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REVIEW

IMAGING OF AUTOIMMUNE ENCEPHALITIS – RELEVANCE FOR CLINICAL PRACTICE AND HIPPOCAMPAL FUNCTION

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Abstract—The field of autoimmune encephalitides associated with antibodies targeting cell-surface antigens is rapidly expanding and new antibodies are discovered frequently. Typical clinical presentations include cognitive deficits, psychiatric symptoms, movement disorders and seizures and the majority of patients respond well to immunotherapy. Pathophysiological mechanisms and clinical features are increasingly recognized and indicate hippocampal dysfunction in most of these syndromes. Here, we review the neuroimaging characteristics of autoimmune encephalitides, including N-methyl-D-aspartate (NMDA) receptor, leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) encephalitis as well as more recently discovered and less frequent forms such as dipeptidyl-peptidase-like protein 6 (DPPX) or glycine receptor encephalitis. We summarize findings of routine magnetic resonance imaging (MRI) investigations as well as ^{18}F-fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET) and single photon emission tomography (SPECT) imaging and relate these observations to clinical features and disease outcome. We furthermore review results of advanced imaging analyses such as diffusion tensor imaging, volumetric analyses and resting-state functional MRI. Finally, we discuss contributions of these neuroimaging observations to the understanding of the pathophysiology of autoimmune encephalitides.

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Key words: hippocampus, autoimmune encephalitis, limbic encephalitis, imaging, MRI, PET.

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INTRODUCTION

The first description of an autoimmune encephalitis dates back to 1888, when Hermann Oppenheim described a patient with neurological symptoms but no underlying brain pathology (Oppenheim, 1888). In the 1960s, post-mortem brain sections of patients with subacute encephalitis presenting with mood and behavioral changes revealed inflammatory changes most pronounced in limbic structures, e.g. hippocampus and amygdala, resulting in the term limbic encephalitis (Brierley et al., 1960; Corsellis et al., 1968). At this time, the relationship between limbic encephalitis and systemic cancer was already established and first hypotheses of an

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Abbreviations: CA, cornu ammonis; CASPR2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein 6; FBDS, faciobrachial dystonic seizures; FDG, 18F-fluoro-2-deoxy-D-glucose; FLAIR, fluid-attenuated inversion recovery; LGI1, leucine-rich glioma inactivated 1; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; NMOSD, neuromyelitis optica spectrum disorder; PET, positron emission tomography; SPECT, single photon emission tomography; VGKC, voltage-gated potassium channel.

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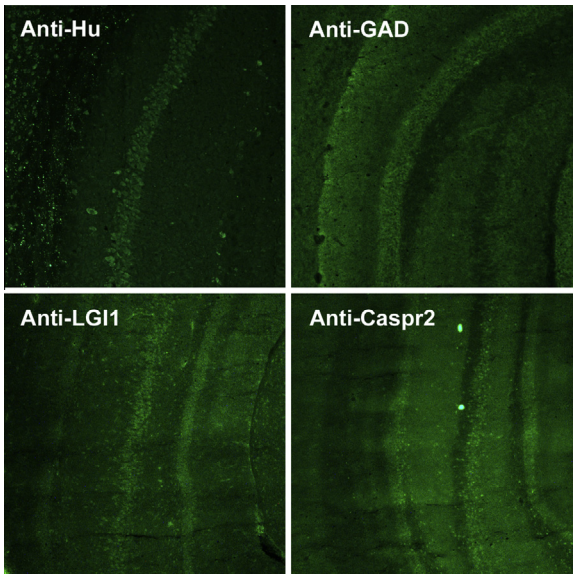

Fig. 1. Antibody-positive patient serum and CSF samples display distinct staining patterns in the hippocampus. Using indirect immunofluorescence on hippocampus sections, patient serum was diluted 1:100 and incubated on rat brains overnight, followed by visualization of specifically bound antibodies with fluorescently labeled secondary anti-human antibodies. Although all patients with limbic encephalitis had strong antibody binding in the hippocampus, the immunohistochemistry pattern in different hippocampal layers varied depending on the target epitope, such as anti-Hu, anti-GAD, anti-LGI1, and anti-CASPR2.

autoimmune-mediated pathogenesis were put forward (Russell, 1961), leading to the discovery of specific neuronal antibodies targeting intracellular neuronal antigens (e.g. Hu, Yo, Ri, Ma2, Tr, CV2) in tumor patients (Wilkinson, 1964; Trotter, 1976; Graus et al., 1985). These onconeuronal antibodies are associated with classic paraneoplastic disorders such as limbic encephalitis and paraneoplastic cerebellar degeneration that respond poorly to tumor removal and immunotherapy. Antibodies are not directly pathogenic and neuronal damage rather seems to be mediated by cytotoxic T cells (Dalmau and Rosenfeld, 2014; Irani et al., 2014a). In recent years, autoimmune encephalitides with antibodies directed against cell-surface proteins were increasingly recognized (Fig. 1). In contrast to classic paraneoplastic disorders, they occur with and without underlying tumor and frequently respond well to immunotherapy (Dalmau and Rosenfeld, 2014; Irani et al., 2014b). By targeting ion channels, receptors or associated proteins such as N-methyl-D-aspartate (NMDA) or GABA receptors, the associated antibodies directly interfere with synaptic transmission and neuronal plasticity. Owing to the variety of antibodies directed against different cell surface proteins, autoimmune encephalitides manifest with a wide range of symptoms and neuroimaging features. Frequently, patients present with cognitive deficits including memory disturbances and imaging shows an affection of the hippocampus, a structure critically involved in the formation of memory (Bartsch et al., 2010, 2011; Finke et al., 2013a). Comprehensive reviews have covered pathophysiology, clinical presentation and treatment strategies of these disorders (e.g., Lancaster and Dalmau, 2012; Bien and Bauer, 2014; Leypoldt et al., 2014; Varley et al., 2014; Irani et al., 2014a). Here, we provide an overview of the neuroimaging characteristics of autoimmune encephalitides with antibodies against cell-surface antigens (Table 1). We summarize observations from clinical routine MR and PET imaging and their relation to clinical characteristics and disease prognosis. Furthermore, we describe results of studies using advanced neuroimaging techniques, e.g. diffusion tensor imaging and resting-state functional magnetic resonance imaging (MRI), which shed light on pathophysiological mechanisms and which may also help in the evaluation of disease prognosis. We start by describing imaging findings in more frequent autoimmune encephalitis variants, e.g. NMDAR or leucine-rich glioma inactivated 1 (LGI1) encephalitis, and continue to include recently discovered antibodies where fewer studies or only case reports are available.

EARLY STUDIES ON LIMBIC ENCEPHALITIS

Before the recent surge in discovery of antibodies against neuronal cell-surface antigens, studies investigating limbic encephalitis frequently combined analysis of patients with and without antibodies or paraneoplastic and non-paraneoplastic manifestations (Gultekin et al., 2000; Lawn et al., 2003; Ances et al., 2005; Urbach et al., 2006). In patients with paraneoplastic limbic encephalitis, uni- or bilateral T2 hyperintense lesions in the medial temporal lobes including the hippocampus were observed in the majority of patients and were accompanied by extra-limbic cortical and subcortical alterations in up to 40% (Dirr et al., 1990; Gultekin et al., 2000; Lawn et al., 2003; Ances et al., 2005; Urbach et al., 2006). Gadolinum contrast-enhancement as an indicator of an increased blood–brain barrier permeability was observed in 15–25% of the patients (Gultekin et al., 2000; Lawn et al., 2003; Ances et al., 2005). In a serial MRI study of limbic encephalitis in patients with onconeuronal antibodies, voltage-gated potassium channel (VGKC) antibodies or without detectable antibodies, swelling of medial temporal lobe structures was observed initially and followed by progressive atrophy, while hyperintensity persisted in most patients (Urbach et al., 2006). This post-inflammatory atrophy of the hippocampus contributes to persistent memory impairment and the neurological disability seen in patients in due course of the disease, representing a large part of the chronic disease burden (Bartsch, 2012). ^{18}F-fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET) imaging significantly increases the sensitivity for abnormalities in limbic encephalitis and can show medial temporal lobe hypo- or hypermetabolism even in normally appearing temporal lobe structures on MRI (Scheid et al., 2004; Basu and Alavi, 2008). Additionally, FDG–PET more often shows extra-limbic abnormalities (mainly hypermetabolism), e.g. in the brainstem, cerebellum or cerebral cortex, and seems to correlate more closely with clinical symptoms than MRI (Ances et al., 2005). Accordingly, serial MRI and PET imaging in an anti-Ma2-positive seminoma and teratoma patient revealed an increasing hypermetabolism

Table 1

Antibody target	Patients with reported neuroimaging*	Magnetic resonance imaging (MRI)	Contrast-enhanced MRI	Positron emission tomography (FDG-PET)	Single Photon Emission Tomography (SPECT)
NMDA receptor	≈ 800	Abnormalities in 23–50% of patients that typically are discrete and non-specific (small white matter lesions in frontal, parietal & mediotemporal areas; thalamic, cerebellar and brainstem involvement in some patients, less frequently basal ganglia abnormalities) **Resting-state fMRI**: disrupted hippocampal functional connectivity **Diffusion tensor imaging**: Widespread white matter damage **Overlap with demyelinating syndrome**: multifocal T2/FLAIR hyperintense lesions **Follow-up**: Hippocampal atrophy and impaired hippocampal microstructural integrity	Mostly transient or faint T1-contrast enhancement of the cortex, meninges and basal ganglia in ≈ 25% of the patients with noncontrast MRI abnormalities Mild contrast enhancement of cortical and subcortical lesions in patients with overlapping demyelinating syndromes.	Increased frontotemporal-occipital gradient (frontotemporal glucose hypermetabolism, occipital hypometabolism) Other patients reported with altered metabolism in frontal, temporal and occipital lobes, in the basal ganglia, cerebellum and brainstem; lateralized effects in some patients	Increased or decreased perfusion in the medial frontal and temporal cortex in single case studies
LGI1	≈ 90	**FBDS stage**: Typically unremarkable, T2/FLAIR hyperintense signal alterations and contrast-enhancing basal ganglia lesions in single cases **Limbic encephalitis stage**: Uni- or bilateral T2/FLAIR hyperintensities of mediotemporal lobes in most patients; basal ganglia signal changes in some patients **Follow-up**: Frequently progression to hippocampal or whole brain atrophy, also affecting patients with formerly unremarkable MRI	**Limbic encephalitis stage**: Mild, ill-defined contrast enhancement of T2-hyperintense brain areas in ≈ 30% of the patients Reduction of contrast-enhanced caudate nucleus and globus pallidus lesion at follow-up in one case	**FBDS stage**: Uni- or bilateral glucose hypermetabolism of basal ganglia in single cases **Limbic encephalitis stage**: Altered basal ganglia glucose metabolism (mostly hypermetabolism) in 63–70% and altered mediotemporal metabolism (mostly hypermetabolism) in 70–75% of the cases Hypermetabolism in cerebellar, occipital and precentral areas or hypometabolism in the anterior cingulate in some patients	**FBDS stage**: Hypo- or hyperperfusion in the medial temporal lobe in single cases
CASPR2	≈ 50	Normal MRI in majority of patients with Morvan's syndrome, T2/FLAIR hyperintensities in frontal and mesiotemporal areas and nonspecific periventricular white matter lesions in some patients Hyperintense medial temporal lobe signal in ≈ 25% of patients with limbic encephalitis,	–	Focal and generalized hyper- and hypometabolism despite normal MRI in Morvan's syndrome involving basal ganglia, orbitofrontal, anterolateral and mediotemporal regions	–

Table 1 (*continued*)

Antibody target	Patients with reported neuroimaging*	Magnetic resonance imaging (MRI)	Contrast-enhanced MRI	Positron emission tomography (FDG-PET)	Single Photon Emission Tomography (SPECT)
		neuromyotonia or Morvans's syndrome; **Follow-up**: In 3/3 patients no progression to hippocampal atrophy or sclerosis			
AMPA receptor	18	Mesiotemporal T2/FLAIR hyperintensities in 90% of the patients, extending to anterior septal nuclei, insula, frontal, occipital or cerebellar regions in some cases **Follow-up**: Bilateral MTL abnormalities developing to hippocampal and amygdalar sclerosis in some patients, progression from unilateral to bilateral involvement over time	Mild, transient contrast enhancement of the left hippocampus in one case	Hypermetabolism predominantly in left hippocampus in one case More widespread bilateral hypometabolism involving the caudate nucleus, frontal, temporal and occipital areas in one case	–
$GABA_A$ receptor	8	MRI abnormal in all patients with extensive multifocal or diffuse cortical and subcortical T2/FLAIR signal alterations Rapid progression from focal mediotemporal and frontal T2/FLAIR abnormalities to atrophy and extensive bilateral lesions in some patients	–	–	–
$GABA_B$ receptor	≈ 65	Uni- or bilateral T2/FLAIR signal increases of the medial temporal lobe, including hippocampus and amygdala, in the majority of the patients Single cases reported with frontal and temporal leukencephalopathy, hippocampal laminar necrosis, brainstem encephalitis, cerebella lesions, basal ganglia lesions, longitudinally extensive myelitis, **Follow-up**: Progression hippocampal atrophy or frontotemporal atrophy	Contrast enhancement of cortical and subcortical lesions in frontal and temporal regions, brainstem, cerebellum and basal ganglia in single cases	Mediotemporal hypermetabolism corresponding to T2 signal increases in two patients; diffuse cortical hypometabolism in one case	Hypoperfusion in thalamus, cerebellum, frontal, parietal and mediotemporal areas together with hyperperfusion in middle and superior temporal, precentral & postcentral cortex in one case
Dopamine D2 receptor	12	T2/FLAIR signal increase in caudate, putamen, globus pallidus and substantia nigra in 50% of the patients **Follow-up**: Basal ganglia atrophy and gliosis in 2 patients	–	–	–
DPPX	20	Normal MRI in majority of patients; unspecific	–	–	–

(*continued on next page*)

Table 1 (*continued*)

Antibody target	Patients with reported neuroimaging*	Magnetic resonance imaging (MRI)	Contrast-enhanced MRI	Positron emission tomography (FDG-PET)	Single Photon Emission Tomography (SPECT)
		abnormalities in 4 of 13 patients; patchy periventricular and subcortical white matter T2/FLAIR signal increases and non-specific white matter changes in single cases			
GAD	≈ 50	Characteristic T2/FLAIR hyperintensities in the medial temporal lobe; higher FLAIR intensity values than in patients with VGKC or NMDAR antibodies; Cerebellar atrophy in ataxia patients **Follow-up**: Hippocampal sclerosis in some patients	–	–	–
Glycine receptor	≈ 60	Normal brain MRI in ≈ 70% of patients; observed abnormalities include T2/FLAIR hyperintense white matter lesions, temporal lobe signal alterations and atrophy; small as well as longitudinally extensive spinal lesions in some patients	T2 lesions were non-enhancing in one case; no contrast enhancement in another patient with unremarkable MRI	–	–

* Estimated based on provided cohort descriptions, corrected for repeatedly reported patients.

in the left medial temporal lobe on PET, which was paralleled by a significant increase in anti-Ma2 antibody titers while left medial temporal lobe hyperintensity on MRI remained unchanged (Scheid et al., 2004).

NMDA RECEPTOR ANTIBODY ENCEPHALITIS

Encephalitis with antibodies against the N-methyl-D-aspartate receptor (NMDAR) ranks among the most frequent forms of autoimmune encephalitis (Granerod et al., 2010). The disease typically affects young women and is associated with an ovarian teratoma in 40–60% of patients (Dalmau et al., 2011; Titulaer et al., 2013). Patients present with a typical clinical syndrome: Following a prodromal phase with low-grade fever, headache and fatigue, patients develop psychiatric symptoms including anxiety, psychosis, delusions, and hallucinations. With further progression, the disease may include abnormal movements such as orofacial dyskinesia and dystonia, autonomic instability, epileptic seizures and disorders of consciousness (Dalmau et al., 2007; Irani et al., 2010b; Titulaer et al., 2013). Immunotherapy and tumor removal lead to substantial improvement in about 80% of the patients, especially when treated at an early disease stage (Titulaer et al., 2013). However, many patients suffer from persistent cognitive deficits, i.e. memory impairment and executive dysfunction (Finke et al., 2012).

Although numerous imaging descriptions exist, large cohort studies reported MRI abnormalities only in 23–50% of the patients (Irani et al., 2010b; Dalmau et al., 2011; Titulaer et al., 2013). This clinico-radiological paradox constitutes one of the main challenges in NMDAR encephalitis neuroimaging. If imaging abnormalities become evident, they are typically mild and unrelated to clinical symptoms. They may involve the frontal, parietal and medial temporal cortex (Dalmau et al., 2007; Dalmau et al., 2008; Irani et al., 2010b), but have also been reported to affect the cingulate gyrus (Wegner et al., 2014), thalamus (Tojo et al., 2011), cerebellum (Vitaliani et al., 2005; Maqbool et al., 2011; Hacohen et al., 2014a) and brainstem (Vitaliani et al., 2005; Dalmau et al., 2008). Basal ganglia imaging changes were observed in a 21-year-old male NMDAR encephalitis patient with T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal and FDG–PET hypometabolism of the caudate head and lentiform nuclei (Tobin et al., 2014b). These MRI signal alterations were, among other symptoms, associated with bradykinesia and dysarthria and resolved following immunotherapy. In another patient with NMDAR antibodies, progressive striatal necrosis was documented (Tzoulis et al., 2013), while in most reported patients with prominent movement disorders no MRI changes were seen (Rubio-Agusti et al., 2011;

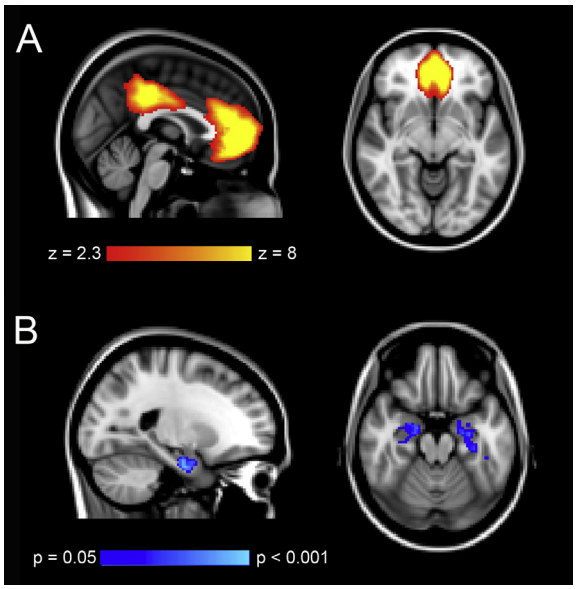

Fig. 2. Reduced functional connectivity of the hippocampus in NMDAR encephalitis. Resting-state functional MRI analysis revealed reduced hippocampal functional connectivity in patients with NMDAR encephalitis. (A) The anterior default mode network (DMN) was identified in patients and controls. The DMN is a functional brain network with increased activity during rest and internally focused tasks. It comprises multiple components, including a distinct medial temporal lobe subnetwork that is involved in memory processing. (B) In patients, functional connectivity between the DMN and both the left and the right hippocampus was significantly reduced in comparison to controls ($p < 0.05$, corrected). The strength of hippocampal functional connectivity correlated with memory performance in patients demonstrating that dysfunction of hippocampal NMDARs is a key pathophysiological mechanism in NMDAR encephalitis-associated memory deficits (not shown). Reproduced with permission from John Wiley and Sons (Finke et al., 2013b).

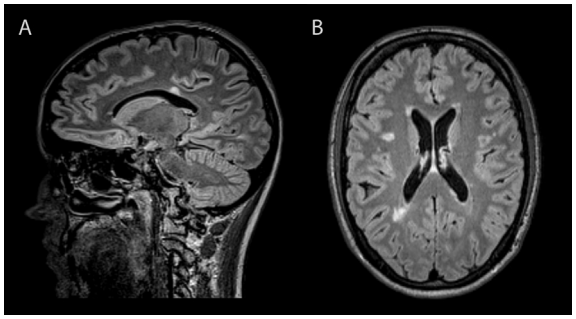

Fig. 3. Overlapping demyelinating syndrome in two patients with NMDAR encephalitis. (A) FLAIR-hyperintense lesions in the corpus callosum of a 20-year-old female patient with NMDAR encephalitis, one lesion with a ''Dawson finger'' aspect typical for multiple sclerosis. Further demyelinating lesions were observed in the periventricular white matter with two of the lesions showing contrast-enhancement. Lesions were detected on a routine follow-up MRI, however the patient had suffered from fatigue during the last six months before MRI. Shortly after MRI, she developed hypoesthesia of both lower legs and bladder dysfunction. A treatment with IV steroids was initiated and symptoms partially remitted. (B) FLAIR-hyperintense lesions in the periventricular white matter of a 26-year-old female patient with NMDAR encephalitis. In total, 14 supratentorial lesions were detected and two lesions showed contrast-enhancement. MRI was performed, because the patient had reported intermittent double vision. The patient was treated with IV steroids and double vision remitted.

Gumbinger et al., 2013; Labate et al., 2013; Aguiar de Sousa et al., 2014; Hacohen et al., 2014b).

Serial MRI and long-term follow-up indicate that severe disease courses can result in predominantly hippocampal or mild global atrophy (Dalmau et al., 2007; Iizuka et al., 2008; Iizuka et al., 2010; Pillai et al., 2010; Dalmau et al., 2011; Frechette et al., 2011; Tojo et al., 2011; Thomas et al., 2013). Interestingly, brain atrophy was partially reversible and accompanied by clinical recovery in two patients with follow-up for 5 and 7 years (Iizuka et al., 2010). A recent investigation of 40 patients after the acute stage of the disease found bilateral hippocampal atrophy that affected the input and output subregions of the hippocampal circuit (Finke et al., 2015). Additionally, hippocampal microstructural integrity was impaired in patients, and both hippocampal volumetric and microstructural integrity measures correlated with memory performance, disease severity and duration. These data thus emphasize the importance of a rapid and adequate immunotherapy to prevent persistent hippocampal damage.

FDG–PET can reveal pathological changes even when MRI and CT scans are normal. Metabolic abnormalities (hypo- or hypermetabolism) have been observed throughout the brain, including the frontal, temporal and occipital lobes as well as basal ganglia, cerebellum and brainstem (Vitaliani et al., 2005; Irani et al., 2010b; Maeder-Ingvar et al., 2011; Leypoldt et al., 2012; Baumgartner et al., 2013; Wegner et al., 2014). A characteristic pattern was described in an FDG–PET imaging study of six NMDAR encephalitis patients with relative frontal and temporal glucose hypermetabolism alongside occipital hypometabolism (Leypoldt et al., 2012). This increased frontotemporal-occipital gradient was associated with disease severity and normalized following recovery in two patients. Similar PET imaging findings were reported in other studies (Vitaliani et al., 2005; Mohr and Minoshima, 2010; Fisher et al., 2012; Wegner et al., 2014), although distinct patterns with occipital hypermetabolism (Irani et al., 2010b), widespread cortical hypometabolism (Pillai et al., 2010; Maqbool et al., 2011) or more lateralized effects (Caballero, 2011; Baumgartner et al., 2013) have been described as well. In accordance with frequent abnormal movements in NMDAR encephalitis, altered basal ganglia metabolism was described in several patients (Maeder-Ingvar et al., 2011; Abers et al., 2013; Baumgartner et al., 2013). For example, sequential PET imaging in a 25-year-old woman with marked limb rigidity showed an increased striatal metabolism in parallel to the diffuse cortical metabolic hypoactivity that normalized upon clinical recovery (Maeder-Ingvar et al., 2011). Single photon emission tomography (SPECT) revealed either increased (Vitaliani et al., 2005; Iizuka et al., 2008) or decreased perfusion in the medial frontal and temporal cortex in single patients (Vitaliani et al., 2005; Iizuka et al., 2010; Tsuyusaki et al., 2014).

Diffusion tensor imaging analyses detected widespread white matter changes, i.e. reduction of fractional anisotropy and increase of mean diffusivity, that correlated with individual disease severity (Finke

et al., 2013b). This observation suggests that white matter damage contributes to the pathophysiology of NMDAR encephalitis and may be mediated by antibodies binding to oligodendrocytic NMDARs (Lipton, 2006). Apart from these observations of white matter damage, an overlap of NMDAR encephalitis with demyelinating syndromes has been described (Takeda et al., 2014; Titulaer et al., 2014; Hacohen et al., 2014a; Fig. 3). A recent assessment of clinical and radiological data of 691 NMDAR encephalitis patients found 23 patients with clinical or MRI features of demyelination (Titulaer et al., 2014). These patients suffered from episodes of neuromyelitis optica spectrum disorder (NMOSD), brainstem or multifocal demyelinating syndromes which preceded, occurred simultaneously with or followed manifestation of NMDAR encephalitis. In some of these patients, antibodies against AQP4 and MOG were detected in addition to NMDAR antibodies. MRI showed new extensive or multifocal T2/FLAIR hyperintense lesions in various brain regions and the spinal cord which contrasted with the typical MRI result in NMDAR encephalitis with no or only small lesions. While the clinical diagnosis was challenging, lesions resolved after treatment in some patients. In a 28-year-old woman with antibodies against both NMDAR and MOG who was followed up for 5 years, recurring T2/FLAIR lesions in the deep gray matter and white matter were reported (Kaneko et al., 2014). These lesions co-occurred with neuropsychiatric symptoms when oral prednisone therapy was discontinued and resolved after IV methylprednisolone treatment. Another patient with multiple sclerosis was tested positive for NMDAR antibodies when she developed severe and persisting cognitive impairment (Fleischmann et al., 2014). In children with NMDAR antibodies, three distinct clinico-radiologic syndromes, i.e. brainstem encephalitis; leukoencephalopathy following herpes simplex encephalitis; and CNS demyelination, were identified and responded well to immunotherapy (Hacohen et al., 2014a). It is therefore important for clinicians to consider such an overlap syndrome in NMDAR encephalitis patients with atypical symptoms and/or spinal or cerebral demyelinating lesions. Conversely, patients with NMOSD or multiple sclerosis with atypical symptoms should be tested for NMDAR antibodies.

Besides structural changes in gray and white matter, functional connectivity was found to be disrupted in NMDAR encephalitis (Finke et al., 2013b). In a resting-state functional MRI analysis, functional connectivity of the left and right hippocampus with the anterior default mode network was significantly reduced in patients and correlated with individual memory impairment (Fig. 2). Remarkably, administration of the NMDA antagonist ketamine resulted in similar functional connectivity alterations and clinical symptoms, e.g. memory impairment and executive dysfunction (Anticevic et al., 2012). Considering the usually unremarkable structural routine MRI in NMDAR encephalitis, the results of these imaging analyses constitute a possible future avenue to address the clinico-radiological paradox of the disease.

In line with these clinical and imaging observations, an animal model of NMDA receptor encephalitis has been established. Animals with intraventricular infusion of patients' cerebrospinal fluid developed progressive memory deficits and anhedonic behavior. Interestingly, post-mortem analysis showed a widespread labeling of NMDA antibodies in the hippocampus, whereas the density of total and synaptic NMDAR clusters and total NMDAR protein concentration decreased in this area. These findings suggest a transient antibody-associated impairment of hippocampal NMDAR function, thus providing a link between hippocampal dysfunction in immune-mediated neuroinflammatory diseases and cognitive deficits. The experiments also provide a rationale for therapeutic approaches by reducing NMDAR antibodies and immune-active cells in these disease states, thereby improving neurological function (Planagumà et al., 2015).

Taken together, these imaging studies indicate that the hippocampus, which contains the highest density of NMDARs in the human brain, appears to be the most affected brain structure in NMDAR encephalitis. This observation is in line with the prominent memory impairments of patients. However, PET imaging highlights that, in contrast to classic limbic encephalitis, almost all brain structures can be affected by the disease, frequently exhibiting a characteristic metabolic pattern. Metabolic or structural alterations of the basal ganglia as demonstrated by MRI and PET are furthermore associated with movement disorders in some patients. Diffusion tensor imaging suggests that white matter damage likewise contributes to the clinical phenotype of the disease. An overlap syndrome should be considered in NMDAR encephalitis patients with atypical symptoms or demyelinating lesions.

VGKC-COMPLEX ANTIBODY ENCEPHALITIS

Antibodies directed against the VGKCs were detected in patients with limbic encephalitis, neuromyotonia and Morvan's syndrome (Liguori et al., 2001; Vincent et al., 2004). Recent research has shown that these antibodies – rather than directly acting on VGKCs – target proteins associated with the VGKC complex, i.e. LGI1 and contactin-associated protein-like 2 (CASPR2) (Lai et al., 2010; Irani et al., 2010a). Imaging studies of autoimmune encephalitis with VGKC-associated antibodies that did not differentiate between LGI1 and CASPR2 antibodies reported pathological changes in the medial temporal lobes with varying degrees of atrophy and cognitive outcomes (Vincent et al., 2004; Ances et al., 2005). In a study of 42 VGKC encephalitis patients, medial temporal lobe structures were uni- or bilaterally enlarged and hyperintense on T2/FLAIR images in 79% of patients, involving both the hippocampus and the amygdala (Kotsenas et al., 2014). These signal alterations showed diffusion restriction in the T2 hyperintense areas in 42% of patients and contrast enhancement in 28% of patients. Only two patients had extra-limbic manifestation in the perisylvian cortex and the caudate nucleus. On follow-up, almost 50% of patients developed hippocampal sclerosis, with an increased risk for patients with restricted diffusion and contrast enhancement. Using an automated

volumetric analysis, Wagner et al. (2014) found increased volumes of amygdala and hippocampus for patients investigated during the first 12 months of the disease. At follow-up 6–12 months later, the volumes had normalized with a trend for smaller hippocampi in patients. FDG–PET imaging in a 67-year-old patient revealed successive mediotemporal hypermetabolism together with hippocampal T2 hyperintensity and swelling, initially affecting the right hemisphere and three months later the left hemisphere (Chatzikonstantinou et al., 2009). At follow-up two years later, hypometabolism of both medial temporal regions had developed, accompanied by right hippocampal atrophy and persistent swelling of the left hippocampus.

Limbic encephalitis with VGKC-associated antibodies has only rarely been described in children. A case study of a 13-year-old girl reported a progression from bilateral swelling with T2/FLAIR signal increase of the amygdala and hippocampus, together with signal increase in the left claustrum and insula, to bilateral hippocampal atrophy within seven months (Kröll-Seger et al., 2009). This case emphasizes that VGKC-associated limbic encephalitis is not restricted to adult patients and may show the same characteristic temporal evolution with rapid progression to hippocampal atrophy in children.

LGI1 ANTIBODY ENCEPHALITIS

Patients with LGI1 encephalitis present with subacute memory disturbances which are accompanied by various neuropsychiatric symptoms, such as disorientation, confusion, temporal lobe seizures and behavioral abnormalities indicating affection of limbic structures. Patients are typically older than 40 years and men are more frequently affected than women (Lai et al., 2010; Irani et al., 2010a). LGI1 encephalitis is only rarely associated with systemic tumors and the overall prognosis is good when immunotherapy is initiated at an early disease stage. Importantly, LGI1 limbic encephalitis is frequently preceded by faciobrachial dystonic seizures (FBDS) – short, jerky and highly stereotyped dystonic episodes that typically affect one arm and the ipsilateral side of the face and occur at a high frequency (median 50/day). Recognition of FBDS is of high clinical importance, since early immunotherapy can prevent progression to limbic encephalitis (Irani et al., 2013). MRI at the stage of FBDS is typically unremarkable, although in single cases T2 hyperintense signal alterations, diffusion restriction and contrast-enhancing lesions of the basal ganglia have been reported (Irani et al., 2013; Plantone et al., 2013). Increased T2/FLAIR signal in the left caudate, putamen and rectus and cingulate gyrus was accompanied by left basal ganglia hypermetabolism in FDG–PET in a patient with a right-sided FBDS (Boesebeck et al., 2013). In a patient with frequent bilateral FBDS but no cognitive deficits, bilateral striatal hypermetabolism was observed with FDG–PET in the absence of MRI basal ganglia abnormalities (Fidzinski et al., 2014; Fig. 4).

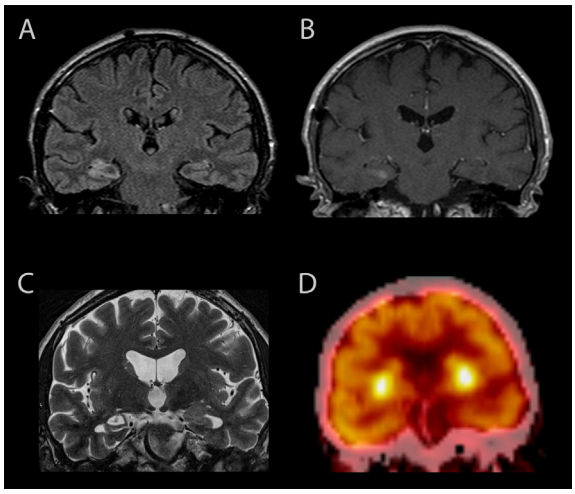

Fig. 4. MRI and FDG–PET imaging in LGI1 encephalitis. (A–C) 60-year-old male patient with LGI1 encephalitis: FLAIR-hyperintense signal alterations in the hippocampus bilaterally (right > left; A), with contrast enhancement on the right side (B). The patient presented with frequent faciobrachial dystonic seizures (FBDS), followed by confusion, agitation, and severe memory impairment. Following immunotherapy with IV steroids, plasma exchange and IV immunoglobulins FBDS ceased while memory impairment persisted. Follow-up MRI 17 months later showed bilateral (right > left) atrophy of the hippocampus as well as moderate global atrophy (C). (D) FDG–PET showing bilateral hypermetabolism in the basal ganglia in a 92-year-old patient that presented with up to 100 FBDS/day but without cognitive deficits. FBDS stopped after two courses of IV immunoglobulin therapy. MRI was unremarkable except mild global atrophy and microangiopathic leukoencephalopathy and especially showed no abnormalities of basal ganglia or medial temporal lobes (Fidzinski et al., 2014).

At the limbic encephalitis stage of the disease, uni- or bilateral T2/FLAIR hyperintensities of the medial temporal lobes are detected in the majority of patients and can likewise be accompanied by basal ganglia signal changes (Lai et al., 2010; Irani et al., 2010a; Irani et al., 2011; Irani et al., 2013; Fig. 4). Patients frequently progress to develop hippocampal atrophy at later follow-up investigations and remain with permanent general cognitive and mnestic impairments (Andrade et al., 2011; Irani et al., 2013; Malter et al., 2014; Kotsenas et al., 2014; Szots et al., 2014; Fig. 4). Importantly, volumetric analysis detected hippocampal and whole brain atrophy also in post-recovery FBDS patients without MRI abnormalities in the medial temporal lobes during the acute illness, indicating that FBDS can cause significant atrophy despite unremarkable clinical routine imaging (Irani et al., 2013). Time to administration of immunotherapy was correlated with time to clinical recovery in these patients, thus again highlighting the need for early immunotherapy in patients with FBDS. It is likely that an early immunotherapy will also be associated with less severe hippocampal and whole brain atrophy in larger longitudinal samples.

FDG–PET at the limbic encephalitis disease stage revealed altered basal ganglia glucose metabolism in 63–70% of patients (hypermetabolism in 11/18; hypometabolism in 1/18) and altered temporal metabolism in 70–75% of patients (hypermetabolism in 11/18; hypometabolism in 2/18) in two recent studies

(Irani et al., 2011; Shin et al., 2013). Normal mediotemporal glucose metabolism was correlated with better clinical outcome, whereas basal ganglia metabolism was unrelated to disease course (Shin et al., 2013). A recent analysis of cerebral glucose metabolism in four LGI1 encephalitis patients in comparison to matched healthy controls found hypermetabolism in the basal ganglia as well as in the cerebellum, the occipital lobe and the precentral gyrus and hypometabolism in the anterior cingulate - but interestingly no significant alteration of medial temporal lobe metabolism (Wegner et al., 2014). This latter finding might partially be related to the disease stage of the investigated patients, since longitudinal PET investigations show waxing and waning of temporal PET metabolism mirroring the clinical course of the disease (Cash et al., 2011; Park et al., 2014).

In summary, LGI1 encephalitis presents with the typical imaging correlates of limbic encephalitis, i.e. T2/FLAIR hyperintense signal alterations in the medial temporal lobes including the hippocampus which frequently progress to hippocampal atrophy. Additionally, prominent basal ganglia involvement is observed in many patients using MRI and FDG–PET imaging. This finding might provide an important clue to the pathophysiology of FBDS in the current debate on whether these episodes represent seizures or extrapyramidal movements (Striano et al., 2011). It has recently been proposed that the concomitant MRI and PET abnormalities in contralateral cortical and extrapyramidal areas might explain the overlap of epileptic (cortical) and movement disorders (subcortical) features in FBDS, thus blurring the traditional borders between these two entities (Boesebeck et al., 2013).

CASPR2 ANTIBODY ENCEPHALITIS

Patients with CASPR2 antibodies develop Morvan's syndrome or, less frequently, limbic encephalitis (Irani et al., 2010a). Morvan's syndrome is characterized by encephalopathy with prominent psychiatric symptoms, insomnia, dysautonomia and neuromyotonia and almost exclusively affects male patients (Lancaster et al., 2011a; Irani et al., 2012). MRI was normal in 23 of 25 patients with Morvan's syndrome, while right frontal T2 hyperintensity was observed in one and bilateral hippocampal T2 high signal with consecutive atrophy in another patient (Fig. 5). Focal and generalized hyper- and hypometabolism were found in all four patients examined with PET, despite normal MRI (Irani et al., 2012). In a 64-year-old patient with VGKC antibodies and Morvan's syndrome, FDG–PET revealed increased basal ganglia metabolism while only nonspecific periventricular white matter lesions were seen on MRI (Spinazzi et al., 2008). Cognitive function improved and cerebral glucose metabolism normalized in this patient following 15 months of immunotherapy with plasma exchange, cyclophosphamide and azathioprine. In a 66-year-old patient with Morvan's syndrome and VGKC antibodies, PET demonstrated reduced FDG uptake bilaterally in the orbitofrontal cortex and anterolateral temporal regions, as well as in the left medial temporal lobe, while MRI was normal (Toosy et al., 2008).

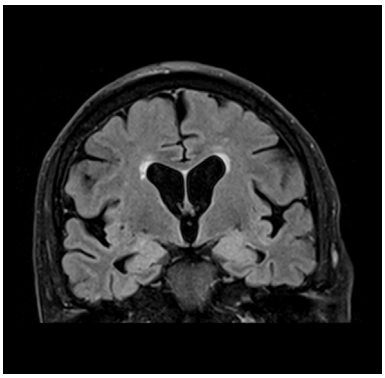

Fig. 5. Medial temporal lobe abnormalities in CASPR2 encephalitis. A 71-year-old male patient with CASPR-2 antibodies presented with complex partial seizures, memory deficits and affective disturbance. MRI revealed symmetric FLAIR hyperintensities in the medial temporal lobes. Following extensive immunotherapy with IV steroids, plasma exchange, IV immunoglobulins and rituximab, a mild improvement of symptoms was observed.

In a sample of CASPR2-positive patients suffering from Morvan's syndrome, neuromyotonia or limbic encephalitis, five of 19 patients had MRI hyperintense signal alterations in the medial temporal lobes, but all five patients with Morvan's syndrome had normal MRI (Irani et al., 2010a). Lancaster et al. (2011b) observed T2 hyperintensities in the medial temporal lobes in two CASPR2 antibody-positive patients, diffuse cortical and subcortical atrophy in one patient and normal MRI in two patients. In a 67-year-old patient with Morvan's syndrome, multiple small T2-hyperintense white matter lesions mostly in the periventricular region, consistent with chronic small vessel changes, were observed (Loukaides et al., 2012). In a 55-year-old patient with epilepsy, dysarthria, and paroxysmal kinesigenic dystonia, acute right subcortical infarction was reported with however uncertain relation to CASPR2 antibody-positivity (Krogias et al., 2013). Another study that only investigated limbic encephalitis patients with T2/FLAIR-hyperintense medial temporal lobe structures found normal MRI at follow-up 11–58 months later in three patients with CASPR2 antibodies (Malter et al., 2014). In contrast to LGI1-positive patients, patients with CASPR2 antibodies did not develop hippocampal atrophy or sclerosis (Kotsenas et al., 2014; Malter et al., 2014).

AMPA RECEPTOR ANTIBODY ENCEPHALITIS

Encephalitis with antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors most frequently affects female patients and is associated with different tumors in 70% of the cases (Lai et al., 2009). It typically manifests as limbic encephalitis with seizures, memory impairment and psychiatric symptoms. Accordingly, T2/FLAIR hyperintense signal alterations were observed in the medial temporal lobes in eight of nine patients in the first reported case series (Lai et al., 2009). In two of these patients, abnormalities extended into anterior septal nuclei and insular,

frontal, occipital or cerebellar regions. Most patients responded well to immunotherapy, with the long-term outcome depending on the management of relapses. Bataller and colleagues (2010) described a 67-year-old woman with confusion, hypersomnia, visual hallucinations, and memory deficits. Mild bilateral FLAIR hyperintensities in the medial temporal lobe were observed on MRI examination. In accordance with the good therapy response in AMPAR encephalitis, her memory impairment alleviated with decreasing antibody titers. Exclusive bilateral mediotemporal T2/FLAIR signal increases were also reported in three patients whose most prominent symptom was short-term memory impairment (Dogan Onugoren et al., 2014). While two initially showed bilateral abnormalities, one patient with left hemispheric involvement became affected bilaterally over time. In the latter case, laminar necrosis-like pattern in the left hippocampal sectors cornu ammonis (CA) 1 and CA 2 was observed. All three patients developed hippocampal and amygdalar sclerosis on follow-up. A similar pattern was found in a 33-year-old female patient with progressive anterograde and retrograde amnesia (Spatola et al., 2014). Left-sided hippocampal edema and hyperintensities on T2/FLAIR images evolved into bilateral affection and finally bilateral hippocampal atrophy. FDG–PET imaging revealed hypermetabolism predominantly in the left hippocampus which persisted after resolution of CSF pleocytosis and hippocampal edema. Antiepileptic therapy was potentiated with the presumption of ongoing temporal seizures, resulting in memory improvement and normalization of left hippocampal glucose metabolism. A fulminant disease course was reported in a 30-year-old pregnant woman. She developed behavioral changes and memory impairment followed by ataxia, nystagmus, quadriparesis, impaired consciousness and status epilepticus (Wei et al., 2013). MRI showed FLAIR hyperintensities bilaterally in the medial temporal lobes, insula and caudate nucleus. Remarkably, follow-up MRI 5 days later revealed severe diffuse cortical atrophy. At a second follow-up on day 37, FLAIR changes had resolved, but cortical atrophy persisted. An FDG–PET performed on day 52 showed widespread bilateral hypometabolism of frontal, temporal, and occipital lobes and the caudate. In contrast, Graus et al. (2010) reported two women with rapidly progressive confusion, personality changes, agitation and aggressive behavior with completely normal MRI. Both patients fully recovered with corticosteroid therapy.

$GABA_A$ RECEPTOR ANTIBODY ENCEPHALITIS

Gamma-aminobutyric acid A ($GABA_A$) receptor antibodies were recently identified in patients with cognitive deficits and prominent seizures (Petit-Pedrol et al., 2014). Six patients with high titers of $GABA_AR$ antibodies in serum and CSF developed a rapidly progressive encephalopathy that eventually resulted in refractory seizures and status epilepticus in five patients. Seizures were preceded or accompanied by cognitive deficits and psychiatric symptoms, including memory impairment, depression, psychosis, confusion and mutism. Further symptoms included opsoclonus, ataxia, chorea and hemiparesis. MRI was abnormal in all patients, showing extensive multifocal or diffuse cortical and subcortical T2/FLAIR signal alterations. For example, a 16-year-old girl presented with multiple T2/FLAIR-hyperintense lesions involving the left temporal lobe and frontal parasagittal regions. Follow-up MRIs revealed considerable progression with increasing size of existing lesions, manifestation of new lesions and diffuse atrophy together with increased ventricular size. MRI performed six months after symptom onset showed resolution of the abnormalities and normalization of ventricular size. In a 51-year-old male patient, MRI changes progressed within 14 days from focal T2/FLAIR signal abnormalities to an extensive involvement of cortical and subcortical regions of both hemispheres. Two of the patients died of sepsis during treatment of refractory status epilepticus and four patients substantially recovered. Twelve patients with low serum titers of $GABA_AR$ antibodies presented with a broader spectrum of diseases including stiff-person syndrome, opsoclonus-myoclonus syndrome and (limbic) encephalitis with seizures. MRI abnormalities included high T2/FLAIR signal in fronto-temporal regions and medial temporal lobes, multifocal lesions and cortical atrophy, as well as normal results in five patients. Ohkawa et al. (2014) reported two patients with invasive thymoma and serum $GABA_AR$ antibodies who developed cognitive deficits and psychiatric symptoms. MRI of both patients showed extensive bilateral multifocal lesions involving the temporal lobes.

$GABA_B$ RECEPTOR ANTIBODY ENCEPHALITIS

Gamma-aminobutyric acid B ($GABA_B$) receptors are expressed throughout the brain, particularly in hippocampus, thalamus, and cerebellum. $GABA_B$ encephalitis typically manifests as limbic encephalitis and is associated with small cell lung cancer or neuroendocrine tumors in 50% of patients (Lancaster et al., 2010). Accordingly, in the majority of patients, uni- or bilateral T2/FLAIR increases in the medial temporal lobes are observed with normal MRI results in some patients (Lancaster et al., 2010; Boronat et al., 2011; Dogan Onugoren et al., 2014). Höftberger et al. (2013) categorized their patient sample according to clinical presentation. Out of 17 patients with limbic encephalitis, MRI showed uni- or bilateral increased T2/FLAIR signal in hippocampus and amygdala in nine patients, increased pial enhancement in one patient and was normal in seven patients. Brain MRI was also normal in a patient with status epilepticus. In a patient with ataxia, MRI showed frontal and temporal leukoencephalopathy and another patient with opsoclonus-myoclonus syndrome had increased signal in T2/FLAIR and contrast enhancement in cortex and white matter of both frontal and temporal lobes and cingulum. Follow-up MRI investigations revealed progressive hippocampal atrophy and signal increase on T2/FLAIR-weighted images demonstrating evolution of hippocampal sclerosis. In two patients, T1-weighted not-enhanced images indicated hippocampal laminar necrosis (Dogan Onugoren et al., 2014).

The clinical spectrum was expanded by Jeffery et al. (2013), who reported a patient with multiple myeloma and $GABA_BR$ antibody-associated encephalopathy and myelopathy. Spinal MRI in this patient revealed longitudinally extensive T2 signal abnormalities in the thoracic spinal cord characteristic of paraneoplastic myelopathy. Other rare manifestations of $GABA_B$ autoimmunity include cerebellar ataxia in a 64-year-old malignant melanoma patient with normal MRI (Jarius et al., 2013) and brainstem encephalitis in a 63-year-old patient with esophageal carcinoma and T2-hyperintense lesion in pons, medulla oblongata and right cerebellar peduncle (Mundiyanapurath et al., 2013). A 33-year-old woman presented with opsoclonus-myoclonus syndrome, followed by a severe episode of limbic encephalitis. Serial MRI studies showed extensive T2/FLAIR hyperintense lesions in the frontal and temporal lobes and the cingulate gyrus which developed into marked fronto-temporal atrophy at follow-up one year later (DeFelipe-Mimbrera et al., 2014). The first pediatric case, a 3-year-old boy, presented with opsoclonus, ataxia, chorea and refractory seizures accompanied by brainstem, cerebellum and basal ganglia involvement upon diffusion-weighted imaging and T2/FLAIR sequences (Kruer et al., 2014).

FDG–PET imaging revealed hypermetabolism in the medial temporal lobes in two out of five patients that was congruent with increased T2/FLAIR signal in MR imaging and diffuse cortical hypometabolism in a third patient (Kim et al., 2014). In a case study of a 62-year-old female patient presenting with limbic encephalitis, ^{123I}-IMP SPECT detected hypoperfusion in thalamus, cerebellum and frontal, parietal, and mediotemporal areas as well as hyperperfusion in middle and superior temporal, precentral and postcentral cortex despite unremarkable MR imaging (Ohta et al., 2011). Remarkably, repeat SPECT imaging following methylprednisolone pulse therapy showed normalization of perfusion in almost all brain regions.

DOPAMINE D2 RECEPTOR ANTIBODY ENCEPHALITIS

Dopamine-D2 receptor antibodies have recently been characterized in children with basal ganglia encephalitis (Dale et al., 2012). Twelve children with this encephalitis presented with Parkinsonism, dystonia, chorea, as well as psychiatric symptoms including emotional lability and psychosis. MRI was abnormal in 50% of these patients, showing T2/FLAIR signal increases in the caudate, putamen, globus pallidus and substantia nigra. Patients with D2-encephalitis may remain with residual motor, cognitive, and psychiatric deficits despite a good response to immunotherapy in some cases. At follow-up examination, basal ganglia atrophy and gliosis was seen in two patients and corresponded to their persistent cognitive and psychiatric symptoms (Dale et al., 2012).

DIPEPTIDYL-PEPTIDASE-LIKE PROTEIN 6 (DPPX) ANTIBODY ENCEPHALITIS

DPPX is a cell-surface auxiliary subunit of the Kv4.2 potassium channel family and antibodies targeting DPPX were detected in four patients with agitation, confusion, myoclonus, tremor and seizures (Boronat et al., 2013). In three patients, these symptoms were preceded by severe diarrhea of unclear etiology, causing substantial weight loss. Cerebral MRI showed only non-specific periventricular and subcortical white matter T2/FLAIR increased signal in a 61-year-old man and non-specific white matter changes and nonacute right frontal infarction in a 58-year-old woman (Boronat et al., 2013). A recent study reported 20 patients with DPPX antibodies with various neurological symptoms including amnesia, psychosis, seizures, eye movement disorders, ataxia, and dysphagia as well as signs of central hyperexcitability including myoclonus, exaggerated startle, diffuse rigidity, and hyperreflexia (Tobin et al., 2014a). Additionally, patients suffered from dysautonomic symptoms such as diarrhea, gastroparesis or bladder dysfunction. Despite the severe neurological deficits, MRI was normal in nine of 13 patients with available MRI and showed only nonspecific abnormalities in the remaining four patients. In three patients with DDPX antibodies and a distinct syndrome characterized by trunk stiffness, hyperekplexia and cerebellar ataxia, cerebral MRI likewise was normal except for one patient with mild cerebellar atrophy 17 years after disease onset (Balint et al., 2014).

GAD ANTIBODY ENCEPHALITIS

Glutamate decarboxylase is an intracellular synaptic antigen concentrated in presynaptic terminals that can be exposed to antibodies during synaptic vesicle fusion and reuptake (Lancaster and Dalmau, 2012). The presence of high titers of GAD antibodies has been associated with different neurological syndromes including stiff-person syndrome, cerebellar ataxia and limbic encephalitis (Saiz et al., 2008). In patients with limbic encephalitis, characteristic T2/FLAIR hyperintensities in the medial temporal lobes are observed (Fig. 6), accompanied by

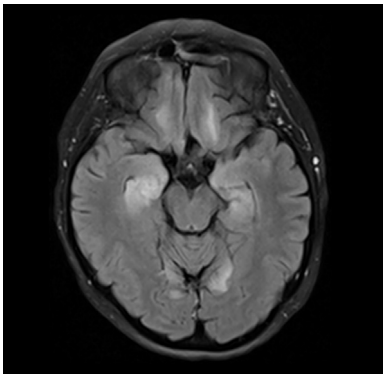

Fig. 6. Medial temporal lobe abnormalities in GAD encephalitis. GAD antibodies were detected in a 53-year-old female patient with generalized seizures, gait ataxia, downbeat nystagmus and cognitive deficits. MRI showed FLAIR hyperintensities in the medial temporal lobes that progressed at follow-up, now extending into insular and frontal cortex. Oncological work-up revealed a gall bladder carcinoma. Immunotherapy with IV steroids, plasma exchange, rituximab and cyclophosphamide resulted in remission of seizures and cerebellar symptoms, while anterograde memory impairment persisted.

anterograde amnesia and language deficits, while disorientation and confusion seem to be less common compared to other antibodies (Saiz et al., 2008; Malter et al., 2010). On follow-up MRI, regression of encephalitic mediotemporal signal was observed, although some patients developed hippocampal sclerosis (Malter et al., 2010). In GAD-antibody-positive patients with cerebellar ataxia, MR imaging showed isolated atrophy of the cerebellum (Honnorat et al., 2001; Ariño et al., 2014). Using an observer-independent postprocessing method, Wagner et al. (2013) found that limbic encephalitis patients with GAD antibodies had significantly higher hippocampal FLAIR intensity values than patients with VGKC and NMDAR antibodies. This observation might be linked to a more severe affection of the hippocampus and worse mnestic and seizure outcome in GAD encephalitis. In a volumetric analysis, amygdala volume was significantly increased in patients with GAD-antibody-positive limbic encephalitis when analyzed within the first twelve months after disease onset and normalized during follow-up. In contrast, hippocampal volumes did not differ significantly from a control group (Wagner et al., 2014).

GLYCINE RECEPTOR ANTIBODY ENCEPHALITIS

Antibodies against the glycine receptor have recently been described in adult and pediatric patients with progressive encephalomyelitis, rigidity and myoclonus (PERM) or stiff person syndrome (Hutchinson et al., 2008; McKeon et al., 2012; Carvajal-González et al., 2014; Wuerfel et al., 2014). Glycine receptors are mainly located in the caudal pontine brainstem and spinal cord, and patients present with the respective brainstem and autonomic signs. In addition, cognitive deficits such as disorientation and memory impairment, and psychiatric symptoms including visual hallucinations, depression or anxiety can be present. Tumors, mainly thymomas and lymphomas, are found in some of the patients. In the largest study so far, brain MRI was unremarkable in 26/36 patients while two patients had signal alterations in the temporal lobes, two had other FLAIR lesions and the remaining patients had unspecific white matter lesions or small vessel disease (Carvajal-González et al., 2014). Interestingly, spinal MRI showed smaller lesion in four patients and, longitudinally, extensive lesions in one, but the majority of patients (18/23) had no abnormalities (Carvajal-González et al., 2014). In a study of 11 patients, MRI changes were found in a 62-year-old male patient with generalized cerebral and cerebellar atrophy and a 42-year-old male patient with nonenhancing T2 abnormalities in the bilateral superior colliculi, superior cerebellar peduncle, left brachium pontis, bilateral occipital white matter (McKeon et al., 2012).

CONCLUSIONS AND FUTURE DIRECTIONS

In the last few years, a variety of new antibodies targeting cell-surface proteins associated with distinct clinical syndromes have been discovered. Despite the wide range of different antibody targets, many of these syndromes present with features of limbic encephalitis and corresponding T2/FLAIR hyperintense signal alterations in the medial temporal lobes including the hippocampus. This includes patients with antibodies directed against LGI1, $GABA_B$ receptors, AMPA receptors or (the intracellular synaptic antigen) GAD and a subset of patients with CASPR2 antibodies. These findings are contrasted by the frequently normal MRI in NMDAR and DPPX encephalitis, extensive multifocal or widespread diffuse abnormalities in $GABA_AR$ encephalitis and basal ganglia lesions in Dopamine D2R encephalitis. It must be noted, however, that the current analysis is based on studies using a wide range of MRI protocols with different MRI sequences and image resolutions, which likely influences the detection rate of imaging abnormalities. Moreover, some advanced imaging methods (resting-state fMRI, diffusion tensor imaging) have so far only been used in NMDAR encephalitis. Future extension of these methods to other autoimmune encephalitis subtypes and advances in imaging methods and analyses as well as the use of multimodal imaging approaches will facilitate the discrimination between different encephalitis variants and will help to identify characteristic imaging profiles of these disorders.

Neuroimaging serves several purposes with regard to autoimmune encephalitides. First, it takes a central role in their diagnosis, given that the corresponding imaging characteristics are now increasingly recognized. While MRI T2/FLAIR hyperintensities in the medial temporal lobes might point to limbic encephalitis caused by $GABA_BR$, AMPAR or GAD antibodies, basal ganglia hypermetabolism in FDG–PET imaging may support the diagnosis of LGI1 encephalitis. As mentioned above, imaging abnormalities in routine MRI and FDG PET are not specific and clinical MR imaging can also return completely normal results, e.g. in NMDAR, DPPX or GlyR encephalitis. Advanced imaging techniques, e.g. automated volumetric analyses, quantification of signal alterations, or the application of new sequences or imaging methods, e.g. resting-state functional MRI will help to bridge the gap between clinical and radiological findings.

Second, neuroimaging can contribute to the pathophysiological understanding of autoimmune encephalitides. The detection of widespread white matter damage in NMDAR encephalitis led to the hypothesis of an involvement of oligodendrocyte NMDA receptors in the pathogenesis of the disease and is particularly interesting with regard to the discovery of overlapping demyelinating syndromes in patients with NMDAR encephalitis. Moreover, a reduced functional connectivity of the hippocampus is a neural substrate of persisting memory deficits in these patients. In LGI1 encephalitis, further analysis of concurrent signal alterations in the medial temporal lobes and the basal ganglia in MRI and PET imaging might help to identify the nature of FBDS. And longitudinal analyses of amygdala and hippocampus volumes in patients with limbic encephalitis are starting to identify distinct volumetric courses depending on the associated

antibody, thus pointing to different pathogenetic mechanisms, including different levels of inflammation and neuronal cytotoxicity.

Third, imaging parameters may serve as prognostic markers. To date, this is typically based on visual inspection, e.g. on the extent and intensity of signal alterations in the medial temporal lobes. Future studies will increasingly use quantitative, observer-independent analyses that provide more robust and reliable measures and allow for a better comparison between patient populations. Moreover, modern imaging techniques will enable the development of new imaging markers and – in association with longitudinal study designs – further improve the predictive value of neuroimaging in autoimmune encephalitis.

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