally (at most, 10% of cases) a pituitary tumor will present as an abruptly expanding mass with an intralesional hemorrhage, brought on by ischemic necrosis when the rapidly proliferating tumor outgrows its available blood supply (■ Fig. 12.5).

During pregnancy, there is a higher risk to vision from an accelerated rate of tumor growth. Pregnancy, trauma, prior radiation therapy, and defects in blood coagulation all increase the risk of pituitary apoplexy.

Treatment of Pituitary Tumors

For microadenomas, which cause no problem with vision, treatment is directed at relieving any hormonal imbalances. For macroadenomas with hormonal activity, medical therapy must usually be accompanied by some degree of surgical reduction in the size of the mass. Favorable effects can occur within 24 h of surgical decompression, after several days of medical management (e.g., bromocriptine, see below), or several months after radiotherapy.

The differential diagnosis of a pituitary adenoma should always include mention of secondary pituitary enlargement. A primary deficit of a pituitary end organ's hormonal production (e.g., primary hypothyroidism) could cause a secondary swelling of the pituitary gland of sufficient size to make contact with the chiasm. In such cases, simple replacement of the missing hormone will lead to a reversal of the syndrome.

! Note

No surgery should be considered for a pituitary tumor prior to a complete endocrinological evaluation.

Prolactinoma

A prolactin-secreting tumor of the pituitary gland can cause a dramatic hyperprolactinemia. One third of all hyperprolactinemias are caused by hypersecreting tumors of the pituitary, and the prolactin level in serum rises to above 200 ng/ml. Typical clinical symptoms are amenorrhea and galactorrhea among women, and loss of libido and erectile function in men, and less commonly, gynecomastia. Prolactinomas in women, who are often alarmed by the endocrinological changes, are usually microadenomas, and are not usually associated with optic disc pallor or visual field defects.

● Pearl

Men often have large prolactinomas with chiasmal compression. It is thought that men commonly repress or ignore the symptoms until late in the course of the tumor's development.

Treatment is tailored according to the size of the tumor. Surgery is indicated in most cases that have:

1. A suprasellar macroadenoma with chiasmal compression.
2. A suprasellar macroadenoma without chiasmal signs or symptoms, but planning for a pregnancy. During pregnancy, prolactinomas can enlarge considerably in 35% of cases.
3. A suprasellar macroadenoma without chiasmal damage, but the patient is intolerant of treatment with dopamine agonists.

If there are no definite indications for surgical intervention, the use of dopamine agonists, e.g., bromocriptine (Parlodel) at doses of 2.5 to 5 or 7.5 mg daily is usually successful. Seventy-three of prolactin-secreting tumors treated with bromocriptine shrink, and in 95% of cases, the blood levels of prolactin will return to normal levels. The drug will show an improvement in symptoms within 72 h of initiating its use. However, it will cause nausea, vomiting, hypotension, and vasospasms in higher doses. Cautious use of lower doses of bromocriptine can usually be toler-

ated without losing its effectiveness for normalizing prolactin levels and reducing the size of the tumor. Alternatively, cabergoline (Dostinex), 0.5 mg, can be given twice weekly, with better tolerance among some patients. Additionally there is a definite risk of tissue necrosis developing during treatment, which can lead to a pituitary apoplexy that requires emergent neurosurgical intervention for its proper management. In addition, tumors can erode the floor of the sella, and when shrinking under the effects of bromocriptine, a CSF leak can develop with an increased risk of bacterial meningitis.

Somatotrophic Hormone–Producing Pituitary Tumors

Endocrinologically these tumors are characterized by elevated production of somatotrophic hormone (STH). The excessive production of growth hormone produces in (preferentially male) children and adolescents with as yet unclosed epiphyses accelerated growth of long bones that can lead to gigantism, whereas among adults (here the female sex is more commonly affected) the effect is to produce acromegaly: enlargement of the acral body parts – nose, chin, fingers and toes with enlargement also of abdominal organs and a deepening of the voice.

The treatment of STH-producing tumors must take a surgical approach, which can usually be done by a transsphenoidal approach (see Chap. 22). For intrasellar tumors, the success rate approaches 90%. In cases where surgery is not possible, analogs of somatostatin are an effective alternative. These agents can normalize the STH levels in 90% of cases, improve the symptoms in 50% of cases, and reduce the size of the tumor in 44% of cases. Initial studies of treatment of acromegaly with a growth hormone receptor antagonist pegvisomant (Somavert) seem encouraging. This drug is used under tightly restricted access in the United States, and access is provided on a case-by-case basis. A trial of treatment with dopamine agonists can be made. Radiation is not useful, since years can pass before the blood levels of growth hormone are reduced. The consequences of STH overproduction include an increase in morbidity that is partly irreversible.

ACTH-Producing Pituitary Tumors

The endocrinological effects of elevated ACTH levels are clinically expressed as Cushing's syndrome (moon face, torso adiposity, diabetes mellitus, and muscle atrophy). The surgical management of ACTH-producing tumors is challenging. Not uncommonly, there is a diffuse growth, often extra glandular, with the source of overproduction of the hormone being located in a microadenoma positioned eccentrically in the pituitary recess. Surgical success is attained in 70 to 90% of cases. Alternatively, treatment with the antiserotonin cyproheptadine results in a clinical remission in 50% of cases. Equally likely is a reduction in the rate of cortisol synthesis by treatment with ketoconazol. For relapses, radiation therapy should be considered.

Endocrinologically Silent Pituitary Adenomas

Hormonally inactive pituitary tumors (up to one third of all pituitary tumors) can with growth and displacement of surrounding tissues result in a hormonal deficit, hypopituitarism with a loss of gonadal function (often the first clinical sign) and hypothyroidism, weakness of the muscles, loss of body hair or with symptoms of hypothalamic disease, including diabetes insipidus, and disorders of sleep, body temperature, and poor motivation.

Chiasmal syndrome is particularly frequent among cases of hormonally inactive tumors, since they are as rule large by the time the correct diagnosis has been made. Regressive changes are more frequent, also due to the large size of these tumors (cysts, necrosis, acute intralesional hemorrhages, and acute chiasmal syndrome). Surgical intervention is often necessary, but the large size and asymmetric extension of these tumors requires an approach by way of a craniotomy. Subtotal resection of the tumor should be followed by targeted radiation therapy.

Craniopharyngiomas

There are two theories to explain the origin of craniopharyngiomas. One assumes that the tumor cells arise from Rathke's pouch, the other that the cells arise through metaplasia of cells in the anterior lobe of the pituitary gland. Tumors with primary intrasellar growth are distinguished from those with the more common behavior of primary suprasellar growth.

One to 4% of all brain tumors are craniopharyngiomas, meaning that they are not common. Craniopharyngiomas among children, however, are second only to optic nerve and/or chiasmal gliomas as a cause of chiasmal syndrome. The incidence of craniopharyngiomas as a function of age is biphasic. Two thirds of all cases are found in patients less than 30 years of age, while adults between 50 and 70 years of age make up most of the remainder. Both sexes are equally represented.

Signs and Symptoms of Craniopharyngiomas

At the time of initial discovery of craniopharyngiomas, especially in the smaller children who are unaware of or cannot easily describe their visual problems, the tumors are usually already over 3 cm in diameter. They grow steadily in size, leading in 19% of cases to a dorsal chiasmal syndrome, compressing the chiasm from a posterior dorsal

position (see Chaps. 3 and 4). Frequently these tumors contain within them cystic spaces that fluctuate in size, filled with viscous fluid that has the color and consistency of motor oil. They often cause fluctuating disturbances of acuity and the visual field, which has detectable defects in more than two thirds of cases. The ocular fundus shows at most an appearance of (sometimes mild) optic atrophy, or (mostly in children) frank papilledema. Acuity is sometimes, but not always reduced.

Pearl

The term acute craniopharyngioma refers to a rupture of the cystic component of the tumor, causing a sterile meningitis.

Calcifications appear in craniopharyngiomas in about 75% of cases. They usually present in company with signs and symptoms of hypothalamic compression. Diabetes insipidus is often present, and disorders of sleep, control of body temperature, and mental alertness are all present. Suprasellar growth of these masses is often heralded by the discovery of papilledema. A hydrocephalus is common in cases of suprasellar growth.

Treatment of Craniopharyngiomas

Surgical removal is the management of choice, but their removal is frequently subtotal, because the tumors, having a capsule of varying thickness, are often firmly adhered to surrounding neural structures. Postoperative radiation therapy following subtotal resections may be necessary.

Low-Grade Astrocytomas

The classification of astrocytomas of low-grade malignancy, as described in various textbooks of histopathology, covers a variable range of severity. A particular type is the pilocytic astrocytoma, found either in the cerebellum or (more frequently) the optic nerve (see above for a discussion of optic nerve gliomas).

About 30% of all gliomas are astrocytomas of low-grade malignancies. They appear in all age groups, but most commonly in men in the 20th to 50th years of life. The older the patient, the higher the grade of malignancy one can expect to find.

Signs and Symptoms Associated with Astrocytomas of Low Grades of Malignancy

Particularly frequent is the location of these tumors in the frontal and temporal lobes, especially in the deeper brain centers (e.g., the thalamus). They often have poorly defined borders in their early stages and are at first difficult to detect by neuroradiological imaging. They have a moderate rate of growth.

Pearl

Epileptic attacks are the presenting sign in 65% of patients.

If the afferent visual pathway is affected, there will typically be a slowly progressive homonymous hemianopia that evolves of a period of months (see Chap. 4), along with simultaneous, nonvisual neurological deficits.

Treatment of Astrocytomas of Low Malignancy

Primary treatment is always surgical. Because of the poor definition of the margins of these tumors, total removal is often impossible. In this case, postsurgical radiation therapy is indicated. Malignant transformation of these tumors due to the radiation therapy is not usually seen.

Gliomas of High Malignancy (Anaplastic Astrocytomas and Glioblastoma Multiforme)

Astrocytomas and glioblastomas can be distinguished from one another histologically. The malignant astrocytomas are highly anaplastic, while glioblastomas have multicolored staining properties. As many as 20% of cases present with signs of a multifocal genesis.

These tumors have a poor prognosis and constitute about half of all primary brain tumors found among middle-aged and elderly patients. Both sexes are equally affected. The patient's age at presentation is an important factor in the prognosis, which is significantly worse for patients over 50 years of age. Malignant gliomas most often arise in the cerebral hemispheres.

Signs and Symptoms of Highly Malignant Gliomas

Growth is rapid, causing a quick succession of multifocal and general neurological deficits, such as an abrupt onset and fast progression of visual field defects. Papilledema is often present, usually reverses its course following surgical intervention, and then reappears, along with a rapid relapse of the signs and symptoms of recurrent tumor growth.

Treatment of Highly Malignant Gliomas

Surgical resection of the mass, including a 2-cm layer of tissue beyond its apparent borders, is current practice, and is followed by irradiation with up to 60 Gy (these tumors are relatively radiation resistant). Additional chemotherapy with temozolomide (TMZ) should be considered a new standard of care for newly diagnosed glioblastoma

multiforme patients. Locoregional therapy with sustained delivery of BCNU (carmustine) from a biodegradable polymer placed around the resection perimeter at surgery (GLIADEL), radioimmunotherapy utilizing radiolabeled monoclonal antibodies against tumor-associated antigens and convection enhanced delivery (CED) – microinfusion catheters placed with stereotactic guidance in the peritumoral region to infuse a therapeutic agent over 3 to 5 days – provide important steps forward in clinical trials. Altogether, recent therapeutic advances have led to modest improvement in outcome for at least some malignant glioma patients. However, recurrence of these tumors can be expected.

Medulloblastoma

Medulloblastomas arise from immature, undifferentiated cells in the cerebellum. Histologically, a characteristic appearance is that of cells with round or elongated shapes that frequently form rosettes and (around blood vessels) pseudorosettes.

About 20% of pediatric brain tumors are medulloblastomas that in two thirds of cases arise during the first 15 years of life. The younger the child, the greater the aggressiveness of growth expected. There is a very high rate of local metastasis via the cerebrospinal fluid in the subarachnoid space, and a high rate of extraneural metastasis (30%). Sixty-five percent of cases are male, and in 90% of cases, the tumors arise in the posterior cranial fossa, most commonly in the cerebellar vermis.

Signs and Symptoms of Medulloblastomas

Internal hydrocephalus is common (40%), caused by obstruction to CSF flow in the region of the fourth ventricle, and there are frequently cerebellar signs, principally ataxia, and ocular findings commonly include papilledema.

Treatment of Medulloblastomas

Radical excision of the tumor is always necessary, followed by postoperative radiation therapy, including irradiation of the spinal canal to treat the so-called drop metastases. In children less than 3 years of age, after surgery chemotherapy is preferred.

Metastases

Between 4 and 20% of brain tumors are metastases. The type of metastases to be expected depends importantly on the patient's age: sarcomas (osteosarcoma, rhabdomyosarcoma) and germinal cell tumors of the testes in children, and carcinomatous metastases in adults (lung, breast, and renal cell carcinomas).

Signs and Symptoms of Intracranial Metastatic Disease

The signs and symptoms of brain metastases depend on the location of the metastatic growth, with the most common ophthalmic sign being papilledema caused by obstruction of CSF flow.

Treatment of Intracranial Metastases

Radical excision of solitary metastases, particularly those of renal cell carcinomas, can have a favorable result. Fifty percent of all patients with brain metastases die, in spite of "successful" surgical procedures, within 6 to 12 months.

Meningiomas

Several forms of meningioma are recognized: meningothelial, fibrous, and transitional are the most common subtypes. They arise ubiquitously. The growth can be nodular or *en plaque* (a laminar spread along the surface of the dura), and there are extracerebral manifestations. Forty percent are basal meningiomas, 50% are tumors of the convexities, and 10% are meningiomas of the posterior cranial fossa. In up to 16% of cases, meningiomas arise multifocally. Typically, there is a long, slow growth that can last for decades, often causing changes in the adjacent bone (an osteoblastic reaction, or so-called blistering), malignant transformation (2 to 10%), and metastasis formation (0.1%). Meningiomas often have a strong tendency to grow rapidly during pregnancy. The association of a meningioma with a carcinoma of the breast is not unusual.

Meningiomas may have a strong familial component. Several associated mutations or deletions on chromosome 22 have been identified. People suffering from neurofibromatosis type 1 and type 2 are at increased risk for the development of meningiomas.

Pearl

Meningiomas make up to 20% of all intracranial tumors. They are rare among children and adolescents; a patient age of 50 years is typical, with women being most frequently affected. Eighty-five percent of all meningiomas arise in women 40 to 60 years old.

Of primary ophthalmic importance are (1) optic nerve sheath meningiomas, (2) meningiomas of the tuberculum sellae, (3) meningiomas of the anterior clinoid process, and (4) sphenoid wing meningiomas. Intrasellar meningiomas are uncommon, rarely cause signs or symptoms and

are usually detected on MRI scans done for unrelated reasons.

Optic Nerve Sheath Meningiomas

Sheath meningiomas of the optic nerves arise either primarily from meningeal cells within the orbit or in the optic canal, or are an extension of intracranial meningiomas that are invading the optic canal. Women in the fifth decade of life are most often affected. Sheath meningiomas also occur in children, where their behavior is one of aggressive growth.

Signs and Symptoms of Optic Nerve Sheath Meningiomas

Typically, these tumors present as painless and insidious progressive monocular loss of vision.

! Note

The initially fluctuating course of visual loss can be misinterpreted as a sign of optic neuritis. Beware the diagnosis of atypical optic neuritis.

Occasionally these tumors cause no initial changes in the appearance of the optic disc, other than slow atrophy. More frequently, however, one sees small vessel hyperemia and tissue swelling on the surface of the optic disc that looks like mild papilledema. Later changes are caused by chronically elevated retinal venous pressure with shunting of retinal venous blood into the peripapillary choroid through optociliary shunt vessels (■ Fig. 12.1 b) that arise in 14 to 33% of cases. CT scanning detects these tumors easily, since they usually contain significant deposits of calcium. Bilateral tumors are also not uncommon.

Treatment of Optic Nerve Sheath Meningiomas

Treatment depends on the extent of visual loss and the distribution of the tumor in the posterior orbit. The more that these parameters indicate an unfavorable prognosis, the more that radiotherapy is to be preferred, since primary surgical excision of the tumor invariably damages the perineural pial vessels of the optic nerve, causing an ischemic infarction. This is the expected outcome, whether or not the tumor is successfully removed.

If visual loss is extensive, or the eye is completely blind, and/or there is contraindication to radiotherapy or if the mass is threatening to invade the chiasm, tumor excision, including amputation of the optic nerve, can help to minimize secondary orbital problems, such as progressive proptosis. For tumors that have already involved the chiasm, surgery is an unacceptable risk to the patient's remaining vision, and radiotherapy is the only treatment option, other than nonintervention.

Tuberculum Sellae Meningiomas

Meningiomas often arise in the suprasellar region. Typically, they cause a rounded elevation of the planum sphenoidale. Less commonly, there can be an associated hyperprolactinemia and/or hypopituitarism (both being late developments). Growth of these masses is usually asymmetric, causing an initially monocular, fluctuating loss of vision with a central scotoma, and frequently an anterior junction syndrome of the chiasm (see Chap. 3). Tuberculum sellae meningiomas constitute 3 to 10% of all intracranial meningiomas, and are first diagnosed in the patient's fourth to sixth decade of life. Women are affected much more (up to 90%) than are men.

Current practice is surgical excision, although complete extirpation is not often achieved. This is particularly true of those tumors having the *en plaque* pattern of growth. Consequently, recurrences are common (up to 50%), and the frequency of recurrence is proportional to the area of dura that has been resected. CT scanning effectively detects the extent and location of bony involvement, while MRI scanning is necessary for the differential diagnosis of pituitary adenomas and for studying the precise relationships between the tumor and neighboring vessels, and the extent of intracanalicular involvement. The most common misdiagnosis of tuberculum sellae meningiomas is recurrent optic neuritis.

Clinoid and Sphenoid Wing Meningiomas

Twenty-five percent of all meningiomas arise near the anterior clinoid processes or along the sphenoid wings. Most affected are women (66%) aged 30 to 50 years. Exophthalmos is caused in 50% of cases, and optic disc swelling occurs (often bilaterally) in half of all meningiomas of this category. Growth through the superior orbital fissure and into the orbit is common, and is usually associated with prominent hyperostosis of the sphenoid wing, as seen on CT scans. Typical visual field findings include:

1. An ipsilateral central scotoma.
2. A unilateral hemianopic defect.
3. A homonymous hemianopia (caused by tract damage).

Most of these tumors can be surgically debulked to the extent that compression of the optic nerves and/or chiasm is relieved. The closer the tumor is to the midline, the more likely that its removal will be incomplete and the more likely that complications will be encountered. Tumors close to the sphenoid midline often extend to the contralateral side, which can require successive operative procedures on one side, and then the other. Stereotactic radiotherapy for these tumors is considered an attractive alternative, given the high rate of complications and postoperative neural

deficits that can be expected with surgical approaches to meningiomas on the skull base.

Conclusion

Visual symptoms are often the first indication of a brain tumor. They must be detected and correctly identified so that appropriate treatment can be quickly started. Following surgical and/or radiotherapeutic treatment, regular ophthalmic monitoring is necessary, to detect early signs of recurrent growth.

Further Reading

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