Chapter 103

Gliomatosis Cerebri

103.1 Clinical Features and Laboratory Investigations

Several synonyms are used for this condition: diffuse glioma of the brain, gliomatosis diffusa, gliomatous hypertrophy, blastomatous type of diffuse sclerosis, and central diffuse schwannosis.

The clinical presentation is variable. Headache is present in most cases, and may be accompanied by focal seizures, changes in mental state, psychiatric syndromes, ataxia, dysphagia, dysphasia, and memory loss. The clinical picture suggests in most cases a multifocal progressive disorder. Initially, however, symptoms may be difficult to interpret, with only loss of concentration, behavioral problems, or psychiatric symptoms. Some patients present with diminished vision only, and papilledema is found at fundoscopy. The clinical symptoms are often discrepantly mild in view of the extensive abnormalities found on MRI, but they are progressive and lead to death. The median survival time is 14 months.

Over the last 5–10 years there seems to have been an increase in the number of cases of gliomatosis cerebri, and younger patients are affected than in former years. The reason for this is unclear.

103.2 Pathology

Macroscopically, there is swelling of the involved structures. Although all parts of the brain may be involved, including the brain stem and cerebellum, there is a preference for the central, periventricular areas and mesolimbic parts of the temporal lobe. The microscopic hallmark of gliomatosis cerebri is the presence of many moderately pleomorphic glial cells, infiltrating pre-existing structures, without significant destruction. Natural borders between structures are not respected. Usually, these cells are astrocytic in type and react positively with glial fibrillary acidic protein (GFAP). In other cases, the infiltrating cells have oligodendroglia-like elements and only a few cells are GFAP-positive astrocytes. Locally further dedifferentiation may take place, and some parts of the lesion may progress to anaplastic astrocytoma or glioblastoma multiforme. Finally, the entire neuraxis may be involved.

103.3 Pathogenetic Considerations

No familial cases of gliomatosis cerebri have been reported. One study looking at the chromosomes of cells of gliomatosis cerebri revealed that the majority of the abnormal cells had the karyotype 44 XY, (del(6)(q25), del(14)(q21), del(15;21)(q10;q10), add(18)(q22), del(19)(p12), add(20)(p13), -21. A smaller proportion of cells had 88 chromosomes with a doubling of the normal karyotype. With the exception of the chromosome 6 deletion, these chromosomal changes do not resemble those found in astrocytomas, suggesting that gliomatosis cerebri is a separate entity (Hecht et al. 1995). Herrlinger et al. (2002) summarize the molecular genetic findings and find that genetic alterations in diffuse gliomatosis are not different from those found in infiltrating astrocytomas. They conclude on these grounds that gliomatosis cerebri should be considered a particularly invasive subform of glioma, rather than a distinct tumor entity that is entirely different from other cerebral gliomas. An extra argument for this is found in the dedifferentiation of gliomatosis cerebri into anaplastic astrocytomas and glioblastoma multiforme.

In one report, gliomatosis cerebri was seen following radiation and chemotherapy for a extraneural metastasis of primary nongerminomatous germ cell tumor in the pineal region, providing evidence for exogenous induction of the tumor.

Fig. 103.1. Series of transverse T_2-weighted images in a 56-year-old woman (*first two rows*). She has a history of changes in personality over the past 2 years, leading to suspicion of frontotemporal dementia. The images show bilateral, nearly symmetrical signal abnormalities of the frontal lobes, connected via the genu of the corpus callosum and spreading toward the deep insular structures on both sides. The affected corpus callosum is markedly swollen. There is diminished gray–white matter distinction in the involved areas. The *third* and *fourth rows* contain diffusion-weighted images (Trace diffusion-weighted images with b = 1000 in the *third row*; ADC maps in the *fourth row*). The Trace diffusion-weighted images show a moderate increase in signal intensity in the involved area, whereas the ADC values are too high, indicating increased mobility of water. Note that this combination of moderately high signal increase on Trace diffusion-weighted images together with high ADC values in the affected area does not reflect vasogenic edema

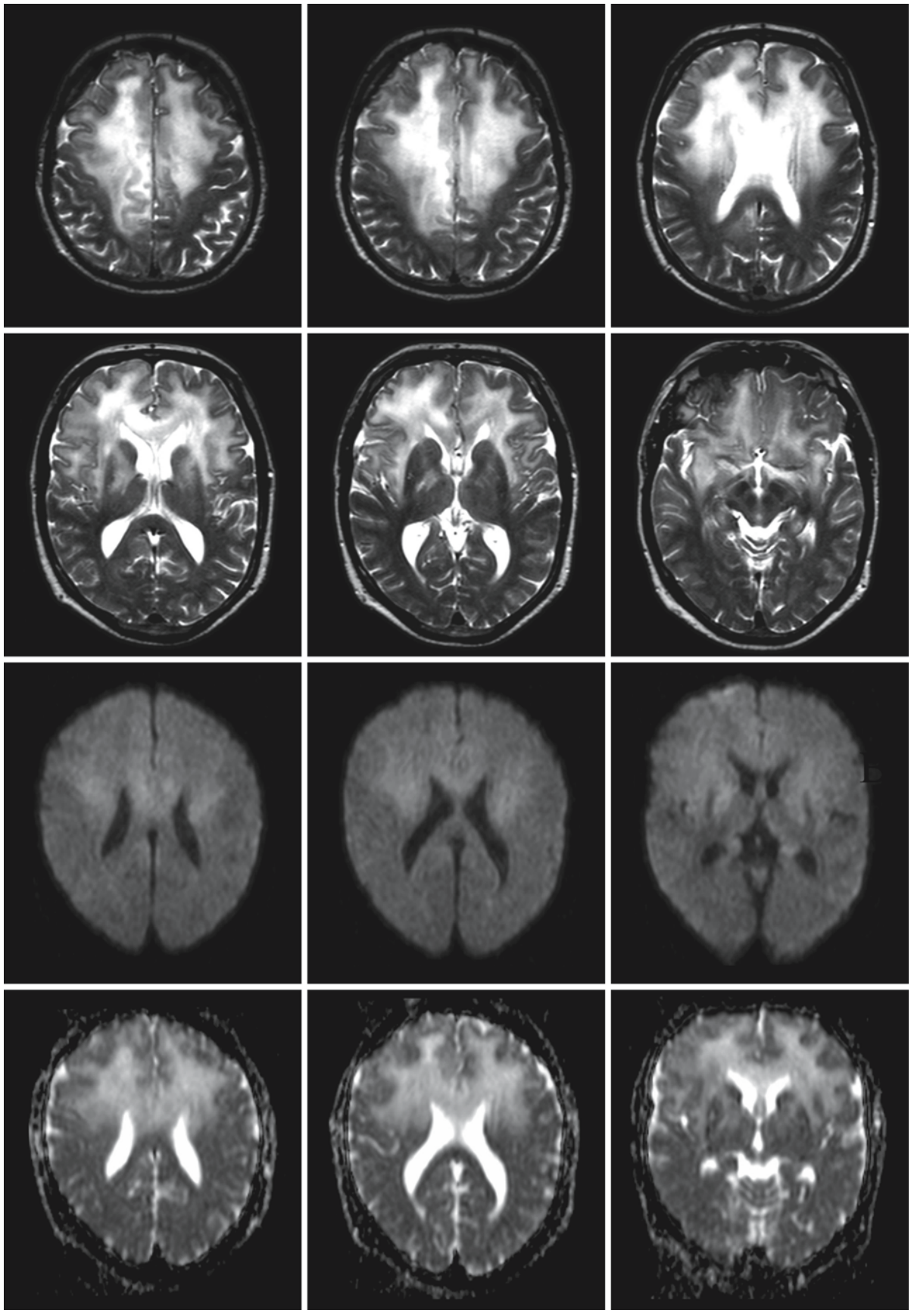

Fig. 103.1.

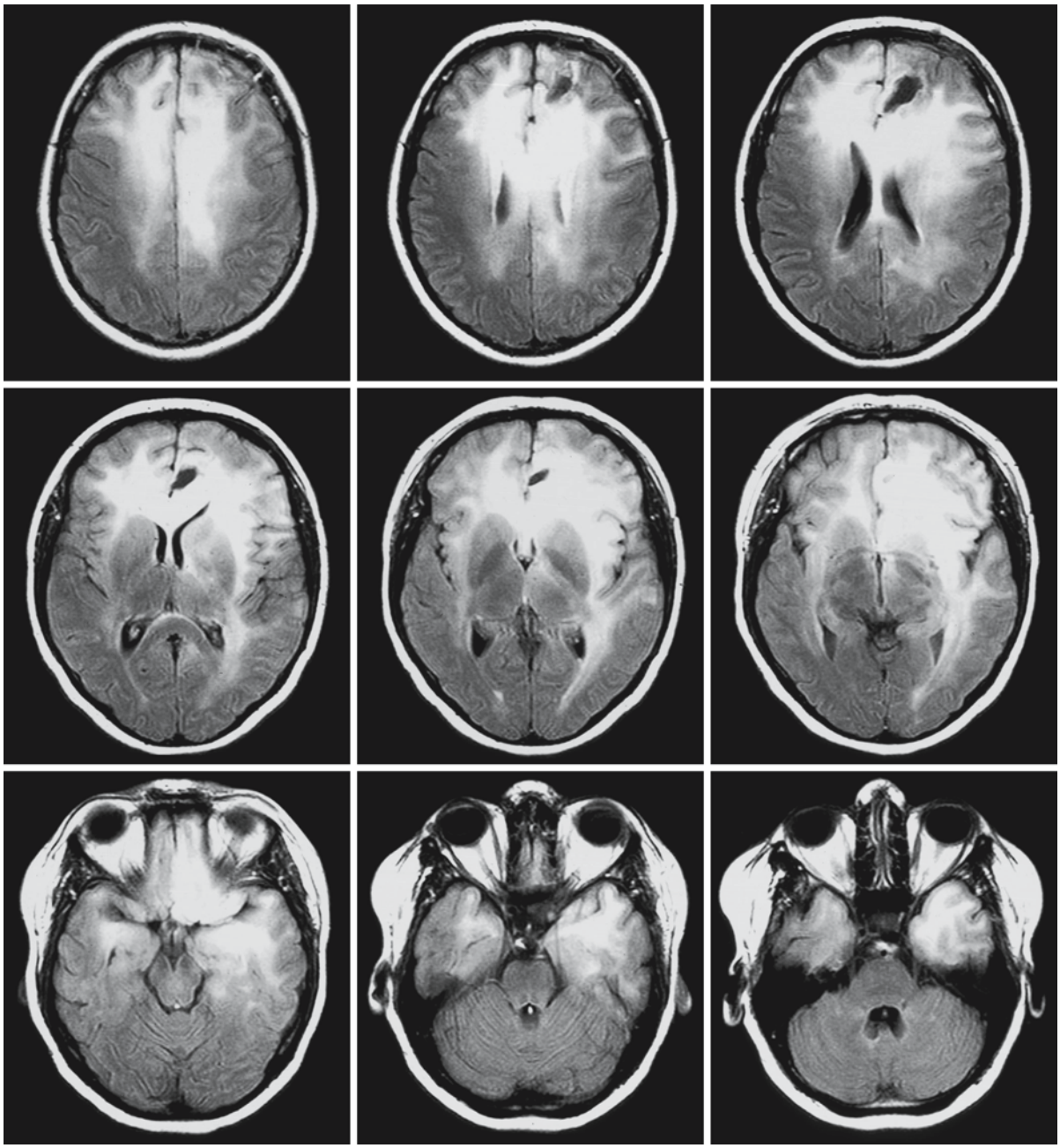

Fig. 103.2. Series of FLAIR images in a 25-year-old man with biopsy-proven gliomatosis cerebri. The biopsy was taken from the left frontal lobe. In this case the abnormalities are mildly asymmetrical and have a prominent mass effect. There is clear involvement of the temporal lobes. In many places where the tumor touches upon the cortico-subcortical junction, the gray–white matter differentiation has disappeared

103.4 Therapy

Because neurosurgery is not an option in most cases, radiotherapy and chemotherapy are the only remaining therapies available. The results have been disappointing for many years, but with the drug temozolomide longer survival has been achieved.

103.5 Magnetic Resonance Imaging

Most useful for the diagnosis of gliomatosis cerebri are proton density, T_2-weighted, and FLAIR sequences. They show increased signal intensity of the involved areas, with poor demarcation from noninvolved tissue, and with mass effect. When the cortico-subcorti-

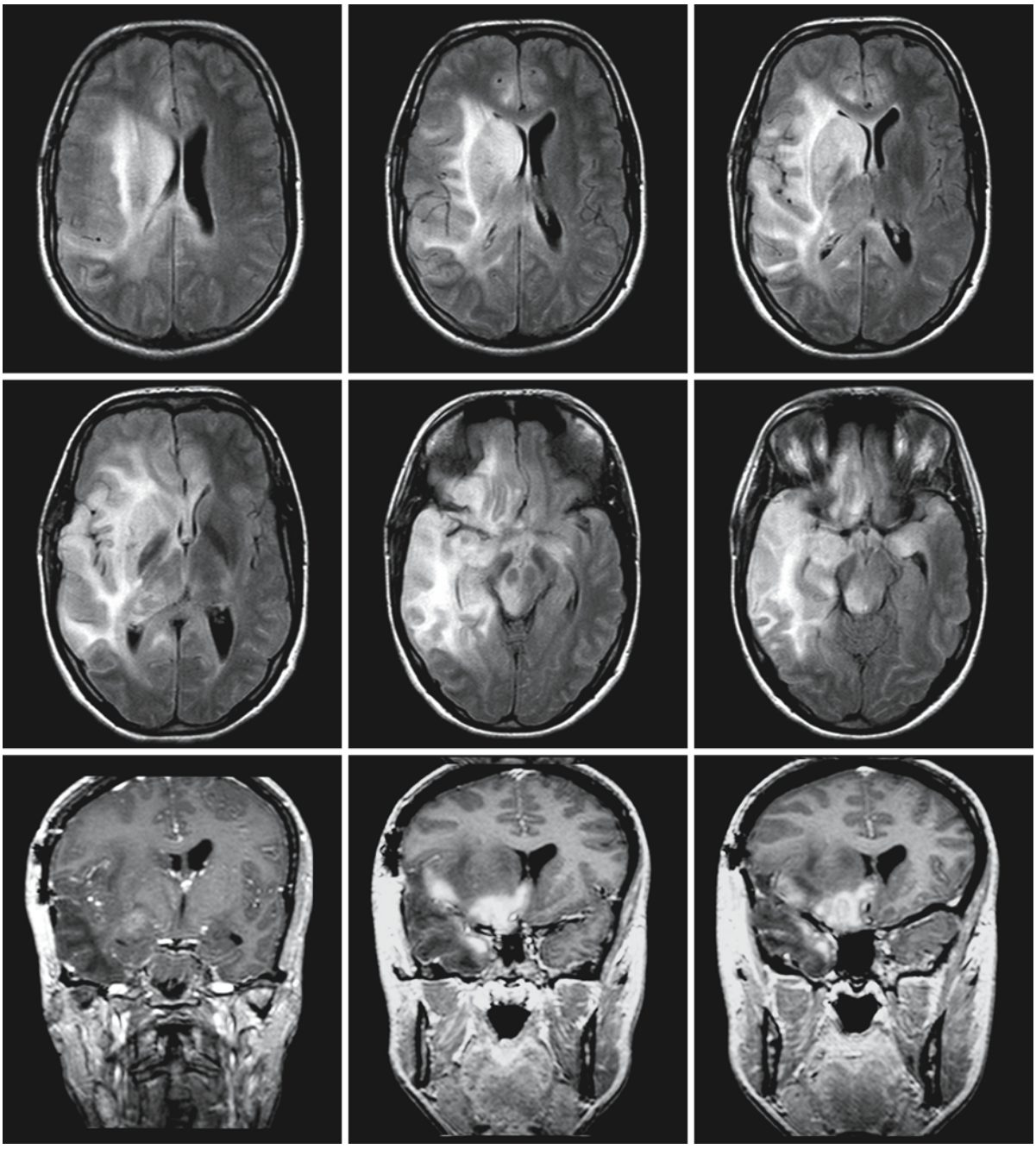

Fig. 103.3. This 17-year-old girl presented with bilateral papilledema and no other neurological signs. The FLAIR images (*upper two rows*) reveal an asymmetrical presentation of gliomatosis cerebri with most prominent abnormalities on the right. The *third row* shows coronal T_1-weighted images with contrast. The *left-hand* image was obtained directly after contrast administration, showing some contrast enhancement in the right frontal lobe. The two images on the *right* were obtained 1 h after the injection and show much more prominent contrast enhancement. The latter images make clear that the damage to the blood–brain barrier is far more extensive than the first postcontrast image would suggest

cal junction is involved, there may be a striking loss of demarcation of gray and white matter and the suggestion of some swelling (Figs. 103.1–103.3). When the periventricular structures are involved, the ventricle will be locally narrowed, with distortion of its normal border (Figs. 103.2 and 103.3). In these centrally located cases, the corpus callosum is nearly always involved and may be severely swollen (Fig. 103.2).

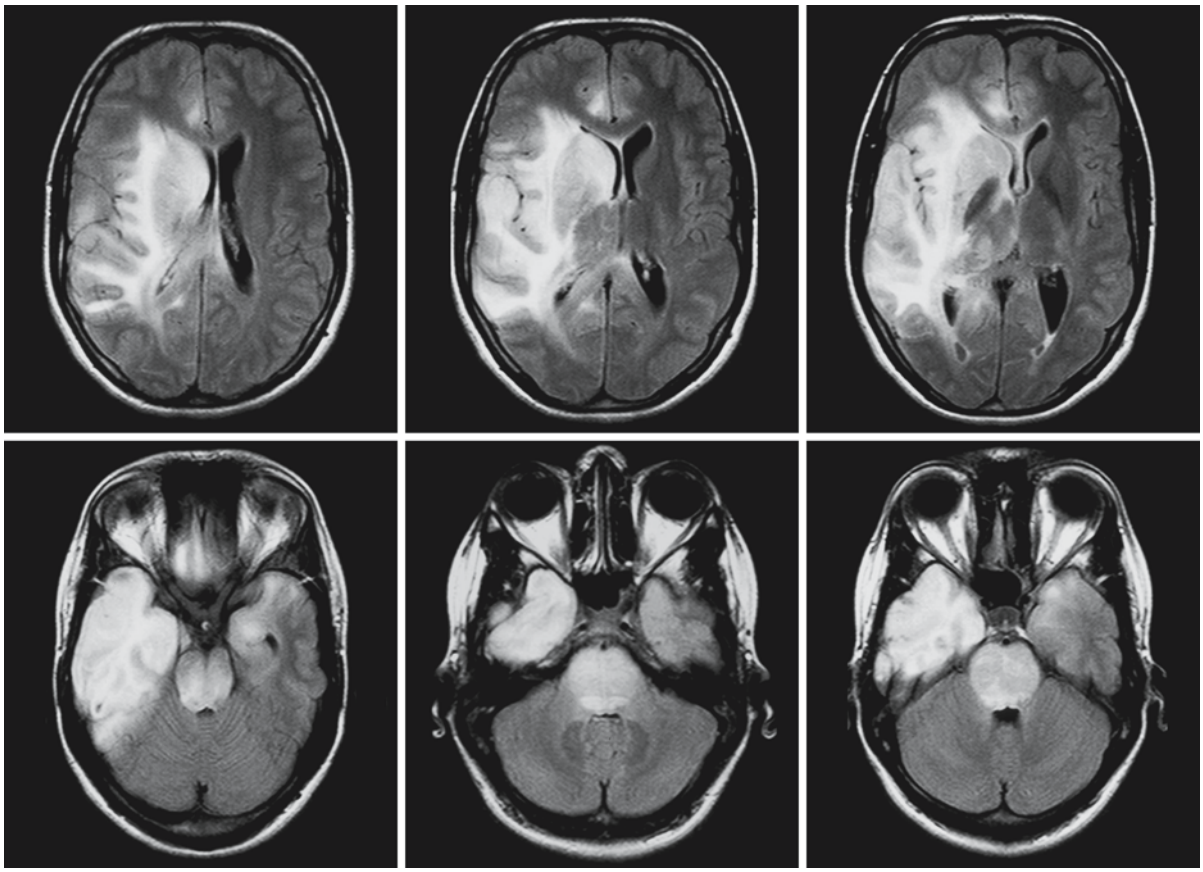

Fig. 103.4. Follow-up study of the same girl shown in Fig. 103.3, 6 months after radiotherapy and chemotherapy. It is clear that the process has advanced and the brain stem is seriously involved

There may be a striking symmetry of the abnormalities (Fig. 103.1), although this may disappear when the disease progresses. The disease may also be highly asymmetrical in the initial stage (Fig. 103.4). In some patients the spread of the disease clearly follows white matter tracts, with less severe involvement of gray matter structures. Focal calcification has been reported.

In most cases, there is no or only partial enhancement of the involved structures after contrast injection. This, however, depends on the technique used. With triple-dose gadolinium one may see some enhancement; a delayed scan (e.g., 1 h delay) may show enhancement in an unexpectedly large area (Fig. 103.3). Leptomeningeal dissemination may be observed, the disseminated lesions showing contrast enhancement.

Diffusion-weighted imaging with ADC maps is useful, in combination with chemical shift imaging and perfusion imaging, to find the places with the highest malignancy to direct a brain biopsy, when considered necessary, or to direct a local boost or intensity-modulated radiotherapy. In the affected areas MRS shows decreased *N*-acetylaspartate, normal or increased choline, and, in some patients, strikingly increased *myo*-inositol. *Myo*-inositol is exclusively present in glial cells.

The MR pattern of the disease is nearly always diagnostic. In cases with central location and symmetrical involvement of the thalamus, central venous thrombosis has to be excluded, for which purpose MRA can be used. Postictal changes may mimic the MR appearance of gliomatosis cerebri. In these cases the abnormalities disappear within 14 days.