Insulectomy for Refractory Epilepsy: Case Series and Literature Review

Insulectomia para epilepsia refratária: Série de casos e revisão de literatura

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Abstract

Surgical resection of the insula (insulectomy) is a procedure used for brain lesions and for refractory epilepsy. It has a difficult surgical access and the need of a wide anatomical knowledge and preoperative planning. There are two types of surgical approaches aiming the exposure of the insular cortex: transsylvian and transcortical. The importance of insulectomies is the efficacy in providing a remarkable decrease in seizures. The objective of the present article is to document the results of a series of 10 patients submitted to insulectomies for refractory epilepsies and compare them with the results of other studies reported in the literature, as well as to describe the main nuances of the surgical approaches and their associated risks. In the new case series, all patients corresponded to preoperative Engel classification IV for; after a mean 2-year follow-up period, they corresponded to Engel classification II. A subtotal resection was performed in six patients, and the remaining four underwent a partial resection, most of them leading to temporary complications. The literature review endorsed the good outcomes of the casuistry. A critical analysis of the presented data reiterates the opinion of several authors that insulectomies are beneficial and safe for the patients. A broad anatomical knowledge of the insular region, preoperative planning (limits of resections), and the use of modern microsurgical techniques must be considered as

Keywords
► island of reil
► insular cortex
► refractory epilepsy
► resective procedures

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Insulectomy for Refractory Epilepsy

Rodrigues et al.

Resumo

A ressecção cirúrgica da ínsula (insulectomia) é um procedimento utilizado para lesões cerebrais e epilepsia refratária. A ínsula possui um acesso cirúrgico difícil com necessidade de um amplo conhecimento anatômico com planejamento pré-operatório. Existem dois tipos de abordagens cirúrgicas que visam a exposição do córtex insular: transsilvianas e transcorticais. A importância das insulectomias é a eficácia em proporcionar uma diminuição das convulsões. O objetivo do presente artigo é documentar os resultados de uma série de 10 pacientes submetidos a insulectomias para epilepsia refratária e compará-los com os resultados de outros estudos relatados na literatura, além de descrever as principais nuances das abordagens cirúrgicas e os seus riscos associados. Na série de casos, todos os pacientes se enquadravam na classificação pré-operatória de Engel IV e, após um período médio de seguimento de 2 anos, eles se enquadravam na classificação de Engel II. Seis pacientes foram submetidos a uma ressecção subtotal e os quatro restantes a uma ressecção parcial, implicando, majoritariamente, em complicações temporárias. A revisão da literatura endossou os bons resultados da casuística. A análise crítica dos dados apresentados reitera a opinião de vários autores de que as insulectomias são benéficas e seguras para os pacientes. O amplo conhecimento anatômico da região insular, o planejamento pré-operatório (limites das ressecções) e a utilização de técnicas microcirúrgicas modernas devem ser considerados princípios básicos para a prevenção de morbidades perioperatórias. As insulectomias são seguras e eficazes, consoante resultem em complicações pós-operatórias temporárias e proporcionem resultados altamente satisfatórios no que diz respeito ao controle das convulsões.

Palavras-chave

► ilha de reil
► córtex insular
► epilepsia refratária
► procedimentos ressrectivos

Introduction

Surgical resection of the insula (insulectomy) is a procedure used for brain lesions and for refractory epilepsy. However, performing this procedure requires a detailed anatomical knowledge of the insula and its surroundings, since its location corresponds to the only cortical region of the brain not visible on the dorsolateral surface of the cerebral hemispheres, which justifies its difficult surgical access and the need of excellent preoperative planning and surgical skills.1,2

There are two types of surgical techniques to approach the insular cortex and perform a total or partial insulectomy: transsylvian and transcortical. Both types of surgical techniques are also associated and combined with other resections of different anatomical locations when needed and, therefore, create different terminologies like operculoinsulectomy (operculum and insula), orbitoinsulectomy (pars orbitalis and insula), or insulectomy plus lobectomy (resection of a brain lobe, for example). In addition, these approaches to the insula are usually associated with good seizure control and acceptable morbidity; nevertheless, it also depends on the histology and location of the lesion.3,4 Besides seizure control, a successful surgical procedure aims to provide a positive impact on quality of life.

The knowledge of the insular anatomy, its functions and the clinical presentation of the seizures arising from this location is important for the surgical treatment.

Anatomy of the Insula

The insula, also known as the fifth cerebral lobe, can be described as an external shield of a true brain block of anatomically well-defined structures, which is arranged, from lateral to medial, as follows: insular cortex, extreme capsule, claustrum, external capsule, lentiform nucleus, internal capsule, and thalamus.5,6

This lobe, unlike the others, is located in the depth of the lateral sulcus, totally covered by the temporal and frontoparietal opercula, which potentially makes the surgical access more difficult, since, to visualize it, it is necessary to dissect the sylvian fissure and retract the opercula or go transcortical. Only then, the characteristic triangular shape of the insula and the perinsular sulci, which are the anatomical landmarks that separate and distinguish it from the surrounding cortical areas, can be recognized (Fig. 1).1,7–9

On the insular surface, there are three short gyri (anterior, middle, and posterior – divided by the anterior and precentral insular sulci), two long gyri (anterior and posterior – divided by the postcentral insular sulcus) and, very often, two additional gyri situated cranially, called transverse and accessory insular gyrus. The short and long gyri are separated from each other by the central insular sulcus (Fig. 1), which divides the insula into two portions, anterior and posterior, which are connected, to the frontal and temporoparietal lobes, respectively. Finally, the insula is delimited by the anterior, superior, and inferior...
limiting sulci, which is also called perinsular sulcus or circular sulcus of the insula. Also considered an important anatomical landmark, located in the most anterobasal portion of the insula, is the limen, corresponding to the level at which the middle cerebral artery (MCA) bifurcates into the M2 branches, laterally to the anterior perforated substance (Fig. 2).

Vascularization of the Insula
The vascular supply to the insula comes from the MCA. The first segment of the MCA is referred to as sphenoidal, or M1, and arises from the ramification of the internal carotid artery (ICA) at the level of the anterior perforated substance, situated superiorly. The lenticulostriate arteries that arise at the M1 level are extremely important perforators that supply the basal ganglia and the internal capsule. These small arteries should be preserved during surgery at this location to avoid neurological deficits.

At the level of the limen, the M1 (insular segment) branches into M2 segments, one superior and the other inferior, supplying the short and long gyri, respectively. The M2 segment is also important because the long perforating branches projecting superiorly and posteriorly irrigate the corona radiata and, therefore, should be preserved during surgery to prevent ischemic injury resulting in hemiparesis.

The vascularization of the insula can be seen in more detail in Figs. 2, 3, and 4.

Functions of the Insula
The function of the insula is not completely understood, probably because there are no isolated insular lesions to better understand its neurological deficits. However, there...
is consistent evidence that this lobe is involved in cognitive functions as well as in sensorimotor and socioemotional processing.

The insular functions related to sensorimotor processing are associated to visceral sensations, autonomic control, interception, somatic, pain and auditory processing, and vestibular and chemosensory functions. The socioemotional processing functions are related to emotional experience, empathy, and risky decision-making. Finally, the cognitive functions are associated mainly to attention and speech. In summary, the insula contributes to multiple cognitive and critical functions for human beings and is considered a part of the limbic cortex.

Connectivity
The insula has reciprocal connections with various regions of the brain. The most important insular networks are with the orbitofrontal, anterior cingulate, supplementary motor areas, the parietal and temporal cortex, as well as with subcortical structures, which explains its involvement in many cognitive functions. These connections can be seen in Fig. 5, a reproduction of an image by Shelley et al.

Semiology of Insular Epilepsies
Since the insula establishes several reciprocal connections with various cortical and subcortical areas of the brain, the semiology of seizures is characteristically heterogeneous, presenting many differences regarding the manifestation of symptoms and clinical signs. The most important types of seizure manifestation involve viscerosensory, somatosensory, olfactory, gustatory, auditory, and tonic clonic presentation, as well as changes in heartbeat pattern, vomiting, abnormal self-motor or hypermotor behaviors, and language disorders.

By analyzing the presence and evolution of clinical symptoms that occur during the development of an ictal discharge inside the insular lobe, it is noted that seizures can arise from any part of the insula, therefore spreading to adjacent opercula regions.

Historically, insular epilepsy has been and still is considered difficult to investigate; therefore, diagnosis, workup, and assessment can take a long time for these patients. Furthermore, insular epilepsy mimics symptoms of frontal and temporal seizures, as well as other types. Because of this cluster of symptoms and signs, a thorough analysis and assessment is usually performed, especially regarding the history of the seizures and the auras, since insular and operculoinsular seizures with preserved consciousness are characteristically associated with asphyxia, painful sensations, and taste auras.

Finally, when insular epilepsy is drug resistant, the resection of the epileptogenic area usually correlates with good to excellent seizure control over time. Also important is the use of invasive electroencephalography (EEG) monitoring when needed to better understand the size and right topography of the epileptogenic area and the seizure dissipation pattern. Therefore, the surgical resection is tailored for each patient and surgical approach performed.

Methods
Study design and patients: Retrospective review of 10 patients submitted to either transsylvian or transcortical insular resection procedures for refractory epilepsy for...
insular lesions. For all patients, medical history, semiology and frequency of the seizures, neurological status, magnetic resonance imaging (MRI) findings, and electrophysiological studies were recorded during the pre- and postoperative periods.

Preoperative procedure: All patients underwent preoperative epilepsy workup assessment. The anatomy and function of the insula were also described and reviewed in the context of the surgical approach description. These patients were operated on by the senior author of the present article.

Surgery and histopathology: For all procedures, intraoperative ultrasonography, neuronavigation, ultrasonic aspirator, and intraoperative neurophysiological monitoring (IONM) were used. Either a transsylvian approach for the left insula or a transcortical approach for the right insula was performed. Despite the approach utilized, tumor resection was performed aiming for gross total resection (GTR). Gross total resection was not feasible due to the high risk for neurological deficits. An extension of the resection was performed to remove the rim of the insular cortex or the epileptogenic surrounding area to achieve seizure control.

Follow-up
All patients were classified preoperatively according to the epilepsy classification by Engel and during the regular follow-ups (FUs). To describe the overall results, the last available outcome was used. Follow-up information regarding seizure reduction and neurological status was obtained from the regular outpatient appointments. The present study began in February 2014 and ended in August 2019. Patients were followed-up, on average, for 27 months.

Results
All 10 patients were right-handed and were left hemisphere-dominant. The mean age was 42.5 years old and there were 6 women and 4 men. The mean FU time was 27.2 months. All patients were Engel IV preoperatively and, after surgery, seven of them became Engel II regardless of the surgical approach, either transsylvian or transcortical, during the FU. Three patients during the study became Engel III (patients 1, 6, and 9). The baseline condition or anatomopathological diagnosis did not correlate with worse or better outcomes regarding seizure control. Regarding postoperative complications, there was a case with permanent hemiplegia in a patient with glioblastoma who died at 12 months of FU, a wound dehiscence with cerebrospinal fluid (CSF) fistula in the same patient, and another deceased patient at 13 months of FU also with a glioblastoma (Table 1).

An awake transsylvian approach was the choice for six patients whose lesions were on the left hemisphere, whereas the transcortical approach was used for the remaining four patients whose lesions were on the right insula (three awake and one asleep). For 6 patients, a subtotal resection (STR) (between 90 and 95%) was performed, and for the remaining 4, a partial resection (PR) (< 90%) was achieved. Gross total resection (> 95%) was not achievable due to the high risk for neurological deficits. Seizure control was better for all

| Case No. | Age (years old) | Gender | Race | Dominance | Preoperative (Engel class) | Surgical approach | Pathology, side | Engagement, awake | Pathologic diagnosis | Type of surgery | Resection | Postoperative (Engel class) | Complications | Follow-up and survival | Postoperative complications | Follow-up and survival | Postoperative complications | Follow-up and survival | Postoperative complications | Follow-up and survival |
|----------|----------------|--------|------|-----------|---------------------------|-------------------|---------------|-------------------|-------------------|------------------|------------|---------------------------|----------------|--------------------------|-----------------------------|--------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|-----------------------------|--------------------------|
| 1        | 55, F          | Black  | Black| Left      | IV                        | Transsylvian, awake| Oligodendrogloma, R | Transsylvian, awake| Partial          | Permanent hemiplegia|            | II                      |               | Death after 12 mos        |                              |                          |                          |                              |                          |                          |                              |                          |
| 2        | 43, F          | Black  | Black| Left      | IV                        | Transsylvian, awake| Oligodendrogloma, L | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 19 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 3        | 34, F          | White  | White| Left      | IV                        | Transsylvian, awake| Oligodendrogloma, L | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 22 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 4        | 54, M          | White  | White| Left      | IV                        | Transsylvian, awake| Oligodendrogloma, L | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 46 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 5        | 19, F          | Yellow | White| Left      | IV                        | Transsylvian, awake| Cortical dysplasia, R | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 34 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 6        | 53, M          | Black  | Black| Left      | IV                        | Transsylvian, awake| Ganglioglioma, L     | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 60 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 7        | 44, F          | White  | White| Left      | IV                        | Transsylvian, awake| Grade II astrocytoma, R | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 11 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 8        | 33, M          | Black  | Black| Left      | IV                        | Transsylvian, awake| Grade II astrocytoma, R | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 21 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 9        | 37, M          | Black  | Black| Left      | IV                        | Transsylvian, awake| Grade II astrocytoma, R | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 34 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |
| 10       | 54, F          | White  | White| Left      | IV                        | Transsylvian, awake| Grade II astrocytoma, R | Transsylvian, awake| Partial          | Subtotal          |            | II                      |               | 60 mos                   |                              |                          |                          |                              |                          |                          |                              |                          |

Abbreviations: CSF, cerebrospinal fluid; F, female; L, left; M, male; mos, months; No, number; R, right.
patients except for the ones with glioblastomas, possibly due to the more aggressive behavior of the condition (►Table 1).

Discussion

From 2009 to 2017, 5 searched articles about insular epilepsy reported the results of 82 patients submitted to lesionectomies plus an insular approach aiming for seizure control (►Table 2). The results showed a significant improvement in seizure control after surgery in all studies. Von Lehe et al.24 presented his results according to the ILAE (International League against Epilepsy) classification. They were able to show that 15 out of 24 patients were seizure free (ILAE 1), 4 presented their results according to the ILAE (International League against Epilepsy) classification. They were able to identify the ILAs, which originate precisely from the M1 segment allows the neurosurgeon to follow and identify the LLAs, which originate from the proximal M1 segment as it runs inferiorly through the anterior perforated substance and up to the region of the limen insulae. From this

Prybylowski et al.4 compared the surgical morbidity of 52 patients submitted to the transsylvian approach with 48 patients operated on by the transcortical approach for glioma resection. The results suggest that both techniques are associated with equivalent and reasonable morbidity profiles, even though gliomas located within the superior-posterior quadrant of the insula are usually considered for a transcortical approach. To date, however, there are no objective and clear criteria that guide the conduct of neurosurgeons to adopt one technique over the other. In fact, most studies reflect a preference for one technique rather than the other based on subjective criteria, such as the historical preference of the institutions themselves and/or personal tendencies of professionals.4

Characteristically, the transpercular approach (►Fig. 6) involves the creation of “cortical windows” above or below the sylvian fissure, through nonfunctional cortical areas of the operculum (by subpial dissection) to avoid blood vessel coagulation and ensure better exposure of the insular cortex. The transsylvian technique (►Fig. 7), developed by Yaşargil, on the other hand, guarantees an alternative strategy, using a natural corridor provided by the sylvian fissure. One of the major advantages of this technique is the ability to identify and control vascular structures during surgical resection, such as the MCA (and its branches) and the lenticulostrate arteries. However, this approach is frequently associated with surgical manipulation of superficial plus perisylvian vessels and, along with opercular retraction, potentially increases the risks of postoperative deficits and of vascular injury or spasm.3,4,28,30–32

The main postoperative complications were hemiparesis and worsening of previous neurological motor and visual deficits (hemianopsias) (►Table 1). Different hypotheses may explain the occurrence of these complications; however, it is important to remember that the insula plays an associative/nonessential role in gustation, olfaction, memory, drive, sympathetic control of cardiovascular tone, somatosensory input and pain processing, motor planning, and language.12,13,15,27,30,33 Hence, transient postoperative deficits may reside in the interruption of motor and/or linguistic functions of the insula during surgery or in the shrinkage of the operculum, being subsequently compensated and even fully recovered due to a secondary nature of the insular cortex in performing these functions, while permanent postoperative deficits would be much more associated with the manipulation of the lenticulostrate arteries or with injury causing deep strokes, for example. (►Figs. 3 and 4).19,27,34

The lateral lenticulostrate arteries (LLAs) have particular importance because the vertical plane formed by their course corresponds to the medial limit of resection in insulectomies. The LLAs supply blood flow to the lentiform nucleus and the internal capsule. Furthermore, early dissection of the proximal M1 segment allows the neurosurgeon to follow and identify the LLAs, which originate precisely from the M1 segment as it runs inferiorly through the anterior perforated substance and up to the region of the limen insulae. From this
<table>
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<th>Authors and Year</th>
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<th>Mean age (years old)</th>
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<td>von Lehe et al., 2009[^24]</td>
<td>24</td>
<td>27 (1–62)</td>
<td>Viscerosensory, emotional and nonspecific sx (including the experience of fear)</td>
<td>n = 7: partial insulectomy with or without lobectomies n = 17: total insulectomy with or without lobectomies</td>
<td>Permanent morbidity: n = 1: increased hemiparesis n = 2: hemianopsia Temporary morbidity: n = 1: hemiparesis and dysphasia Other complications: n = 1: aseptic inflammatory meningeal response</td>
<td>37.5 months (12–168 months)</td>
<td>Seizure outcomes according to ILAE classification: n = 1: Class 1 n = 2: Class 2 n = 2: Class 3 n = 5: Class 4</td>
<td>n = 2: cavernoma n = 2: DNT (WHO grade I) n = 3: gliosis n = 5: other gliomas (WHO grades II–III) n = 6: ganglioglioma (WHO grade I) n = 6: cortical dysplasia</td>
</tr>
<tr>
<td>Park et al., 2009[^26]</td>
<td>6</td>
<td>4.2 (4–7 years)</td>
<td>Unspecified</td>
<td>Pt.1: total insulectomy Pt.2: frontal and temporal lobectomy and total insulectomy Pt.3: hemisphreectomy and total insulectomy Pt.4: frontal lobectomy and partial insulectomy Pt.5: frontal lobectomy and total insulectomy Pt.6: temporal lobectomy and partial insulectomy</td>
<td>None</td>
<td>17.8 months (6–33 months)</td>
<td>Seizure outcomes according to the Engel classification: Pt.1,2,3,4,6: Class I Pt.5: Class II</td>
<td>Pt.1: cortical dysplasia Pt.2: could not be diagnosed Pt.3: could not be diagnosed Pt.4: cortical dysplasia Pt.5: hypertrrophic astrocyte Pt.6: microgyreogenesis</td>
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<td>Malak et al., 2009[^27]</td>
<td>9</td>
<td>29.4 (16–36)</td>
<td>Somatosensory, viscerosensory, and somatomotor sx; paresthesia; throat constriction; tonic posturing; nausea; dysphasia</td>
<td>Pt.1: temporal lobectomy and partial (ant) insulectomy Pt.2: partial (post) insulectomy Pt.3: frontal lobectomy and total insulectomy Pt.4: frontal, parietal, and temporal operculoinsulectomy Pt.5: frontal operculoinsulectomy Pt.6: temporal lobectomy and total insulectomy Pt.7: frontal and parietal operculoinsulectomy Pt.8: total insulectomy Pt.9: partial insulectomy</td>
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<td>54 months (14–122 months)</td>
<td>Engel Class I was achieved in all patients</td>
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<td>18</td>
<td>35 (22–53)</td>
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<td>Permanent morbidity: n = 1: arm, tongue, and cheek hypeesthesia and foot dysesthesia Temporary morbidity: n = 3: trans hemiparesis (or increase) n = 3: trans aphasia n = 1: trans brachyfacial paresis and/or: trans depression, hyperosmia, facial asymmetry, altered pain and thermal sensation, etc.</td>
<td>21.8 months (5–142 months)</td>
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<td>n = 1: tuberous sclerosis n = 1: congenital encephalomalacia n = 2: hippocampal sclerosis n = 4: cortical dysplasia</td>
</tr>
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(Continued)
point, the M1 bifurcates into M2 segments (Fig. 1B), whose branches originate the short and long perforating arteries that supply the insular cortex and the corona radiata, respectively. For this reason, it is important to preserve the long perforating branches to avoid ischemic lesions and motor deficits.\textsuperscript{12,13,35,36}

\textbf{Conclusions}

Surgical resection of insular lesions can be a challenge regarding the extent of resection and maintaining quality of life with minimal neurological deficits. The present case series presented results comparable with the most recent ones in the literature in terms of seizure control, life expectancy, and quality of life. Despite complications associated with these procedures, in general, the benefits outweigh the risks since, for many patients, the natural history of the baseline condition could be more devastating, thus reinforcing surgical indication. Finally, it is paramount to better understand the insular surgical anatomy when performing a procedure in this complex region. The utilization of modern
microsurgical techniques, ultrasound, neuronavigation, and specially IONM, are important to prevent neurological deficits. Insulectomies can be performed in the context of achieving not only oncological resection but also to accomplish seizure reduction by adding to the lesion resection an extension to include the epileptogenic surrounding cortex.

Conflict of Interests
The authors have no conflict of interests to declare.

References

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