Chapter 80

Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Encephalomyelitis

80.1 Clinical Symptoms and Laboratory Investigations

Acute disseminated encephalomyelitis (ADEM) is an uncommon inflammatory disorder within the CNS, predominantly within the white matter of the brain and spinal cord. "Postinfectious/postvaccination encephalopathy" is a synonym. Poser used the term "disseminated vasculomyelinopathy," indicating the probably causative small vessel vasculopathy (Poser 1969). Many other synonyms exist.

ADEM and acute hemorrhagic encephalomyelitis (AHEM) represent two clinical variants of a single pathological process. They follow a viral infection or vaccination or occur without recognized antecedent. Implicated viral infections are measles, chickenpox, rubella, smallpox, infectious mononucleosis, herpes simplex, herpes zoster, mumps, influenza, and *Mycoplasma pneumoniae* infection. They rarely occur following a bacterial infection. A nonspecific upper respiratory tract infection is the most common antecedent. The latent period varies from several days to several weeks, the mean being 4–6 days. Onset of the neurological symptoms is often abrupt, with convulsions and progression to somnolence and coma. Illness may also commence subacutely with symptoms of headache, fever, irritability, drowsiness, and vomiting. Nuchal rigidity may be present. The neurological signs are quite polymorphic and consist of hemiplegia, diplegia or tetraplegia, cerebellar ataxia, cranial nerve palsies, optic neuritis, nystagmus, sensory loss, and bladder dysfunction. Subcortical blindness is rare. Extrapyramidal movement abnormalities such as chorea, athetosis, and ballismus occur. The progression of the disease is variable. Patients with AHEM have a more severe clinical course and progress more rapidly into delirium and coma. The highest mortality is seen during the first week of the illness, and in fact most patients who survive the first week eventually recover, with varying degrees of disability. Prolonged disturbances in level of consciousness entail a poor prognosis both for morbidity and mortality. Possible neurological sequelae include epilepsy, spastic paresis, ataxia, decreased vision, and cognitive and psychiatric disturbances, but many patients have no remaining deficits. Most of the neurological syndromes have a monophasic course lasting several weeks. Recurrent attacks of ADEM/AHEM may occur. The occurrence of the neurological abnormalities is apparently independent of the nature and severity of the antecedent infection or immunization.

There is a close relationship with the Guillain–Barré syndrome, and in fact a combination of ADEM and Guillain–Barré syndrome has been described. Clinically, ADEM can usually be distinguished from multiple sclerosis, because it presents with signs of severe multifocal involvement of the CNS at the same time. If initially monosymptomatic with optic neuritis, the optic neuritis tends to be bilateral. No clinical feature, however, is exclusive to one or the other disorder.

Laboratory investigations reveal a peripheral leukocytosis. The CSF shows pleocytosis. The cellular exudate is mainly lymphocytic and rarely exceeds 100 cells/ml in ADEM. In AHEM the initial cells are granulocytic, and erythrocytes are also often seen. Glucose concentration is normal. There is usually a mild elevation of the CSF proteins, with an oligoclonal banding pattern and a heightened IgG index as signs of intrathecal IgG synthesis. An elevated level of myelin basic protein is shown, indicating myelin destruction. CSF abnormalities may persist for a long time after clinical recovery. Rarely, the CSF is completely normal throughout the course of the illness. The EEG often shows bilateral slow activity. These abnormalities are nonspecific and add little to the diagnosis.

80.2 Pathology

Edema is often the most conspicuous gross finding in ADEM, but the external appearance of the brain may also be completely normal. Microscopic examination demonstrates a diffuse inflammatory process in the brain, brain stem, and spinal cord, with inflammatory cells around veins and venules. Sometimes the perivascular infiltrates are associated with signs of vasculitis, showing inflammatory cells in vessel walls with or without frank necrosis. The cerebral hemispheres are usually more or less symmetrically involved. Both the white matter and gray matter are affected, but the white matter shows more severe changes. The most distinctive histological change is perivascular demyelination. Within the lesions myelin sheaths are lost, but the axons are relatively unaffected. Occasionally the demyelinating lesions are confluent and form large demyelinated areas. At

later stages of the disease, the inflammatory exudate is replaced by fibrous gliosis.

In AHEM, necropsy reveals the brain to be swollen and soft in consistency. On sectioning, numerous small hemorrhages are seen, mainly in the white matter. The cerebral cortex and basal ganglia are often spared. The hemorrhagic lesions are often but not always symmetrical. Confluence of many small lesions leads to large hemorrhagic lesions. On microscopic examination the abnormalities are seen to be related to blood vessels, predominantly small veins but also small arteries. There is necrosis of vessel walls, with fibrinous exudation, perivascular edema, hemorrhages, neutrophilic granulocytes in the vessel walls, perivascular spaces, and adjacent brain tissue, and perivascular demyelination. The demyelination is usually associated with necrosis and at least some loss of axons. In severely necrotic areas all axons may disappear. Perivascular demyelination is also seen surrounding apparently normal vessels.

Both in ADEM and in AHEM the severity, type, and localization of the pathological changes are unrelated to the type of preceding disease. In both syndromes the parenchymal pathology is often associated with meningeal lymphocytic infiltrates.

80.3 Pathogenetic Considerations

The early theories on ADEM and AHEM speculated that these syndromes might represent a delayed but direct invasion of the CNS by a virus or reactivation of a latent virus. There has, however, been a considerable amount of evidence against these theories. The pathological changes are fairly uniform and quite unlike those of the viral encephalitides, the demonstration of viral antigens or viral particles in the brain or the CSF being an exception.

Some observations led to the theory that ADEM and AHEM represent an autoimmune response to myelin constituents. First of all, the same neurological syndrome was found in patients vaccinated with rabies vaccine grown in rabbit spinal cord. Secondly, a comparable neurological syndrome was reported in animals after the repeated injection of CNS homogenate in combination with Freund's adjuvant. This syndrome is known as experimental allergic encephalomyelitis. Pathologically, the lesions of ADEM and experimental allergic encephalomyelitis have marked similarities. The white matter shows perivascular cuffing by inflammatory cells and demyelination. The cerebral hemispheres, cerebellum, brain stem, and spinal cord are involved. A hyperacute form of allergic encephalomyelitis has been induced in animals with alteration of the immunization regimen. Pathologically, more hemorrhagic features are present, similar to AHEM. Sensitization of lymphocytes to nervous tissue antigen and especially to myelin basic protein has been shown in a variety of postinfectious neurological disorders, including ADEM and AHEM. Experimental allergic encephalomyelitis results from T cell sensitization to myelin basic protein. The delayed hypersensitivity to myelin basic protein leads to an attack on myelin sheaths with subsequent demyelination. The demyelination is predominantly perivascular as the responsible T cells originate from the blood. ADEM and AHEM may represent the human counterparts of experimental allergic encephalomyelitis with breakdown of tolerance to myelin antigens. It is possible that the viral proteins serve as an antigen that cross-reacts with myelin antigens. It is also possible that during the initial phase of viral invasion there is subclinical involvement of the CNS, with release or exposure of sequestered neural antigens and subsequent sensitization to them. These theories, however, do not explain the rarity of ADEM and AHEM following a viral infection of the CNS, such as herpes virus or cytomegalovirus, nor its low incidence in general. How a wide variety of infections and vaccinations can induce similar sensitization to myelin antigens has also not been explained satisfactorily.

An alternative theory stresses the importance of the vascular changes, which are almost invariably present, and has coined the term "disseminated vasculo-myelinopathy." The detection of circulating antigen–antibody complexes in the serum of patients with a variety of postinfectious neurological disorders led to the assumption of a vascular lesion due to the entrapment of immune complexes in vessel walls and the subsequent inflammatory response. Because perivascular demyelination can result from vascular injury alone, the participation of delayed hypersensitivity would not be necessary. The presence or absence of immune complexes, the size and the number of the complexes, and not the antecedent illness would thus be the major factor in the development of ADEM and AHEM, and the development of delayed hypersensitivity to myelin antigens would be merely an epiphenomenon resulting from nervous tissue damage. However, it is not clear why the nervous system should be preferentially involved in immune-complex-mediated vasculitis. Only some indirect evidence supports this theory: the detection of circulating complexes in some patients with various postinfectious neurological disorders, the presence of systemic features compatible with immune complex disease in occasional patients, and the occurrence of similar nervous system abnormalities in other human disorders caused by immune complexes. Immune complexes have, however, not been found at sites of vessel injury, and it is not impossible that the complexes themselves only represent an epiphenomenon.

The two hypotheses presented here are not mutually exclusive. Immune complex vasculitis results in increased vascular permeability. Changes in vascular permeability and perivascular inflammation can either alter the antigenicity of myelin or release an antigen previously sequestered by a competent blood–brain barrier. The cell-mediated immune response could then perpetuate the damage and lead to demyelination. In some patients perivascular demyelination is seen, whereas in others the pathological picture is dominated by perivascular necrosis. It is hypothesized that pure demyelination may be caused by delayed hypersensitivity to myelin antigens alone and that necrosis associated with inflammatory infiltration occurs when there is production of antibodies directed against several components of the brain parenchyma.

80.4 Therapy

Corticosteroids are central in the management of ADEM and AHEM. Dramatic clinical improvement may be seen. Relapses may occur when steroids are withdrawn, and improvement may then recur when steroids are reinstituted. The fact that the improvement is sometimes absent or only slight may be explained by the presence of irreversible structural damage prior to institution of the steroid therapy. It is recommended that corticosteroid therapy be initiated as soon as possible in the treatment of these syndromes.

In desperate cases, alternative therapeutic strategies may include more drastic immunosuppression and plasmapheresis.

80.5 Magnetic Resonance Imaging

In ADEM, CT scan of the brain shows multifocal or diffuse white matter damage, but it may be normal in the acute stage, or may remain normal throughout. Not all lesions show enhancement after contrast injection. CT can seldom explain the full extent of clinical disability, and, conversely, several lesions may be seen for which no correlative clinical signs are observed. Clinical improvement is accompanied by disappearance of contrast enhancement and complete or partial resolution of low-density lesions.

In AHEM the white matter lesions are characterized on CT by extensive edema with prominent mass effect and the presence of hemorrhages.

MRI in ADEM shows multiple, usually large white matter lesions with an asymmetrical distribution (Figs. 80.1–80.3). In very extensive cases, in which almost all white matter is involved, the asymmetrical distribution becomes less clear. Symmetry of lesions is exceptional. Smaller, multiple sclerosis-like lesions occur in a small number of patients. The lesions have a preference for the occipital and parietal area. The white matter lesion may "spill into" the cortex with some focal cortical involvement (Fig. 80.3). Mass effect is rare but tumefactive lesions in the frontal and parietal lobes have been described. It should be noted that less frequently ADEM presents with involvement of the basal ganglia and brain stem (Fig. 80.4). Spinal MR is mandatory for a comprehensive inventory of lesions (Fig. 80.4). In nearly all cases spinal lesions can be demonstrated. Incidentally spinal lesions are the sole MR presentation of the disease. Some patients have optic neuritis (Fig. 80.4). After contrast injection the white and/or gray matter lesions may enhance (Fig. 80.3), but usually not all lesions enhance, and contrary to what is usually stated, our experience is that in many cases enhancement is at most subtle (Fig. 80.2), or is not present at all (Fig. 80.1). The enhancement is often patchy, while sometimes the whole lesion enhances. Ring enhancement may occur. The presence of both enhancing and nonenhancing lesions argues in favor of the lesions' being in different stages of development, despite the supposed monophasic character of the disease. Repeated MRI during the course of the disease may show disappearance of some lesions and concurrent appearance of others. These observations modify the view that ADEM is always simply monophasic. Disappearance of white matter lesions is sometimes rapid (Fig. 80.5), but may also take a long time, as much as 18 months, and part of the white matter damage may be permanent (Fig. 80.6). New lesions may appear despite clinical improvement.

Diffusion-weighted imaging in ADEM reveals similar results as in multiple sclerosis. In the peracute phase of the lesion ADC values may be low; after 2–3 weeks, the ADC values are higher than average in the core of the lesion and mixed in the borders; in the late phase the abnormal findings tend to disappear.

Magnetization transfer ratios (MTRs) have been estimated in ADEM. Histogram MTR analysis of normal-appearing white matter in patients with multiple sclerosis and ADEM show significantly lower MTRs and peak positions and significantly higher diffusivity in multiple sclerosis than in ADEM, suggesting that

Fig. 80.1. A 2-year-old girl with ADEM. The T_2-weighted transverse images (*first* and *second rows*) show large, bulky lesions in the centrum semiovale, predominantly in the frontal lobe. There are also lesions in the midbrain and pons. This is the "common" pattern of ADEM. On the T_1-weighted contrast-enhanced images (*third* and *fourth rows*) no enhancement of lesions is seen, despite the acute clinical presentation

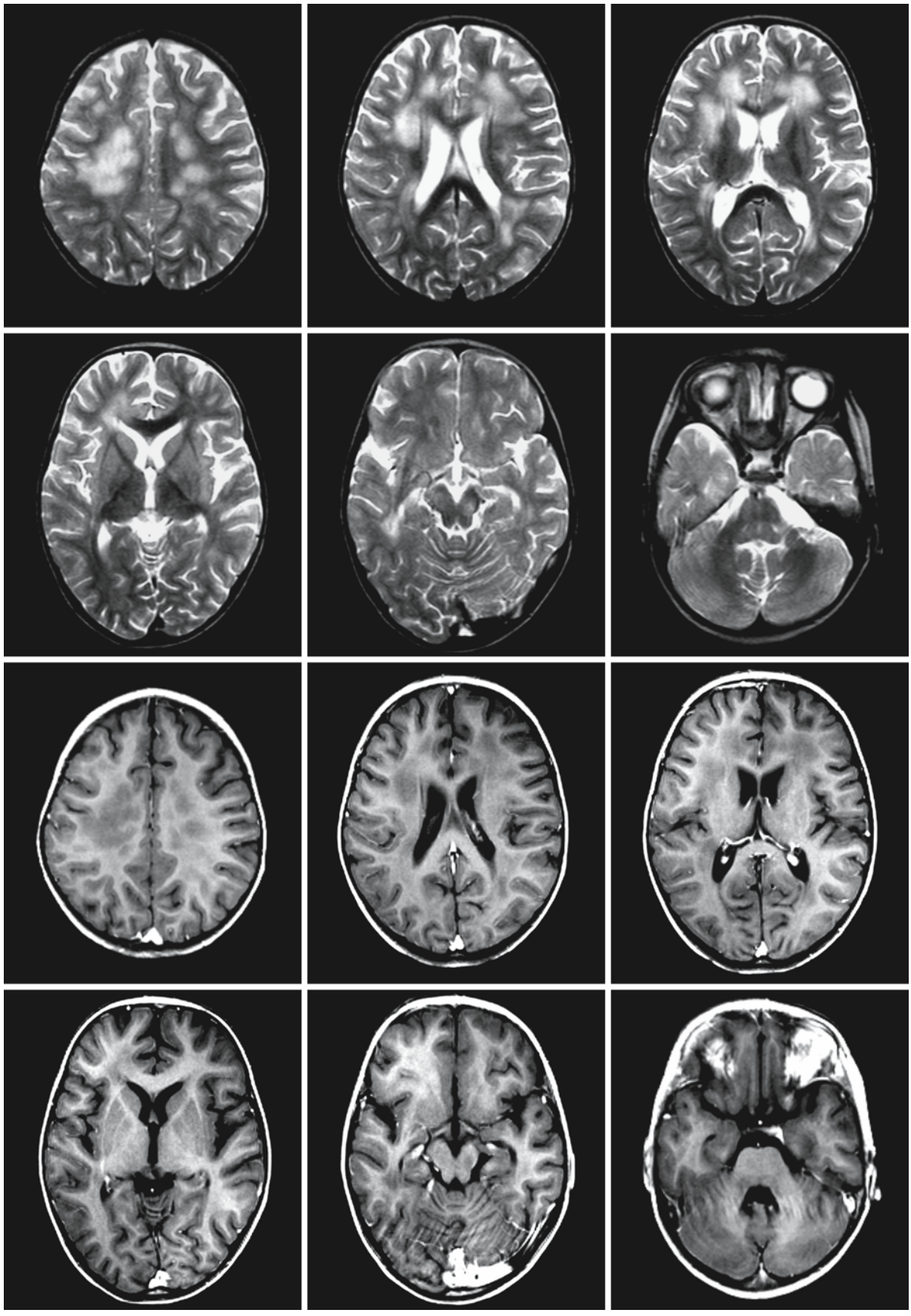

Fig. 80.1.

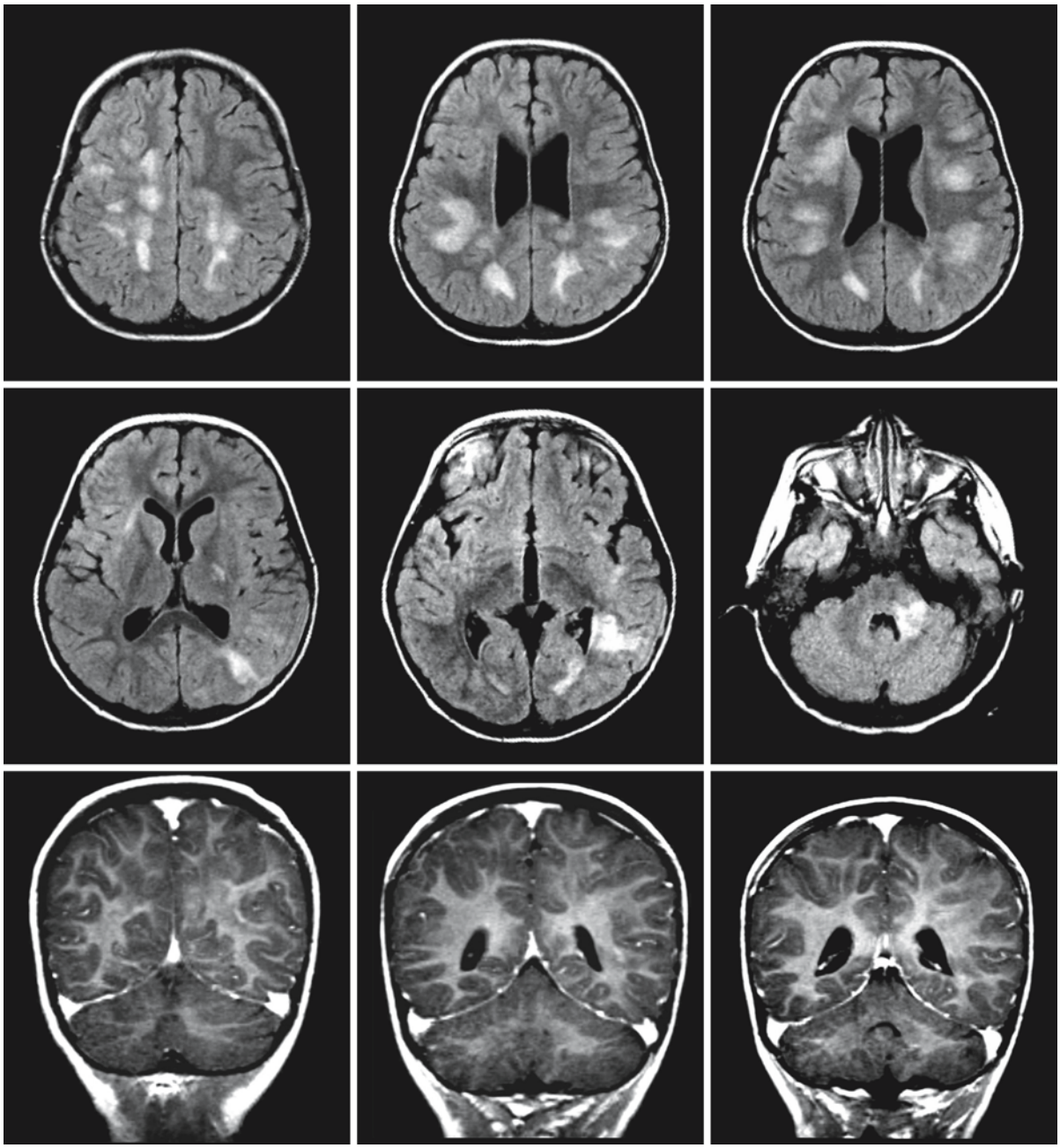

Fig. 80.2. A 5-year-old girl with a rapidly progressive presentation of ADEM. The transverse FLAIR images (*upper two rows*) show many lesions dispersed throughout the brain, with exception of the temporal lobes. There is also a large lesion in the left middle cerebellar peduncle. T_1-weighted coronal contrast-enhanced images (*third row*) show only a few tiny spots of enhancement

in ADEM the normal-appearing white matter is less involved than in multiple sclerosis. These measurements have been made outside of the acute phase.

Apart from the difference in preferential involvement of brain structures, it may be difficult to distinguish ADEM from multiple sclerosis in the initial phase. Without a clinical history of a preceding infection or vaccination, or when the disease presents with a single symptom such as optic neuritis, it is impossible to differentiate between acute multiple sclerosis and ADEM on basis of MR images. In a later phase, comparison as described of MTRs and MRS in normal-appearing white matter can help in the decision. Repeated MRI examinations over a long period of

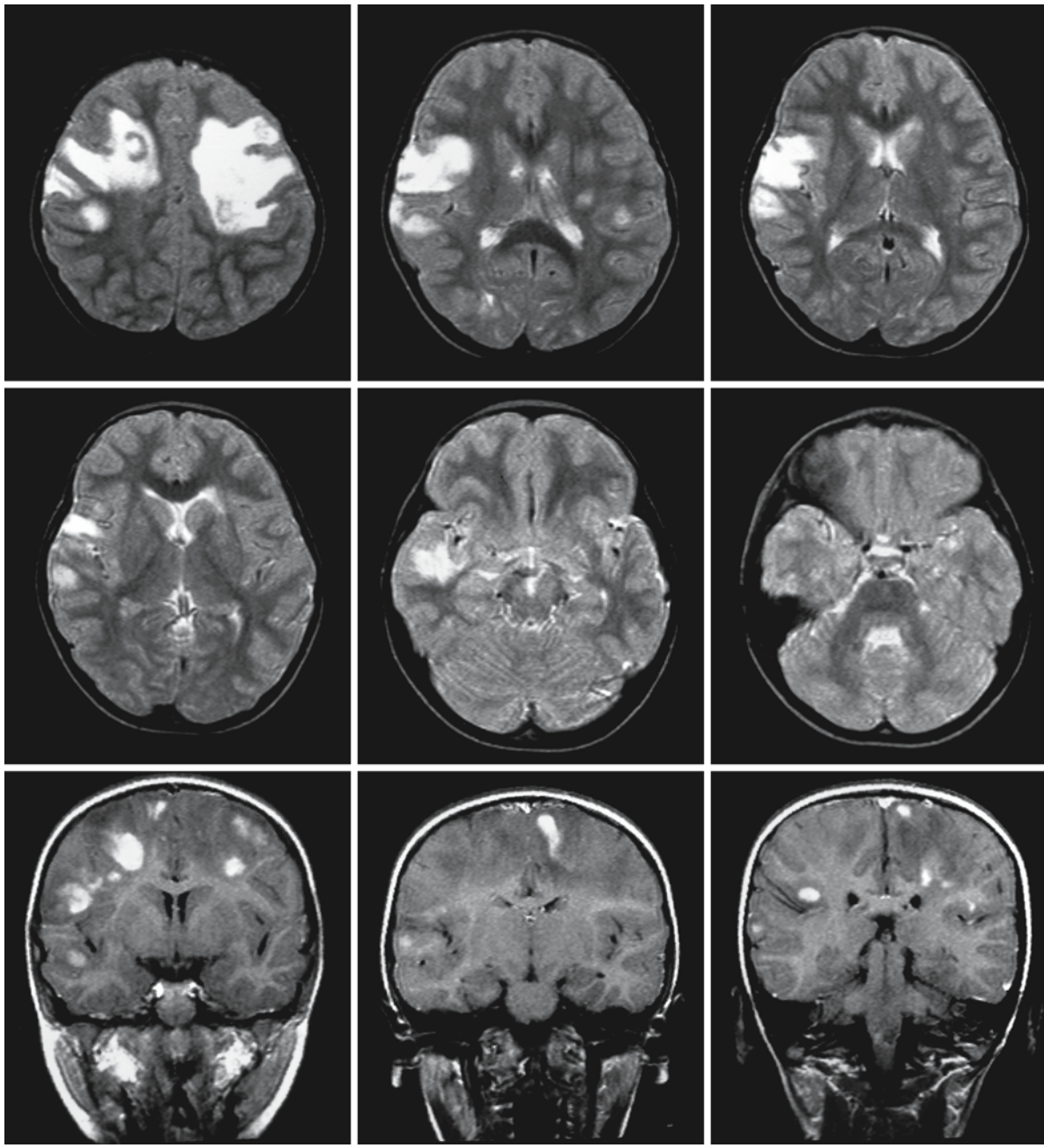

Fig. 80.3. In this 3-year-old girl with ADEM the T_2-weighted transverse images (*upper two rows*) show large lesions that involve the subcortical white matter, with extension into the cortex. After contrast injection the T_1-weighted images (*third row*) show enhancement of many lesions

time may also be helpful, in particular in combination with follow-up of the clinical course. Stationary lasting lesions are indicative of ADEM, while newly appearing lesions argue against this diagnosis, but this is not an absolute rule. New lesions may appear in ADEM despite ongoing clinical improvement, but new lesions do, as a rule, not appear after the attack when the patient is asymptomatic. New lesions on MRI repeated 3 months after the attack is considered to be predictive of multiple sclerosis. However, some ADEM patients have multiple episodes in the course of several years.

In exceptional cases, one may find a clinical picture suggestive of ADEM while MRI shows predominantly

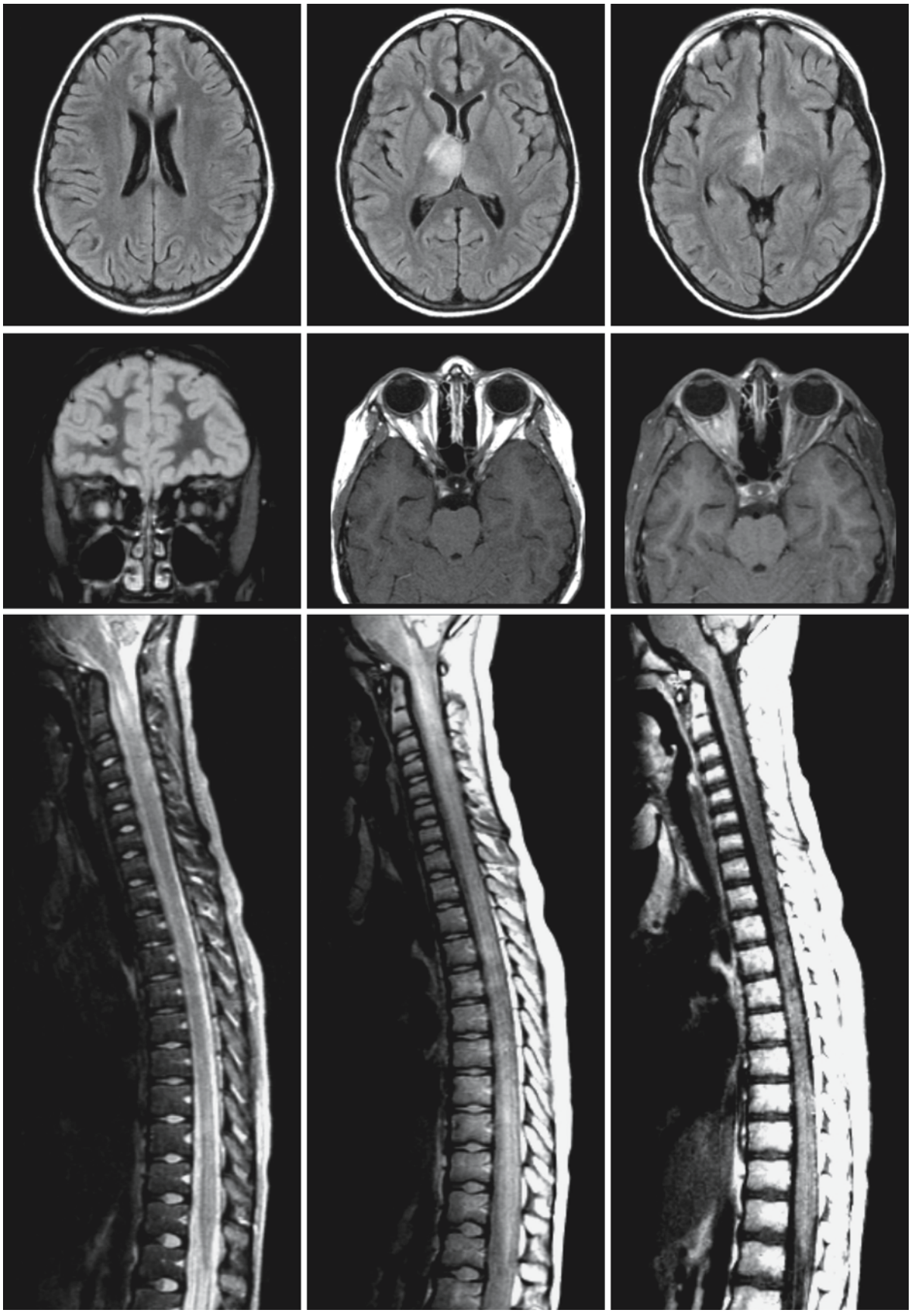

Fig. 80.4.

or exclusively gray matter lesions (Fig. 80.7). These gray matter lesions may disappear. Probably the "gray matter ADEM" is the counterpart of the "regular ADEM," just as Guillain–Barré syndrome is usually a demyelinating polyneuropathy, but is sometimes axonal.

In AHEM, the hemorrhagic component can be identified on CT, but also with confidence by MRI, either by FLAIR or by gradient echo techniques. The hemorrhagic aspect, which is highly unusual in multiple sclerosis and its variants, may help to establish the correct diagnosis (Fig. 80.8).

Fig. 80.4. MRI in a 6-year-old girl presenting with lowered consciousness, spastic paraparesis, and diminished vision of the right eye. The FLAIR images (*first row*) show a gray matter lesion, a large lesion in the right thalamus with some mass effect. A coronal STIR image (*second row*, *left*) shows swelling and too high a signal in the right optic nerve, representing optic neuritis. The transverse T_1-weighted images after contrast injection (*second row*, *middle* and *right*) show enhancement of the right optic nerve. The *third row* shows the spinal images. A T_2-weighted sagittal image of the cervical and upper thoracic cord (*left*) shows a large intramedullary lesion in the upper cervical cord. The proton density image (*middle*) reveals multiple additional smaller lesions in the thoracic cord. A T_1-weighted contrast-enhanced sagittal image of the spinal cord (*right*) shows enhancement of multiple lesions

Fig. 80.5. An 11-year-old boy with ADEM. In the acute stage (*first two rows*), the T_2-weighted transverse images show extensive, patchy involvement of the white matter in the centrum semiovale, bilateral and symmetrical involvement of the internal capsule, involvement of the pulvinar, and also symmetrical involvement of structures in the pons. At follow-up, 2 weeks later (*third* and *fourth rows*), the lesions have disappeared completely, reflecting full clinical recovery.
(Fig. 80.5 see next page)

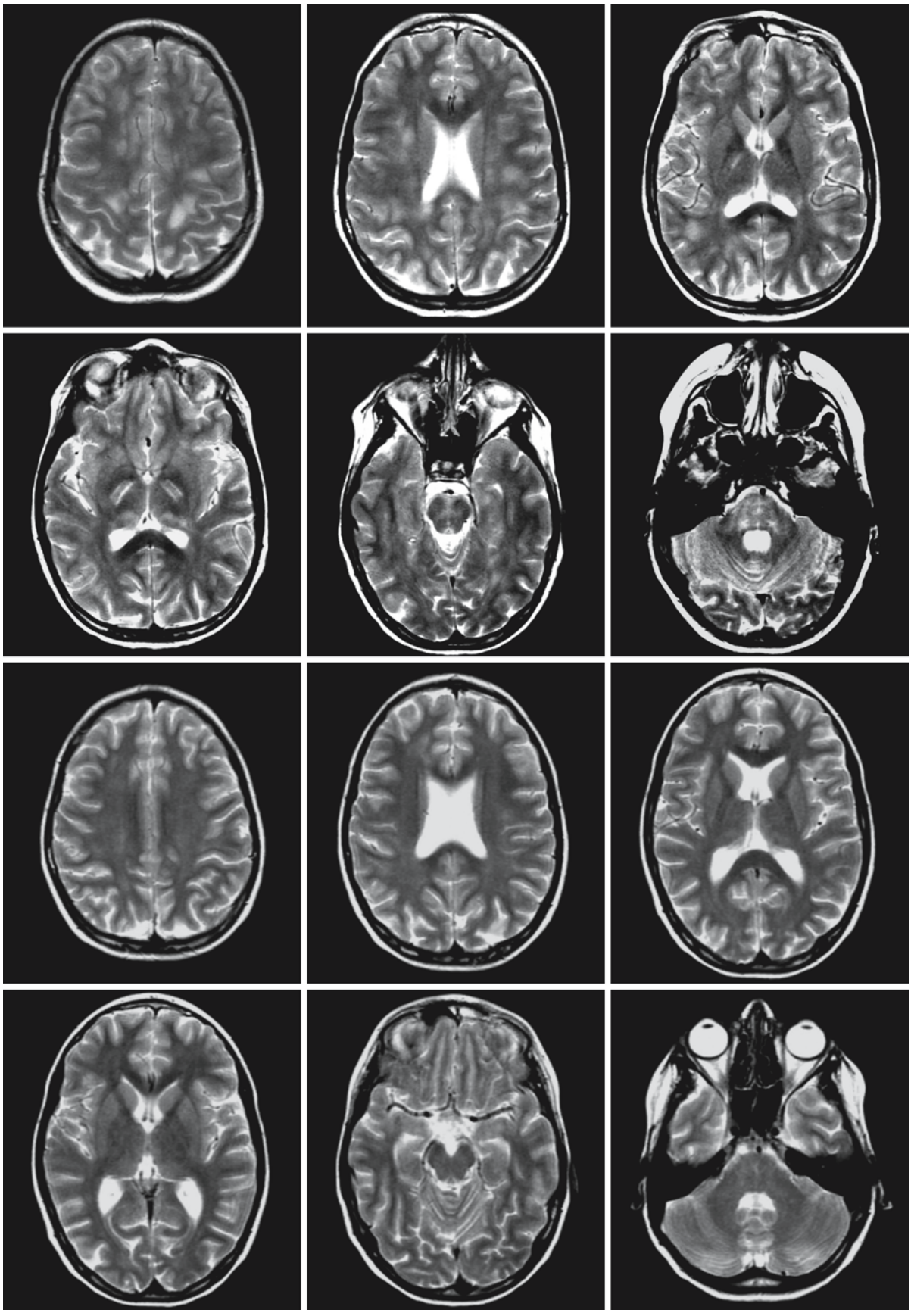

Fig. 80.5.

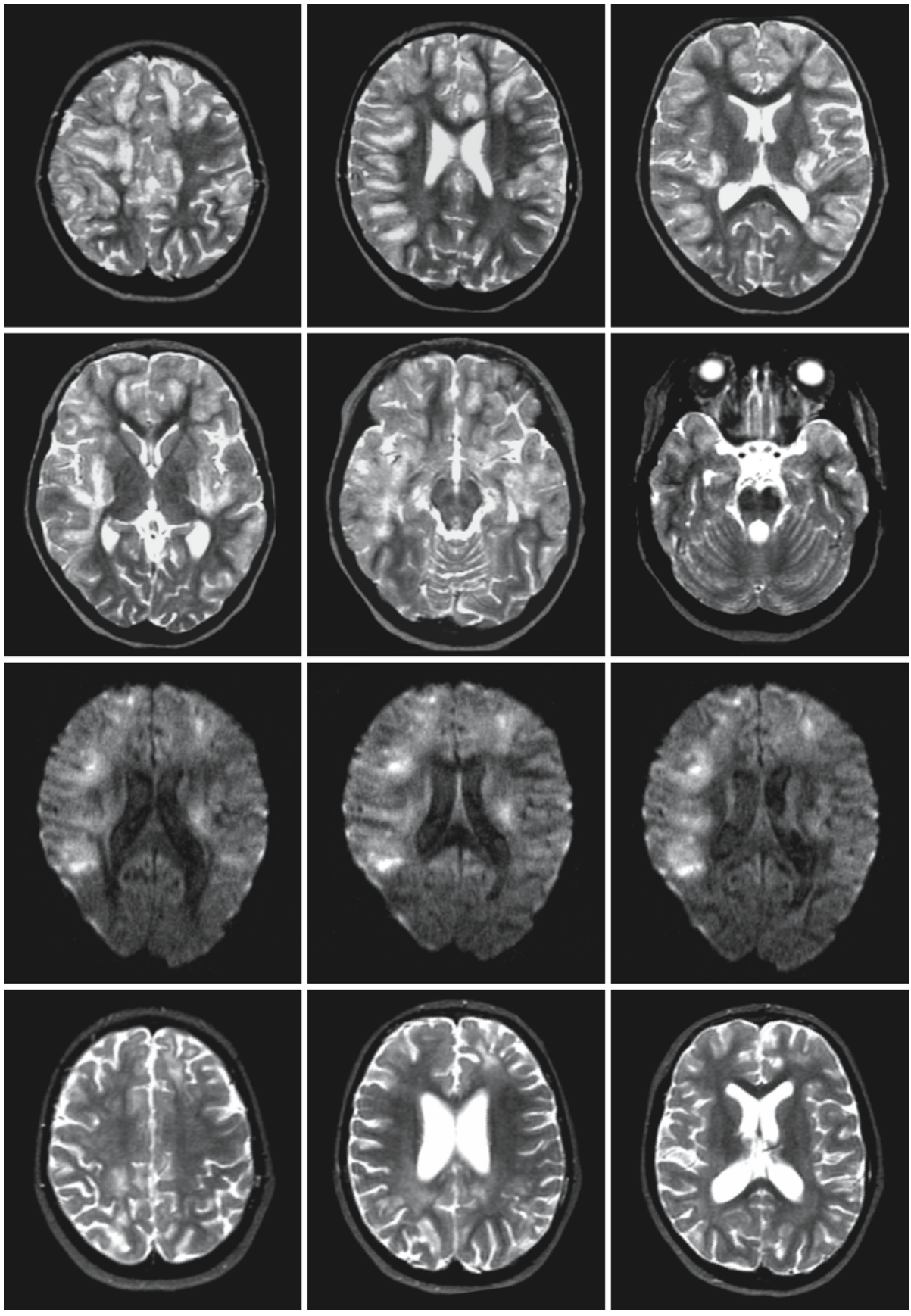

Fig. 80.6.

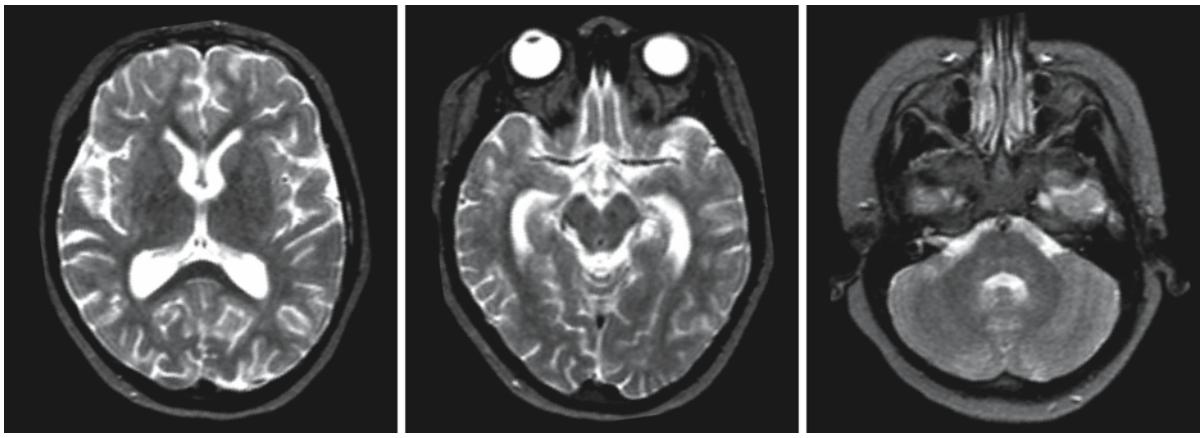

Fig. 80.6. (*continued*). In a 6-year-old girl with ADEM and a serious presentation, the T_2-weighted images (*upper two rows*) show multifocal involvement of subcortical and deep white matter. Diffusion-weighted–Trace (b = 1000) images (*third row*) show high signal in the affected regions with greater conspicuity. The ADC values were low (–30 %). Follow-up MRI after 6 months (*fourth* and *fifth row*) shows cortical and central atrophy and some ill-defined areas of signal abnormality in the cerebral white matter

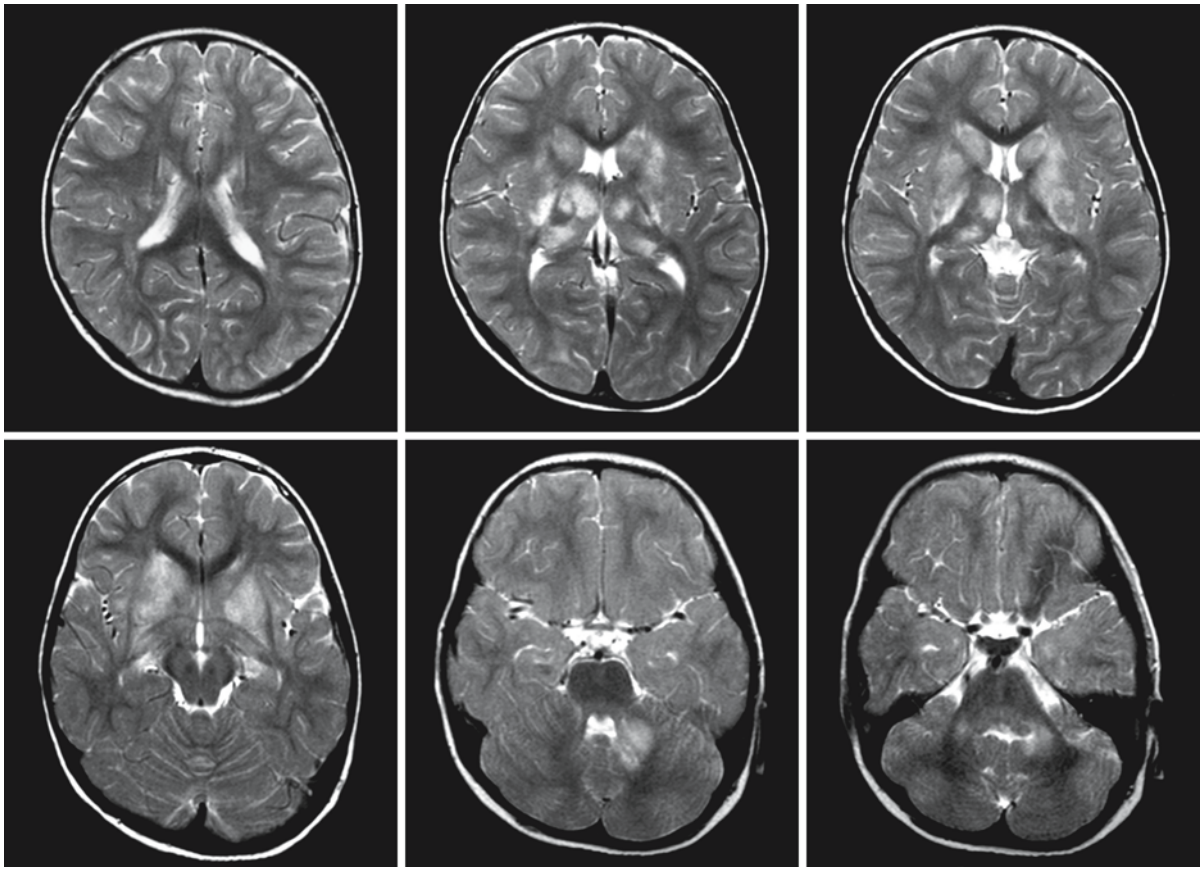

Fig. 80.7. In this 2.5-year-old boy with ADEM, the lesions are predominantly located in the gray matter. Exceptions are lesions in the middle cerebellar peduncle on the left side

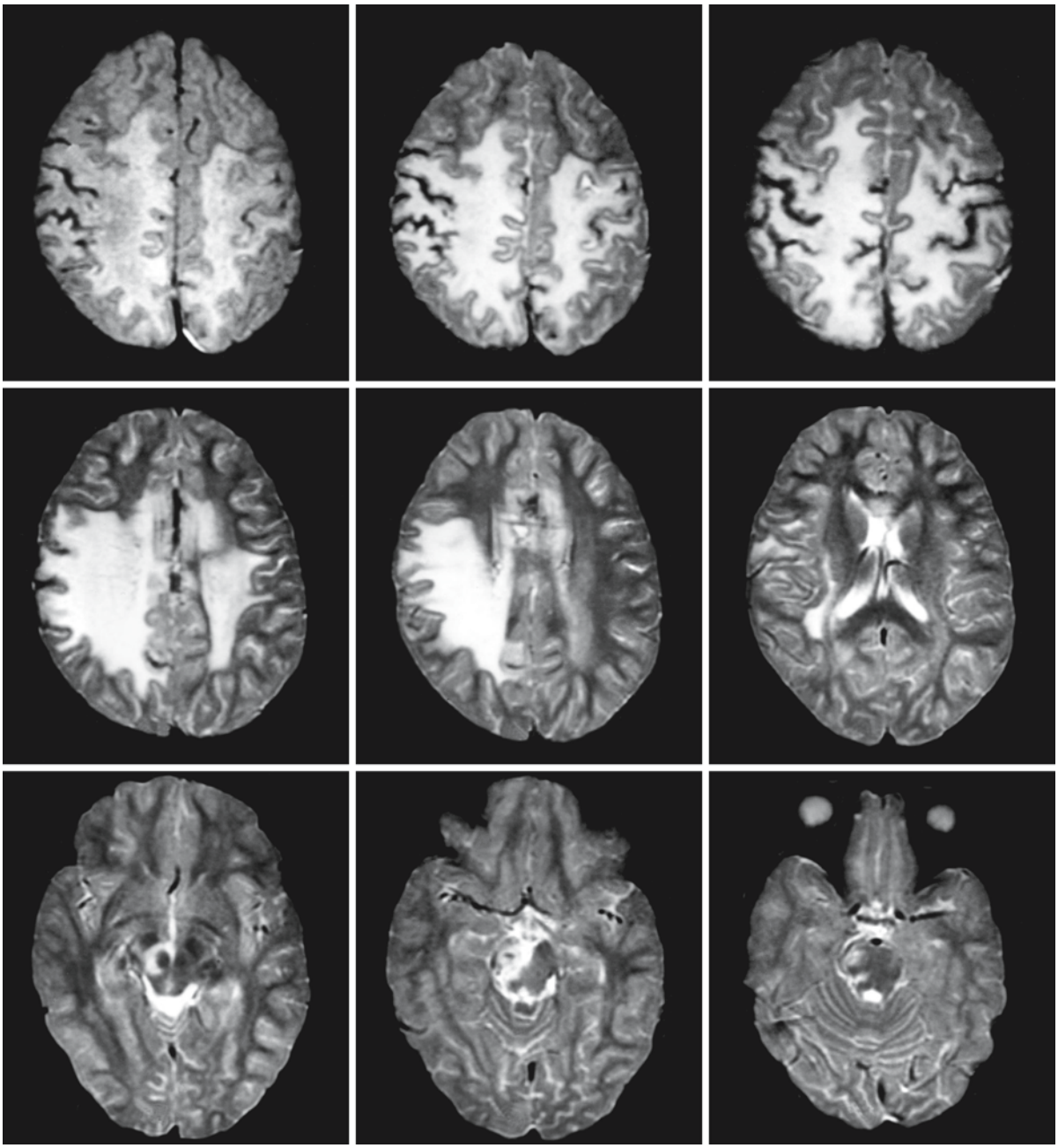

Fig. 80.8. An 8-year-old boy, acutely ill following a minor infection a few weeks before admission. The T_2-weighted images show involvement of the pons and mesencephalon, especially on the right side, and large, confluent areas of abnormal white matter in the cerebral hemispheres. The gyral pattern in the rolandic area shows too low a signal intensity, caused by the presence of breakdown products of blood, including hemosiderin. The presence of considerable hemorrhage classifies this patient as a case of AHEM. Courtesy of Dr. A. Goulao, Lisbon, Portugal