
**Association between mesial temporal
sclerosis and suicidal behavior in
patients with temporal lobe epilepsy:
A 5-year prospective cohort study**

END OF TERM PROJECT

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*“Melancholics ordinarily become epileptics, and epileptics, melancholics:
what determines the preference is the direction the malady takes;
if it bears upon the body, epilepsy, if upon the intelligence, melancholy”*

Hippocrates, 400 B.C.

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1. ABSTRACT

Background: Epilepsy is the most common neurologic disorder worldwide. As a chronic condition, it provokes a great burden for people who suffer it and it is a source of a lot of complications. In addition, it also predisposes to a loss of life expectancy because it increases the risk of suffering accidents and other pathologies. One of the leading, and poorly studied causes of death in epileptic patients is suicide, which may affect an important part of them. Numerous risk factors have been described, especially mental disorders, psychosocial or familiar stressors, antiepileptic drugs, type and frequency of seizures or presenting refractory epilepsy. Although 60% of patients with refractory epilepsy correspond to people with mesial temporal sclerosis, this lesion is not included among the risk factors for autolytic behavior.

Objective: The aim of this study is to analyze whether the presence of mesial temporal sclerosis is associated independently with a major risk of developing suicidal behavior in patients with temporal lobe epilepsy.

Methods: The study will be an observational analytic prospective cohort study with a follow-up of 5 years performed at Hospital Josep Trueta de Girona and Hospital Santa Caterina de Salt. Using a non-probabilistic consecutive sampling, patients aged 14 or more with current or new diagnosis of temporal lobe epilepsy will be recruited and divided depending on the presence of mesial temporal sclerosis. The two groups will be followed in order to analyze suicidal behavior appearance (ideation, attempt or completed suicide).

Key words: epilepsy, suicide, behavior, temporal lobe epilepsy, mesial temporal sclerosis, psychiatric disorders

2. ABBREVIATIONS

MTS	Mesial temporal sclerosis
TLE	Temporal lobe epilepsy
HS	Hippocampal Sclerosis
CNS	Central Nervous System
mTLE	Mesial temporal lobe epilepsy
HJT	Hospital Josep Trueta
HSC	Hospital Santa Caterina
MDD	Major depressive disorder
SLE	Schizophrenia like psychosis of epilepsy
ILAE	International League Against Epilepsy
AED	Antiepileptic drugs
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
PET	Positron Emission Tomography
EEG	Electroencephalogram
EKG	Electrocardiogram
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases (ICD)
PD	Psychiatric disorder
HADS	Hospital Anxiety and Depression Scale
CEIC	Comisión Ética en Investigación Clínica
M.I.N.I	Mini International Neuropsychiatric Interview
WHO	World Health Organization

3. INTRODUCTION

3.1. EPILEPSY: A REVIEW

Epilepsy is the most common neurologic disorder worldwide, affecting about 50 million people (1). The prevalence of active epilepsy (people in treatment or with seizures in the last 5 years) is 5-8 per 1000 population in high-income countries, whereas the number rises to 10 per 1000 population in low-income countries and even higher in rural areas (2). The annual incidence in Spain is 31-57/100.000 inhabitants, being higher between 6 and 14 years, adolescents and elderly people (especially above 60 years with an incidence of 134/100.000). Approximately 5-10% of general population will suffer a seizure during their lifetime and until 20% of them will have recurrent seizures (3).

Epilepsy is characterized by the recurrence of seizures, which translate continuous simultaneous discharges of a large group of neurons, leading to the interruption of their normal function. In order to clarify concepts, it is important to distinguish the terms *seizure* and *epilepsy*. The first one is defined by the International League Against Epilepsy (ILAE) as “*a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*”, whereas the second one is characterized as “*an enduring predisposition of the brain to generate epileptic seizures, with neurobiological, cognitive, psychological, and social consequences*” (4).

Due to its difficult interpretation in clinical settings, the ILAE recently proposed a new operational clinical definition that can be used in everyday practice (5). Thus, epilepsy can be diagnosed if we have one of the following:

1. At least two unprovoked (or reflex) seizures occurring > 24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%) occurring over the next 10 years
3. Diagnosis of an epileptic syndrome.

In addition, epilepsy is considered to be resolved in individuals who (5):

- a. Either had an age-dependent epilepsy syndrome but are now past the applicable age
- b. Those who have remained seizure free for at least 10 years and without antiepileptic drug (AED) for 5 years.

3.1.1. Classification of epilepsies

Since 1981 and later in 1989, the ILAE Commission on Classification and Terminology proposed a nomenclature to classify epilepsies. Later, Berg AT et al. (6) suggested changes regarding terminology and groups but these changes still constitute a topic of debate and they are far to be accepted. For practical reasons, this report will focus on the old ILAE classification because it is still widely used for clinical management and research.

Regarding to 1981 classification, there is a major dichotomy involving three main groups (*see Annex 2*):

- (1) **Generalized seizures** when “*the discharge bilaterally and diffusely involves the entire cortex*” (7) with six subtypes
- (2) **Partial or focal seizures** when “*the neuronal discharge is thought to originate within one region of the cerebral cortex*” (7) which are sub-classified in:
 - a. Simple partial (without impairment of consciousness)
 - b. Complex partial (with impairment of consciousness)
 - c. Partial seizures evolving to secondarily generalized seizures
- (3) **Unclassified epileptic seizures** when there is insufficient evidence to characterize as partial, generalized or both.

On the other hand, the 1989 Epilepsy classification and Epileptic syndromes grouped it depending on causative agent into idiopathic, symptomatic and cryptogenic; and made an organization of epileptic syndromes depending on their origin (partial or generalized) and etiology.

3.1.2. Clinical manifestations

In general, focal seizures are more common than generalized ones and, among the first, those with temporal lobe epilepsy (TLE) represent the 60% (8). Anyway, the most frequent manifestation that brings a patient to the physician is a tonic-clonic seizure (type of generalized seizure). The clinical expression will vary depending on type and area of the brain involved.

3.1.2.1. Generalized seizures

Generalized seizures affect both hemispheres and are classified clinically into convulsive or *grand mal seizure*, consisting in excessive abnormal muscle contractions that usually are a

combination of tonic and clonic phases; and not convulsive or *petit mal seizures*, which includes typical and atypical absences and often begin in childhood (see *Table 1 for a summary*).

Table 1. Clinical classification of Generalized Seizures			
	TYPE	SUBTYPE	CLINICAL EXPRESSION
CONVULSIVE	Myoclonic	May be atonic or tonic	Sudden brief involuntary unique or multiple muscle contractions
	Tonic		Sustained increase in muscle contraction lasting seconds to minutes
	Clonic		Regularly repetitive contractions involving the same muscle groups at a rate of 2-3 cycles per second
	Tonic-clonic		Sequence involving a first tonic contraction followed by a clonic phase
	Atonic		Sudden loss or decrease in muscle tone lasting 1-2 seconds, involving head, trunk, jaw or limb musculature
	NON-CONVULSIVE	Absence	Typical
Atypical			Longer than typical absence, usually with myoclonic, tonic, atonic, autonomic features and automatisms

3.1.2.2. Focal seizures

Focal seizures vary depending on which cortical zone is stimulated. For instance, in those with frontal origin, motor symptoms can be observed if there is a stimulation of the primary or supplementary motor cortex (clonias, Jacksonian march, fencing posture...); somatosensory perceptions such as tingling, pins and needles, numbness or burning if parietal lobe is implicated; or visual hallucinations (flashing colored lights, geometrical figures, loss of vision, strange faces, etc) if occipital lobe is involved. Special mention deserves those from temporal lobe origin, which are characterized by auras (epigastric sensations, emotions like fear and anxiety), oroalimentary automatisms, head turning, auditory hallucinations and other.

3.1.3. Diagnosis

Any patient with a clinical suspect of epilepsy should have an accurate medical history with a personal (age of onset, febrile convulsions history, seizure type, obstetric complications, AED

used, psychomotor development, etc) and family history. It is also mandatory a 12-lead ECG to rule out cardiac abnormalities, an EEG (preferably intra-ictal) to determine stimulated areas, a neuroimaging (CT or MRI) to discard organic involvement, and proper laboratory tests (serum glucose, sodium, magnesium and calcium levels), urine analysis for toxicology and lumbar puncture if required (9). The diagnosis of epilepsy may be difficult because other afflictions may have similar symptomatology (syncope, pseudo-seizure, stroke, transient global amnesia, vertigo, migraine, etc).

3.1.4. Treatment, prognosis and mortality

The base of treatment are antiepileptic drugs (AED), which will be prescribed depending on epileptic type, seizure recurrence, likelihood and severity of physical or psychosocial consequences with further seizures and always when benefits outweigh the risks. It is also important to recognize and change any environmental, physiologic or lifestyle trigger (sleep deprivation, irregular sleep habits, alcohol abuse) which can reduce the seizure threshold.

To add on, these patients are at higher risk of suffering medical complications, poor psychosocial outcomes and stigmatization; decreasing their quality of life. They also have less life expectancy and increased mortality, mainly due to seizure-related deaths (status epilepticus, drowning, trauma, fatal drive crashes, sudden unexpected death syndrome, etc), medical or surgical treatments (reactions to AED, etc), underlying medical diseases (especially neurologic) and suicide; which is the main issue of the present study.

3.2. SUICIDE: AN OVERVIEW OF THE PROBLEM

Suicide is a public health problem which encompasses approximately 1 million deaths around the world each year, representing an annual global age-standardized rate of 11.4 per 100.000 inhabitants (10). Nonetheless, these numbers tend to be underestimated because, as a sensitive issue and even illegal in most countries, is often under-reported. Regarding to age and gender, suicide tends to be higher in elderly for both sexes but, in some countries, rates are higher among the young (especially 25-45 years), being one of the first causes of premature death (10).

The American Psychiatric Association defines suicide as a “*self-inflicted death with evidence (either explicit or implicit) that the person intended to die*” and they also introduce three key concepts: *suicidal ideation* (thoughts of engaging in suicidal behavior), *suicidal attempt* (non-fatal intent) and *completed suicide* (fatal intent) (11).

Suicide also affects community health. For instance, survivors of an attempted suicide often present previous mental disorders and may have serious injuries like bone fractures, spinal cord injuries and brain or organ damage. Likewise, their families and friends may usually feel shock, anger, guilt, hopeless and depressive, often requiring professional help. Therefore, the medical costs and lost wages associated also take their toll on the community.

3.2.1. Risk and protective factors

There are several risk factors for suicide; among the most common we can find:

- **Sociodemographic:** age (adolescence and elderly), gender (males during elderly and females in the adolescence), race, marital status, sexual orientation or occupation.
- **Mental disorders:** the most prevalent are mood disorders (especially major depressive disorder (MDD)). Other conditions include schizophrenia, anxiety and eating disorders, attention deficit hyperactivity disorder, substance abuse disorders and other.
- **Previous suicidal behavior:** may rise even 50-fold the risk of committing suicide.
- **Physical illness:** may influence in several ways: increasing the risk by themselves, promoting psychiatric conditions, act as a psychological stressor, etc. Among physical illness we should emphasize: CNS diseases (epilepsy, multiple sclerosis, Huntington disease, etc), malignant neoplasms, human immunodeficiency virus, etc.
- **Family history of suicide:** apparently through genetic as well as environmental factors.
- **Psychosocial features:** lack of social support and relationships, gender violence, childhood traumas, etc

On the other hand, there are also several protective factors: religiosity, pregnancy, life satisfaction, good coping and problem solving skills, positive social support or a good family unity are some examples of it (11).

3.2.2. Can we prevent suicide?

Even if suicide is preventable, it requires coordination and collaboration among multiple society sectors such as health, education, labor, law, defense, politics or media. It is necessary to give up stigmatizing and to begin working on it. Several measures can be taken in laws, hospitals and primary care professionals and some of them should include: reducing access to suicide, treating substance abuse, training healthcare professionals in identifying this behavior early, to control people with previous history and identifying those illnesses which increase risk.

3.3. PSYCHIATRIC COMORBIDITY IN EPILEPSY

Psychiatric conditions are frequent in epileptic patients and it has important clinical and therapeutic implications. Tellez JF et al. (12) reported an annual incidence of mental disorders of 24%, whereas the number raised to 35.5% during lifetime. Among psychiatric diagnosis the most frequent are depression, psychosis, personality disorders and/or behavioral problems. On one hand, epilepsy can precede, co-occur or follow the diagnosis of mental disorder; and on the other hand, psychiatric symptoms can be classified according to the temporal relationship with seizures into **peri-ictal** (during and related to the seizure) and **inter-ictal** (between seizures).

As reviewed by Valente KD & Busatto G (13) and Tellez JF et al. (12) depression is the most frequent psychiatric disorder, affecting 15-50% of epileptic patients and especially those with temporal lobe origin. Several factors have been involved in determining this strong association, including: endogenous condition, psychosocial effects, adaptive processes, iatrogenic factors, a bidirectional relationship with high incidence of secondary epilepsy in prior depressed patients and vice-versa or a functional dysregulation of limbic circuits and “*dysfrontality*” (14).

Despite its frequent comorbidity, depression in epilepsy still remains underestimated, probably because there is a lack of patient’s reporting, minimization of symptoms or a possible atypical presentation (14). Part of this phenomenon may be explained by the lack of specific diagnostic criteria. Neither in the current DSM-V nor the ICD or ILAE classification is considered this entity. Furthermore, the lack of evidence concerning the use of antidepressant drugs for MDD prevents physicians treating these patients.

On the other hand, schizophrenia-like psychosis of epilepsy (SLE) also appears as a comorbid condition. Psychotic symptoms affect 5.6% of epileptic patients and even 7% if they are affected by temporal lobe epilepsy (TLE); representing 7.8 times more than non-epileptic patients (15). Several mechanisms have been implicated, including: neurotoxic effect, adverse effects of AED, unknown neurobiological networks, shared genetic mutations, etc. Also, both conditions share similar brain structural abnormalities such as enlarged ventricles and grey matter reduction especially in temporal lobes. Clinically, SLE is similar to common schizophrenia, presenting paranoid or influence ideas that may become systematized and auditory hallucinations often of a menacing content. Differences with classic schizophrenia include: common religious content of the paranoia, preserved insight and a lack of typical deterioration to the hebephrenic state. Auditory hallucinations are common but visual ones are relatively rare. In case of traumatic brain injury, also other forms of delusions (grandiose, referential, religious and *Schneiderian* symptoms) can be observed (16).

As previously mentioned for major depression, there is also a lack of diagnostic criteria for SLE, making difficult to differentiate between those symptoms related to epilepsy from those due to schizophrenia. Furthermore, as seen in MDD, SLE also complicates epilepsy management and worsens its prognosis.

Common comorbidity between epilepsy and psychiatric disorders emphasizes the need for proper psychiatric screening and to purpose a systematic approach to identify and treat it correctly. Furthermore, suffering from mental disorders also may have other complications such increased suicidality risk, a negative impact in quality of life and an impact on costs and overuse of medical services (17).

3.4. TEMPORAL LOBE EPILEPSY AND MESIAL SCLEROSIS

Temporal lobe epilepsy is included in the classification of the ILAE under the group of focal seizures as localization-related symptomatic epilepsies; representing the 24% and 60% of the overall and focal epilepsies, respectively (8). The same classification also divide seizures coming from the lateral temporal area from those coming from the medial temporal area (7), and among the last one, it distinguishes an important form called mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS), also known as mesial temporal sclerosis (MTS). MTS is defined as a symptomatic focal epilepsy that can be subcategorized as limbic epilepsy (or neocortical epilepsy) and is one of the most common types of epilepsy referred to surgery.

MTS is defined histologically by neuronal loss and gliosis particularly affecting CA1 and CA3 sectors of the hippocampus, with relative sparing of CA2. Patients with mTLE and hippocampal sclerosis usually have a previous history of febrile seizures, predominantly in late childhood or adolescence (18). Hippocampal sclerosis is usually detected on MRI (which shows decreased volume and increased T2 signal in hippocampus) and PET (which shows temporal hypometabolism predominantly in the mesial temporal region). The presence of MTS predicts poor response to antiepileptic drugs, which leads often to classify the majority of these patients as refractory epilepsy.

In addition, neuropsychological evaluation generally demonstrates memory dysfunction, specially verbal or visual-spatial memory, when left or right hemisphere is involved, respectively. It is important to consider that psychiatric comorbidities (with special mention to depression and schizophrenia) are also more frequent among patients with MTS. It is assumed that the rate of depression ranges from 20 to 55% in patients with refractory epilepsy, especially considering those with temporal lobe epilepsy caused by mesial temporal sclerosis (13). Some studies have examined the relationship of depression with MTS. For instance, Sanchez-Gistau V

et al. (19) examined the possible relationship between mesial temporal sclerosis and future major depression appearance, and found that there is an strong association between MTS and “post-seizure onset” MDD and that this phenomenon is more of a chronic than of a state-dependent condition.

Despite this known clinical relationship, only few studies have investigated whether patients with MDD display a characteristic pattern of pathological and imaging findings. Intriguingly, neuronal circuits implicated in MTS and major depression often includes the temporal lobes and the alterations that may be found usually are shared: hippocampal volume loss and higher amygdala volumes in MRI, smaller frontal lobes with cingulate gyrus or alterations in entorhinal, neocortical cortex and subcortical structures (such as basal ganglia and thalamus) with its connecting pathways (13).

Moreover, schizophrenia-like psychosis is also a frequent condition in patients with TLE. Some symptoms include psychic or experiential phenomena: intellectual aura or dreamy states, complex visual or auditory hallucinations or illusions, memory “flashbacks”, *déjà vu*, *jamais vu* and emotions (especially fear). However, there are controversies about a feasible relationship between specific brain pathology as MTS and the development of prior or future schizophrenia. Recent neuropathological studies made in patients with MTS show common findings at a cellular level, including neuronal loss, shrinkage or disarray in the cortical layers and occasional gliosis; and structural level, affecting prefrontal cortical areas, the pons, the *nucleus accumbens*, the hypothalamus, the *substantia innominata*, the cingulate, superior, middle and inferior temporal gyri, the amygdala and the hippocampus (20). Even though, the relationship between schizophrenia and MTS still remains unclear and unsolved. Some authors have reported that the presence of MTS is a risk factor for SLE appearance, while others have stated the opposite. Despite this, recent neuropathological evidences suggest that there is a structural basis for psychiatric symptoms in TLE patients with hippocampal sclerosis. It has been found neuronal loss in Ammon’s horn and entorhinal cortex layer II and reduced density of the interneurons in a left hemisphere of post-mortem brains of schizophrenic patients, being more noticeable in paranoid than in catatonic patients (21).

Finally, it is well-known that patients with refractory epilepsy have increased risk of suicide respect to the general population and even in general epileptic patients (22) (23). Consequently, we could assume that the risk in TLE with MTS, which is cause of refractory epilepsy, could be even higher, and expect the presence of other reasons that could explain this phenomenon.

3.5. EPILEPSY AND SUICIDE: A CLOSE RELATIONSHIP

Suicide is an important cause of death in patients suffering from epilepsy. Several authors have already reported higher rates compared to the general population and they have found that the lifetime prevalence of suicidal behavior ranges between 12-15% in this population (22).

Several researchers have been fascinated by this curious association. Pompili M et al (24) investigated 29 cohorts of people suffering from epilepsy and traced the deaths by suicide among countries according to year and age group. They concluded that suicide was an alarming cause of death in this population and that there were differences between countries, being more frequent in Finland than in other European countries. Jones J et al. (22) reported a results of a multicenter study, using a specific test of the Mini International Neuropsychiatric Interview (M.I.N.I.) as part of the assessment, that suicidal ideation was common in patients with epilepsy, showing a prevalence of current suicidal ideation of 12.2%. Another study from Sweden investigated a cause-specific mortality in people with a hospital discharge diagnosis of epilepsy and they also reported an excess rate of mortality due to suicide (25).

Nowadays, it is still unclear which factors could explain this phenomenon. The World Health Organization (WHO) stated that the increased suicidal mortality seen in epileptic patients is linked to the increased aggression, impulsivity, chronic disability and alcohol and drug abuse (10). Additionally, other risk factors published include: psychological stressors, previous suicide attempt, psychiatric disorders, early age at epilepsy onset, frequency of seizures, cognitive deterioration, previous epileptic surgery (25) and seizure type; especially TLE (26). Special mention deserves psychiatric disorders, which always have been considered the most important factor for suicidal behavior in the general population, and, as expected, in patients with epilepsy, too. Interestingly, recent research supports the hypothesis that approximately a third of epileptic patients that presented suicidal ideation were euthymic or had only mild or subclinical depressive symptoms (27)

Besides, some researchers have studied different neural networks, suggesting a possible dysfunction or disturbances of neurotransmitters. In relation to TLE, Kanner AM (28) proposed a possible underlying mechanisms between suicide, epilepsy and depression. He found a reduction in serotonin receptors 5-HT_{1A} in the temporal lobes of patients with TLE and a dysregulation of serotonin in patients with psychiatric disorders. Curiously, neurotransmitter disturbances were found principally in limbic structures, which correspond to the affected part seen in mesial temporal sclerosis. These data suggest not only a behavioral factor but also an existence of a complex mechanism in neurobiology of epilepsy, mood and suicidal behavior.

Furthermore, there is evidence suggesting that suicide rate in this population is underestimated. For instance, Pompili M et al (29) conducted a meta-analysis to compare data reported in representative studies about suicide rates in epilepsy with data on mortality in general epileptic population. They found that the form of death often was not included in mortality rates and, according to data analyzed; an important part of it could be attributed to suicide. They concluded that, although results were only representative of their population, mortality rates in people with epilepsy probably did not include suicide, greatly underestimating these deaths.

To summarize, despite the existence of different hypothesis, the mechanism of suicidal behavior in epileptic patients remains uncertain. It would be desirable that future research will focus on determining which factors play a key role in this process and which ones could serve as a marker to prevent earlier suicidal behavior in epileptic patients. According to this, primary healthcare professionals should be the first to recognize possible suicidal behavior and to promote preventive strategies among higher-risk patients, including those with epilepsy.

4. JUSTIFICATION

Suicide is an important cause of death among epileptic patients, especially in those who present psychiatric comorbidities as major depressive disorder, schizophrenia and anxiety. Interestingly, in epileptic patients, and particularly in those with temporal lobe epilepsy, the presence of psychiatric comorbidities and suicidal behavior are more frequent. Most of patients suffering temporal lobe epilepsy are difficult to control with antiepileptic drugs, fulfilling criteria of refractory epilepsy; and the vast majority of them, correspond to people with mesial temporal sclerosis. It is also intriguing that psychiatric disorders (especially major depression and schizophrenia) are more frequent in people with mesial temporal sclerosis and that they may also present more prevalence of suicidal behavior (22). Oliveira GN et al. (30) discuss about the possible relationship between TLE and refractory epilepsy with the increased risk of suicide, but they do not focus about the possibility of the existence of an underlying lesion (which could be mesial temporal sclerosis) that could predispose these patients to have autolytic tendencies.

The purpose of this study is to investigate if a lesion such as mesial temporal sclerosis, with a known physiopathology, localization and implicated structures, could explain alone an increased risk of patients with refractory epilepsy (especially those with TLE) to develop suicidal behavior (in form of ideation, attempt or consumed suicide).

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6. HYPOTHESIS

6.1. Primary

The presence of mesial temporal sclerosis is associated with a higher risk of developing suicidal behavior in patients with temporal lobe epilepsy regardless of the presence of major depression or psychosis.

6.2. Secondary

There are differences in suicidal behavior among patients with TLE depending on which antiepileptic drug is used.

7. OBJECTIVES

7.1. Primary

To analyze whether the presence of mesial temporal sclerosis is associated independently with a major risk of developing suicidal ideation, suicidal attempt or completed suicide in patients with temporal lobe epilepsy regardless of the presence of major depression or psychosis.

7.2. Secondary

To determine whether the antiepileptic drug used is associated with a major tendency of having suicidal behavior among patients with temporal lobe epilepsy.

8. METHODOLOGY

8.1. STUDY DESIGN

The study consists in an observational prospective cohort study with a follow-up of 5 years that will be performed at Hospital Josep Trueta de Girona (HJT) and Hospital Santa Caterina de Salt (HSC).

8.2. STUDY POPULATION

The population of the study will be patients aged fourteen years or more with current or new diagnoses of temporal lobe epilepsy.

8.3. INCLUSION AND EXCLUSION CRITERIA

The **inclusion criteria** to participate in the study are:

1. Patients aged fourteen or more
2. Patients with current or new diagnosis of temporal lobe epilepsy defined by clinical, electroencephalographic (EEG) and neuroimaging findings (MRI) (the last one are not mandatory) (31):
 - One or more of the following *clinical features*:
 - Seizures typically lasting more than 2 minutes with a slower evolution and more gradual onset/offset.
 - Typical medial temporal (epigastric, cephalic, affective or autonomic) or lateral temporal (auditory hallucinations or illusions) auras.
 - Partial awareness commonly preserved.
 - Prominent motor arrest with loss of awareness.
 - Post-ictal confusion and dysphasia.
 - Oroalimentary or gestural automatisms (lip-smacking, chewing, swallowing, fumbling, fidgeting, undressing, etc).
 - Typical *inter-ictal EEG* with epileptiform abnormalities (anterior or midtemporal spikes/sharp waves) or without epileptiform abnormalities (regional slowing in temporal lobe regions or ictal EEG with rhythmic temporal alpha or theta activity within 30 seconds of onset).
 - *Magnetic resonance imaging* showing hippocampal sclerosis defined by unilateral decrease in hippocampal volume and increase in signal on T2-weighted MRI scan.

The **exclusion criteria** to participate in this study include:

1. Patients who have not signed or are not capable to sign the informed consent.
2. Previous suicidal behavior (ideation or attempted suicide).
3. Modified Rankin scale (mRS) score of more than 3 points (*see Annex 4*).
4. Mini Mental State Examination test score of less than 21 points (32) (*see Annex 8*).

5. Previous temporal lobe epilepsy surgery
6. Intellectual disability defined by percentiles of less than 5 in the general scale of Raven's Progressive Matrices (RPM) test. RPM consists in geometric analogy problems in which a matrix of geometric figures is presented with one entry missing, and the correct missing entry must be selected from a set of answer choices.
7. Current or previous history of substance abuse (except tobacco) assessed by modules I and J of the Mini International Psychiatric Interview (M.I.N.I v6.0) (33) (*see Annex 9*).
8. Non-epileptic seizures.

8.4. SAMPLE PROTOCOL

8.4.1. Sample selection

A non-probabilistic consecutive sampling method will be used. The patients will be recruited during their attendance in the medical department of epilepsy of HJT and HSC and they will be revised to fulfill the inclusion criteria and none of the exclusion criteria stated above. All participants will be informed about the purpose of the study and will be invited to read and sign the information sheet and the informed consent (*see Annex 1*). They only will be included in the study if they sign and agree with the conditions.

8.4.2. Sample size

To calculate the sample size the power calculator GRANMO® will be used. The minimum relative risk of presenting suicidal behavior in patients with TLE with and without MTS will be calculated according to previous data published (23). In the group of TLE without MTS the expected prevalence is 11.5%, corresponding to general epileptic patients; whereas in patients with TLE with MTS, estimated with refractory epilepsy patients, the number raises until 5-fold, and thus, the prevalence expected is 16% (22,23,28). Due to a lack of epidemiological data regarding suicidal behavior in patients with MTS, the estimated risk used in the study will be 2, which includes the previously estimated risk of 5-fold (23).

Accepting an alpha risk of 0.05 and a beta risk lower than 0.2 in a bilateral contrast, it is needed 115 subjects in TLE-MTS+ patients and 230 in TLE-MTS- patients to detect a minimum relative risk of 2 if the prevalence of non-exposed is 11.5%. It has been estimated a follow-up losses tax of 5%.

8.5. VARIABLES AND MEASUREMENT TOOLS

8.5.1. Independent variable

The independent variable will be the presence of probable mesial temporal sclerosis (definite diagnose requires biopsy). The assessment will be done using clinical manifestations and neuroimaging (MRI) and is defined by:

- *Magnetic resonance imaging*: showing hippocampal sclerosis (*see Annex 10*) (demonstrable by unilateral decrease in hippocampal volume and increase in signal on T2-weighted MRI scan) *plus one or more of the following*:
 - Typical clinical features: epigastric auras, oral automatisms as lip-smacking, chewing, swallowing and/or absence of generalization.
 - Childhood history of prolonged febrile convulsions.

8.5.2. Dependent variable

The dependent variable will be the appearance of suicidal behavior that includes one or more of the following situations:

- *Suicidal ideation*: thinking about, considering or planning suicide. It may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent.
- *Suicidal attempt*: a non-fatal, self-directed, potentially injurious behavior with intent to die as a result of the behavior; it might not result in injury.

These two situations will be assessed with the *Columbia Suicide Severity Rating Scale (C-SSRS)* (*see Annex 5*). Nowadays it is considered to be the definitive suicidal rating scale and is widely used in research, primary care and clinical practice. It also evaluates the behavior severity, intensity and lethality. It employs a scale of 1-5 with increasing severity from ideation to attempted suicide (34).

- *Completed suicide*: death caused by self-directed injurious behavior with intent to die as a result of the behavior. This variable will need either a proper implicit or explicit evidence of a self-injurious behavior supported by pathological (autopsy), toxicological, investigatory, psychological evidence or by statements of the decedent or witnesses. For its registration, it only will be valid a proper judicial, medical or forensic report.

8.5.3. Confounding variables

8.5.3.1. Mental disorders

- **Major depressive disorder (MDD):** defined by the DSM-V criteria for major depression (35) (*see Annex 6*) and supported by the use of the Hospital Anxiety and Depression Scale (HADS) (*see Annex 7*), which has been validated to be used in epilepsy by several researchers (36). The HADS is a tool designed as a screening for use in hospital outpatient clinics. It is composed of seven items both for depression and anxiety, scored from 0 to 3 according to frequency. Several authors recommend a cut off of >7 for both HADS-D (the depression subscale) and HADS-A (the anxiety subscale), but combined total scores (HADS-T) can also be used.
- **Schizophrenia (SLE):** defined by the DSM-V criteria for Psychotic disorder due to another medical condition (35) (*see Annex 6*).
- **Anxiety disorder:** this item will be assessed using the HADS (*see Annex 7*) scale due to a lack of current specific criteria in DSM-V.

All data concerning mental disorders will be assessed by a psychiatrist who will be trained at the beginning of the study to pass and interpret the tests used. The psychiatric assessment will be repeated during the first, the third and the fifth year.

8.5.3.2. Sociodemographic data

Current sociodemographic information will be collected by the neurologist in charge of the patient who will bring her/his a standardized sheet (*see Annex 3*) after they agree to join to the study. The standardized sheet will ask for:

- I. Age: measured in years.
- II. Gender: female, male or intersex.
- III. Race: caucasian, afro-American, Asian, etc.
- IV. Schooling: without schooling, compulsory education, A level, graduate.
- V. Family history of suicidal behavior.
- VI. Marital status: single, married, coupled, widow/er.
- VII. Employment: student, employed, unemployed, unemployable.

8.5.3.3. Functional and cognitive assessment

Functionality assessment will be repeated 3 times during the study (at 1, 3 and 5 years) in order to evaluate possible deterioration.

- a) *Patient disability*: defined by the modified Rankin scale (mRS) (*see Annex 4*). The mRS is a useful scale for measuring the degree of disability or dependence in the daily activities of individuals with present or past neurological condition and is the most widely used clinical outcome in neurological clinical trials. The assessment requires only five minutes to complete and the scores vary from 0 (without symptoms) to 6 (death).
- b) *Development of neurocognitive disorder*: assessed by the Mini Mental State Examination (MMSE). We will consider the results if there is a decrease of ≥ 5 points respect to baseline (32) (*see Annex 8*).

8.5.3.4. Clinical data concerning temporal lobe epilepsy

Clinical data of epilepsy will be gathered in the patient's report sheet (*see Annex 3*) by the neurologist in the first visit and the information recruited will be the following:

- 1) Age of onset.
- 2) Frequency of seizures: number per month.
- 3) Use of antiepileptic drugs: type, doses and possible observed side effects.
- 4) Electroencephalogram previous data
- 5) Lateralization: left or right temporal lobe epilepsy. Will be recruited using the MRI and/or EEG previous data.

8.6. DATA COLLECTION AND VISITS SCHEDULE

All data regarding neurological assessment (sociodemographic data, neurological clinical examination, epilepsy, hippocampal sclerosis, EEG, etc) will be collected by a neurologist; whereas the psychiatric assessment will be responsibility of the psychiatrist. During the first visit, the neurologist will request for a MRI and EEG if there is no previous data, which will be done by a radiologist and neurophysiologist, respectively. So as to facilitate data collection and organization, here is proposed a schedule with the activities developed in each visit and its frequency:

DATA COLLECTION	Inclusion	1 ST year		2 ND year		3 RD year		4 TH year		5 TH year	
		M6	M12	M18	M24	M30	M36	M42	M48	M54	M60
Information sheet and informed consent reading and sign	X										
Sociodemographic data	X										
General and neurological clinical examination	X	X	X	X	X	X	X	X	X	X	X
Clinical data of epilepsy	X	X	X	X	X	X	X	X	X	X	X
Functional and cognitive assessment: Rankin scale and MMSE	X		X				X				X
Intellectual disability: Raven test	X										
Psychiatric assessment: Depression, psychosis, anxiety, substance abuse.	X		X				X				X
Suicidal behavior assessment: CSRRS	X	X	X	X	X	X	X	X	X	X	X
Magnetic resonance imaging previous data revision	X										
EEG previous data revision	X										
Number of visits	2 visits each year separated each 6 months										
*Psychiatric assessment will be done by the psychiatrist											

9. STATISTICAL ANALYSIS

The data will be analyzed using IBM SPSS® for Windows®. The independent variable (mesial temporal sclerosis) as well as the dependent variable (suicidal behavior) will be considered as categorical variables. In the same way, most covariates will be considered as categorical, with the exception of age, frequency of seizures and all questionnaires/scales, which are quantitative variables. The results will be expressed as percentages or relative frequencies for categorical variables and as mean \pm SD or median for continuous variables, depending on whether they are normally distributed or not. Comparisons between exposed and non-exposed groups will be carried out with the Chi² test for categorical variables, whereas the t-student or Mann-Whitney test will be used to compare between quantitative variables.

Considering that in this study the time until the event occurrence (suicidal behavior) is not relevant, the influence of mesial sclerosis on admission to determine the future appearance of suicidal behavior (ideation, attempt or consumption) during the patient follow-up will be evaluated by logistic regression analysis. On the other hand, with regard to adjust for confounding variables the multivariate analysis will be used.

10. ETHICAL ASPECTS

The research protocol will be presented to both *Comisión de Ética para la Investigación Médica* (CEIC) located in HJT and HSC of Girona before the study is initiated.

The main investigators and collaborators guarantee that the study will be conducted in accordance to the human rights and the ethical considerations gathered in the World Medical Association Declaration of Helsinki of “*Ethical Principles for Medical Research Involving Human Subjects revised in 2013*”; as well as the Spanish law concerning medical investigations “*Ley 14/2007, de 3 de julio, de Investigación biomédica*”.

Any patient information will be used without their previous consent. At the time of admission, study information and purposes will be explained to each patient and they will be invited to sign the informed consent. To maintain the confidentiality and data security, no names, postcodes, addresses, birth dates or other numbers will be collected. The security of data will be ensured on a locked network which only will be accessible for the principal and responsible researchers of the project. According to the national and international laws regarding patient’s autonomy, the study will be governed by:

- *Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal.*
- *Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.*

The authors declare that they have no conflicts of interest.

11. STRENGTHS AND LIMITATIONS

As any study design, it presents different limitations that may interfere in the proper study performance and their final results. These can be classified in biases, study design and sample limitations.

11.1. Biases

Regarding to selection biases, the age of patients stated in the inclusion criteria exclude those under fourteen, which correspond to patients with an early TLE onset. This criterion is not modifiable due to the current management of these patients who are usually submitted directly to epileptic surgery since the beginning.

The radiological and neurophysiological diagnosis of TLE and MTS with MRI and EEG is often difficult because there is heterogeneous presentation and there are often few image changes or electroencephalographic alterations. To try to avoid this selection bias, the radiological and EEG interpretation will always be revised by the same radiologist and neurophysiologist.

The same problem can be found regarding psychiatric assessment, in which although there are specific diagnostic criteria to determine psychiatric conditions (DSM-V or ICD-10), there still not exist a 100% reliable method. Although the criteria used correspond to DSM-V, which are the most accepted and used currently in medical practice; the diagnostic of mental disorders continues to be very subjective yet, and thus, the same psychiatrist will review all patients.

With respect to information biases, we have to take into account possible observer biases. These biases will be minimized using standardized case report sheets and training physicians during the informative meetings to homogenize data collection method. On the other hand, concerning patient's information, the most important bias refers to the dependent variable studied (suicidal behavior), which, as a sensitive area, sometimes is difficult to explore or talk about. In order to avoid this, the assessment of suicidal behavior will be done using standardized tests (C-SSRS) which are self-administered and strictly anonymous.

Finally, confusion variables will be considered during the statistical analysis as well as in the design and data collection protocol.

11.2. Study design

Concerning the type of study, we assume that the duration of the study will be long, making it more expensive, difficult to carry out and more tedious for the patients. But, in favor of the study design, we consider that to do a reliable suicidality assessment, using a long prospective follow-up study increases its validity, because the response variables are recruited during their appearance and can be validated and managed at the same time.

On the other hand, as a long study, it is important to consider two key factors. First of all, we have to contemplate the possible loss of an investigator during the study, which will be solved assigning a back-up for each investigator who will replace him/her in case of need; and second,

the loss of patients due to the lost to follow-up, which will be avoided encouraging the physicians to use motivational interviewing in order to engage patients to the study. In case of possible patient relocation, they will be asked if they want to continue participating in the study via telephone survey. To analyze possible factors involving patient's decision to abandon the study, the statistical analysis will allow us to assess its magnitude and identify those with more abandoning rates.

At last, although there is a long cohort study, it has a low cost because only psychiatrists have to be paid for their services and the questionnaires and tests are available for free in clinical practice.

11.3. Sample limitations

Taking into account the clinical presentation of epilepsy, it is necessary to use a non-probabilistic consecutive sampling, because the majority of patients are only diagnosed after their first and posterior seizures. We assume that, although using that sampling method we will include patients attending neurology department of both hospitals, we can expect missing mild forms of temporal lobe epilepsy, which may be under or misdiagnosed. On the other side, as a sample recruitment of a limited region such Girona, the results only will be representative for this region and it would be difficult to generalize the results.

12. WORKING PLAN

The study will be performed in 9 years and 6 months and it will be composed of 5 phases with different objectives and activities in each part. Following, it is detailed and outline of the study plan proposed and what activities will be done:

Phase 1: Study setting-up and Coordination (6 months)

- **Study setting-up:** during this period of time, the principal investigator and co-workers will make a literature review, propose objectives and hypothesis, develop a methodology used and write a draft of the protocol design (M1-2)
- **First informative meeting:** once the principal investigator had a draft of the protocol designed he/she will present it to the collaborators and they will agree an execution plan and organization. He also will manage the participation of the different centers during this period. (M2)
- **Final project design and writing** (M3)

- **Protocol revision and approval:** the protocol will be brought to the CEIC for its revision and approval (M4-M5)
- **Second informative meeting:** after CEIC approval, the principal investigator will organize a session with all implicated professionals (neurologists, psychiatrists and statistician) in which they will be trained about information collection. This session will be used to homogenize and agree a standardized method of action (M6)

Phase 2: Participants recruitment, evaluation and data collection (8 years)

- **Subject's recruitment:** this part will last for 3 years and it will consist in the recruitment of patients with the desired inclusion criteria. During the first visit, the information sheet and informed consent will be facilitated to the patients (M6-M42).
- **Subject's evaluation:** this period will start at the same time of patient's recruitment and it will finish five years after the inclusion of the last participant. Each patient will be followed during five years. (M6-M102)
- **Data collection:** data from the first and successive visits will be gathered. Data collected from the first visit will correspond to the neurologist and psychiatrist, whereas the successive visits will be the neurologist the main responsible. Patients will be assessed coinciding with their epilepsy control. All data will be gathered in a standardized case report sheet (*see Annex 3*). (M6-M102)

Phase 3: Data analysis (3 months)

- **Data analysis:** a statistician will take all collected data and will proceed to analyze it with specific statistical program. (M102-M105)

Phase 4: Results interpretation and final report elaboration (3 months)

- **Results interpretation:** with the statistical data obtained, investigators will analyze and discuss the obtained data (M105-M106)
- **Final report writing** (M106-M108)

Phase 5: Results publication and dissemination (6 months)

- **Results publication:** the results will be presented in specific conferences and meetings. (M108-M111)
- **Final report dissemination:** the final report will be submitted to scientific journals to be published (M111-M114)

13. STUDY CHRONOGRAM

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Phase 1. STUDY SETTING-UP AND COORDINATION										
Study setting-up										
First informative meeting										
Final project design and writing										
CEIC revision and approval										
Second informative meeting										
Phase 2. PARTICIPANTS RECRUITMENT AND EVALUATION AND DATA COLLECTION										
Subject's recruitment and evaluation										
Subjects evaluation										
Data collection										
Phase 3. DATA ANALYSIS										
Data analysis										
Phase 4. RESULTS AND FINAL REPORT WRITING										
Results interpretation										
Final report writing										
Phase 5. PUBLICATION AND DISSEMINATION										
Results publication										
Final report dissemination										

14. BUDGET

TYPE OF COST	UNIT COST (€)	HOURS/UNITS	TOTAL
PERSONEEL/STAFF			
Psychiatrist	50 €	375 h x 3 visits	56.250 €
Statistician	35 €	120 hours	4.200 €
Person who collect information	15 €	100 hours	1.500 €
PUBLICATION AND DIFFUSION COSTS			
Article publication and diffusion			1.500 €
OTHER JUSTIFIED COSTS			
Information and informed consent, case report and tests printing	0.30 €	1500 units	450 €
TOTAL			63.900 €

Neurologists are part of the neurologic department of HJT and HSC and their cost are not included in the budget. Psychiatrist collaboration will be paid 50€per visit and they will have 3 visits during the study.

The diagnostic tests, the MRI and EEG form part of the usual management of the epileptic patients, so, it is not stated in the budget.

The tests or questionnaires used in the study are available for free in clinical practice and its cost only belongs to its printing.

15. FEASIBILITY

Both HSJ and HSC provide neurological assistance to approximately 800.000 inhabitants of the region of Girona. Taking into account an annual incidence of epilepsy of 30-51 new cases per 100.000 inhabitants (3) and the prevalence of patients suffering TLE (8), the population of Girona can provide 87-150 new cases per year. For the purpose of this study, a recruitment period of three years would have to be enough to achieve the number of 345 patients required.

On the other side, both centers are totally equipped medically and technologically to accomplish the objectives of the study.

The study coordinator will submit the project to different grants (*Acadèmia de ciències mèdiques, Societat Catalana de Neurologia, la Marató...*) in order to achieve the budget.

For all mentioned above, this protocol is feasible to be brought out in our province and clinical centers.

16. IMPACT TO THE NATIONAL HEALTHSYSTEM

As a prevalent and preventable issue, suicide should be a priority for our national health system. Lots of deaths could be avoided if there was an early proper screening; and the authorities, health professionals and the general population would be concerned about that. Related to this, some autonomous communities have already started some programs regarding this issue, like *Codi Risc de Suicidi* recently started in Catalunya, which tries to make a quickly assessment of this patients and coordinate the work among healthcare professionals.

During the last years, new insights have been learned about suicide. We have realized that it is not only due to a specific factor but also it is a multifactorial pathology with several risk and protective factors. For instance, it is widely accepted that suffering from mental disorders, a poor socio-economic status or having a chronic medical disease increases dramatically the suicide risk. Thus, it should be a priority for the health system to try to detect earlier patients at risk and to promote preventive measures.

Accordingly, the present study would provide better knowledge about the role of a chronic medical condition such epilepsy in the predisposition of presenting suicidal behavior, and maybe, the discovery of a potential risk factor which could serve, first as a “marker” for potential future suicide behavior, and second; to develop future prevention strategies that might be used in the daily clinical practice.

17. ANNEXES

ANNEX 1. INFORMATION SHEET AND INFORMED CONSENT

INFORMATION SHEET

You are being asked to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information.

TITLE OF STUDY

Association between mesial temporal sclerosis and suicidal behavior in patients with temporal lobe epilepsy: A 5-year prospective cohort study

WHAT IS THE PURPOSE OF STUDY?

Epilepsy is one of the most common neurologic disorders worldwide and as a chronic condition; it predisposes to suffer a lot of medical, psychological and social complications. Patients with epilepsy also have less life expectancy, usually due to cardiac, neurologic or epilepsy-related complications. Among causes of death, suicidal behavior has been frequently associated with this condition. Several risk factors have been commonly related with this phenomenon (mental disorders, family history, genetic predisposition, suffering from temporal lobe epilepsy, etc) but it still remains unclear and topic of debate. Thus, this study may help as to better understand this frequent association, to investigate new important risk factors and to know why epileptic patients present a higher tendency to develop suicidal behavior.

Then, the purpose of this study is to determine if a specific lesion involved in suffering temporal lobe epilepsy is associated with an increased risk of developing suicidal behavior.

WHAT I HAVE TO DO DURING THE STUDY?

If you want to take part in the study, you will be asked to:

- Answer several questions related to your sociodemographic and clinical data
- Respond a couple of tests for psychiatric assessment in order to explore psychopathology and possible suicidal thoughts
- To submit to a general and neurologic clinical examination.

In the first visit and in order to classify your possible epilepsy, the physician may ask you to submit to a magnetic resonance imaging (MRI) and an electroencephalogram (EEG). During the EEG it is possible that the physician uses a video to recorder possible seizures. During the next visits, which will take part each 6 months during five years, the physician will ask you again about several questions concerning your epilepsy and possible new autolytic behavior.

The first visit will take part in approximately 1 hour, whereas the consecutive visits will last for 30 minutes approximately.

ARE THERE ANY RISKS?

All the procedures that have to be done during this study do not have any risk for your health. Only in case that during the magnetic resonance imaging the physician needed to use a dye injection (gadolinium) to improve the image quality, the procedure would require an arm puncture. Although extremely rare, there are few cases which reported an allergic reaction to gadolinium.

In case of epilepsy diagnosis, the physician will prescribe you an antiepileptic drug (AED). AED have possible side effects which will be explained to you by your physician-in-charge and should be taken into account. It is also important that you record any change of doses or adverse effect which you think could be related with your treatment.

Finally, you may decline to answer any question and you may finish your study involvement at any time if you choose.

WHAT ARE THE BENEFITS OF THIS STUDY?

Except for a good management of your epilepsy and possible related complications, there will be no economic benefit to you for your participation. However, we hope that the information obtained may have enormous benefits for other people suffering from epilepsy. It may allow us to better understand why some epileptic patients present suicidal behavior and to identify new unknown determinant factors which could be used for the development of new screening methods to recognize patients at risk.

CONFIDENTIALITY

Your responses to this study and all the information extracted will be anonymous. Please do not write any identifying information on your case report sheet. Every effort will be made by the researcher to preserve your confidentiality including the following:

- Assigning code names/numbers for participants that will be used on all research notes and documents.
- Keeping notes, interview transcriptions, and any other identifying participant information in a locked file cabinet in the personal possession of the researcher.

Participant data will be kept confidential except in cases where the researcher is legally obligated to report specific incidents. These incidents include, but may not be limited to, incidents of abuse, when there is a risk for a 3rd person or public health or others.

CONTACT INFORMATION

If you have questions at any time during the study or you experience adverse effects as a result of your participation, you could contact the principal researcher whose contact information will be provided at the beginning of the study.

VOLUNTARY PARTICIPATION

Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. If you decide to take part in this study, you will be asked to sign a consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be returned to you or destroyed.

INFORMED CONSENT

I, _____, confirm that:

I have read and I understand the provided information and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without cost.

I understand that my participation in the present study will be confidential

I understand that I will be given a copy of this consent form.

I voluntarily agree to take part in the study *“Association between mesial temporal sclerosis and suicidal behavior in patients with temporal lobe epilepsy: A 5-year prospective cohort study”*.

Participant's signature _____ Date _____

Investigator's signature _____ Date _____

ANNEX 2. THE ILAE CLASSIFICATION OF EPILEPSY (1981 and 1989)

International League Against Epilepsy Classification of Epileptic Seizures
Generalized seizures
<ul style="list-style-type: none"> A. Absence seizures <ul style="list-style-type: none"> 1. Typical absence seizures 2. Atypical absence seizures B. Myoclonic seizures C. Clonic seizures D. Tonic seizures E. Tonic-clonic seizures F. Atonic seizures
Partial (Focal, Local) Seizures
<ul style="list-style-type: none"> A. Simple partial seizures (consciousness not impaired) <ul style="list-style-type: none"> 1. With motor symptoms 2. With somatosensory or special sensory symptoms 3. With autonomic symptoms 4. With psychic symptoms B. Complex partial seizures (with impairment of consciousness) <ul style="list-style-type: none"> 1. With simple partial onset followed by impairment of consciousness 2. With impairment of consciousness at onset C. Partial seizures evolving to secondarily generalized seizures <ul style="list-style-type: none"> 1. Simple partial seizures evolving to generalized seizures 2. Complex partial seizures evolving to generalized seizures 3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures
Unclassified Epileptic Seizures

International League Against Epilepsy Classification of Epilepsies and Epileptic Syndromes
Localization-related (focal, local, partial) epilepsies and syndromes
<ul style="list-style-type: none"> 1.1. Idiopathic (with age-related onset) 1.2. Symptomatic 1.3. Cryptogenic
2. Generalized epilepsies and syndromes
<ul style="list-style-type: none"> 2.1. Idiopathic (with age-related onset, listed in order of age appearance) 2.2. Cryptogenic or symptomatic (in order of age) 2.3. Symptomatic <ul style="list-style-type: none"> 2.3.1. Nonspecific etiology 2.3.2. Specific syndromes
3. Epilepsies and syndromes undetermined as to whether they are focal or generalized
<ul style="list-style-type: none"> 3.1. With both generalized and focal seizures 3.2. Without unequivocal generalized or focal features
4. Special syndromes
<ul style="list-style-type: none"> 4.1. Situation-related seizures <ul style="list-style-type: none"> 4.1.1. Febrile convulsions 4.1.2. Isolated seizures or isolated status epilepticus 4.1.3. Seizures occurring only when there is an acute metabolic or toxic event

COGNITIVE AND FUNCTIONAL ASSESSMENT

	First visit	1 st year	3 rd year	5 th year
Rankin				
MMSE				

IQ (Raven Test) score:

DATA OF EPILEPSY

Age of onset

- Infancy Childhood
 Adolescence Young adult or late adulthood

Frequency and duration of seizures : _____ (number per day/week and minutes/hours)

Description of symptoms:

Magnetic resonance imaging report:

Electroencephalogram report:

Antiepileptic drugs use:

Name:

Dose prescribed:

Possible side effects observed:

Seizure control : _____ (number of seizures per month)

Lateralization of TLE: Left Right

PSYCHATRIC ASSESSMENT

Substance abuse

- Tobacco Alcohol Other drugs

The consume causes a functional/cognitive disability that impede to join in the study?

- YES NO

Major depressive disorder

She/he fulfill DSM-V criteria

YES

NO

Score in HADS:

Schizophrenia/Psychosis

She/he fulfill DSM-V criteria

YES

NO

Anxiety

Score in the HADS scale:

	First visit	1 st year	3 rd year	5 th year
Major depression				
Schizophrenia				
Anxiety				

SUICIDAL BEHAVIOUR ASSESSMENT

Using the Columbia Suicide Severity Rating Scale CSSRS you have to complete the following table:

SUICIDAL BEHAVIOUR	Suicidal ideation		Suicidal attempt		Completed suicide		Not valuable	
	1VISIT	2VISIT	1VISIT	2VISIT	1VISIT	2VISIT	1VISIT	2VISIT
First visit								
1 st year								
2 nd year								
3 rd year								
4 th year								
5 th year								

Put an to fill in each box if the behavior is present during the follow-up visit. In case that at the same time there are two types of behavior, please, fulfil both options.

ANNEX 4. RANKIN SCALE

MODIFIED RANKIN SCALE	
SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

SUICIDE IDEATION DEFINITIONS AND PROMPTS	Past month	
	YES	NO
Ask questions that are bolded and <u>underlined</u>.		
Ask Questions 1 and 2		
1) Wish to be Dead: Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <u>Have you wished you were dead or wished you could go to sleep and not wake up?</u>		
2) Suicidal Thoughts: General non-specific thoughts of wanting to end one's life/commit suicide, " <i>I've thought about killing myself</i> " without general thoughts of ways to kill oneself/associated methods, intent, or plan. <u>Have you actually had any thoughts of killing yourself?</u>		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act): Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. " <i>I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it....and I would never go through with it.</i> " <u>Have you been thinking about how you might kill yourself?</u>		
4) Suicidal Intent (without Specific Plan): Active suicidal thoughts of killing oneself and patient reports having <u>some intent to act on such thoughts</u> , as opposed to " <i>I have the thoughts but I definitely will not do anything about them.</i> " <u>Have you had these thoughts and had some intention of acting on them?</u>		
5) Suicide Intent with Specific Plan: Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out. <u>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</u>		
6) Suicide Behavior Question: <u>Have you ever done anything, started to do anything, or prepared to do anything to end your life?</u> Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc. <u>If YES, ask: How long ago did you do any of these?</u> • Over a year ago? • Between three months and a year ago? • Within the last three months?		

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ANNEX 6. DSM-V CRITERIA FOR MAJOR DEPRESSION AND SCHIZOPHRENIA

Criteria for Major Depressive Episode: DSM-5

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

Source: DSM-V, American Psychiatric Association

Diagnostic Criteria for Schizophrenia

- A. **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
- delusions
 - hallucinations
 - disorganized speech (e.g., frequent derailment or incoherence)
 - grossly disorganized or catatonic behavior
 - negative symptoms, i.e., affective flattening, alogia or avolition
- Note:** Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
- B. **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
- C. **Duration:** Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
- D. **Schizoaffective and Mood Disorder exclusion:** Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no major depressive episodes or Manic Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
- E. **Substance condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

Source: Diagnostic and Statistical Manual (DSM-V), American Psychiatric Association

ANNEX 7. Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

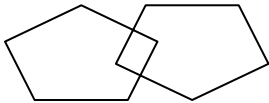
ANNEX 8. MINI MENTAL STATE EXAMINATION

Mini-Mental State Examination (MMSE)

Patient's Name: _____

Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) <div style="text-align: center;">  </div>
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

ANNEX 9. MINI INTERNATIONAL PSYCHIATRIC INTERVIEW (M.I.N.I.). MODULES I AND J

I. ALCOHOL DEPENDENCE / ABUSE

() MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

11	In the past 12 months, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	() NO	() YES
12	In the past 12 months:		
a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? <small>IF YES TO ANY, CODE YES.</small>	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES
	ARE 3 OR MORE 12 ANSWERS CODED YES?		
	* IF YES, SKIP 13 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.		
		NO YES* ALCOHOL DEPENDENCE CURRENT	
13	In the past 12 months:		
a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? <small>(CODE YES ONLY IF THIS CAUSED PROBLEMS.)</small>	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

- | | | | | |
|----|---|---|------|-----|
| J1 | a | In the past 12 months, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood? | (NO | YES |
|----|---|---|------|-----|

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "Peace Pill", "Tranq", "Hog"), or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

- | | | | |
|-----------------------------|--|----|-----|
| a | Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it? | NO | YES |
| b | When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? | NO | YES |
| IF YES TO EITHER, CODE YES. | | | |
| c | Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would? | NO | YES |
| d | Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed? | NO | YES |
| e | On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or recovering from the drug, or thinking about the drug? | NO | YES |
| f | Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? | NO | YES |
| g | If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it? | NO | YES |

ARE 3 OR MORE J2 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

* IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO	YES *
SUBSTANCE DEPENDENCE CURRENT	

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

- | | | |
|----|---|---|
| J3 | <p>a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem?</p> <p>(CODE YES ONLY IF THIS CAUSED PROBLEMS.)</p> <p>b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)?</p> <p>c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct?</p> <p>d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it?</p> | <p>NO YES</p> <p>NO YES</p> <p>NO YES</p> <p>NO YES</p> |
|----|---|---|

ARE 1 OR MORE J3 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO	YES
SUBSTANCE ABUSE CURRENT	

ANNEX 10. MESIAL TEMPORAL SCLEROSIS IMAGING

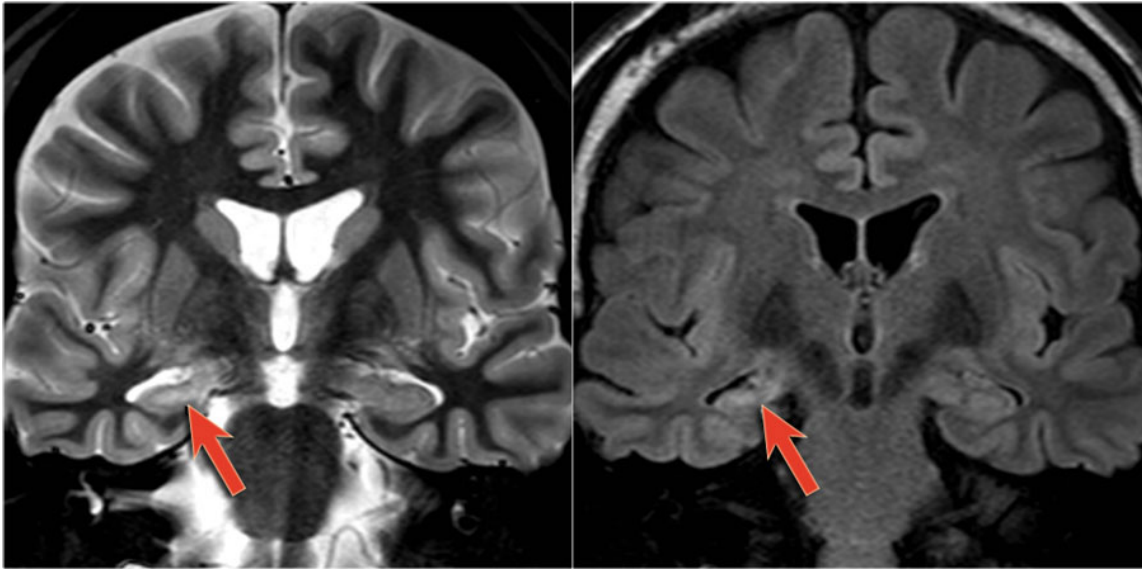


Figure 1. The coronal T2WI and FLAIR images show right-sided mesial temporal sclerosis. Notice the volume loss, which indicates atrophy and causes secondary enlargement of the temporal horn of the lateral ventricle. The high signal in the hippocampus reflects gliosis.

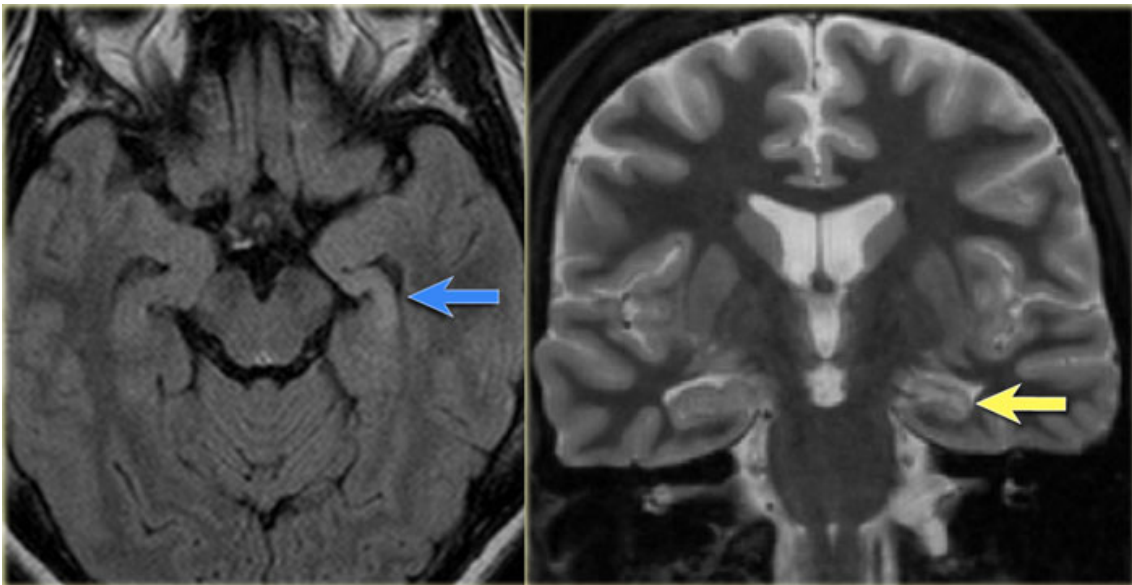


Figure 2. Left mesial temporal sclerosis. Subtle gliosis of left hippocampus (blue arrow) and atrophy (yellow arrow).

Source: <http://www.radiologyassistant.nl/en/p4f53597deae16/role-of-mri-in-epilepsy.html>.

Consulted at: 02/11/2015