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Rasmussens encephalitis: Early diagnostic criteria in children

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ABSTRACT

Rasmussens encephalitis (RE) is a rare chronic inflammatory brain disorder resulting in progressive neurodegeneration in one cerebral hemisphere. The inflammatory process is accompanied by progressive loss of function of the affected hemisphere, associated with drug-resistant partial epilepsy. The diagnosis is based on a range of clinical, electroencephalographic, radiological and biochemical arguments, without any specific formal marker, which makes the diagnosis of the disease complex, especially in its initial phase. Seizures are refractory to anti-seizures medication (ASM) and to classical immunomodulatory treatments. These treatments are also ineffective to stop the degenerative process. Only surgical treatment with hemispherotomy (surgical disconnection of a cerebral hemisphere) allows definitive cessation of seizures but this leads to definitive motor and cognitive deficits. The etiology of RE is not known, but there is strong evidence for an immunopathogenic mechanism involving T-cell mediated immunity. The emergence of biotherapies targeting against various cytokines offers potential therapeutic perspectives. This disease is currently a real challenge in terms of: (i) early diagnosis, before the constitution of marked hemispheric atrophy and the appearance of neurological and cognitive consequences; (ii) recognition of incomplete form; (iii) therapeutic management due to advances in the field of targeted treatment of inflammation; (iv) surgery and recovery possibilities.

1. Introduction

Rasmussens encephalitis (RE) is a rare chronic inflammatory brain disorder resulting in progressive neurodegeneration in

one cerebral hemisphere. The inflammatory process is accompanied by progressive loss of function of the affected hemisphere, associated with drug-resistant partial epilepsy [1–3]. The diagnosis is based on a range of clinical, electroencephalographic, radiological and biochemical arguments,

without any specific formal marker, which makes the diagnosis of the disease complex, especially in its initial phase. Seizures are refractory to anti-seizures medication (ASM) and to classical immunomodulatory treatments. These treatments are also ineffective to stop the degenerative process [4,5]. Only surgical treatment with hemispherotomy (surgical disconnection of a cerebral hemisphere) allows definitive cessation of seizures but this leads to definitive motor and cognitive deficits [4-6]. The etiology of RE is not known, but there is strong evidence for an immunopathogenic mechanism involving T-cell mediated immunity. The emergence of biotherapies targeting against various cytokines offers potential therapeutic perspectives [7,8]. This disease is currently a real challenge in terms of: (i) early diagnosis, before the constitution of marked hemispheric atrophy and the appearance of neurological and cognitive consequences; (ii) recognition of incomplete form; (iii) therapeutic management due to advances in the field of targeted treatment of inflammation; (iv) surgery and recovery possibilities.

2. History and diagnosis

RE is a rare disease, affecting both sexes indiscriminately and with no known ethnic or geographic predisposition. The incidence is estimated to be between 0.18 per 100,000 people [8].

The clinical history of typical RE was described in the late 20th century by Oguni et al. [2] from 48 observations in Montreal. In 30-50% of cases, there was an infectious or inflammatory event within six months prior to disease onset [2,9,10]. The disease was described in three stages: an early stage (stage 1) characterized by the onset of partial epilepsy, the possible presence of a transient motor deficit and the absence of cognitive deficit; an acute stage (stage 2) characterized by the installation of constitutive deficits (hemianopia, hemiparesis), the presence of cognitive deficit responsible for progressive cognitive deterioration while the epilepsy worsens; and a late stage (stage 3), when seizures are less frequent with persistent severe and stable motor and cognitive deficits. At the beginning of the disease focal and/or generalized seizures can be observed and continuous partial epilepsy is present in a quarter of patients, the latter reaching 50 to 90% of patients in the acute stage depending on the studies.

Because of the difficulty of the diagnosis, diagnostic criteria were developed and published in 2005 by Bien et al. [5]. These criteria are grouped in two parts with three criteria for each (Table 1). Part A contains clinical, electromyography (EEG) and radiological criteria. To fulfill the diagnostic conditions in part A there are in fact five and not three criteria: two clinical criteria-focal seizures and motor deficit; one electrophysiological criterion-the EEG pattern (Table 1); and two radiological criteria, magnetic resonance imaging (MRI) identification of unilateral cortical atrophy with a T2 hypersignal or Flair in the white matter and the gray matter, or atrophy of the head of the caudate nucleus. In part B, two out of three clinical criteria are required. The clinical and radiological criteria require a progression of the symptoms in two successive exams (Figs. 1-5). The last criterion is histological obtained by a brain biopsy. The histology must demonstrate the presence of T cells with activation of microglial cells and astrocytic gliosis [1,11-13]. The brain biopsy may be risky if it is in a functional area. However, this biopsy may be negative since the foci of inflammation are scattered.

Currently, there are no biological markers that can be used to conclude or exclude the diagnosis of RE. The presence of oligoclonal bands, elevated protein levels and hypercellularity in the cerebrospinal fluid (CSF) are found in about 50% of cases [5].

3. Different forms of RE

Several forms of RE have been described since the 2000s [5,10]. The early childhood-onset rapidly progressive type fulfills the conditions of Biens criteria. It affects young children with an onset before the age of 10 years with an average age at disease manifestations of six years of age. Stages 1 and 2 described by Oguni et al. [2] are clearly identifiable. The prodromal stage (stage 1 of Oguni et al.) may be rather non-specific with a relatively low seizure frequency and rarely mild hemiparesis with a median duration of 7.1 m (0 months - 8 years). Following this, the worsening phase is clear and rapid. All patients enter an acute stage (stage 2 of Oguni et al.) characterized by frequent seizures. One-third of patients start the disease at this acute stage. It is characterized by high frequency seizures, mostly focal motor seizures, often in the form of *epilepsia partialis continua* (EPC). The neurological deterioration beco-

Table 1 – Clinical criteria for Rasmussen encephalitis, adapted from Bien et al., 2005.

Part A	Need 3/3 – 5 criteria
Clinical	Focal seizures (+ <i>epilepsia partialis continua</i>) AND unilateral cortical deficit(s)
EEG	Unihemispheric slowing ± epileptiform activity AND unilateral focal seizure onset
MRI	Gray or white matter T2/Flair hyperintense signal, hyperintense signal or atrophy of ipsilateral caudate head
Part B	Need 2/3
Clinical	EPC or progressive ^a unilateral cortical deficit(s)
MRI	Progressive ^a unihemispheric focal cortical atrophy
Histopathology	T-cell dominated encephalitis with activated microglial cells (cerebral biopsy)

Patient has to meet A or B criteria.

^a Progressive means that at least two sequential clinical examinations and MRI studies are necessary to conclude.

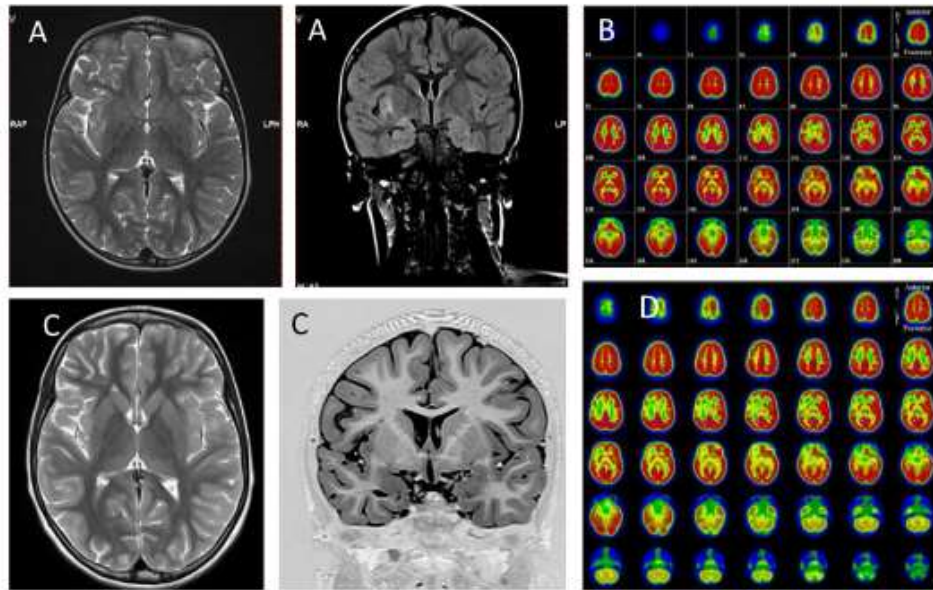


Fig. 1 – Girl, 3.5 years old. Left opercular seizure. A. First MRI three months after the first seizure Flair and T2 hyperintensity in the right peri-insular region. B. PET Scan: hypometabolism affecting the right orbital region, the temporal pole and the opercular region C. 5 years later: slight right hemiatrophy predominant around the peri-insular area. D. PET scan: marked hypometabolism in the frontal, orbital, opercular and right insular regions.

mes manifest by progressive hemiparesis, hemianopia, cognitive deterioration and aphasia if the language dominant hemisphere is affected. Hemispheric cortical atrophy occurs rapidly.

The slow progressive late-onset form concerns adolescents and adults. The age of onset ranges from six years to 58 years across studies. The different stages described by Oguni et al. [2] are difficult to distinguish. The usual presentation is drug-resistant partial temporal or temporoperinsular epilepsy. Hemispheric atrophy is slow and may develop after several years of epilepsy. The motor deficit is inconstant. Cognitive deterioration is slow. In these forms, females are strongly represented (79%), the EPC is present in 31% of cases. Thus, the absence of EPC, cognitive deterioration and the absence of hypersignal and/or atrophy on MRI should not exclude the diagnosis. This slow evolution with the absence of motor or cognitive deficits explains the delay in diagnosis of these forms [14].

Atypical forms of RE correspond to RE in which epilepsy does not precede motor and or cognitive deficits. Rare cases have been reported with motor impairment (chorea, athetosis, hemiparesis) or cognitive impairment. Epilepsy starts later or is absent. MRI reveals damage to the caudate nucleus, the lenticular nucleus, and or hemispheric atrophy which may precede the onset of epilepsy [15–20]. Other atypical features of RE has been reported by Olson et al. [21] such as signal change without atrophy, ipsilateral or contralateral cerebellar atrophy on MRI, lack of epilepsy or generalized seizures, bilateral slowing and epileptiform activity on EEG, dual

pathology with cortical focal dysplasia and RE on histopathology [22].

Bilateralization of RE is probably very exceptional: only nine cases out of more than 200 patients were reported before 2005 [5], but three of them were probably not RE [5]. There has been no report of a patient with contralateral hemisphere involvement after surgical treatment of RE.

The diagnosis of RE is therefore based on the clinical course and coexistence of clinical, electroencephalographic, radiological symptoms and cognitive deficit and/or cognitive and behavioral deterioration. The absence of strong biological markers is a limitation for diagnosis. The differential diagnoses are described in Table 2.

4. Diagnostic orientation towards RE

At the beginning of the epilepsy and/or in case of drug-resistant epilepsy, one might believe that focal cortical dysplasia (FCD) with normal MRI is the cause of the disease [23].

The EEG is the main complementary examination. EEG analyses in RE show that there is asymmetric slowing of the background activity, with unilateral paroxysmal abnormalities on the same side. The EEG may show one or more foci on the same side of seizure onset. The paroxysmal abnormalities may be bilateral [24]. One study compared EEG performed in the first four years of epilepsy in patients with RE and FCD [25]. The diagnosis of RE was based on Biens criteria. The analysis

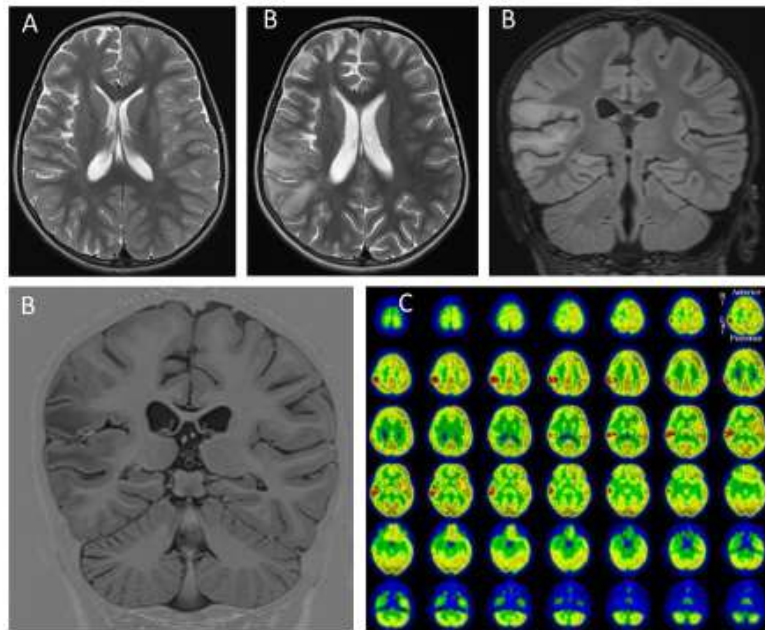


Fig. 2 – Girl, 4.5 years old. CPE started one week after the first left brachiofacial seizure. A. First MRI one week after the first seizure: atrophy of the right hemisphere with predominant frontal insular area atrophy B. Second MRI, 3 months later: CPE on the left side including the face, the arm and the leg. T2 and Flair hyperintensity in the right peri-insular and frontal areas with T1 (inversion recovery) hypointensity. C. Intense focal hypermetabolism involving the rolandic and right opercular region with a relative right hemispheric cortical hypometabolism.

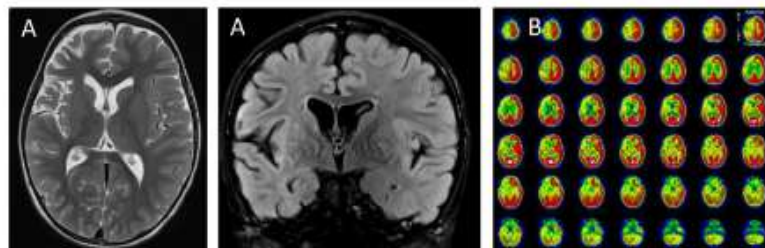


Fig. 3 – Girl, 3.5 years old, left hemiclonic seizures. A. MRI one month after the beginning of the epilepsy. Atrophy of the right hemisphere. B. PETscan at the same time: large hypometabolism on the right hemisphere.

on the first year of epilepsy concerned 10 patients with RE and six patients with FCD. Altered background activity was possible in both diagnoses at three months of epilepsy onset (8/10 for RE versus 6/9 for FCD). However, it was always more asymmetric in patients with RE. This article also confirmed the negative cognitive impact of contralateral paroxysmal abnormalities in RE (Figs. 6 and 7).

Positron emission tomography (PET) studies show focal or multifocal hypometabolism or hypometabolism extended to a

hemisphere. This hypometabolism in RE is larger than the epileptic area expected from the clinical, EEG and MRI analysis [26–28]. PET and single photon emission computed tomography (SPECT) are not suitable for defining the inflammatory nature of the disease. However, they may help in confirming the unihemispheric nature in suspected early RE findings.

In conclusion, the diagnosis of early infantile forms is quickly made because Biens' criteria are efficient. The diagnosis is more difficult for slowly evolving forms and

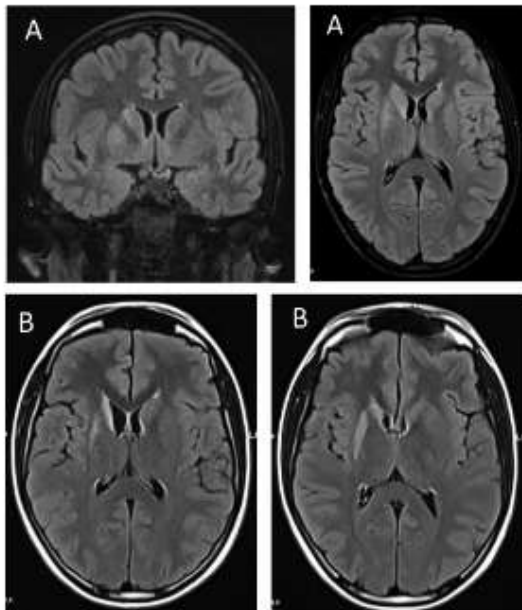


Fig. 4 – Boy, 13 years old, rapidly progressive left hemidystonia. Frontal and temporal focal seizures at 14 years. A. First MRI at 13 years: Flair hyperintensity in the right putamen and caudate nucleus. B. Two years later: slight atrophy of the right hemisphere, with Flair hyperintensity of the right putamen and marked atrophy of caudate nucleus.

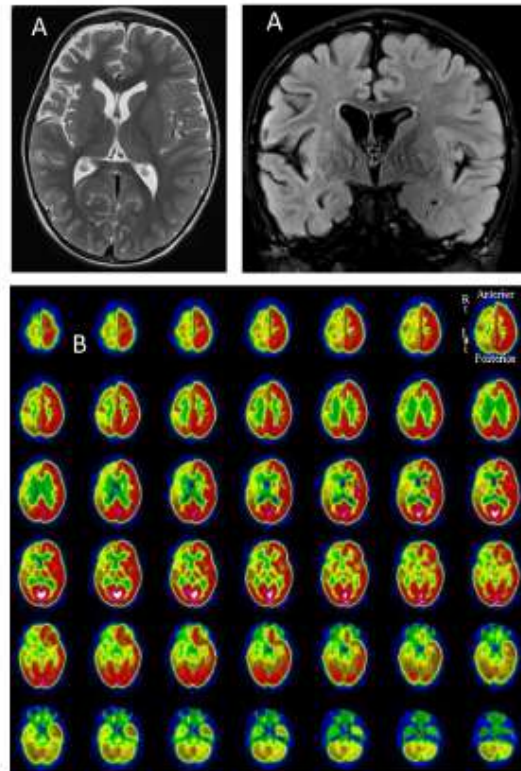


Fig. 5 – Girl, 3.5 years old, left hemiclonic seizures. A. MRI one month after the beginning of the epilepsy. Atrophy of the right hemisphere. B. PETscan at the same time: large hypometabolism on the right hemisphere.

atypical forms. Slowly evolving forms only meet Biens criteria very late. The diagnosis of RE should be evoked in patients with a presentation of “refractory temporal epilepsy”. In case of atypical forms, the absence of partial epilepsy at the beginning of the clinical symptoms (motor or cognitive deficit) leads to diagnostic erraticism.

5. Place of the RE in the immune-mediated diseases of the central nervous system in childhood

The clinical spectrum of these conditions is increasingly expanding, and the underlying mechanisms of dysregulation of the immune system can vary greatly. Different pathogenic mechanisms have been identified, such as cell-mediated and antibody-mediated, infection-triggered, paraneoplastic, and genetically defined mechanisms that can occur in previously healthy children and can contribute to different stages of the disease. The majority of these disorders have an acute onset and a self-limited course, but at other times, they can represent the first episode of a more chronic condition. Their detection and appropriate management is of paramount

importance, due to the possible chronic sequelae and disease burden they could cause [8,29].

The challenge is therefore to diagnose RE as early as possible in order to start immunosuppressive therapies before neurocognitive deterioration and before the development of hemispheric atrophy. Even in the absence of an etiology, immunological data converge on the major role of T lymphocytes in the inflammation and of memory T lymphocytes. The reactivation of the latter at the onset of epilepsy or during an infectious event is one of the hypotheses for the onset of the disease [30]. ASM, corticosteroid therapy [31], immunoglobulin treatments and plasmapheresis and protein A IgG immunoadsorption [5,32–34] allow a certain, usually transient, stabilization but do not control the seizures or slow down the cognitive and motor deterioration in rapidly evolving forms. In this rapidly progressive form, hemispherotomy is the effective treatment to stop seizures and cognitive decline [5]. In contrast, the interest of immunotherapy has been highlighted for patients in whom hemispherotomy is relatively or absolutely contraindicated (e.g.,

Table 2 – Differential diagnosis and explorations according to Bien et al. [5].

Unihemispheric epileptic syndromes	Clinical and laboratory criteria
Cortical dysplasia, hemimegalencephaly, tuberous sclerosis, Sturge-Weber-syndrome, stroke, tumor Hemiconvulsion-hemiplegia-epilepsy-syndrome	Focal seizures in infancy or early childhood MRI with gadolinium No progression on MRI Usually occurring in infancy, initial (tonic-) clonic unilateral seizures presenting as status epilepticus Early MRI: diffuse cytotoxic edema of the whole hemisphere Hemiparesis, hemiatrophic hemisphere on MRI and focal epilepsy
Epilepsia partialis continua (EPC) due to metabolic disorders Diabetes mellitus: Ketotic/non-ketotic hyperglycemia, type I diabetes and anti-GAD-65-antibodies, renal or hepatic encephalopathy Metabolic or degenerative progressive neurological diseases MELAS and other mitochondrialopathies Alpers syndrome or polymerase gamma-related disorders	History, blood tests, anti-GAD-65-antibodies Blood-lactate, mitochondrial DNA genetic testing for mutations, muscle biopsy fi, progressive illness, EEG: bilateral abnormalities, MRI: T2 hyperintensity in the occipital lobes and thalami, liver impairments Autosomal recessive mutations in the DNA Polymerase gamma, catalytic subunit (POLG) gene
Inflammatory/infectious diseases Cerebral vasculitis in systemic connective tissue disease (e.g. lupus erythematosus)	History, other clinical features, blood abnormalities (ANA, ANCA), antiphospholipid antibodies (anticardiolipin antibody, anti-beta-2-glycoprotein-I (a β ,GPI) antibody) anti-Ro/SSA antibody anti-double-stranded DNA (anti-dsDNA) antibodies anti-thyroglobulin, anti-thyroid peroxidase History, others clinical features, movement disorders, psychiatric features
Autoimmune encephalitis Antibodies: autoimmune encephalitis with intracellular antigens Autoimmune encephalitis with cell-surface antigens Paraneoplastic syndrome	Autoantibodies (blood and CSF), anti-neuronal antibodies, anti GQ1b, GD1b, GM1, GM2, anti-HU (a,b)
Subacute sclerosing panencephalitis and other delayed subacute measles encephalitis with or without immunodeficiency Multiple sclerosis	History, vaccination status, early measles, EEG: periodic discharges, measles-antibodies in CSF History of previous episodes, additional deficits, MRI, CSF; oligoclonal bands
Creutzfeldt-Jakob-disease Infectious diseases	CSF, EEG, MRI antibody tests: HIV, HSV1, HSV 2, Syphilis, CMV, EBV, HHV6, mycoplasma, chlamydiae, Borrelia burgdorferi, Bartonella henselae

For more details about auto-immune encephalitis see (i) Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis. American Journal of Neuroradiology June 2017, 38 (6) 1070-1078 and (ii) Muniz-Castrillo S, Joubert B, Vogrig A, Honnorat J. Diagnostic des encéphalites auto-immunes [Diagnosis of autoimmune encephalitis: An update] Pratique neurologique-FMC, vol 11, issue 4, dec 2020, 227-237.

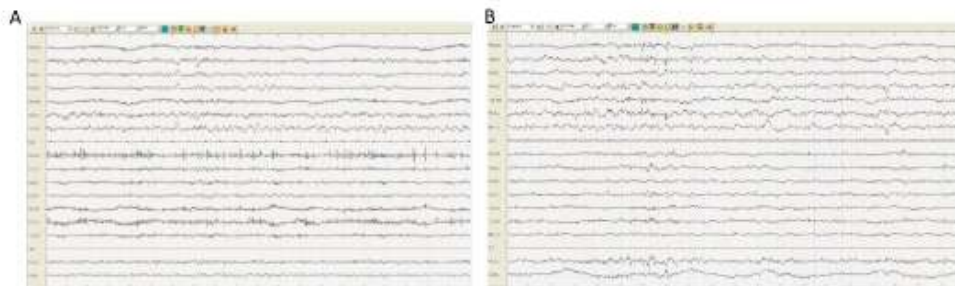


Fig. 6 – A. Slow background activity on the right hemisphere. CPE of the felt upper lip, recording of the muscular contraction on FP1-F3; F7-T3. B. Multifocal spikes on the right hemisphere.



Fig. 7 – Three consecutive EEGs if the same child A. One month after the first seizure: slow activity on the right central area. B. Two months after the first seizure, CPE increased slow activity on the right hemisphere, normal background activity on the left hemisphere C: three months after the first seizure: diffusion of the slow activity on the left hemisphere.

those with late-onset forms, dominant hemisphere disease or mild existing deficit). Due to the contribution of T cells to RE, specific immunotherapy, such as tacrolimus [35–37], rituximab [38] as well as adalimumab [39] could be an interesting treatment.

5.1. Treatment management

After the onset of epilepsy, and often before the diagnosis of RE, treatment with ASM is usually initiated because partial seizures are predominant symptoms. Any patient suspected of having RE should be referred to a specialized epilepsy center. Immunomodulatory therapies are proposed when the diagnosis is suspected or confirmed.

5.2. Immunotherapy

Corticosteroids: there are different protocols: boluses of intravenous methylprednisolone (400 mg/m²/day or 30 mg/kg/day for 5 days) followed or not by prednisolone or prednisone (1–2 mg/kg/day per os). Corticosteroid pulse therapy is proposed at an interval of once a month for several months to several years, depending on response.

Intravenous immunoglobulin (IVIg) therapy: the protocol for regular IVIg therapy can be 2 mg/kg for three to five days at an interval of once a month for several months to several years depending on response.

It is possible to propose a treatment combining corticosteroids followed by immunoglobulins every month.

Specific immunotherapy: adalimumab 24 mg/m² with a maximum of 40 mg via subcutaneous injection every seven or 14 days [39]; rituximab 375 mg/m² two infusions 15 days apart [38]; tacrolimus starting dose of 0.1 mg/kg/day (for children) with dose escalation after two months, depending on blood levels of tacrolimus (5 and 20 ng/ml) [35–37].

Evaluation of the benefit of these treatments is necessary and surgery should be regularly discussed with the family to avoid cognitive deterioration and to stop the seizures.

6. Conclusion

According to the International League Against Epilepsy, patients displaying drug-resistant epilepsy (failure of two ASMs) must be referred to an epilepsy center. Complementary investigations such as video-EEG seizure recording, cognitive

evaluation, CSF exploration and brain imaging including MRI and PET scan should be performed. A strong suspicion of RE should allow the use of immunomodulatory therapies in association with ASMs. The appearance of a unilateral cortical deficit and unihemispheric atrophy will confirm the diagnosis. If pharmacological treatments fail, surgical treatment (hemispherotomy) should be considered.

Early diagnosis of RE may allow to propose anti-inflammatory therapies before visible neurological deterioration. Evoking the diagnosis of RE in case of drug-resistant epilepsy should become a reflex for neuropsychiatrists and neurologists.

Disclosure of interest

The authors declare that they have no competing interest.

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