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MRI of high-grade astrocytic tumors: early appearance and evolution

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Abstract The clinical management and prognosis of patients with diffusely infiltrating astrocytomas are dependent on neuropathological grading of the tumors. The characteristics of MR images of high-grade astrocytic tumors are well known, but the early MRI appearance and the MRI evolution of high-grade astrocytic tumors have rarely been examined. We retrospectively reviewed MR images obtained from 4 months to 3 years and 3 months before admission, as well as MR images on admission, for five patients with pathologically proven high-grade astrocytic tumors (two glioblastomas and three anaplastic astrocytomas). In two patients, neoplastic lesions were not detectable on initial MRI, even retrospectively. In the remaining three patients, however, hyperintense areas with little or no mass effect were demonstrated on T2-weighted imaging. These lesions were misinterpreted as non-neoplastic processes, such as ischemic lesion or infarction, or demyelinating processes. All tumors showed gadolinium enhancement on admission, that emerged from the previously existing hyperintense areas on T2-weighted images without gadolinium enhancement, except for one de novo glioblastoma. Development of a small central cyst without gadolinium enhancement was demonstrated in one case before the emergence of an enhancing area.

Keywords Brain tumors · Astrocytic tumors · Diffusely infiltrating astrocytomas · MRI

Introduction

Nowadays, MRI is available in many hospitals and institutions. Patients with various signs and symptoms undergo MRI of the head, and some gliomas are unexpectedly demonstrated in patients without typical clinical manifestations. In these cases, gliomas with characteristic MRI appearances are readily diagnosed, whereas others may be misinterpreted as non-neoplastic conditions. Delay in diagnosis of high-grade gliomas may lead to a serious outcome for the patient. Therefore, early diagnosis of glioma is mandatory, and assessment of early MRI appearances of high-grade gliomas is important to neuroradiologists for making a correct diagnosis at the earliest opportunity.

We retrospectively reviewed previously obtained MR images in patients with histologically confirmed anaplastic astrocytomas or glioblastomas at the initial diagnostic procedures, in order to identify the early MRI appearances of high-grade astrocytic tumors.

Patients and methods

In addition to MR images obtained on admission to our university hospital, previously acquired MR images from outside hospitals were retrospectively reviewed in five patients with histopathologically diagnosed high-grade astrocytic tumors (two men and three women; age range from 36 to 84 years, mean 61.6 years): two glioblastomas and three anaplastic astrocytomas. Histological diagnosis was made in each patient by initial diagnostic intervention performed soon after admission: stereotaxic needle biopsy in

three patients, surgical tumor resection in the other two. Patients who had been observed for a period under a tentative diagnosis of low-grade glioma were not included in this study.

Initial MR images were obtained 4 month to 3 years and 3 months prior to admission because of various symptoms: vertigo, unconsciousness attacks, general convulsions, dysesthesia, and hemiparesis. Additional MRI examinations were performed 8 and 9 months before admission in two patients for evaluation of the efficacy of steroid therapy in one case, with a tentative diagnosis of multiple sclerosis, and for decreased activity in the other. All images were obtained with 1.5-T imagers, and a total of 12 MRI examinations was studied.

Because of the retrospective study, and because previous MRI studies were performed in different outside hospitals, MRI protocols were not uniform. However, in all patients, spin-echo (SE) T1-weighted, SE or fast SE (FSE) proton density- and T2-weighted images were obtained, with the following parameters: TR 380–600 ms, TE 10–20 ms, number of excitations 2–3 for SE T1-weighted images; TR 2,520–4,000 ms, TE 90–100 ms, number of excitations 2 for SE or FSE proton-density and T2-weighted images, echo train length of 7–12 for FSE; field of view 22–23 cm, a matrix of 192–256×256 or 512, and slice thickness of 5–6 mm with interslice gap of 1 mm. Post-contrast T1-weighted imaging was also added in nine examinations, except for the initial studies in three patients.

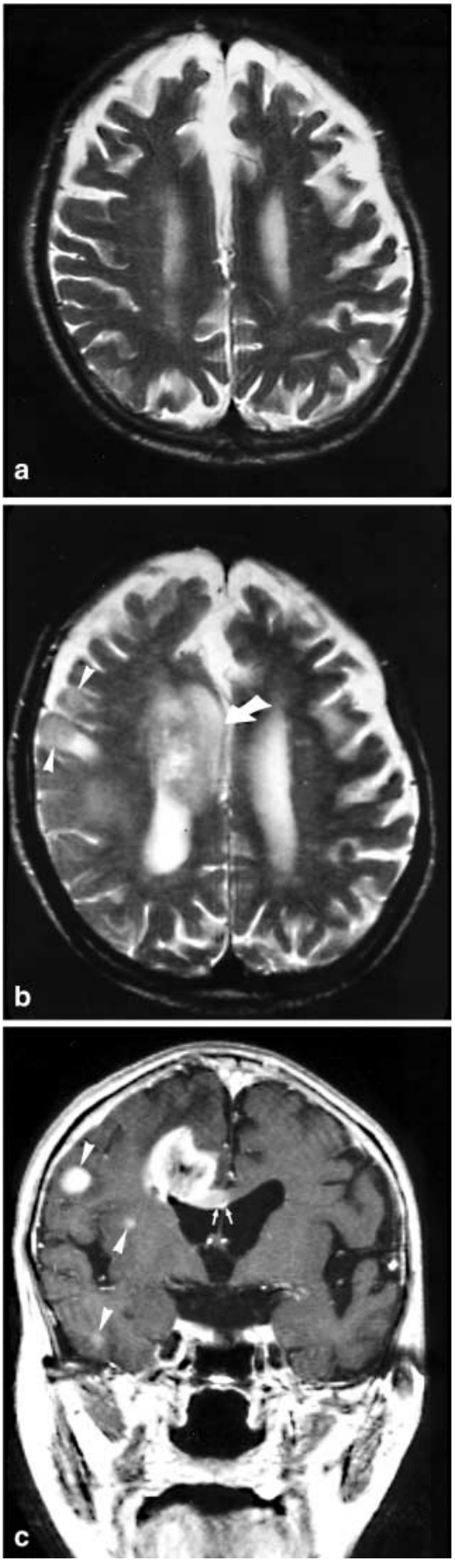
Results

Clinical and MR features are summarized in Table 1. Gliomas could not be detected on the initial MR studies in two patients, even retrospectively. In these patients, post-contrast images were not obtained at that time. In one case of multicentric glioblastomas (case 1), multiple enhancing tumors were demonstrated on admission (Fig. 1b, c), but no abnormal signal intensity could be found at the sites of the tumor development on the initial MR images 4 months earlier (Fig. 1a). In the other patient with anaplastic astrocytoma (case 3), there were multiple small hyperintense areas in the cerebral white matter on the T2-weighted images from the initial MRI (Fig. 2a), but making a diagnosis of glioma was impossible. A homogeneously hyperintense area was demonstrated in the left frontal white matter on the T2-weighted images from the second MRI 2.5 years later (Fig. 2b). Unfortunately, occlusion of the middle cerebral artery was demonstrated on MR angiography at the same time, and the lesion was misinterpreted as an ischemic lesion. This lesion showed no gadolinium enhancement, but evolved into a solid enhancing tumor with necrosis and marked surrounding edema 9 months after the second examination (Fig. 2c).

In the remaining three patients, hyperintense lesions with little or no mass effect were found on the T2-weighted images from the initial MRI, but they were misinterpreted as non-neoplastic diseases. An ill-defined subtle hyperintensity area in the left anterior temporal white matter was considered to be an ischemic change initially in a hypertensive elderly man (case 5, Fig. 3a) because confluent ischemic lesions were distributed in other areas of the cerebral white matter. Subsequently, a ring enhancing tumor emerged from the lesion (Fig. 3b). In the other two female patients in their fourth decade (cases 2 and 4), the hyperintense lesion was diagnosed as demyelinating process or cerebral infarction. Both lesions showed no gadolinium enhancement. Initial diagnosis of a heterogeneous hyperintensity area in the left parietal white matter, without mass effect, was multiple sclerosis (case 2, Fig. 4a), which was not depicted as a definitive lesion on pre- and post-contrast T1-weighted images (Fig. 4b). The patient was treated with steroids for 2 months. Although the size of the lesion showed no interval change, a small non-enhancing cyst emerged

Table 1. Patients' clinical and MR features. Time in parentheses is an interval between the MR study and the diagnosis. *Dx* diagnosis, *GB* glioblastoma, *SNB* stereotaxic needle biopsy, *ND* not detectable, *F* focal lesion, *Ne* necrosis, *GE* gadolinium enhancement and surrounding edema, *NG* no gadolinium enhancement, *AA* anaplastic astrocytoma, *D* diffuse lesion

Case	Age (years)/ gender	Symptom	Pathological Dx	Means of Dx	Initial MR study	Second MR study	MR study at Dx	Survival after Dx
1	77/male	Vertigo	GB	SNB	ND (4 months)		Multiple F with Ne, GE	4 Months
2	38/female	Dysesthesia	GB	Removal	F, NG (10 months)	Add a small central cyst (8 months), NG	Multiple Ne in F, GE	1 Year 8 months
3	84/male	General convulsions	AA	SNB	ND (3 years 3 months)	Patchy F, NG (9 months)	Irregular Ne in F, GE	10 Months
4	36/female	Left hemiparesis	AA	Removal	D + F, NG (5 months)		D + F, ring GE	1 Year 3 months
5	73/male	Unconsciousness attack	AA	SNB	D (9 months)		Ne in F, ring GE	1 Year 4 months
Mean	61.6							1 Year 1 month



within the central portion of the lesion (Fig. 4c). Eight months later, the lesion turned into a large enhancing tumor with multiple cystic or necrotic portions and marked perifocal edema (Fig. 4d). The diagnosis of glioblastoma was confirmed. In the other patient (case 4), a hyperintense lesion was demonstrated in the right high prefrontal gyrus on T2-weighted MR images obtained 5 days after sudden onset of left hemiparesis (Fig. 5a). This lesion was hypointense on T1-weighted images without gadolinium enhancement, and was erroneously diagnosed as cerebral infarction. In this case, the right pyramidal tract in the internal capsule and pons showed increased signal intensity on T2-weighted images (Fig. 5b, c). In addition, other subtle hyperintense areas with structural enlargement were retrospectively seen on T2-weighted images at the right insular cortex (Fig. 5b), and the right amygdaloid nucleus and hippocampus (Fig. 5c). However, these lesions were not recognized at that time. Five months later, a ring enhancing tumor with accompanying edema developed in the high precentral gyrus (Fig. 5d). Although multiple, irregularly enhancing tumors developed from other hyperintense areas on T2-weighted images over 14 months after the diagnosis, hyperintensity of the right pyramidal tract did not change in the disease course.

Discussion

The clinical management and prognosis of patients with diffusely infiltrating astrocytomas are dependent on accurate neuropathological grading of the tumors [1]. The diffuse astrocytoma is the most benign of them [2, 3]. Typical range of survival is more than 5 years for diffuse astrocytomas WHO grade II [2], and post-operative survival usually ranges from 3 to 10 years [4]. On the other hand, high-grade astrocytic tumors have poor prognoses. The average post-operative survival for anaplastic astrocytomas is approximately 2 years, and that of glioblastomas is usually less than 1 year [1, 2, 4]. The mean survival after the diagnosis was 1 year and 1 month in our five patients: 1 year in two glioblastomas, and 1 year and 2 months in three anaplastic astrocytomas.

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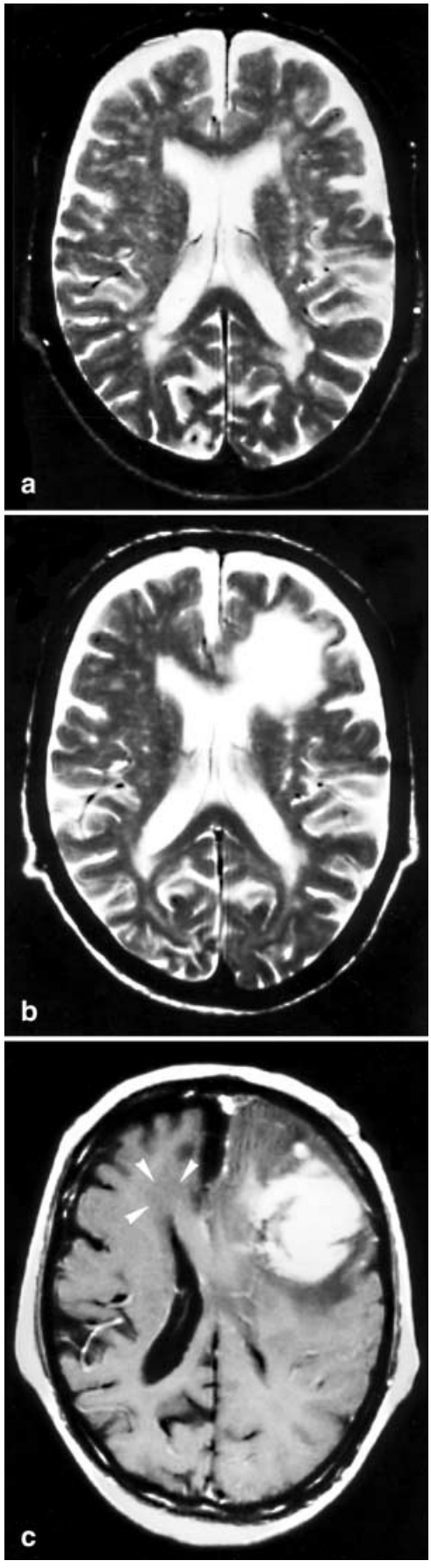
Fig. 1a–c. Case 1. A 77-year-old man with multicentric de novo glioblastoma. **a** T2-weighted (4,000/90/2, TR/(effective) TE/excitations) image from the initial MRI 4 months before admission shows no neoplastic lesion. **b** T2-weighted (3,100/90/2) image on admission shows a heterogeneously hyperintense tumor in the right centrum semiovale (*arrow*) and small slightly hyperintense areas in the right frontal gyri (*arrowheads*). **c** Post-contrast T1-weighted (460/12/2) coronal image shows a heterogeneously enhancing tumor in the right centrum semiovale extending into the corpus callosum (*small arrows*) and other small enhancing nodules at the junction between gray and white matter in the right cerebral hemisphere (*arrowheads*)



Glioblastomas can be of two types: the majority, that arise in diffuse astrocytomas and anaplastic astrocytomas [3], and those that originate de novo without undergoing malignant transformation from lower-grade tumors [3, 5]. Early detection of both malignant change in diffuse astrocytomas and occurrence of de novo high-grade astrocytic tumors on MRI is mandatory to improve survival in patients with astrocytic tumors. In our study, de novo type glioblastoma was demonstrated in case 1. Initial MR studies obtained 4 months earlier could not depict any neoplastic abnormality (Fig. 1a), but multiple, enhancing tumors developed on admission (Fig. 1b, c). In cases of such a de novo glioblastoma with rapid growth, both the making of earlier MRI diagnosis and the improvement of patient survival seem still to be difficult.

Well-known MRI appearances of untreated diffuse astrocytomas are iso- to hypo-intense to adjacent brain on T1-weighted images, and homogeneously hyperintense on T2-weighted images [6]. These tumors characteristically are well defined; display little mass effect, vasogenic edema, heterogeneity, or contrast enhancement, and are non-hemorrhagic [1, 6, 7, 8]. A lesion suggesting diffuse astrocytoma with the above-mentioned MRI features was demonstrated in the left frontal white matter at the second MRI in case 3 (Fig. 2b). Punctate hyperintense areas were seen at the site on T2-weighted images from the initial MRI 2.5 years earlier (Fig. 2a), but a neoplastic nature was not detectable. Even if one of the punctate lesions in the left frontal white matter was a bud of the astrocytic tumor, it could not be differentiated from other multiple ischemic white matter lesions. Eventually, the patchy, left frontal white matter lesion enlarged and showed heterogeneous enhancement with an irregular necrotic area and marked surrounding edema, resulting in a midline shift to the right (Fig. 2c). In addition, the tumor extended into the right frontal white matter through the corpus callosum. These MRI appearances were characteristic of high-grade astrocytoma, especially glioblas-

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Fig. 2a–c. Case 3. An 84-year-old man with anaplastic astrocytoma. **a** T2-weighted (2,520/90/2) image from the initial MRI 3 years and 3 months before admission shows multiple small ischemic lesions in the cerebral white matter. **b** T2-weighted (2,700/90/2) image from the repeated MRI 2.5 years after the initial MRI shows a patchy, hyperintense lesion with little mass effect in the left frontal white matter. The lesion showed no gadolinium enhancement (not shown). **c** Post-contrast T1-weighted (600/15/2) image on admission shows an irregularly enhancing tumor with peripheral necrotic portion and a surrounding edema in the left frontal white matter. Also demonstrated are compression of the left lateral ventricle with the midline shift to the right, and enlargement of the genu of the corpus callosum. The tumor extending into the right frontal white matter through the corpus callosum is shown as a slightly hypointense area anterior to the right anterior horn (*arrowheads*)

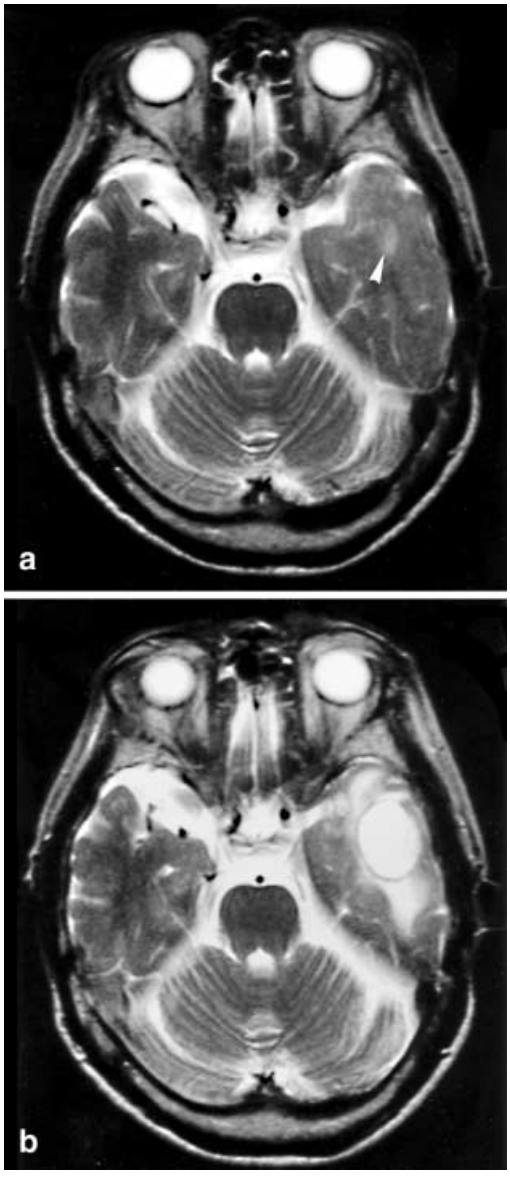

Fig. 3a, b. Case 5. A 73-year-old man with anaplastic astrocytoma. **a** T2-weighted (4,000/100/2) image from the initial MRI shows a small subtle hyperintense area in the left anterior temporal white matter (*arrowhead*). Signal intensity of the surrounding white matter is similar to that of gray matter. **b** T2-weighted (4,000/100/2) image 9 months later shows a cystic tumor with surrounding edema in the left anterior temporal lobe

toma [1, 2, 3, 6, 8, 9]. However, the histopathological diagnosis by stereotaxic needle biopsy was anaplastic astrocytoma. Diagnosis of glioblastoma is easily made when necrosis is present in the biopsy specimen, but a diagnosis of anaplastic astrocytoma is rendered if a limited tissue sample does not contain evidence of necrosis [1, 9].

Histopathologically, diffuse astrocytomas are ill defined and show a consistent tendency for diffuse infiltration of the surrounding brain [2]. Tumor cells extend as far as the borders of the high-signal intensity areas shown on T2-weighted images, in some cases [8]. Diffuse infiltration with gradual incorporation of preexisting cells often leads to an enlargement and distortion of the invaded anatomical structures, e.g., cortex and compact myelinated pathways [2]. Ill-defined, increased T2-signal lesions demonstrated on initial MRI in two patients (cases 4 and 5) represented these pathological findings, with an enlargement and distortion of the adjacent structures (Figs. 3a, 5a–c).

Approximately 80% of low-grade gliomas ''dedifferentiate'' into more aggressive forms [5]. In general, more anaplastic elements are found in the centers of higher-grade tumors, while their peripheries contain better-differentiated cells [5]. A small cystic area without gadolinium enhancement emerged in the midportion of the lesion in case 2 (Fig. 4c), central hyperintense areas were seen on T2-weighted images in cases 4 and 5 (Figs. 3a and 5a), from where enhancing tumors developed. However, these central areas were not recognized as dedifferentiating or more anaplastic elements in diffuse astrocytomas, initially. Single or multiple cysts containing a clear fluid may be seen in diffuse astrocytomas [2], but cyst formation or necrosis is a significant, positive predictor of higher tumor grade [1]. Although some cases of anaplastic astrocytomas without previous use of steroids show no gadolinium enhancement [10], high-grade astrocytic tumors generally show contrast enhancement [5, 6, 8, 9]. In the present study, all tumors showed gadolinium enhancement on MRI on admission. The presence and degree of gadolinium enhancement is one of the most reliable predictor of higher tumor grade [8, 9, 11], and contrast-enhancing foci within an otherwise benign-appearing mass may be the initial harbingers of more aggressive disease [6]. In addition, a central hyperintense area on T2-weighted imaging and a non-enhancing cystic area emerging in the center of the lesion might be additional MRI features of initial malignant change, even though no accompanying contrast enhancement is demonstrated.

However, these hyperintense lesions in astrocytic tumors can be indistinguishable from non-neoplastic white matter diseases [6], such as ischemic lesions in elderly patients, or the demyelinating process of multiple sclerosis (MS) in younger patients. Although a variety of MR appearances may be seen in MS patients, a solitary ill-defined lesion with a central area, as seen in case 2, may suggest brain neoplasm rather than MS [12, 13].

Wallerian degeneration showing hyperintensity along the pyramidal tract in the brain stem should be differentiated from tumor extension along the pyramidal tract [14, 15, 16]. In case 4, hyperintensity along the right pyramidal tract on T2-weighted images might be Wallerian degeneration, because the hyperintense signal did not change in the disease course, whereas multiple,

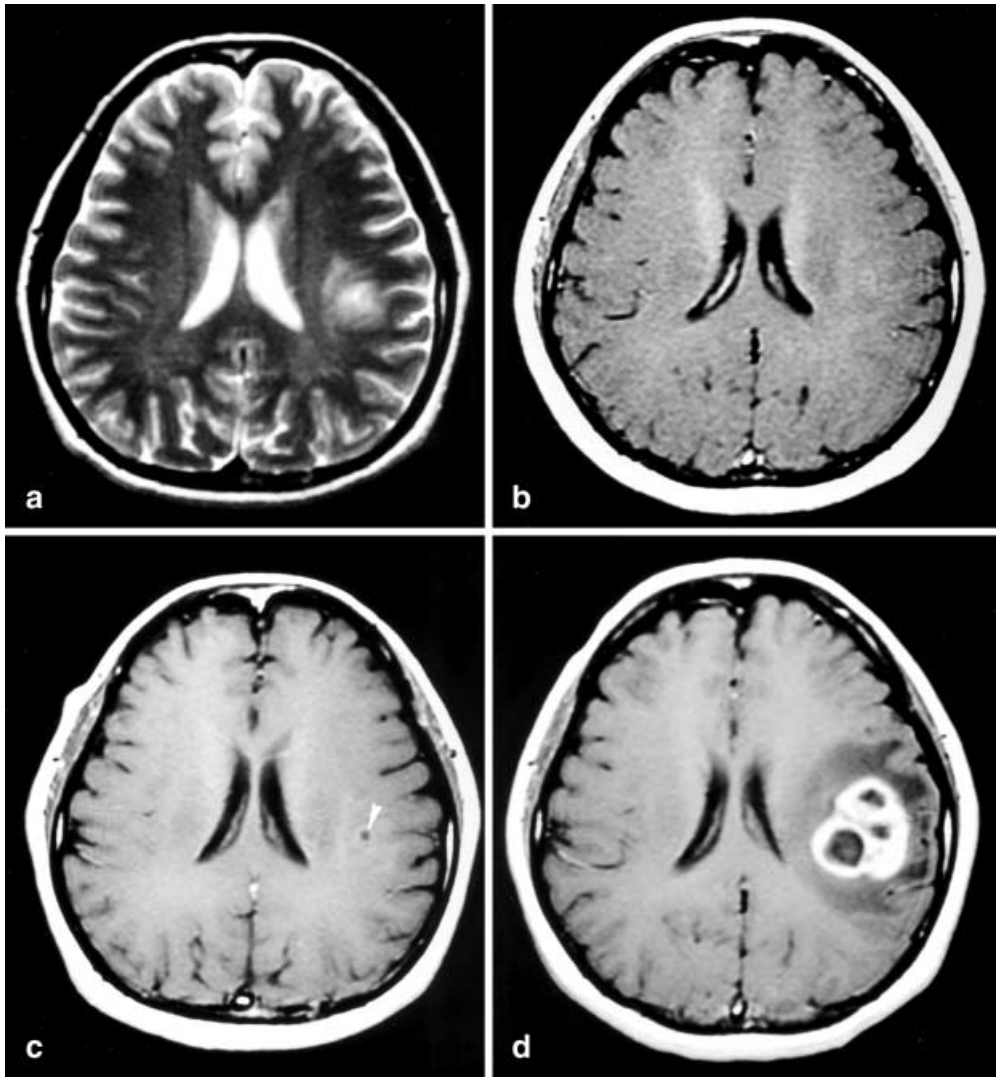

Fig. 4a–d. Case 2. A 38-year-old woman with glioblastoma. **a** T2-weighted image (3,000/96/2) from the initial MRI shows an ill-defined hyperintense area in the parietal white matter. **b** Post-contrast T1-weighted (600/10/3) image from the initial MRI. A tiny subtle hyperintense area can be seen retrospectively at that site on T1-weighted image (not shown). No gadolinium enhancement is demonstrated on post-contrast T1-weighted image. **c** Post-contrast T1-weighted (600/10/3) image from the repeated MRI 2 months later shows a small cystic area in the center of the lesion (*arrowhead*). **d** Post-contrast T1-weighted (600/10/3) image obtained on admission shows an enlarged enhancing tumor with multiple cystic or necrotic portions. Surrounding edema is also demonstrated as a surrounding hypointense area

enhancing tumors developed from the other hyperintense areas. Differentiation of these two conditions is difficult on T2-weighted imaging only, but diffusion-weighted imaging is useful. Tumor invasion in the white matter tract increases anisotropy of the tract [17, 18], whereas anisotropy of the pyramidal tract is reduced in chronic Wallerian degeneration [19]. These conditions should not be confused at patient management. A supratentorial lesion with hyperintense signal on T2-weighted images along the pyramidal tract could not be a fresh infarction, because Wallerian degeneration is demonstrated on MRI 1 month after the event [19].

In conclusion, early MRI appearances of high-grade astrocytic tumors were solitary or multiple ill-defined hyperintense areas on T2-weighted images, with little or no mass effect and no gadolinium-enhancement. Some lesions were subtle even on T2-weighted images, and were overlooked. Therefore, fluid attenuated inversion recovery (FLAIR) imaging should be added, because various lesions, including gliomas, are best evaluated with FLAIR imaging [20]. Differentiation of diffuse astrocytomas from non-neoplastic diseases is important for making a correct diagnosis. Diffusion-weighted imaging is useful to differentiate astrocytic tumors from fresh infarction [18, 20], and tumor infiltration from Wallerian degeneration [18, 19]. The latency and rapidity of progression of diffuse astrocytomas to anaplastic astrocytomas vary considerably, and classical histopathological features fail to predict which tumors will progress in individual cases. Some studies suggest that in diffuse astrocytomas WHO grade II, the proliferative potential correlates inversely with survival and time to recurrence, but this finding is inconsistent, and in individual cases, the size of the growth fraction as determined by the MIB-1 labeling index cannot be regarded as being prognostic [2]. Therefore, early diagnosis and

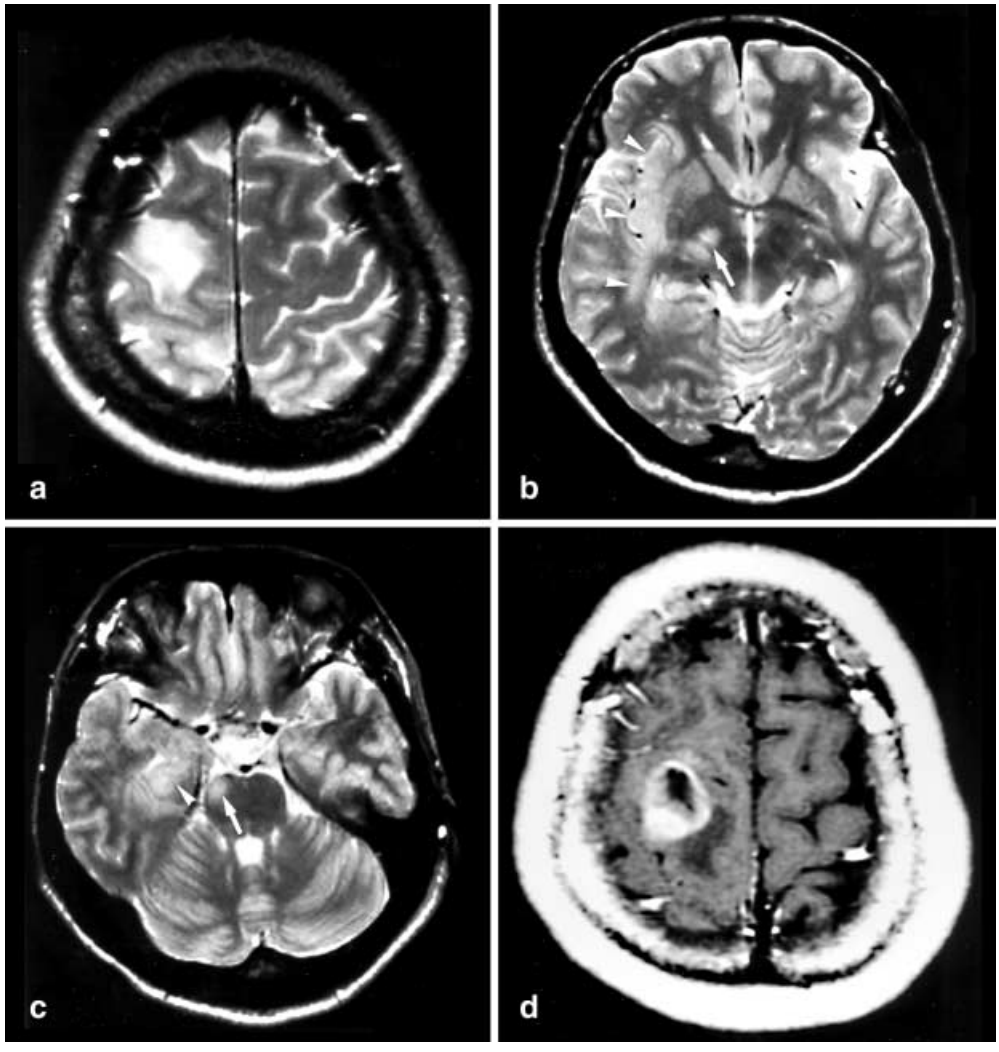

Fig. 5a–d. Case 4. A 36-year-old woman with anaplastic astrocytoma. **a** T2-weighted (3,000/80/1) image obtained 5 days after the ictus shows a hyperintense lesion with a concentric, more hyperintense area in the right high precentral gyrus. Enlargement of the gyrus is observed. This lesion shows no gadolinium enhancement (not shown). **b** T2-weighted (3,000/80/1) image at the level of the anterior commissure acquired at the same time as **a**. Both enlarged right insular cortex and obscured external capsule are demonstrated, but these lesions were not recognized at that time. Slightly increased signal intensity area of the right insula extends posteriorly (*arrowheads*). Increased signal intensity is also seen at the posterior limb of the right internal capsule (*arrow*). **c** T2-weighted (3,000/80/1) MR image at the level of the inferior horns obtained at the same time as **a** and **b** shows hyperintense signals at the right amygdaloid nucleus and hippocampus (*arrowhead*). The right pyramidal tract in the upper pons is also hyperintense (*arrow*). **d** Post-contrast T1-weighted (380/20/2) MR image obtained on admission shows a ring-like enhancing tumor in the enlarged right precentral gyrus. Perifocal edema is demonstrated posteromedial to the tumor

treatment are recommended, and observation is not warranted for low-grade astrocytomas [7]. Patients with such lesions should not be observed for more than 2 months. If a central hyperintensity on T2-weighted imaging or a small cystic or necrotic area develops in the center of the lesion, high-grade astrocytic tumor should be considered even if gadolinium enhancement is not demonstrated.

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