Hippocampal Sclerosis

Horst Urbach

Contents

Abstract

Hippocampal sclerosis is by far the most common cause of temporal lobe epilepsy. The familiar reader detects it on MRI in more than 95% of cases but should be aware of typical "pitfalls", namely bilateral hippocampal sclerosis, "dual pathology" and insufficient image Quality.

1 Terminology

Hippocampal sclerosis, Ammon's horn sclerosis and mesial temporal sclerosis are used synonymously.

2 Epidemiology

First histopathological description by the German psychiatrist W. Sommer in 1880. By far the most common cause of temporal lobe epilepsy (TLE) and found in 50–65% of patients undergoing resective surgery.

3 Pathogenesis

Half of the patients undergoing surgery have experienced a precipitating injury before the age of 4 years (complex fever seizures, 70%; birth trauma, meningitis, head injury, 30% Blümcke et al. 2002). Mean age at the onset of complex partial seizures is between 9 and 11 years, and mean age at the time of epilepsy surgery around the age of 30 (Blümcke et al. 2002). The long latency between a possible initial precipitating injury, the onset of epileptic seizures, and epilepsy surgery renders assessment of the pathogenesis of hippocampal sclerosis difficult.

Current concept is a genetically determined susceptibility and a precipitating injury induce temporo-mesial seizures and hippocampal sclerosis. A substantial argument is the fact, that 1/3 of non-affected individuals in families

H. Urbach (✉)
Department of Neuroradiology,
University Hospital Freiburg, Germany
e-mail: horst.urbach@uniklinik-freiburg.de

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Table 1 Neuropathological grading of hippocampal sclerosis [adapted from Wyler et al. (1992)]

Grade	Classfication	Neuropathological description	MRI
Wyler I	Mild mesial temporal damage	Gliosis with slight (<10%) or no hippocampal neuronal dropout involving sectors CA1, CA3, and/or CA4	Not visible
Wyler II	Moderate mesial temporal damage	Gliosis with moderate (10–50%) neuronal dropout of CA1, CA3, and/or CA4. If Involvement limited to CA3 and 4 = end folium sclerosis	Loss of internal structure on high resolution T2-weighted images
Wyler III	"Classical" ammon's horn sclerosis	Gliosis with >50% neuronal dropout of CA1, CA3, and CA4, but sparing CA2	Atrophy and increased T2/FLAIR signal
Wyler IV	"Total" ammon's horn sclerosis	Gliosis with >50% neuronal dropout of all sectors	Atrophy and increased T2/FLAIR signal visible

Table 2 Neuropathological grading of hippocampal sclerosis [adapted from Blümcke et al. (2007)]

Grade	Description	Frequency (%)	MRI
Blümcke MTS 1a	Severe neuronal loss in CA1, moderate neuronal loss in other subfields	23	Atrophy and increased T2/FLAIR signal
Blümcke MTS 1b	Extensive neuronal loss in all subfields	68	Atrophy and increased T2/FLAIR signal
Blümcke MTS 2	Severe neuronal loss restricted to CA1	7	?
Blümcke MTS 3	Severe neuronal loss restricted to hilar region = end folium sclerosis	5	Loss of internal structure on high resolution T2-weighted images

with familial TLE show hippocampal sclerosis on MRI (Kobayashi et al. 2002).

If patients develop temporal lobe seizures or subacute memory deficits after the age of 20, one has to think of limbic encephalitis, which is mediated via antibodies and found in up to 30% of patients in this age group (Soeder et al. 2009).

4 Clinical Presentation

A typical mesial temporal lobe seizure starts with an epigastric aura (definition of aura = initial part of a partial seizure, that is remembered after the seizure has terminated). The aura is followed by objective phenomena like staring, restlessness, oroalimentary automatism, and (ipsilateral) head deviation, which last from around 30 seconds to several minutes. In the postictal phase, gradual reorientation occurs which may be accompanied by dysphasia and other sympoms.

5 Pathology

Hippocampal sclerosis is characterized by neuronal loss and gliosis, most prominent in the CA1 field of the hippocampus, followed by the hilus, CA3 field, and dentate granule layer, while the CA2 field is relatively spared. These alterations are accompanied by a dispersion of the dentate granuale layer with ectopic neurons being found in the molecular layer.

Extent of hippocampal sclerosis is graded according to Wyler et al. (Table 1) or more recently according to Blümcke et al. (Table 2) (Wyler et al. 1992; Blümcke et al. 2007). Note that more than 90% of patients, who undergo selective amygdalohippocampectomy with MRI suspected hippocampal sclerosis have Wyler grade III and IV hippocampal sclerosis. Both are easily recognized on perfectly angulated high resolution T2- and FLAIR images due to their atrophy and increased signal intensity. In contrast, only a minority of patients (3–5%) has atypical variants either confined to the CA1 field or CA4 field (= end folium sclerosis). These atypical variants do not show significant atrophy and may be only detected due to a loss of the internal hippocampal structure (Fig. 1). However, if a hippocampus is normal on MRI an unrevealing histology is more likely.

6 Imaging

MRI correlate of hippocampal slerosis are atrophy and increased signal intensity, which are best visualized on coronal FLAIR and T2-weighted fast spin echo images angulated perpendicularly to the hippocampal long axis. Increased signal intensity T2-signal abnormalities appears to correlate with gliosis and may not be directly related to the degree of neuronal loss (Briellman et al. 2002). On FLAIR sequences, contrast to noise ratio (C/N) is higher

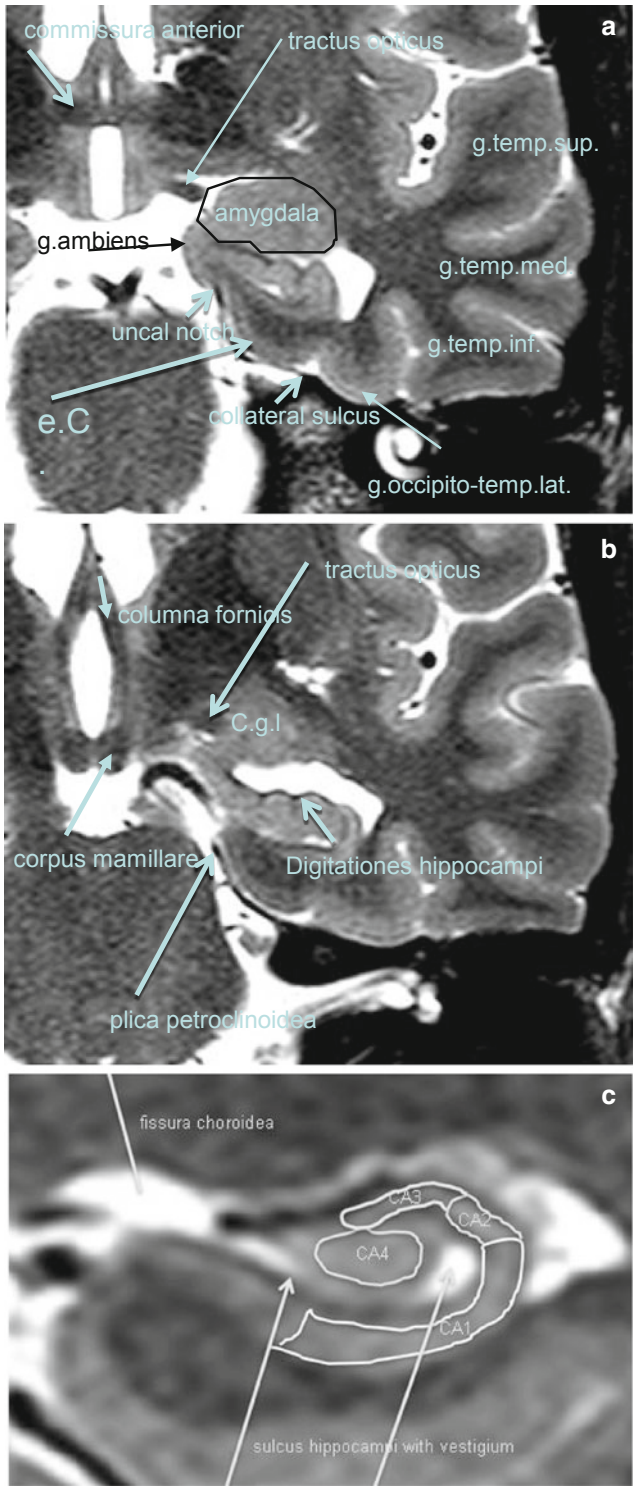

Fig. 1 Temporomesial MR anatomy on coronal 2 mm thick T2-weighted images. **a** shows a slice at the level of the amygdala, **b** at the level of the hippocampal head, and **c** at a level of the hippocampal body. Note that slices are displayed with different magnifications depending on the structures of interest

than on T2-weighted sequences, however, one has to be aware that normal limbic structures already have a higher FLAIR signal than the remaining cortex (Hirai et al. 2000). T2-weighted sequences display the hippocampal substructures in more detail and are complementarily used to diagnose hippocampal sclerosis. In order to assess atrophy and signal intensity, side comparisons are helpful. An accurate angulation avoiding tilting in the coronal plane is fundamental (Fig. 2). However, 10–20% of patients have bilateral hippocampal sclerosis (Margerison et al. 1966, Malter et al. in press), which can be overlooked when side comparison is the only criterion and no "engramm" of a normally sized hippocampus exists. T2 volumetry or T2 relaxometry can be helpful in these cases.

Hippocampal sclerosis is usually diagnosed on coronal slices through the hippocampal head, which displays the highest relative volume of hippocampal tissue on a slice. The neuropathological diagnosis relies on slices through the hippocampal body allowing to assess the single CA subfields (Fig. 3).

More subtle hippocampal sclerosis signs are a loss of the internal structure and loss of hippocampal head digitations (Oppenheim et al. 1998; Howe et al. 2011), which are both best appreciated on high resolution T2-weighted images (Fig. 4). Dilatation of the temporal horn is common, but occurs also in healthy persons as variant and even contralateral to the sclerotic hippocampus as falsely lateralizing finding (Wieser and ILAE Commission on Neurosurgery of Epilepsy 2004).

Hippocampal sclerosis with atrophy but without increased signal intensity has been described in 5% of patients. However, it is likely due to poor image quality not suited to visualize increased signal intensity.

Hippocampal sclerosis as incidental finding is extremly rare. There may be signal increase in healthy patients, however, signal increase and atrophy together almost never occur (Labate et al. 2010; Menzler et al. 2010).

MRI scans of older patients, however, often show some degree of atrophy including loss of digitations of the hippocampal head and increased signal intensity (on FLAIR) images. The histopathological substrate typically remains unclear, it may be related to normal ageing or Alzheimer's disease or so-called pure hippocampal sclerosis which occurs in around 10% of individuals older than 85 years and which is often misdiagnosed as Alzheimer's disease (Dickson et al. 1994; Ala et al. 2000; Nelson et al. 2011).

Secondary findings: Apart from hippocampal sclerosis the following structures of the limbic system can be atrophic: amygdala, entorhinal cortex, ipsilateral mamillary body, ipsilateral fornix, posterior thalamus (with increased signal), cingulate gyrus, contralateral cerebellum (Chan et al. 1997; Urbach et al. 2005) There is more often a temporal lobe or even hemispheric atrophy with atrophy pronounced in the anterior temporal lobe. The anterior temporal lobe shows reduced white matter volume and white matter signal is increased as compared to the opposite side or remaining white matter. Findings may be subtle and obscured or falsely highlighted by B1 field inhomogeneities

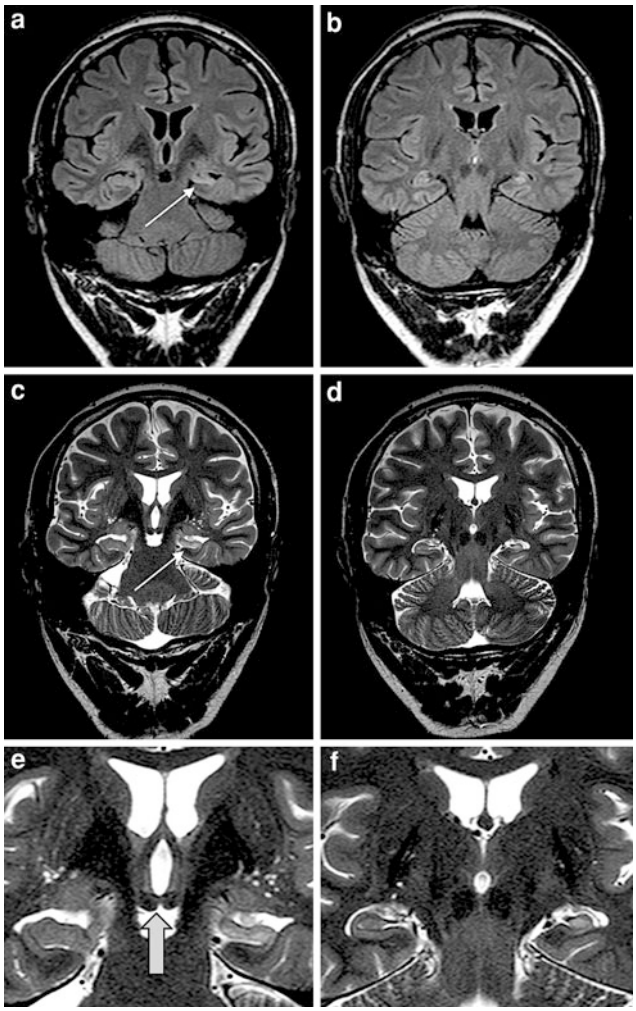

Fig. 2 Left-sided hippocampal sclerosis (**a**, **b**: coronal 3 mm thick FLAIR, **c**–**e**: coronal 2 mm thick T2-weighted fast spin echo images) indicated by increased signal intensity and atrophy of the left hippocampus. These findings are best appreciated on slices through the hippocampal head (**a**, **c**, **e**: *arrow*) since they contain the highest amount of hippocampal tissue per slice. In contrast, neuropathological diagnosis is based on slices through the hippocampal body (**b**, **d**, **f**), which allow a better anatomical orientation with respect to the CA subfiels. In order to allow side comparisons tilting in the coronal plane must be avoided. Exact angulation is proven by displaying small pairy structures (e.g. columnae fornicis (**e**: *hollow arrow*); semicircular canals) on one slice.

and narrow "windowing". There is usually an a.p. gradient with a higher white matter signal in the temporal pole that gradually diminishs and is already absent if slices through the amygdala or hippocampal head are inspected. Since white matter has a higher signal, contrast to gray matter is reduced and the term "gray white matter demarcation loss" has been designated to describe this condition.

The histopathological substrate of "gray white matter demarcation loss" is not clear. Some describe a higher amount of ectopic neurons within the white matter, however, a higher amount of white matter neurons in the anterior temporal lobe is also physiologic. Some consider "gray white matter demarcation loss" as mild maformation of cortical development (Palmini et al. 2004; Blümcke et al. 2011), others as focal cortical dysplasias (FCD) type I (Fauser et Schulze-Bonhage 2006), and others as maturation disorder, in which the process of cerebral myelination is disturbed due to an early precipitating injury (Mitchell et al. 2003; Schijns et al. 2011). Recent work investigating the pathological substrate of gray-white matter demarcation loss with 7 Tesla MRI revealed dishomogeneous myelin staining of the white matter, reduction in the number of axons and presence of axonal degeneration (Garbelli et al. 2012). A hint for a maturation disorder are early precipitating injuries and early seizure onset (often before the age of two) of patients with a "gray white matter demarcation loss" as compared to those who do not have these changes (Mitchell et al. 2003; Schijns et al. 2011). (Figs. 5, 6).

In around 10% of patients hippocampal sclerosis is associated with another extrahippocampal epileptogenic lesion (Fig. 7). This is called *dual pathology* and associated with a poorer prognosis regarding postsurgical seizure outcome. Most common dual lesions are cortical dysplasias and gliotic lesions acquired in early childhood. Note that in the initial description 30% of patients had dual lesions (Levesque 1991). This high number is explained by the fact that 10% of patients in this series had gliomas and temporal lobe seizures. They underwent hippocamopectomy and showed only mild hippocampal cell loss on histopathology. Some authors consider "gray white matter demarcation loss" of the anterior temporal pole as type I dysplasia and thus a dual lesion (Fauser et Schulze-Bonhage 2006). In order to have a strict definition of dual pathology, the ILAE proposed the following definition: *Dual Pathology* refers only to patients with hippocampal sclerosis, who have a second principal lesion affecting the brain (which may be located also outside the ipsilateral temporal lobe), that is, tumor, vascular malformation, glial scar, limbic/Rasmussen encephalitis, or MCD (including FCD Type IIa/IIb). Ipsilateral temporopolar atrophy with increased T2 signal changes on MRI is not included as its histopathologic correlate has yet to be specified. Histopathologically confirmed architectural abnormalities in the temporal lobe associated with hippocampal sclerosis should not be diagnosed as FCD Type I or ''Dual Pathology'' but FCD Type IIIa (Blümcke et al. 2011).

PET: positron emission tomography (PET) has become part of the presurgical evaluation in many epilepsy centers. The central finding is that the temporal lobe is hypometabolic for uptake of glucose on the side of the seizure focus during the interictal period. The region of hypometabolism can be both medial and lateral, and commonly exceeds the size of tissue that needs to be removed for cure of seizures.

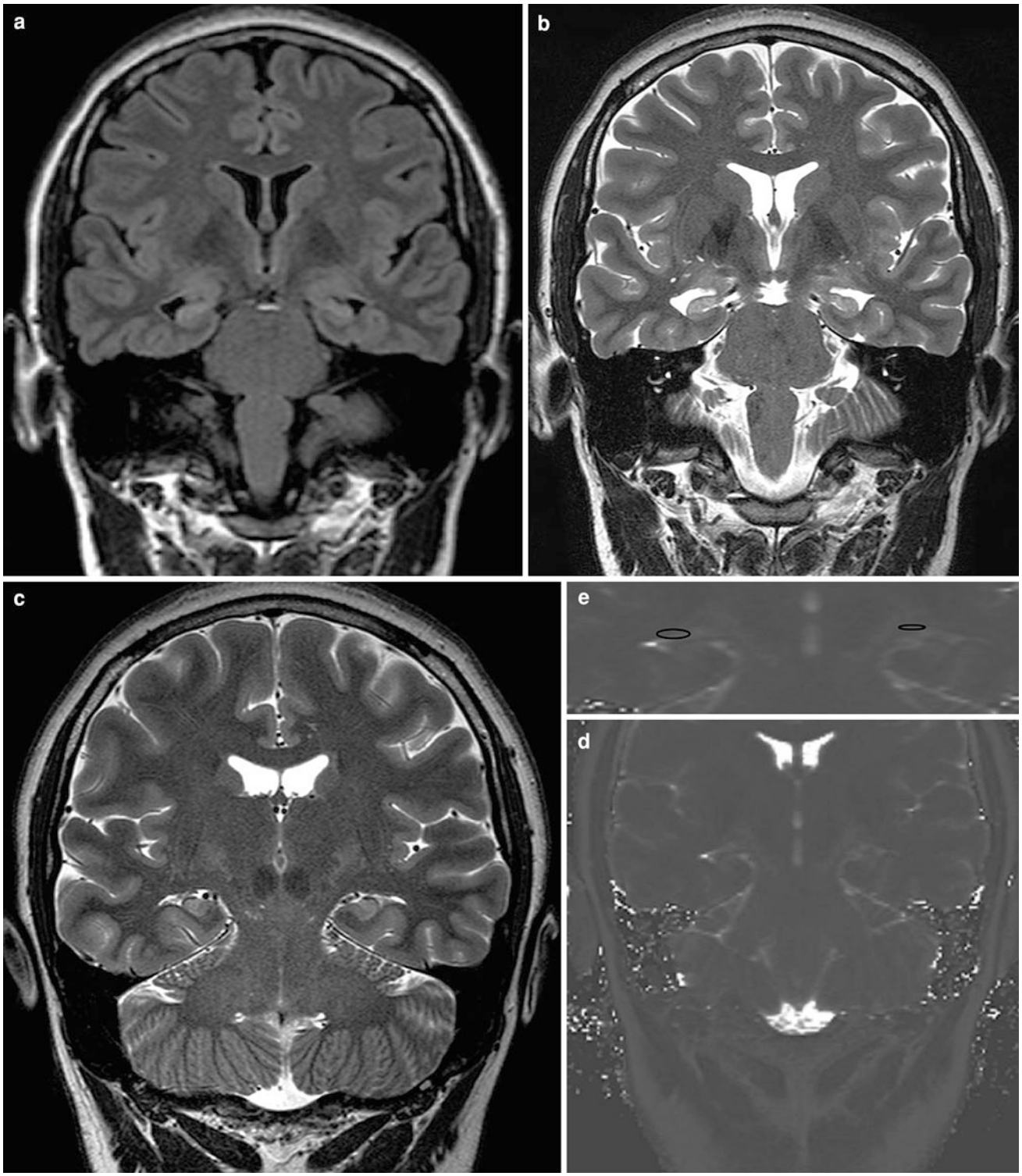

Fig. 3 Bilateral hippocampal sclerosis indicated by bilateral atrophy and increased signal intensity on FLAIR (**a**) and T2-weighted (**b**, **c**) fast spin echo images through the hippocampal heads (**a**, **b**) and bodies (**c**). If one has no engramm of a normal hipppocampus, T2 relaxometry (**d**) is helpful which revealed T2 relaxation times (**e**: ROI placements) with a mean of 132 ms in both hippocampi

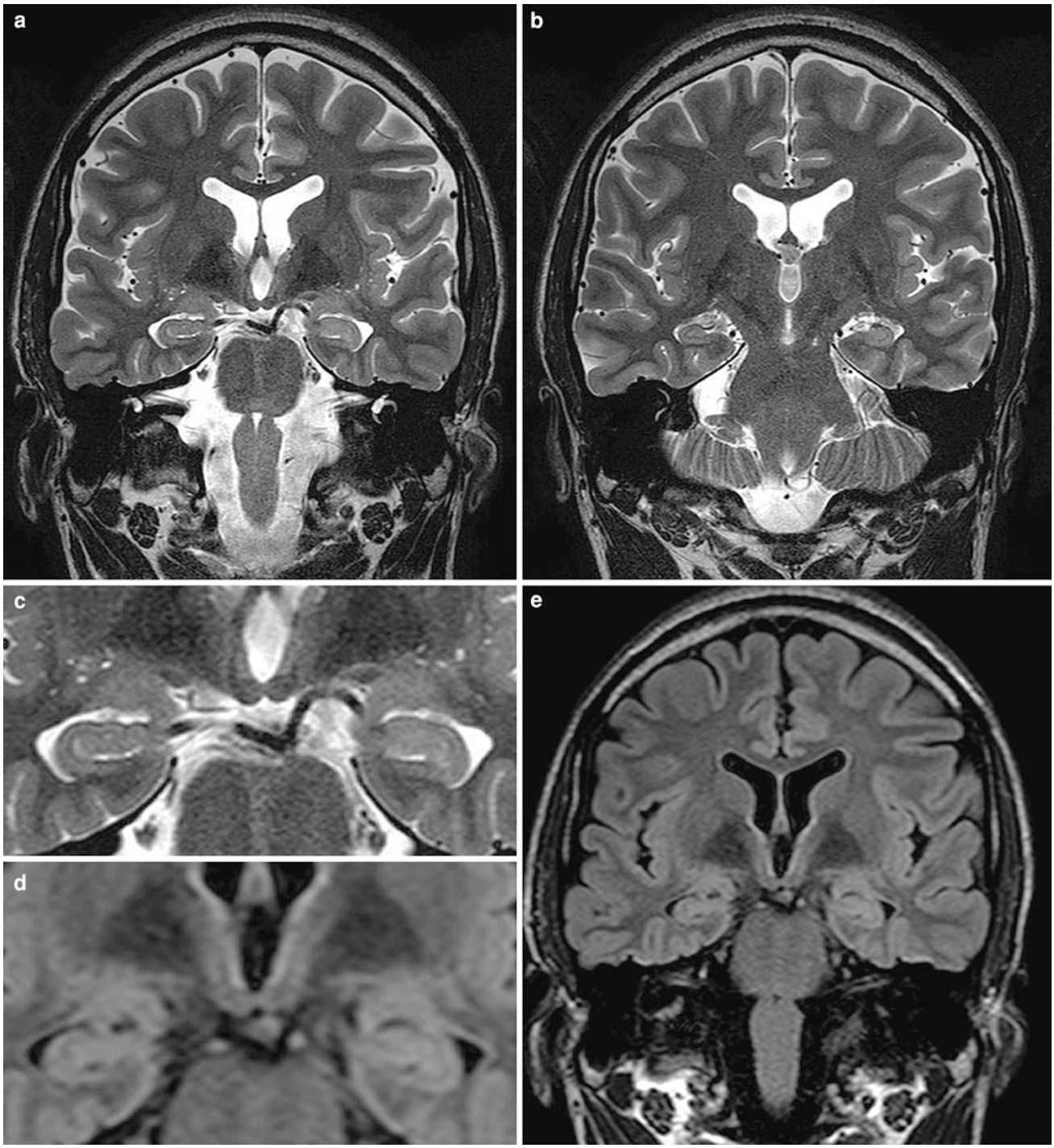

Fig. 4 A 21 year old man with complex partial seizures since the age of 18 underwent left-side selective amgydalohippocampectomy. On MRI, the left hippocampus is of normal size (**a**–**c**: 2 mm thick T2-weighted fast spin echo images, **d**, **e**: 3 mm thick FLAIR fast spin echo images). If there is an abnormality at all, hippocampal head substructures (digitationes hippocampi, CA fields) are better to delineate on the *right* (**c**) than on the *left* side

7 Treatment

Selective amygdalohippocampectomy (removal of amygdala, hippocampus and part of the parahippocampal gyrus) and anterior temporal lobectomy (additional removal of the anterior 4.5 cm on the left and 5.5 cm on the right side) are the most appropriate treatments and lead to seizure freeness (Engel-class I) in 75% of patients. Another 12% benefit with a distinct reduction of seizure frequency (Engel class II). With antiepileptic drugs only 8% of patients get seizure free (Engel et al. 1993; Wiebe et al. 2001). Note that

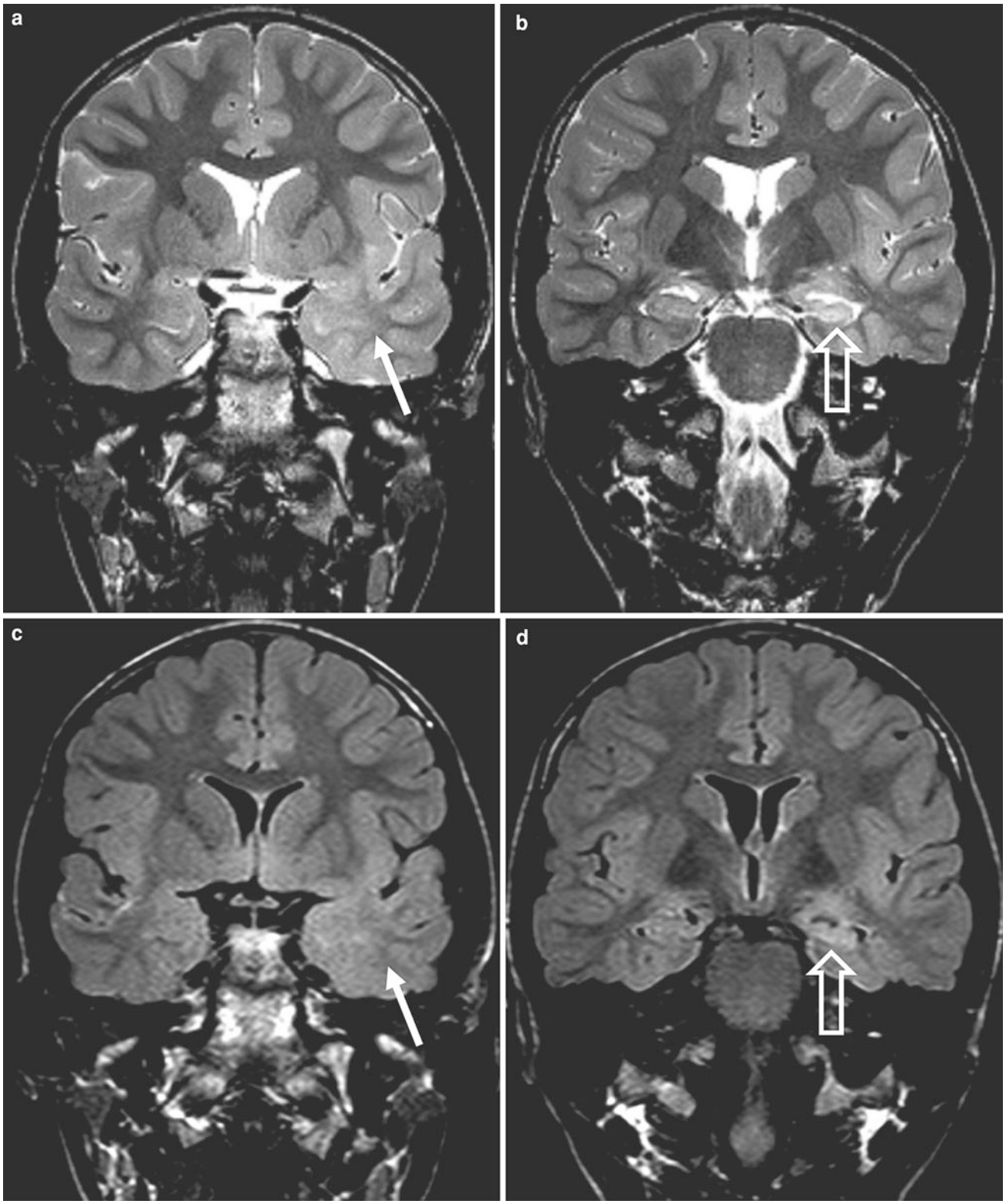

Fig. 5 Left-sided hippocampal sclerosis (**b**, **d**: *hollow arrow*) and "gray white matter demarcation loss" of the anterior temporal lobe (**a**, **c**: *arrow*) in a 32 year old man with varicella zoster virus infection as infant and complex partial seizures since this time

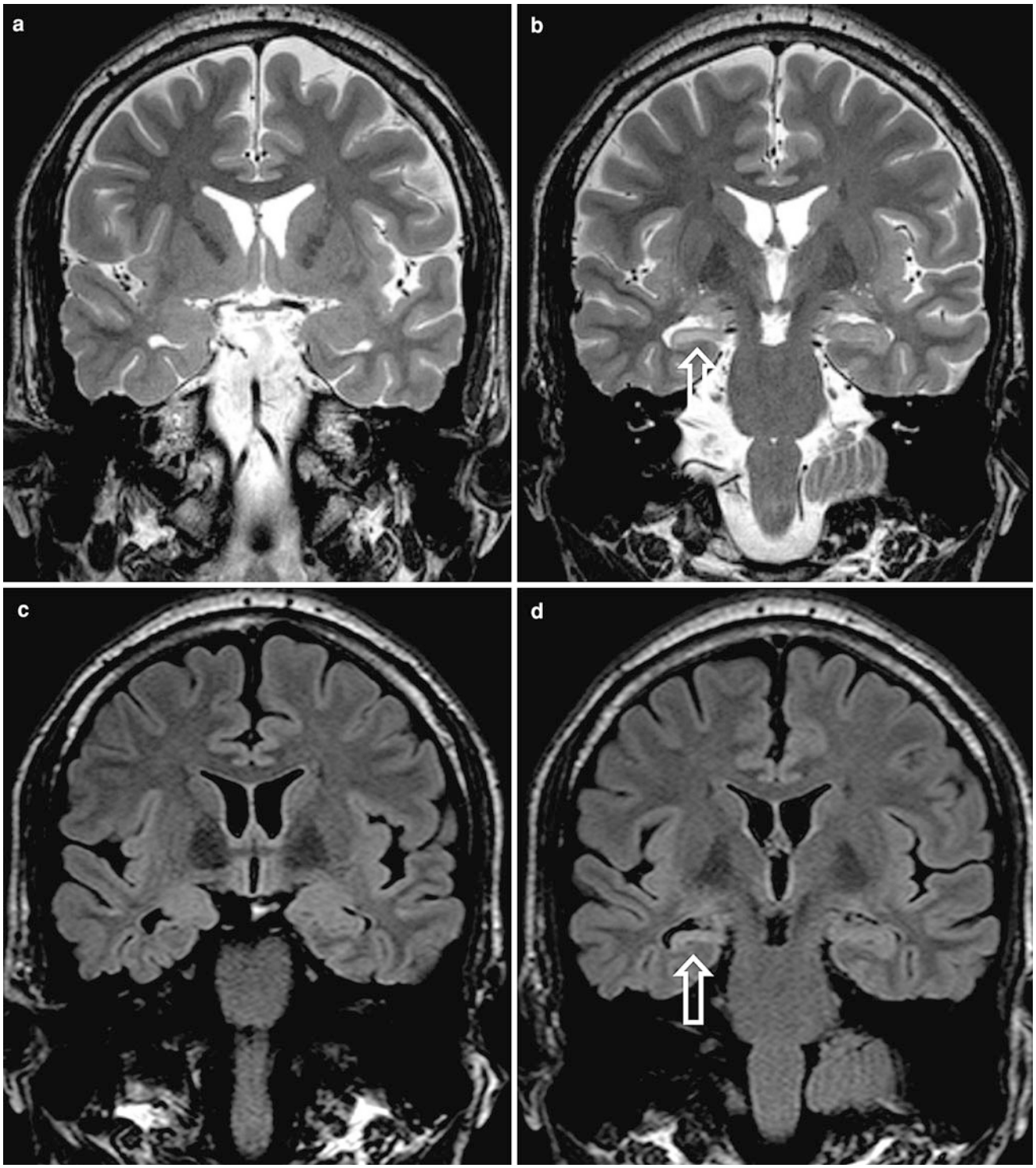

Fig. 6 Right-sided hippocampal sclerosis (**b**, **d**: *hollow arrow*) with slight atrophy of the anterior tempopral lobe but without "gray white matter demarcation loss"(**a**, **c**) in a 30 year old man without precipitating injury and complex partial seizures since the age of 5

seizure freeness is even reached, if only the anterior parts of the hippocampus and adjacent structures are removed.

Bilateral hippocampal sclerosis (20% of patients) was for a long time considered a knock-out-criterion for epilepsy surgery, since memory capacity of the non-resected hippocampus and chance for seizure freedom were considered low. However, individual patients can be operated successfully: If intrahippocampal depth electrodes show seizure origin in one hippocampus and event-related potentials sufficient memory capacity of the contralateral

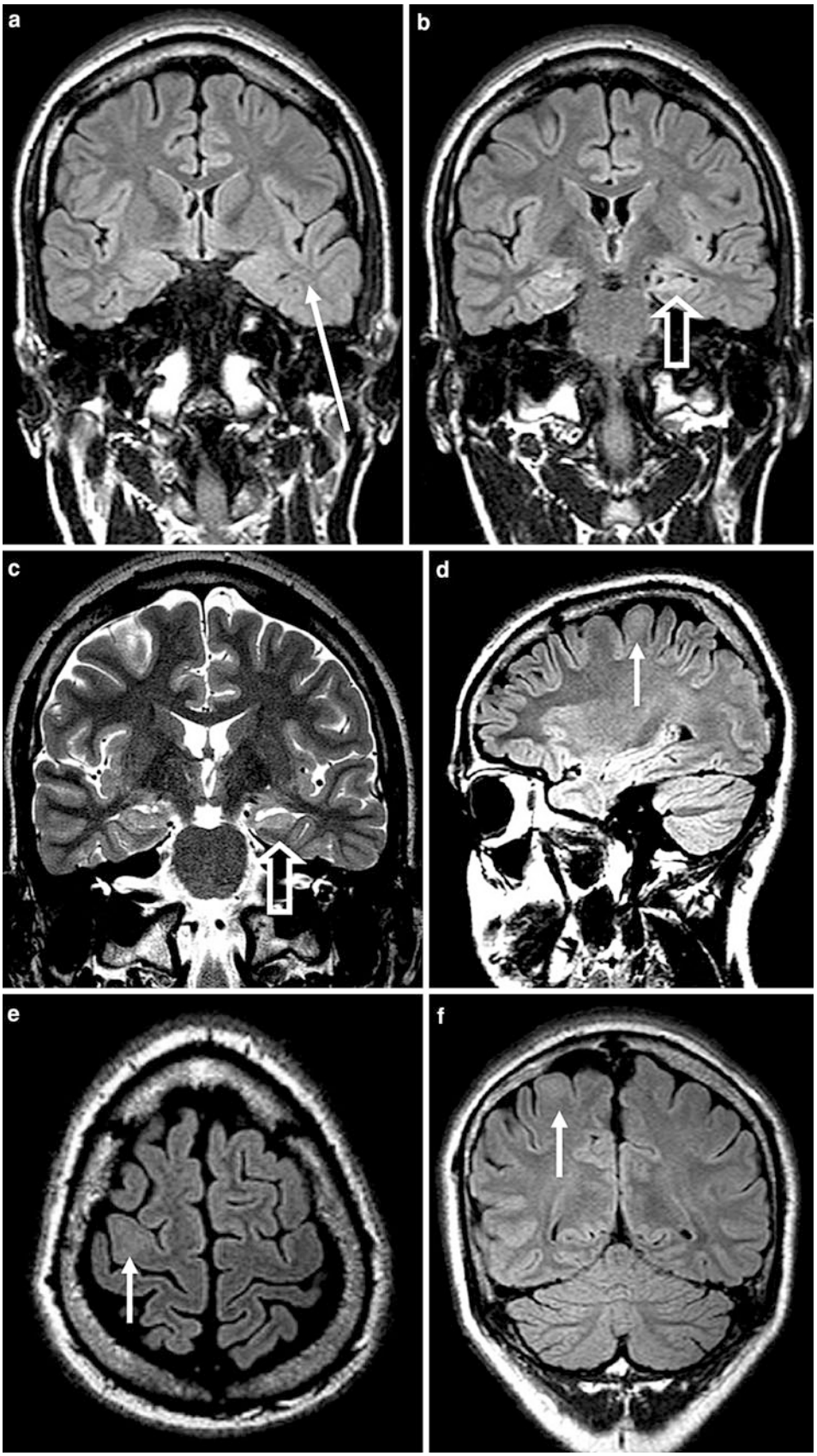

Fig. 7 16 year old male with complex focal seizures and left sided hippocampal sclerosis (**b**, **c**: *hollow arrow*l) and "gray white matter demarcation loss" of the anterior temporal lobe (**a**: *arrow*) as well as a dysplasia in the right precentral gyrus (**d–f**: *arrow*). The "gray white matter demarcation loss" is rather a maturation disorder of the anterior temporal lobe which myelinates latest. It is often seen in patients who have a precipitating injury and start to have temporal lobe seizures within the first two years of life. The dysplasia in the right precentral gyrus is a "dual pathology" strictu sensu

hippocampus, selective amygdalohippocampetcomy leads to seizure freedom without significant memory impairment in the more than 70% of patients.

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