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Review Article

Drug resistant epilepsy of the insular lobe: A review and update article

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ABSTRACT

Background: Epilepsy is a chronic disease that affects millions of people around the world generating great expenses and psychosocial problems burdening the public health in different ways. A considerable number of patients are refractory to the drug treatment requiring a more detailed and specialized investigation to establish the most appropriate therapeutic option. Insular epilepsy is a rare form of focal epilepsy commonly drug resistant and has much of its investigation and treatment involved with the surgical management at some point. The insula or the insular lobe is a portion of the cerebral cortex located in the depth of the lateral sulcus of the brain; its triangular in shape and connects with the other adjacent lobes. The insular lobe is a very interesting and complex portion of the brain related with different functions. Insula in Latin means Island and was initially described in the 18th century but its relation with epilepsy was first reported in the 1940–1950s. Insular lobe epilepsy is generally difficult to identify and confirm due to its depth and interconnections. Initial non-invasive studies generally demonstrate frustrating or incoherent information about the origin of the ictal event. Technological evolution made this pathology to be progressively better recognized and understood enabling professionals to perform the correct diagnosis and choose the ideal treatment for the affected population.

Methods: A literature review was performed using MEDLINE/PubMed, Scopus, and Web of Science databases. The terms epilepsy/epileptic seizure of the insula and surgical treatment was used in various combinations. We included studies that were published in English, French, or Portuguese; performed in humans with insular epilepsy who underwent some surgical treatment (microsurgery, laser ablation, or radiofrequency thermocoagulation).

Results: Initial search results in 1267 articles. After removing the duplicates 710 remaining articles were analyzed for titles and abstracts applying the inclusion and exclusion criteria. 70 studies met all inclusion criteria and were selected.

Conclusion: At present, the main interests and efforts are in the attempt to achieve and standardize the adequate management of the patient with refractory epilepsy of the insular lobe and for that purpose several forms of investigation and treatment were developed. In this paper, we will discuss the characteristics and information regarding the pathology and gather data to identify and choose the best therapeutic option for each case.

Keywords: Insular lobe, Insular epilepsy, Refractory epilepsy, Epilepsy surgery, Thermocoagulation, SEEG

INTRODUCTION

Epilepsy is traditionally understood as a set of changes characterized by recurrent seizures that afflict humanity for a long time. Historical reports show situations that describe epileptic

seizures in ancient times. The increasing interest in the last century and technologic development provided complementary information about the disorder and started to be characterized not only by its basic epiphenomenon, the seizures, its considered "a brain disorder" characterized by a predisposition to generate epileptic seizures with the neurobiological, cognitive, psychological, and social consequences of it.[25]

Epilepsy is a chronic neurological disease caused by various etiologies and characterized by recurrences of unprovoked epileptic seizures. It can be conceptualized as a temporary and reversible change in brain functioning that has not been caused by fever, drugs, or metabolic disorders and is expressed by repeated seizures at irregular time intervals.[23] After an unprovoked seizure, the chance of another is 40–52%. After the second unprovoked non-febrile seizure, the average chance of another is 73% (59–87% $P < 0.05$) in the next 4 years period.[11]

It is estimated a worldwide prevalence of epilepsy around 0.5–1.0% of the whole population.[3] In absolute numbers would be 65 million people worldwide and about 30% of them are called refractory, they continue to have seizures despite the appropriate treatment with anti-epileptic drugs (AED).[26] Data about the occurrence of epilepsy vary substantially between the studied populations and indicate that in developed countries the annual incidence of epilepsy is 50 / 100.000 (or 1 in 2.000) inhabitants, while the prevalence is close to 700 / 100.000 people. In low- and middle-income countries estimates of the corresponding rates are generally higher. In Brazil, Noronha *et al*.,[37] in 2007, found a prevalence of 9.2 per 1.000 inhabitants and we also have an older study, Fernandes *et al*.[10] from 1992, in Porto Alegre, with prevalence around 16.5 per 1.000. Epilepsy places a substantial burden on public health worldwide.[13]

The incidence of epilepsy is higher in the 1st year of life and increases again after 60 years of age. The overall probability of being affected by epilepsy lifelong is about 3%.[26] This pathological condition has neurobiological, cognitive, psychological, and social consequences with directly impairment in the patient's quality of life.[44]

Epilepsy is not necessarily life long and is considered "resolved" for individuals with an age-dependent epileptic syndrome but has already exceeded its age limit or those who have been seizure free for at least 10 years without AED for at least the past 5 years.[11]

The currently accepted concept of refractory epilepsy or drug resistant epilepsy is: epilepsy in which seizures persist and complete seizure control is very unlikely to be achieved with further association/manipulation of drug therapy. And failure is the appropriate use of two or more well tolerated and appropriately chosen AED used as mono or polytherapy without achieving seizure control.[24]

Kwan *et al*.[24] studied 525 patients with epilepsy and those using medication reported a rate remission of 63%. About the 470 patients with no history of previous treatment, 47% achieved clinical remission (seizure free for at least 1 year) using a first AED, while only 13% responded completely to a second drug and only 3% would respond with any other drug association.

Mortality rates are higher in people with most types of epilepsy and it can be attributed to the direct consequences of seizures and also the effects of some underlying diseases that give rise to epilepsy.[26] Sudden unexpected death in people with epilepsy, known as SUDEP, is at higher rates than unexpected death rates in the general population. These deaths are directly caused by epilepsy and not as a consequence of seizures (traumas, falls, and accidents in general after or during the epileptic event).[13] de Almeida *et al*.[8] found in a cross-sectional study a probable incidence of SUDEP of 29:1.000 epileptic patients. The combined and population-adjusted mortality rate is up to three times as for the general population. In adolescents and young adults, the risk of sudden death increases by 24 times.[13]

Practically, epilepsies can be classified according to two major axes: topographic and etiological. On the topographic axis, the epilepsies are separated into generalized, focal and unknown types. A generalized manifestation occurs in an epileptic seizures whose onset involves both hemispheres simultaneously or large neuronal network with rapid bilateral involvement. Most of time they are genetically determined and accompanied by altered consciousness; when present, motor manifestations are always bilateral.[52]

In focal epilepsies, the ictal onset begins localized in a specific area of the brain and its clinical manifestations depend on the ictal site and areas that the ictal discharge may propagate. A range of seizure types can be seen including focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures. The term "Unknown" is used to denote when is understood that patient has epilepsy but it is unable to determine if the epilepsy is focal or generalized because there is insufficient information available.

On the etiological axis, epilepsies are divided into idiopathic (without underlying structural lesion), symptomatic (with lesion), or cryptogenic (presumably symptomatic but without lesions available at images). The most frequent lesional causes of symptomatic focal epilepsies are: mesial temporal lobe epilepsy (TLE) with hippocampal sclerosis, primary brain neoplasms, vascular malformations, and cortical development abnormalities (focal cortical dysplasia).[12]

Among all newly diagnosed cases, 40–60% of them are focal epilepsy and up to 30% of them will develop drug resistant epilepsy.[26]

Diagnosis of an epileptic seizure, in most cases, can be made clinically by obtaining a detailed anamnesis, a detailed general and neurological examination and basic psychiatric evaluation. Often an eyewitness description is important to describe in detail and to classify the seizure. The diagnosis of epilepsy is clinical and the correct differential diagnosis with other paroxysmal disturbances of consciousness such as syncope and psychogenic non-epileptic seizures is critical.[11]

Complementary examinations should be guided by history and physical examination findings. The main exam is the electroencephalogram (EEG) whose role is to help the physician to make an accurate diagnosis of brain electrographic changes and their location. The EEG can answer three important diagnostic questions in patients with suspected epilepsy: (1) Does the patient have epilepsy? (2) Where is the epileptogenic zone located? (3) The treatment is being adequate?[9] Imaging tests such as magnetic resonance imaging (MRI) and computed tomography (CT) of the brain should be ordered and may demonstrate focal structural brain lesions such as congenital abnormalities, tumors, vascular malformations, hippocampal sclerosis, cortical dystrophies, and signs of neuronal migration disturbance.[23] The diagnosis of an underlying structural cause has therapeutic implications; it may support the indication of surgical treatment for the epilepsy looking for a good seizure free outcome.

About 75% of patients evaluated in specialized centers for refractory epilepsies have brain MRI abnormalities and in general half of epileptic patients have structural abnormalities detected on imaging exams.[28,29] Nowadays, the gold standard image exam for epilepsy investigation is a brain MRI with gadolinium, in a high definition image system.

Patients with drug resistant epilepsy and frequent disabling epileptic seizures should have at least the basic procedures as follows to assist in the investigation and management for possible surgical intervention:

- Brain MRI with gadolinium is mandatory in the investigation for all patients with refractory epilepsy, except for those with absolute contraindications
- Complete medical report with clinical description, medications with doses already used and the results
- Neuropsychological assessment to detect cognitive impairment and the prognosis of possible negative cognitive events
- Video EEG (VEEG) is also a mandatory exam to evaluate and identify the electrographic findings with synchronous semiology on each case.[45]

Up to 20% of refractory patients will not present structural alterations at image exams and sometimes these structural alterations may not coincide with the findings of other complementary exams and/or the seizure clinical findings.[44] For such cases, we do have a large armamentarium and among them we can mention the functional MRI, DTI tractography, and spectroscopy. We can also use nuclear exams focused on brain metabolism, such as positron emission CT (PET-CT), which uses 18Fluorodeoxyglucose as marker. Furthermore, the single photon emission computerized tomography (SPECT), which uses technetium (99mTc-HMPAO) as marker for imaging and assessment of brain metabolism.[45]

In the same non-invasive way, we can use electromagnetic encephalography (MEG) in the attempt to determine the epileptogenic zone and correlate it with the clinical and radiological findings.

However, in some patients even after extensive non-invasive investigation, the results are not sufficient to determine accurately the epileptogenic zone and need an invasive investigation. This type of investigation aims to collect electrographic data directly from brain electrodes surgically implanted, in a cortical subdural way or with depth electrodes. Thus, there is the possibility for more reliable electrographic information about the ictal onset. As well its possible to make a cortical stimulation map of brain eloquent areas, which may be affected by the epileptogenic focus. In selected cases, the treatment can be performed with radiofrequency thermocoagulation (RFTC) using the same deep electrodes implanted for diagnosis and mapping.[58]

The goal in the epilepsy treatment is to provide the best quality of life for patients, looking for seizure control, and minimal adverse effects or complications. Thus, the treatment aims for the complete remission of seizures.[44]

The Insular Lobe

The insular lobe is a thin barely visible cerebral cortex structure located deep in the lateral sulcus (Sylvian fissure), covered by a rich vascular network of the middle cerebral artery branches and hidden by the frontal, parietal and temporal opercules (in Latin "curtain"). The insula owes its name from the German physician and anatomist Johann Christian Reil, who in 1819 called this hidden part of the cerebral cortex as "insel" (in Latin "island"). Since that, the terms "Reil's insula" and "Reil's Island" and finally "insula" were used to designate this structure.[54]

Embedded between the frontal and temporal lobes of each cerebral hemisphere and constituting the basis of the sylvian fissure, the insula has an anterior and a lateral surface that is covered by the opercules. While the anterior insular surface is covered by the fronto-orbital operculum (portion of the posterior orbital gyrus and orbital part of the inferior frontal gyrus), its lateral surface is covered superiorly by the fronto-parietal operculum (pars triangularis and opercularis of the inferior frontal gyrus, subcentral gyrus, and superior part of the supramarginal gyrus) and inferiorly by the temporal

operculum (superior temporal gyrus and inferior portion of the supramarginal gyrus).[41]

The insula looks like an inverted pyramid with a medial base, whose antero-inferior vertex constitutes the limen of the insula. The insula is divided by the insular central sulcus into an anterior and posterior portion. While the anterior portion is generally composed by three short girus (anterior, medial, and posterior), the posterior portion is generally composed of two long girus (anterior and posterior).[41]

The insular lobe covers the lateral surface of the central core, a deep block anatomically constituted in each hemisphere by the insula itself, basal ganglia, thalamus, and internal capsule.

Despite its name, the insula - the island - has reciprocal connections to most areas of the brain, especially the orbito-frontal region, anterior cingulate gyrus, supplementary motor areas, parietal lobe, temporal cortices, and subcortical structures especially the amygdala, globus pallidus, and thalamus.[27]

The insula is part of the limbic system and is considered as the fifth lobe. This lobe is closely associated with visceral, psycho-emotional activities and interrelation with the motor, sensory, and language areas. The insular cortex has a variety of functions and acts in memory, direction, and different types of emotion, as well as visceral autonomic control, taste sensation, and smell. Overall, it is a complex structure with seven cyto-architectural subdivisions encompassing five gyrus and four different functional areas (cognitive, socio-emotional, chemical-sensory, and sensory-motor) that overlap themselves without precise boundaries.[17]

Its vascular supply become from the insular segment (M2) of the middle cerebral artery which covers the insular cortex, constitutes the essential blood supply, and appears to be the main cause of high surgical risk to the region. Venous drainage of the insula is almost exclusively by the superficial and deep Sylvian veins which should be preserved in all surgeries.[53]

There is a great connectivity in all insular regions and eventual epileptic seizures originating from the insula are great mimics of seizures originating from other areas. Epilepsies with frontal, temporal, and parietal characteristics may actually start at the insular lobe, causing difficulty on diagnosis and treatment failure. The anterior insula has a great connection with the frontal lobe while the posterior portion has a great connection with the parietal lobe. Regarding these special characteristics insular epilepsy is reported as a form of epilepsy that remains difficult to recognize, evaluate and treat.[19]

Insular Lobe Epilepsy

The idea of "insular lobe epilepsy" was proposed for the first time in the 1950s, with the observation that epileptic symptoms resulting from insular electric stimulation were similar to those of TLE and was very difficult to differentiate between the two. Early in the 50s Guillaume and Mazars; and Penfield, Jasper and Faulk in the following years got clinical data and showed that patients with TLE who were surgically treated had an approximately 70% satisfactory results and the main reason for treatment failure was suggested to be the insular cortex involvement. They observed interictal electroencephalographic changes at insula during intraoperative electrocorticography (ECoG) in patients with TLE and could also generate the same symptoms with intraoperative insular stimulation as the spontaneous temporal lobe seizures do.[21]

Approximately 10 years after this observation Silfvenius *et al*.[46] reported that the addition of insular resection to temporal lobectomy did not improve seizure outcome but morbidity, especially hemiparesis, increased from 3% to 21%. Penfield in his publications also concluded that insular cortex ECoG-guided resection after temporal lobectomy did not significantly increase seizure control compared to temporal lobectomy alone and the risk of complications was extremely higher. Demonstration of these results led to relative disinterest in insular lobe epilepsy for a few years. For a long time and in many places, the epilepsies were classified based only on the four cerebral lobes: frontal, temporal, parietal, and occipital.[47]

The onset of seizure at the insular cortex is very difficult to record and recognize by the surface EEG due to its deep anatomical location and the rich middle cerebral artery branches coverage. Therefore, routine scalp EEG, which is considered the most useful and valuable initial approach in epilepsy, plays a minor role in insular lobe epilepsy. Using just the EEG data are difficult to determine whether the discharge originate at mesial temporal lobe and spread to insula or if it starts in fact at the insular cortex. However, with improvement of the investigative techniques such as stereo-electroencephalography (SEEG) and the advances on imaging exams enhanced the knowledge and research interest on this specific field.[22]

After the 1960s with the development of SEEG in France, enabling extra-operative monitoring of the insular cortex, the electrographic investigation of insular epilepsy returned to the focus. The idea to use deep intracerebral electrodes implanted with stereotactic technique, described by Talairach and Bancaud,[50] made possible an invasive investigation for longer periods, which increases the chance of recording ictal information beyond just the interictal ones. SEEG was described and accepted as an innovative and reliable technique for deep electrode implantation; however, the need to traverse the perisylvian opercula still posed major risks and complications, leading the community to somehow abandon the insular epilepsy momentarily.[22]

The application of SEEG in Europe has always been widely used and widespread after its conception, but in other continents this technique has been less practiced routinely since it needs a special apparatus and was time consumable.[23]

Insular lobe epilepsy regains major global attention between the 1980s and 1990s when brain image exams evolve dramatically, allowing an anatomic-electro-clinical correlation between insular lesions and seizure symptoms. Due to evolution on the imaginological exams with a fine resolution for brain blood vessels and the opportunity to fuse different image techniques together with stereotactic devices allowed the chronic invasive study with depth electrodes at the insular lobe to be used with great precision and reduced risks. So this investigative tactic got more acceptances and started to be widespread throughout different epilepsy centers worldwide.[23]

The first report of specifically insular invasive monitoring, extra operatively, was in 1993 by Roper *et al*.[42] using subdural electrodes at the insular cortex surface. The Lyon group in France performed the first insular-specific SEEG implantation in 1996.

In the beginning of the 21st century, Isnard *et al*.[20,21] reported the first ictal record of an insular seizure using intracranial electrodes in patients with atypical TLE. In a follow-up of 50 patients with TLE using SEEG, 86% of seizures spread to the insula and only 12% actually arose from the insular lobe. He also could describe the semiology of insular seizures using electrical stimulation of the insular cortex. It starts with a feeling of laryngeal constriction and always-unpleasant paresthesias affecting large cutaneous territories, most often at the ictal onset and most of time without compromising consciousness. Subsequently dysarthria and focal motor symptoms could be developed. This clinical sequence on the onset of seizures in patients with TLE strongly favors the diagnosis of insular epilepsy.[21] Curiously, these findings were the same as those previously reported by Wilder Penfield in 1951, when he wrote: "The description of the initial phenomenon is markedly similar from one case to another. The sensation begins in the epigastrium and rises to the throat when consciousness is usually lost. The sensation may be pain or tightness and may end up as a choking sensation." (Penfield and Kristiansen).[39] At present, invasive investigation of insular lobe epilepsy is preferably performed with SEEG in most of specialized epilepsy centers and is the gold standard technique for the drug resistant insular lobe epilepsy study.

Etiology

Most cases of insular epilepsy reported in the literature have obvious and visible MRI lesions. These lesions include mainly low-grade brain tumors, most commonly gliomas and dysembrioplastic neuroepithelial tumors; also cavernomas and cortical dysplasias are common lesions on insular cortex.[57] In patients with insular epilepsy and negative magnetic resonance, no evidence of lesions on image exams, the most common pathology is cortical dysplasia.[21,29,30] Chevrier *et al*.[7] recently reported a study of 48 patients with epilepsy of the insular/peri-insular cortex. MRI revealed a neoplasic lesion in 27% of patients, a focal cortical dysplasia in 21%, a vascular malformation in 19%, atrophy/gliosis in 17%, a normal result in 8%, and a few other different lesions.

Semiology and General Characteristics

Regarding insular numerous connections with other lobes, insular seizures can simulate seizures from other locations. It is well known that seizures of insular origin may also have predominant motor manifestations, which are linked to the spread of the insular ictal discharge to the frontal lobe, especially to the fronto-mesial regions.

The hypothesis of insular lobe seizure should always be considered when a combination of somatosensory, visceral, and motor symptoms is observed at the onset of the seizure, or even in a TLE with different presentation. Most cases with insular lesions as cortical dysplasia, tumors, and gliosis/atrophy commonly present as a drug resistant epilepsy.[35]

Somatosensory manifestations are often found, particularly when the ictal discharge develops at the posterior region of the insula. Patients often report diverse sensations due to the multisensory nature of this region, but migratory/disseminated paresthesias such as tingling or low-intensity electrical shock are the most common reports, it typically involves a large cutaneous area such as limbs and hemi-body or only delimited areas such as peri-oral region. When these symptoms are bilateral and symmetrical or thermal sensation (hot/cold), they are even more favorable to be from an insular origin. In addition, it may be described a painful feature of the seizure which is considered pathognomonic of an insular seizure.[26]

Discomfort reported in the cervico-laryngeal region, ranging from a simple difficulty in swallowing to even a terrifying sensation of suffocation or strangulation is very frequent and usually points to an origin at the anterior insula.[22] This unpleasant sensation is often accompanied by dyspnea or a prolonged breathing pause.

Visceral-sensory and visceral-motor manifestations are also frequently observed. They include nausea and epigastric or abdominal sensation, similar to those described in mesial TLE and occasionally vomiting. Visceral symptoms typically suggest an ictal discharge at the anterior insula. However, only with the clinical observation it's not possible to certainly know the topographic place of the initial discharge.[26]

Hypermotor seizures of insular origin occurs predominantly at night and have often pedal-like motor disturbances and may or may not have elevation of the upper limb in association, which often leads to the mistaken suspicion of pure frontal epilepsy. Symptoms can range from a discrete gesture movements (brief pedaling, bimanual, or swinging trunk movements) to sometimes spectacular motor phenomena characterized by disordered agitation with kicking or pelvic rotation and even dystonic features as asymmetrical tonic posture, hemiballistic movements, or facial dyskinesia.[43]

Classically nocturnal hypermotor attacks have been associated with foci in the orbitofrontal, lateral-prefrontal, or medial frontal regions and in their presence there are warning signs that should raise the suspicion of a possible ictal onset at the insular cortex. These are the seizures preceded by visceral, somatosensory, taste, and/or hearing auras characteristics that are more evident preceding diurnal motor seizures when compared to nocturnal ones. Nocturnal seizures generally make it impossible to report auras.[45] The effective motor behavior only occurs when the ictal discharge reach the frontal portions of the brain, it can be evidenced by the latency (8–20 s) observed between electrographic onset and motor events, suggesting an extra frontal lobe seizure.[34,43]

There are some symptoms that are less frequently seen or recognized:

- Auditory hallucinations - Usually a simple elementary sounds, but can present complex sounds. May originate not only from the temporal operculum (Heschl's gyrus), but also from the posteroinferior portion of the insula. These auditory symptoms are occasionally associated with somatosensory symptoms around the ear[26]
- Taste or olfactory symptoms - Taste symptoms are rarely found but are of high value for insular localization, according to cortical stimulation data these symptoms are evoked by stimulation of the middle portion of the insular lobe. Olfactory symptoms have also been identified in the same insular sub region and are even rare than taste symptoms[21,35]
- Vestibular symptoms - Rarely found, vestibular symptoms are usually located at the back of the insula. Patients describe hallucinations of body movement as flying, rising, falling, or rotating head sensations[35]
- Speech disorders - Rarely encountered symptom, the degree of which varies from a complete speech interruption or only missing words or impaired fluency.[21]

It is still uncertain that insular seizures can cause bradycardia, atrioventricular block and/or asystole during the onset leading to SUDEP, but tend to be a rare symptom that in some cases may potentially increase the risk of death in these patients.[51]

Insular seizures may be confused with non-epileptic psychogenic seizures or not yet identified as insular onset due to the lack of clear electrographic subsidies and so the patients sometimes maintain their treatment for temporal or frontal lobe epilepsies but without the expected results. Thus, it is clear the need for a detailed investigation of the history and characteristics of the events with special interest on the presenting auras.[36]

Investigation and Diagnosis

Basically, there are two forms of investigation to prove the topographic diagnosis of epilepsy and the recognition of the epileptogenic zone. They are commonly referred as invasive and noninvasive studies. Invasive when they need any surgical approach on the process or noninvasive when performed with complementary examinations without surgical procedures.[48]

As we have seen before, the clinical and semiological characteristics of insular epilepsy are heterogeneous and sometimes nonspecific requiring the use of exams and complementary information to accurately identify the insular focus. The symptoms described previously are highly suggestive of insular cortex involvement but do not always mean that seizures start at the insula, they may have ictal discharge in a nearby area and quickly dissipate through it.[48] To really confirm the epileptogenic zone and the ictal onset area, we have some tools:

Non-invasive studies

EEG

It is the basic exam initially performed in all patients with epilepsy. Patients with insular lobe or operculo-insular epilepsy usually exhibit interictal epileptiform discharges at frontal, temporal, and/or central electrodes.[38] As the scalp EEG requires synchronous or temporally overlapping activation of a relatively large area of cortex to determine a spike and the insula is located at the depth; in some cases, the discharges may not be clearly identified on surface EEG. In most cases, these interictal epileptiform discharges will allow lateralization of the epileptic focus at least. However, some seizures are associated with diffuse changes and sometimes not even lateralization is possible.[48]

The earliest ictal changes may take the form of rapid low-voltage activity or rhythmic slow-wave discharges; most often they are clearly lateralized. During hypermotor seizures the muscle artifacts can run over and compromise the interpretation of the deep seizures discharges.[15]

VEEG

Complementary examination regularly performed in all patients with refractory epilepsy and in preoperative

investigations. Its the use of scalp EEG coupled with visual video record in a sync real time with electroencephalography, it enables electro-clinical association for initial investigation. Auras are not usually captured by video but clinical signs such as faces of pain; movement of the hand toward the throat; the time latency between clinical and electrographic manifestations and hypermotor manifestations may suggest an insular focus.[7]

MRI

It is an image exam witch is also part of the basic investigation in all refractory epilepsy. High-resolution images should be made according to specific epilepsy protocols and thoroughly evaluated by experienced personnel. The diagnosis of insular epilepsy is highly suggestive when the images demonstrate an epileptogenic lesion in the insula. But unfortunately, non-lesional cases are found very often on daily practice.[22,28]

Rates and the radiological findings vary depending on the published series regarding the focus of each study. In a recent publication of 25 patients undergoing non-tumoral epilepsy surgery involving the operculum-insular region, preoperative MRI was normal or had nonspecific findings in 18 patients (72%) of the cases and in 20% the findings were cortical dysplasia.[22,28]

Magnetoencephalography (MEG)

MEG is one of the most useful noninvasive tests to identify possible patients with insular epilepsy. It is a newer imaging modality used in preoperative evaluation of focal epilepsy, which has been shown to be useful for detecting epileptic foci even in patients with other inconclusive traditional noninvasive studies. MEG is sensitive to neuronal activity and like EEG is more sensitive to the neuronal activity in superficial than deep structures.

MEG-guided epilepsy surgery usually results in favorable seizure control especially when complete resection of the visualized MEG cluster is performed.[32,38]

Interictal PET-CT and ictal SPECT

They are functional images of brain metabolism using specific markers, the radiopharmaceuticals previously described. Despite having a well-established role in the investigation of mesial TLEs, PET-CT and SPECT have a moderate value in topographic confirmation of peri-insular epilepsies. In interictal and ictal images, the brain areas with interconnections with the insula can often lead to misleading epileptogenic stimuli. Therefore, it is not recommended to use such modalities alone to confirm the diagnosis and to indicate the surgical treatment for insular lobe epilepsy.[49]

Genetic tests

When MRI does not identify an epileptogenic lesion, one possible explanation is that in fact really exist an underlying lesion but it is so subtle that it is not detected by MRI scans currently in use. This is increasingly supported by histopathological studies performed on epileptogenic insulas of patients with normal MRI who underwent surgical resection. The results demonstrated subtle focal cortical dysplasias.[38]

Some cases of insular epilepsy have been already reported to have genetic defects, including mutations on CHRNB2 and CHRNA4 genes and also a DEPDC5 mutation in a patient with familial focal epilepsy syndrome. A large temporo-insular epileptogenic neuronal network was reported in a family with focal epilepsy syndrome associated to a Q555X mutation of synapsin1 (SYN1) on chromosome Xp11-q21.[36,58]

These two ideas are not mutually exclusive because genetic mutations can lead to neuronal migration defects and consequently focal cortical dysplasia.

Invasive studies

Because of insular deep location and complex connections, non-invasive examinations are frequently unable to accurately differentiate between true insular seizures or seizures from temporal, parietal, or frontal lobe. Once insula epilepsy is suspected an intracranial electrode recording and cortical stimulation are generally required to evaluate the electro-clinical-radiological data on each case. Like all patients with refractory epilepsy those with insular epilepsy should be evaluated and treated individually with causal hypotheses and treatment plans drawn up on a case-by-case basis.[38]

There are several approaches described for insular electrodes implantation. Invasive investigation may include depth electrodes (located inside the insula), subdural electrodes (located on the insular surface), or the combination of both. The use of depth electrodes for insular EEG monitoring has been shown to be safe and reliable since you follow some basic orientations and has a clear hypothesis with the purpose of always avoiding a "fishing expedition." The risks and costs must be calculated and compared with the benefits of performing an invasive investigation and even some surgery procedure to control seizures.[22,44]

In a general way when the patient has clinical and semiological characteristics that strongly suggest seizures from the operculum-insular region with MRI without visible lesions, known as negative MRI, the invasive study should be performed. Patients with warning signs that suggest temporal plus epilepsy – cases of TLE in which the epileptogenic zone

extend to neighboring regions – should be investigated invasively before undergoing direct surgical treatment of the temporal lobe, which risk of treatment failure is higher.[22,44]

Subdural electrodes

Subdural electrodes are commonly used in the preoperative evaluation of patients who are candidates for refractory epilepsy surgery in general. They are a kind of electrodes placed directly on the surface of the cerebral cortex and used to determine epileptogenic regions when the non-invasive study cannot adequately identify the epileptogenic zone. Subdural electrodes have a much higher resolution than scalp electrodes and have a much clearer identification of small activity sites that are difficult to find with the surface EEG.[22] They are sets of electrodes from 2 to 4 mm in diameter separated from each other every 10 mm, inserted in a polyurethane/silicone base such as grids or strips. It is the most common used method for chronic recording in the majority epilepsy centers worldwide.[34] Subdural electrodes are implanted after a craniotomy or trepanation and are also used for electrocorticography and functional mapping. The benefits of subdural grid placement include precise mapping of superficial zones (language and motor areas) and the possibility to be used in any patient regardless of age. Disadvantages of the subdural study include the need for relatively large craniotomies, limitations for bilateral explorations and difficulty in assessing deep cortical structures such as the insula.[27]

For insular epilepsy study, due to its deep localization and rich covering by arterial branches that hinder the accuracy of the subdural cortical electrodes the deep electrodes have been shown to be more effective in locating the epileptic focus and the involved neuronal network.[34] The combination of subdural and deep electrodes implanted after craniotomies in an attempt to delimit the epileptogenic zone has been widely used for the management of epilepsy.[49]

Deep electrodes

As we know, 2/3 of the brain cortex are not viewed at the surface, similar to insula, so the depth electrodes are the preferred technique for invasive investigation of insular lobe refractory epilepsy. It has evolved considerably in recent years and the common denominator for safe implantation is a detailed vascular study.[14]

Deep electrodes are the electrodes implanted in the brain depth for monitoring and mapping deep cortical areas, especially those with difficult to access/contact with subdural electrodes. They are arranged in line and circumferentially in a cable with a thickness of few millimeters (2 mm), with varied number of contacts and sizes.[26] To be implanted they progressively penetrate the superficial cortex, white matter, travels close to the brain vessels and are finally located at the deep cortical portions to get the electrographic data. Its advantages in addition to three-dimensional electrographic monitoring and the ability to stimulate and map deep areas are the possibility of simultaneous bilateral recording and in some cases to perform a thermocoagulation treatment with the same electrodes; all of this can be achieved after a percutaneous stereotactic-guided implantation with high precision and safety.[2,14] The major disadvantages are infection, cerebral hemorrhages and cerebrospinal fluid leakage. It also has some more difficult to fix it in little children. This technique was first published in the 1950's, in Paris.[50] Using multiplanar measurements and stereotactic coordinates can be performed less invasively using a percutaneous implantation technique with good accuracy, allowing the spatial study of the neuronal network involved in the beginning and dispersion of the epileptogenic discharge.[14]

The technique was called SEEG and initially it required a special and complex technical apparatus, consuming a long time and multiple stages for implantation; it also had a high risk of intracerebral hemorrhage. The technique was not globally used routinely becoming more restricted to European countries, especially France and Italy. With the progressive technological evolution on MRI images allied with the widespread knowledge and the easily accessible digital stereotactic fusion, SEEG has returned with great force and importance on the invasive investigation for refractory epilepsies, especially those from insular/peri-insular region. At present, the SEEG is the modality of choice for investigation and surgical planning to treat insular lobe epilepsy.[1]

Findings of the invasive investigation of insular epilepsy

With the invasive study, interictal and ictal electroencephalographic monitoring can be performed and specific patterns and characteristics of the insular lobe recognized. However, there is relatively less information on the invasive EEG of the insula compared with invasive EEG from other areas.[21]

Insular ictal findings recorded with SEEG usually consist of low-voltage activities evolving to high-frequency rhythmic spikes, usually limited to one part of the insula initially. This restricted location may spread to other areas of the insula, opercular regions or other related structures. Insular discharges seem to propagate to mesial temporal lobe structures rarely while the reverse is very frequent.[21,35]

The low voltage fast activity that may start abruptly or be preceded by predictive discharges is the most common finding.[35] Insular low voltage activity can spread to the contra lateral insula very fast, causing false lateralization sometimes.

One of the great advantage using invasive electrodes, specially the depth ones, is the possibility to do deep cortical stimulation on each different contact and collect their clinical response. Those clinical responses can be compared with the seizure semiological findings and then be used to confirm the topographic diagnose.[31]

Treatment

After an extensive investigation and confirmation that seizures in fact arise from the insular cortex and the epileptogenic zone is defined, surgical treatment strategies become the main end point. Surgical resection of the epileptogenic zone remains the first-line treatment for patients with refractory epilepsy.[23] The expansion use of invasive EEG increased the diagnosis of insular epilepsy and the literature supports surgical resection for insular lobe epilepsy; however, insular and peri-insular surgery still remain a great challenge for the neurosurgical team and this is directly related to its difficult approach and the high morbidity associated with insular resections.[26]

Microsurgical resection

The first resections of the insular cortex were proposed early in the 1950's to improve the surgical outcome of temporal lobectomies, but the idea was abandoned due to the higher surgical morbidity and the inability to improve results as expected. Interest for insular surgery returned with the advent of microsurgical techniques and in 1992 Yasargil *et al*.[59] reported a series of 177 paralimbic tumors including 80 insular tumors, 92.5% of patients were seizure-free after surgery with a few complications.[22]

With the advancement of neuroimaging and microsurgical techniques, became safer to perform insular resections for vascular malformations and tumors with a good surgical results and low risk of complications.[30,57]

According to von Lehe and Parpaleym,[56] who analyzed five independent series involving 74 patients with refractory insular epilepsy treated with surgical resection and an average follow up of 3.5 years, an epilepsy free ratio from 60% to 85% was achieved. Numbers are similar to the results obtained in patients with TLE. However, the complication rate is also very variable on analyzed papers, it is estimated that permanent postoperative deficits are around 8–20% and the transient ones from 9 to 45%, generally related to vascular insults.[22]

Bouthillier and Nguyen in 2017[6] summarized the experience of Montreal Neurological Institute epilepsy group, presenting a series of 25 patients with an Engel I result in 20 cases (80%) after microsurgery.

Surgical resection is the gold standard when it's feasible. Those patients with no conditions or desire for a surgery can still be treated with the so called minimally invasive techniques as laser ablation (laser interstitial thermal therapy [LITT]), SEEG RFTC or less frequent radiosurgery.

Laser therapy - LITT

The laser therapy called LITT uses a stereotactically implanted thermal energy source for a local ablative process (5–20 mm in diameter lesion) and should be visually controlled in a real-time MRI exam to confirm localization and thermo-lesion measurement. The laser thermal ablation for epilepsy treatment has good results when used on mesial TLE and deep locations causes.[4,59] Especially for insula epilepsy control it seems to be a good option for non-surgical candidates as published,[19] reporting a satisfactory outcome in up to 80% of patients treated with LITT for insular epilepsy; however, more investigational series and longer follow-ups are necessary to confirm that. Recent papers regarding insular epilepsy in children treated with LITT shown a good seizure free outcome (Engel 1 and 2) in 43 to 55% with a complication rate from 20 to 30% presenting temporary deficits. However, all authors confirms the necessity of more research about LITT on the treatment of insular epilepsy.[18,40]

Radiofrequency thermocoagulation - RFTC

Using the same electrodes already implanted (SEEG) and connecting a radio frequency generator to their contacts, we can choose which one will be activated for the treatment. Radiofrequency causes a progressive rise in temperature between the determined contacts and leads to cell death, generating the injury.[58] They cause focal lesions of 5–7 mm in diameter with minimal risks, even because the electrodes are already implanted and the thermal dissipation is relatively small.[16] Unlike LITT the lesion caused by the TCRF cannot be visually monitored in real-time by images; however, in the same way as Laser ablation it has a less seizure control rate than that found with the resective surgeries.[58]

RFTC for insular lobe seizure control seems to be an effective choice in selected cases as shown on published series but further information is needed.[55] Mullatti and cols described a good seizure control (Engel 1 and 2) in 74% of cases and 53% of them seizure free. However, a longer follow-up study must be done. They report complication in up to 40% of patients most of them transient.[33]

According to a recent meta-analysis,[5] who did not exclusively study insular epilepsy, the authors said that results are encouraging but without a clear evidence of complete seizure control since numbers ranged from 4 to 71% seizure free, and a pool ratio of 23% of cases being completely controlled. The complication rate reported was 2.5% of permanent deficits.

Palliative procedures

In some cases, when the epileptogenic zone cannot be safely surgically treated neuromodulation is a feasible alternative. There are three different types of modulation, responsive neurostimulation, deep brain stimulation, or vagal nerve stimulation; however, we should understand that these modalities provide partial reduction of seizures and rarely total epilepsy control and so they are considered as palliative treatments. Compared to the potential total control with surgical resections, neuromodulation is considered inferior and should only be done when resection is not an option.[26]

MATERIALS AND METHODS

A literature review was performed using MEDLINE/PubMed, Scopus, and Web of Science databases, in addition to manual search (bibliographic reference list of the included articles). The terms epilepsy/epileptic seizure of the insula and surgical treatment was used in various combinations. To direct the search strategies in each database, the official terms and their synonyms of the Medical Subject Headings (MESH) were used combined through Boolean operators AND and OR in addition to words that identified the studied interventions.

We included studies that were published in English, French, or Portuguese; performed in humans with insular epilepsy who underwent some surgical treatment (microsurgery, laser ablation, or RFTC); the primary outcome was the results in seizure control (Engel I), whether or not included the complication rates; and published from 2008 to September 2019.

The exclusion criteria were studies that included patients with other brain disease than epilepsy; patients not submitted to the surgical treatments described above; case reports or series with less than 5 patients; and when the full text and/or bibliographic references were not available.

RESULTS

In the initial search, a total of 1267 articles were obtained. After removing the duplicates, 710 remaining articles were analyzed for titles and abstracts applying the inclusion and exclusion criteria. 70 studies that met all inclusion criteria were selected and were fully analyzed.

Insular epilepsy is a well-known and characterized disease related to drug resistant epilepsy and has been progressively studied. Among all published papers about the theme most of them are focused in some particular point of the pathology, here we present a compilation of recent and consolidates studies regarding the insular lobe drug resistant epilepsy; a complete overview since its history, anatomo-clinical considerations, diagnostic techniques, and treatment options. Without knowing the signs diagnose must be compromised and the treatment may be failure.

CONCLUSION

Insular epilepsy is rare entity but may be responsible for a considerable number of patients who do not present the expected positive postsurgical results. As insula is a deep-seated intracranial region, many times non-invasive studies are unable to make the topographic diagnosis of insular epilepsy accurately. In such cases, the investigation must be performed with deep electrodes, capable to capture electrographic data directly from the deep cortical area. SEEG is the gold standard technique for insular epilepsy investigation nowadays.

After diagnose and the definition of the epileptogenic zone, to choose the treatment option is the next step. Very often patients show insular lesions on MRI and when a surgical resection is feasible, it must be done. If the resection will be done by microsurgery, laser ablation or RFTC is something that should be defined case by case, counting the patient's choice and the surgeon experience. An insular resection is a safe method and is the most effective approach for refractory insular epilepsy and should be considered as the first line of choice.[26] There is not a one fits all recipes for insular epilepsy and there is not a single line treatment option for all patients.

The take home message is to elucidate the importance of known and recognize insular seizure signs to provide the most appropriate investigation, diagnose, and treatment.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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