Insular Neurocysticercosis: Our Findings And Review Of The Medical Literature

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Abstract

Forty six patients with radiographically proven NCC primarily involving the right insula lobe, the left insular lobe or both, attending to neurocysticercosis clinic and/or neurology clinic at Umtata General Hospital or Nelson Mandela Academic Hospital (South Africa) between January 1999 and January 2005 were selected for this study. All patients were assessed for neglect, dysphagia, dysphasia, cardiac disturbances and insular epilepsy among other disorders. CT scan, Elisa test for cysticercosis, ECG, and EEG tests were done. Commonest problems found were functional dysphagia, visual and somesthetic neglect, neurogenic heart, ECG abnormalities such as: ST segment depression and QT interval prolongation. Insular epilepsy was characterized by laryngeal discomfort, thoracic oppression, unpleasant paresthesia, and sensation of levitation. Similar findings about insular NCC were not reported before. Insular neurocysticercosis should be listed among causes of sudden death, SUDEP, and neurogenic heart.

INTRODUCTION

One day, somebody asked to our medical students: “How large of the different lobes of the brain relative to each other?” And the most advantaged one answered: “The percentages of total cerebral cortex volume for the different lobes are: frontal lobe = 41%, temporal lobe = 22%, parietal lobe = 19%, and occipital lobe = 18%” therefore he answered correctly, but as you can see many peoples refer to cerebral lobes as: frontal, parietal occipital and temporal. Nevertheless, in addition to these four lobes, a fifth one exists called the insular lobe (IL) the IL or the island of Reil was first referred to by Vic d’Azyr in 1786 as the “circonvolutions situated between the sylvian fissure and the corpus striatum”, the first description was done by J. C. Reil in 1809 and further detailed anatomic descriptions of this structure were made independently by Guldberg and Eberstaller in 1887. Remembering the lost island of Atlantis this lobe remains hidden and lies submerged beneath the parietal, frontal, and temporal opercular cortices, buried under a tangled web of middle cerebral artery branches. IL is internal and is not visible from the surface of the brain, its the best protected region of the whole cerebral cortex, and the poorest studied region all over brain; IL represents a remarkable challenge for further researchers among new generations of neurologists, neurophysiologists, neuroimmunologists, and neuropathologist among others.

Some functions of the right insular lobe are little bit known such as its role in taste perception its intensity and recognition for the ipsilateral tongue (rostrodorsal insula) and some functions of the left insula cortex for intensity of the stimulus ipsilateral to the tongue and taste recognition bilaterally, gustatory mechanism, movements of the mouth, and oropharyngeal swallowing (anterior insular) are not well known neither, and almost nothing has been demonstrated about the role of insular lobe over the amygdala complex and emotional behavior.

The human IL is also considered as paralimbic cortex, because of its connections with limbic and sensorimotor cortices, the IL is believed to play a role in affective and attention aspects of human behaviour as well. Paralimbic insular regions have functional specialization for behaviours requiring integration between extra personal stimuli and the internal milieu. Based on these connections, one might expect that lesions of the insular cortex may result in disorders of neglect. This was recently observed in a right-handed individual who developed severe multimodal neglect after injury to the right insular lobe, adjacent white matter, and the inner face of the overlying operculum.

The incidence of neglect in patients with isolated insular infarctions due to ILNCC has not been previously investigated. Previous studies showed greater
severity of somesthetic, audition, and visual neglect among patients with right compared with left insular damage. These findings are consistent with anatomic connections that have been identified between insular cortex and various cortical regions from animal studies. 13,14

The present findings also provide empirical support for observations of neglect associated with right insular infarction reported in case studies. 8

Scant information is available about the role of the human insular cortex in cognitive processes. Altered behavior following insular damage in humans has previously been described in case reports and associations between right insular lobe damage and neglect 4 and left insular damage and aphasia 15,16 have also been reported. Berthier et al 12 reported the case of a right-handed patient who, after an ischemic infarction that involved the entire right insular cortex and adjacent white matter, developed a severe neglect syndrome, oral apraxia, mutism, and ideomotor apraxia on the right hand.

Although the presence of neglect is usually considered a sign of parietal lobe dysfunction, it should not be surprising to find neglect in association with non-parietal lesions. A review of neglect syndromes in monkeys and humans suggests that several regions provide an integrated network for the mediation of directed attention. 2 The 3 cortical components of this network are the posterior parietal lobe, frontal eye fields, and the cingulate gyrus. Heilman et al 10 have described a neuroanatomic system involving cortical-limbic-thalamic-recticular components that lead to preparatory activation or arousal toward meaningful stimuli in the contra lateral hemi space. In humans, neglect is most commonly associated with lesions that involve the right inferior parietal lobe, which includes Brodmann's areas 40 and 39. However, there are other areas where lesions in humans have been reported to induce neglect, including the dorsolateral frontal lobes, the mesial frontal lobes including the cingulate gyrus, and the thalamic and mesencephalic reticular formation. 1 Moreover, several reports have clearly shown that lesions elsewhere in the right hemisphere may result in neglect. 12,16

Although clinical descriptions of cases with restricted insular lesions are rare, insular anatomy, connectivity, and physiology have been extensively studied in monkeys and humans 18. The insular lobe sends neural efferent to cortical areas, from which it receives reciprocal afferent projections. Considering both afferents and efferent, the insular lobe has connections with principal sensory areas in the olfactory, gustatory, somesthetic (SI and SII), and auditory (AI and AII) modalities as well as the paramotor cortex (area 6 and perhaps MII), polymodal association cortex, and a wide range of paralimbic areas in the orbital, temporo-polar, and cingulate areas.

It should also be noted that the insular cortex has reciprocal connections with the anterior inferior parietal cortex, that produces classical parietal neglect when damaged. On the basis of the above data and anatomic connections, the present finding might be construed to indicate that insular lesions probably disrupt connections with areas that are normally involved in arousal, attention, and activation. Right insular damage, similar to right parietal lobe damage, may impair awareness of external stimuli and lead to neglect.

Neurocisticercosis (NCC) is a parasitic infection of central nervous system (CNS) caused by the larval stage (Cysticercus cellulosae) of the pig tapeworm Taenia solium. This is the most common helminthes to produce CNS infection in human beings. The larvae of Taenia solium (Cysticercus cellulosae) cause neurocisticercosis. This pork tapeworm can vary in size, but is notable for a scolex (head) with approximately 25 hooklets, 4 suckers, and a body with 700-1200 proglottids and 500-600 eggs each one. The ova of the tapeworm are spread via the fecal-oral route and are approximately 40 microns in diameter with a radially striated shell. The intermediate host is the pig, which harbors the larvae after eating ova, while the definitive host is the human being. If pig products infected with larvae are ingested, a tapeworm infection in the intestines will ensue; however, if ova are ingested, cisticercosis may occur in this normally intermediate host. The ingested ova develop into larvae (cysticerci) and lodge in soft tissues, especially skin, muscle, and brain (NCC). Cysticerci are fluid-filled oval cysts, approximately 1-2 cm in diameter, with an internal scolex. In the central nervous system, T solium is deposited in the cerebral parenchyma, meninges, spinal cord, and eyes. Unless large numbers of cysts are present, the body's immune system will not act to destroy the organism, and cysts can live for many years undetected. A live cyst can go undetected for as long as 5 years before dying or causing symptoms in the host. The occurrence of acquired epilepsy or the syndrome of raised intracranial pressure in a person living in or visiting a region where taeniasis is endemic or even in one living in close contact with people who have taeniasis should suggest a diagnosis of cysticercosis; the NCC may remain asymptomatic for months to years and...
sometimes its diagnosis is made incidentally when neuroimaging is performed. Symptoms and signs are related both to the parasite, and to the inflammatory-immunological response of the host. NCC is the most common cause of acquired epilepsy worldwide and most of the patients taking phenytoin or carbamazepine for a proper control of their seizures, respond very well. For interested peoples, many other aspects concerning to NCC from our region are available on line. According with the publications made in the last decade, very little is know about NCC on the IL. The main aim of this study is to report the clinical manifestations found in a serie of patients affected by NCC on the IL from hereinafter called insular neurocysticercosis (ILNCC) and correlates our finding with those reported on the medical literature.

**MATERIAL AND METHOD**

Fourty six patients with radiographically proven NCC primarily involving the insula, attending to neurocysticercosis clinic and/or neurology clinic at Umtata General Hospital or Nelson Mandela Academic Hospital (South Africa) between January 1999 and January 2005 were included in the study. The study consisted of a prospective analysis. Patients who could be included in this prospective group were identified on admission to the hospital and underwent a detailed evaluation. Once accepted into the study, subjects were scheduled for a subsequent visit for a computerized tomography (CT) scan of the brain, if the CT was confirmatory, they were evaluated both clinically and radiologically at each review visit. The serum from each patient was tested for cysticercus antibodies by enzyme linked immunosorbent assay (ELISA). For most of the patient a routine 12-lead electrocardiogram (ECG) was done. All patients underwent a full neurological examination with detailed seizure history. Dysphagia was confirmed when patients presented cough or swallowing disturbances after instillation of 5 ml of tap water into the mouth.

Impairment for recognition of fear or disgust on facial expression on selected photo were present in 2 patients but we were unable to confirm t therefore this aspect will not be considered for analysis.

Inter ictal EEG was performed in all epileptic patients: 28 males and 18 females. The mean duration of follow-up in the study was 27.8 (+/-20.86) months. Exclusion criteria: previous history of any other neurological disease apart from epilepsy, concomitant disorders such: metabolic disorders, meningoencephalitis, head injuries, coronary diseases, disorders commonly associated with dysphagia. Other exclusion criteria included alternative cause for intracranial calcifications or suspicion of tuberculomas, pyogenic brain abscesses, mycotic granulomas, and primary or brain's metastases., Jervell-Lang-Nielsen Syndrome, Romano-Ward syndrome or the classical QT Syndrome or Drug-induced QT prolongation.

**RESULTS**

Commonest disturbances found in our serie are summarized in Table I, and medical reports about these issues are also reflected on that Table. In general, most relevant clinical manifestations from our serie were: neglect (n=6), disturbances of gustation (metallic taste as aura, n=4), functional dysphagia (n=8), cardiac asystole (n=3), signs of neurogenic heart (n=6), ECG abnormalities such as: Prolonged QT (QT interval in excess of 0.44 seconds) and ST depression (horizontal or down-sloping ST segment depression of 0.1 mV or more for 80 milliseconds), (n=4), ECG abnormalities were more commonly observed in patients presenting INCC on the right anterior or right posterior IL (Graphic 2) Disturbance of taste were confirmed almost exclusively in patients with INCC on the anterior left. (Table II)

**Figure 1**

Graphic 2: Correlation between ECG changes and IL affected
Insular epilepsy was characterized by: pilomotor seizures (n=3), laryngeal discomfort and, thoracic oppression (n=3), unpleasant paresthesia, dysarthria and sensation of levitation without loss of consciousness (n=3). Inter-ictal EEG done did not show remarkable abnormalities.

No significant correlation between INCC and Elisa for NCC was found. Dysphagia was observed in patients presenting NCC on the left IL (Table I) and most of those patients presented simple focal seizures (Graphic 1).

Table 1

<table>
<thead>
<tr>
<th>Associated problems</th>
<th>Left insula</th>
<th>Right insula</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior insula</td>
<td>3</td>
<td>3</td>
<td>X</td>
</tr>
<tr>
<td>Posterior insula</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Graphic 1: Correlation between epileptic seizures and dysphagia

Calcified NCC on IL was confirmed only in epileptic patients (Figure 1) while CT showing active NCC in colloid or granular stages on the IL were found in patients presenting ECG abnormalities, neurogenic heart, SUDEP, neglect and dysphagia (Figure 2).

Table 2: Correlation between disturbances of taste and affected insula

<table>
<thead>
<tr>
<th>Gustation</th>
<th>Left Insula</th>
<th>Right Insula</th>
<th>Anterior Insula</th>
<th>Posterior Insula</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Salty</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Bitter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sour</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Metallic</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Alkaline</td>
<td></td>
<td></td>
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Table: Other problems

- Sexual arousal
- Receiving pain
- Empathy for pain
- Depression
- Auditory agnosia
- Recognition of disgust and fear from facial expression
- Emotional symptoms
- Visceral symptoms
- Autobiographical memory
- False offers
- Dysphagia
- Slow phase eye velocity
- Nystagmus
- Deactivation of the caloric
Figure 6
Figure 1: CT (coronal view) Shows calcified NCC on left insular cortex

Figure 7
Figure 2: CT scan of the brain (axial view): Show enhancing cystic lesions on both cerebral hemisphere (in colloid stages) including both insula lobes. Scolex is present in some of them and perilesional edema is also seen. Other lesions in advance granular stage are seen as well. Signs of severe damage on the left insular cortex are present.

DISCUSSION
In our opinion, except epilepsy almost all neurologic manifestations to be discussed thereafter arise from ILNCC when the encysted worm is on the way of death by natural cause or other conditions causing an irritative/inflammatory response due to events such as: polarizing the immune response to Th2, suppressing interleukin 2, 5 and 6, and TH1 cytokine. Increased IgG, interleukin-2-5 in serum and interleukin 5-6 plus neopterin in the CSF, accumulation and phenotype heterogeneity of mast cell with increased secretion of numerous powerful mediators such as endorphins, serotonin, histamine, heparin, kinins, leukotriens, prostaglandin, vasoactive intestinal peptide, proteolytic enzymes, cytokines and phospholipases which are well known to have significant pathophysiological effects on vascular and neuronal tissues, among other problems.
Neglect: We confirm visual and somesthetic neglect in 3 patients with right INCC, our finding were congruent with those previously reported on the medical literature. Gemeiner et al. Dysphagia: Dysphagia may occur in patients with unilateral stroke affecting the IL particularly the anterior part which has important connections with the primary ans secondary motor cortex, the ventroposterior medial nucleus of the thalamus, and the nucleus of tractus solitarius, all these structures play important role on the mechanism of oropharyngeal swallowing, therefore to observed dysphagia in patient affected by anterior IL lesions by INCC is something that we expected.

Dysphasia: Cases of insular damage with variable involvement of the superior temporal gyrus and inferior parietal region have presented with conduction aphasias, although we could not identify patients presenting only disturbances for spoken language such as motor, sensory or global dysphasia on this serie. It is well known that infarction of the anterior insula may result in difficulty in initiation of speech, for the other hand patients with infarction of the insula have revealed global aphasia when the dominant lobe was involved. Involvement of the non-dominant lobe resulted in mutism, neglect, apraxias or bilateral opercular syndromes, and other deficits include object naming, articulatory planning deficits, auditory processing disorders, ictus emeticus and dyslexia.

Pain: Rostral agranular insular cortex is one of the few cortical areas consistently activated by painful stimuli and we also know that the cerebral cortex contains pathways that raise or lower pain thresholds but we did not assess this function on this serie therefore this aspect is not discussed in this article.

Impairment for recognition of facial expression: It was present in at least two patients from this serie however because our limitations for a proper documentation of these finding we decide do not include it for analysis, and we just want to mention it. Facial expression recognition is impaired in schizophrenia, some types of dementia, and Huntington’s disease. All this disorders may sharing same topographic diagnosis: Left insular cortex.

Cardiac disturbances: In one of our patients with ILNCC on the right insula lobe (Figure 3) almost all reported pathological features were well documented during post-morten examination and this patient presented ictal tachycardia, ECG changes (prolonged QT interval and ST depression), subendocardial hemorrhage (neurogenic heart) and/or SUDEP being it one of the more important finding from this serie. The insula of the right cerebral hemisphere may have a major role in cardiac autonomic control as you can see in Figure 4. Here, we present our graphical hypotheses about the neurogenic mechanism for ECG abnormalities found in our serie. Neurogenic ECG alterations are often transient, but cause diagnostic problems, mimicking acute myocardial infarction (MI). Some features of T waves may be suggestive of heart pathology, but they are non-specific, making it important to consider a neurogenic genesis to avoid unsuitable therapies. In cases of ILNCC, associated insular stroke, and ECG abnormalities such as: ST depression and inverted T wave or aberrant Q wave the differential diagnosis between IL’s ischemic stroke secondary to cardiac embolism (acute coronary syndrome) and cardiac damage (focal myocytolysis) secondary to increased local cardiotoxic catecholamines, increase production of 3',5'-cyclic adenosine monophosphate (cAMP) which causes the opening of the calcium channels resulting in the influx of calcium (and efflux of potassium ions), actin-myosin interaction with subsequent prolonged muscle contraction (calcium channels failure) and cell death due to intracellular metabolic derangement (subendocardial hemorrhages/focal myocytolysis) due to INCC and associated ischemic stroke, its may be extremely difficult to perform taking into consideration that elevated cardiac enzymes and ECG abnormalities are present in both situations. Here if fractal dimensions of HRV confirm autonomic disturbance the more probable diagnosis may be neurogenic heart secondary to INCC and final diagnosis of cardiac damage related to coronary disease must be done by myocardial perfusion imaging (Thallium 201 or Technetium Tc 99m). Single-photon emission computed tomography (SPECT) imaging is indicated for patients with intermediate pretest probability of coronary artery disease based on clinical history or results of aprevious exercise tolerance test, patients who cannot exercise or ECG shows exertional ST depression associated with left ventricular hypertrophy, other choices are cardiac magnetic resonance angiography with or without contrast or dobutamine, nad Carotid intima-media thickness. In 2004 Colivicchi et al. designed a study to assess the effects of acute right insular ischemic damage on heart rate variability (HRV) and arrhythmias finding that the right insula is implicated in the autonomic control of cardiac activity and that acute right insular damage may lead to a derangement of cardiac function with potential prognostic implications. We agree
HRV is one of the most reliable tests to confirm autonomic dysfunction of the heart, and we previously demonstrated that fractal dimension for HRV is even the best choice. Nevertheless, signs of neurogenic cardiac disturbances found in our series such as: cardiac asystole, ictal bradycardia and neurogenic heart are useful to support the hypotheses that left insula play an important role in neurogenic cardiac disturbances as well. According with Locatelli, left insular stimulation and right vagal nerve stimulation cause same effect on cardiac rhythm because the fiber from the left cortex must cross to stimulate the right brainstem vagal nuclei therefore treatment of choice for this problem is pacemaker.

**Figure 8**
Figure 3: Lateral view of the right insula lobe. One cyst with the scolex inside (in vesicular stage) on anterior insula is seen, other cyst without scolex with turbid fluid-filled oval cysts and local inflammatory reaction on the middle-anterior (agranular) insula is observed. Left insula was normal and no other cysts were found all over the brain. Cause of death: SUDEP/Neurogenic heart (subendocardial hemorrhage)

Insular epilepsy in Neurocysticercosis (IENCC): Insular lobe epilepsy (ILE) and insular lobe seizures are still not included in the current classification for epileptic seizures, epilepsy or epileptic syndromes belong to The International League Against Epilepsy therefore most of neurologist, epileptologist, clinician and pediatrician do not include this syndrome in the list of their differential diagnosis for patients presenting “aberrant types of TLE”, “stereotype simple focal seizures” and others. The electroencephalographic studies of the insula are difficult since it is hidden from the brain surface. There was a general consensus about the most persistent finding associated with damage to the insula presenting as complex partial seizures, especially with involvement of the visceral sensations, however we only identified these type of seizures in patients presenting TLE.

In 2004, Isnard et al studied fifty patients performing video and stereoelectroencephalographic ictal recordings and direct electric insular stimulation of the insular cortex for presurgical evaluation of temporal lobe epilepsy and they found an ictal sequence of event in fully conscious patients characterized by a sensation of laryngeal constriction and paresthesiae, often unpleasant, affecting large cutaneous territories, most often at the onset of a complex partial seizure (five of the six patients). It was eventually followed by dysarthric speech and focal motor convulsive symptoms. The insular origin of these symptoms was supported by the data from functional cortical mapping of the insula by using direct cortical stimulations and they concluded saying: “This sequence of ictal symptoms looks reliable enough to
characterize insular lobe epileptic seizures. Observation of this clinical sequence at the onset of seizures on video-EEG recordings in TLE patients strongly suggests that the seizure-onset zone is located not in the temporal but in the insular lobe; recording directly from the insular cortex should occur before making any decision regarding epilepsy surgery”. Other authors a year later were able to characterize insular onsets in the following set of symptoms—memorization of which may benefit all epileptologists. A fully conscious patient with laryngeal discomfort, dyspnea, unpleasant perioral or somatic paresthesias, and dysarthric speech, followed by somatomotor symptoms, implies an insular onset. The final proof is in the response to surgery. The authors provide both positive and negative evidence, that is, two patients who underwent only insular ablation were cured, whereas two who underwent only temporal ablation had persistent seizures.

IENCC has not been well described before probable because little is known about insular seizures, because most of the symptoms and signs did not recall attention from patients and relatives, because these type of seizures are not very common and because other manifestations like disturbances of cardiac function, gastrointestinal symptoms, associated behavioral disorders, and major complications including SUDEP are more relevant even for the attention of health professionals. We would like to emphasized that if these clinical features are not in mind, its diagnosis never going to be done. Based in our observations ILE can be differentiated from TLE if patients remains fully conscious during the attack but when epileptic activity spread from IL to temporal lobe or vice versa that clinical differentiation can be almost impossible to perform. If CT shows calcified NCC on the IL, final diagnosis can be supported by it(Figure 4)

A few weeks ago a comprehensive estimate of the monetary burden of cysticercosis in our region is published.

obviously this interesting study did include IENCC and its desvastating consequences. Nevertheless, we hope after a better understanding of this problem more patients will be early diagnosed and the mortality rate due to NCC will be dramatically decreased contributing to alleviate poverty from this region. Insular neurocysticercosis should be listed among causes of sudden death, SUDEP, and neurogenic heart.

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