Imaging of Autoimmune Epilepsies

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Abbreviations:

CSF:	Cerebrospinal fluid
CT:	Computed tomography
DTI :	Diffusion tensor imaging
FDG :	18F-fluorodeoxyglucose
FLAIR :	Fluid-attenuated inversion recovery
HE :	Hashimoto encephalitis
HHV6 :	Human herpes virus 6
GET2 :	Gradient echo T2
MRI :	Magnetic resonance imaging
MRS :	Magnetic resonance spectroscopy
PNLE :	Paraneoplastic limbic encephalitis
SWI :	Susceptibility weighted imaging
VGKC-Ab:	Voltage-gated potassium channels antibodies (VGKC-Ab)

Summary

Epilepsy due to an autoimmune disease is a recently recognized entity. Among the best-known diseases are paraneoplastic limbic encephalitis, limbic encephalitis associated with voltage-gated potassium channels (VGKC)) antibody glutamic acid decarboxylase antacid, antireceptor antibodies N-methyl-D-aspartate, Rasmussen and Hashimoto encephalitis.

More efficient imaging technics and immunologic laboratory analyses have allowed us to deepen our knowledge concerning these diseases that are most common in adults.

In this article we will describe the most common imagery findings and the most appropriate methods of image analysis.

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Key words: epilepsy, MRI, autoimmune diseases, paraneoplastic encephalitis, voltage-gated potassium channels encephalopathy, anti GAD

Imagerie des épilepsies auto-immunes

L'épilepsie causée par une maladie auto-immune est une entité récemment reconnue. Les étiologies les plus fréquentes sont l'encéphalite limbique paranéoplasique, l'encéphalite limbique associée à l'anticorps anticanaux potassiques voltage dépendant, l'encéphalite à anticorps antiacide glutamique decarboxylase, l'encéphalite à anticorps antirécepteur du N-methyl-D-aspartate, l'encéphalite de Rasmussen et l'encéphalite de Hashimoto.

Ces maladies sont rares et méconnues. Les avancées techniques en imagerie et en laboratoire nous ont permis d'approfondir nos connaissances.

Dans cet article, nous allons décrire les anomalies radiologiques les plus souvent rencontrées dans chaque maladie ainsi que les méthodes d'imagerie les plus adaptées pour leur analyse.

Mots clés : Epilepsie, IRM, maladies autoimmunes, encéphalite paranéoplasique, encéphalopathie canaux potassiques voltage-dépendant, anti AGD

Bildgebung der autoimmunen Epilepsien

Durch Autoimmunerkrankungen verursachte Epilepsien stellen eine erst seit kurzem bekannte Entität dar. Die häufigsten Ursachen sind die paraneoplastische limbische Enzephalitis, die limbische Enzephalitis mit gegen spannungsabhängige Kaliumkanäle gerichteten Antikörpern, die Enzephalitis mit Anti-Glutamatdecarboxylase-Antikörpern, die Enzephalitis mit Antikörpern gegen N-Methyl-Aspartatrezeptoren, die Rasmussen-Enzephalitis sowie die Hashimoto-Enzephalitis.

Es handelt sich hierbei um seltene und wenig bekannte Erkrankungen. Fortschritte in der Bildgebung und in Labortechniken haben es jedoch ermöglicht, unsere Kenntnisse zu erweitern. In dieser Arbeit werden die häufigsten radiologischen Befunde obengenannter Autoimmunerkrankungen beschrieben, mit Empfeh-

lungen zur Optimierung der Bildgebungstechnik.

Schlüsselwörter: Epilepsie, MRI, Autoimmunerkrankungen, paraneoplastische Enzephalitis, Enzephalitis mit gegen spannungsabhängige Kaliumkanäle gerichteten Antikörpern, Anti-GDA

Introduction

In this paper we will describe the most frequent findings detected by imagery in autoimmune diseases associated with epilepsy.

The imaging technic of choice is resonance magnetic imaging (MRI), we will describe the most adequate technical protocols as well as the anomalies found in these diseases.

Imagery and autoimmune laboratory studies play a key role in the diagnosis and follow up.

Imaging technic

The imagery of choice is magnetic resonance imaging (MRI) at 3T using a 32 channel brain coil, the technical protocol recommend is: coronal fast spin echo T2 (FSET2), repetition time (TR) 7520 ms; echo time (TE) 114 ms; voxel size 0.5 × 0.4 × slice thickness 3 mm, the position of the slices is perpendicular to the hippocampi as well as in the axial plane, 3D Fluid inversion recovery(FLAIR) TR 5000; TE 419; inversion time (TI) 1800; isotropic voxel size 0.9 × 0.9 × 0.9 mm (**Figure 1**), diffusion tensor imaging (DTI) TR 8000 ms; TE 84 ms, 30 directions, arterial spin labeling (ASL) TR 4000 ms; TE 12, voxel size 3.4 x 3.4 x slice thickness 4 mm and spin echo (SE) T1 before and after contrast medium and 3DT1 after contrast medium, TR 1750 ms; TE 2.29 ms; isotropic voxel size 0.7 × 0.7 x 0.7 mm [1].

The use of contrast medium is recommended.

The gradient echo T2 (GET2) TE 20 ms, TR 832 ms, slice thickness 4 mm or susceptibility weighted imaging (SWI) are helpful particularly in limbic paraneoplastic encephalitis and limbic encephalitis associated with voltage-gated potassium channels where microbleeds are common.

Computed tomography (CT) is usually realized in the emergency room upon patient arrival but does not allow the diagnosis of this type of epilepsy as the hippocampal abnormalities are difficult to analyze and detection of microbleeds is limited.

Whole PET-F-fluorodeoxyglucose (FDG) is used for detecting malignances in patients where a paraneoplastic encephalitis is suspected.

Paraneoplastic limbic encephalitis (PNLE)

Paraneoplastic limbic encephalitis is a rare disorder affecting 1% of patients with a systemic cancer [2]. It was first described in 1960 by Brierley [3], incidence in males or females depends on the type of tumor implicated. It is characterized by memory loss, personality changes, seizures and dementia.

Around 60% of patients with PNLE have antineural antibodies in the serum or CSF [4].

Anomalies of the hippocampi and limbic system are detected by MRI, hyperintensities on FLAIR/T2 in both or one of the temporal lobes and hippocampi, the inferior frontal region, the insular cortex and cingulate gyrus can also be affected. The symptoms and imaging anomalies appear frequently before detection of the primary neoplastic disease.

The imaging of choice for analysis of these anomalies is MRI.

The most common antibodies associated are the:

- Anti-Hu: associated with small-cell carcinoma of the lungs, the most common cause of paraneoplastic limbic encephalitis (**Figure 2**)
- Anti-Ta: associated with tumors of the testis
- Anti-Yo: associated with breast and ovarian cancers
- Anti NMDAR: associated with tumors of the ovaries, frequently teratomas
- Anti-CRMP5 (anti-CV2): associated with small-cell carcinoma of the lungs and thymoma
- Anti Tr: associated with Hodgkin disease

The common MRI findings are hyperintensities and enlarged hippocampi and amygdala in FLAIR and FSE T2 in the early stages of disease followed by atrophy (**Figure 2**). These anomalies may extend to the striatum and thalamus, the brainstem and the cerebellar peduncles. Microbleeds are rare and enhancement is some-

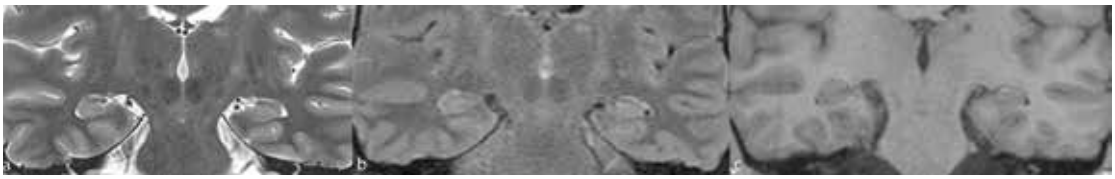

Figure 1: Normal hippocampus on coronal FST2, FLAIR and T1 weighted images (a, b, c)

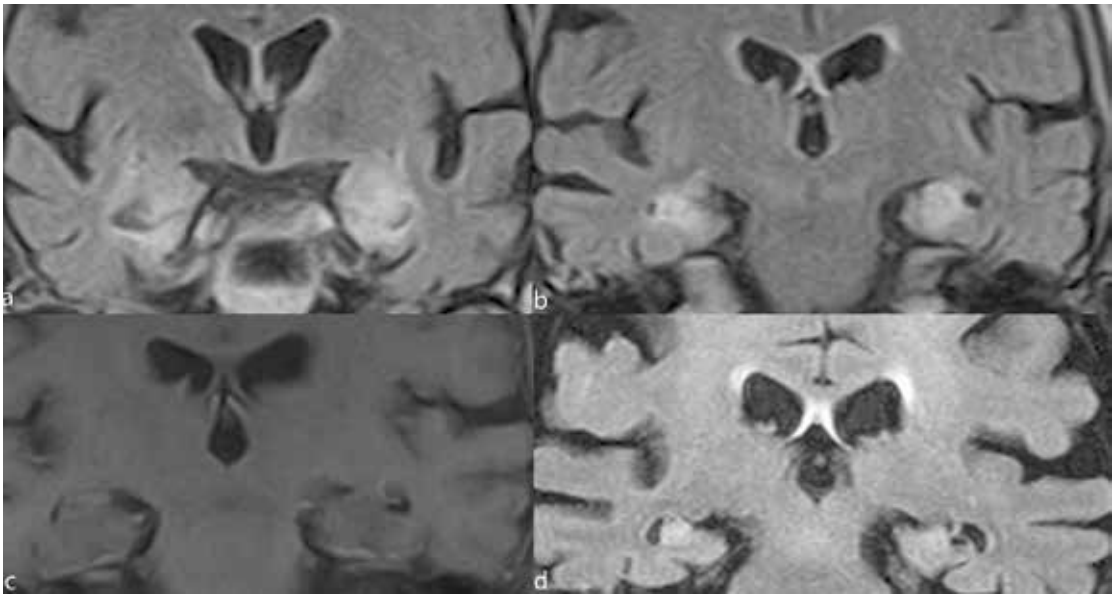

Figure 2: Paraneoplastic encephalitis: 82 year-old woman with carcinoma of the lung, note the hyperintense and enlarged hippocampi and amygdala on T2 (a, b). No enhancement is noted in (c), follow-up 8 months later shows an atrophy of the hippocampi (d).

times associated.

The differential diagnosis of imaging findings includes the human herpes virus 6 (HHV6) [5] encephalitis and other non-paraneoplastic encephalitis such as voltage-gated potassium channel antibody encephalitis, bilateral glioma and gliomatosis cerebri.

Isolated involvement of the pulvinar nuclei may open the differential diagnostic with Creutzfeldt-Jakob disease [6].

The anomalies may regress in the early stages if the primary tumor is removed but often this is not possible due to advanced malignant and infiltrative disease [7].

Whole PET-18 F-fluorodeoxyglucose (FDG) is used for detecting malignances but is rarely used at the level of the brain. However, non-specific medial temporal and extra-temporal hypermetabolism can be observed in patients with autoimmune epilepsy in the earlier phases [7], and a diminution of intake of FDG in the most advanced phases [7, 8].

Voltage-gated potassium channels antibodies encephalitis (VGKC-Ab)

Voltage-gated potassium channels antibodies disease is an autoimmune non-paraneoplastic reversible limbic encephalitis characterized by memory loss, confusion and seizures.

The imagery is indistinguishable from paraneoplastic encephalitis in the early stages when only the hippocampi and amygdala are affected. They appear hyperintense on T2 and FLAIR and are enlarged in the early stages of disease followed by atrophy [9]. Findings can be unilateral or bilateral (**Figure 3**). A restriction of diffusion can be observed in the same location of the T2/FLAIR anomalies [10] and enhancement can be seen.

Microbleeds have been described in this pathology [9]. A generalized atrophy of the brain is also observed in chronic stages (**Figure 3**).

Findings can be reversible and in some cases this is not treatment dependent.

Normal imaging at the onset is possible.

Treatment includes immunotherapy, plasmapheresis and oral prednisone.

Rasmussen encephalitis

Rasmussen encephalitis is an uncommon progressive encephalitis of unknown cause, however recent research has shown that it is a chronic T-cell mediated disorder [11], with onset in the first decade of life and less common in adults. It is characterized by mental impairment, progressive hemiparesis and drug-resistant epilepsy.

Diagnostic criteria were established in 2005 by Biel et al. [4] and adapted by Olson et al. in 2013 [11] and include clinical symptoms (focal seizures and unilateral cortical deficits) and EEG findings (epileptiform activity and unilateral seizure onset). MRI criteria include hyperintensity of white matter and cortex on FLAIR and

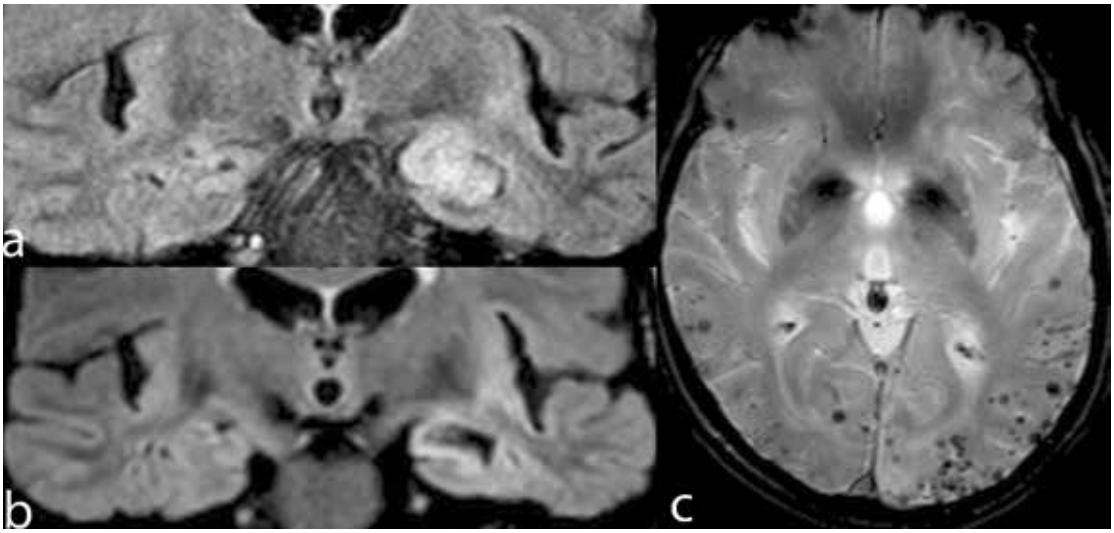

Figure 3: Voltage-gated potassium channels antibodies encephalitis: Coronal FLAIR sequence shows an enlarged left hippocampus (a) observe the atrophy 3 months later associated with diffuse cortical and subcortical microbleeds.

FSET2, unilateral progressive atrophy and no enhancement (**Figures 4, 5**). All of these criteria must be met for the diagnosis as well as 2 of 3 of the following criteria: epilepsia continua or progressive unilateral cortical deficits, progressive unilateral atrophy at MRI and T-cell dominated encephalitis with activated microglial cells.

Pradeep et al. [12] had modified the imaging criteria and proposed 4 stages as follows (**Figures 4, 5**):

Stage 1: swelling of the cortex, with a hyperintense T2/FLAIR signal;
Stage 2: normal volume and hyperintense signal;
Stage 3a: mild atrophy with hyperintense signal;
Stage 3b: moderate atrophy with hyperintense signal; and
Stage 4: severe atrophy with normal signal.

Magnetic resonance spectroscopy (MRS) studies show decreased NAA levels and increased (cho) peaks, resulting in a decreased NAA/cho ratio suggestive of neuronal loss or dysfunction and elevated lactate [12 - 15].

Longo et al. have described a case showing an association between Parry-Romberg and Rasmussen encephalitis [16].

Hashimoto encephalitis

Clinical presentation of Hashimoto encephalopathy is variable and observed in the pediatric, adult, and elderly populations. Common clinical manifestations include stroke-like symptoms, movement disorders, dementia, and focal or generalized seizures. Diagnosis is confirmed by an elevated antithyroid antibody level encephalopathy when other more common infectious, metabolic, and toxic causes of encephalopathy have been completely excluded [17].

Hashimoto encephalitis (HE) presents a wide range of MRI findings such as enlarged and hyperintense unilateral or bilateral hippocampi, transient subcortical ischemia, cortical atrophy, and unilateral cerebral atrophy. Bohnen et al. reported diffuse reversible white matter anomalies that mimic a leukodystrophy and resolve after treatment [18].

In other cases, HE my simulate tumors, granuloma, infection or degenerative disorders [19, 20] however patients may have a normal MR.

Findings in MRS are diverse for example Singh H et al. described a peak of lactate in MR-spectroscopy in the symptomatic phase with a normalization of values with clinical improvement of the patient [21]. Su et al. reported a decrease in N-acetylaspartate (NAA/Cr=1.19) and myo-inositol peaks, and an elevation in lipid, lactate, glutamate/glutamine multiplet and choline (Cho/Cr = 1.21) peaks, which supported a cerebral inflammatory change.

Diverse physiopathologic mechanisms have been proposed such as the role of anti-thyroid antibodies produced intrathecally [22, 23], perivascular lymphocyte infiltration involving leptomeninges and the brain stem, signs of vasculitis, cerebral hypoperfusion, and toxic effects of thyrotropin-releasing hormone.

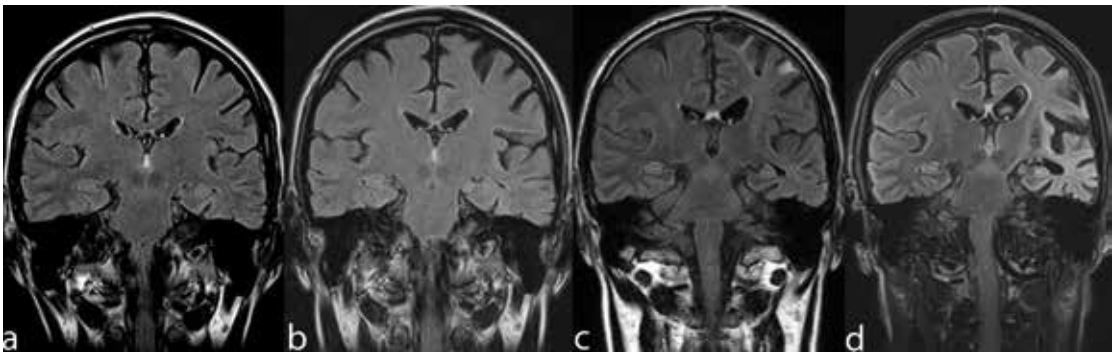

Figure 4: Rasmussen encephalitis: Evolution of this disease is shown on coronal FLAIR MR, in the first control the MRI is normal in 1999 (a). In 2002, left cortical-subcortical atrophy is present.
In 2006, note the high signal of the left frontal lobe and the left hemispheric cortical-subcortical atrophy.

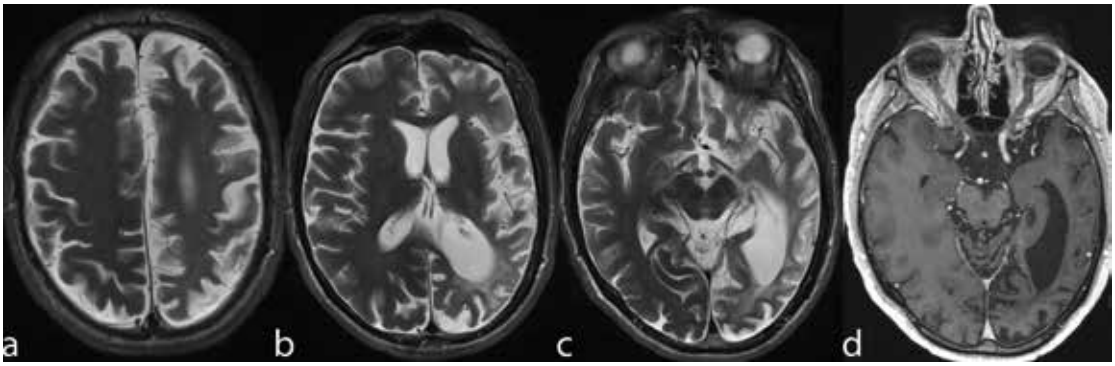

Figure 5: Rasmussen encephalitis: Axial FSE T2 illustrates the last control of this patient in 2013, note the important cortico-subcortical atrophy of the left cerebral hemisphere associated with a diffuse high signal (a, b, c). Enhancement is absent (d).

Anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis

This entity has been reported in 60% of women with ovarian cancer [24] but recently it has also been identified in infants and adolescents without tumors [25]. NMDARE symptoms in the initial phase include a flu-like illness followed by psychiatric disorders such as psychosis, hallucinations, anxiety, agitation, and paranoia; hyperactivity dominates in children. Altered levels of consciousness, severe dysautonomia, central hypoventilation, orofacial dyskinesias and seizures are common [26].

CT scans of the brain are normal. MRI may also be normal or demonstrate nonspecific anomalies in T2-weighted or FLAIR sequences in the mesial temporal lobes, cerebral cortex, cerebellum, basal ganglia or brainstem. Contrast enhancement is infrequent, a meningeal or cortical enhancement can be observed. In the chronic stage cerebral atrophy can be encountered [24].

Antibodies directed against glutamic acid decarboxylase (anti-GAD)

Anti-GAD is a rare encephalitis characterized by psychiatric symptoms, stiff syndrome, subacute memory loss, and seizures [27] and is potentially partially reversible if the diagnosis is early.

MRI may be normal or can show anomalies implicating the mesial temporal lobe and the hippocampi [27] which are enlarged with a high signal. Follow-up MR shows an atrophy of the hippocampi and of the cerebral parenchyma.

Glutamine and glutamate levels are increased in the region of seizure onset in patients with anti-GAD antibodies compared to the contralateral side or in control subjects leading to atrophy [28].

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