Infectious Disease

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Inflammation is mediated through cytokines, chemokines, and leukotrienes. These and the cellular constituents of the inflammatory response represent potential targets for PET imaging in the investigation of inflammatory and infectious diseases. Given that inflammatory cells utilize glucose at a much higher level than noninflammatory cells, the most commonly employed PET tracer, fluorodeoxyglucose (18F) (FDG), remains invaluable in the study of inflammatory disease states.

Infectious lesions demonstrate intense uptake of 18F-FDG (Fig. 51.1) [1], and 18F-FDG PET has been widely used in the diagnosis of infectious/inflammatory diseases such as pyogenic abscess [2], tuberculosis [3], HIV-related CNS infectious diseases [4], tuberculosis meningitis [5], and autoimmune encephalitis [6], among others. Given the well-established role of MRI in the evaluation of these diseases, it stands to reason that combining metabolic information provided on PET imaging with structural information derived from MRI may improve our ability to diagnose these entities and also to monitor their response to treatment. In addition, hybrid PET/MRI allows a 20% reduction in radiation exposure compared to PET/CT if attenuation correction only is used or up to 60-73% when both attenuation correction and diagnostic quality CT studies are acquired with PET/CT [7, 8]. The use of MRI is also advantageous in that physiologic tracer accumulation in brain gray matter makes it difficult to detect inflammatory foci in brain tissue by FDG-PET alone, which leads to false-positive/false-negative findings in the evaluation of intracranial inflammatory lesions.

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Therefore, some investigations utilize new PET tracers which specifically target neuroinflammation. Indeed, PET imaging with specific inflammation tracers will immensely enhance our understanding of the mechanisms facilitating inflammatory processes in the CNS and increase clinical diagnostic specificity and accuracy for detection of brain inflammatory and infectious lesions.

TSPO and Neuroinflammation

Translocator protein (TSPO) is an 18 kDa macromolecular protein with a structure of five alpha-helices across the membrane lipid bilayer and is the most widely used target for PET imaging of neuroinflammation. TSPO is upregulated by the activation of microglia and astrocytes due to immunomodulation and is a sensitive biomarker of neuroinflammation [9]. TSPO is highly expressed in activated microglia, but it is always expressed at a lower level in the cerebral gray matter [10]. Examples of radiotracers specific for activated microglia which bond to TSPO and are used to study neuroinflammation include [11C]PK11195, [11C] PBR18, [11C]DPA-713, and [11C]PBR28. Many second- or third-generation TSPO ligands, including some that utilize [18F] isotopes with longer half-life, are currently used primarily in the research setting.

Amino Acid Tracers

Although 11C-methionine (MET)-PET has primarily been employed for neuro-oncologic indications and demonstrates promising results in detection and delineation of viable tumor, especially in low-grade gliomas [11], it may also have a role in inflammatory and infectious CNS disease. Although MET-PET demonstrates relatively low uptake in inflammatory lesions, it is advantageous to FDG since there is no expected tracer uptake by normal brain tissue. On the other hand, while F18-FDG strongly accumulates in inflammatory

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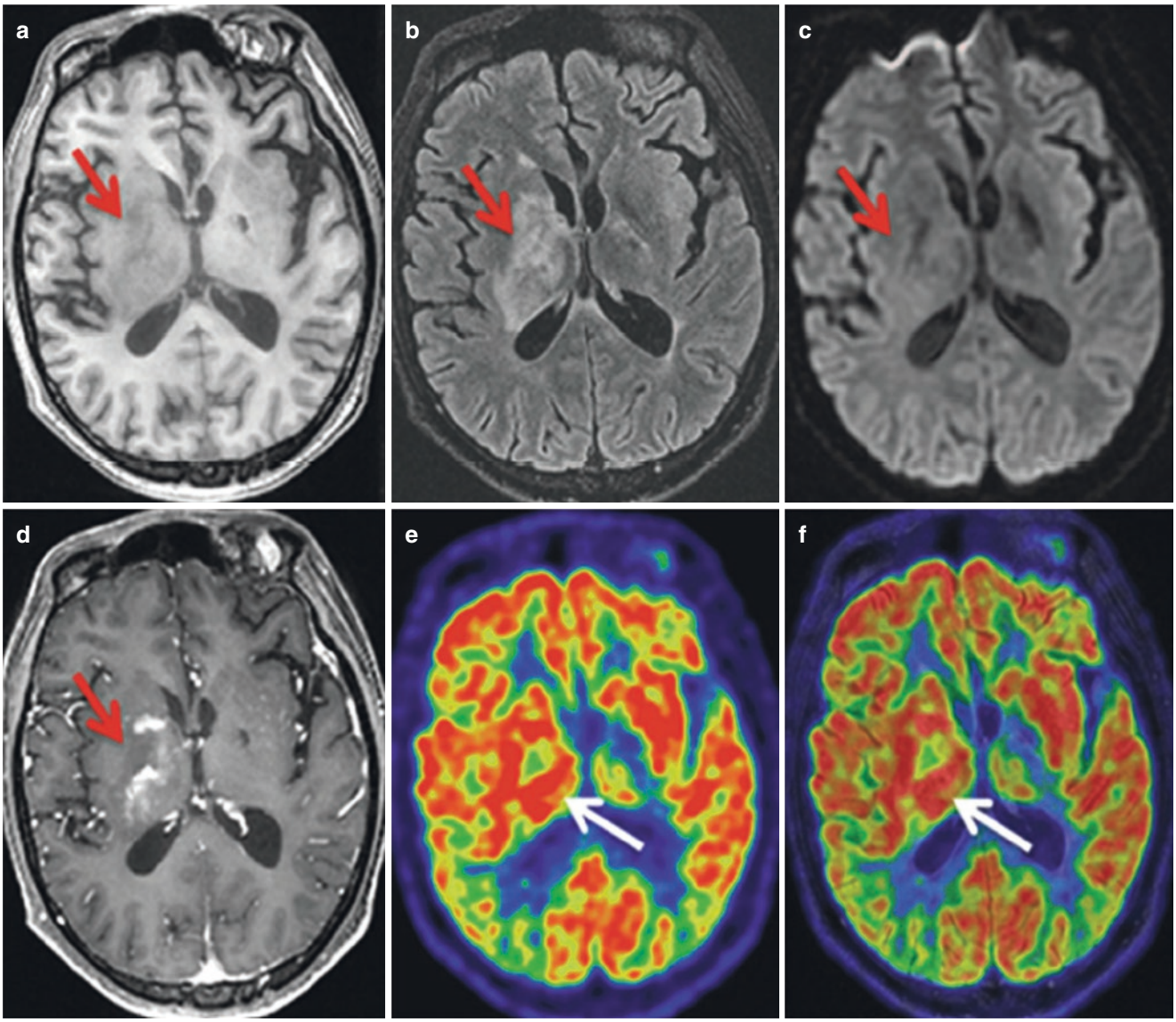

Fig. 51.1 A 28-year-old male patient with encephalitis of right basal ganglia and thalamus. (**a**) The lesion showed low intensity signal on T1WI (red arrow), (**b**) high intensity signal on T2-FLAIR (red arrow), (**c**) questionable slight restricted diffusion on DWI (red arrow), (**d**) heterogeneous enhancement on T1WI + C (red arrow), (**e**) hypermetabolism on 18F-FDG PET image (white arrow), and (**f**) hypermetabolism on PET/MRI fusion image (white arrow). (Adapted with permission from Gao et al. [1])

states, it also shows high physiological background uptake in normal brain tissues, resulting in low lesion-background contrast. The mechanism of MET accumulation in encephalitic lesions is considered to be increased density of inflammatory cells and, consequently, activated transport of amino acids.

Few studies in the literature describe the use of MET-PET in inflammatory brain lesions.

Hirata et al. published a case of encephalitis with elevated 11C-methionine uptake in the right cerebral hemisphere [12]. They observed high MET uptake in the active phase of the disease, normalizing with recovery (Fig. 51.2a, b), suggesting that MET-PET can be useful to monitor disease activity. Maeda et al. reported a patient with Rasmussen encephalitis with elevated MET uptake in the involved cerebral tissues [13].

There are also a few reports of increased MET uptake in brain abscesses which corresponded closely to the enhancing lesion on CT and MR in both acute phase of disease and following treatment, suggesting that PET studies, more directly, reflect the degree of inflammatory response in brain abscess than enhancement on CT or MRI and, therefore, may be a useful adjunct modality in assessing the clinical effects of antibiotic treatment in brain abscesses [14].

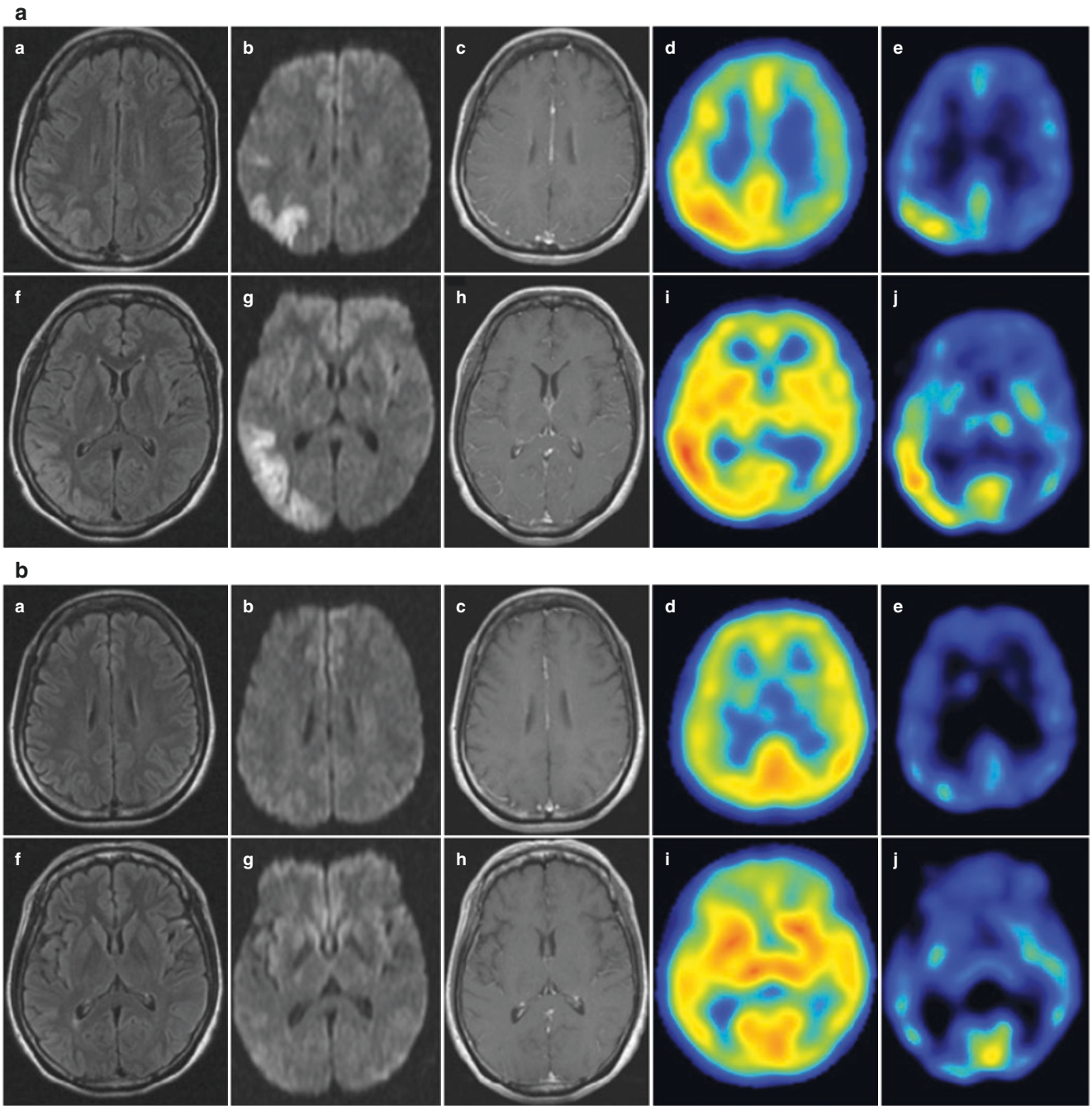

Fig. 51.2 (**a**) On MR fluid-attenuated inversion recovery (FLAIR) images, high signal intensity was observed in the right parietal, temporal, and occipital lobes (**a** and **f**). Diffusion-weighted imaging (DWI) also showed high signal intensity in these regions (**b** and **g**). Gadolinium enhancement was not observed (**c** and **h**). 99mTc-hexamethylpropyleneamine (HMPAO SPECT) revealed increased blood flow in the lesion (**d** and **i**). PET images scanned 30 min after injection of 148 MBq 11C methionine (MET) demonstrated increased tracer accumulation in the corresponding area (e and j). (**b**) After therapy, MR FLAIR (**a** and **f**) and DWI (**b** and **g**) showed normalized signal intensity in the right parietal, temporal, and occipital lobes. Gadolinium enhancement was absent (**c** and **h**). 99mTc HMPAO SPECT showed no abnormal blood flow (d and j). On MET-PET images, the abnormal uptake previously observed was normalized (**e** and **j**). (Adapted with permission from Hirata et al. [12])

MR Imaging Patterns of CNS Infectious Diseases

MRI changes in infectious CNS disease fall into four broad patterns: parenchymal involvement or cerebritis (including abscess formation), meningeal involvement, and ventricular involvement.

Non-purulent parenchymal involvement presents as increased T2-FLAIR signal intensity without or with patchy contrast enhancement. Meningeal involvement is identified as abnormal enhancement in the sulci and basal cisterns, along cranial nerves and over the convexities of the brain. These two patterns are commonly seen in CNS viral and fungal infections. Basal cistern enhancement is most commonly seen in tuberculosis. Abscess formation is defined as ringlike enhancement pattern surrounding an area of central necrosis. Ventricular involvement is diagnosed when abnormal hyperintensity on FLAIR or linear enhancement is found along the ependymal lining, sometimes in association with layered intraventricular purulent debris. This may arise from rupture of an abscess into the ventricular system, given that abscess walls tend to be thinner along the sides that face the ventricles. Choroid plexitis may coexist. Empyema can also be seen in some bacterial CNS infections, manifesting as hyperintense fluid collections within the subdural space, with associated capsular enhancement.

Encephalitis

Encephalitis is an acute inflammation of the brain, usually caused by a viral infection. The clinical manifestations are characterized by fever, headache, and altered level of consciousness. Examination of the cerebrospinal fluid (CSF) obtained by a lumbar puncture procedure is essential. The detection of viral DNA in CSF as well as antibodies to virus is a rapid, specific, and highly sensitive method for the diagnosis of viral encephalitis. CT and MRI can provide useful and sometimes complementary information. However, PET has rarely been performed for the diagnosis of encephalitis, with the literature limited to a few case reports, some of which are reviewed here.

Viral Infections

HSV Encephalitis

Different patterns of 18F-FDG distribution have been recognized in HSV encephalitis. Brain single-photon emission computed tomography (SPECT) data previously reported in the literature has demonstrated focally increased cortical perfusion predominantly in the bilateral temporal lobes in acute HSV, followed by hypoperfusion of the affected region in the recovery phase (between 3 and 6 months) [15]. A previous report of FDG-PET findings in HSV-1 encephalitis demonstrated hippocampal hypermetabolism acutely, then hypometabolism at 3 and 9 months [14]. In the acute phase, 18F-FDG hypermetabolism may be the result of active inflammation, but seizure activity can also be a contributory factor. In chronic phases of the infection, 18F-FDG hypometabolism is likely the consequence of neuronal loss [16].

Schillaci and colleagues reported a case of HSV encephalitis with subacute presentation [17]. PET/MR images (Fig. 51.3) showed extensive hypometabolism in the left temporal, parietal, and occipital lobes (a, b) in agreement with the neurological symptoms of the patient. This metabolic pattern corresponded to white matter and cortical hyperintensity in the involved areas on T1- and T2-weighted MR images likely due to hemorrhagic necrosis (arrowhead in c and d). PET images also showed reduced left thalamic and striatal 18F-FDG uptake (arrowhead in a), without corresponding MRI signal abnormality (c), likely a consequence of transsynaptic degeneration due to the ipsilateral cortical necrosis.

A focal area of increased FDG uptake in the left inferior temporal gyrus (arrowhead in b) corresponding to focal gyral enhancement on postcontrast-T1WI images was also noted (arrowhead in d); this finding has been interpreted as focal inflammation with local meningeal vasodilatation.

Atypical (Fungal and Protozoan) Infections

Several studies have shown 18F-FDG PET/CT scans to be particularly useful in differentiating atypical infections including toxoplasmosis from malignant lesions such as lymphoma or metastases in HIV-positive patients. PET/CT scan typically demonstrates 18F-FDG uptake in toxoplasmosis to be less than that of the normal brain cortex, while malignant lesions such as CNS lymphoma show increased binding compared to normal gray matter. Interestingly, CNS tuberculosis may also present with decreased FDG uptake.

There are only a few published case reports highlighting correlation of PET with MRI imaging in atypical CNS infections, which demonstrate the benefit of combining metabolic and anatomic imaging in clinically and radiologically difficult cases, which are briefly reviewed here.

CNS Histoplasmosis

A 66-year-old HIV-positive female reported by Makis et al. [18] presented with dizziness and unsteady gait. Initial MRI showed several irregular ringlike enhancing T2 hyper-

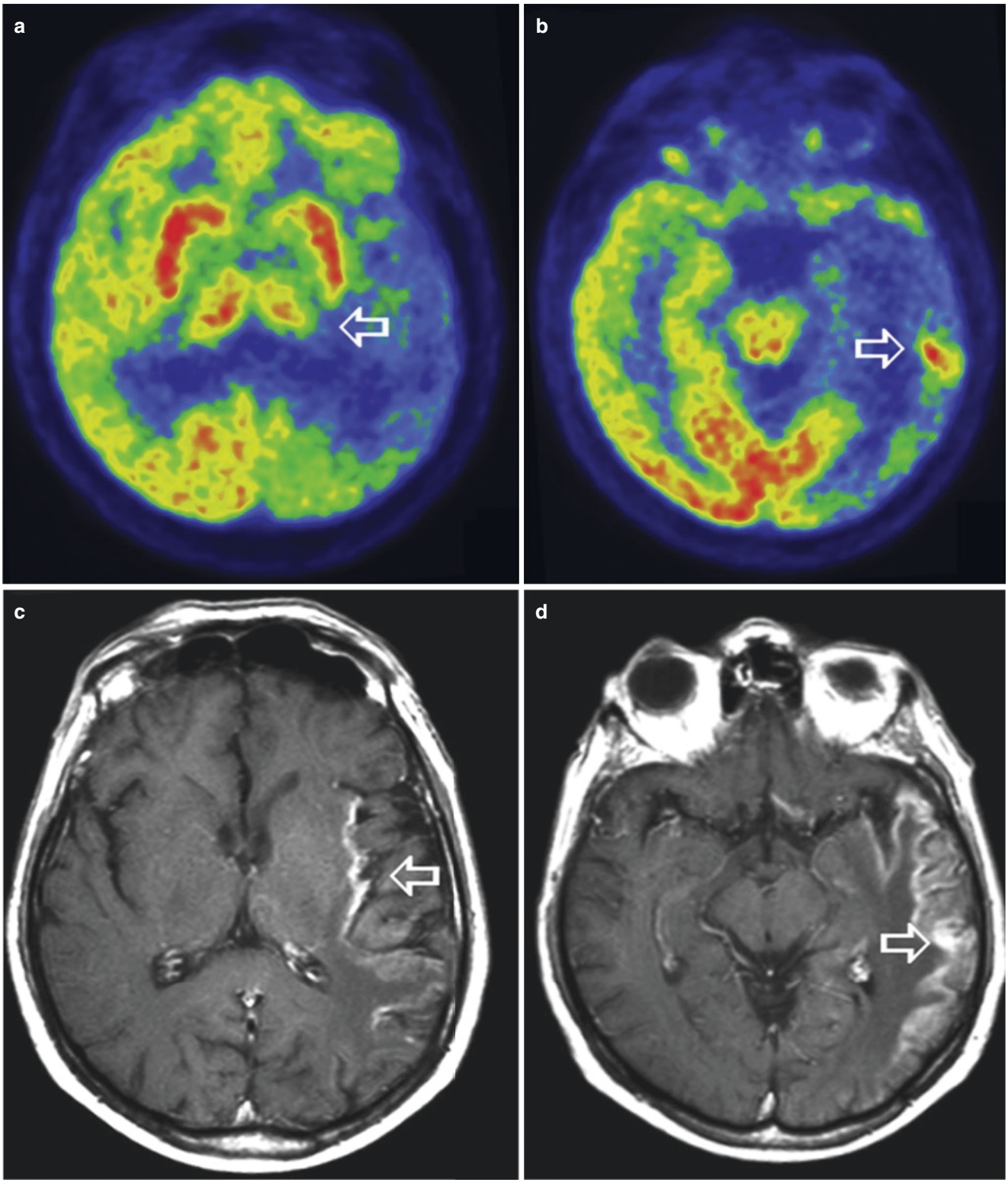

Fig. 51.3 Axial 18F-FDG PET showing a wide reduction of glucose metabolism at a cortical level in the left hemisphere (**a**, **b**). Reduced tracer uptake is detectable in left basal ganglia and thalamus (arrow in **a**). A focal area of 18F-FDG increased uptake is detectable in the left temporal lobe (arrow in **b**). T1-weighted MR axial slices (**c**, **d**) showing the morphological correlate of the PET findings (arrows in **c** and **d**, see text). Coregistered PET/MR axial views are shown in (**e**) and (**f**). (Adapted with permission from Schillasi et al. [17])

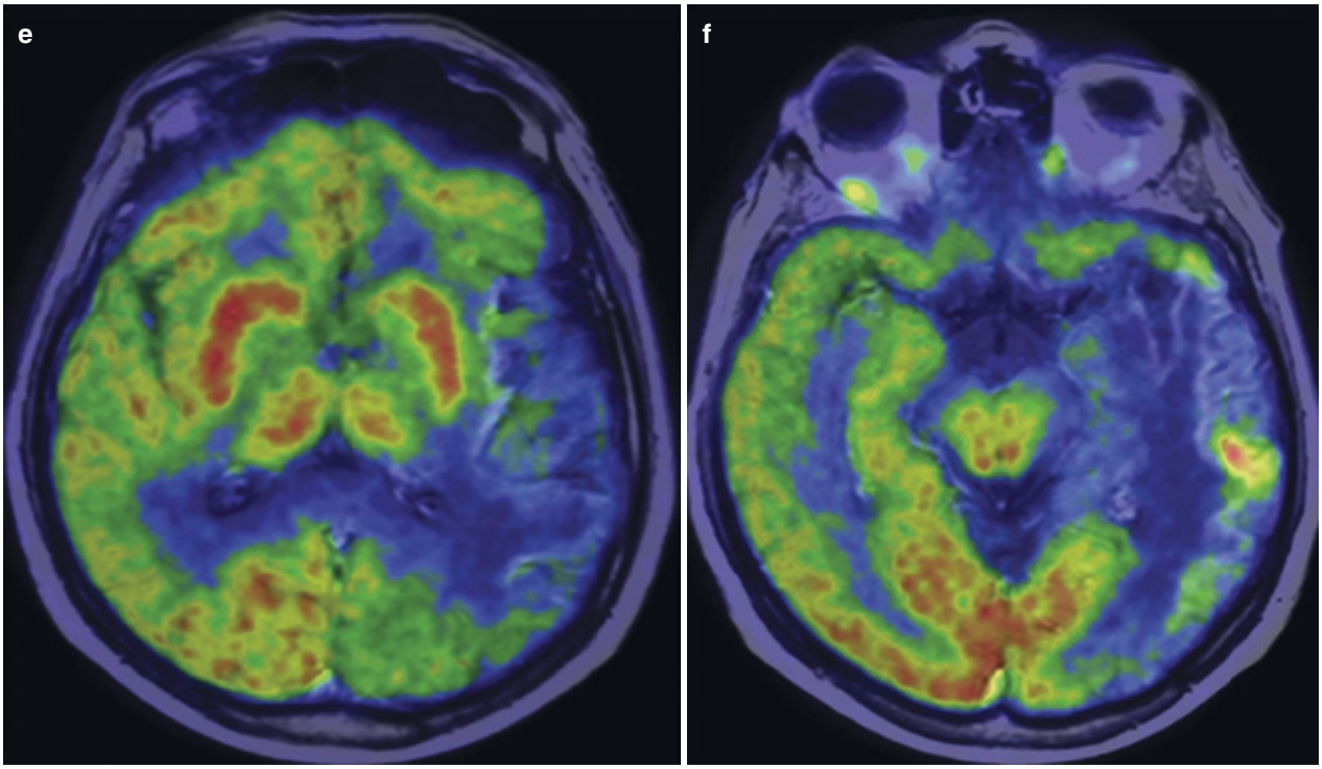

Fig. 51.3 (continued)

intense lesions in the right temporal lobe (Fig. 51.4d). The differential diagnosis includes high-grade astrocytoma, lymphoma, metastases, and infection. The PET/CT scan failed to demonstrate extracerebral FDG-avid lesions, and the intensely enhancing cerebral lesions described on MRI were hypometabolic when compared with normal gray matter (Fig. 51.4b, c), which increased the likelihood of an infectious etiology. Following the failure of a diagnostic/therapeutic trial of antimicrobials for toxoplasmosis, a brain biopsy and culture confirmed the presence of *Histoplasma capsulatum*.

Cryptococcal Choroid Plexitis

Dubbioso et al. described an immunocompetent 63-year-old female with CNS cryptococcosis [19], presenting with behavioral disturbances and seizures of temporal lobe onset. MRI revealed choroid plexitis with surrounding temporal lobe edema without features of meningitis, intraparenchymal cryptococcoma, or hydrocephalus. The patient underwent serial MRI and FDG-PET before and after antifungal therapy that resulted in marked clinical improvement. These findings support a potential role of FDG-PET in monitoring antifungal therapeutic efficacy (Fig. 51.5).

Granulomatous Amebic Encephalitis

Dowell et al. [20] report the case of a 41-year-old male presenting with 3 months of general malaise, night sweats, cough, confusion, and worsening mental status requiring intubation. The patient was found to have CD4 count of 4 cells/mm^3.

Unenhanced head CT demonstrates a right cerebellar hypodense lesion (Fig. 51.6a). Subsequent MRI revealed scattered white matter T2 and FLAIR hyperintense foci, diffuse leptomeningeal enhancement within the cerebellum and brain stem, and a focal enhancing lesion in the right posterior cerebellar hemisphere (Fig. 51.6b–d). The differential diagnosis of these MRI findings includes atypical tumors such as lymphoma, metastatic disease, or inflammatory/infectious process. 18F-FDG PET was performed for further evaluation and revealed focal hypometabolism in the right cerebellar lesion (Fig. 51.7a, b). These findings suggest an inflammatory etiology, rather than lymphoma in the HIV-positive

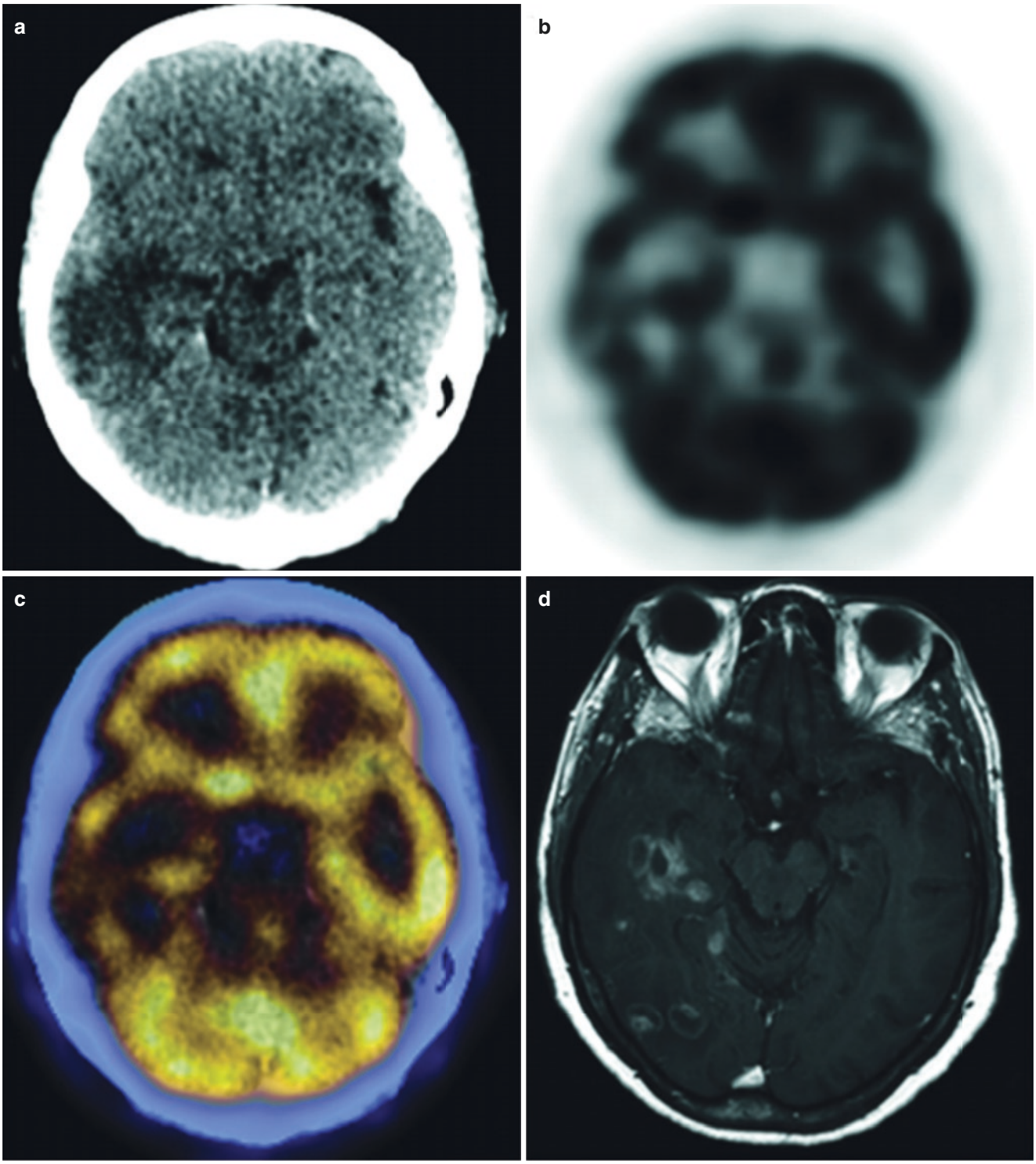

Fig. 51.4 (**a**) Transaxial CT, (**b**) FDG-PET, (**c**) FDG-PET/CT fusion, and (**d**) MRI T1 post-gadolinium images. The intensely enhancing cerebral lesions seen on MRI appear hypometabolic on the PET/CT images when compared to normal gray matter. (Adapted with permission from Makis et al. [18])

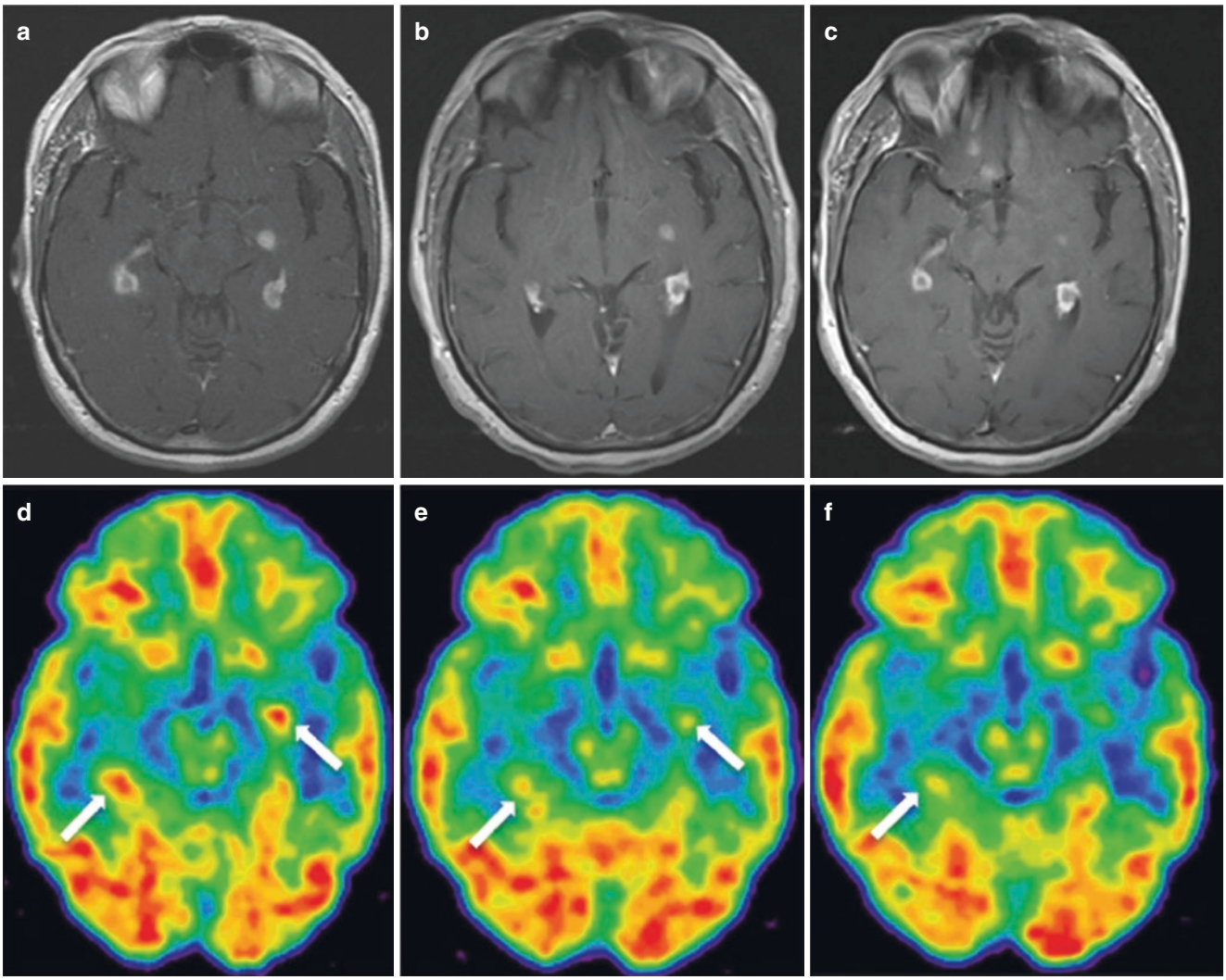

Fig. 51.5 MRI T1 images after gadolinium injection (top) and axial FDG-PET (bottom) showing enhancing enlarged choroid plexus in bilateral temporal horns corresponding to increased uptake of FDG (arrows) before therapy (**a**, **d**), after 1 month (**b**, **e**), and following 6 months (**c**, **f**) of therapy with incremental improvement. (Adapted with permission from Dubbioso et al. [19])

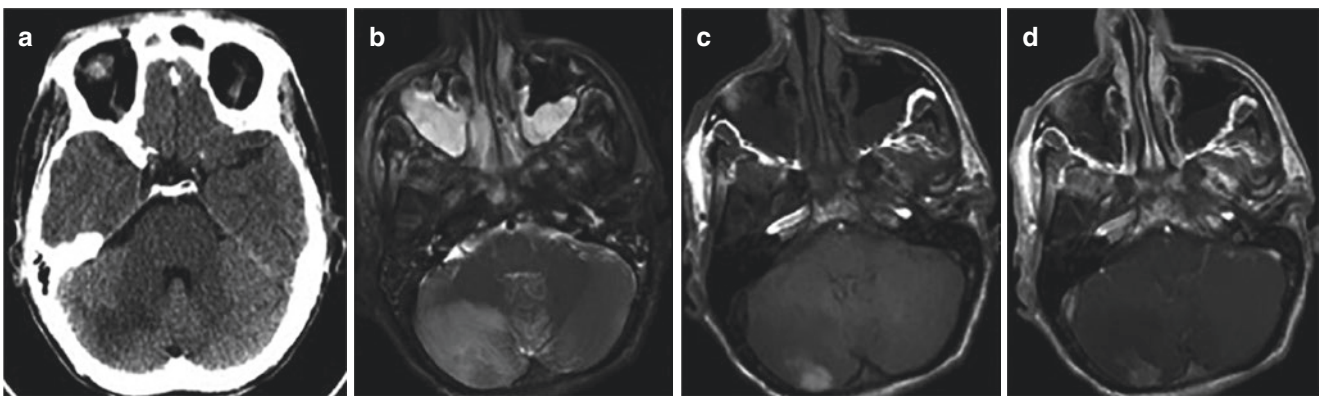

Fig. 51.6 Unenhanced head CT demonstrates a right cerebellar hypodense lesion with mild mass effect on the fourth ventricle (**a**). Correlative MR images of the right cerebellar lesion demonstrate significant edema on T2 weighted (**b**) with associated edema and mass effect. Note patchy T1 shortening (**c**). Postcontrast T1-weighted MR image (**d**) demonstrates enhancement of the right cerebellar lesion as well as of the leptomeninges overlying the cerebellum and brain stem. (Adapted with permission from Dowell et al. [20])

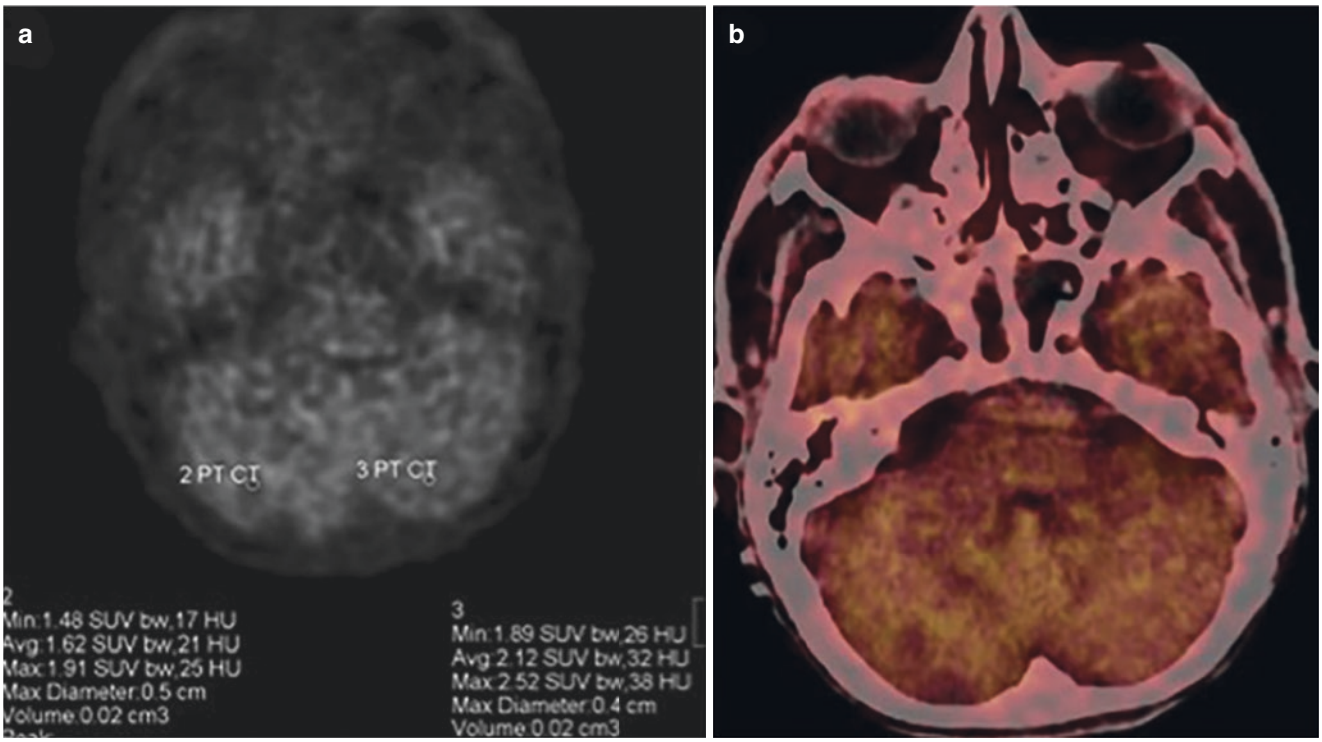

Fig. 51.7 Brain PET reveals focal F-18 fluorodeoxyglucose (FDG) hypometabolism within the right cerebellum (**a**, **b**) correlating to the lesion identified on CT and MR. (Adapted with permission from Dowell et al. [20])

patient. Brain biopsy of the right cerebellar lesion yielded the diagnosis of *Balamuthia mandrillaris* amebic meningoencephalitis.

These findings support a possible synergistic benefit of FDG-PET and MRI in the diagnosis of granulomatous amebic encephalitis.

Brain Abscess and Bacterial Infections

Tsuyuguchi and colleagues evaluated 18F-FDG and 11C-methionine PET before and after treatment in four patients with brain abscess [21].

After treatment, as the enhancing lesion volume decreased, a decline in tracer uptake was also noted. The pre-treatment FDG-PET demonstrated smaller size of lesion compared to the area of peripheral enhancement on MRI, and on follow-up posttreatment imaging, FDG uptake was noted to decrease faster than the intensity of contrast enhancement (Figs. 51.8 and 51.9). The MET-PET findings in the pre- and posttreatment stages were found to correspond more closely to the enhancement observed on MRI, suggesting that the mechanism of MET uptake may be related to disruption of the blood-brain barrier in these patients, while the mechanism of FDG binding is related to a higher metabolic rate and, in addition, increased density of inflammatory cells.

Therefore, PET studies more directly reflect the degree of inflammatory response in brain abscess than enhancement CT or MRI and may serve as a useful adjunct technique for detecting infectious CNS lesions and assessing the clinical effects of antibiotic treatment for brain abscess.

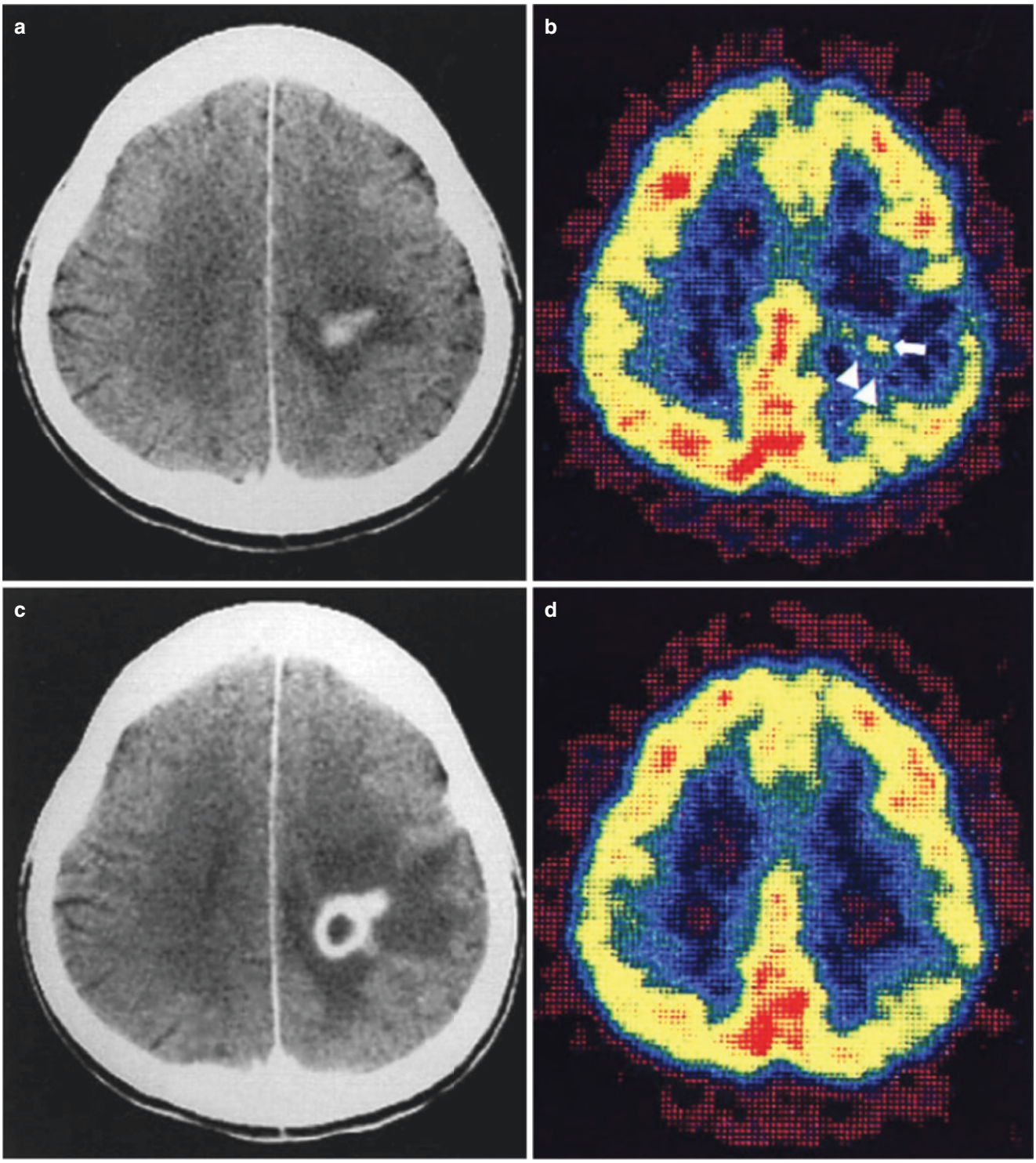

Fig. 51.8 Brain abscess in the left frontal lobe. Before antibiotic treatment, a contrast CT scan (**a**) shows a ringlike enhanced lesion with brain edema. FDG-PET (**b**) shows faint accumulation (arrow) and low accumulation (arrowheads) in a portion of the ringlike lesion (arrow) and decreased uptake around it. After 2 months of administration of antibiotics, contrast CT (**c**) shows a small residual enhancing lesion and decreased edema. FDG-PET (**d**) shows no uptake. (Adapted with permission from Tsuyuguchi et al. [21])

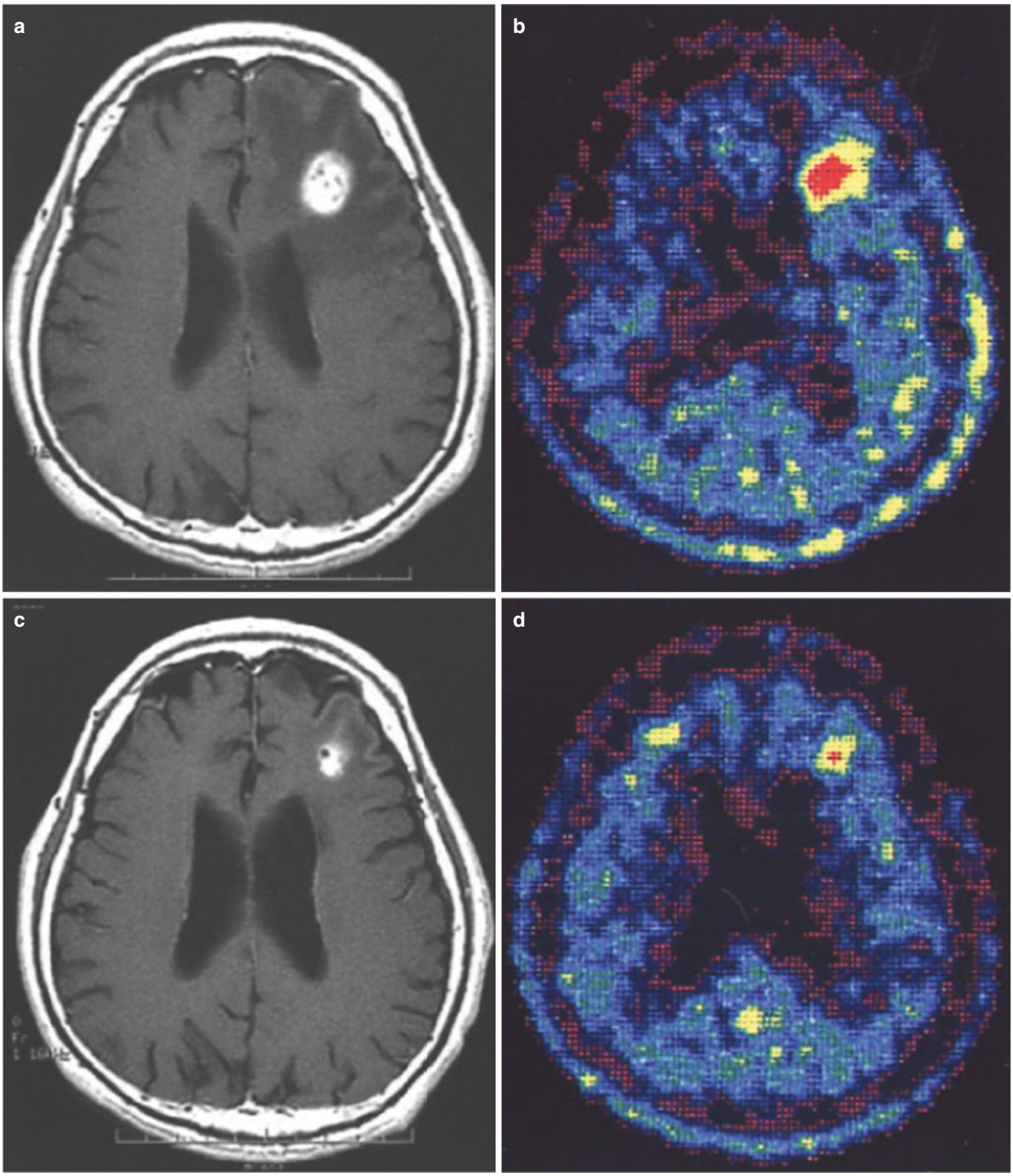

Fig. 51.9 Brain abscess in the left frontal lobe. Before antibiotic treatment, gadolinium-enhanced MRI (**a**) shows an enhancing lesion with surrounding brain edema. MET-PET (**b**) shows avid uptake in the lesion. After administration of antibiotics for 7 weeks, gadolinium-enhanced MR (**c**) shows a small residual enhancing lesion. MET-PET (**d**) similarly shows small focal tracer uptake in the lesion. (Adapted with permission from Tsuyuguchi et al. [21])

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