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LIMBIC ENCEPHALITIS SPECTRUM

Thesis

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By

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Herpetic encephalitis

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SUMMARY

INTRODUCTION

Limbic encephalitis are neurological manifestations associating in general anterograde memory disorders, an epilepsy and neuropsychiatric disorders of acute or sub-acute evolution.

Their etiologies are often inflammatory, dysimmune or infectious.

The diagnosis of limbic encephalitis, the most frequent and the most urgent to spread, corresponds to the herpetic encephalitis. It is about a therapeutic emergency given the risk of necrotic lesion progression with the irreversibility of symptomatology.

Until the end of 1990s, non-infectious encephalitis were considered as paraneoplastic. For 12 years, the spectrum of encephalitis has widened, especially with the discovery of antibodies against antigenic membrane or intracellular neuronal targets by Dalmau and his (her) collaborators in cases of limbic encephalitis, which revolutionized the field of paraneoplastic and autoimmune encephalitis.

Initially restricted to paraneoplastic limbic encephalitis associated with ovarian teratomas, the field of encephalitis anti-NMDA-R spread over the publications of the last three years with the description, in particular in males and in children of autoimmune forms without associated tumor.

The clinical spectre of the induced neurological disease by the presence of these antibodies is however remained remarkably constant in its descriptions: picture is stereotyped and very evocative.

This is what makes the importance of the evocation of diagnosis because the spontaneous prognosis is severe while effective therapeutic attitude are available though not codified and that the precocity of their implementation is probably an important prognostic factor.

The limbic encephalitis are defined clinically and pathologically by the

inflammatory disease all or part of the limbic system. This system which comprises the inner part of the temporal lobes, hippocampus and amygdala, Cingulate Gyrus, the fornix, the septum, fronto- basal structures and hypothalamus.

Neurological dysfunction associated with the disease of these structures include memory disorders (anterograde amnesia), behavioral and emotional disorders (aggressiveness, fear, anxiety, apathy), vegetative disorders (thermoregulation, ventilation, arterial pressure, and, hypersalivation), sleep disorders, epileptic seizures and, in a very characteristic way anti-NMDA-R encephalitis, abnormal movements

The clinical suspicion of limbic disease can be consolidated by the EEG data and magnetic resonance imaging (MRI).

The treatment of limbic encephalitis always respects two axes, etiological and symptomatic.

Etiological treatment may appeal to anti -infective agents (antiviral or antibiotic) as it can be immunological order in case of limbic autoimmune or paraneoplastic encephalitis. Thus, when a tumor is highlighted it is on its treatment that depend the prognosis and the clinical evolution of the limbic encephalitis

Symptomatic treatment is based on the treatment of epilepsy, hyponatremia, disorders of ventilation, insomnia, intestinal pseudo-obstruction, psychiatric disorders and dysautonomia.

The descriptions of the cognitive disorders involved in the long-term prognosis of this disease were little discussed in the literature. Indeed, crossed the acute episode, residual cognitive disorders determine the return at home and the autonomy of the patients. A more precise description is necessary to better support patients, possibly adapt professional recovery and better anticipate the difficulties.

We describe in this work 22 cases of Moroccan patients retrospectively

collected within the University Hospital Hassan II, from which we shall try to approach more exactly these various aspects of the disease.

OVERVIEW

Anatomical reminder

The structures of the telencephalon with their marginal areas and their connections to sub-cortical centers are gathered under the name of the limbic system. It is not here about a system of compact or orderly individualized pathways, but rather about a core assembly and cortical areas very functionally linked. We also describe this system as the visceral or emotional brain to evoke the importance of its functional significance. This concept of limbic system is based on functional considerations; the anatomical structures that underlie it are only defined imprecisely.

The limbic system is buried inside the temporal lobe of the brain and it can be likened to the emotional brain. The limbic system has also an essential role in memory and learning ability.

The limbic system is at the origin of the emotions and it has a center of reward, seat mechanisms of euphoriants action, so addictive effects of drugs such as opiates but also chocolate or extreme sports. When we think, perceive, feel, we estimate automatically the produced effect: positive, neutral or negative, we automatically evaluate the effect: positive, neutral or negative. This evaluation is ultrafast (less than 100 milliseconds) and takes place unconsciously. Our limbic system reacts instantly to our thoughts and sends the information to the brainstem, causing various reactions in our body.

The limbic system consists mainly of 4 formations:

- The limbic lobe
- The intra-limbic convolution
- The nuclei (central) amygdalia
- Septal area

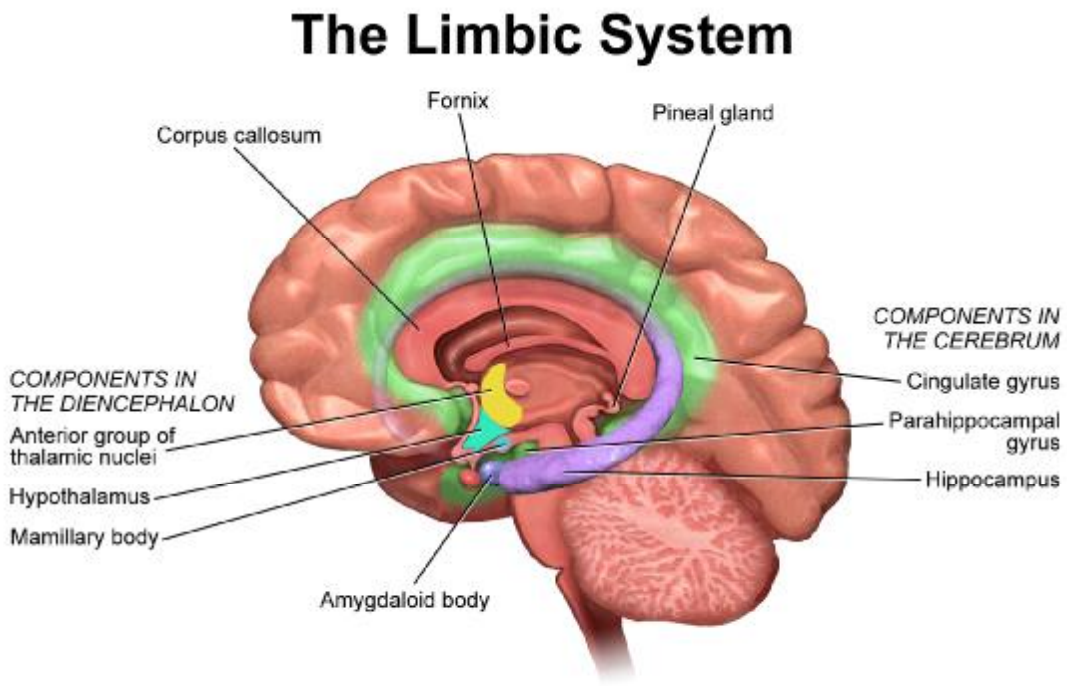


Fig. 1 : median sagittal section of the brain showing the structures of the limbic system.

The cortical regions belonging to the limbic system form a ring complex to the medial aspect of the hemispheres including: parahippocampal gyrus, the cingulate gyrus, subcallous area. The cingulate gyrus also described as limbic gyrus, gave its name to the system. At the medial surface of the hemispheres, we can distinguish an internal arc and an outer arc. The outer arc is formed by marginal areas and by the gray indusium of the corpus callosum. The internal arc is constituted of the hippocampal formation, of fornix, of the septum region, of the diagonal band of Broca and of para- terminal gyrus. Amygdala is another important component. Some subcortical nuclei having close connections with the limbic cortex are also included in this system such as: mammillary body, the anterior thalamic nucleus, habenulaire ganglion, and at the midbrain, the dorsal tegmental nucleus, the ventral tegmental nucleus and the inter- pedicle nucleus.

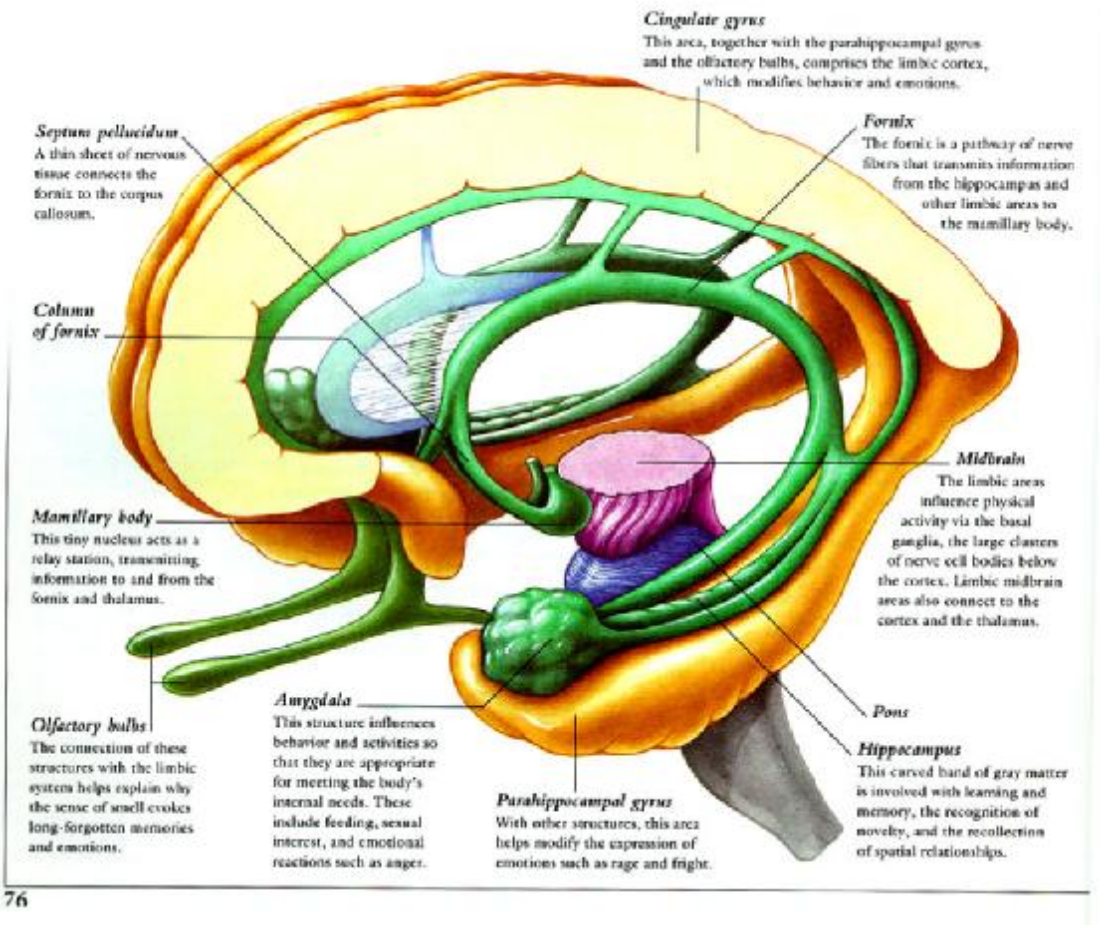

Cingulate gyrus
This area, together with the parahippocampal gyrus and the olfactory bulbs, comprises the limbic cortex, which modifies behavior and emotions.
Septum pellucidum
A thin sheet of nervous tissue connects the fornix to the corpus callosum.
Fornix
The fornix is a pathway of nerve fibers that transmits information from the hippocampus and other limbic areas to the mamillary body.
Column of fornix
Midbrain
The limbic areas influence physical activity via the basal ganglia, the large clusters of nerve cell bodies below the cortex. Limbic midbrain areas also connect to the cortex and the thalamus.
Mamillary body
This tiny nucleus acts as a relay station, transmitting information to and from the fornix and thalamus.
Pons
Hippocampus
This curved band of gray matter is involved with learning and memory, the recognition of novelty, and the recollection of spatial relationships.
Amygdala
This structure influences behavior and activities so that they are appropriate for meeting the body's internal needs. These include feeding, sexual interest, and emotional reactions such as anger.
Olfactory bulbs
The connection of these structures with the limbic system helps explain why the sense of smell evokes long-forgotten memories and emotions.
Parahippocampal gyrus
With other structures, this area helps modify the expression of emotions such as rage and fright.
76

Fig. 2

The limbic system is attached to the olfactory centers via several fiber bundles. The fibers of the lateral olfactory streak end in the cortical parts of the amygdala.

The limbic system influences the hypothalamus via three ways:

- The fornix, of which pre-commissurales fibers lead to the preoptic area and in the nuclei of the tuber cinereum.
- Stria terminalis that the amygdala also goes to the nuclei of the tuber.
- The ventral amygdalfuges fibers.

The connections of which the nuclei of midbrain tegmentum are assured by the downlink beams of the Habenular Nucleus through channels of mammillary body. On this occasion, the efferent mamilo-tegmentale beam and the relative peduncle of mammillary body constitute a neural circuit.

Within the limbic system walks the neural circuit of Papez, multi- synaptic. The efferent fibers of hippocampus affect the mammillary body via the fornix. Hence, the influx are transmitted to the beam of Vicq d' Azyr, which goes to the anterior thalamic nucleus. The latter is projected on the cortex cingulate gyrus from which the fiber bundles return to the hippocampus through the cingulum.

The connections of neocortex with the limbic system exist particularly at the entorhinal cortex para- hippocampal gyrus, which is projected on the hippocampus.

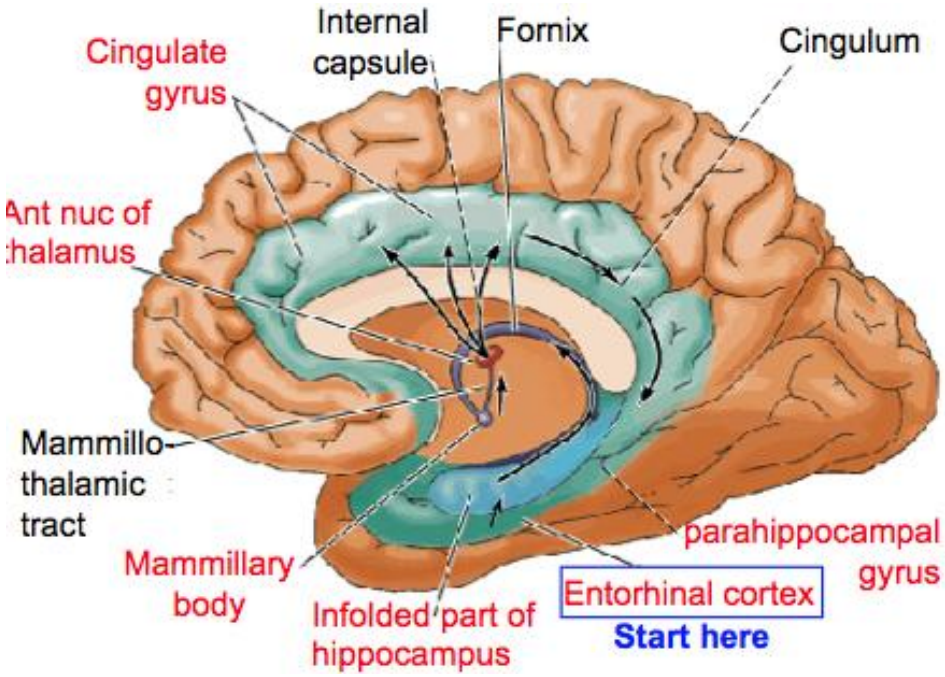


Fig. 3 : Papez circuit.

The encoded information is going to circulate in Papez circuit also called “Memory road”. The information passes through the anterior thalamic nucleus, the cingulate cortex, the fornix, the entorhinal cortex, hippocampus, the mammillary bodies, and then the anterior nucleus of the thalamus and so on. After several passages, the memory is stored.

I. The limbic lobe

The limbic lobe is a disposed ring around the penetration commissures within each hemisphere; its peripheral limit is shown clearly on top by the cingulate furrow and its sub- parietal extension; the collateral furrow constitutes its lower limit.

This territory is a component of the rhinencephalon, the brain of olfaction, which is an ancestral structure, presents even at anosmatic animals, without smell. It reached its full development in reptiles.These structures have declined sharply in primates and especially humans; therefore, olfactory function becomes secondary compared with other functions acquired in connection with the process of memory and emotional behavior.

It includes three formations; the two arranged in concentric rings, they are:

- The limbic lobe (LL) per se ; it circumscribes
- A threadlike ring, intra-limbic lobe (LL); the third is
- The olfactory lobe (OL) which constitutes the sensory component of rhinencephalon.

The ring of the limbic lobe itself includes:

- The cingulate gyrusor the convolution of the corpus callosum occupying the area between the groove of the same name and the groove of the corpus callosum.

- The hippocampal gyrus, corresponding to the fifth temporal convolution (T5); the ring is completed by the area under calloused in front, and the Isthmus backwards.

The intra-limbic lobe, it is about a filamentary or banded ring by location, vestige of an atrophied convolution.

The olfactory lobe is situated in the pre- chiasmal area, under each frontal lobe, close to the midline.

This lobe contains:

- the actual olfactory nerve
- The posterior olfactory lobe consisting of the uncal and the underlying the amygdala

II. The intra-limbic convolution

1. Hippocampus

It was originally thought that the hippocampus played a major role in the expression of the emotional behavior, because the subject, presenting serious injury of the hippocampus and nearby temporal structures, showing clear signs of emotional disturbances. Thereafter, it becomes clear that the most emotional changes produced by temporal lobe lesions were the result of the only damage of the amygdala. Although the hippocampal formation may have a role in the expression of emotion, circumscribed damage to the hippocampus show that it has a specific role in learning and memory processes.

The hippocampal formation is a cluster of laminated structures, which is above the parahippocampal gyrus, on the ventral side of the temporal lobe. Located just behind the amygdala, the hippocampal formation extends along the temporal horn of the lateral ventricle until it arrives at the splenium of the corpus callosum.

The hippocampal formation includes:

- The dentate gyrus
- The subiculum
- The Entorhinal cortex

The contoured shape of these structures reminiscent of a hippocampus, hence its name.

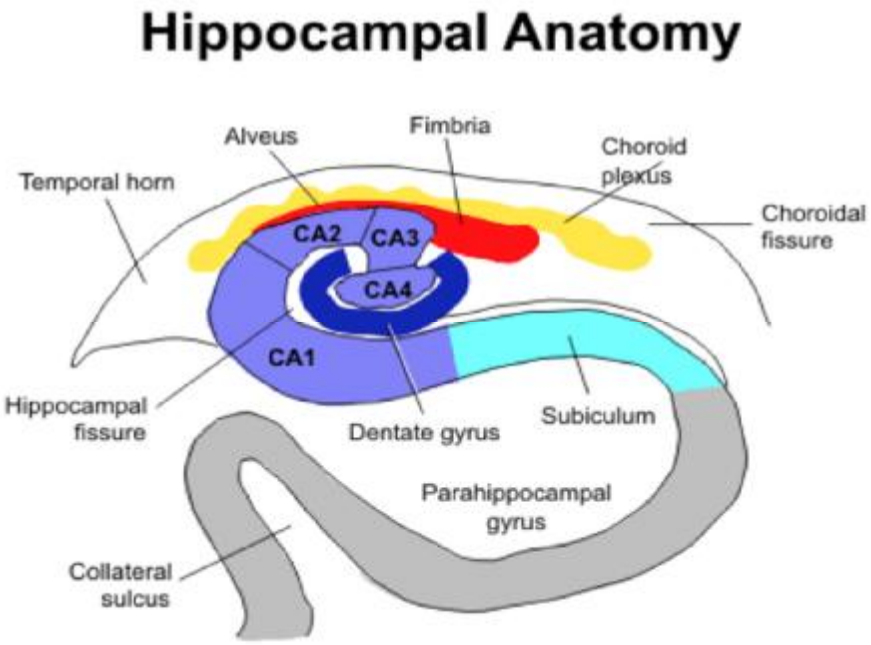

Hippocampal Anatomy
Alveus
Fimbria
Choroid plexus
Temporal horn
Choroidal fissure
CA2
CA3
CA4
CA1
Hippocampal fissure
Dentate gyrus
Subiculum
Parahippocampal gyrus
Collateral sulcus

Fig. 4

2. The fornix

The cerebral hemispheres are joined one to another by disparate formations called inter- hemispheric commissures: the corpus callosum, the fornix, the septum pellucidum and the anterior and posterior corners.

The cerebral fornix is not a corner in the strict meaning of the term since substantially all of its fibers remain ipsi –lateral.

III. Amygdaloid body

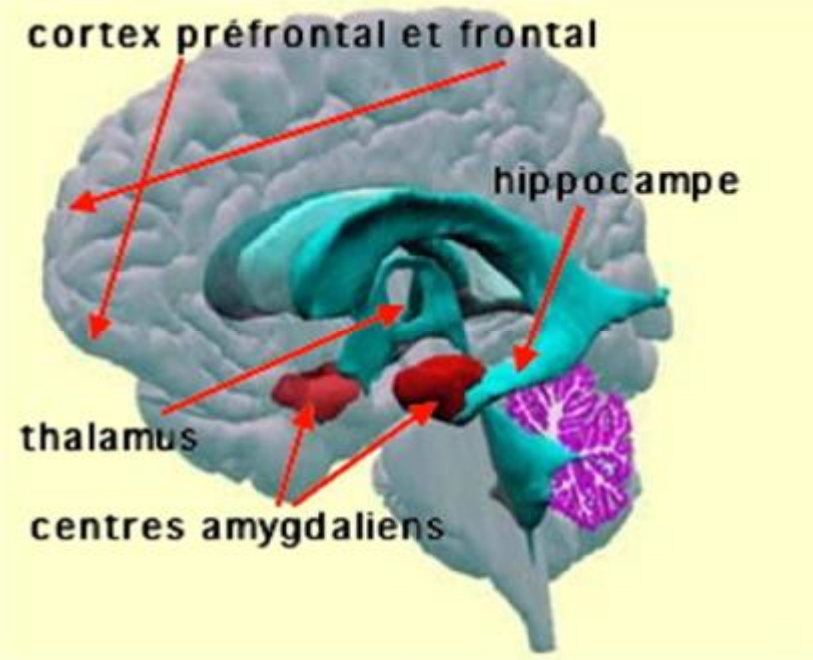


Fig. 5

The amygdala is a part of the brain, which takes its name from its shape reminiscent of an almond. As for the most structures of our brain, we have two tonsils. They are located close to the hippocampus in the front part of the temporal lobe.

The tonsil is essential in our ability to feel and perceive in others certain emotions. This is the case of fear, anger, acts of struggle, flight or stunning, but also medium-term sadness, the anxiety, and anguish and all physical changes that it causes.

The amygdala contains several nuclei, which differ in their neurochemical composition and in their afferent and efferent connections.

IV. Septal area:

It has massive connections with the hippocampus, which is the central structure of the limbic system. Cholinergic and GABAergic nuclei of the septal region project into the hippocampus and the dentate gyrus.

Electrical stimulation of the septal region as the amygdala stimulation can also trigger oral activities (lick, chew, swallow), excretory (defecation, micturition) and sexual (erection), the stimulation of the area of anterior commissure in humans, revealed a euphoric reaction and a general feeling of well-being.

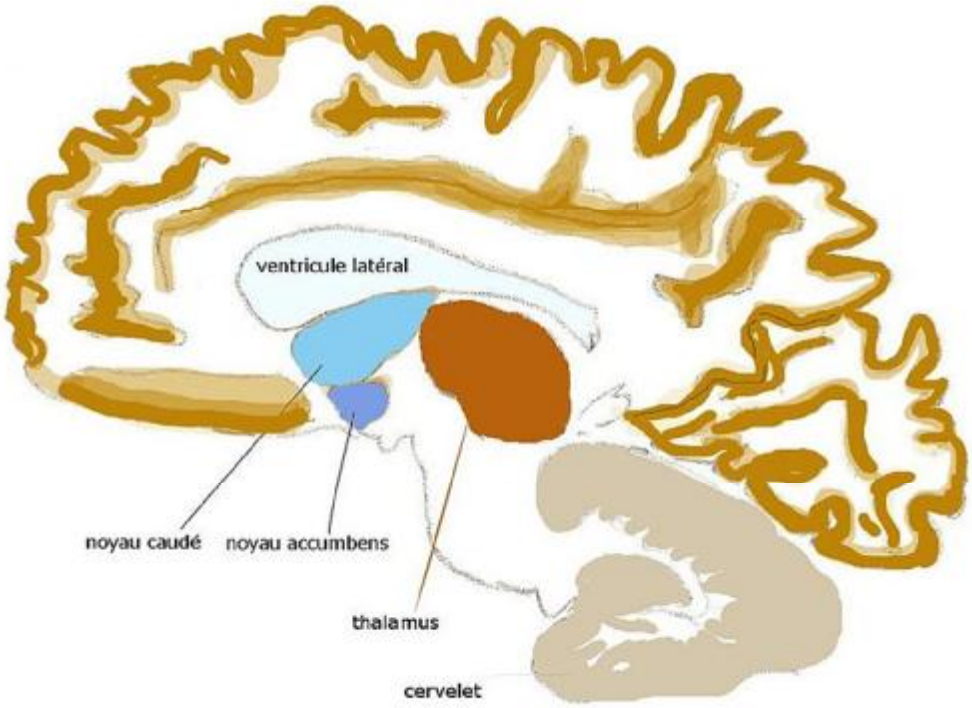

ventricule latéral
noyau caudé
noyau accumbens
thalamus
cervelet

Fig. 6

OUR STUDY

I. Material and methods :

We carried out a retrospective study between September 2008 and June 2015 in the case of twenty-two patients hospitalized within the service of neurology of the UHC (University Hospital Center) HASSAN II of Fes.

All our patients had the clinical picture of acute or subacute encephalitis associating to varying degrees cognitive disorders, behavioral change, clinical or infraclinical epileptic seizures, psychiatric impairment, meningeal syndrome, disorders of consciousness.

These patients all benefited from neurological and general clinical examination as well as from paraclinical examinations:

- Radiologic: nineteen patients benefited from a cerebral magnetic resonance imaging (MRI) (with sequences T2, Flair, Diffusion, T2 *, T1 without and with gadolinium), a cerebral tomography was realized in the case of three patients; a thoraco-abdominal pelvic tomography was realized in the case of five patients. An abdominal-pelvic and testicular ultrasound was realized in the case of the other patients.
- The biological exams : realized on the patients included: blood ionogram, creatininemia, uremia, glycemia, complete blood count (CBC), lumbar puncture with electrophoresis of proteins in the blood and cerebrospinal fluid, syphilitic serology, serology of lyme, viral serologies including HIV, dosage of the vitamin B12, TSHus, dosage of the thyroid hormones, antibody anti-thyroglobuline, anti-thyroperoxydase, dosage of the SPA(Specific Prostate Antigene). Onconeuronal antibodies (antibody anti Hu, anti Yo, anti CV2, anti My, amphiphysin, anti VGKC, anti NMDA,) were only realized in five cases due to lack of financial means in the case of the other patients.

A neuropsychological evaluation was carried out in almost all the patients with at least an Arabic MMSE version (mini mental state evaluation).

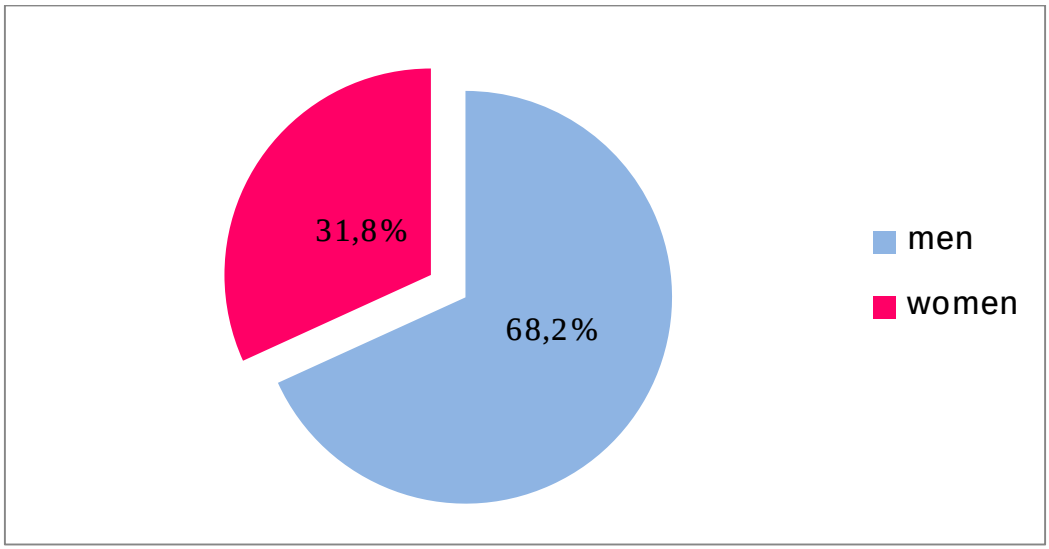
The clinical, paraclinical, therapeutic and evolutionary data were brought together.

II. Results :

1. Epidemiological data :

a. Distribution by sex :

We identified twenty-two patients including 15 men and 07 women with a male predominance of (68.2% of patients).



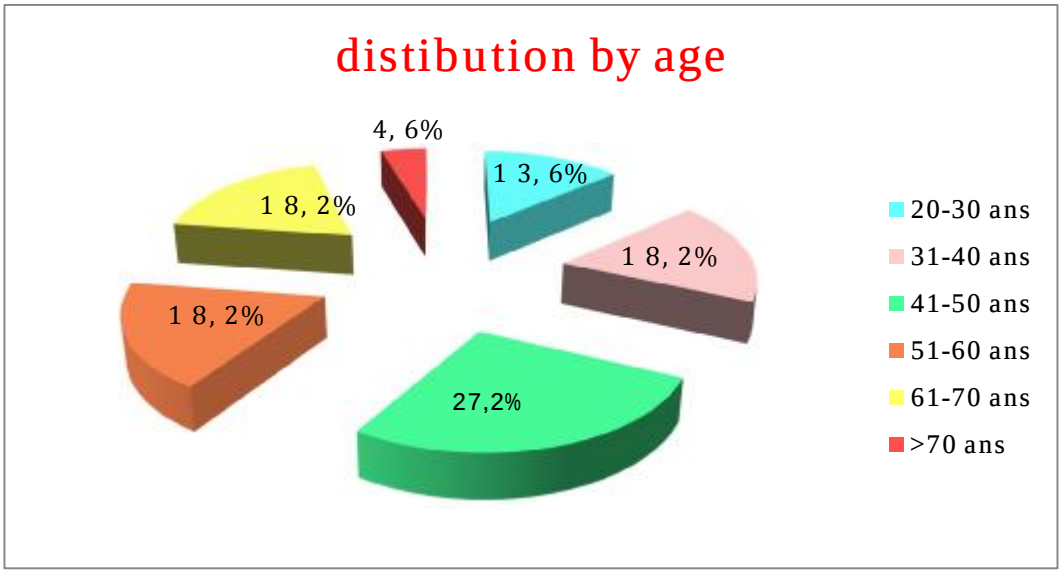
graphic 1 : distribution of our patients by sex

b. Distribution by antecedents :

We found an antecedent of hypothyroid in a female patient under Levothyrox, an antecedent of ovarian tumor in a female patient, cutaneous melanoma and another recent discovery of nasopharyngeal cancer in another female patient. Antecedent of cardiovascular disease: high blood pressure (hypertension) (n = 2), an acute coronary syndrome (n = 1). Finally, an antecedent of diabetes with insulin in the case of a male patient.

c. Age Distribution :

The average age of our patients is 47 years, mainly ranging from 24 to 75 years (Table 2), with a maximum of patients aged 41 to 50 years (6 patients representing 27.2% of cases). With an average follow up of 24 months. Ten patients disappeared, nine are still followed and three others died.



graphic 2 : distribution by age

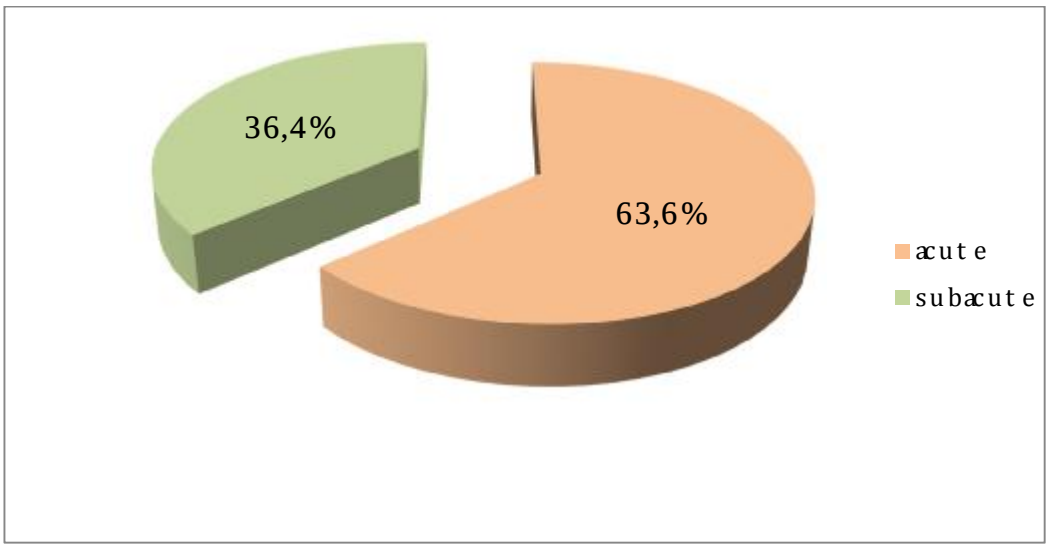
Table 1 : general characteristics of our patients.

Patient	Age	sex	Neoplastic history	Immunological history	Clinical history
1	38 ans	M	No	No	No
2	45 ans	M	No	No	No
3	50 ans	M	No	No	No
4	32 ans	M	No	No	No
5	24 ans	M	No	No	No
6	47 ans	M	No	No	No
7	53 ans	F	No	No	Coronary syndrome
8	36 ans	F	No	No	No
9	75 ans	M	No	No	HTA
10	34 ans	M	No	No	No
11	65 ans	F	Ovarian tumor	No	No
12	63 ans	M	Nasopharyngeal tumor	No	HTA
13	45 ans	M	No	No	No
14	54 ans	M	No	No	No
15	70 ans	F	Melanoma thigh	No	No
16	65 ans	M	No	No	No
17	53 ans	F	No	No	hypothyroidism
18	50 ans	M	No	No	No
19	24 ans	F	No	No	No
20	60 ans	M	No	No	diabetes
21	26 ans	F	No	No	No
22	50 ans	M	No	No	No

2.Clinical :

a. Clinical presentation :

The Clinical presentation was acute in fourteen cases (63.6%) or sub-acute in eight cases (36.4%) over several weeks.



graphic 3 : distribution by the onset mode

b. Clinical signs :

- Triggers and prodromes :

Six patients (27.2% of cases) presented viral type syndrome prodromes (fever, cephalees, vomiting) the day preceding the start of the infection.

- Psychiatric Presentation :

Neuropsychiatric impairment with behavioral disorders (hallucinations, agitation, delirium) being the fourth signal, is found in 10 patients (45.5% of cases).

- Epileptic disorders :

Ten patients (45.5% of cases) presented generalized tonic-clonic seizures including three cases of convulsive status epilepticus. One male patient had only presented inaugural generalized epileptic seizures without epilepsy events thereafter.

Three patients (13.6% of cases) have shown partial seizures at the beginning then subsequently the seizures became generalized. Clinical symptoms such as clonus of the face or of the limbs were attributed to partial seizures.

- Cognitive disorders :

Cognitive disorders, so evaluable, were constant. When patients were able to participate, complementary exams were performed remotely from the first symptoms. Neuropsychological achievement with anterograde memory disorders was observed in 50% of patients (11 patients) in relation to a limbic injury.

Language disorders associated with cognitive impairment were found in a female patient who presented aphasia.

The triad of temporal epilepsy, anterograde amnesia and neuropsychiatric manifestations was only found in five patients (22.7%)

- Consciousness troubles :

Twelve of our patients (54, 5% of the cases) developed consciousness disorders (ranging from a simple confusion to coma) during Epileptic seizure requiring mechanical ventilation.

The concomitant respiratory disorders are difficult due to the only pathology in case of patients who are sensible to status epilepticus or to repeated convulsive seizures treated with antiepileptic drugs. The other patients showed no ventilation problems.

- Dysautonomia :

Dysautonomia was found in five patients (22.7% of cases). It was manifested by Sphincter disorders (urinary incontinence in two patients) and a Tachycardia in three patients.

- Abnormal movements :

The Abnormal movements having appearance of non-epileptic nature occurred in two patients. It has been described an activity of chewing with the mouth bypass in a patient, and chorea upper limbs in the other.

The EEG did not find any epileptical features correlated to those manifestations

- Other symptoms :

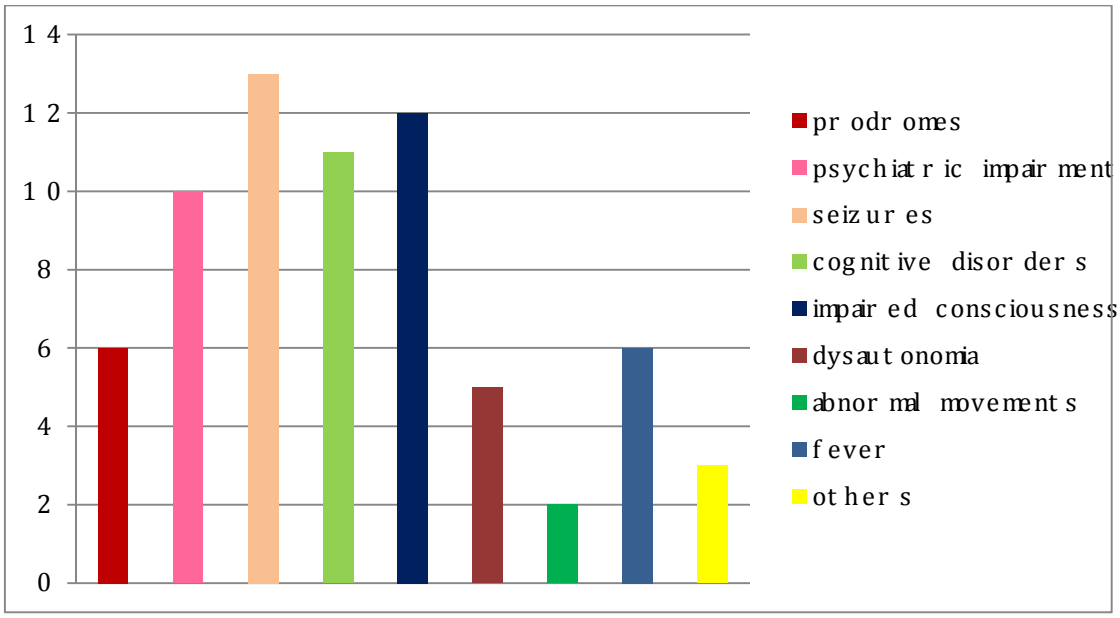
Other less typical clinical symptoms were identified. It is a chronic fever in six patients, headache in two patients and insomnia in a single patient.

A febrile meningeal syndrome was found in 32% of cases.

Table 2 : main clinical signs

Clinical signs	Number of cases	Percentage
neuropsychological impairment with anterograde memory disorders	11	50%
Seizures (status epilepticus inaugural)	13 (4)	59,10%
Neuropsychiatric impairment with behavior disorders	10	45,50%
fever	6	26,20%
Triad (temporal lobe epilepsy, anterograd amnesia, neuropsychiatric disorders	5	22,70%
Impaired consciousness	12	54,50%
Febrile meningeal syndrome	7	32%

Seizures and consciousness disorders are the most frequent signs as well as neuropsychological impairment with anterograde memory disorders and neuropsychiatric impairment with behavioral disorders.



graphic 4 : number of patients with each clinical symptom

Table 3 : distribution of different clinical signs in our patients

Patient	seizures	Neuropsychological and psychiatric impairment	Memory problems	Other clinical signs
1	partial seizures with secondary generalization	Behavioral disorders	Memory disorders	–
2	Widespread seizure	–	Memory disorders	–
3	Partial seizures with secondary generalization	–	–	–
4	–	Impaired consciousness	–	fever
5	Generalized TC seizures	Behavioral disorders	Memory disorders	–
6	Generalized TC seizures	–	Memory disorders	Headach, fever, vomiting
7	Generalized TC seizures	Psychiatric disorders	Memory disorders	–
8	–	–	Memory disorders	–
9	–	Impaired consciousness	–	–
10	–	confusion	–	fever
11	Generalized TC seizures	–	Memory disorders	–
12		confusion		fever
13	–	Psychiatric disorders, confusion	–	headach
14	Status epilepticus	Psychiatric disorders	–	–
15	–	Psychiatric disorders	–	–
16	Status epilepticus	Behavioral disorders	–	–
17	–	Behavioral disorders	dementia	–
18	Generalized TC seizures	Behavioral disorders and impaired consciousness	Memory disorders	Hypertension of both upper limbs
19	Status epilepticus	Impaired consciousness	–	Motor deficit
20	–	Behavioral disorders and impaired consciousness	Memory disorders	Fever, aphasia
21	Partial seizures with secondary generalization	Impaired consciousness	–	Fever, micturition burns
22	Generalized TC seizures	–	Memory disorders	–

3. Paraclinical characteristics :

a. The radiological data :

- Cerebral MRI (Magnetic Resonance Imaging) :

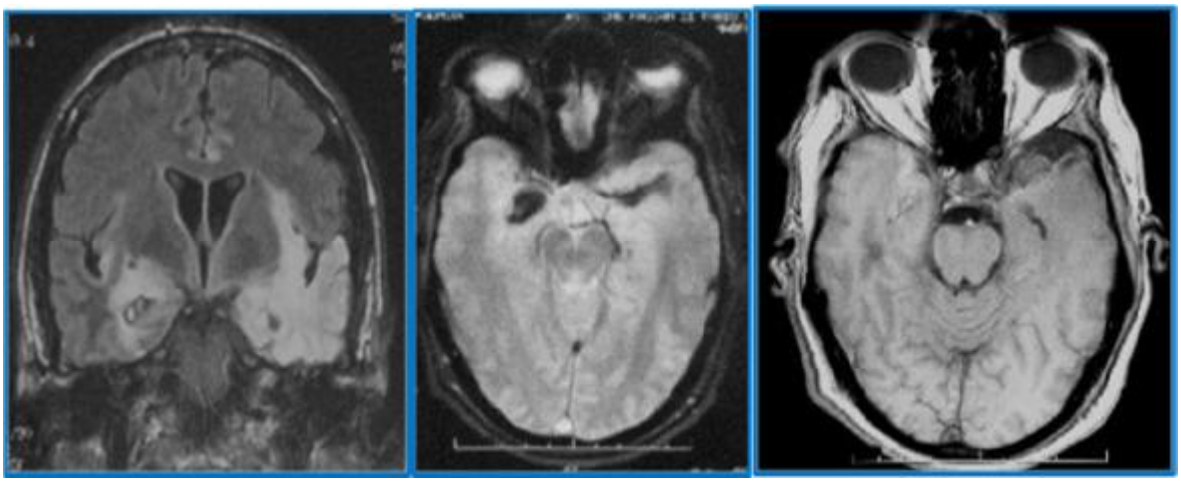
The MRI was performed on 19 patients with T2 and T2 FLAIR sequences. It showed a unilateral or bilateral medial temporal hyperintense in15 patients (78.9% of cases).

It also showed a hypersignal at cerebellar level without thrombosis in the sinuses in single male patient (5.2% of cases).

MRI was normal in three patients (15.6% of cases).

Table 4 : appearance of MRI in our patients

Patient number	MRI
1	Limbic encephalitis
2	Limbic encephalitis
3	Limbic encephalitis
4	Limbic encephalitis
5	Normal
6	Right temporo-insular hyper-signal
7	Limbic encephalitis
8	Limbic encephalitis
9	Limbic encephalitis
10	Limbic encephalitis
11	Bitemporal, bifrontal, insular and cortico-subcortical hyper-signal
12	Limbic encephalitis
14	Bilateral hyper-signal predominant in left cortico-subcortical interesting the temporal lobe, cingulate gyrus and insular gyrus
15	Limbic encephalitis
16	Limbic encephalitis
17	Limbic encephalitis, cerebral granulomatosis
19	Cerebellar hyper-signal
21	Normal
22	Lesions in the hippocampus, hyper-signal on T2 and FLAIR

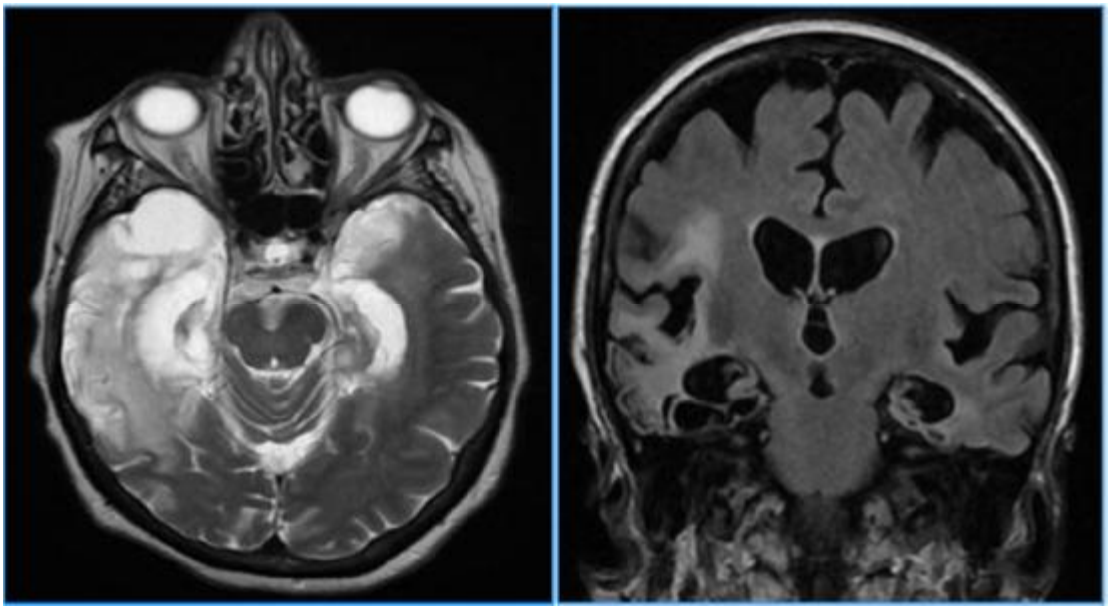


(a) (b) (c)

figure 7 : Brain MRI showing a bilateral temporo-insular and left cingulate lesion at FLAIR hyperintense sequence (a), including hypo- signals in T2* sequence (b) and hypersignal on T1 sequence (c)et en hypersignal en T1 (c).

Patient (n° 14) 54 years old, with no history, who presented a meningeal syndrom. Brain MRI for a limbic encephalitis. The infectious exams are negative. The patient improved under Zovirax.

Herpetic origin was established.

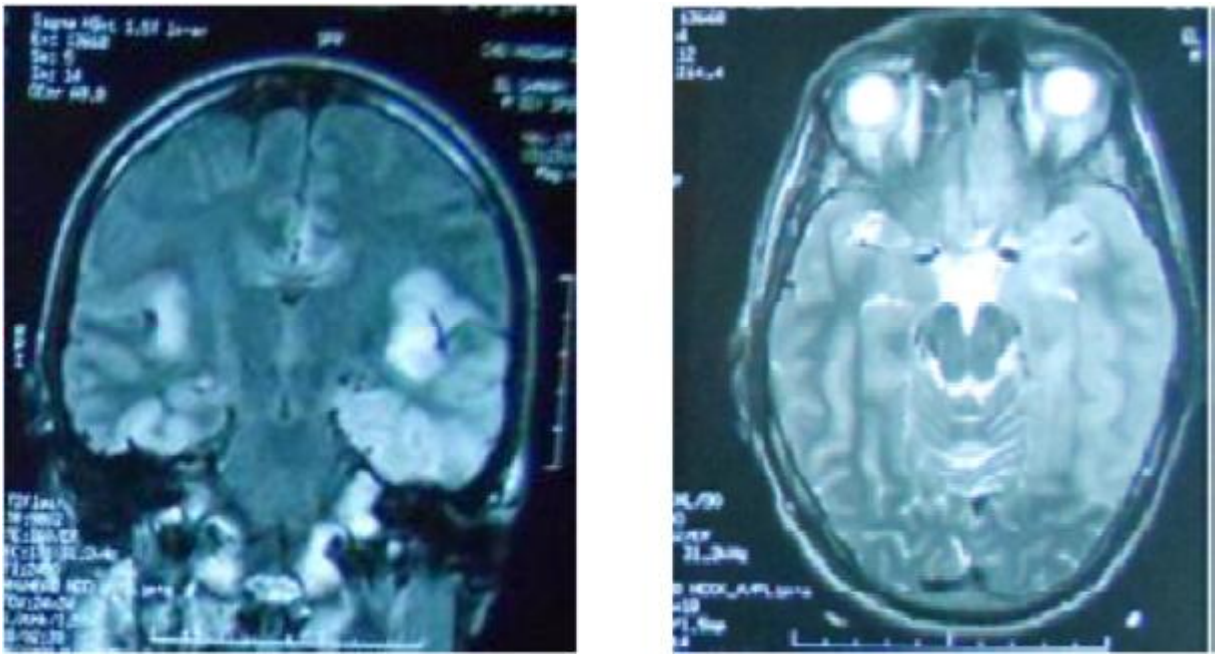


(a) (b)

Figure 8 : Cerebral MRI axial sections in weighed sequence Flair (b) and T2 (a) showing bitemporal hyper-signal, bifrontal and insular cortico sub -cortical.

Patient (n° 11), 65 years old, with history of ovarian tumor and high blood pressure (Hypertension) admitted by seizures and memory disorders. The Cerebral MRI is in favour of limbic encephalitis, the onconeural antibodies are negative. The thoraco-abdominopelvic CT (TAP) showed a relapse of Ovarian Carcinnosarcoma, no improvement under acyclovir.

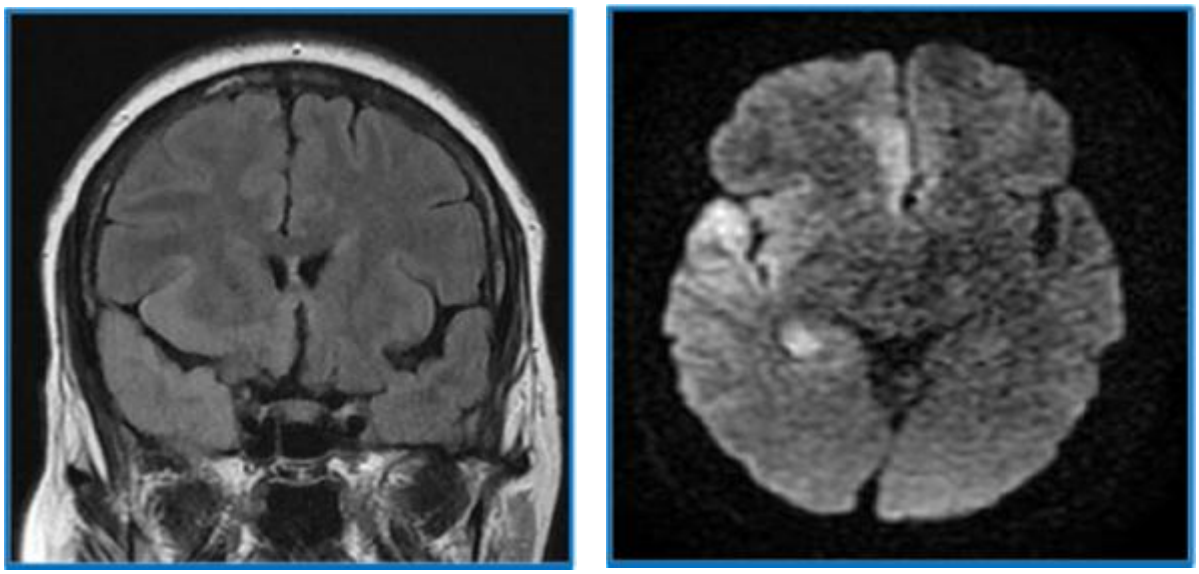
Paraneoplastic etiology was performed.



(a) (b)

Figure 9 : cerebral MRI coronal and axial sections, in sequence FLAIR (a) and T2 (b) showing a predominant left cortico sub-cortical hyper-signal interesting the temporal lobe, insular gyrus and cingulate gyrus.

Patient (n° 14), 54 years old, with no antecedents, presenting an epilepticus status generalized, the cerebral MRI is in favour of limbic encephalitis, the thoraco-abdominal-pelvic CT showed a suspicious lung injury, the onconeural antibodies are negative. Paraneoplastic origin is more likely.



(a) (b)

figure 10: Brain MRI showing a right cingulate and temporo- insular hyperintense on FLAIR sequence (a) with restricted diffusion as shown by the net hyperintensity on diffusion sequence (b).

Patient (n° 4), 32 years old, with no history, admitted for febrile consciousness disorders. The infectious examinations are negative.

The herpetic etiology was performed.

- Cerebral CT scan :

CT (Computerized Tomography) was performed among 15 patients. A single cerebral scan without MRI (Magnetic Resonance Imaging) has been done in three patients. The CT showed a normal aspect among 10 patients (66,6% of the cases), a right fronto-insular lesion in one single patient (6,66% of the cases),a left temporal lobe lesion in 2 patients (13,3% of the cases), a right temporal lobe lesion in one patient (6,66 % of the cases), multifocal ischemic focus in one patient (6,66% of the cases).

The function imaging (PET scan, SPECT) has not been used (not yet available at CHU Hassan II).

Table 5 : CT appearance in our patients

Patient number	CT
1	Normal
2	Normal
3	Normal
5	Normal
7	Normal
10	Right fronto-insular lesion
13	Left temporal lesion
14	Normal
15	Normal
16	Normal
17	Multifocal ischemic focus
18	Left temporal lesion, cerebral edema
20	Normal
21	Normal
22	Right temporal lobe hyperdensity

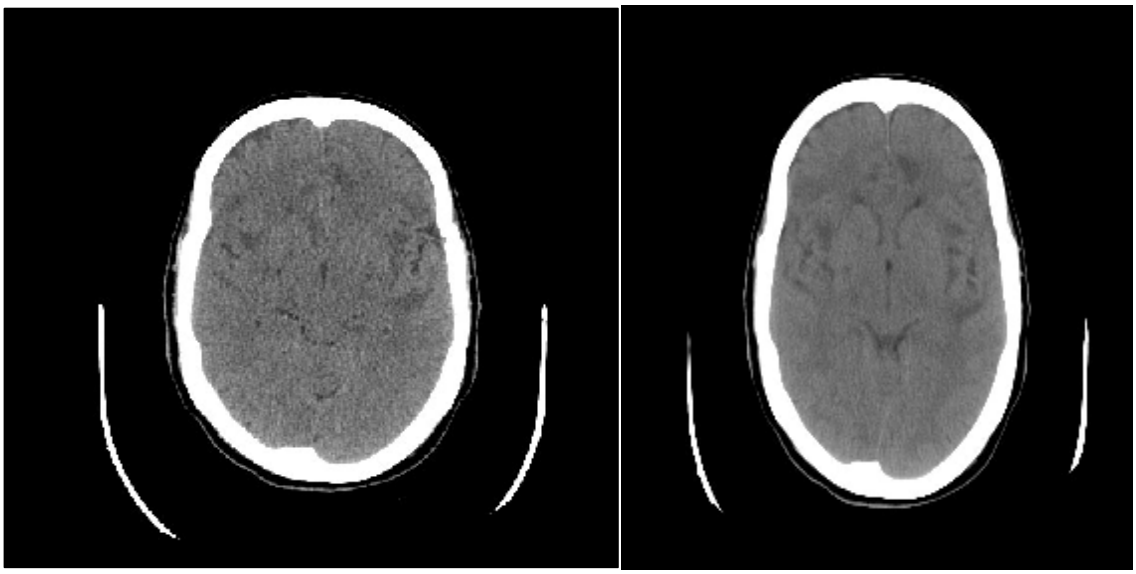


fig. 11 : brain CT scan : asymmetric and bilateral fronto-temporo-insular hypodense lesions

- EEG (Electroencephalogram) :

.The Electroencephalogram was performed among twelve patients. It showed either temporal waves (figures 4 and figure 5) with a slowing background curve in seven patients (58, 3% of the cases) or a diffuse cerebral suffering among three others (25%).

It was normal in the case of two patients.

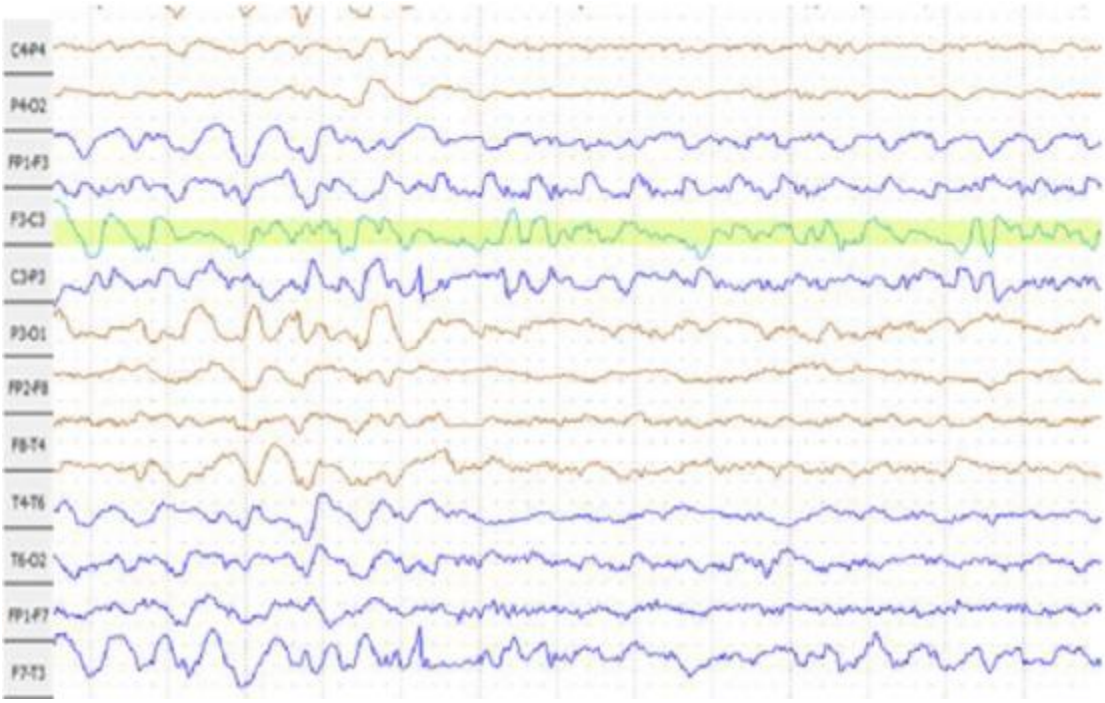


Figure 12: EEG signal of bilateral fronto-temporal suffering with slow wave and tip-waves.

Patient aged 65 years, admitted for behavioral disorders, status epilepticus and memory disorders. The CT scan showed a pulmonary mass. The onconeural antibodies are negative. The Paraneoplastic cause was the most probable cause.

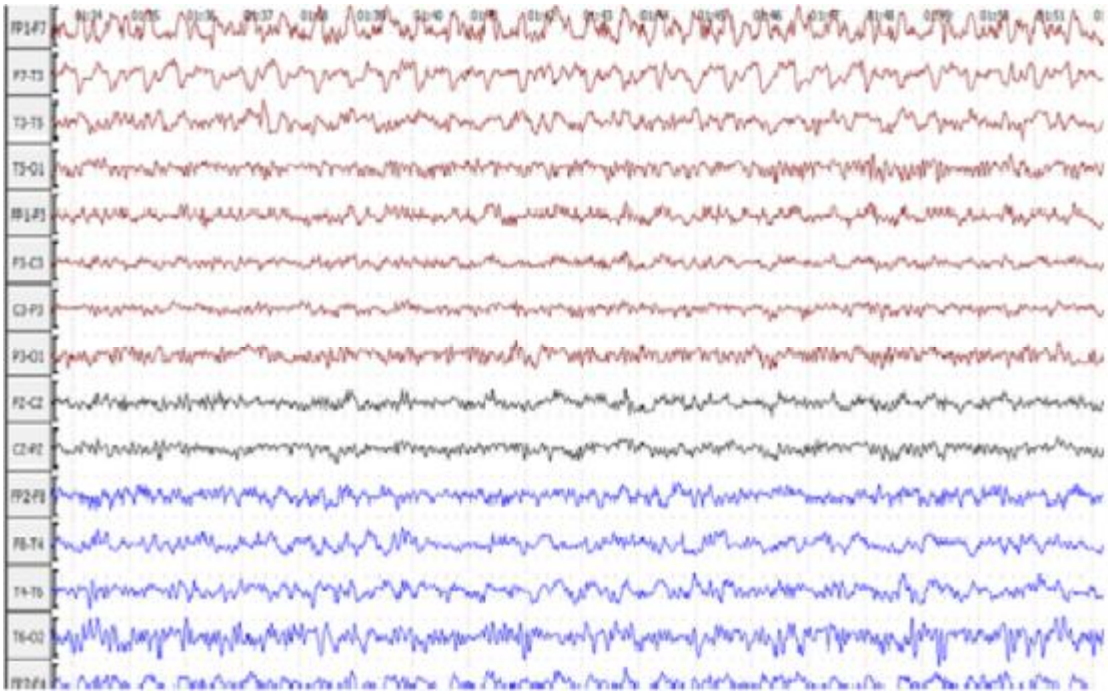


Figure 13 : EEG of patient objectifying the bilateral fronto-temporal theta slow waves more proeminant at left.

Patient aged of 24 years, without history, admitted for convulsive seizures and behavioral disorders.

Cerebral MRI in favor of limbic encephalitis with the EEG of the fronto-temporal sharp waves more proeminant at left.

b. Biological data :

- Lumbar puncture :

The study of cerebrospinal fluid (CSF) with cytochemical analysis and research of oligoclonal band was performed in twenty-one patients and was abnormal in 17 patients (81% of cases) with hyperleuocutose Lymphocytic predominance and hyperproteinorachie less than or equal to 1 g / l, the research of intrathecal immunoglobulin synthesis was negative. The cytobiochimical analysis is interpreted as normal in five patients.

- Serology :

The Syphilitic serology were positive in blood and CSF (cerebrospinal fluid) in four patients (18.2%). HIV (Human Immunodeficiency Virus) serology and the rest of the infectious serology were negative.

- Inflammatory examinations :

The examinations detects an inflammatory syndrome in 10 patients: increased CRP *(C-reactive protein)* and VS or elevation of CRP with inflammatory reaction on the electrophoresis of the serum protein. Positive CRP values ranged from 15 to 134mg / l. The PCR *(Polymerase Chain Reaction)* Herpes in CSF *(Cerebrospinal fluid)* was made in nine patients and was negative; it could not be done in other cases due to financial problems of patients

- Immunological examinations :

An immunological examinations without neurological specificity was conducted in 06 patients. It was negative:

Antinuclear antibodies (ANA), anti-native DNA (Deoxyribonucleic acid), Antithyroperpxydase antibody (TPO) and anti-thyroglobulin antibody.

Anti-onconeural antibodies were made in five patients and were negative in all cases.

c. Other exams :

Thoraco-abdomino-pelvic CT was performed in the case of nine patients, with a normal aspect in four patients and abnormalities in others, a tissue lung mass in two patients; a recurrence of ovarian tumor was found in the case of one female patient, a nasopharyngeal cancer in the case another male patient, inguinal lymph nodes in the case of one female patient in whom a cutaneous melanoma has been diagnosed.

The neuropsychological evaluation with at least a Mini Menta State Evaluation (MMSE) has been altered (with variable degrees) among 13 patients: 59, 1% of the cases.

The cancer's research revealed a cutaneous melanoma in the case of one female patient, a recurrence of ovarian carcinosarcoma in the case of another patient, suspicion of lung cancer among two male patients, nasopharyngeal cancer in the case of another male patient.

Table 6 : CSF study of our patients

Patient number	CSF study
1	TPHA, VDRL positive in blood+CSF
2	TPHA, VDRL positive in blood+CSF
3	TPHA, VDRL positive in blood+CSF
4	Limphocytic meningitis, no intrathecal immunoglobulin
5	Limphocytic menegitis, no intrathecal immunoglobulin
6	Normal
7	Normal
8	Limphocytic meningitis, no intrathecal immunoglobulin
9	Limphocytic meningitis, no intrathecal immunoglobulin
10	Normal
11	Limphocytic meningitis, no intrathecal immunoglobulin
12	Limphocytic meningitis, no intrathecal immunoglobulin
13	Limphocytic meningitis, no intrathecal immunoglobulin
14	Limphocytic meningitis, no intrathecal immunoglobulin
15	Normal
16	Normal
17	Limphocytic meningitis, no intrathecal immunoglobulin
19	Limphocytic meningitis, no intrathecal immunoglobulin
20	Limphocytic meningitis, no intrathecal immunoglobulin
21	Limphocytic meningitis, no intrathecal immunoglobulin
22	TPHA, VDRL positive in blood+CSF

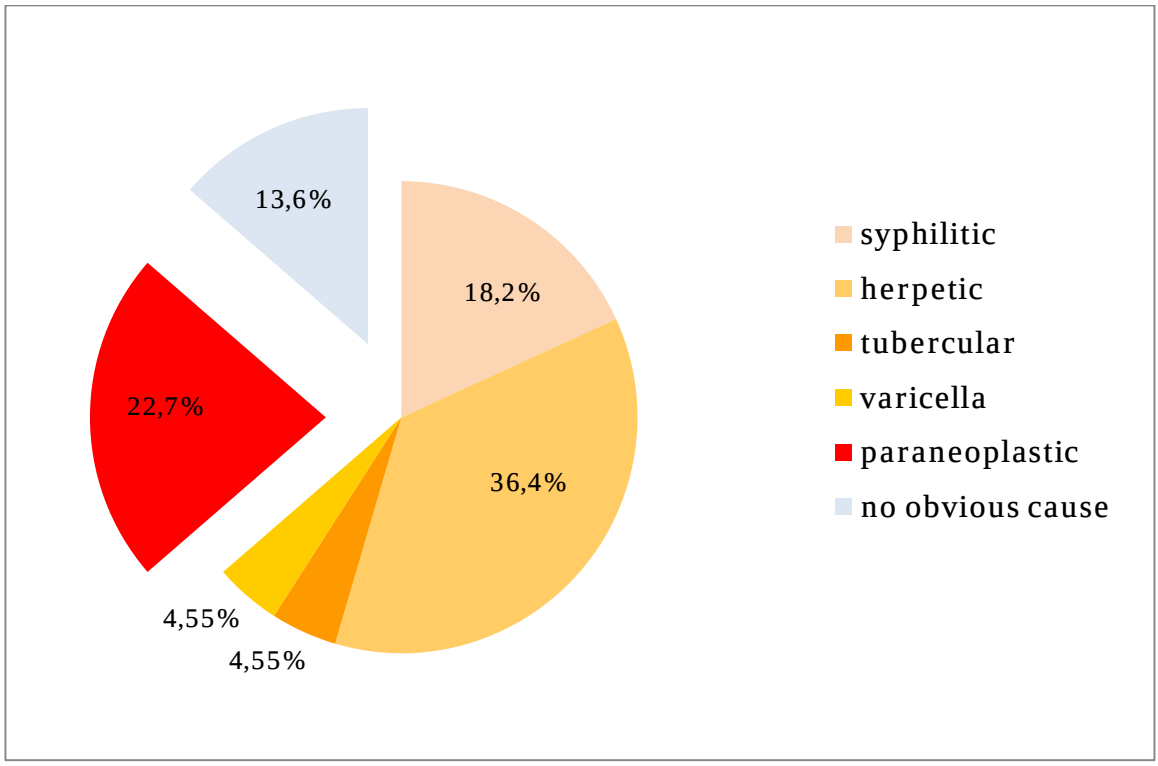
4. Causes :

In our study, we found 14 cases (63,6% of patients) of infectious limbic encephalitis, of which 04 were of syphilitic origin, 08 were of herpetic origin, a single case of limbic encephalitis due to tuberculosis and another whose cause was varicella.

We also noted the presence of 05 patients (22,8% of cases) with paraneoplastic limbic encephalitis origin.

Three patients in our series (13,6% of cases) had limbic encephalitis without obvious cause.

We could not detect any case of immunological limbic encephalitis origin.



graphic 5 : distribution of patients according to the cause of limbic encephalitis

5. Treatment :

a. Support in ICU :

An ICU stay was required in 09 of 22 patients, orientation in acute care is justified by neurological criteria of consciousness disorder (n=5) or status epilepticus (n=4).

b. Etiological treatment :

An initial treatment with acyclovir IV was administred in 16 patients (72.7% of cases). An antiepileptic treatment was started in almost all patients with seizures (n=9) or status epilepticus (n=4).

We administred cures of peni G or oral cyclins in four patients diagnosed limbic encephalitis of syphilitic origin.

Immunomodulatory therapy with intravenous immunoglobulin and immunosuppressant was prescribed in a patient who does not improve as acyclovir.

After treatment, a complete improvment was noted in 6 patients (28.5% of cases), partial in 12 patients (57.2% of cases). Three patients died (14.3% of cases).

c. Symptomatic treatments :

It was administred neuroleptic or anti depressants in the case of psychiatric disorders. Sedatives and anticonvulsivants were administred against neuropathic pain or even against abnormal movements. No treatment was effective against abnormal movements, tried in three patients. However seizures or status epilepticus responded on electroencephalographic plane, sometimes partially the strengthening of treatment, in some cases requiring the use of powerful anti-epileptic or even sedation sometimes.

Antibiotic treatments were administred as developed infections, treatment with acyclovir was often initiated before knowing the diagnosis.

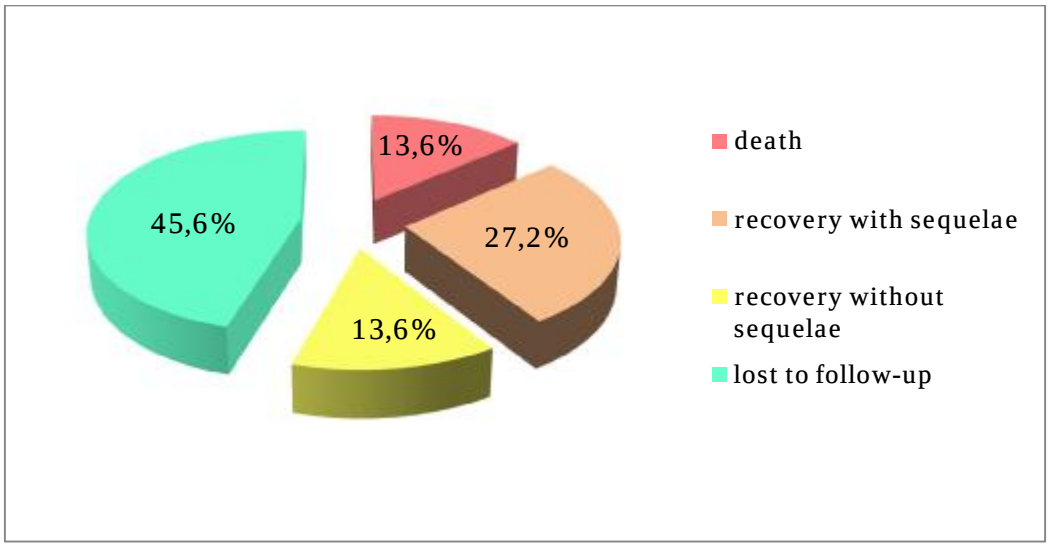
6. Evolution :

Clinical follow-up showed a variable evolution. Three deaths were deplored.

For these three patients : a patient admitted for psychiatric disorders complicated by impaired consciousness, died a few days after his admission at ICU. A second patient died one day after her melanoma biopsy in pulmonary embolism table. The third patient died six months after the diagnosis of limbic encephalitis with recurrence of ovarian carcinosarcoma.

Clinical recovery was noted with sequelae in 6 patients and with no sequelae in 3 patients.

Sequelae were multiple (cognitive, psychiatric impairment, persistence of seizures with the need to maintain an antiepileptic background therapy). Furthermore nine patients in our series were lost to follow-up.



graphic 6 : evolution in our patients after treatment

DISCUSSION

I. Epidemiological Data:

1. By age:

In literature, the average age of onset of symptoms is 27 years, with a peak of occurrence between 20 years and 50 years [1], while in our study, the average age is 47 years with maximum of interference between 41 years and 50 years and extreme ages ranging from 24 years to 75 years, this would be due to selection bias given non-recruitment of the pediatric population within our service

2. By sex :

There is a slight male predominance in our patients with sex ratio of 2.14, while several publications found the opposite with a female predominance [1][2]. In some series; the female sex represented even 100% of the patient (study done at Nantes in the case of 09 female patients) [111]. In certain studies the immunological etiology of limbic encephalitis, which can be related to the teratoma of the ovary, can explain this feminine predominance in the foreign studies; whereas in our study there is no case of limbic encephalitis of a confirmed immunological origin. On the one hand, this predominance can be explained by the size of the sample under study. On the other hand, the other series were devoted to the study of auto-immune encephalitis and not to infectious origin. Moreover, the infectious etiology is frequent in our series with 18.2 % of the cases of syphilitic limbic encephalitis which is met exclusively in male patients.

3. According to medical history :

Some reports of available cases in the literature allow drawing a relatively stereotypical clinico-radiologic picture. Limbic encephalitis associated with teratomas with presence of anti-NMDA-Receptors antibodies affect young women between 14 and 44 years.

In the initial publications, 65 % of the cases of encephalitis of Ac anti-NMDA-R were associated with a tumor [21][36]. This proportion tends actually to decrease as the number of published cases increases. 79 % of the tumors are pelvic, mainly mature or immature teratomas of the ovary [36], and they are sometimes microscopic. Cases of mediastinal, testicular teratoma; tumor of the sexual cord, stromagonadic or lung cancer with small cells were also reported [37].

In a study, of the 19 cases of limbic encephalitis reported by J.Dalmau, 17 patients had an underlying tumor.

In our study three cases of néoplasie were registred with a percentage of 13.6%.

Other medical histories can be noticed with patients suffering from a limbic encephalitis such as a coronary syndrome or an high blood pressure, but there is no relation between these pathologies and limbic encephalitis.

Diabetes type 1 can also be met, especially within patients having a limbic encephalitis in anti-GAD syndrome.

II. Diagnosis

1. Clinical symptomatology

The clinical descriptions reported in our study are coherent with those of the literature, both at the level of the clinical presentation and at the level of the response to the treatment and the outcome.

The most striking semiological traits are the acute or sub-acute onset, within a few days or a few weeks, of temporal epileptic seizures, an anterograde amnesia or psychiatric disorders typical of depressive syndrom, irritability, disorders of behavior or delirium with hallucinations. This clinical triad is the cornerstone of the clinical diagnosis of limbic encephalitis. Nevertheless, the chronology of appearance of these signs and the predominance of the one over the other symptoms can vary in time according to the type of limbic encephalitis and the evolutionary stage of the latter. So, the disorders of memory are often masked at the time of the diagnosis by epilepsy or psychiatric disorders. On the other hand, impairment of memory is the longest to improve and often constitutes the functional outcome of limbic encephalitis. Furthermore, it is frequent that the patients also present an extra limbic impairment which can mislead the diagnosis. Even there, the type of extra neurological limbic impairment varies according to the etiology. One of the most important elements of the diagnosis is the mode of acute or sub-acute onsetinstallation of the disorders in almost all of the cases. A differential diagnosis must be systematically evoked and eliminated.

In certain studies [111], the clinical presentation comprises globally the same procession of symptoms with variable degrees of impairment varying from a mainly psychiatric presentation to severe disorders of consciousness requiring a prolonged reanimation. The cause of this disparity is not known but it has been observed a

link between the rate of antibody and the severity of impairment. The presence of a tumor is also associated with more severe forms of the disease.

In other studies, less typical clinical presentations were described, as myelitis or clinical syndromes being similar to the NMO spectrum (Neuromyelitis Optica).

a. Triggering factors and prodromes :

In 70 % of the cases, the neuropsychiatric presentation is preceded within 15 days, by the prodrome which can evoke a viral episode with headaches, nausea, vomiting, fever, diarrhea or respiratory symptoms of the non-specific superior airways [3][4][5].

Headaches, non-specific viral syndrome or little high fever were noted in 86 % of the cases in the two weeks preceding the admission of a series of 100 cases published by Dalmau and al in 2008. Another study made in Nantes in 2014 showed that 55 % of the patients presented the prodrome typical of viral syndrome; whereas in our study, these symptoms were only reported in 27.2 % of the patients: six patients showing fever, two showing headaches and one patient showing vomiting.

b. Epilepsy

Epileptic seizures are extremely frequent and are reported in more than 80 % of the cases [3][5]. The epilepsy arises most of the time prematurely and three main types of seizures are observed.

First of all, the temporal seizures whose semiology can be discreet but always typical. These seizures are sometimes the only revealing clinical signs of limbic encephalitis [6][7]. The semiology is stereotypical and reproducible in the same patient. The progress of a temporal epileptic fit just at the mesial starting point comprises an aura often with an increasing oppressive epigastric sensation. Then, there is most of the time a loss of contact with gestual and oral automatisms. To this, is associated a dystonic posture of the contralateral upper limb at the starting

point of the seizure. When the temporal lobe controlling language is involved, an aphemia or a per-critical aphasia which continues in a post critical stage by speech difficulties typical of motor aphasia is frequently noticed. Following a temporal seizure, the patient can be confused during several minutes. In particular a state of agitation or aggressiveness succeeding the seizure is also noticed when it involves the temporal right lobe. The majority of the patients alternate right and left temporal seizures.

Sometimes, the development of the epileptic fit can be very quick, without the typically temporal signs being identified. The diffusion in the other intellectual areas can then give rise to generalized tonico-clonic seizures. The generalized seizures are brief (never more than two minutes) but are followed by a long period of recovery where the patient is confused, sleepy and hypotonic.

The status epilepticus, both in the initial stages or during the evolution of the disease, are frequent and require an early and energetic treatment. They are usually the acutisation of one of the two types of seizures previously cited and constitute a stable epileptic condition. The status epilepticus associated with limbic encephalitis are most of the time drug-resistant and care in the midst of a reanimation service is systematic.

Finally, a particular attention is given to the confusional syndrome. It is met in 46 % of the cases [8]. If the confusion can directly result from the impairment of limbic regions, the presence of a tempo-spatial disorientation and\or a change of vigilance can result from the epilepsy. First of all, the seizure itself is not always highlighted and the patient is examined in the post critical period of confusion. Besides, the states of the status epilepticus, involving the temporal or frontal lobes, can imitate a confusional syndrome. Thus it is necessary to realize an EEG (Electroencephalography) with any confusional syndrome in these patients, in

particular if the symptoms are unstable, recurring or in the case of a sudden onset.

In a study concerning 419 patients carried out by the team of Dalmau in 2011, 76 % presented the seizures among which 45 % were generalized tonico-clonic and 10 % were complex partial ; while our study showed that 59.1 % of the patients presented seizures among which 77 % are generalized and 23 % are partial [3]. The partial seizures are often unnoticed, and the environment keeps only the memory of the secondary tonico-clonic generalization. On the other hand, the temporal or frontal seizures are sometimes wrongly taken for abnormal movements in particular when they last for a long time within the framework of a state of partial complex status epilepticus. EEG is very useful to support the diagnosis. It is to remind that epileptic seizures represent one of the factors that foretell limbic encephalitis .

c. Amnesic Syndrome

The disorders of the short-term memory proceed with a bi-hippocampal impairment and thus show themselves essentially by an anterograde amnesia with forgetfulness and in the most severe cases, establishing a syndrome of Korsakoff. The amnesic disorders are characteristic of limbic encephalitis and are practically constant but can be masked at the beginning of the disease by epilepsy or psychiatric disorders. At the time of the diagnosis, the limbic encephalitis is never in the form of an isolated amnesic syndrome but the amnesic disorders foretell the limbic encephalitis. So, these can continue in the subsequent stage of the disease in an isolated way. As such, the psychometric evaluation allows to detect and to follow the disorders of memory. This examination also allows to lead a possible rehabilitation.

Contrary to the literature, in our study, the patients did not show any relation between the amnesic disorders and the outcome of limbic encephalitis, but the outcome depended especially on the precocity of the treatment.

In several publications, it is reported that amnesic disorders in 86 % of the cases affect in particular the working memory and the episodic memory, but there are few impairments of the semantic or procedural memory. They also show that the amnesic disorders are frequent but do not seem to be in the foreground, although the limbic system plays an important role in memory and learning. These studies showed that patients exceeding 45 years would show more memory disorders.

In our series, the disorders of anterograde memory were observed in 50 % of our patients. We also notice that younger patients (less than 45 years) were affected by these disorders. This could be explained by the frequency of the herpetic encephalitis in our studied population.

d. psychiatric and cognitive disorders

The psychiatric disorders are reported in 42 % of the cases of LE in the series published by Gultekin and al [8].

The psychiatric symptoms are diverse, manifesting themselves by a behavior modification and by the appearance of anxious disorders, deficiency symptoms with insomnia, withdrawal, social retreat, loss of memory and productive symptoms with visual or hearing hallucinations and delirious ideas. The language is generally affected, with various symptoms the most frequent of which is the echolalia, loss of word, jargonophasia or dumbness. The evolution can be made in a progressive way towards a catatonic state including phases of agitation.

In children, this first phase is characterized by change in behavior with irritability, anxiety, insomnia, hyperactivity and sometimes the appearance of sexualized or violent behavior, with a decrease of the language and even dumbness [4][5].

The disorders of humor are present in 1/3 of the cases and about 1/4 of the patients report hallucinations. In 15 % of the cases, the psychiatric signs amount to a

change in personality, most of the time associated with a disinhibition.

The cognitive disorders are mainly of a practical type and are reported in 15 % of the cases.

Sometimes, the association of mood disorder and the cognitive impairment as well as the presence of an amnesic syndrome can lead to the constitution of a picture of dementia.

Concerning these psychiatric disorders, most of the authors insist on their heterogeneousness. A recent review of the literature [23] tried to characterize the psychiatric demonstrations according to the various types of autoimmune limbic encephalitis (according to the current classification, that is according to the managed associated antibodies either against an intracellular antigen, or against an antigen of the surface). No specific psychiatric picture was highlighted. However, the psychiatric disorders are frequently in the foreground of the scene, making the diagnosis difficult [24]. So, in the particular form of limbic encephalitis associated with anti-receptors and antibodies in the NMDA affecting the young adult, on 200 published cases, 75 % had initially been examined by psychiatrists because of psychological disorders. This form of limbic encephalitis is interesting and can certainly establish [23][25] a physiopathological model of psychiatric disorders. Indeed, the study of the glutamate and the receptors of the NMDA had already allowed to suggest a neurobiological hypothesis of schizophrenia [26]. A link between the receptor of the NMDA and the thymic symptoms was supported by a more uncertain result [25]. The examinations realized within the framework of limbic encephalitis of M.H. did not show the presence of auto-antibody. It would suggest that the model of the encephalitis with anti-receiving auto-antibodies in the NMDA cannot report the whole spectre of the disorders of the mood. However, we formulate the hypothesis that the major depressive episode was favored in certain

patients showing a depressive vulnerability by the encephalitic injuries of the limbic system whose role in the emotions is well sustained [27].

The patients affected by schizophrenia can show cognitive disorders typical of dysexutif syndrome and of the episodic memory disorders, identical to the neuropsychological picture of the patients suffering from limbic encephalitis. It would be interesting to compare the neuropsychological assessments of schizophrenic patients and encephalitic ones. The semiological link of these two affections could find its source in a common physiopathology, by a hypofunctioning of the NMDA receptors also described in schizophrenia in several studies.

In a study led by Dalmau and al., 100 % of the patients presented neuropsychiatric disorders among which 77 % were seen at first by a psychiatrist and 23 % were seen by a neurologist at the beginning.

Contrary to the literature, only 45.5 % of the patients of our series presented neuropsychiatric disorders.

e. Extra-limbic neurological symptoms

So, the clinical diagnosis of limbic encephalitis. is based on the triad of symptoms: amnesia, epilepsy and psychiatric disorders. However, the inflammatory impairment responsible for limbic encephalitis can extend beyond the limbic structures to other structures of the nervous, central system as well as peripheral. This impairment of extra–limbic structures is not arbitrary and more specifically not associated with the one or the other of the autoantibodies and so guides the etiological diagnosis. The picture below sums up the extra-limbic signs met and the frequently associated autoantibodies.

extra-limbic symptoms	suspected autoantibodies
pure sensory neuropathy myelopathy multifocal involvment	anti-Hu
sensorimotor neuropathy chorea	anti-CV2/CRMP5
insomnia with REM sleep disorders neuromyotonia	anti-VGKC
stiff-person syndrom	anti-amphiphysine, anti-GAD
diencephalon and/or hypothalamus reaching	anti-Ma2
facial dyskinesias or dystonic movements	anti-NMDAr

Main extra-limbic symptoms and suspected autoantibodies

So, the coexistence of a neuropathic impairment evokes the presence of an anti-Hu or of one anti-CRMP5. Indeed, such an impairment is present in respectively 86 % and 57 % of the SNP associated with these autoantibodies [14]. The existence of a neuropathic impairment with sensory predominance is more suggestive of the presence of an anti-Hu [15] in particular if it preferentially involves the superior limbs. On the other hand, a neuropathic sensory motor impairment is more suggestive of the presence of one anti-CV2 / CRMP5, especially if a uveitis or choreic movements are present. The anti-Hu associates willingly with medullary impairment and with the brainstem [16]. The diencephalic impairment with diurnal hypersomnia is present in 1/3 of the SNP associated with an anti-Ma2 [17]. A cerebellar impairment is associated with the presence of an anti-CV2 / CRMP5, of an anti-GAD or an anti-Hu [14][18]. The existence of a neuromyotonia, associated with sleeping disorders (Morvan syndrome) leads to a search of anti-VGKC antibody [19]. A particular case is the digestive pseudo-obstruction, little known by the gastroenterologists and which is present especially in the case of antibody anti-Hu and also anti-CV2 / CRMP5.

In a study concerning 16 patients made in 2012 at the level of the university hospital of Strasbourg, nine patients constituting (56.25 % of the cases) showed extra-limbic clinical signs, while in our series, only 13.6 % of the patients presented the extra-limbic signs [20].

f. Abnormal movements

The abnormal movements are met in 90 % of the cases [3][5] most frequent and typical of which are the orofacials dyskinesis which can come along with secondary labial or lingual injuries due to the repeated bites: forced opening-closure of the mouth, the prodrive of the tongue, even anxious mimes of terror, diverse oral noises and shouts. It can also involve more diffuse choreic, athetosic, mixed movements of

the extremities or the pond or still a hypertonia and dystonic postures up to the opisthotonos [3][21].

Limbic encephalitis gives rise to extremely polymorphic and often severe abnormal movements. The movements of the patients described in a study made in Nantes in 2014 represent this diversity well. In another study made in 2011, the abnormal movements were met in 86 % of the cases, they were various types. The bucco-facial dyskinesis (grimaces, movements of chewing) are the most characteristic and are present in more than half of the cases (55 % of the cases). In a little less than half cases (47 % of the cases), the patients show ample choreic movements of the limbs or the belly, ballic movements, dystonias, rigidity or an opisthotonos. In certain cases, repeated, badly classifiable stereotypical movements are observed and can persist during several hours or days. In our experiment, abnormal movements of a non-epileptic nature were only observed in two patients (9.1 % of the cases), seen that some abnormal movements of the patients were listed in the repertory of epileptic cases.

g. Central alveolar hypoventilation

During the evolution, an alveolar hypoventilation of central origin appears frequently (66 % of the cases) [3], which may require recourse to the invasive mechanical ventilation whether or not the patients present a coma. The median deadline of mechanical ventilation would be of eight weeks (2-40 weeks) [3]. At the same time, this stereotypical presentation seems very specific in the literature [22] and in other experiments. Indeed, from a historic series of 505 subjects from 18 to 35 years old hospitalized in intensive care, a German team recently identified seven patients presenting the association of encephalitic signs with psychiatric symptoms (agitation, paranoid ideas, hallucinations), convulsions, inflammation of the CSF and the absence of identification of a bacterial or viral infectious agent [22], which may

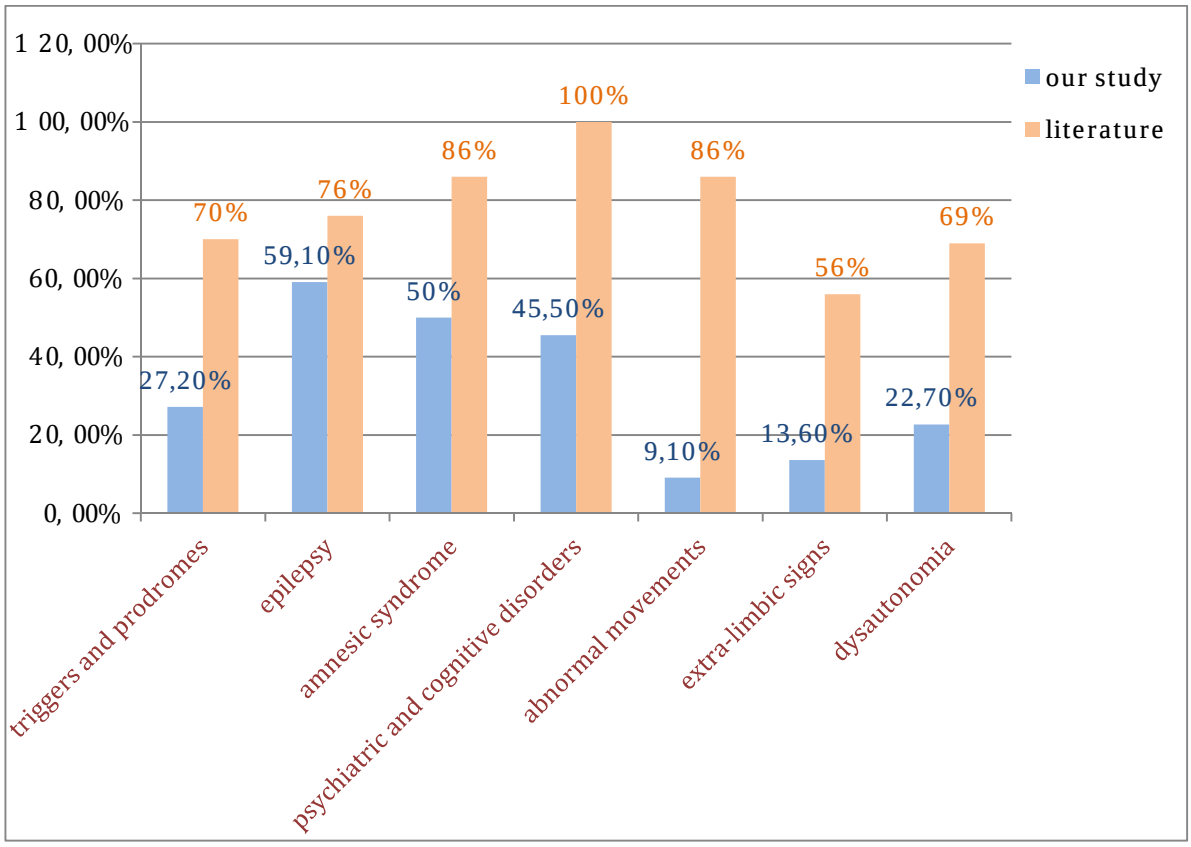
''a posteriori'' evoke the diagnosis of encephalitis with antibody anti-R-NMDA. The retrospective analysis on serotheque allowed the confirmation of the diagnosis for six out of seven patients (85 % of the cases). Another study conducted by Dalmau and al. 2011 showed the presence of an alveolar hypoventilation in 66 % of the listed patients.

The notion of central alveolar hypoventilation remains unknown in our practice and could report bad predications in certain patients.

h. Dysautonomia

The dysautonomic picture is rarely in the foreground and first of all must always evoke a state of shock in a patient in intensive care. This picture, though frequent during the disease (approximately two thirds of the cases) [3][21], can comprise a high blood pressure or a low blood pressure, rhythmic disorders with palpitation or a bradycardia sometimes requiring the use of a pacemaker, a fever, a hypersalivation, an erectile dysfunction or a urinary incontinence.

Contrary to our study in which we noted that 22.7 % of the patients suffered of dysautonomia (sphincter disorders or palpitation), the literature shows that dysautonomia is present in 69 % of the cases. This may be related to the lack of the systematic research of the signs of dysautonomia in the patients.



graphic 7 : comparison of different clinical signs between literature and our study.

2. Additional examinations:

Paraclinical examinations will contribute to the positive diagnosis by revealing abnormalities of limbic structures. The magnetic resonance imaging (MRI) of the brain, the electroencephalography (EEG) and possibly position emission tomography (PET) with fluoro deoxy glucose allow the highlighting of these abnormalities.

Moreover, lumbar puncture (PL) contributes to demonstrate the existence of an inflammatory phenomenon at the level of the central nervous system. With the blood test, it also contributes to the differential diagnosis.

Finally, the search for onconeuronal auto antibodies is systematic in front of an array of non-infectious limbic encephalitis and allows positive diagnosis.

In front of an initial presentation of limbic encephalitis, lumbar puncture, electroencephalogram (EEG), computed tomography (CT) or magnetic resonance imaging (MRI) are often made even before evoking the diagnosis precisely. The results to be expected from these reviews about the disease are given in the table below.

results of additional explorations in LE	
electroencephalogram	
abnormal	92%
slow activity (widespread activity delta or theta or predominant in frontotemporal regions)	71%
epileptic activity	71%
cerebral MRI	
abnormale	55%
temporal lobes	22%
cerebral cortex	17%
cerebellum	6%
brainstem	6%
noyaux the basal ganglia	5%
prise de contrast enhancement	14%
others	8%
cerebrospinal fluid	
abnormal	95%
lymphocytic pleocytosis	91%
CSF protein increased	32%

a. Imaging:

- Magnetic resonance imaging (MRI):

Brain MRI is the radiological examination of the most sensitive routine to highlight inflammation of the temporo-mesial structures and participates in the differential diagnosis. In almost 80% of the cases; the imaging is abnormal at the time of diagnosis. The most frequent anomalies encountered are:

- A hypersignal T2 and T2 flair of the bihippocampus (Fig.1).this signal abnormality willingly involves adjacent structures and notably includes the tonsils, the temporal poles and the insular cortex.
- Abnormal hippocampal volume: in the acute phase of limbic encephalitis, it highlights a relative increase in the volume of the bihippocampus that appear in an edematous form. This sign is very fleeting and done quickly to an aspect of bihippocampal atrophy which can be asymmetric
- Contrast enhancement, usually little intense and without hemorrhagic alterations except in herpes encephalitis [28]. The presence of contrast enhancement of leptomeninges evokes an associated meningitis.

In order to highlight the abnormalities which are sometimes subtle, this exploration of the brain must always have at least a T2 sequence in spin echo, a coronal sequence weighted in T2 FLAIR, a spread sequence, a T1 sequence with inversion-recovery in the coronal plane and a 3DT1 acquisition after injection of galolinium with reconstruction in the three plans. All the sequences are done in relation to bihippocamic plan in order to allow an accurate analysis of temporal lobes [29][30].

If the previously described anomalies are characteristic, they are not always present. In addition, the inflammatory reaction may extend beyond the hippocampal structures.

This, hyperintense T2 may be associated with cortical localization and contrast enhancement which are usually little intense.

Each of the cortical structures may be involved. The meninges gadolinium enhancement is an argument for the existence of an associated meningitis.

In literature, the MRI is normal in 17% to 43% of cases according to the series, while justifying the realization of a functional imaging to highlight a disorder of the temporal regions (Gultekin and al., 2000) Lawn et al., 2003). The temporal suffering of_ imaging is rarely isolated (a little less than 40% of the cases). In order to highlight this extra-temporal disease, functional imaging is more sensitive than MRI. In 2005, Ances and al. have shown that these two techniques are complementary but the results are not superimposed in around 50% of cases (Ances et al., 2005)

In a study conducted in 2012, the initial magnetic resonance imaging was abnormal in 63% of cases with an involvement extending beyond the temporal regions in 44% of cases. The functional imaging type SPECT or PET brain was abnormal in 94% of cases to highlight more extensive abnormalities than the brain MRI in 29% cases and temporal anomalies while MRI was normal in 29% of cases. Outside the limbic regions, the most affected areas are the frontal lobe, insula, midbrain and cerebellum. [20].

In another publication dating from 2011, brain MRI is abnormal only in 50% of patients [1]. Furthermore, the anomalies found are often discreet and nonspecific. The most frequently abnormalities found are hyperintense in sequence weighed in T2 or FLAIR at the level of the hippocampus and the cerebral cortex. Region fronto-basal and insular, basal ganglia, cerebellar cortex, brainstem or spinal cord are less frequent [5]. It should be noted that the observed abnormalities can be fleeting and variable from one MRI to another.

In our study, 89,5% of MRI made were abnormal with an extension beyond the

temporal regions in 31% of cases. The most affected regions are the temporal lobe, the frontal lobe, the hippocampus and the insula and the cerebellum.

It seems reasonable to suggest controls of brain MRI of the patients with severe clinical presentation to monitor the absence of complications that might require therapeutic adaptation especially if the clinical course is unfavorable and clinical examination non-contributory.

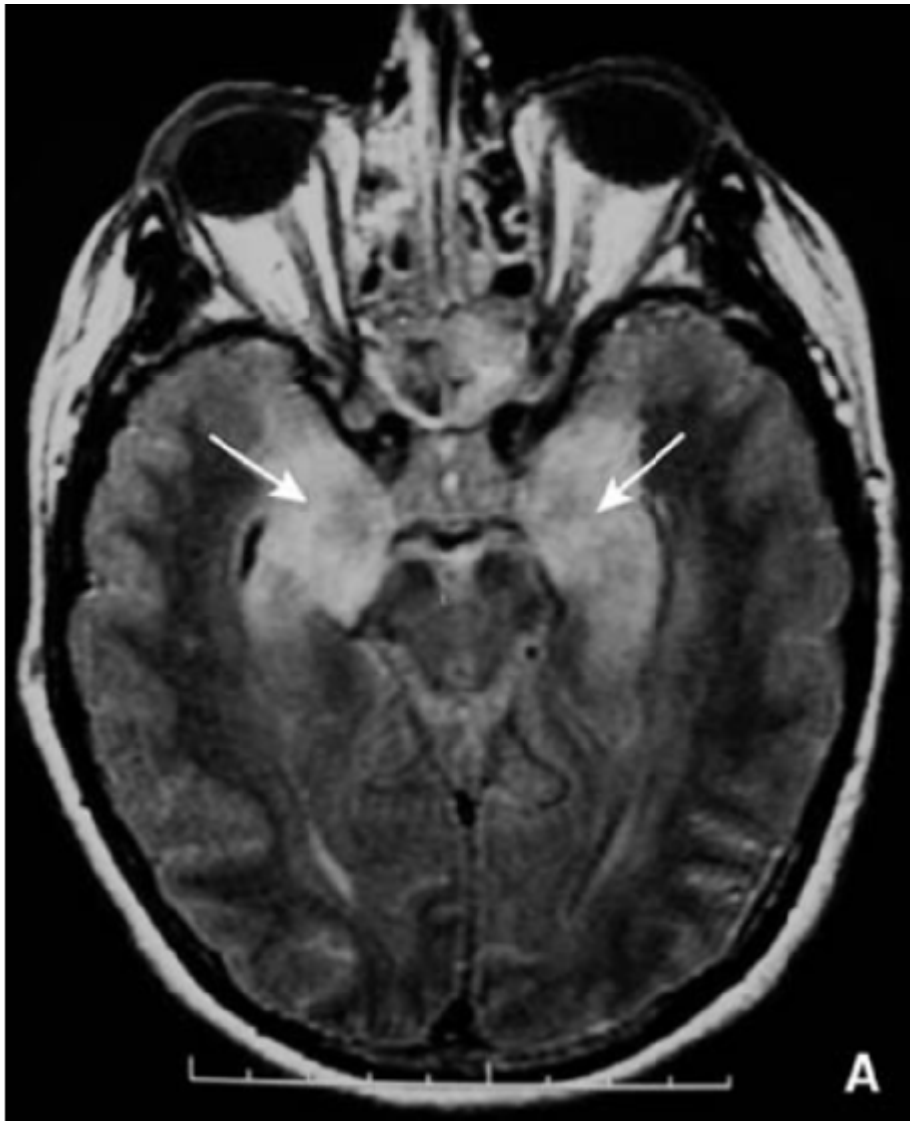


Fig. 14 : brain MRI with characteristic bihhipocampic damage.

FLAIR in axial slices with bihippocampic hyperintensities.

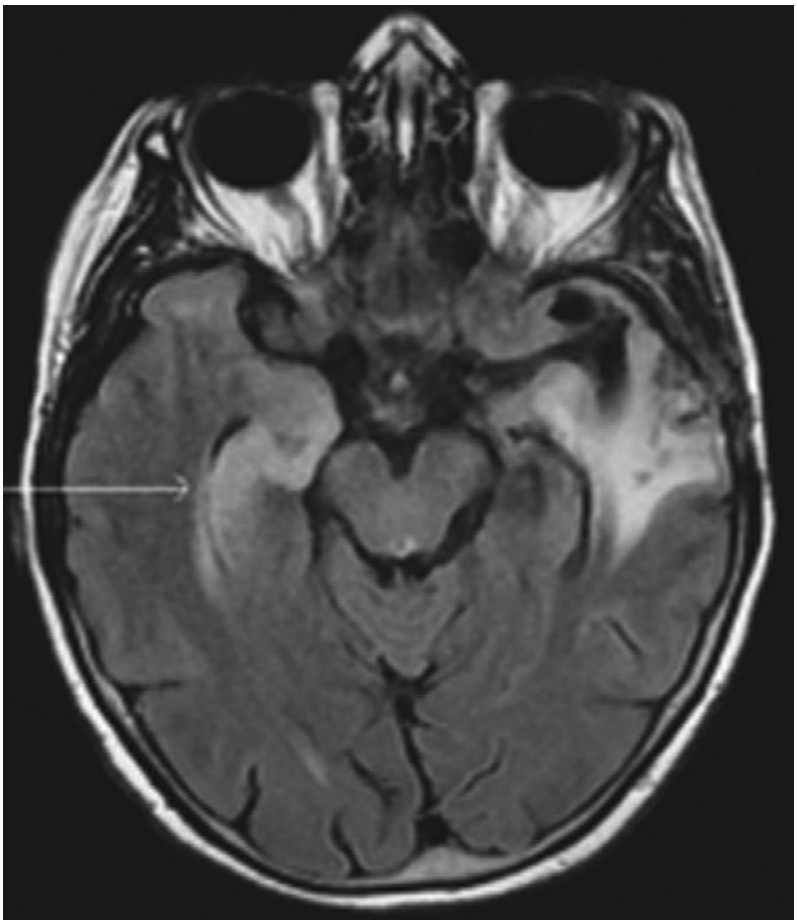


Fig. 15 : cerebral MRI T2 FLAIR, hypertintense of the right and left medial temporal regions. Hyperintensity of porencephalic left temporo-polar cavity associated with lesions of post radiation gliosis.

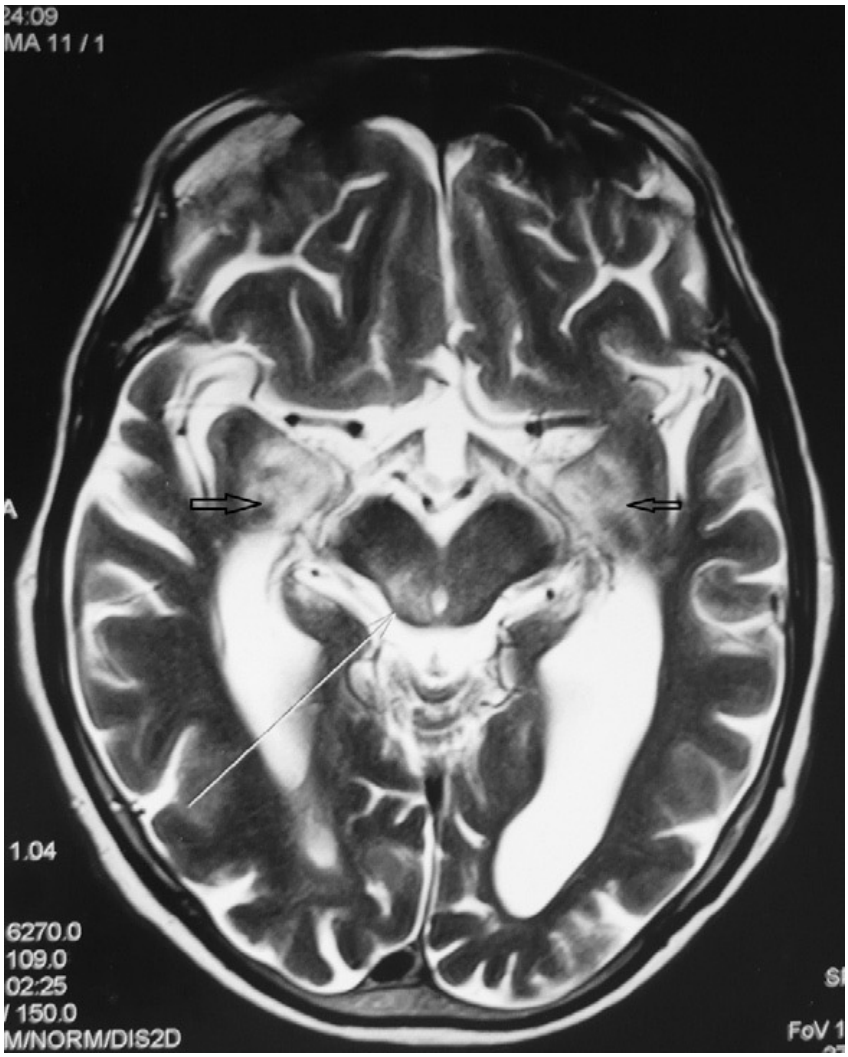


Fig. 16 : cerebral MRI T2, midbrain and temporal hyperintensities.

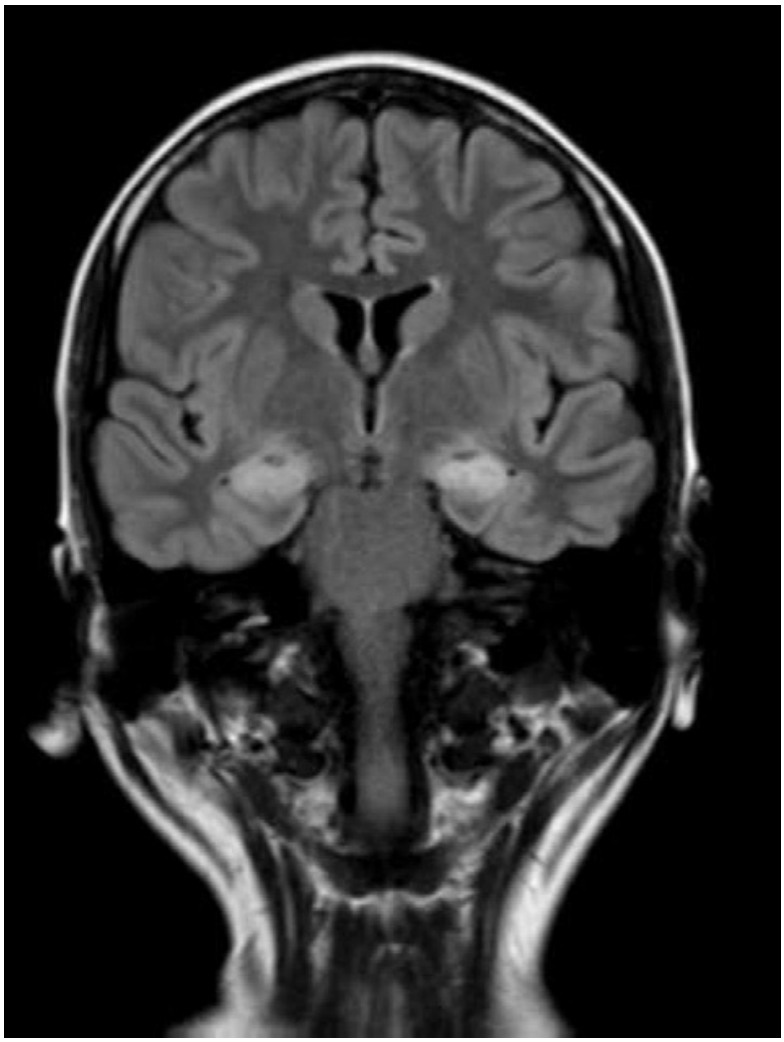


Fig. 17 : brain MRI, frontal slice, FLAIR sequence : hyperintensities of medial temporal regions

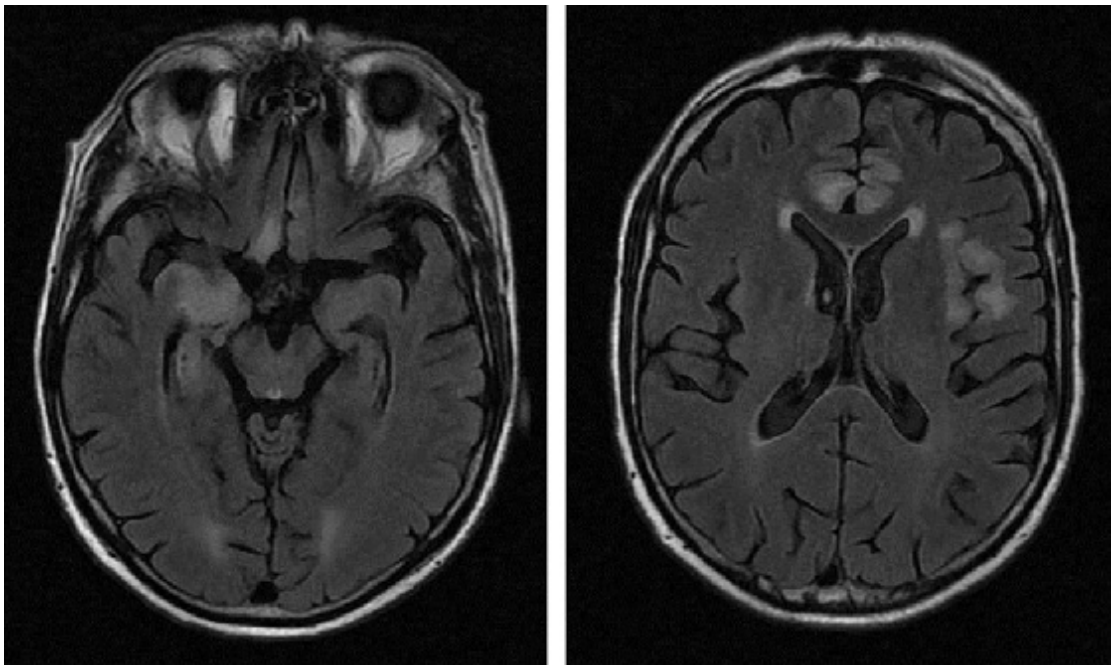


Fig. 18 : temporal hyperintensity associated with the hyperintensity of the cingulate gyrus and contralateral insula (paraneoplastic limbic encephalitis without onco-neuronal antibodies demonstrated)

- The brain computed tomography (CT):

The scanner is fairly insensitive due to its low resolution in the temporal regions, often artefactees by dental and bone structures. It is not contributory to diagnosis, often normal, it can, however, eliminate other diagnoses such as a tumor lesion. This is a tool of orientation in an emergency.

The normality of the CT scan does not eliminate the diagnosis of limbic encephalitis. At an advanced stage of the disease, it can reveal a temporal lobes' hypodensities, edema and, sometimes, contrast enhancement.

In our study, brain CT scan was performed in 15 patients, it was normal in 10 cases (66.66% of cases), in the others, we found temporal lesions, fronto-insular or multifocal ischemic foci.

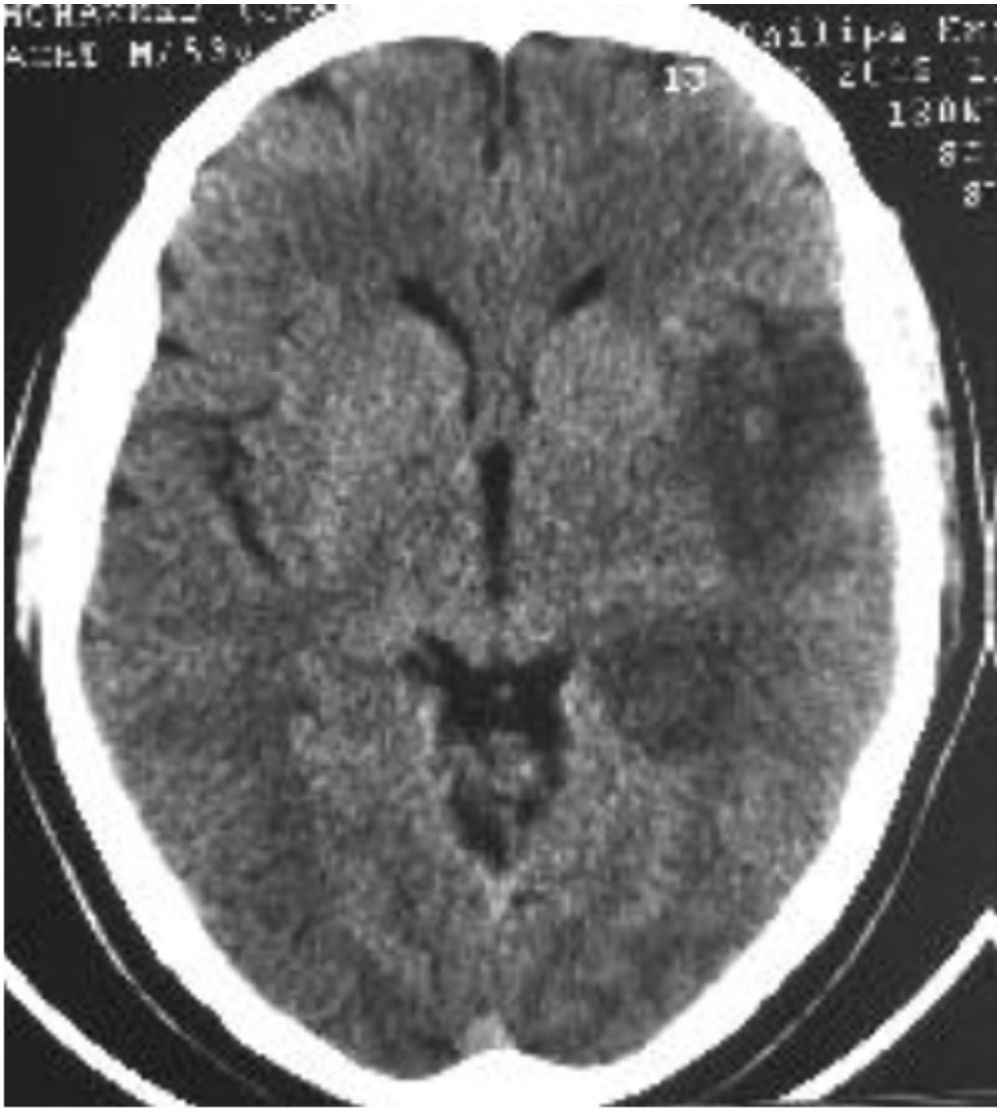


Fig. 19 : brain CT : axial section without contrast injection : left temporo- insular hypodense lesion.

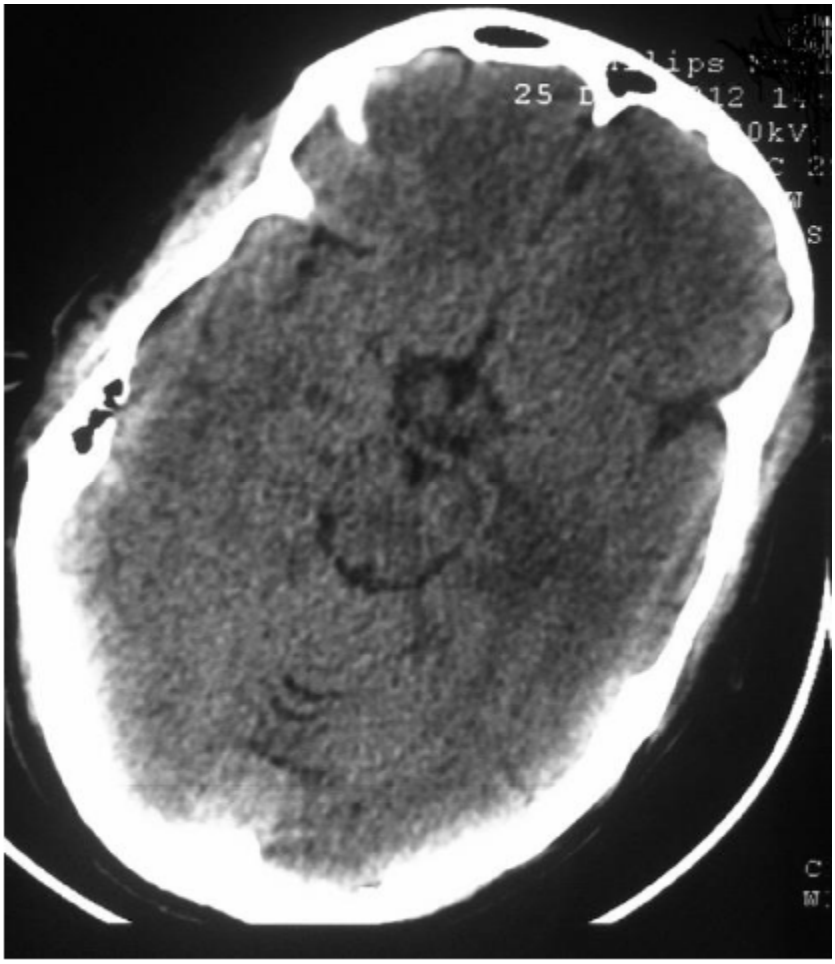


Fig. 20 : brain CT : left medial temporal hypo- density

- Electroencephalography (EEG)

It is abnormal in nearly nine out of ten cases. The most characteristic abnormalities are spikes or focal slow waves in temporal regions. These abnormalities are either unilateral or bilateral more readily. This disturbance of the cerebral electrogenesis demonstrates parenchymal suffering at this level.

Regardless of these signs of suffering, epileptic abnormalities can be saved. It is subclinial temporal recrutant activities or even, more rarely, authentic temporal electroclinical seizures. Most often, the patient is registered in inter-ictal period and there may be only a focal temporal slowdown. In a context of limbic encephalitis with confusion, a focal slowdown of EEG activity is suggestive of an epileptic origin. After generalized tonic-clinical seizures, EEG is less specific and presents a global slowdown of the cortical electrogenesis.

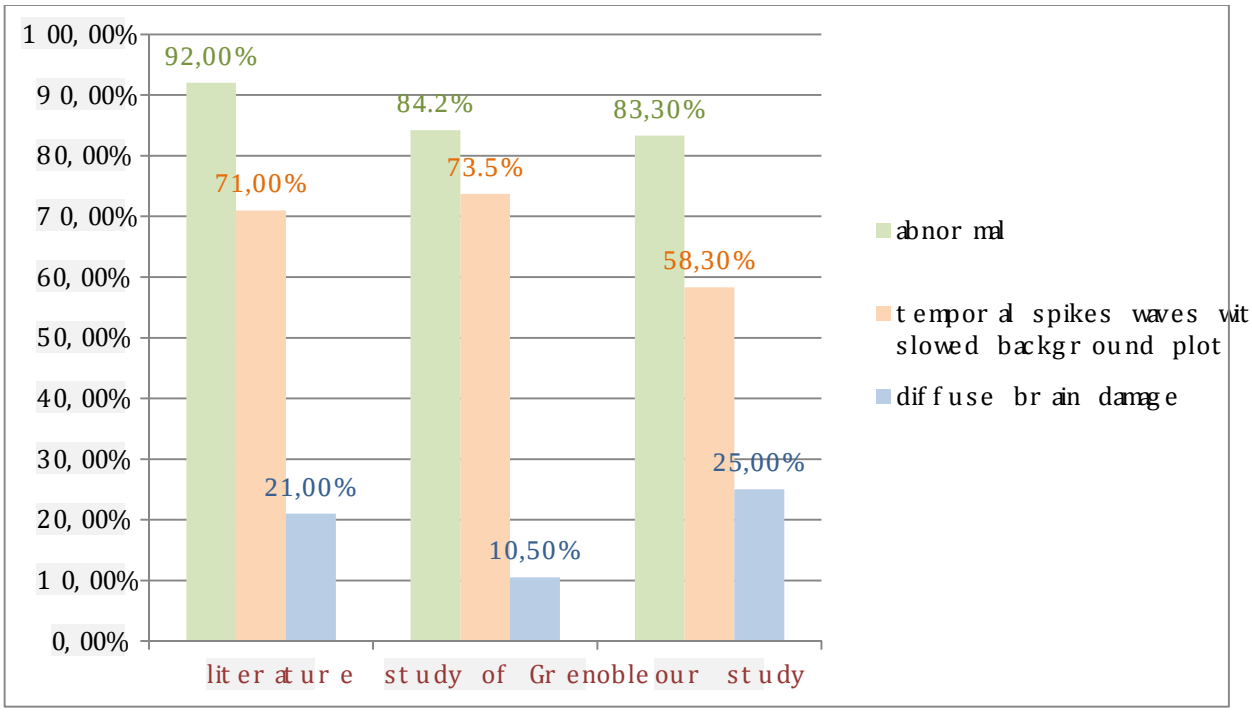
The EEG may also be disrupted when no seizure is found. The most characteristic anomaly is the presence of pseudo-periodic spikes next to the temporal regions, unilateral or bilateral [34]...

In a survey made in 2011, the EEG was abnormal in 92% of cases, it was noted a slower activity in 71% of cases and an epileptic activity in 71% of cases [3].

In a publication of Grenoble in 2012, all patients (19 patients) received an EEG examination: it was normal in 3 patients (15.8% of cases), diffusely slow without focusing in 2 patients (10.5% of cases), or with focusing signs in 14 patients (73.7% of cases).

This focused organization of the track corresponds to a slow wave activity sometimes bi- or tri - phasic predominantly temporal, frontal or even hemispheric. Finally in some patients ,it is about an activity of focused tips (n=4): State of poorly partial hemispheric left predominant in the frontal region (n=1), Left hemispheric crises (n=2) and temporal spikes without critical organization (n=1).

While in our series, the EEG was conducted in twelve patients and showed either spikes temporal waves with a slow background track in seven patients (58.3% of cases), a diffuse brain injury in three others (25%), it was normal in two patients.



graphic 8 : comparison of aspects oh the EEG in diffenrent studies.

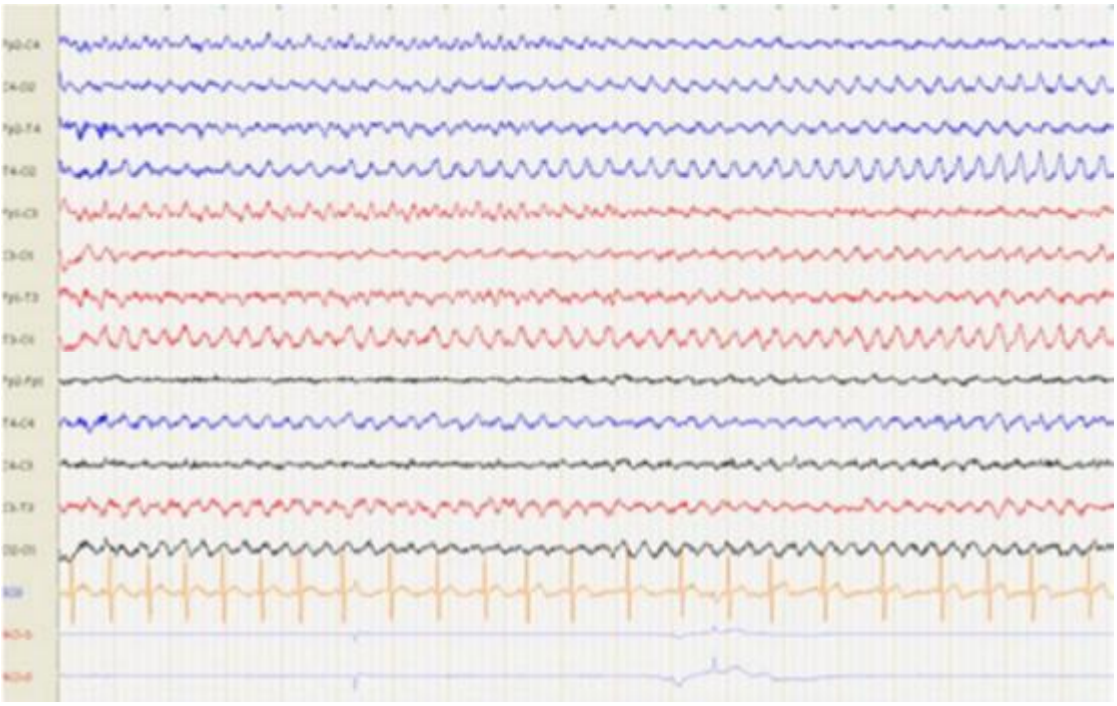


Fig. 21 : rythmic delta waves diffuse 3 Hz, arréactives

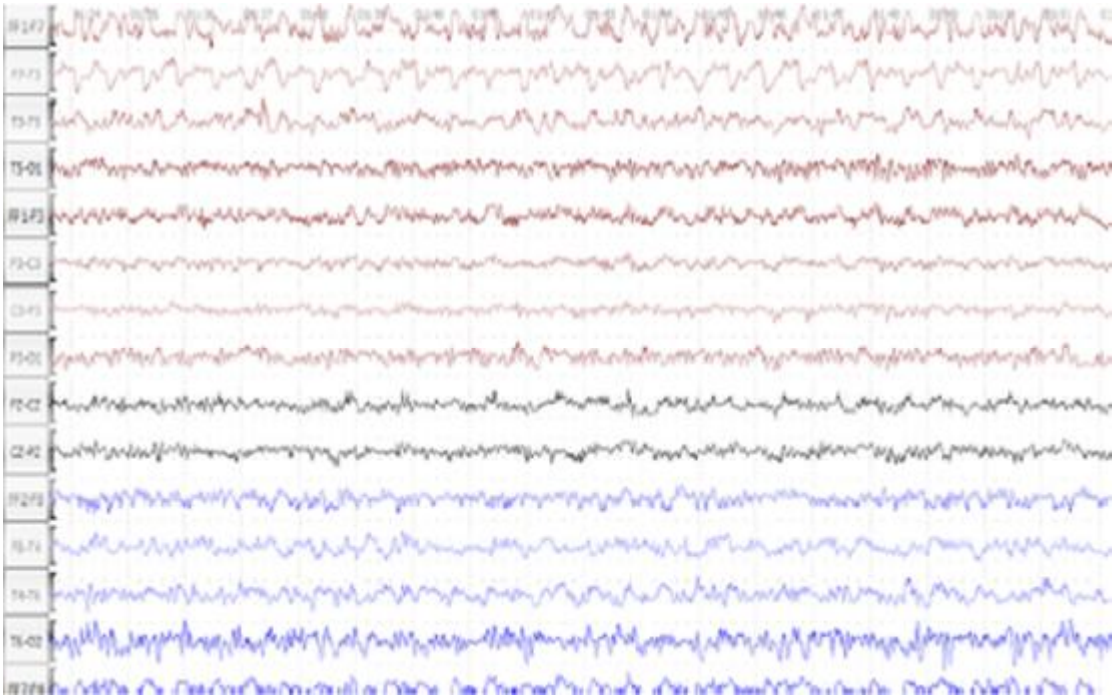


Fig. 22: EEG of a patien objectifying slow waves predominant in left frontotemporal.

Patient of 24 years old without disease history admitted for seizures and behavior disorders. Brain MRI in favor of limbic encephalitis with left frontotemporal slow spikes in the EEG.

- The positron emission tomography (PET –SCAN)

In a more marginal way as for the current clinical practice, it has been reported by the cases associating limbic encephalitis and extended temporal hypermetabolism demonstrated by Emission Tomography with fluorodeoxyglucose.This hypermetabolism is highlighted, including when the brain MRI is normal. Positions (PET-CT) emission may bring a help to the diagnosis by highlighting a cortical and sub-cortical multifocal hypermetabolism which modifies during the diseaseand which could have its place in the prediction of the evolution and the response to the treatment. These signals would be visible even in the absence of anomalies in the MRI [31][32].

The PET-CT in the 18FDG, allows to visualize a bilateral hypermetabolism in the temporal cortex, typical of the limbic encephalitis, to monitor the responce to treatment, but also to look for the primary tumor [17][35]. A PET-CT in the 18FDG should be repeated as early as possible when lung cancer is suspected to be able to avoid the lymph node metastatic stage on the second PET-CT to 18 FDG.

it can also show an increase of the regional blood flow in one or several internal temporal regions.

The most evocative aspect TEP is the association of hyper and of hypometabolisms, but tables with hypermetabolism or isolated hypometabolism are possible. The changes can be unilateral or bilateral (often asymmetrical) and variable scope (correlated in the clinical severity). In encephalitis with anti-NMDAR antibody, the most evocative aspect is the existence of an antero-posterior cortical metabolic gradient with fronto-temporal hypermetabolism and parietal-occipital hypometabolism. Hypermetabolism of the basal ganglia is possible.

In encephalitis with antibody anti-LGI1, we find more often a pictureof hypermetabolism affecting the temporal regions and the basal ganglia. The hyper-

association and hypometabolism is rarer and no single hypometabolism was described. In other cases published by limbic encephalitis, we find rather temporal hypermetabolisms.

In a publication of Nantes in 2014, three CT-scan were performed and were all normal, in our series, we were not able to perform functional explorations because of their non-availability in our region.

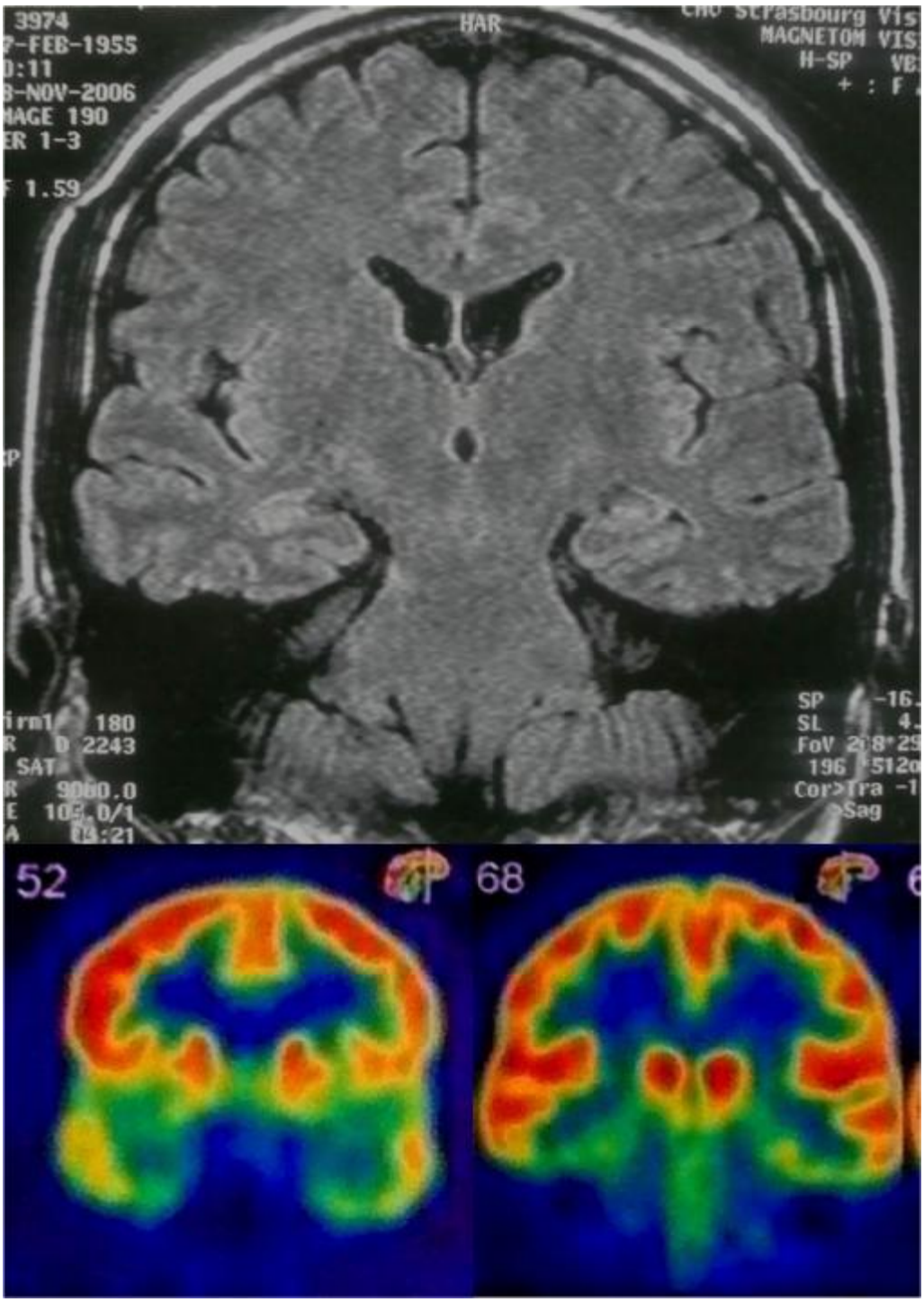


Fig. 23 : lack of temporal hyperintensity on MRI. Bitemporal hypometabolism on PET-FDG (limbic encephalitis antibody anti-LGI1)

- Other explorations:

Because of the frequent association with tumor, particularly in a teratoma [3][5][22], it is recommended to realize a search of a tumor with a thoraco-abdomino-pelvic CT scan (TAP) and a pelvic MRI for women.

The abdominal ultrasound by transvaginal ultrasound,often realized, does not seem sensitive enough. The probability of discovery of an underlying tumor is dependent on the age, sex and ethnic origin. The link to an ovarian teratoma is the most frequent, especially among black women over 18 years, the reason why it is necessary to practice a pelvic MRI for any diagnosis of limbic encephalitis in a woman in the absence of obvious cause.

Only 5 % of men over 18 years have an underlying tumor, which, according to the experts [5][39], still requires the search for a testicular cancer, lung or lymphoma by thoraco-abdomino-pelvic CT scan. The clinical supervision and necessary paraclinical at the patients not presenting a tumor to the diagnosis remains controversial, but various experts propose:

- In woman, a clinical and radioalogical follow-up for two years.
- In man, no special monitoring because of the weakest association [5][39].

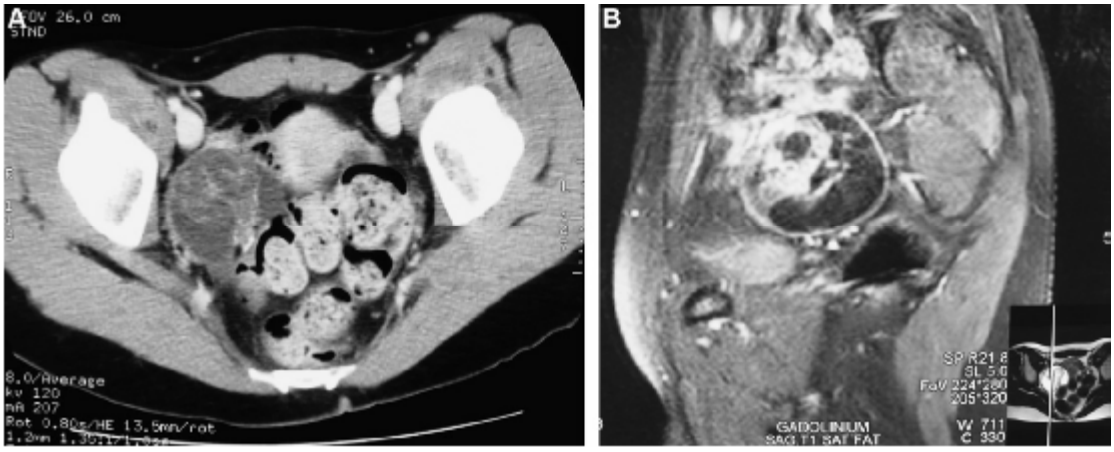


Fig. 24 : right abdomino-pelvic adnexal heterogeneous and cystic tumor, with contrast enhancement.

A : pelvic scan with contrast injection, horizontal section.

B : Pelvic MRI T1 sequence with fat saturation and gadolinium injection, sagittal saction.

In our study, thoraco-abdomino-pelvic CT scan was performed in nine patients; with normal aspect in four patients of them and abnormalities in the others, a pulmonary tissue mass in two patients, a recurrence of ovarian tumor was objectified in a female patient, a nasopharyngeal cancer in another patient, inguinal adenopathy in a female patient who has been diagnosed a cutaneous melanoma.

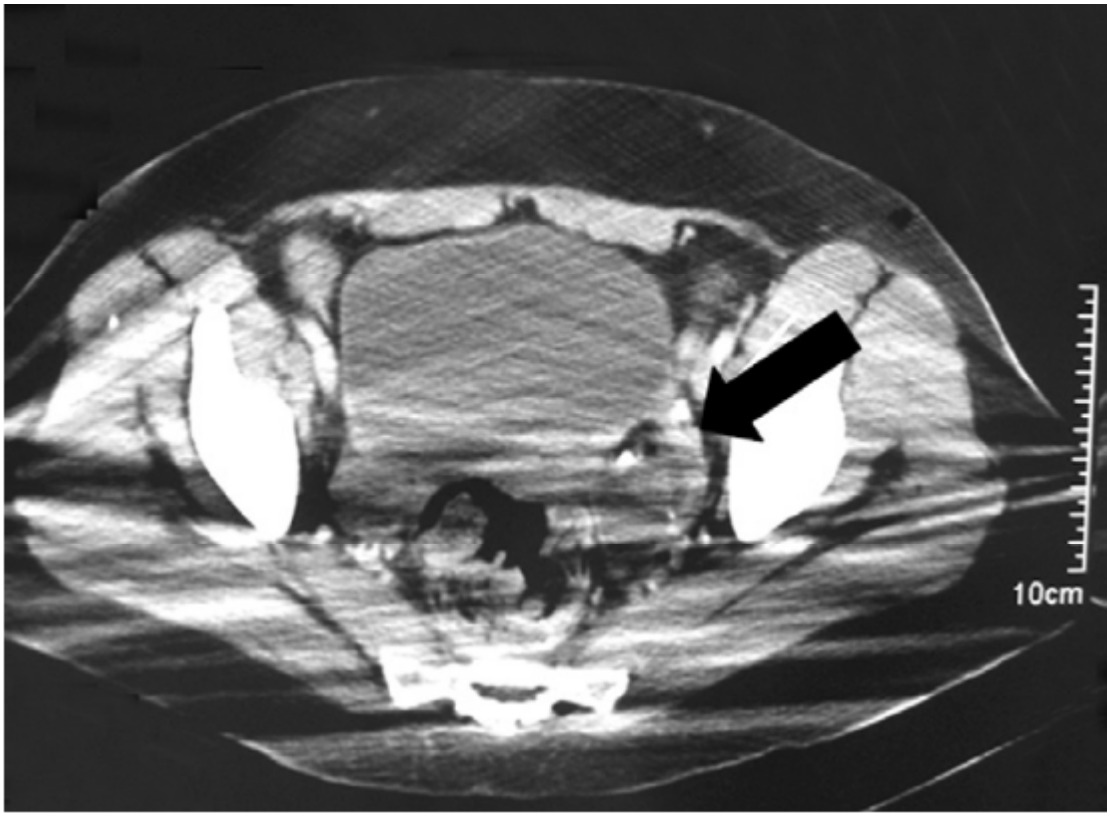


Fig. 25 : TAP CT scan : axial section showing a teratoma of the left ovary.

On one hand, in the study conducted in Nantes in 2014, thoraco-abdomino-pelvic CT was performed in seven patients with normal aspect in two female patient (28.5% of the cases) and abnormalities in the others, an ovarian lesion in two female patients a thyroid goiter and renal hypodensity in a female patient, atelectasis in one female patient and the team was not informed concerning another patient.

On the other hand, in the study of Grenoble of 2012, an etiologic review looking for a primary neoplasm was performed on thirteen patients by TAP CT scan. a functional imaging by TEP scan was performed on eight patients. A tumor was found only in two female patients: an ovarian teratoma supported surgically and an ovarian adenocarcinoma treated by surgery and cancer chemotherapy. For six patients, abnormal images have been described without being able to be reported to neither a precise etiology nor encephalitis picture.

The brain biopsy has no place in the diagnosis. Among the fifteen patients, who underwent a brain biopsy, nonspecific abnormalities like perivascular lymphocytic infiltrates, mainly B, low T lymphocyte infiltration and microglial activation were found [2][16]. autopsy data are similar[5][17]

b. Biology:

- Lumbar puncture:

CSF (Cerebrospinal fluid) examination is performed after eliminating an engagement risk by brain imaging.

The analysis of cerebrospinal fluid is abnormal in more than 90% of the cases [10]. It allows to highlight inflammation within the central nervous system and spreads a differential diagnosis

Thus, the cerebrospinal fluid has an inflammatory profile more or less marked depending on the case with lymphocytic hypercellularity usually moderate (one to a few tens of lymphocytes/mm3). The hyperproteinorrachia is usually less than 2g/l.

CSF proteins of the immuno-electrophorese often highlights the oligoclonal bands and there is an intrathecal immunoglobulin G

The herpes research viridae PCR must be systematic in front of any table of limbic encephalitis. The absence of abnormal cells and the normoglycorachie eliminate carcinomatous meningitis.

In the case of hyperbasophiles lymphocytes, the immunophenotyping allows to exclude brain lymphoma, which, although rare, is also a differential diagnosis.

The detection and titration of antibody anti-onconeural in blood and CSF is by immunohistochemistry.

In literature, the CSF is abnormal in 80% of patients at diagnosis. It finds a moderate lymphocytosis (9–219 elements/µl; median value: 24 elements/µl, a hyperproteinorrachia (56–129 mg/dl; median value: 67 mg/dl) with a normal glucose level [21].

Researches show that, specific oligoclonal bands were found in CSF in 60% of the patients [5].

In a serie of 100 cases published by Dalmau et al. in 2011, cerebrospinal fluid (CSF) was abnormal in 95% of cases with pleocytosis lymphocytic in 91% of cases (median 32 cells / mm3, 5-480), hyperproteinorrhachia in 32% of cases (0.49 g / l to 2.13 g / l) and oligoclonal distribution of gamma globulin in 26% of cases.

In another study of 2012, the lumbar puncture was abnormal in 93% in cases showing an inflammation of the central nervous system. These results are consistent to those found in the literature (Gultekin et al., 2000; Bataller et al., 2007). Although in some series dealing with complex LGI1 and VGKC antibodies, the CSF can be normal in the majority of cases (Lai et al., 2010; Vincent et al., 2004). These results show (demonstrate) that the normality of CSF does not eliminate the possibility of dysimmune encephalitis notably to anti-LGI1, but this review remains fundamental

in orientation toward an immune origin of a temporal epilepsy or a limbic damage(affection). The PL also helps, undeniably, to eliminate the other infectious etiologies in particular.

Another series of nineteen patients, published in Grenoble in 2012, showed that 68% of the PL was abnormal, with a lymphocytic reaction in 69% of cases, a hyperproteinorrhachia in 77% of cases and oligo-clonal bands in 7.6% of cases.

In our series, CSF analysis was performed in twenty-one patients, abnormal aspect was seen in seventeen patients 81% of cases, with Lymphocytic leukocytosis predominance and hyperproteinorrhachia in 100% of the cases, and oligo-clonal bands in 70% of the cases.

Table 7 : comparing CSF analysis between different series and literature

CSF analysis	Dalmau 2011	Grenoble 2012	Our study
abnormal	95%	68%	81%
Lymphocytic leukocytosis	91%	69%	100%
CSF protein increases	32%	77%	100%
Oligo-clonal bands	26%	7,60%	70%

- Research for onconeural auto-antibodies :

The immunological study consists of the research for biological arguments in favour of a disimmune etiology, having eliminated other differential diagnoses. It is divided into two major parts. On one hand, the study of onconeuronal antibodies and, on the other hand, the study of antibodies said to be "systemic", which are a marker of a more global inflammatory disimmune mechanism.

They allow the positive diagnosis of limbic encephalitis and determine the therapeutic care. This research is systematically made in front of a limbic encephalitis of a non-determined origin. A first commercial test (Ravo-test) allows the screening by dot blot of seven main onconeural antibodies (anti-Hu; anti-CV2 / CRMP5; anti-amphiphysin; anti-Ma1 and anti-Ma2; anti-Tr and anti-Yo). A research of anti-GAD must also be systematically carried out. When the clinical context is suggestive, a research of anti-NMDAr in the cerebrospinal fluid for CSF: (Cerebrospinal fluid) and/or of anti-VGKC in the serum is made in reference laboratories. The research for anti-AMPAr receptor is not routinely realized performed.

These antibodies can also be measured in the blood, but it is their presence in the cerebrospinal fluid which endorses the diagnosis. This research in the laboratory is made in two phases: a first stage of immunofluorescence on brain cut slices of a rat where it is possible to highlight the existence of an antibody in the cerebrospinal fluid of the patient capable of settling on the brain slices of a rat. A second specific stage (Cell Based Assay) using HEK293 cells over expressing the NMDAr (heteromers NR1 / NR2B) thanks to which it is possible to demonstrate the specificity of antibodies for the R-NMDA.

The important series of limbic encephalitis of Gultekin had then only allowed he description of three types of onconeural auto-antibodies associated with limbic

encephalitis: anti-HU, anti-your (or Ma2) and anti-my (or Ma1) [8]. It is about antibodies directed against intracellular neuronal antigens, which are at the origin of neuronal death by apoptosis phenomena. The research for antibody was negative in 40 % of the cases of his series. The later studies pursued by a small number of teams were interested, in the case of seronegative patients for classic onconeural antibodies, in the search of antibody against the antigens of neuropil [41][42]. Among these, antibodies anti-VGKC [43][44][45] and the antireceptor antibodies NMDA of the glutamate (NMDA-R) were individualized [21][46][47][48]. In certain patients, the rate of antibodies in the serum and in the cerebrospinal fluid evolved at the same time with the improvement.

In another study carried out in Strasbourg between 2000/2010 and published in 2011, onconeuronal antibodies were found in 56 % of the cases. Based on these two experiments, we notice that the presence of onconeuronal or systemic antibody is not necessary, but sufficient if associated with the health clinic to evoke the diagnosis of disimmune and/or paraneoplasic encephalitis.

The data of our study remain insufficient to draw conclusions, because five patients in whom we looked for onconeuronal antibodies had negative results.

- The PCR (polymerase chain reaction) tests :

The tests of amplification of nucleic acids such as the PCR are fast and more sensitive/ significant than the tests by cell culture. They are mainly used to detect the simplex herpes virus (SHV) at the level of the cerebrospinal liquid during an infection of the central nervous system (CNS). They are especially useful for the etiological diagnosis of encephalitis. Specific baits primers allow the identification of various genes of SHV-1 or 2 in the cerebrospinal fluid. The detection of the SHV by PCR demonstrates a sensitivity superior to 95 % and a specificity of about 98 %. However, positive and negative controls must be included in the various stages of

the process of preparation of the sample and the genomic amplification to avoid a bad interpretation of the results by false negatives and/or false positives. Furthermore, in the premature stage of the disease, it is possible to obtain false-negative results. In this case, it is necessary to redo lumbar punctures 1 to 2 days later. The best sensitivities are the ones obtained with samples taken between 2 and 10 days after the beginning of the symptoms.

In our study, herpes PCR tests were realized in the case of nine patients and were all negative. The diagnosis of herpetic encephalitis was based on the clinic and the cerebral MRI as well as the evolution.

Limbic encephalitis of herpetic origin arises at any age and appears as an acute necrotizing temporal encephalitis. It starts fast (less than 48 hours), with fever, headaches ;character, language and memory disorders. In the state of the case, a mental clouding precedes the coma, which can come along with convulsions or with paralyses. The cerebral MRI shows hypersignals T2 and flair affecting the limbic structures. The evolution of herpetic encephalitis is very serious with approximately 20 % rate of mortality, and grave sequels in the case of the surviving patients.

- Serological tests

Serological tests are indicated in case of the other techniques are not decisive. Such situations are observed when the patients develop recurring infections and during the absence of active lesions. Serums can be analyzed up to a few weeks after the appearance of the symptoms. Because of the deadlines of the humoral response, antibodies anti-SHV are not detectable during the acute phase of a primary infection. The use of this technique is useful to estimate the risk of the partners of the patients having clinical signs and immuno compromised people who are more susceptible to develop chronic recurrences. At present, the available tests can differentiate the infections caused by the SHV-1 and 2 with a high degree of

sensitivity. However, they cannot determine with certainty the site of infection.

- Other biological examinations:

On the biological plan, a hyponatremia by SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion) is very often found and represents a specificity of limbic encephalitis in anti-receptor antibody VGKC: 80 % versus very rare in the other limbic encephalitis (including in anti-NSA), except in case of an associated lung neoplasia [43][44][49]. The rest of the examinations is not generally contributory apart from sometimes an inflammatory syndrome in the paraneoplasic forms, and allows to eliminate the differential diagnoses: infectious, metabolic and deficiency encephalopathies, infiltering tumor, prion and other auto-immune diseases.

Clinical suspiscion of encephalitis :

Cognitive or psychiatric disorders,

confusion, epilepsy

Acute or subacute onset

Eliminate differnetial diagnoses :

(especially infectious)

CSF : viral serology (HSV, VIH) and bacterial (Syphilis, Lyme), INFα.

Biology : serum electrolytes, creatinine clearance, amoniémie, NFS, ASAT, ALAT, γGT, PAL, B1, B6, B9, B12, Glycémie, Gaz du sang.

MRI : brain tumor, posterior cerebral infarction, arguments for a Creutzfeldt-Jakob or a Gayet-Wernicke encephalopathy

EEG : arguments for a Creutzfeldt-Jakob, or a metabolic encephalopathy

Brain MRI (+FDG PET if MRI normal)
Atteinte temporale

CSF : GB, CSFprotein, CSF glucose, DOC
« inflammation »

EEG : temporal seizures, status epilepticus, intercritical focus

Paraneoplastic systematic review directed by the clini and found antibodies :
TAP CT completed by a whole body FDG-PET if normal ; testicular ultrasonography in men, +/-diagnosis orchiectomy if Ma2 and testicular cancer risk factors ; pelvic and transvaginal ultrasound in women, +/-pelvic MRI if anti NMDA-R ; mammography ; tumor markers(αFP, βHCG, CA125, ACE, cyfra21) have only a guidance value.

Comprehensive immunological tests :
Systemic antibodies : AAN, anti-DNA, anti-ENA, anti-phospholipides, anti-TPO and anti TG
Intracellular onco-neuronal antibodies : anti-Hu, Ma2, CV2, Amphiphysine, GAD
Membrane onco-neuronal antibodies : VGKC (LGI1 et CASPR2), NMDA-R, neuropile

Diagnosis of inflammatory limbic encephalitis (auto-immune and paraneoplastic)

III. Etiologies:

In addition to the infectious causes, other autoimmune limbic encephalitis conditions must be evoked. In the front row of these is encephalitis associated with antibodies anti-VGKC. The discriminating elements are most of the time insufficient to allow an immunological test. The series of Tan and al. [104], in 2008, allows to delimit the typical outlines of this condition described by Vincent and al in 2004 [44]. Compared with the patients affected by encephalitis with anti-NMDAR antibody, the patients having an encephalitis with anti-VGKC antibody were older (average 65 years) and presented myoclonia, impairment of the peripheral nerves, and the brainstem or the cranial nerves in respectively 29%, 25% and 19 % of the cases. Qualified as acute or as subacute, the mode of the beginning is described as slower and more progressive. The EEG (Electroencephalography) was not discriminating. The MRI was abnormal in 54 % of the cases, but the pattern of the lesions was not different from that described in encephalitis with anti-NMDA-R antibody. The cerebrospinal fluid was abnormal in a case out of two. In a remarkable way other auto-antibodies associated with anti-VGKC were described in this series and in that of Thieben and al of 2004 [43][104]. It was about intracellular onconeuronal antibodies, calcic anti-channels, antireceptor of the acetylcholin, anti-striatum, anti-thyroglobulin and anti-thyroperoxydase. The explorations in search of a neoplasia did not reveal teratomas among the cases of found neoplasia. These included mainly carcinomas and hematological cancers, and were found in less than half of the cases. It is to be noted that the therapeutic principles are identical to those of encephalitis with anti-NMDA-R and that the forecast seems similar [44]. The encephalopathy of Hashimoto, characterized by the presence of antibody anti-thyroglobulin and anti-thyroperoxydase, is also a differential diagnosis but this

auto-immunity is little specific, because it is frequent among the patients having an autoimmune neurological pathology, and it is possible that the progress to come will allow to dismember this syndrome which is very close to encephalitis with anti-VGKC antibody [43]. A new cause of autoimmune limbic encephalitis has been recently described [105]. These ten cases of limbic encephalitis associated with anti-receptor antibodies AMPA of the glutamate concerned patients from 38 to 87 years old. There were nine women and a man. The clinical presentation did not contain either abnormal movements or dysautonomia contrary to encephalitis with anti-NMDA-R. A neoplasia was present in seven cases out of ten (lung, breast, thymus). All the patients except one responded to the oncological or immunological treatment. Neurological relapses affecting the forecast, without a tumor recurrence being associated, were observed in six cases out of ten [105]. Finally, among the diseases of the system, the neurolupus and the neuro-Sjögren can be discussed and eliminated by the systemic and auto-immune balance sheet. Finally, the differential diagnosis with a psychiatric condition (pathological anxiety, psychogene crises, hysteria, pernicious catatonia) arises frequently at the beginning of the disease, especially as the explorations (EEG and MRI) cannot indicate an organic pathology.

In our study, we found 14 cases (63.6 % of the patients) of limbic encephalitis of infectious origin among which 04 were of syphilitic origin, 08 of herpetic origin, a single case of limbic encephalitis of tubercular origin and another whose cause was the varicella.

We also noted the presence of 05 patients (22.8 % of the cases) with limbic encephalitis of paraneoplasic origin, with three cases of limbic encephalitis without obvious cause.

Table 8 : limbic encephalitis causes in our study and literature

Limbic encephalitis	série Aupy	série M.Vaillant	Our study
Infectious origin	éliminée	éliminée	63,60%
Paraneoplastic origin	30%	30%	22,80%
Auto-immun origin	60%	30%	0%

IV. Differential Diagnosis:

In so far as the psychiatric disorders and the presence of abnormal movements only become secondarily obvious having questioned the family, the initial picture is often one of an encephalitis or a meningo-encephalitis. So It is necessary to eliminate quickly the infectious causes. Therefore, according to the French and English recent epidemiological studies [99,100], it is necessary to eliminate a herpetic meningo-encephalitis with Simplex Herpes virus, VZV (varicella-zoster virus), Mycobacterium tuberculosis and other classic germs. 21 % of the cases of infectiously supposed meningo-encephalitis in the English study were finally encephalitis of autoimmune causes [99]. Among these, the ADEM (Acute Disseminated Encephalomyelitis) is the most frequent cause [101-103]. Other paraneoplasic or autoimmune encephalitis (encephalitis of Hashimoto, neurolupus) can be evoked. A cerebral vasculitis or a multiple sclerosis under an atypical shape are rarer.

In the case of immunosuppressed patients, it is necessary to know how to look for rarer causes of viral encephalitis (VZV, cytomegalovirus, Epstein-Barr virus, Human herpes virus 6, virus JC), parasitic (toxoplasmosis, cryptococcosis) or bacterial (listeria, pneumococcus) [99]. Autoimmune or paraneoplasic encephalitis or is rarer in this context.

In every case, the entry into a psychiatric disease has to remain a diagnosis of exclusion. The presence of anomalies of the cerebrospinal fluid or the MRI make it impossible for a primitively psychiatric disease to exist.

1. Infectious encephalitis:

Viral encephalitis represents the main differential diagnosis. The clinical picture of a limbic encephalitis being very close to herpetic encephalitis, a treatment by acyclovir must be immediately established in front of any suspicion of limbic encephalitis. The highlighting of the herpetic virus in the cerebrospinal fluid has a 94 % sensitivity and a 98 % specificity, but it can be negative if it is realized more than 72 hours after the beginning of the symptoms. In the case of a viral impairment with SHV, the symptoms quickly evolve towards a deterioration of the state of consciousness associated with a focal deficit. Then the MRI shows frequently a cerebral oedema and a hemorrhagic encephalitis.

Other less frequent viral causes, such as the Varicella-Zoster Virus (VZV) and the cytomegalovirus (CMV) are often evoked. Nevertheless, the cerebral MRI rarely shows the anomalies of the temporal lobes described previously. The only exception is encephalitis with Human Harpes Virus 6 (HHV 6) which can mime a limbic encephalitis in immune-suppressed patients, in particular after a transplant of a bone marrow or of hematopoietic stem cells.

2. Autoimmune encephalitis:

a. Encephalitis of Hashimoto:

It is a rare, probably under-diagnosed encephalitis that affects patients between 2 years 10 months and 84 years. Marked by clinical neurological electroencephalographic disorders as well as the positivity of the antithyroid antibodies and a good response to corticoids.

The most reported clinical signs are shivers, transitory aphasia, headaches, and convulsive crises, sleep disorders, myoclonia, cognitive decline, psychosis /

hallucination, ataxia and a state of epileptic pain. The biological balance sheet shows a high blood rate of the antithyroid antibodies (anti-thyroid peroxydase, anti-thyroglobulin) with a hypothyroidism (63 % of the cases) or an euthyroidism (23 % of the cases). The lumbar puncture shows a hyperproteinorachia, normal immunoglobulins, rare oligoclonal bands and no pleiocytosis. The electroencephalogram is not specific and can sometimes be normal. The MRI is not specific with individual and temporal variability. It can be normal, as it can show a cerebral atrophy, or anomalies of the focal white and confluent substance, or a cortical irregularity and a vascular modification or even a cerebral oedema.

b. Neurolupus:

The systemic lupus erythematosus is an autoimmune disease affecting mainly the skin and the joints. The central and peripheral neurological manifestations are frequent during the systemic lupus but are not always attributable to lupus itself. The most frequent manifestations are cognitive dysfunction and headaches (50% to 80% of the cases); neuropsychiatric manifestations (91%) and other manifestations such as anxiety, chorea, convulsions and myelitis.

The study of the cerebrospinal fluid is not specific; it can show a hyperproteinorrachia (22 %), a lymphocystic pleiocytosis (22 %) or oligoclonal bands (22 %). The MRI is most of the time the reference examination. It is most often pathological in case of focused anomalies (19% to 70%), on which we can find lesions of the white periventricular and sub-cortical substance or lesions of the grey substance especially in the sequence T2. The MRI can be normal where from the necessity of other techniques such as the PET or the SPECT (Single-photon emission computerised tomography) arises. The treatment is based on the general corticosteroid therapy and the rituximab, which seems very promising in the case of neurolupus.

c. Encephalitis of Rasmussen:

Rasmussen encephalitis is an inflammatory disease affecting a single cerebral hemisphere. It is a rare and severe pathology, which is characterized by a focal drug resistant epilepsy, progressive cortical deficits (hemiparesis, cognitive decline, hemianopsia, phasic disorder) and a monohemispheric atrophy. In the encephalitis of Rasmussen, the PET is a good complement to the MRI to get a sure and fast diagnosis. The PET reveals a diffuse monohemispheric hypometabolism well correlated with the visualized atrophy on the MRI. There can exist hypermetabolic foci in case of important epileptic activity [26]. The antiepileptic treatments always have a limited efficiency. Only the hemisphrotomy improves the epilepsy, but with functional sequels. In this context, the use of immunotherapy has recently been reported.

V. Treatment:

Because of the recent description of the disease, no randomized study comparing the various proposed treatments is available for the moment. Hence, it impossible to propose a validated care based on evidences.

However, an immuno-modulatory therapy must be systematically proposed later or concomitantly in the oncological care. For encephalitis membrane antibodies, the treatment of choice remains the IgIV in the vector dose of 2g / kg on five days, as monthly cures initially, to adapt then according to the clinical response [5][44]. For intracellular antibody encephalitis, the effect of IgIV is more modest and hypothetical [17][67], the best treatment remains to this day to the treatment of underlying cancer. This is because of certain" intercellular" antibodies probably have no pathogenic role because the immunity involvement would be rather of cellular

mediation [8][17]. An Immuno-modulatory therapy can still be proposed but rather will be type of as immuno-suppressant cyclophosphamide [109] or type of monoclonal antibody like rituximab [110] even both. It could allow at least a stabilization of symptomatology and may be used only in second line in encephalitis with “membrane” antibodies [5]. Encephalitis in anti-GAD syndrome represent a particular case, elsewhere in unecohorte, they perfectly responded to immuno-modulators. In fact, the anti-GAD are intracellular but directly pathogenic (particularly in the cerebellar ataxias and stiff -man syndrome [98], by acting on the GABA synthesis enzyme.

The treatment by IgIV has demonstrated its efficiency in the care of the stiff man syndrome but remains empirical in the absence of study on big troops within the framework of the cerebellar syndromes and the limbic encephalitis .We propose a therapeutic algorithm based on our experience in clinical practice and the data of the literature.

1.Immuno-modulatory treatment

The proposed initial care is based on a treatment associating a corticosteroid therapy by methylprednisolone 1 g/d during five days which may or may not be associated with immuno-globulins IV in 0, 4 g / kg a day during five days [5]. A treatment by plasmapheresis was proposed instead of the IgIV or the association of corticosteroid therapy-immunoglobulin IV. In the absence of a response within ten days, Dalmau and al propose, for patients having a tumor, a second line treatment associating orituximab (375 mg / m2 every week during four weeks) and/or cyclophosphamide (750 mg / m2 at the same time as the first dose of rituximab, followed by one dose a month). The treatment is interrupted when a clinical

improvement is noticed [5].

This first-line therapeutic strategy seems effective in 80 % of the cases in case of ablation of the tumor [5]. In case of the absence of a tumor, only 48 % of the patients will have a favorable evolution with the same treatment. There is no study comparing the corticosteroid therapy or the immuno-globulins with plasmaphereses.

For the second line treatment, in the case of patients without a diagnosed tumor or with a delay in the diagnosis, a treatment of second line associating of rituximab (375 mg / m2 every week during four weeks) and of cyclophosphamide (750 mg / m2 at the same time as the first dose of rituximab, followed by one dose per month) was proposed with a clinical benefit in the case of 65 % of the patients [5].

Certain teams prefer to try plasmapheresis before envisaging a treatment by rituximab. There is no datum as for the duration and the number of necessary sessions of plasmapheresis.

Because of the risk of relapse, certain teams suggest maintaining an immunosuppression by mycophenolatemofetil or azathioprine during at least one year [3][5]. The evolution of the concentration of antibodies in the cerebrospinal fluid can be used to monitor the treatment and to determine its duration.

In our study, seen that 63.7 % of the patients had limbic encephalitis of infectious origin and that the treatment by acyclovir was effective in almost all the patients followed, the immuno-modulatory treatment by intravenous immunoglobulins and immuno-suppressor was prescribed in the case of patients who did not initially improve under acyclovir.

2. Removal/resection of the tumor at issue

In case a tumor is highlighted, the surgical ablation is the rule [3]. It is on its treatment that depends the outcome of limbic encephalitis, and it would seem that the outcome is better as long as the surgical operation is early [3]. Therefore, a cancer is looked for systematically in the case of a limbic encephalitis by a thoraco-abdomino-pelvic scanning and a TEP with fluorodeoxyglucose. According to the type of identified autoantibody, the carcinologic search must be oriented. As indicated previously, a teratoma of the ovary is to be looked for (pelvic MRI and/or endovaginal ultrasound) in the case of women presenting an anti-NMDAr. For men presenting a limbic encephalitis with anti-Ma2 and the risk of cancer of the testicle (calcifications or cryptorchidism), a systematic orchidectomy with anatomopathologic examination may be indicated. Finally, the prolonged follow-up of patients with an anti-Hu demonstrates that this antibody joins in practically all the cases with cancer, especially, bronchial cancer with small cells. The anatomopathologic examination of the operating specimen finds in women a mature ovarian teratoma in 35 % of the cases, an immature teratoma of the ovary in 14 % of the cases and in men an immature teratoma of the testicle in 1 % of the cases [3]. A case of neuroblastoma was described in a four-year-old child [108].

Spontaneous improvements were however described without treatment [46]. The recovery could be longer, the deadline of hospitalization could be longer and the relapses could be more frequent.

3. Anti-infectious and anti-viral treatment

To handle a herpetic encephalitis, acyclovir is administered by intravenous way at a dose from 10 to 15 mg / kg every eight hours for a period from 10 to 21 days. Certain studies suggested that higher doses (up to 60mg / kg a day) can be considered despite the neurotoxicity that this treatment can cause. It is preferable to introduce the treatment as fast as possible to reduce the neurological sequels which can be associated with the infection [112][113]. Furthermore, the duration of the treatment can be extended as long as the viral DNA is detected in the cerebrospinal fluid. The emergence of HSV (Herpes Simplex Virus) strains resistant to acyclovir can in some cases result in a therapeutic failure. Indeed, mutations located in the gene of the TK (Thymidine Kinases), which intervenes in the first stage of phosphorylation of the acyclovir reduces the efficiency of the latter.

In the case of some patients affected by herpetic encephalitis, the MRI highlights a deviance of the secondary median line to a cerebral oedema. In this case, corticosteroids, which are anti-inflammatory drugs, are administered in combination with the antiviral agent to control the inflammatory response [114][115]. Clinical studies realized on 45 patients suggested that the administration of corticosteroids in the acute phase improves the outcome of the disease. In spite of the limits of these studies related to the limited number of the patients, there are obvious facts that the administration of an anti-inflammatory agent could be considered in a treatment combined with acyclovir. However, no cohort study which allows to establish a guide of clinical recommendations for the administration of anti-inflammatory drugs to patients affected by herpetic encephalitis has been carried out up to now [116].

In our study, an initial treatment with acyclovir IV was administered in the case

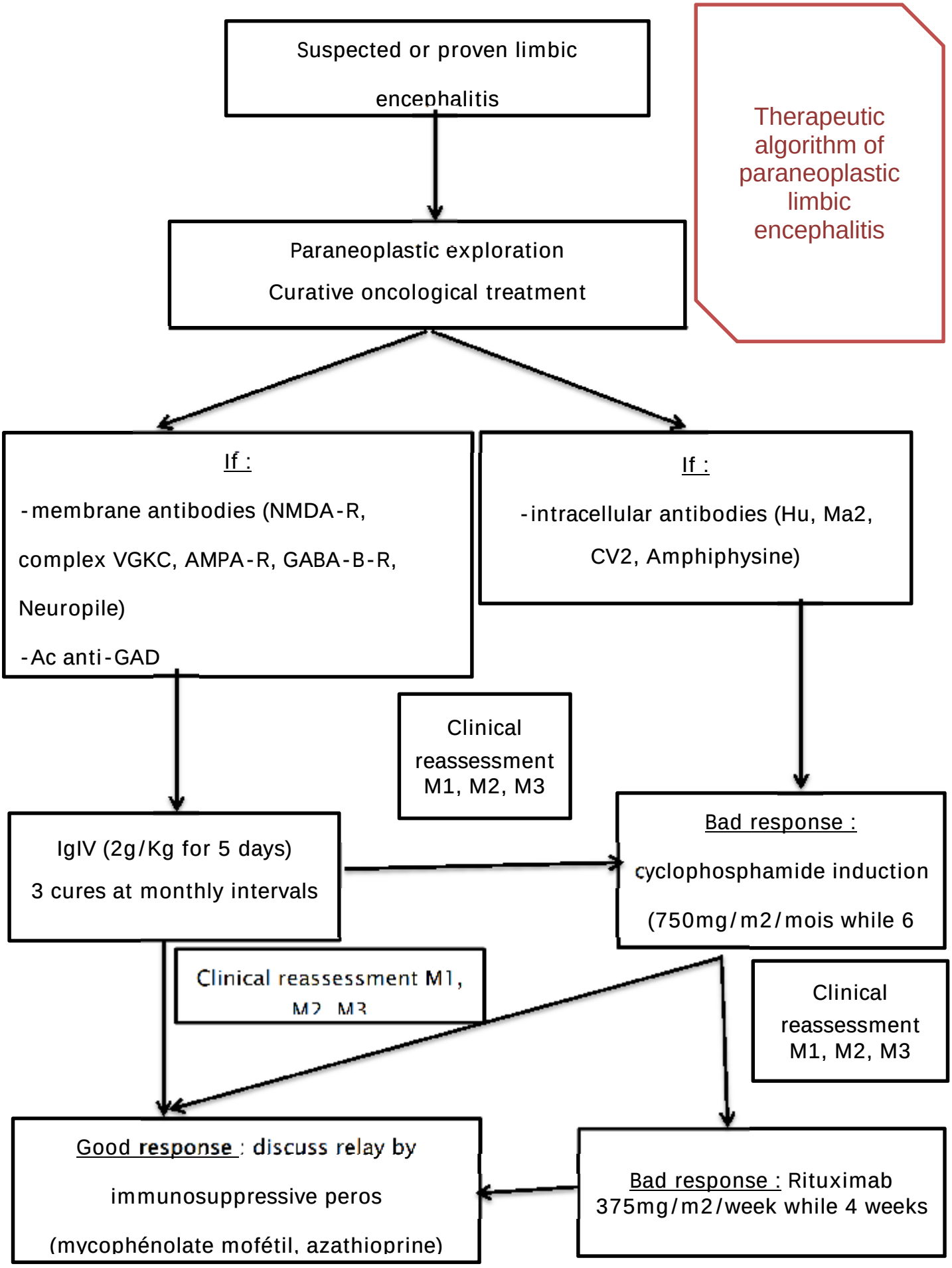
of 16 patient (72.7 % of the cases), Only a single patient did not respond positively.

4. Symptomatic treatment

As for the symptomatic treatment, it is administered for the semiology appropriate to such or such variety. In a concomitant way, a symptomatic global care is necessary. It goes through a treatment of the epilepsy, a neuropsychological and motor rehabilitation, a care for the inappropriate secretion of anti-diuretic hormone (SIADH) and the treatment of the hyponatremia which results from it in particular potassium canalopathies treatment of the disorders of ventilation during the forms with antibody anti-NMDAr, treatment of insomnia, the intestinal pseudo-obstruction, the psychiatric disorders and the dysautonomia.

On the symptomatic plan, neuroleptics or antidepressants were administred within the framework of the psychiatric disorders. Painkillers and antiepileptics were administered with an antiepileptic aim or even against abnormal movements. Antibiotic treatments were administered according to the developed infection.

Whereas in a study led by Dalmau, the conduct of the specific treatment is based on immunomodulatory drugs or immunosuppressors : In the absence of tumor and in the first intention, use of immunoglobulins associated with corticoids and possibly with plasmapheresis of difficult implementation in the case of a child or an agitated and non-cooperative patient; in the presence of tumor, in addition to the aforesaid treatment, are carried out. In the second intention, in case of bad response to the first line of treatment, rituximab or cyclophosphamide, and even their association, are then indicated, pursued by a monthly cure of cyclophosphamide.


Therapeutic algorithm of paraneoplastic limbic encephalitis
Suspected or proven limbic encephalitis
Paraneoplastic exploration
Curative oncological treatment
If :
-membrane antibodies (NMDA-R, complex VGKC, AMPA-R, GABA-B-R, Neuropile)
-Ac anti-GAD
If :
-intracellular antibodies (Hu, Ma2, CV2, Amphiphysine)
Clinical reassessment M1, M2, M3
IgIV (2g/Kg for 5 days)
3 cures at monthly intervals
Bad response :
cyclophosphamide induction
(750mg/m2/mois while 6
Clinical reassessment M1, M2, M3
Clinical reassessment M1, M2, M3
Good response : discuss relay by immunosuppressive peros
(mycophénolate mofétil, azathioprine)
Bad response : Rituximab 375mg/m2/week while 4 weeks

VI. Evolution

The mortality is 4 % with a median deadline until death of 3.5 months (one-eight months) [3][5]. Most of the patients died in ICU because of toxic shock, heart attack, acute respiratory distress syndrome and a state of refractory disorder.

With an immunomodulatory treatment possibly associated with surgery in case of a diagnosed tumor, the regression of the symptoms is classically made in the inverse order of their appearances with a slow and progressive awakening, a stabilization of the autonomous system, the disappearance of the central hypoventilation, the recovery of language and executive functions [5]. Approximately 75 % of the patients have a favorable evolution without sequels or the continuation of moderate disorders of consciousness, impulsiveness, disinhibition, sleeping disorders with hypersomnia or modification of the circadian rhythm [5]. It would seem that the patients remotely keep a complete and persistent amnesia of the episode. The average deadline between the beginning of the symptoms and the first signs of improvement is of eight weeks (between 2 and 24 weeks) in the case of patients early taken care of for a tumor, of 11 weeks (4 - 40) in the case of patients handled late for their tumor and of ten weeks (2 to 50) for those having no underlying tumor [3].

These patients are often hospitalized for a few months in the acute phase (between three and six months on average and until 15 months in reanimation_ personal data). A long period of rehabilitation is then often necessary.

The risk of relapse is estimated at 25 %, increasing on average in the first 18 months, more frequently in patients taken care of late for a teratoma or without diagnosed tumor or following a tumoral relapse [5].

Spontaneously favorable evolutions were described in every case in a series of

four cases without ablation of the teratoma at issue which was present in three cases [46]. But the deadline of improvement going from one month to one year, and the severity of the symptoms, requiring staying in ICU for several months and the amputation of both lower limbs in one case, induce a fast aggressive therapeutic conduct which could shorten the deadline of clinical improvement and decrease the risk of complications, even fatal evolution, including tumoral resection when a tumor is highlighted.

The follow-up of the patients shows that most of them find a normal and even an improved cognitive functioning [21][46][48] unlike limbic encephalitis within the framework of paraneoplasic syndromes whose neurological outcome remains reserved.

The treatment by acyclovir by intravenous way must be started once the diagnosis is evoked. The evolution of herpetic encephalitis is very serious: approximately 20 % of mortality, with severe sequelaes in the case of the surviving patients. Among the predictive factors of death: age and especially the deadline acyclovir is introduced.

Sixteen of our patients benefited from a treatment by acyclovir IV, and fifteen among them responded well the to treatment (93.75 % of the cases), whereas the sixteenth was put under immunomodulatory treatment.

Several observations are today showing a better prognosis of encephalitis with antibodies run against antigenic membrane targets because they are probably directly pathogenic.

In a study carried out in Strasbourg, the improvement was significant in 76 % of the cases, complete in 31 % of the cases. Relapses were observed in 25 % of the cases. A stabilization of the symptomatology was obtained in 12 % of the cases. 12 % of the patients presented a progressive detereoration until death. In the same

study, the evolution of the epilepsy was good with a disappearance of the seizures in 100 % of the cases.

In the series of Dalmau and al. 2011, 47 % had a complete recovery, 28 % had a recovery with light sequels, 18 % with heavy sequels and 7 % died.

In our study, the clinical follow-up showed a variable evolution. Three deaths were noticed. These three patients had a limbic encephalitis of paraneoplasic origin. A patient was admitted for psychiatric disorders complicated with disorders of consciousness, and died a few days after her admission into ICU. The second patient died one day after biopsy of her melanoma in a picture of pulmonary embolism. The third patient died six months after the diagnosis of limbic encephalitis with carcinoma relapse of the ovary. A clinical recovery with sequels was observed in six patients, a complete recovery was noticed in three patients. Besides, we lost contact with nine patients. Epileptic seizures in our study persisted only in the case of a single patient, that is an improvement in 95.5 % of the cases.

CONCLUSION

Limbic encephalitis are neurological pictures associating in general disorders anterograde memory, an epilepsy and neuropsychiatric disorders of acute or sub-acute evolution.

Their etiologies are often inflammatory, dysimmune or infectious.

The diagnosis of limbic encephalitis, the most frequent and the most urgent to spread, corresponds to the herpetic encephalitis. It is about a therapeutic emergency given the risk of necrotic lesion progression with the irreversibility of symptomatology.

The frequency of auto-immun encephalitis, especially encephalitis with antibody anti-receptor NMDA glutamate, is probably underestimated due to lack of appropriate diagnostics until recent years.

This pathology is more common in young patients. Both sexes are affected with a slight female predominance.

The most salient semiologic characters are acute or subacute facility, within days or weeks of temporal seizures, an anterograde amnesia or psychiatric disorders like depression, syndrome, irritability, behavior disorders ou delirium with hallucinations.

The clinical triad consists of temporal epilepsy, anterograde amnesia and neuropsychiatric disorders is the cornerstone of the clinical diagnosis of limbic encephalitis.

It is frequent that patients have extra-limbic reached which also depends on the etiology of limbic encephalitis.

It is possible that these symptoms are preceded by prodromes consisting of headaches, fever and vomiting.

Limbic encephalitis diagnosis is not based solely on clinical but also on additional examinations, especially ; the magnetic resonance imaging ; the EEG ; and

the study of cerebrospinal fluid.

PET scan is also important for the diagnosis of limbic encephalitis, but was not used in our study because of the non availability of the device.

Auto-antibodies search could help in etiological diagnosis of limbic encephalitis.

Limbic encephalitis causes are different, next to the infectious origin (63.6% of our patients) which is dominated by herpetic encephalitis (36.36% of our patients) and syphilitic encephalitis (18.18% of our patients). Non-infectious origin, auto-immune or paraneoplastic, is the second etiology to searcg after eliminating herpetic encephalitis and other infectious causes.

The management of paraneoplastic limbic encephalitis is mainly based on the specific cancer treatment. The treatment includes, in addition to the removal of a possible tumor, an immunological treatment whose protocol is relatively standarised even if it has not been subject of randomized trials.

However, an immunomodulatory therapy should be systematically proposed after or concomitanly with oncological therapy. For encephalitis membrane antibodies, the treatment of choice remains IVIg to the classic dose of 2g/kg for five days, in the form of monthly courses initially, to then adapt depending on the clinical response. For encephalitis intracellular antibodies, the effect of IVIg is much more modest and hypothetical, and the best treatment to date remains underlying cancer treatment.

The evolution of limbic encephalitis varies from complete recovery without sequelae to death.

The evolution of herpetic encephalitis is extremely serious : 20% of mortality, with serious sequelae among surviving patients.

The mortality rate is 4% with a median time to death of 3.5 months.

Approximately 75% of patients had a favorable evolution without sequelae or persistent moderate attention disorders, impulsivity, disinhibiting, sleep disorders with hypersomnia or modification of the circadian rhythm.

The risk of relapse is estimated at 25%, occurring on average in the first 18 months.

Abstract

Thesis : limbic encephalitis spectrum

Author : Ahmed FILALI ADIB

keywords: encephalitis, limbic system, seizures, anterograde amnésia, herpeticencephalitis.

Limbic encephalitis are neurological manifestations associating in general anterograde memory disorders, an epilepsy and neuropsychiatric disorders of acute or sub-acute evolution.

In this work translated into english, we are interested in limbic encephalitis whatever the clinicalpicture; acute or sub-acute ; combining cognitive disorders or behavior changes and especially : seizures, anterograde amnesia and psychiatric disorders.

Therapeutic modalities depend on etiologies : infectious, immunological or paraneoplastic.

Outcome in limbic encephalitis is very variable, ranging from full recovery without sequelae to death.

The aim is to emphasize that the limbic encephalitisis a disease that could have a good prognosis if it is supported on time.

Résumé

Thèse : spectre des encéphalites limbiques

Auteur : Ahmed FILALI ADIB

Mots clés : encéphalite, système limbique, épilepsie temporale, amnésie antérograde, encéphalite herpétique.

Les encéphalites limbiques sont des tableaux neurologiques associant en général des troubles de la mémoire antérograde, une épilepsie et des troubles neuropsychiatriques d'évolution aigüe ou subaigüe.

Dans ce travail traduit en anglais, nous nous intéressons aux encéphalites limbiques quelque soit le tableau clinique ; aigü ou subaigü ; associant des troubles cognitifs ou des modifications comportementales et plus particulièrement des crises épileptiques, une amnésie antérograde et de troubles psychiatriques.

Les modalités thérapeutiques dépendent des étiologies infectieuse, immunologique ou paranéoplasique.

L'évolution des encéphalites limbiques reste très variable allant de la guérison totale sans séquelles jusqu'au décès.

L'objectif étant d'insister sur le fait que l'encéphalite limbique est une pathologie qui pourrait avoir un bon pronostic si elle est prise en charge à temps.

ملخص

العنوان : طيف التهاب الدماغ الحوفي

من طرف : أحمد فيلالي أديب

الكلمات الأساسية : التهاب الدماغ - التهاب الدماغ الحوفي - الصرع - اضطرابات الذاكرة - الهربس - التهاب الدماغ

التهاب الدماغ الحوفي هي الجداول العصبية التي تقدم اضطرابات في الذاكرة قدمية والصرع والاضطرابات العصبية والنفسية وهي ذات تطور حاد أو شبه حاد.

في هذا العمل المترجم للإنجليزية ، نهتم بدراسة أعراض المرض الذهنية والسلوكية وخاصة النوبات الصرعية واضطرابات الذاكرة والاضطرابات النفسية.

ترتبط الأشكال العلاجية بأسباب المرض المتنوعة: مناعية ، أو ورمية.

يختلف تطور المرض باختلاف الأسباب بين الشفاء الكامل والوفاة.

الهدف من هذه الدراسة هو التأكيد على ضرورة العلاج المبكر لتفادي قدر الإمكان مضاعفات المرض.

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