Neurocysticercosis and related seizures

by

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Abstract

Neurocysticercosis, the major global cause of acquired epilepsy, is a parasitic disease caused by *Taenia solium* larvae. Patients may have seizures whether larvae in brain are alive or degenerated (calcified). We assessed whether parasitic lesions produce changes in structural brain scans that are associated differentially with the presence of seizures. Using magnetic resonance imaging (MRI) of brain, including diffusion tensor imaging (DTI), with the metrics of fractional anisotropy (FA), axial diffusivity (AD or L1), and mean diffusivity (MD) we examined relationships of clinical findings with white matter pathologic features (ischemia, myelination, axonal damage, inflammation, and edema). We also focused on susceptibility weight imaging (SWI). In the first study, we examined DTI results from 51 patients, with (n=38) or without (n=13) seizures in the fifteen days before scanning, under treatment for a single lesion. We measured FA, AD, and MD, over regions of interest (ROIs), defined within the lesion area, and in part of the brain hemisphere (i.e., half brain minus ventricle and infratentorial region), respectively. Metrics of DTI over the ROIs were compared between hemispheres to calculate an index of asymmetry. Patients exhibiting seizures and single lesion had higher brain asymmetry for AD and MD. DTI did not differ between groups, comparing lesion implantation site and the surrounding nervous tissue with the symmetrical contralateral area. These findings support the idea that inflammatory processes related to neurocysticercosis lesions can affect large

areas of brain hemispheres, in the context of recent seizures. In the second study, we examined 92 brain lesions in 64 patients under treatment for neurocysticercosis: comprising 71 lesions with seizures and 21 lesions without. With seizures, peak lesion frequencies were observed in precentral gyrus, hippocampus and areas proximal to these structures. Lesions in this group were closer to the brain cortex than non-seizure group lesions. Brain volume affected by the disease was also bigger in the seizure group. Characteristics of lesions included: contours that can be smooth or rough; the presence of parasite's head; the peri-lesion gradient; the intra-lesion double gradient, and the enhancement of the nourishing vessel (*vasa nutricia*). Odds of having seizures were higher in the absence of peri-lesion gradient, resembling a shadow between the image of the lesion and the nervous tissue. Finally, sites of lesion implantations follow anatomical patterns of the brain diseases caused by emboli. This innovative finding (related to the deployment of lesions similarly to other emboli) is consistent with the transit paths of larvae from intestine through blood to the brain. These results indicate that *in vivo* MRI analysis of brain lesions in neurocysticercosis is a useful approach for increasing our understanding of determinants of seizures in this disease. Further examination of lesion–symptom relationships with MRI and using parallel electroencephalographic (EEG) studies may yield clinically useful information about seizures in this patient population that may be identifiable through more widely available EEG technology. Such clinical translational advances would be extremely helpful in attempts to combat and treat this disease in areas where MRI analysis may be neither accessible nor affordable.

Preface

The research embodied in this thesis was possible due to an ongoing international research collaboration, between the Department. of Radiology Shri Guru Ram Rai Institute of Medical & Health Sciences (SGRRIMHS), Dehradun, India and the Department of Psychiatry at the University of Alberta, led by. Dr. Rajiv Kumar Azad, MD, PDCC, Neuroradiology Professor & Head at SGRRIMHS and Dr. Andrew J. Greenshaw, PhD, Professor & Associate Chair (Research), Department of Psychiatry at the University of Alberta. For the research presented in this thesis, Dr. Azad selected patients and supervised the brain scanning in his unit at SGRRIMHS. Image data extraction for the DTI and SWI images referred to in the methodology section was led by Dr. Matthew Brown, PhD, Adjunct Professor, Department of Computing Science and Research Associate, Department of Psychiatry at the University of Alberta. The experimental design, data analysis and concluding analysis are my original work, as well as the literature review.

Portions of the text presented in the literature review of this thesis are components of papers that were accepted for publication as Dametto E. et al., "Neurocysticercosis in asplenic patient, case report" and Dametto E., "Neuropsychiatric Manifestations and Epidemiology of Neurocysticercosis" in the *Brazilian Journal of Neurology*, vols. 52(4) and 53(1), respectively.

Acknowledgement

Some words of gratitude: I would like to express my gratitude to all persons who supported this work. Specifically, I would like to acknowledge the anonymous patients whose experience of this disease permitted the development of the research. I consider the brain images studied here as a symbolic reference to their lives. In the same way, I want to dedicate this thesis to future patients that may be helped with this work. May God, the source of all goodness, inspire us.

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List of symbols and abbreviations

(a)	Index of asymmetry between hemispheres
(a')	Index of asymmetry between punctual sites
(n)	Metrics FA, L1, MD, RD, MG, or PH
A	Index of asymmetry
AD	Axonal diffusivity
ANOVA	Analysis of variance
BET	Brain extraction tool
cc	Cubic centimeters
DTI	Diffuse tensor imaging
EITB	Enzyme-linked immunoelectrotransfer blot
ELISA	Enzyme-linked immunosorbent assay
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
FOV	Field-of-view
HDI	Human development index
MCA	Midle cerebral artery
MD	Mean diffusivity
MG	Magnitude derived from SWI
mm^3	Cubic millimeter
ms	milliseconds
n.	Number of subjects in the sample

n1	Metric ipsilateral to the lesion
n2	Metric contralateral to the lesion
NEX	Number of excitations
PH	Phase derived from SWI
RD	Radial diffusivity
SE	Spin-echo
SD	Standard deviation
SWI	Susceptibility weight imaging
T. solium	*Taenia solium*
TE	Echo Time
TR	Repetition Time
x	Maps of SWI or DTI
μ	Micron

C H A P T E R

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I N T R O D U C T I O N

1.1. Overview

Neurocysticercosis is a brain infection caused by larval stages of the parasite *Taenia solium*. The *taenia*-cysticercosis complex refers to pathologic interactions between the humans and the parasite, this complex encompasses extra-intestinal and intestinal parasitosis. Intestinal parasitosis allows adult development of the parasite. Additionally, extra-intestinal parasitosis allows persistent occupation of the larvae in various organs and tissues, and from this stage there is extensive damage to the host.

The most severe form derived from this interaction results in neurocysticercosis. It is considered the most severe form due to the diversity of neurological and psychiatric manifestations that accompany it, and because of the alarming epidemiological data, i.e., it is a frequent etiology for acquired epilepsy and it occurs worldwide. Estimates indicate that 7.6 million cases of epilepsy are associated with neurocysticercosis, in the world population (Berkowitz et al. 2015). The neurological presentations include motor and sensory deficits, which are associated with lesions in the large sensorimotor pathways, cranial nerves, spinal cord, etc. Depression and cognitive decline are among the most prevalent psychiatric symptoms (Srivastava et al. 2013). Endemic areas include South and Central America, Asia, sub-Saharan Africa, and India (Willingham & Engels 2006). It is also

emerging in non-endemic areas due to migration and travelers, particularly in European countries, the United States of America, and Canada (Coyle et al. 2012, Del Brutto 2012, Wallin & Kurtzke 2004). Neurocysticercosis is considered the leading cause of preventable neurological diseases in the world (White 1997).

Human participation in the life cycle of *T. solium* is essential, as it is in humans that the parasite reaches its adult form and releases eggs. *Taenia solium* eggs can be transmitted between humans. Such interpersonal transmission can lead to neurocysticercosis or can result in harboring the adult parasite in the intestines, which perpetuates the worm's life cycle. For non-human hosts, the parasitic disease is restricted to infections caused by larval forms (except for experimental animal models and rare reports) usually in pigs (Carpio 2002, Ambrosio et al. 2011).

Although appropriate prophylaxis for neurocysticercosis exists, the disease remains as a common cause of epilepsy and is associated with a variety of sensory and motor deficits. In studies of prophylaxis the use of 400 mg albendazole for three consecutive days, 2 times a year, has been demonstrated to produce significant reduction of *taeniasis* (and other forms of helminthiasis) when administered to participants who are over six years old, who are not pregnant or breastfeeding, and who do not suffer from acute diseases (Ash et al. 2015). The means of prevention include sanitation of animal farming, hygiene and inspection of food and water origin. The individual means of prophylaxis include thorough cooking of pork, evaluating the origin of fruits and vegetables, and proper hygiene practices.

The optimal therapeutic approach is currently the use of anti-parasitic drugs (e.g. albendazole, praziquantel), anti-inflammatories, treatment of associated conditions (e.g. seizures, intracranial hypertension), and some cases require surgery to extirpate the parasite (García et al. 2012, Xiao et al. 2016).

The biological characteristics of the parasite favor the parasite's interspecies interactions. Host-parasite interactions allow the parasite to gain nutrients and guarantee success in the perpetuation of its life cycle. The intestinal infestation contributes to the release of thousands of eggs, which have the potential to contaminate water and food. The extra-intestinal infection allows the parasite to reach new hosts, because infected meat of animal origin may be inadvertently consumed, particularly pork.

The parasite has a flat body that allows it to absorb nutrients by diffusion from the tegument (Riutort et al. 2012). The absorption strategy is incremented by body extension and numerous villi at the surface of the parasitic body. *T. solium* is classified as a flatworm because the extension of the body reaches meters, while the thickness is the range of a few millimeters. The absence of internal cavities that were intended for the digestive tract, and circulatory system allows the body to be sectioned, which favors the parasite in its reproductive strategies. The individual segments of the body are called strobila, this special anatomical segmentation is present in living creatures that reproduce by releasing body fragments (Kamiya et al. 1991). *T. solium* releases from the final ends of the body numerous fragments that are home to thousands of eggs. Each unit is independent in both food and reproductive functions. Strobili have reproductive ap-

paratus common to both genders, allowing male and female gametes to merge by self-fecundation or halo-fecundation (Maravilla et al. 2011, Willms et al. 2003). These characteristics contribute to the production of large amount of reproductive units that are also infective agents. The adult *T. solium* can liberate 300,000 eggs daily, which can contaminate water and foods (Hui et al. 2000, p. 220). The genu *Taenia* has eggs with an external shell (oncosphere) composed of concentric layers, the shell protects the embryo (Galán-Puchades et al. 2016). The host's digestive secretions such as bile salts act on the oncospheres and externalize the embryos, which are also known as hexacanth larvae because of their six hooks (Conn & Swiderski 2008). The embryos adhere to the intestinal mucosa, later reaching adulthood, or invade the submucosa vessels to disseminate through the bloodstream to the host's organs. The embryos' adhesion is attained by means of muscular structures (suckers), while the hooks and secretory glands permit the embryos' invasion (Willms 2008). The submucosal blood vessels take the hexacanths to the hepatic portal vein. From the liver embryos may reach the heart and arterial circulation.

The anatomy of human arteries may contribute to the implantation of the embryo in specific brain areas. The internal carotid artery delivers the embryos via three main branches the anterior cerebral artery, the posterior cerebral artery and the middle cerebral artery (MCA). The MCA is a terminal branch of the common carotid artery and receives frequently foreign particles circulating in the blood (Ng Yee et al. 2007, Wolf et al. 1978). Considering that the larvae circulate in the

blood as emboli, the sites of brain lesion implantation may follow patterns of other embolic diseases.

The parasite can disrupt the host's defenses through various invasive mechanisms. Some methods are biochemical, for instance the presence of secretory glands, yielding products that allow the parasite to break the structural continuity of cells and penetrate body tissue. In addition, other methods of invasion are physical, for example the hooklets, which are thorns placed in the cephalic portion of the parasite. As muscular fibers permit movement of the parasite's head, consequently the hooks scarify the host tissue (Flisser 2013). The presence of microtriques (filaments) on the surface of the parasite's tegument blinds the host's defenses. The entire body surface of the parasite is covered with microscopic filaments, which attach glycoproteins secreted by the parasite, as well as the host's substances. The combinations of parasite's and host's molecules form an almost perfect camouflage for the parasite as it is covered with molecules from the host, the parasite tegument even binds to human immunoglobulins (Willms & Arcos 1977) .

Effectiveness in warding off the host's defenses is strengthened by aggressive strategies against the immune system, considering that the *Taenidae* can inhibit lymphocyte mitotic factors (Letonja et al. 1987). Despite evading the host's defenses, the cyst degenerates after reaching four developmental stages. The pathological sages of the these cysts, based on Escobar (2002) are:

1. Vesicular: viable parasite with intact membrane and therefore no host reaction.

2. Colloidal vesicular: parasite dies and the cyst fluid becomes turbid. As the membrane becomes leaky, edema surrounds the cyst. The host's inflammatory reaction can increase the edema volume.
3. Granular nodular: edema decreases as the cyst retracts further.
4. Nodular calcified: end-stage quiescent calcified cyst remnant, no or little edema.

In the early stages of parasite-host interactions, inflammation elicits edema close to the infective tissue (**Fig**. **1**). The parasite degenerates and the scar is formed by calcifications, granulomas and fibrosis. The inflammatory reaction around the cyst is chronic. The inflammation on vessel walls and gliosis happen close to the site of infection, at any stage. It is assumed that the debris of the parasite may be a source of long term antigenicity. The immune system, in order to combat the larvae, recruits the participation of several cells (including eosinophils, lymphocytes, monocytes, plasma cells, macrophages) and chemical mediators (including lymphokines, interferons, tumor necrosis factor, see Sciutto et al. 2013). Immune mediated inflammatory responses to causative agents in brain lead to granulomatosis, fibrosis, and calcification in order to isolate the cyst from the nervous tissue. Granulomae are formed by macrophages and their derived cells (giant cells, epithelioid), while fibrosis are formed by fibroblasts. Nonetheless, the infection affects also the nervous tissue, gliosis is frequently seen at the inflammatory site. Immunological tests using enzyme-linked immunoelectrotransfer blot (EITB) and enzyme-linked immunosorbent assays (ELISA) are useful for detection of antibodies against parasite antigens in serum.

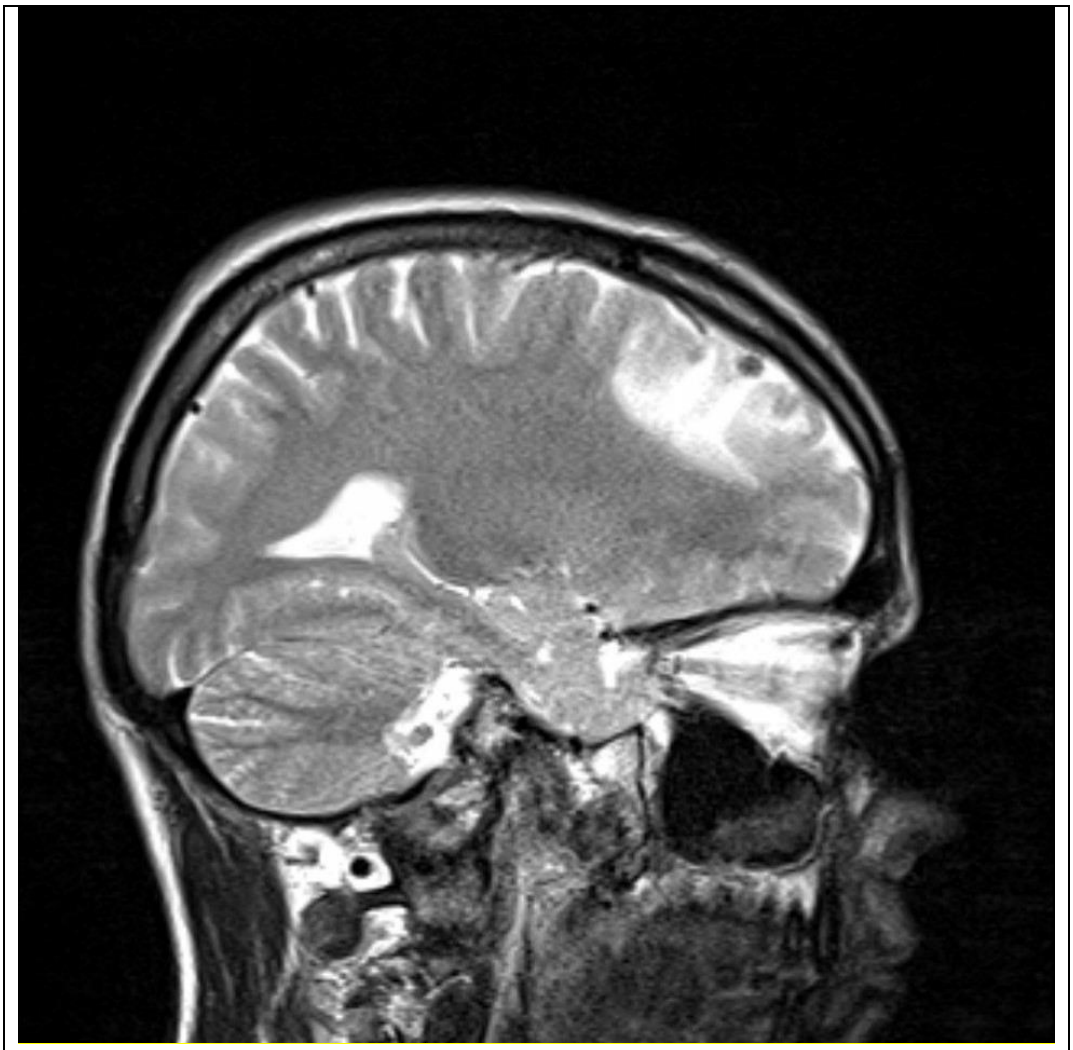

Figure 1: Brain edema close to lesion in superior frontal gyrus.

A positive serum antibody reaction can be due to the presence of the adult worm in the human intestine (*taeniasis*) or caused by larval worms in extra-intestinal sites (cysticercosis).

Cerebral areas involved in the genesis and propagation of seizures has been proposed by literature, for instance mesial temporal lobe is considered an epileptogenic zone (Bragin et al. 2000). The participation of the hippocampus, as well as that of the amygdala to a lesser extent, has been reported in several studies (Wieser 1983). Other mesial temporal lobe structures may also play a key role in seizure genesis, such as the entorhinal cortex (Spencer & Spencer, 1994; Bartolomei et al. 2008) or piriform cortex (Gale 1992) and the limbic part of the temporal pole (Chabardes et al. 1999). In relation to the participation of brain regions (e.g. hippocampal area) in the origin of seizures due to neurocysticercosis lesions, a main focus has been the mesial temporal lobe (Del Bruto, 2016). Similarly, single precentral gyrus neurocysticercosis lesion has being described in association with seizures in a case report (Azzopardi & Quirk 2012).

Seizures are signs or symptoms due to excessive or synchronous neuronal activity in the brain, while epilepsy manifests as unprovoked seizures occurring at least 24 hours apart. Provoked seizures have proximal time associations with brain impairments, for example infections, trauma, and intoxications (Fisher et al. 2005). The concept of seizure states for repetitive discharges of groups of neurons, addresses the electrophysiological principle of polarization. A dielectric pole is formed when electrical charges move from higher to lower areas in concentration of electrons. In the dielectric pole, the electrostatic fields are separated

by a medium that makes opposition to the passage of charges. Based on the concept of a dielectric pole, pathological brain changes result in seizure by two mechanisms that facilitate the movement of electrons: a) decreasing the resistance of the medium, b) increasing the density of charges (or electrical capacitance), i.e., the ratio between the number of charges and the supporter area (Getet et al. 2000, Amzica & Neckelmann 1999).

Opposition to the passage of electrons is related to myelin sheaths, in the brain, myelin sheaths separating the cortex of subcortical layers. Electron density can be normally high in brain structures with reverberation circuits (e.g. hippocampus) and in areas with increased number and sizes of neurons (e.g. motor cortex). Electron density can be normally low in subcortical layers. The motor cortex and hippocampus are well-established as major seizure-associated areas (Bonini 2013, Hoffmann, 2008).

In relation to pathological changes, damage to white matter (e.g. demyelination and edema) may decrease the resistance of brain tissue to the passage of discharges. Following damage to gray matter (e.g. mineral deposits in the motor cortex) there may also be an increase in electron density in reverberation circuits and in the high electrical capacitance areas.

Neuroimaging is relevant in the diagnosis of neurocysticercosis; however, brain scans must be correlated with clinical presentation, epidemiology and serological tests. Typically, the parasite is located within an encapsulated liquid medium (cyst). The most identifiable cysts show the presence of a scolex, i.e., the cephalic region of the parasite. The presence of the scolex on neuroimaging is considered a major di-

agnostic criterion. The stages of lesions based on neuroimaging has been used to infer the risk of seizures, with limited success. Generally, a cyst is considered active when presenting inflammatory reactions surrounding it, which are identified by the presence of edema or peri-lesion enhancement. After calcification of the cyst, it would be considered inactive. However, calcified lesions may be associated with the presence of seizures, and not all lesions surrounded by edema or enhancement have convulsive symptoms.

Magnetic resonance imaging is a non-invasive method. It has been used routinely for diagnosis of NCC due to the high resolution in detecting cysts, as well as edema frequently related to the inflammatory processes.

Susceptibility Weight Imaging (SWI) and Diffusion Tensor Imaging (DTI) look promising to characterize pathological changes associated with seizures. SWI is a magnetic resonance technique that measures the ability of a material or tissue to be magnetized in an external magnetic field, which results in neuroimaging with different gradients for the substances ferromagnetic (iron), diamagnetic (bone, calcifications), and paramagnetic (deoxyhaemoglobin, hemosiderin and ferritin). SWI indicates whether the tissue is attracted into or repelled out of the magnetic field. Specially, the DTI-Phase neuroimaging can be sensitive to substances that change the neuronal tissue like deoxygenated blood, hemosiderin, ferritin, and calcium (Mittal et al. 2009). DTI technique measures water molecules' direction, which can have an anisotropic diffusion (water molecules move in a preferred direction) or an isotropic diffusion (water molecules move in every direction).

The DTI metrics fractional anisotropy (FA), axial diffusivity (AD), and mean diffusivity (MD) may show subtle white matter pathologic features (ischemia, myelination, axonal damage, inflammation, and edema) (Le Bihan et al. 2001), in brain areas related to epileptogenesis.

Seizures can be a result of a larger impact in the brain, rather than local changes in the infective tissue. In addition, the changes in brain tissue may not follow the chronology of the cyst's evolution. Damage in the cerebral hemisphere may persist after apparent resolution of inflammation, i.e. improvement of edema or peri-lesion enhancement. Considering seizures as result of repetitive discharges of neurons, there are two main system related to the movement of electrical charges. One relies on the cortical layer where most discharges are triggered. The other relies on the white matter tracts where the discharges are transmitted throughout the brain. These two systems allow us to understand of seizures in the context of neurocysticercosis at two levels. One system points to the cortex in terms of location of lesions and number, and the other points to white matter in terms of extension of brain damage.

1.2. Statement of the problem and research questions

1.2.1 Statement of the problem

Neuroimaging is the preferred diagnosis modality for detection of neurocysticercosis, however, this approach frequently fails to explain the pathological mechanisms underlying the seizures, which are frequent manifestations of neurocysticercosis.

The effort to understand the seizures associated with the neurocysticercosis has focussed on better characterization of the stages of development of cysts, however this focus may be misdirected. It is argued that calcified foci are not as innocuous as they are made out to be and can harbor persistent inflammation and gliosis around these lesions, which may be responsible for occurrence of seizure activity in these patients. Nonetheless, the seizures may result from alterations in the whole brain, instead of alterations in the nervous tissue surrounding the neurocysticercosis lesion. There are inconsistencies in the association between presentation of seizures and lesion stages, which were observed by Scobar (2002) in describing the evolutionary chronology of parasitic cysts. It seems more proper to look for whole brain changes, rather than local cyst changes in the context of seizures associated with neurocysticercosis, as structural changes in brain tissue may not follow the same chronology as the cyst does during its degeneration.

Another failure in the understanding of the seizures in the context of neurocysticercosis is the lack of correlation between neuroimaging results and the concepts of parasitology. The larvae reach the brain from the blood, in this process certain brain sites are affected due to the larvae dimensions and host’s vessels anatomy, such factors may have a bearing on the presence of seizures. In the same way, there are failures in correlating neuroimaging and host-parasite interactions. The lesions can have a bigger size or be more numerous, the sum of the volume of nervous tissue affected by all may relates with the presence of seizures.

Advances in terms of new techniques in neuroimaging may reveal aspects not yet described in the literature on neurocysticercosis, particularly as little is known about neurocysticercosis, especially as a causative agent of repetitive seizures.

1.2.2 Research questions

The following questions were addressed:

I. What are the frequencies of location, size and number of the neurocysticercosis lesions comparing the groups of patients with and without seizures?

II. Are there differences between groups with seizure or without seizure, considering the distance from cortical surface and the layer where the lesions were settled (grey matter, white matter or both)?

III. How can we characterize the brain-lesion interface by SWI, DTI, and MRI-T2 considering the inflammatory process derived from host-parasite interaction?

IV. Are the characteristics in the brain-lesion interface related to the presence or absence of seizures?

V. Are there alterations in DTI in the whole brain or in the local site of implantation related to the presence of seizures?

The stages of lesions based on neuroimaging has been used to infer the risk of seizures despite predictive failures. Generally, a cyst is considered active when presenting inflammatory reactions surrounding it, which are identified by the presence of edema or peri-lesion enhancement. After calcification of the cyst, it would be considered inactive. However, calcified lesions may be associated with

the presence of seizures, and not all lesions surrounded by edema or enhancement are associated with convulsive symptoms.

Seizures can be a result of a large impact in the brain, rather than local changes in the infective tissue. In addition, changes in brain tissue may not follow the chronology of the cyst's evolution. The damage in the cerebral hemisphere may persist after apparent resolution of cyst inflammation, i.e. improvement of edema or peri-lesion enhancement. Several pathological changes were identified in the brains of epileptic patients: ischemia, edema, axonal damage, demyelination, tissue deposits of hemosiderin and ferritin, etc.

C H A P T E R

2

LITERATURE REVIEW

2.1 Morphology and vital functions of Taenia solium

Taenia solium has a complex morphology responsible for respiratory, nutritive, nervous, reproductive, secretory and excretory functions. Despite complexity, it does not have respiratory, digestive, and circulatory organs. Vital functions are integrated at the level of the tissues and cells, such arrangement allows the body to reach several meters of length. Morphologic aspects enable the parasite to achieve maturation and reproduction by deriving nutrients from the host's species, and to furthermore evade from host's defenses.

2.2 Taxonomy

Taenia solium belongs to the family *Taenidae*, to the class *Cestoidea*, to the order *Cyclophyllidea*, to the phylum *Platyhelminthes* and to the kingdom *Animaliae* (Flisser et al. 2014). Platyhelminthes (Greek "*platy*", flat and "*helminthes*", worms) have a planar morphology that permits substances to diffuse throughout the tegument to the cells underneath the body's surface (Riutort et al. 2012). Cestodes (Latin "*cestus*", belt) do not have internal body cavities, neither specialized circulatory, nor respiratory organs. Cestodes are endoparasites because they

need to live inside the body of hosts to grow and reproduce. *Cyclophyllidea* include parasites in which life cycle involves at least one intermediate host before developing into the adult form in the definitive host (Nakao et al. 2013). A primary host is a host in which the parasite attains maturity for reproduction. A secondary host (or intermediate) is a host that harbors the parasite for a transition period, before maturity (De Queiroz et al. 1998).

Adult *Taenia solium* inhabits the small intestine of humans, whereas the larval stage can dwell at least two families *Hominidae* and *Suidae* (swine). Typically, humans are primary hosts, and pigs are the intermediate. Exceptionally, humans act as the secondary host when infected by larval forms of *T. solium* (Ferraris Jr et al. 2000, Thanchomnang et al. 2014). *Taenia solium* is the causal factor in the etiology of two different diseases, *taneiasis* that results from the adult infestation in the intestinal mucosa, or cysticercosis that is the invasion of the larval stages in tissues and organs. Particularly, the human brain infection of larval stages is responsible for histological alterations such as edema, necrosis, fibrosis, gliosis and calcification, which can lead to several neuropsychiatric manifestations, or become fatal.

2.3 The organism of Taenia solium

The organism of *Taenia solium* comprises three compartments: head, neck and body.

The head is called : head, neck andions, , it allows to distinguish species of the family *Taenidae*. *T. solium* scolex is spheroidal with a double circular line of hooklets, while that of T. *saginata* is cuboidal without hooks (Jeri et al. 2004, Swastika et al. 2012). The apical end of the scolex is called 2004, Swastika et al*rostrum"* ostrumcal end, it has the shape of a cone. The *Taenia solium* rostellum presents two rings of hooks. The inner circle has larger hooks, while the outer circle has smaller ones. Hooks alternate with each other, length is positively correlated with sharpness of the blade (apex of the hook). Hooks have a chemical composition responsible for their shape and hardness, they are a derivative of chitin, which is a long polymer of N-acetylglucosamine. Chitin gives resistance to protective structures such as exoskeletons in insects, shells in crustaceous, cell walls in bacteria and fungi (Merzendorfer et al. 2006). Muscular fibers permit movement of protrusion and retraction of the rostelum, and consequently to its hooks. The hooks movements result in scarifying the host's tissue during invasive strategies.

The scolex is surrounded by four circular muscles, they act as an adhesion device on the intestine mucosa of the host. This specialized attachment organ is named sucker (Merchant et al.1998, Flisser 2013, García et al. 2003, Leventhal and Cheadle 2011). The neck is an unsegmented zone adjacent to the scolex. The organism grows from the neck region towards the body. Because this area permits the expansion of the worm it has been termed the growth zone or the area of proliferation.

The body is called the strobila. Strobilation consists in the transverse fission of the body by independent units. The strobila is composed of several hundreds of successive segments called proglottids. Each proglottid is self-sufficient for reproductive, digestive and excretory functions. The transverse fission is an expedient to achieve reproduction by releasing proglottids containing eggs outside from the host (Kamiya et al. 1991). As the body gradually elongates, it matures reproductive organs (Wang et al.1999). Notably, the segments close to the head are small, and have the rudiments of the genitalia. Those in the middle of the body contain developed genital organs, while the posterior proglottids are full of eggs. Proglottids are classified as immature, mature and gravid (Willms et al. 2003, Maravilla et al. 2011).

The body of *Taenia solium* is divided transversely by three layers: tegument, intertegumentary muscles and parenchyma. The tegument covers the surface of the worm's body. The basal membrane outlines borders between muscles and the tegument. We know from the effects of dyes that the basal membrane is acidophilic.

The intertegumentary muscles are organized in transversal and longitudinal fibers. The two layers of muscles (longitudinal and transversal) allow vermicular movements and retain proglottids together. Motility is more prominent during larval stages when the worm seeks hosts to grow and achieve maturation. The musculature atrophies in gravid segments, while the uterus expands. This results in the detachment of the gravid proglottid and releasing of the eggs. The tegument has small folds of cortical parenchyma projected towards the external face,

they are called microvilli and increase the contact surface with the medium to improve metabolic changes (Voge and Brown 1979). Along the length of the *Taenia* body extends tegument, nerve cords, excretory ducts and longitudinal muscles (Willms and Arcos 1977, Yong-Jie et al. 2003).

2.4 Tegument structure and function

The tegument main functions are protection, absorption, secretion, and excretion.

Secretory cells lodged inside the mesenchyme (referred to as mesenchymal cells) reach the tegument, perforating the basal membrane and intertegumentary muscles by pore canals. Soluble substances transit throughout tegument. The outermost external layer is formed by the microtriches and the glycocalyx, which is a molecular layer of glycoprotein and polysaccharide originating from the parasite, or from the host. Microtriches are tiny projections in the external surface that allow adhesion of the glycocalyx and foreign molecules to the tegument. Glycocalyx is also present in diverse organisms, e.g. bacteria, and permits identification of invading organisms. Parasites are camouflaged from the host's defenses by a covering of the tegument's glycocalyx with host molecules (Arana et al. 2013).

The tegument resembles an alimentary mucosa and, across it, nutrients are absorbed from exterior; absorption is maximized by the flattened shape and folds.

Glucose enters the microvilli cells via an energy-dependent sodium-dependent co-transporter, analogous to that in vertebrate intestinal epithelium, correspondingly the consumption of nutrients is similar (Dalton et al. 2004).

Platyhelminths, in general, use carbohydrates as source of energy and use amino acids and fatty acids for the synthesis of macromolecules. The tegumentum equally exhibits enzyme catalysis. The worm's covering is the site where enzymes break down diverse complex substrates into simple molecules. Cysteine proteases, which exist over the tegument, act on complex proteins. This illustrates how, the tegument, by secreting enzymes extra-corporeally can digest external substrates (Molinari et al. 2000). This mechanism enables nutrition, invasion and protection of the worm. However, cysteine proteases in fruits or latex of the papaya, pineapple and fig may attack intestinal worms.

2.5 Respiratory function

Taenia solium is a facultative aerobic: it lives and grows in the absence of molecular oxygen. It may take oxygen to form energy, but is capable of switching to anaerobic respiration if oxygen is absent (Cervantes-Vazquez et al. 1990). The parasite may obtain energy by catabolism of glucose and glycogen and it excretes a diversity of substances, including lactic, pyruvic, acetic, and succinic acids (von Brand et al. 1961).

Glycogen is the main stored nutrient and the chief source of energy. Respiratory function occurs at the cellular level through mitochondria, but the organelle is

absent in certain cells (e.g. spermatozoa). Free oxygen is also consumed by the worm. Another key point is that rate of consumption is higher in the anterior proglottids where immature proglottids develop, and it declines towards the posterior end where gravid proglottids have already achieved maturation.

2.6 Nervous system

The central nervous system is comprised of a pair of cephalic ganglia (cerebral ganglia) which extend peripheral nerves to the head and to the body. The cerebral ganglia project fibers to form two circles: a circumcerebral nerve ring and a rostellar nerve ring.

The circumcerebral nerve ring forms a circle over the rostellum. This circuit connects the two cerebral ganglia each other. Four pairs of radial nerves, called rostellar nerves, emerge from the circumcerebral nerve to innervate the rostellum (Vasantha et al.1992). These radial nerves are linked to each other at the base of the rostellum. This second circle constitutes the rostellar nerve ring. The muscular structures in the head are supplied by the cerebral ganglia via nerves to suckers. Two nerves to the body, on each side, emerge from the circumcerebral nerve ring. They transit along the body subjacent to the tegument, and are called posterolateral nerves. The pair of posterolateral nerves are joined by transverse commissures within the scolex and strobila. Secondary branches arise from the transverse commissures and break into tertiary branches to form a rich plexus of

subtegumental nerves. The presence of short nerve endings at the tegument suggests sensory reception (Vasantha et al.1992).

Two pairs of posteromedial nerves also emerge from the cerebral ganglia; however, their extensions are visible up to the region of the neck. The innervation to the suckers and rostellum controls head movement related to adhesion and penetration into the crypts of the host's intestinal mucosa. The peripheral nervous system performs motor and possible sensory functions, considering the presence of short nerve endings. It may also regulate the excretory and secretory functions of the parasite. The nervous fibers, via modulation of muscular contraction, may regulate the propulsion of fluid in the excretory ducts.

2.7 Excretory and osmoregulatory system

The basic structure of the excretory and osmoregulatory system consists of the flame cell and the tube cell. The flame cell has a projection of cilia which is involved by the tube cell (Valverde-Islas et al. 2011). Hydrostatic pressures in flame cells move through the cilia liquids to the tube cell. While flame cells collect waste solutes from mesenchyme, tube cells drain them to the excretory canals and pores. Calcareous corpuscles are found in the excretory canals (Varga-Parada et al. 1999). There are two longitudinal excretory canals: one is dorsal other one is ventral. They continue inner to the muscular layer along the body of the worm, except the dorsal that is restricted to the anterior part of the body. At the scolex they are all connected by the nephridial plexus. At the last proglottid,

the ventral canals join each other to form a caudal vesicle that opens to the exterior by an excretory pore, before the last proglottid ventral canals connect to form the transverse excretory canal.

2.8 Reproductive system

Mature proglottids are hermaphrodite: they have male and female reproductive organs originated from the mesenchyme, where they remain situated. Male organs differentiate before female organs, a condition termed protandrous. Maturation starts from the neck. Anterior segments possess only male genital organs, in contrast posterior segments have both.

2.9 Reproductive system: Male Genital Organs

Testes exist in hundreds in mature segments, for this reason they have numerous male reproductive cells. Testes lie along the (mesenchyme) interstitium close to excretory ducts and ovary. The spermatozoon in *Taenidae* has an anterior extremity that is the apical cone (about 0.5 μ m) and a filiform and elongated body. Several microtubules are present, but it lacks mitochondria (Miquel et al. 2009). The *vasa efferens* derives from testes and these numerous ducts unite into a common duct called the vas deferens. The terminal part of the *vas deferens* is the cirrus that ends in the genital atrium, and then in the genital pore. Receptacles

develop on the *vas deferens* to stock spermatozoa. Those dilatations are named seminal vesicles. If a vesicle grows in the part of the *vas deferens* outside the cirrus sac, it is called an external seminal vesicle; however, when a dilatation on the *vas deferens* develops within the cirrus sac it is classified as an internal seminal vesicle. The prostate gland is represented by a cellular group of glands around the *vasa efferens*.

2.10 Reproductive system: Female Genital Organs

The ovary or germinarium has a ventral position in the medullary parenchyma. It is lobed and the lobes are linked by a narrow isthmus (ovarium bridge). Ova transit from the ovary along the oviduct and are fertilized in its proximal part, the fertilization duct. The fertilization duct is connected to the vagina and to the seminal receptacle. Seminal receptacle stores sperms in the female organs briefly. Fertilized ova from the oviduct goes to the uterus passing through ootype and uterine canal. The ootype is a spherical dilation where secretions from vitelline glands (or yolk-glands) and Mehli's gland form the egg-shell. The uterus consists of a proximal narrow part (uterine duct) and a distal large part (uterine expansion) where numerous branches accommodate the fertilized eggs (Maravilla et al.1998, Kumar et al. 2015, Mendlovic 2006).

2.11 Fertilization and first embryonic stages

Fertilization is internal: ova in the fertilization duct meet spermatozoa originating from the same proglottids (self-fertilization) or from different proglottids

(cross-fertilization). The zygote goes to the ootype where it is surrounded by yolk cells from the viteline gland. Yolk cells become associated with the zygote, and their secretion forms a chorionic membrane (egg shell). The zygote, a unique cell formed by the combination of male and female gametes, divides into two cells one large (megamere) and another small (embryonic cell). The megamere produces other megameres, while the embryonic cell produces mesomeres (medium size cells) and micromeres (small size cells). The embryo is formed by the micromeres, while mesomeres and megameres form external capsules.

The egg has different layers, they are: egg shell, vitelline layer, outer embryonic membrane, embryophore, granular layer, basal membrane, oncospheral membrane, and oncospheral tegument (Galan-Puchades et al. 2016). *Taenia* eggs survive outside the proglottids in the environment, where they can contaminate water and food. After ingestion, the egg hatches the hexacanth embryo, in the intestinal mucosa of hosts by the actions of digestive secretions. The hexacanth embryo attaches to the intestinal mucosa of the host by means of hooks, and the secretion of its penetration glands allows it to reach the submucosal tissues. Submucosal blood vessels take the hexacanth to the portal vein. From the liver the embryo reaches the heart and arterial circulation. Its final destination may be: the central nervous system, eyes, muscles, skin, and other organs (Chamaria et al. 2014, Corstjens 2014, Chile et al.2012). At host organs, the embryo settles to develop into a bladder-worm or cysticercus. The metacestode is either a bladder-like larva, or a derived form: the cysticercus. Two morphological types differen-

tiate the cysticerci: the c*ysticercus cellulose,* which is characterized by the vesicle containing scolex, and the c*ysticercus racemous* that has the appearance of a bunch-of-grapes due to folds of the vesicular capsule.

The embryo presents three pairs of chitinous hooks, secreted by specialized cells called oncoblasts. A hexacanth embryo has six hooks and a pair of penetration glands, it may adhere to the intestinal mucosa of the host, and can invade submucosal vessels. The oncosphere is the hexacanth embryo enclosed by one or two embryonic envelopes (Conn and Swiderski 2008). The hexacanth embryo can remain attached to the intestinal mucosa of the definitive host, in which the parasite attains maturity for reproduction and perpetuation of the parasite life cycle.

2.12 Discussions about morphology and vital functions

For many decades, the literature has referred to two nomenclatures for the morphological types of cysts, yet they are not distinct species. C*ysticercus cellulose* has an oval or round shape. It is smaller (3 to 18 mm, approximately); the *cysticercus racemous* has an irregular and lobular shape, it is bigger (5 to 90 mm, approximately). *Cysticercus racemous* is associated with more extensive lesions (Biagi et al. 1961).

Taenia solim infection is the cause of two different disease in humans. *Taeniasis* results from worm adhesion on the intestinal mucosa, and cysticercosis results from the invasion of the worm to submucosal tissues and organs. Emphasis on

the role of suckers and hooks in the adhesion and to the function of perforating glands in the invasion, has produced dichotomous concepts of the function of these morphologic structures. However, the parasite uses nonselective apparatus in its interaction with host tissues. Host tissue close to the suckers can be damaged, and presents necrosis of epithelial and submucosal cells (Willms 2008).

In a like manner, secretions help in the adhesion. For instance, Anexin-A present on the glycocalix enables adhesion (Verastegui et al. 2007). The adhesion of the oncosphere to the mucosa depends on the structural action of microvilli. A diversity of molecules exists on the glycocalix of the worm. These molecules correlate the glycocalix with functions of protection and invasion. The role of protection is equally outlined by microtriches, structural projections that cover the entire body. The action of enzymes on the surface of the worm is not restricted to alimentary substrates. Several enzymes can act on host tissues, e.g.: cysteine proteases, secreted by metacestodes deplete human CD4 lymphocytes *in vitro* (Molinari et al. 2000).

Several active substances on the surface of the worm can also interfere the host defenses, these include: sialic acid, N-acetyl-D-glucosamine, Nacetylneuraminic, alpha-methyl-D-mannoside, and D-mannose/glucose (Landa et al. 2010). Sialic acid on the surface of bacteria can provide resistance to the host's innate immune response (Severi et al. 2007). N-acetyl-glucosamine showed a mild inhibitory effect of elastase enzyme release from human polymorphonuclear leukocytes (Kamel et al. 1990). N-acetylneuraminic acid can act as a receptor for infectious agents including influenza viruses in mammal cells (Ng Preston et al. 2014).

Studies suggest that the worm can carry other infective agents to host tissues; in this context virus-like particles in the metacestodes may play a role in impairing host defenses (Laclette et al. 1990). The presence of host's molecules (e.g. immunoglobulins) bound on the *Taenia* surface suggests that the parasites evade external attacks covering their body with host molecules (Navarrete-Perea et al. 2016). Furthermore, antibodies can fail to kill the metacestode, interfering with both cellular and humoral immune responses (White Jr et al. 1992). Despite the importance of chemical messengers in the host-parasite defenses, emphasis must be placed on the morphology of the metacestodes. The cells of immunological system have to neutralize and phagocyte a multicellular organism with dimensions incomparable to the usual microorganisms. The proliferative nature of the capsule can regenerate itself after external aggressions. Its folds enclose the excolex (a vital core) from the host's attacks.

Molecular mediators related to neuroendocrine function have been investigated for this parasite. Acetylcholine was identified in the nerve tissue of *Taenia solium* (Vasantha et al.1992). Prolactin was found in the cerebral ganglia in the region of the sucker, in the main nerve cords, and in a few fibers of the transverse nerve commissure (Liu et al. 1996). The enzyme glutamate-carboxylase that catalyzes decarboxylation of glutamate to GABA and CO_2 was also found in *Taenia solium* (Monteoliva et al.1965), as were sex steroid hormones and corticosteroids (Romano et al. 2015, Valdez et al. 2014).

Frequent sites of cyst implantations are the brain and the eyes, in contrast opposing to rare occurrences in the lungs (Jain et al. 2015, 2010). This suggests that

the anaerobiosis of the worm permits cyst development in tissues where the oxygen supply has no surplus, and where oxidative reactions may not affect cyst development.

Fertilization by spermatozoa occurs in conditions of lower oxygen availability in the mature proglottidis, evidence that supports this hypothesis is the absence of mitochondria in male reproductive cells. The main function of mitochondria is the production of energy in the form of ATP, which can be used in the case of spermatozoa of several species, including humans, for sustaining sperm motility (Piomboni et al. 2012). The mature spermatozoon of *T. solium* lacks mitochondria, whereas this organelle is present in other cells of the worm (Willms et al. 2003). Moreover, the mitochondrial gene is present in *T. solium* as it is in other parasitic flatworms (Nakao et al. 2003). Taken together these data suggest that the worm uses alternative sources of energy, for instance in the movement of spermatozoa. Alternative sources of energy were identified in studies that block glucose uptake in *Taenidae* (Fraga et al. 2012).

Finally, the massive discharge of eggs may be the most powerful strategy for reproduction and success in achieving host infection, since one cyst implanted may correspond to numerous oncospheres eradicated by host defenses.

C H A P T E R

3

NEUROPSYCHIATRIC MANIFESTATIONS AND EPIDEMIOLOGY

3.1 Neurocysticercosis manifestations

Taenia solium is a flat helminth whose developmental stages before adulthood (metacestodes) may be executed in host's organs, causing cysticercosis. The metacestodes of this parasite can reach various humans organs where they develop an encysted living form. Contamination occurs by ingesting food or water infected by oncospheres (embryos within a capsule) or meat infected by metacestodes (Singhi 2016). Neurocysticercosis is a major cause of epilepsy in endemic areas, and leads to a diversity of motor and sensitive deficits, manifestations vary from headache to severe intracranial hypertension.

The diagnosis consider manifestations (neurological and psychiatric), neuroimaging findings, and if the patients lived or traveled to endemic areas. Potentially fatal conditions include arteritis, encephalitis and hydrocephalus. Depression and cognitive decline remain among the most important psychiatric manifestations. The world regions affected by this parasitic disease include all continents. The World Health Organization estimates 50 million neurocysticercosis cases world-

wide (Bouteille 2014). It is endemic in Central and South America, Asia and Sub-Saharan Africa. Table 1 presents main world regions affected by this parasitic disease (see **Table 1**). Countries with a low Human Development Index (HDI) are more affected by *Taenia solium* diseases. The HDI is low to medium in endemic areas of the parasite, while it is high in areas where the parasite is rare. The HDI is a summary measure of having a long and healthy life, being knowledgeable and having a decent standard of living. It does not reflect on inequalities, poverty, human security, empowerment, etc. (See endnotes for links to maps of HDI and endemicity of *Taenia solium*).

Immunologic assays (Enzyme Linked Immunosorbent Assay, Western blot) are not specific to CNS infection. Cerebrospinal fluid may show pleocytosis, increased protein, and low glucose levels (Varghese et al. 2016). Lesion biopsy is reserved for times when surgery was necessary (e.g. ocular, spinal cord, fourth ventricle locations: see Seddighi et al. 2016, Abud et al. 2016); in subcutaneous lesions; or exceptionally, in the brain to conduct differential diagnosis (e.g., suspicion of tumors, abscess, mycosis and tuberculosis) (Xiao et al. 2016).

Neuroimaging provides clear information about the characteristics of the parasite stage. Active neurocysticercosis has one or more lesions surrounded by inflammatory signals (e.g. edema or peri-lesion enhancement). In earlier parasite stages, typical lesions have vesicular morphology within a parasite scolex (head); in later stages lesions are calcified (Carpio et al. 1994, Venkat et al. 2016) (**Fig**. **2**).

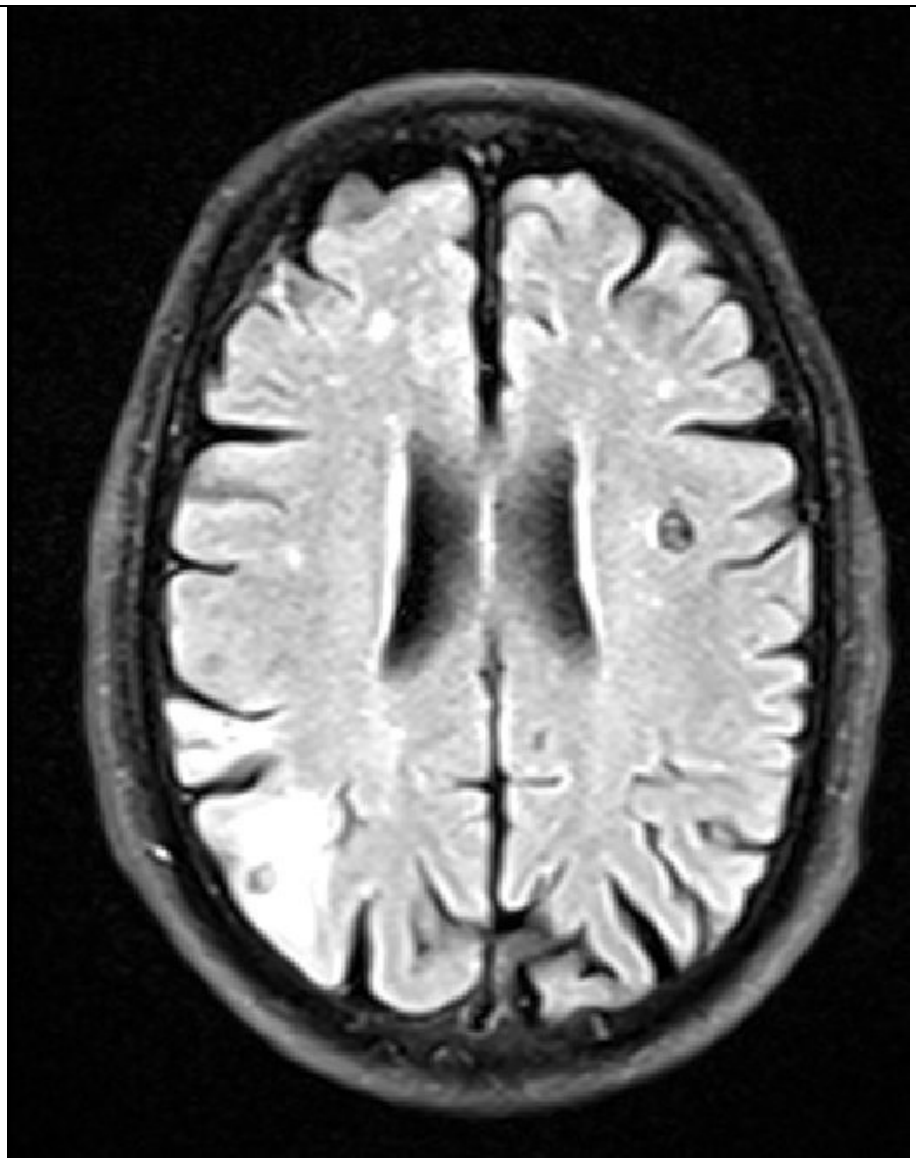

Figure 2: Brain edema (left) and eccentric dot in the lesion (right).

Treatment consists in use of antiparasitic drugs (albendazol, praziquantel) and drugs to treat associated conditions (anticonvulsants, corticosteroids).

Treatment for cysticercosis uses albendazol at a recommended dose of 15 mg/kg/day, the duration varies as 1 month, 15 days and 1 week, or praziquantel in a dose of 50 mg/kg/day for 15 days. In case of 10 days of treatment, a combination of albendazole and praziquantel was more effective than one cysticidal alone (García et al. 2016).

Dexamethasone is prescribed to reduce brain edema, with doses ranging from 4.5 to 12 mg/day.

Mannitol can treat acute intracranial hypertension (García et al. 2002).

Surgery is reserved to extirpate the parasite from particular locations (eyes, spinal cord, cerebral ventricles) or to differentiate neurocysticercosis from tumors, tuberculosis, mycosis, etc.

Prevention includes treatment of intestinal helminthiasis, sanitation in animal farming, food preparing hygiene and quality control of water and food.

All neurocysticercosis sequelae would be avoided by prevention and early treatment.

The diversity of neurocysticercosis presentations encourages health professionals to consider it in diagnoses, especially in endemic countries but also in non-endemic areas because migrants and travelers are subject to contagion.

In the human brain, the signs and symptoms diversify according to the number, size, localization and pathological stages of cysts.

Table 1: Epidemiology of Neurocysticercosis.

Locations	
Worldwide	*The frequency of NNC ranged from 0.2% to 52% worldwide, and its association with epilepsy ranged from 0.11% to 1.32% (Ndimubanzi et al. 2010).* *The World Health Organization estimates 50 million cases worldwide, it causes about 50,000 deaths each year (Bouteille 2014).* *Neurocysticercosis causes approximately 5 million cases of epilepsy in the world (Nash et al. 2013).*
Latin America	*It was estimated infection in about 350,000 individuals, in Latin America (Takayanagu & Leite 2001).*
Asia	*Neurocysticercosis was the cause of epilepsy in up to 50% of Indian patients presenting with partial seizures. It was also a major cause of epilepsy in Bali (Indonesia), Vietnam and possibly China and Nepal (Rajshekha et al. 2003).*
West Africa	*In Togo and Benin, the prevalence of cysticercosis was 2.4% and 1.3%, respectively (Zoli et al. 2003).*
Central Africa	*Human cysticercosis was characterized as endemic in Rwanda, Burundi, the Democratic Republic of Congo and Cameroon.* *Cysticercosis may be one of the major causes of epilepsy in Cameroon with figures as high as 44.6%.* *Cysticercosis was present in 7% of 300 autopsies carried out in a*

	region of Butare (Zoli et al. 2003).
Europe	*Cases of neurocysticercosis were 176 in 17 European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Sweden, United Kingdom, and Croatia, Norway, Switzerland). A particular epidemic situation was described in Spain and Portugal (Fabiani & Bruschi 2013).*
United States of America	*Neurocysticercosis has emerged as a serious public health problem (Willingham & Engels 2006).* *Data in the Nationwide Inpatient Sample for 2003–2012 estimated 18,584 hospitalizations for neurocysticercosis (charges >US $908 million). Hospitalization was highest among Hispanics. The charges to cysticercosis exceeded those for malaria and were greater than for other neglected tropical diseases combined (O'Neal SE & Flecker 2015).*
Canada	*Literature reported 60 cases, in the past two decades (Del Brutto 2012).*
Mexico	*Cysticercosis was present in 2.4% of autopsies in Mexico (n. 20,026) (Sarti et al. 1992).* *Serological studies revealed infection rate from 4.9 to 12.2% for human cysticercosis, in rural areas, the prevalence was 9.1% as determined by CT (Flisser et al. 2003, Fleury et al. 2006).*
Brazil	*Prevalence of neurocysticercosis was approximately 24% in individuals hospitalized for diagnosis of epilepsy in Chapecó/SC (Trevisol-Bittencourt et al. 1998)* *In Uberaba-MG, cysticercosis frequency in autopsies was 3.3%,*

the brain location was 79.2% (n. 53, age 15-86 years) (Lino et al. 1999).

Percentage of neurocysticercosis was 5.1% in patients with epileptic seizures, in Recife City (Valença & Valença 2000).

Brazilian literature showed incidence of 1.5% in autopsies and 3.0% in clinical trials (Agapejev 2003).

3.2 Psychiatric manifestations

Depression and cognitive decline are among the most frequent psychiatric manifestations of neurocysticercosis (see **Table 2**). The incidence of depression associated with this parasitic disease was higher than in the general population, as follows: 83% of patients had neurocysticercosis plus depression and epilepsy; 88% had neurocysticercosis and depression without epilepsy, according to the study of Almeida and Gurjão (2010). Cognitive decline was associated with 87.5% of the cases in a group of 38 patients (Forlenza et al. 1997). Dementia was diagnosed in 12.5% of patients, in a sample size of 40 patients (de Andrade et al. 2010). Generally, neurocysticercosis patients seek medical care due to neurological and psychiatric symptoms. It is important to investigate the presence of emotional manifestations not reported by the patients. In major depressive disorders, typically patients have a history of losses and negative feelings (guilt, fear, low self-esteem, diminished interest or pleasure) towards experienced situations. Health professionals are recommended to investigate, in neurocysticercosis patients, depressive symptoms e.g.: sadness, alterations of sleep-wake cycle, appe-

tite changes, memory impairments, and behavioral changes in family or social environment.

In neurocysticercosis patients, there may be evidence for disinterest in rewarding or enjoyable activities, related to the patient's inability to cope with performances that they previously were able to execute. That is, patients give up favorite occupations because neuronal deficits, and negative feelings are justified by sequelae. Major depressive disorders frequently have alterations of thinking such as low attention, worsening of intellectual performance, pessimistic ideas, suicidal thoughts, and exaggerated concern about serious diseases. Considering the presence of brain lesions due to the parasite, impairment of intellectual performance and attention persist while lesions are present. Different from depressive disorders, the worsening of cognition does not happen as traits, it does not recover when emotion are better.

Cognitive decline and dementia have been imputed to brain damage or complications such as hydrocephalus (Jay et al. 2016). Brain damage can be characterized by multiple calcifications on neuroimaging scans; this is an evidence of neurocysticercosis in the past. Hydrocephalus or blockage in the cerebrospinal fluid circulation through ventricles and cisterns can be consequences of protein deposits or physical obstruction by the presence of cysts (Kurz et al. 2016).

Brain imaging in dementia commonly demonstrates enlargement of cerebral ventricles and spaces between gyri that are filled with cerebrospinal fluid (Rayment et al. 2016); brain scans can help to manage both chronic and acute hydrocephalus (Zhao et al. 2015).

The drainage of cerebrospinal fluid by ventriculoperitoneal derivations is used to relieve hydrocephalus, however the use of antihelminthic medication that seems to increase shunt longevity is also recommended (Kelley et al. 2002). Psychosis has been correlated with neurocysticercosis, although less frequently than cognitive decline and depression. The estimated proportion of psychotic patients was 14.2% and depressed was 52.6 % in a cross section of 38 outpatients (Forlenza et al. 1997).

Psychiatric manifestations frequently happen together with neurological diseases. The frequencies ranges from: 79% of neurocysticercosis patients have seizures/epilepsy, 38% severe headaches, 16% focal deficits and 12% signs of increased intracranial pressure. Several other symptoms happened in less than 10% of patients (Carabin et al. 2011).

Table 2: Psychiatric Manifestations of Neurocysticercosis.

Manifestations	
Depression	*Percentage of depression was higher than in the general population, as follows: neurocysticercosis with epilepsy (83%), neurocysticercosis without epilepsy (88%), sample size 65 patients (Almeida & Gurjão 2010).* *Depression was the most frequent psychiatric diagnosis (52.6%), in a sample of 38 patients (Forlenza et al. 1997).*
Mixed anxiety and depression	*Anxiety and depression were the most common in 50 patients with neurocysticercosis and epilepsy, compared to 50*

	patients with epilepsy only. Psychiatric disorders had frequency of 68% in patients with neurocysticercosis and epilepsy, compared to 44% of those only with epilepsy. Left sided lesions had greater psychiatric morbidity (Srivastava et al. 2013).
Decline in cognitive function	*Decline in cognitive function was present in older children with neurocysticercosis, sample size 83 patients (Prasad et al. 2014).*
Dementia	*Dementia was found in 1.3% of neurocysticercosis patients, sample size 592 (Varma & Gaur 2002).*
Manic syndrome	*Case report of manic syndrome secondary to neurocysticercosis was responsive to risperidone (Monedero et al. 1996).*
Psychotic symptoms	*Case report of neurocysticercosis presenting as delusion (Chakraborty et al. 2014).*
Schizophrenia	*Case report of neurocysticercosis presenting as schizophrenia (Bhatia et al. 1994).*
Personality changes	*Case report with negative self-evaluation, low self-stem, feelings of shame directed to the diagnosis of the neurocysticercosis (Capitão 2016).*

3.3 Neurological manifestations

Neurocysticercosis is a manifold disease concerning the diversity of signals and symptoms. Neurological manifestations (**Table 3**) can include disturbances of

movement, gate, speech and motor coordination. Neuroendocrine syndromes may follow lesions in the hypothalamic-pituitary axis.

Seizures and epilepsy are considered the most common manifestations of neurocysticercosis. In endemic areas, this parasitic disease may count for 29% of acquired epilepsy (Mandel et al. 2016, Nash & Garcia 2011). They can be associated with psychiatric symptoms. Such associations complicate the management of medications because many psychoactive drugs have the risk of seizures. Psychoactive drugs must be diligently prescribed in this parasitic disease, considering that the occurrence of seizures can reach 70% to 90% of neurocysticercosis patients (Carabin et al. 2011).

Seizures are signs or symptoms due to excessive or synchronous neuronal activity in the brain (Fisher et al. 2005), while epilepsy involves unprovoked seizures occurring at least 24 hours apart. Provoked seizures have close temporal associations with brain impairments, for example infections, traumas, and intoxications (Beghi et al. 2010). Some authors classify the seizures according to the evolutionary stages of the parasite in brain images. When seizures are concomitant with inflammation (edema or peri-lesion enhancement) they should be classified as acute symptomatic seizures (Beghi et al. 2010), while recurrent seizures after edema resolution or cyst calcification should be categorized as unprovoked (epilepsy) (Carpio et al. 2013). A calcified lesion can reactivate the host immune response, which is characterized by the presence of cyst inflammation and clinical manifestations. Reactivation occurs due to the presence of residual antigens, or living cells of the parasite capsule.

There is no consistency in reports of the proportion of types of seizures in patients with neurocysticercosis. Some researchers associate a higher percentage of focal seizures in single calcified lesions (Murthy & Reddy 1998), while others conclude that generalized seizures are more frequent (Mwape et al. 2015).

Although the mechanisms that lead patients to seizure and epilepsy are not completely known, importance has been attributed to histological changes as perilesion gliosis, fibrosis, and edema (Leite et al. 2000, Antoniuk et al. 2001, Rathore et al. 2012). Particularly if those changes happen in the temporal lobe structures such as the amygdala, the piriform cortex and the hippocampus (Liu et al. 2014, Bianchin et al. 2015).

Epileptogenesis in neurocysticercosis can be related to changes in the blood brain barrier permeability, gliosis, fibrosis, hippocampal lesions, and other factors. Those pathological changes has also been found in association with a diversity of psychiatric diseases (Rupprecht et al. 2010, Cotter et al. 2001, Raison et al. 2006), suggesting that neurologic and psychiatric manifestation coexist due to similar mechanisms. Pathologic mechanisms related to neurologic manifestations may underlie the mental changes. The host-parasite interactions (inflammatory and immunologic reactions) are responsible for neuronal damage due to edema, fibrosis, inflammation, cellular infiltrate and calcifications (White 2000). The destruction of nervous tissue at the site of implantation by the parasite, and ischemia around larger cysts are other mechanisms of brain injury. Complications associated with neurocysticercosis are cerebrovascular sequelae, increased

intracranial pressure, meningitis and encephalitis. Motor and sensory deficits occur also due to extra cerebral lesions (spinal and ocular locations).

Cerebrovascular complications of neurocysticercosis include ischemic, lacunar infarcts and hemorrhage. Lesions may also be responsible for paresis or plegias, involuntary movements, gait disturbances, and paresthesias (Barinagarrementeria & Cantú 1992, Barinagarrementeria & Del Bruto 1989, Jha & Kumar 2000, Cantú et al. 2003).

Table 3: Neurologic Manifestations of Neurocysticercosis.

Manifestations	
Seizure and epilepsy	*Seizures were generalized in 121 patients and partial in 82. CT showed parenchymal brain calcifications in 53 patients and cysts in 150. Use of anticysticercal drugs improved seizure control (Del Brutto et al. 1992).*
Headache	*Headaches occur:* *a. as migraine and tension-type,* *b. as result of increased intracranial pressure* *(Fogang et al. 2014).*
Sensory-motor Deficits	*Focal deficits were the third most frequent manifestation, behind seizures or epilepsy and headache, in a systematic review (Carabin et al. 2011).*
Hydrocephalus	*The majority of patients presented with a chronic and relatively normotensive hydrocephalus, in a sample of 11 pa-*

	tients. Impairment of CSF flow required permanent CSF shunting. Exceptionally, one cyst was removed by surgery (Lobato et al. 1981).
Cerebrovascular disease	*It was reported three cases of stroke secondary to neurocysticercosis. MRI demonstrated cortical and subcortical infarction areas and cisternal cysts. Angiographic showed arteritis of basilar and carotid arterial system.* *Infarcts happened in small arteries in most cases, but middle cerebral and carotid arteries can be affected (Rocha et al. 2001).*
Spinal cord lesions	*In the spinal regions cervical and lumbosacral was found cystic lesions, in a patient. Anthelmintic and anti-inflammatory treatment was initiated with albendazol (2×400 mg/day) and steroids (prednisone 60 mg/day) for 4 weeks. The patient was retreated (Hackius et al. 2014).* *Spinal cysticercosis presented mainly with motor symptoms (21/27 patients): paraparesis and paraplegia were the most common signs; one-third of patients had sphincter dysfunction (Cárdenas et al. 2015).* *Intramedullary spinal cord neurocysticercosis presenting as Brown-Séquard syndrome, i.e. , paralysis and loss of proprioception on the same side as the lesion, and loss of pain and temperature sensation on the contralateral side (Noguera et al. 2015).*
Neuroendocrine syndromes	*The signs of cysticercosis in the sellar region include headache, vision loss, hypopituitarism, seizures, and meningitis (Zada et al. 2016).*
Papilledema	

	Case report of papilledema due to neurocysticercosis in brain ventricle (Huang & Sridhar 2015).
Claude's syndrome	*Case report due to neurocysticercosis lesion in the mid-brain characterized by contralateral hemiataxia and oculomotor cranial nerve palsy (Song et al. 2010).*
Loss of Vision and ataxia	*Case report of non-communicating hydrocephalus with headaches, ataxia and loss of vision due to intraventricular cyst (Pamplona et al. 2015).*
Dizziness and ataxic gate	*Case report of a rare racemose cysticercose in the cerebellar hemisphere (Kim et al. 2010).*
Parkinsonism	*A patient with parkinsonism secondary to neurocysticercosis. Neuroimaging showed edema in the midbrain. Parkinsonism symptoms were exacerbated after albendazole treatment. The symptoms improved after methylprednisolone pulse therapy for 5 days, and levodopa and carbidopa for 8 months (de Lima et al. 2012).*

3.4 Mortality associated with Neurocysticercosis

Proportions of death due to neurocysticercosis range according to age of population and countries of studies.

a) In children in India, frequencies of mortality ranged from 18.5% (5/27) (Puri et al. 1991) to 2.0% (1/50) (Kalra & Sethi 1992); considering that

meningoencephalitis and raised intracranial pressure was responsible for higher incidence (18.5%) of death.

b) In children in Mexico, the proportion of death was 1.6% (2/122) due to chronic arachnoiditis (Ruiz-García et al.1997).

c) In adults, in Ecuador it was 3.2% (1/31), mortality was associated with hemorrhagic cyst (Alarcon et al.1992).

d) In Portugal, mortality was 5.3% (2/38 - average age at onset of symptoms was 36 years in the sample) (Monteiro et al. 1993).

e) Mortality was 0.9% (1/112) of patients in Houston, Texas (Shandera et al. 1994).

3.5 Rare manifestations of Neurocysticercosis

Rare presentations related to neurocysticercosis encompasses Bruns syndrome, i.e., hydrocephalus episodic due to cyst movement in ventricular space (Rodriquez et al. 2012), frontotemporal dementia with mutism (Satler et al. 2012), epileptic and psychiatric manifestations of temporal lobe (Costa et al. 2007), trigeminal neuralgia (Aguiar et al. 2000), and association with Lennox-Gastaut syndrome (Agapejev et al. 2000).

3.6 Conclusion about manifestations of Neurocysticercosis

The multiplicity of brain areas affected by lesions may justify the variety of neurocysticercosis clinical manifestations. In general, signs and symptoms associat-

ed with neurocysticercosis depend on the number and size of lesions, developmental stage of the parasite and the host's immune response. Manifestations can be associated with potentially fatal conditions, for example arteritis, encephalitis, and hydrocephalus. Neuropsychiatric manifestations are imputed to brain damage. The host-parasite interactions (inflammatory and immunology reactions) result in histopathological changes such as edema, fibrosis, vascular changes, and gliosis. Those changes happen in neurological and psychiatric disorders, which suggests a common cause for neuropsychiatric manifestation of neurocysticercosis.

Accurate diagnosis of neurocysticercosis is possible after interpretation of clinical data together with findings of neuroimaging studies and results of immunological tests. Enzyme-linked immunoelectrotransfer blot and Enzyme-linked immunosorbent assay are the tests most frequently used for diagnosis, but they can be positively reactive in patients with *taeniasis* or cysticercosis.

Treatment guidelines recommend antiparasitic drugs depending on the stage of the illness (e.g. praziquantel, albendazole), steroids (to treat encephalitis and brain edema), and anticonvulsants. Surgical resection is reserved for some cases of hydrocephalus, giant cysts, spinal and ocular implantations.

Neurocysticercosis is an important cause of acquired epilepsy worldwide. Seizures, psychiatric manifestations and cognitive decline are strong arguments to focus on prevention of this disease, which can be achieved through educational initiatives, early treatment and diagnosis of *taeniasis* and cysticercosis. The diversity of neurologic and psychiatric presentations encourages health profession-

als to add neurocysticercosis to their list of differential diagnoses, especially in endemic countries.

Low endemicity of *Taenia solium* is consistent with a high index of a long and healthy life, being knowledgeable and having a decent standard of living.

C H A P T E R

4

METHODOLOGY

4.1 Introduction

Routinely, the neuroimaging demonstrates inflammatory changes in brain against the NCC lesions.

The inflammation is commonly characterized by edema, which comes from the increased vascular permeability.

The inflammation is presumed to be the cause of signals and symptoms including the seizures.

The increasing vascular permeability happens at any stage of the cysts, generally it is expected in the early interaction between parasite and immune system. Therefore, the common effort of neuroimaging, in the context of NCC, is to demonstrate the presence of edema and evaluate the stage of the lesions.

The lesions stages, location, as well as number and size of lesions seem to be reasonable factors to evaluate seizures associated with neurocysticercosis, those factors must be diligently considered, as well as the presence of edema (**Fig**. **3**).

Additionally, it is important to consider the participation of brain regions (e.g. hippocampal area, and precentral gyrus) in the origin of seizures.

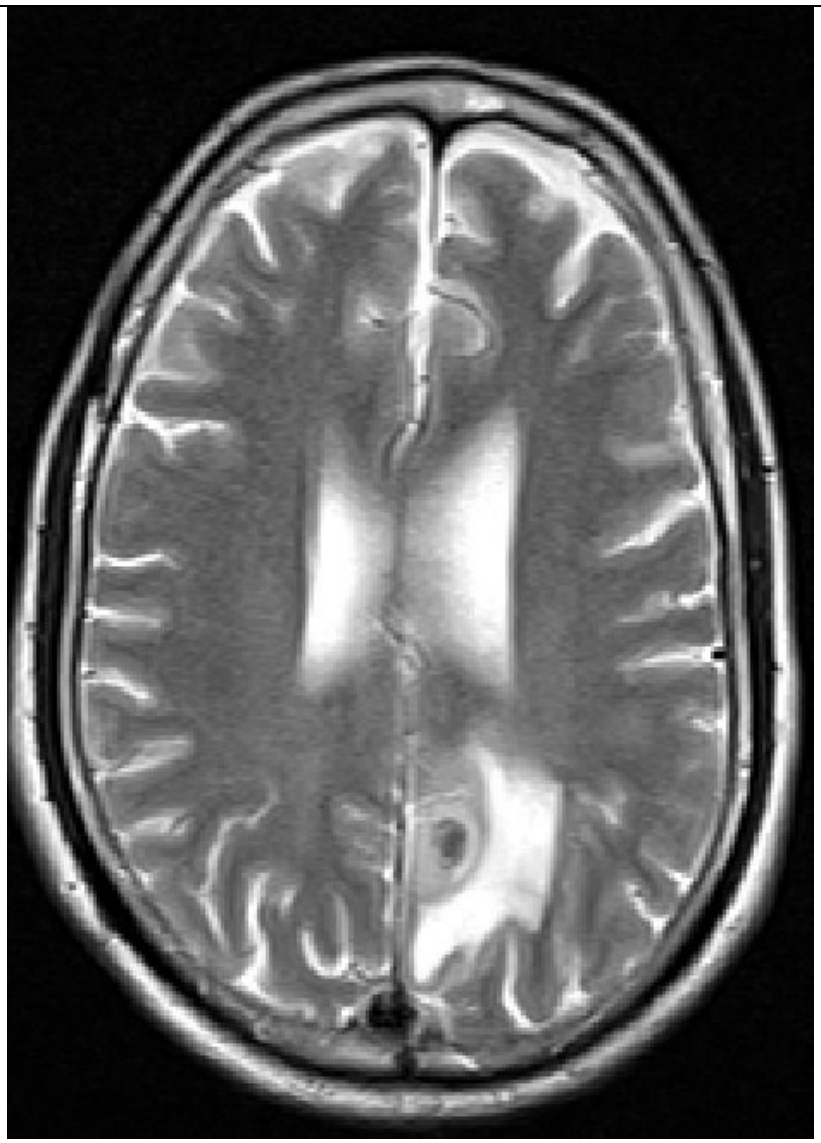

Figure 3: Lesion with scolex and edema peri-lesion.

4.2 Statement of the problem

Lesion stages may not correspond to the brain inflammatory chronology. The inflammatory chronicity in the brain may be in curse while the cyst may have its life cycle completed, which is usually assumed by the presence of mineral deposits (calcified lesion). A mineralized cyst can elicit chronic inflammation, which is usually attributed to a long-term immune response.

It is believed that the phases of cyst maturation differ from the phases of inflammatory response in the nervous tissue, considering that macrophage and fibroblast proliferation continue after the presence of parasite calcification. It is important to evaluate the site of lesions with respect to areas related to epilepsy (e.g. hippocampus). However, the parasite has particularities as for the dissemination through bloodstream and size of larvae that may elect specific sites (e.g. grey matter), which can be related to the presence of seizures.

The impact of lesions over the integrity of brain is usually evaluated in term of number and size of lesions. These effects should be considered as integrated factors, because a single and big lesion may have similar volume impacting the brain as would have several lesions with smaller dimensions. Additionally, the brain can be affected by the volume of edema external to the lesions.

The specific techniques of DTI and SWI may detect others pathologic findings. The brain alterations may be related to the local of implantation or to the entire

hemisphere. The characteristics of lesions may not be fully described by the techniques of DTI and SWI.

4.3 Experimental design methods

In order to understand brain changes in neurocysticercosis associated with seizures we analyzed map scans derived from the techniques Susceptibility Weighted Imaging, Diffusion Weighted imaging, and Magnetic Resonance Imaging T2 in a set of patients under treatment for neurocysticercosis divided in two groups with or without seizures.

The neuroimaging techniques of DTI may detect pathological changes to the white matter related to epilepsy in neurocysticercosis, by focusing parameters of water diffusion in the vicinity of neurocysticercosis lesions and in the extended brain hemisphere. Additionally, SWI combined with MRI-T2 may help to characterize the phases of lesions because it accurately identify its mineral deposits.

The present research comprises two studies. Firstly, we studied DTI from 51 patients under treatment for a single neurocysticercosis lesion. Patients were divided in two groups with (n.38) or without (n.13) seizures in the last fifteen days. We measured parameters of FA, AD, and MD, over regions of interest (ROIs), which were drawn in the lesion, and in part of the brain hemisphere (i.e., half brain minus ventricle and infratentorial region). The metrics of DTI over the ROIs were compared between the lesioned and contra-lateral side calculating the index of asymmetry.

Secondly, we studied 92 brain lesions in 64 patients under treatment for neurocysticercosis: 71 lesions in patients with seizures and 21 lesions patients without seizures.

We classified the sites of lesion implantation according to anatomical references (brain hemispheres, cerebral lobes, cerebral gyri, and cerebral arteries).

Characterization of the brain-lesion interface evaluated the contours of the lesions that can be smooth or rough, the presence of parasite's head, the peri-lesion gradient, the intra-lesion double gradient, and the enhancement of the nourishing vessel (*vasa nutricia*).

The volume of brain affected by the lesions were measured by adding the volume of each lesion with the volume of brain edema (if present).

Finally, the relationship between lesions and the cortex. We measured the distance from cortical surface, as well as we considered the layer where the lesions were settled, i.e., implantation within the grey matter, in the white matter or in both (**Fig. 4**).

4.4 Experimental questions

We addressed the following questions:

I. What are the frequencies of location, size and number of the neurocysticercosis lesions comparing the groups of patients with and without seizures?

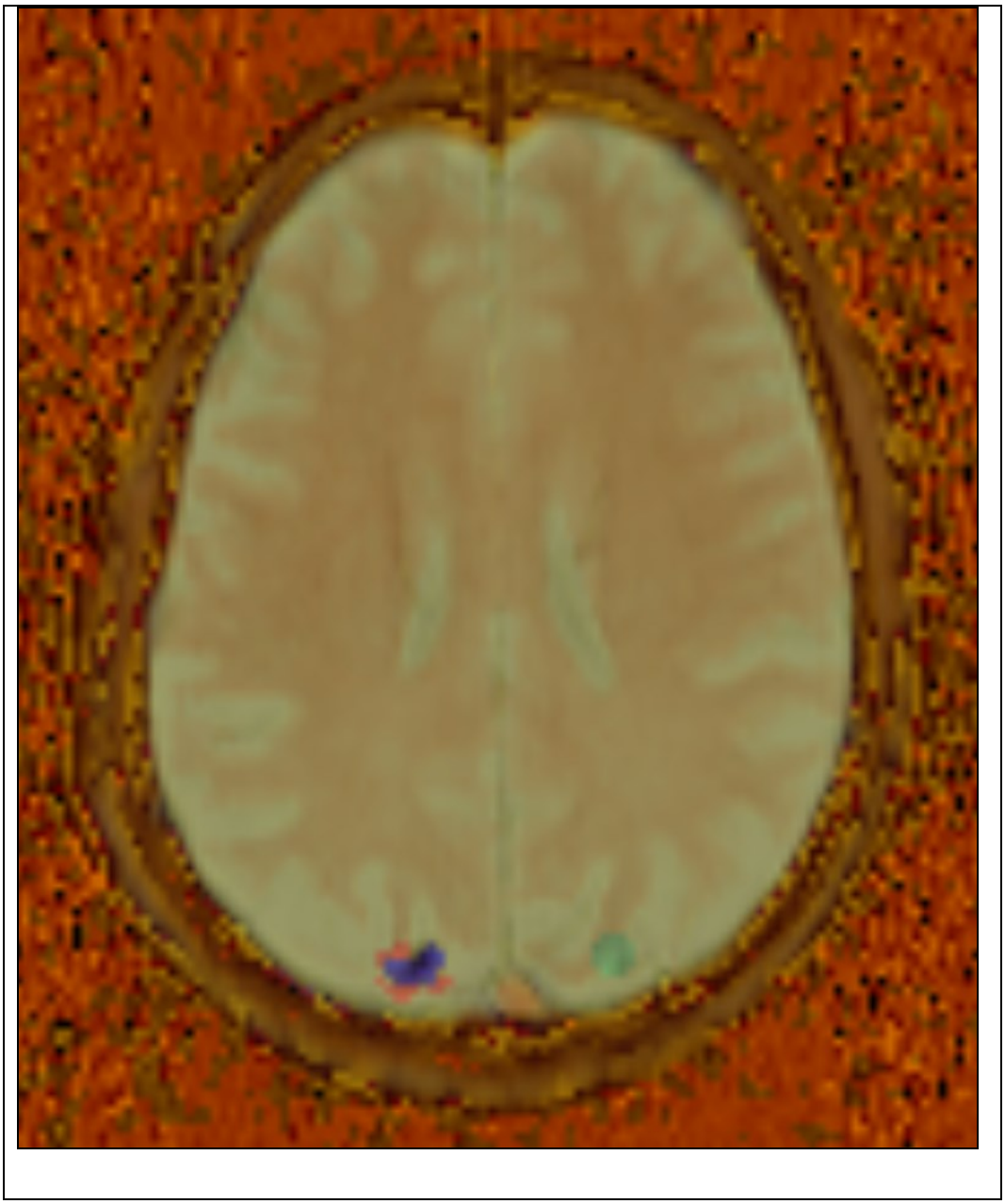

Figure 4: ROIs over lesions located in the transition grey and white matter.

II. How to characterize the brain-lesion interface by SWI, DTI, and MRI-T2 considering the inflammatory process derived from host-parasite interaction?

III. Are the characteristics in the brain-lesion interface related to the presence or absence of seizures?

IV. Are there alterations in DTI in the whole brain or in the local site of implantation related to the presence of seizures?

V. Are there differences between groups with seizure or without seizure, considering the distance from cortical surface and the layer where the lesions were settled (grey matter, white matter or both)?

4.5 Experimental execution of the methods and techniques

4.5.1 Patients recruitment

Data collection was hospital-based study in the Department of Neuroradiology, Shri Mahant Indiresh Hospital and Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun - India. Patients in treatment for neurocysticercosis were recruited by Dr. Azad regardless gender and ethnicity.

We recruited 64 patients under treatment for neurocysticercosis, the total had 92 NCC lesions 71 lesions were in patients with seizures and 21 lesions were in

patients without seizures. The average was 1.44 lesions per patient for all subjects (minimum 1 and maximum 4 lesions). For the female participants the number of lesions were 46, and for the male participants the number of lesions were 46. The age of patients ranged from 5 to 58 years old (mean 25.5 and standard deviation 14.26). Half of the participants (n. 32) were between the ages 5 to 21 years and half were between the ages 22 to 58 years. The average lesions per patient was 1.46 in the younger group and it was 1.40 in the older group. The specific studies included some additional criteria for the patients (described in details in the following sections).

All research was conducted in concordance with the Code of Ethics of the Shri Mahant Indiresh Hospital and Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun. The Human Research Ethics Board of the University of Alberta approved the research in this thesis based on the SGRRIMHS ethics approval and the understanding that my analysis represents secondary analysis of the anonymized patient data set provided by Dr. Azad at SGRRIMHS.

Inclusion criteria were: presence of neurocysticercosis lesion(s) in brain scans evaluated by neuroradiologist and neurologist; the lesion(s) must have the presence of scolex, or be typical for neurocysticercosis; the patients must be in treatment for neurocysticercosis.

Exclusion criteria were: patients with more than 4 neurocysticercosis lesion; patients having more than 60 years old; scans with artifacts (e.g. head movements).

4.5.2 Image acquisition

Each patient was whole brain scanned for MRI-T2, DTI and SWI; all acquisitions were performed in the axial plane. The image acquisitions followed standard procedures of the Department of Radiodiagnosis, Shri Mahant Indiresh Hospital and Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun - India.

MRI data acquisition was performed using a 1.5 Tesla scanner (Magnetom, Siemens, Erlangen, Germany). The imaging protocol includes T1- and T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI) and Diffusion Weighted imaging (DWI). Imaging parameters for various sequences were: axial spin-echo (SE) T1-weighted sequence (TR = 450–650 ms, TE = 10–20 ms, section thickness = 5mm, matrix = 256 × 192, NEX = 2, FOV = 230 x 222 mm), axial, coronal and sagittal T2-weighted sequence (TR = 3000–4500 ms, TE = 80–90 ms, echo-train length = 22–27, section thickness = 5mm, matrix =256 × 256, NEX = 2, FOV = 172 x 220 mm), axial fluid-attenuated inversion recovery (FLAIR) sequence (TR = 7000–9000 ms, TE = 80-100 ms, inversion time = 2000–2300 ms, section thickness = 5mm, matrix = 256 × 256, NEX = 1, FOV = 230 mm) and axial magnitude and phase corrected SWI sequence (TR=54 ms, TE= 40 ms; acquisition time, 3:40 minutes; slice thickness 3 mm; one average; and flip angle, 15°, matrix = 256 × 256, FOV = 286 x 286 mm). Diffusion tensor images (DTI) were obtained in 20 (and either 30) directions using an echo-planar sequence with TR- 3420, TE of 85 ms, acquisition time: 4:44 minutes; 3 mm section thickness, 20 to 26-cm FOV, 128 x 128 matrix

size and a b-value of 1000 s/mm^2. Further thin coronal T1 inversion recovery (IR) and FLAIR sequences were acquired.

After administration of intravenous gadodiamide (Omniscan, GE Healthcare) in the dose of 0.1mmol/kg body weight, post-contrast T1 weighted (PCT1W) sequence with fat sat (FS) (556/10/58/230x256) [TR/TE/Echo-Train Length/Matrix] was acquired in all the standard planes.

4.5.3 Image preprocessing

The image files were preprocessed and analyzed by Dr. Matthew Brown at the Department of Psychiatry at the University of Alberta.

DTI images were preprocessed using the FSL software package (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library).

Data were corrected for different sizes and translation using the normalization in the console tool of the FSL program.

Additionally, the brain extraction tool (BET) was used to extract non-brain tissue (e.g. skull) from the whole head. The FSL program also was used to execute Eddy current correction, that corrects for head motion and image blurring. The images had a brain registration to the SWI template of the FSL program, using correlation ratio cost function and a tri-linear intepolation in FLIRT function.

FSL's DTIFIT program from the eigenvalues (λ 1 , λ 2 and λ 3) of the diffusion tensor calculated MD, AD or L1, and FA .

The formulae for FA, MD and L1 are (Özarslan et al. 2005, Basser & Pierpaoli, 1996):

$$FA = \sqrt{½}\frac{\sqrt{(\lambda 1 - \lambda 2)^2 + (\lambda 2 - \lambda 3)^2 + (\lambda 3 - \lambda 1)^2}}{\sqrt{\lambda 1^2 + \lambda 2^2 + \lambda 3^2}} \quad \text{..... (3.1)}$$

$$MD = \frac{\lambda 1 + \lambda 2 + \lambda 3}{3} \quad \text{..... (3.2)}$$

$$L1 = \lambda 1 \quad \text{..... (3.3)}$$

4.5.4 Regions of interest in the lesions

The images were displayed on the image viewer software MRIcron (Chris Rorden's MRIcron software).

Brain maps of DTI (FA, L1, and MD), SWI (MG and PH) and MRI-T2 images were displayed and overlaid on MRIcron to better identify changes involving the nervous tissue due to neurocysticercosis and to draw regions of interest (ROIs).

For each lesion in each patient, five regions were created. These included a region encompassing the lesion itself, a contralateral control region, and three perilesion regions of different sizes.

ROIs were manually drawn by the console of tools on the software MRIcron in all the sections where a lesion was visible and in the surrounding tissue. The ROIs over the lesions were flipped to create symmetrical masks in the contra-lateral side.

The Matlab software (MATLAB Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States) applied flip operation to binary MR data in NIFTI files; the image derived was in standard orientation for left-right side along the midline.

Matlab was used to create ROIs in the peri-lesion tissue. The software applied a radial increase (technically, a "dilatation") by one, two, and three voxels. Also, Matlab subtracted the area of the cyst, that resulted in three ROIs of the tissue surrounding the lesion (expansion 1, 2 and 3) (**Fig**. **5**).

To study the hemispheres, we outlined manually in MRIcron one half of the brain in all sections from the vertex to the tentorium. The draw was flipped by Matlab to generate a symmetrical contralateral mask.

The totality of ROIs was checked around orientation and symmetry. Subtraction for bone tissue, cerebrospinal fluid and artifacts (e.g. air or calcified structures) was applied in all regions of interest.

The anatomical concept of cerebral hemispheres refer to the paired halves of the cerebrum. However, in this work we adopt the term hemisphere (for short) to the area of study from the vertex to the tentorium minus lateral ventricles. The ventricles subtraction was done in the Matlab program.

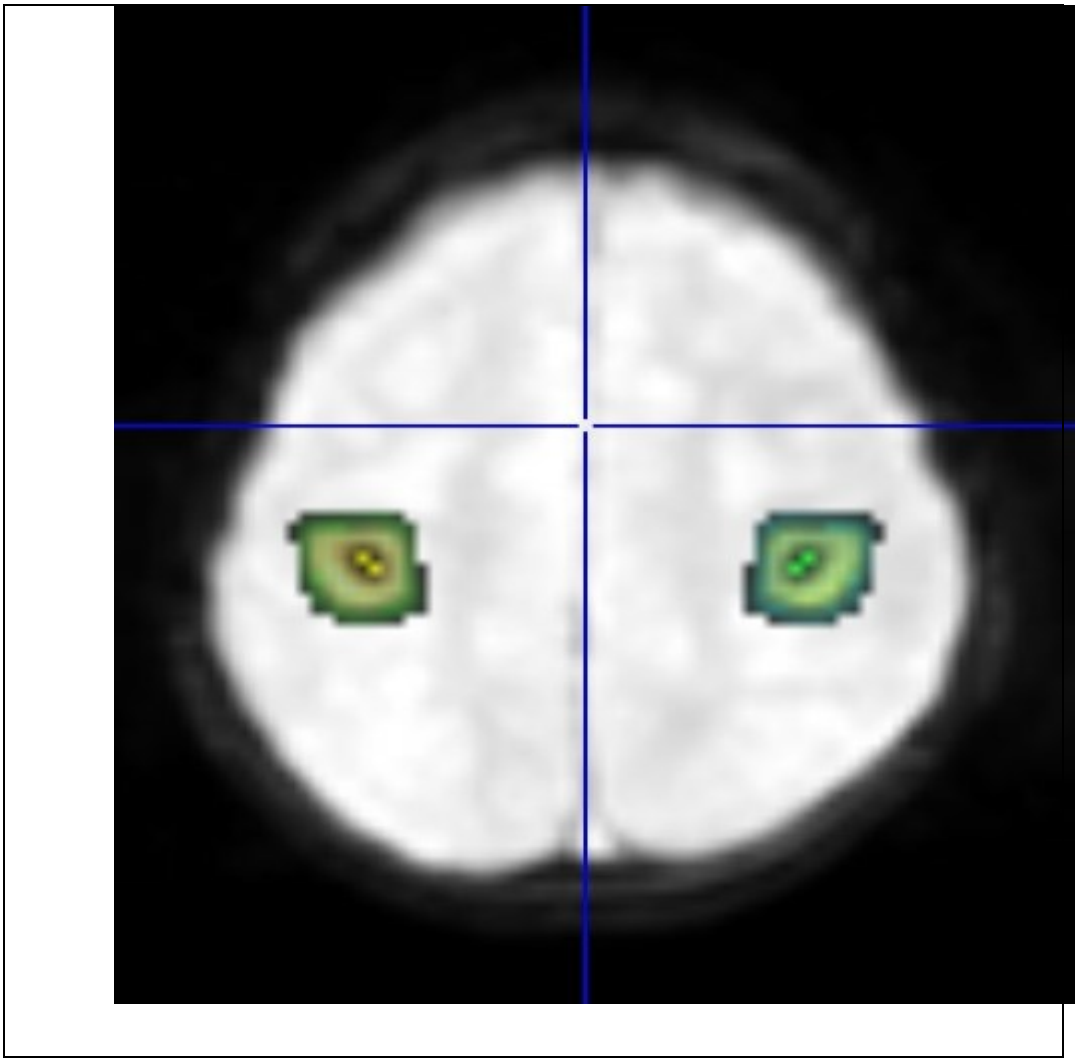

Figure 5: ROIs over the lesion, surrounding tissue and symmetrical areas.

4.5.5 The interface

The extraction of data from ROIs over the DTI maps (FA, MD, L1) were collected by the Matlab and they were organized in a statistical table.

We computed the values of FA, MD and L1 in the regions: a) within the cyst, b) peri-lesion expansion 1, 2 and 3; and c) contralateral control regions, and d) hemisphere. Symmetrical measurements in the side not affected were also collected, that is FA, MD, L1 were extracted for the contralateral control regions as well. Matlab was used to calculate the volume of each lesion and the volume of edema.

4.5.6 The volume of each lesion and edema

We outlined manually in MRIcron all the sections where a lesion was visible. The sum of the areas for each section gave us the volume of the lesion, the same procedure was done to the tissue affected by edema, exploratory assessments of the volume of edema volume adjacent to lesions were performed in raw data of T2 images. The volume of each lesion was evaluated in the technique magnitude derived from SWI (MG). We measured the volumes of edema in cubic millimeters (mm^3), before normalization.

4.5.7 The lesions and the cortical surface

Lesions were visualized on MRI-T2 in three directions (anterior-posterior, superior-inferior and lateral-medial), and the distances between the lesions and the brain surface were measured in terms of millimeters in all three axes.

The distance was computed as the mean of the three measurements.

4.5.8 The characteristics in the interface

Characteristics of lesions in MRI-T2, DTI and SWI were tabulated considering the occurrence of edema, roughness on the boundary, eccentric dot intra-lesion , intra-lesion double gradient, peri-lesion gradient, and *vasa nutricia*.

The SWI technique distinguishes the presence of mineral deposits which are identified as a double gradient intra-lesion in the phase component of SWI.

MRI-T2 and DTI techniques allow identification of the edema, which has similar intensity to the cerebrospinal fluid.

The RMI-T2 also shows: the contours of the lesions that can be smooth or rough, the presence parasite's head (scolex) identified by the characteristic shape of eccentric point inside the cyst, and the enhancement of the nourishing vessel (*vasa nutricia*) (**Fig**. **6**).

The peri-lesion tissue was characterized in terms of presence or absence of intensity variations in the signal of SWI magnitude.

SWI-magnitude revealed the peri-lesion gradients, that are heterogeneous intensity gradients around some lesions, which give them the appearance of shading. The homogeneity of signal surrounding the lesion characterized the lesion as without double gradient, while the heterogeneity of signal surrounding the lesion gave the criteria of double gradient peri-lesion present.

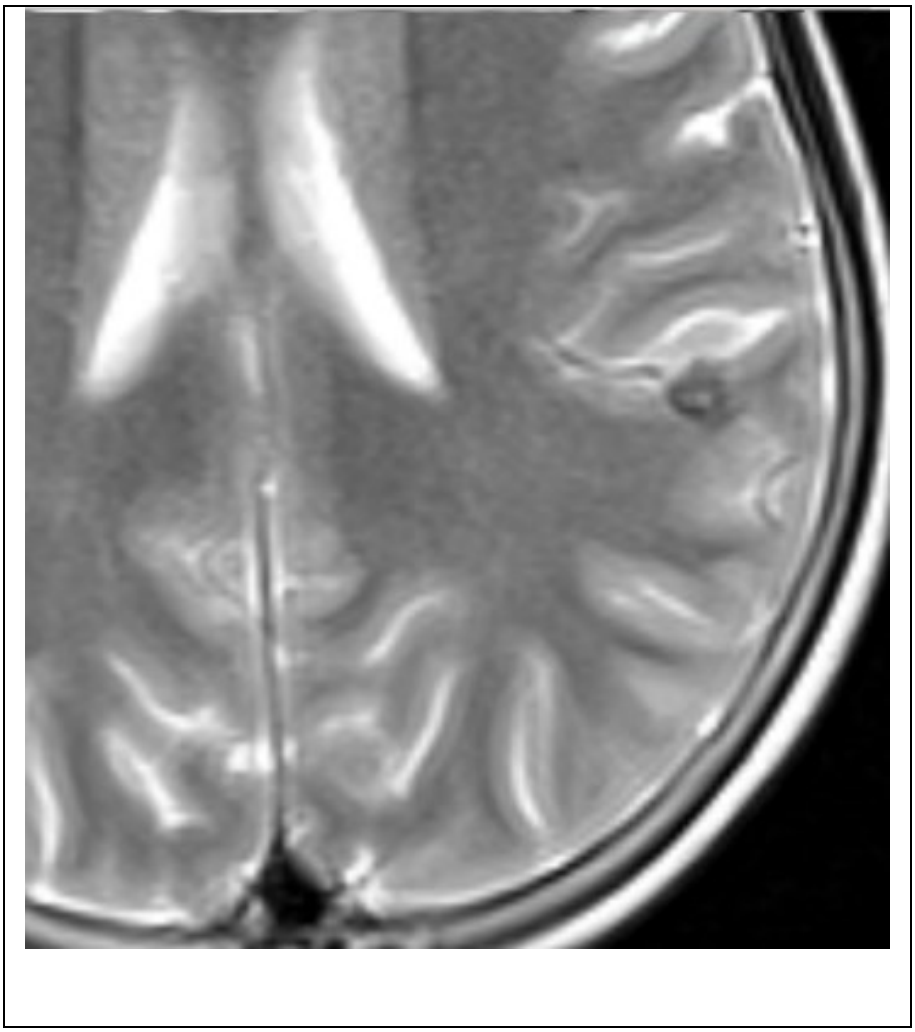

Figure 6: Vasa nutricia.

4.5.9 The classes

We assigned the brain-lesion interface into four phases. The first phase stands for the absence of changes in the brain-lesion interface. The second phase is defined by the presence of edema. The third does not have edema nor minerals deposits. The fourth has the presence of mineral deposits regarding if the lesion has or has

not edema, the mineral deposits are identified by double gradient inside the lesion in SWI-PH (**Fig**. **7**).

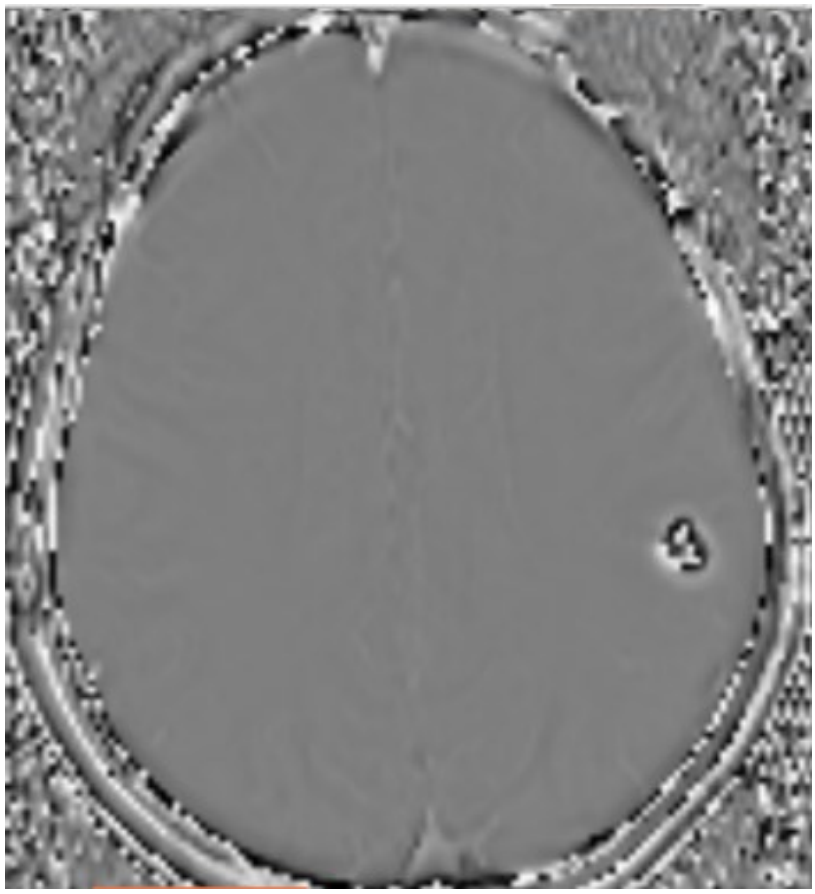

Figure 7: Double gradient intra-lesion.

4.5.10 The index of asymmetry

We calculated differences of FA, MD and L1 between brain sides only for patients with a single lesion.

The side where the lesion is located is termed the ipsilateral (ipsi) and the other one is the contralateral (contra). The index of asymmetry between brain sides

were calculated by the formula of Steinmetz et al. (1991), which were adapted to the terms “ipsi” and “contra”. The index of asymmetry was measured by a modified form of a commonly used equation that relates differences between each brain hemispheres to the total measurement in both hemispheres:

$$A\,(a\ or\ a')\ for\ x(n) = \frac{(n1 - n2)}{(n1 + n2)} \quad \text{..... (3.4)}$$

A = Index of Asymmetry

(a) = between hemispheres

(a’) = between punctual sites

x = maps of SWI or DTI

(n) = metrics FA, L1, MD, RD, MG, or PH

n1 = metric ipsilateral to the lesion

n2 = metric contralateral to the lesion

where the Index of Asymmetry *(A)* between hemispheres *(a’)* or between the site of implantation and contralateral corresponding area (a’) for the maps of SWI or DTI *(x)* considering the metrics *(n)* FA, L1, MD, RD, MG or PH is equal to the value of the metric ipsilateral to the lesion *(n1)* minus the value of the metric contralateral to the lesion *(n2)*, divided by the sum of both.

C H A P T E R

5

- STUDY 1

5.1 Hypothesis 1

Based on the concept of the dielectric pole, pathological brain changes result in seizures by two mechanisms that facilitate the movement of electrons: a) decreasing the resistance of the medium, b) increasing the density of charges (or electrical capacitance), i.e., the ratio between the number of charges and the supporter area. The myelin sheaths execute opposition to the passage of electrons.

In pathological changes, damage to the white matter (e.g. demyelination and edema) may decrease the resistance of brain tissue to the passage of charges.

We hypothesized that the neurocysticercosis lesion may damage white matter in the surrounding tissue or in the large part of the brain (hemisphere).

5.2 Study 1 design

We studied DTI brain scans from 51 patients under treatment for a single neurocysticercosis lesion. Patients were divided in two groups with (n.38) or without (n.13) seizures in the last fifteen days. We measured parameters of FA, AD, and

MD, over regions of interest (ROIs), which were drawn in the lesion, and in part of the brain hemisphere (i.e., half brain minus ventricle and infratentorial region). The metrics of DTI over the ROIs were compared between the lesioned and contra-lateral side calculating the index of asymmetry (**Fig**. **8**).

5.3 Statistical Analysis

The statistical analysis was performed using the SPSS statistical software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The measurements of central tendency for the DTI variables FA, L1 and MD were computed in each hemisphere separately, i.e., before applying the formula to create the index of asymmetry.

Between-group differences for DTI variables were compared using independent samples t tests; this analysis was utilized to determine group differences for variables presence of seizure or absence of seizure in the last 15 days. The DTI variables FA, L1 and MD were computed as index of asymmetry for t tests. The t test was used to examine asymmetry between brain sides of patients with seizure ($p < 0.05$) by checking means differences for DTI indexes over the ROIs: intra-lesional, peri-lesion expansion 1, 2, 3 and hemisphere.

The effect size and quantitative measure of the strength of the correlation between seizures and hemisphere asymmetry were assessed by Cohen's d.

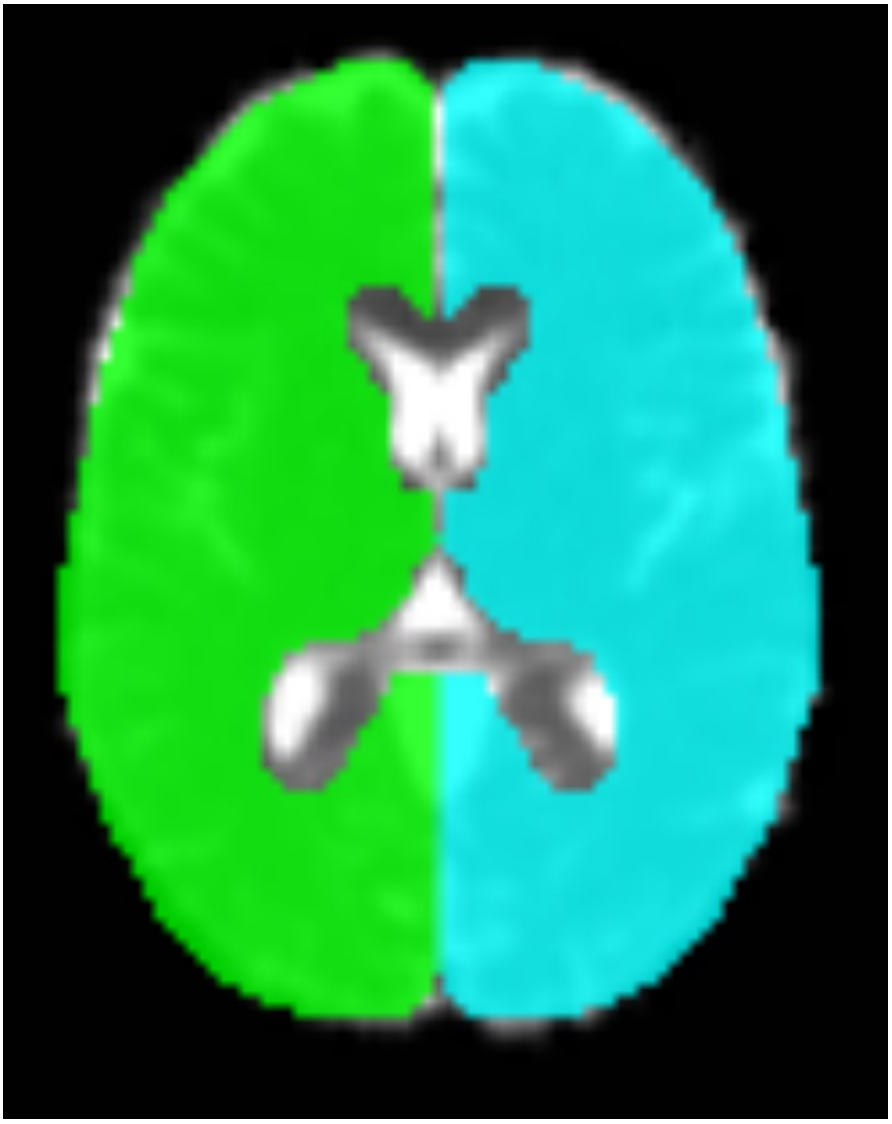

Figure 8: ROIs over hemispheres.

The correlation between the DTI variables and volume of edema was evaluated by Pearson-correlation. The effect of age and gender were covaried for each DTI variable.

The relationship between lesions and nervous tissue were evaluated by percentage of lesions localized in grey, white matter or both.

Characteristics of lesions (edema, double gradient intra-lesion, gradient peri-lesion, and lesion contour) were grouped in four classes. In the class I, the interface neuronal tissue and parasite contour are unchanged, that is, the boundary is smooth, there is no edema. In the class II, the edema is present. In the class III, the edema is absent, the outline of the cyst is irregular, and the neural tissue surrounding the cyst has heterogeneous intensity graduations. In the class IV, double gradient appears within the lesion.

5.4 Results

5.4.1 Demographic variables

We studied 51 patients (31 male and 20 female) each with a single brain lesion due to Neurocysticercosis. The number of neurocysticercosis patients with seizure were 38 (25 male and 13 female). The number of neurocysticercosis patients without seizure were 13 (06 male and 07 female). The participant's ages were organized in three groups, ranging from 5 to 58 years old. The number of

participants between 5 and 12 years old were 17 (12 with seizure and 5 without seizure). In the group between 21-39 years old were 26 subjects (21 with seizure and 5 without). The group between 40-58 years old had 8 participants (5 with seizure and 3 without).

5.4.2 The means for FA, L1 and MD between hemispheres and groups

The analysis of means for DTI parameters computed the parameters FA, L1 and MD in the hemisphere same lesion side and opposite lesion side. The parameters were compared in the group with seizures (**Table 4**) and in the group without seizures (**Table 5**).

Table 4: Group with seizures means for DTI parameters.

	Hemisphere same lesion side			Hemisphere opposite lesion side		
	FA	L1	MD	FA	L1	MD
Mean	213.12921	1.0696334	0.8833747	211.54763	1.0577461	0.8745471
SD	11.917146	0.11433995	0.10280808	11.548253	0.11534068	0.10349894
N	38	38	38	38	38	38

(DTI Parameters X 1000)

Table 5: Group without seizures means for DTI parameters.

	Hemisphere same lesion side			Hemisphere opposite lesion side		
	FA	L1	MD	FA	L1	MD
Mean	220.68462	1.0586854	0.8702554	218.76769	1.0653177	0.8777715
SD	13.117199	0.08174185	0.07680711	12.568229	0.08167726	0.07526626
N	13	13	13	13	13	13

(DTI Parameters X 1000)

The data show that the hemispheres have asymmetric values for L1 and MD, and that this asymmetry is more pronounced in the group with seizures. The parameters L1 and MD are higher in the same lesion side for the group with seizures; in opposition, the parameters L1 and MD are lower in the same lesion side for the group without seizure.

a) Comparison between hemispheres in group with seizures

The DTI (FA, L1, MD) parameters are higher in the hemisphere same side of lesion in the group with seizures.

b) Comparison between hemispheres in group without seizures

The DTI (FA) parameter is higher in the hemisphere same side of lesion in the group without seizures. The DTI (L1 and MD) parameters are lower in the hemisphere same side of lesion in the group without seizures.

c) Comparison hemispheres same lesion side between group with seizures

The DTI parameter FA for the hemisphere same lesion side is lower in the group with seizures compared to the group without seizures. The DTI parameters L1 and MD for the hemisphere same lesion side are higher in the group with seizures compared to the group without seizures.

d) Comparison hemispheres opposite lesion side between group with seizures

The DTI parameters (FA, L1, and MD) are lower in the hemisphere opposite lesion side in the group with seizures compared to the group without seizures.

5.4.3 The normality of distribution in the index of asymmetry

The means for the asymmetry of DTI parameters for the groups with and without seizures were computed to analyze the normality of distribution (**Table 6** and **7**).

There is an increased L1 and MD asymmetry in the group with seizures compared to the group without seizures. The smaller the index, the bigger the asymmetry.

Table 6: Group with seizures means for asymmetry in DTI parameters.

	FA ASYMMETRY	L1 ASYMMETRY	MD ASYMMETRY
Mean	4.1387493	5.1947701	4.5251879
Std. Deviation	11.54022657	11.97327635	12.57191981
N	38	38	38

(DTI Parameters X 1000)

Table 7: Group without seizures means for asymmetry in DTI parameters.

	FA ASYMMETRY	L1 ASYMMETRY	MD ASYMMETRY
Mean	4.304707	-3.128593	-4.358496
Std. Deviation	10.55318	8.790284	9.348059
N	13	13	13

(DTI Parameters X 1000)

The Kolmogorov-Smirnov and Shapiro-Wilk tests demonstrated that the values for asymmetry between hemispheres in DTI parameters are normally distributed in the groups with and without seizures (**Table 8** and **Table 9**).

Table 8: Group with seizure tests Kolmogorov-Smirnov and Shapiro-Wilk.

	Kolmogorov-Smirnov [a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
FA ASYMMETRY	0.100	38	0.200	0.960	38	0.186
L1 ASYMMETRY	0.080	38	0.200	0.975	38	0.553
MD ASYMMETRY)	0.064	38	0.200	0.990	38	0.979

a. Lilliefors Significance Correction

Table 9: Group no seizure tests Kolmogorov-Smirnov and Shapiro-Wilk.

	Kolmogorov-Smirnov [a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
FA ASYMMETRY	0.142	13	0.200	0.935	13	0.396
L1 ASYMMETRY	0.123	13	0.200	0.960	13	0.749
MD ASYMMETRY)	0.149	13	0.200	0.935	13	0.393

a. Lilliefors Significance Correction

The normality of distribution in the index of asymmetry for FA, L1 and MD between groups with and without seizures was assessed also in Q-Q plots. The Q-Q Plots demonstrated that the values for asymmetry between hemispheres in DTI parameters are normally distributed in the groups with and without seizures (**Fig. 9** to **Fig. 14**).

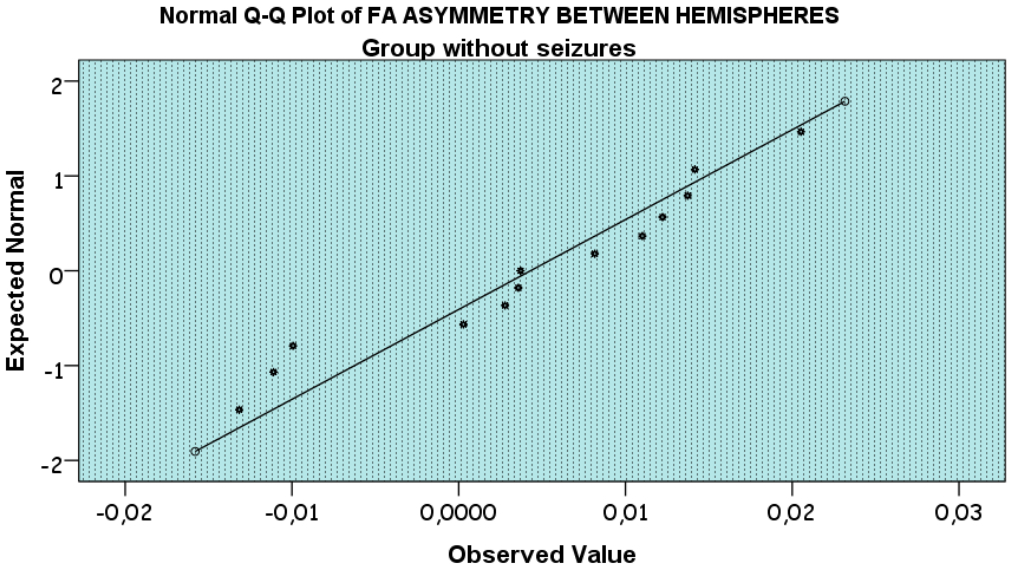

Figure 9: Normal Q-Q Plot FA - Group without seizures.

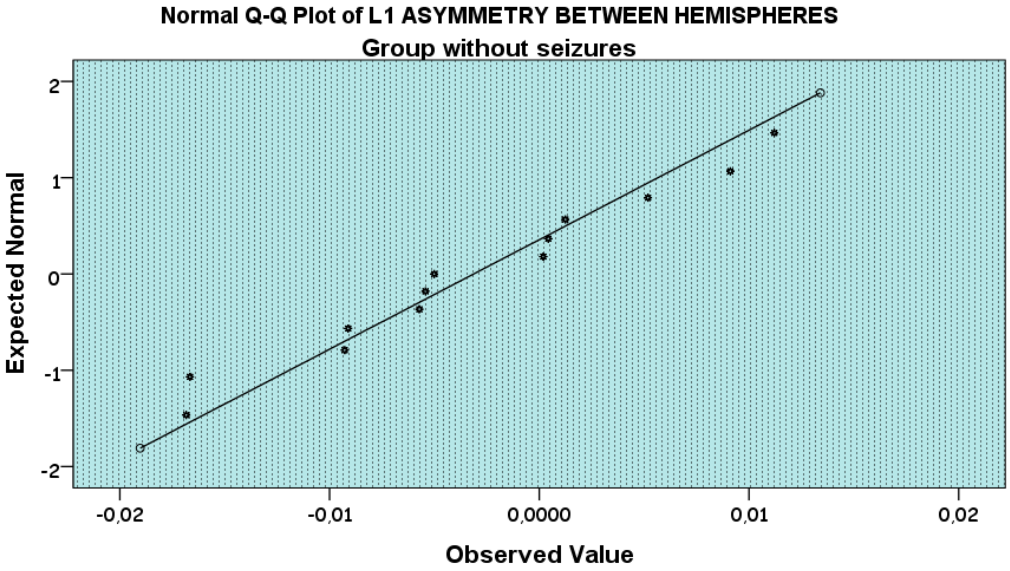

Figure 10: Normal Q-Q Plot L1 - Group without seizures.

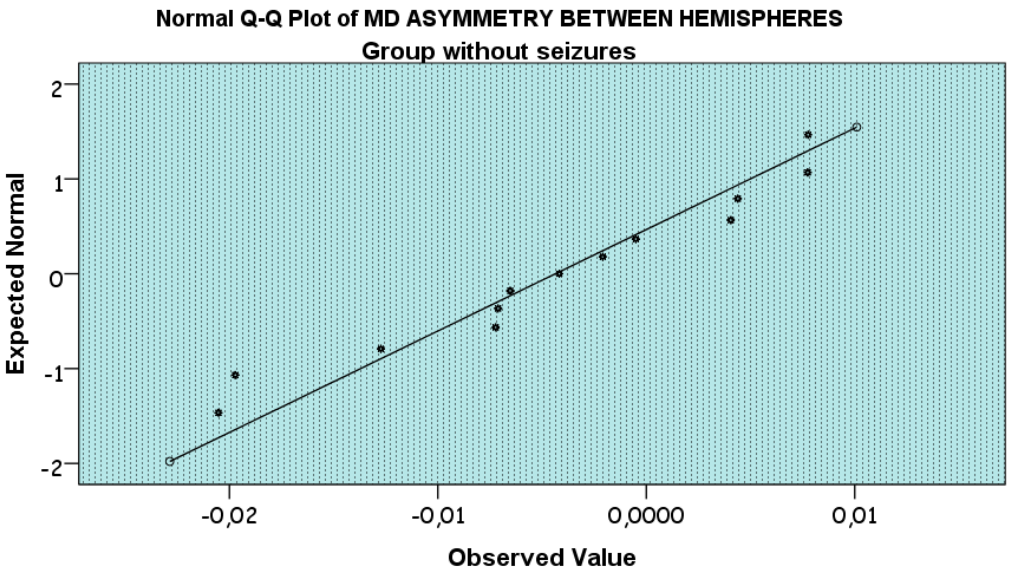

Figure 11: Normal Q-Q Plot MD - Group without seizures.

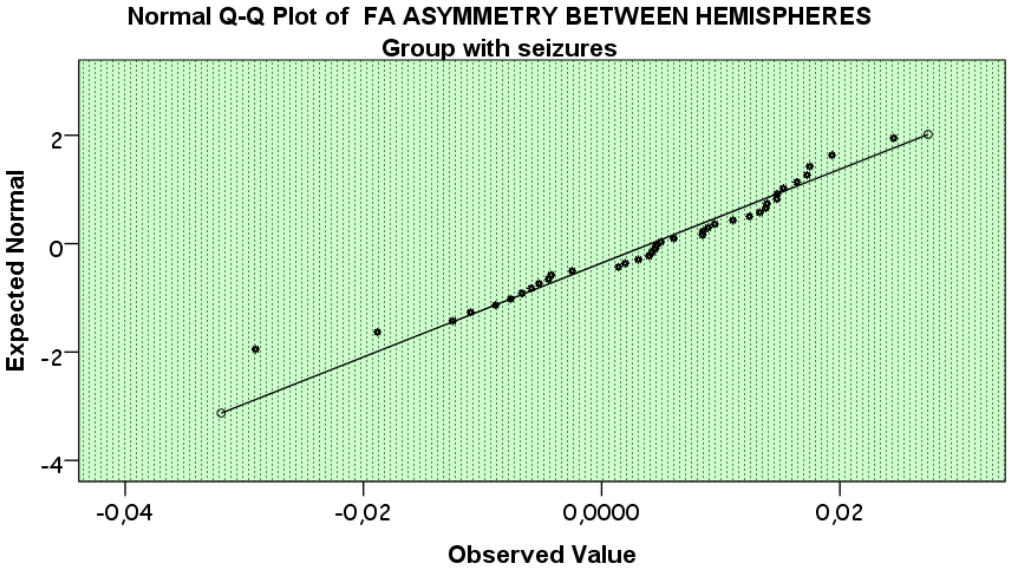

Figure 12: Normal Q-Q Plot FA - Group with seizures.

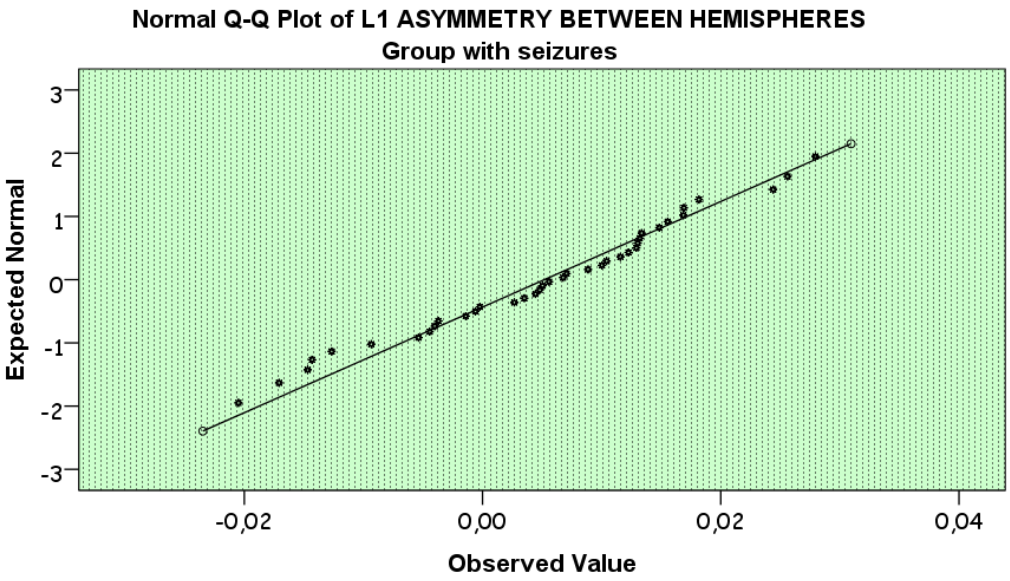

Figure 13: Normal Q-Q Plot L1 - Group with seizures.

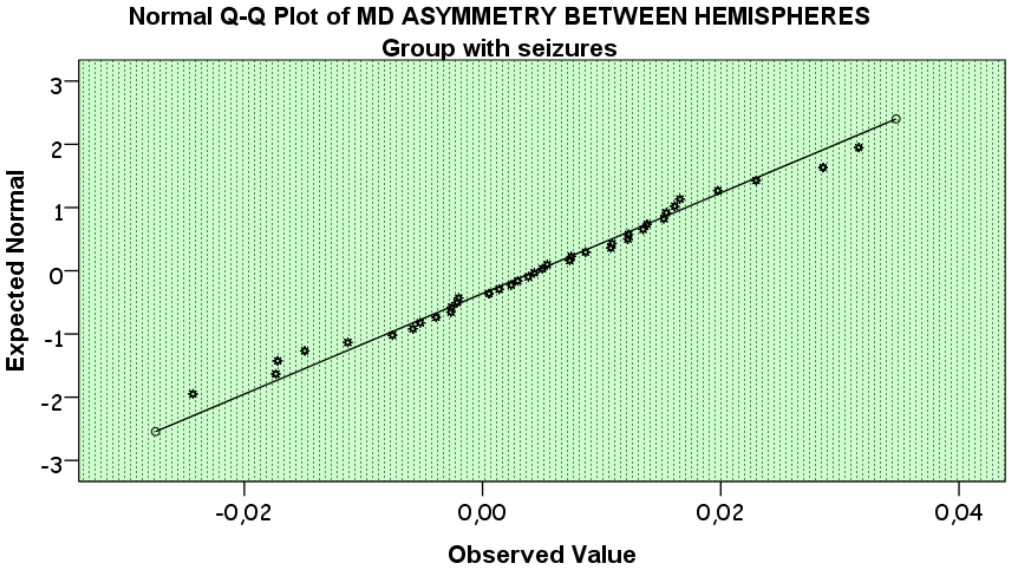

Figure 14: Normal Q-Q Plot MD - Group with seizures.

5.4.4 The t tests considering ROIs over the hemispheres

The inspection of Q-Q plots revealed that FA, L1 and MD were normally distributed for both groups (with and without seizure) and that there was homogeneity of variance as assessed by Levene's Test for Equality of Variances. Therefore, an independent t test was run on the data with a 95% confidence interval (CI) for the mean difference. The assumption was that the increased means L1 and MD asymmetry observed in the group with seizure compared to the group without seizure would be significantly different. By rejecting or accepting the null hypothesis (no significant differences between means) we will conclude that there are grounds for believing that asymmetry between hemispheres is associated with seizures in patients with neurocysticercosis single lesion. The t tests at α=0.05 and confidence interval 95%, demonstrated that L1 has t (49)=-2,297, p = 0,026 and MD has t (49)=2,331, p = 0,024.

The results confirm the assumption that there was a correlation between DTI measures and seizure. It was demonstrated that the asymmetric index has statistical difference between groups with compared to without seizure in the last 15 days, considering the differences of L1 and MD in the hemisphere affected by a single lesion, when compared with the contralateral hemisphere not affected (**Table 10**).

The table also demonstrates the equality of variance and means between groups with seizures compared to without seizures.

Table 10: Independent t-test Asymmetry between hemispheres.

Asymmetry of DTI metrics of ROIs over hemispheres			FA	L1	MD
Levene's Test for Equality of Variances	F		0.131	1.347	1.220
	Sig.		0.718	0.251	0.275
t-test for Equality of Means	t		0.046	-2.297	-2.331
	df		49	49	49
	Sig. (2-tailed)		0.964	0.026	0.024
	Mean Difference*		0.16595753	-8.3233627	-,8.883684
	Std. Error Difference*		3.63286018	3.62343721	3.81189687
	95% Confidence Interval of the Difference*	Lower	-7.1345483	-15.604932	-16.543977
		Upper	7.46646338	-1.0417930	-1.2233905

* (Mean Difference, Std. Error Difference, 95% Confidence Interval Difference X 1000)

5.4.5 The effect size was assessed by Cohen's d

The effect size based on the differences of means were assessed by Cohen's *d*. Cohen's *d* is defined as the difference between two means divided by a standard deviation for the data. Cohen's *d* was for L1 = 0.6528 and for MD = 0.666, that means a medium effect size.

5.4.6 The Pearson-correlation for edema and DTI metrics

The correlation between the DTI variables and the volume of edema per each brain was computed to assess whether edema would or would not be responsible

for differences in the index of asymmetry for L1 and MD, between groups with and without seizures, considering ROIs over the hemispheres.

There were 9 patients with edema in the group with seizure and 3 patients with edema in the group without seizure. The mean for volume of edema was 1.86 in the group with seizures, and 0.047 in the group without seizures and (**Table 11**).

Table 11: Means of edema volume between groups.

		N	Mean	Std. Deviation	Std. Error Mean
Edema volume per brain	Without Seizure	13	0.0477	0.09506	0.02636
	With Seizure	38	1.8655	5.86260	0.95104

Pearson correlations demonstrated that there were no significant correlations between the variables FA, L1 and MD and the volume of edema per each brain. The Pearson correlations for edema and FA was r=-0.052, n=51, p=0.718; for edema and L1 was r=0.257, n=51, p=0.069; and for edema and MD was r=0.250, n=51, p=0.076 (**Table 12**).

Table 12: Pearson correlation for edema volume and DTI metrics.

	Edema	FA
Pearson Correlation	1	-0.052
Sig. (2-tailed)		0.718
N	51	51
	Edema	L1
Pearson Correlation	1	0.257
Sig. (2-tailed)		0.069
N	51	51
	Edema	MD
Pearson Correlation	1	0.250
Sig. (2-tailed)		0.076
N	51	51

We checked by scatterplots the bivariate edema volume and each index of asymmetry, which resulted in three charts:

1) Scatterplot for edema volume and index of asymmetry for FA (**Fig. 15**).

2) Scatterplot for edema volume and index of asymmetry for L1 (**Fig. 16**).

3) Scatterplot for edema volume and index of asymmetry for MD (**Fig. 17**).

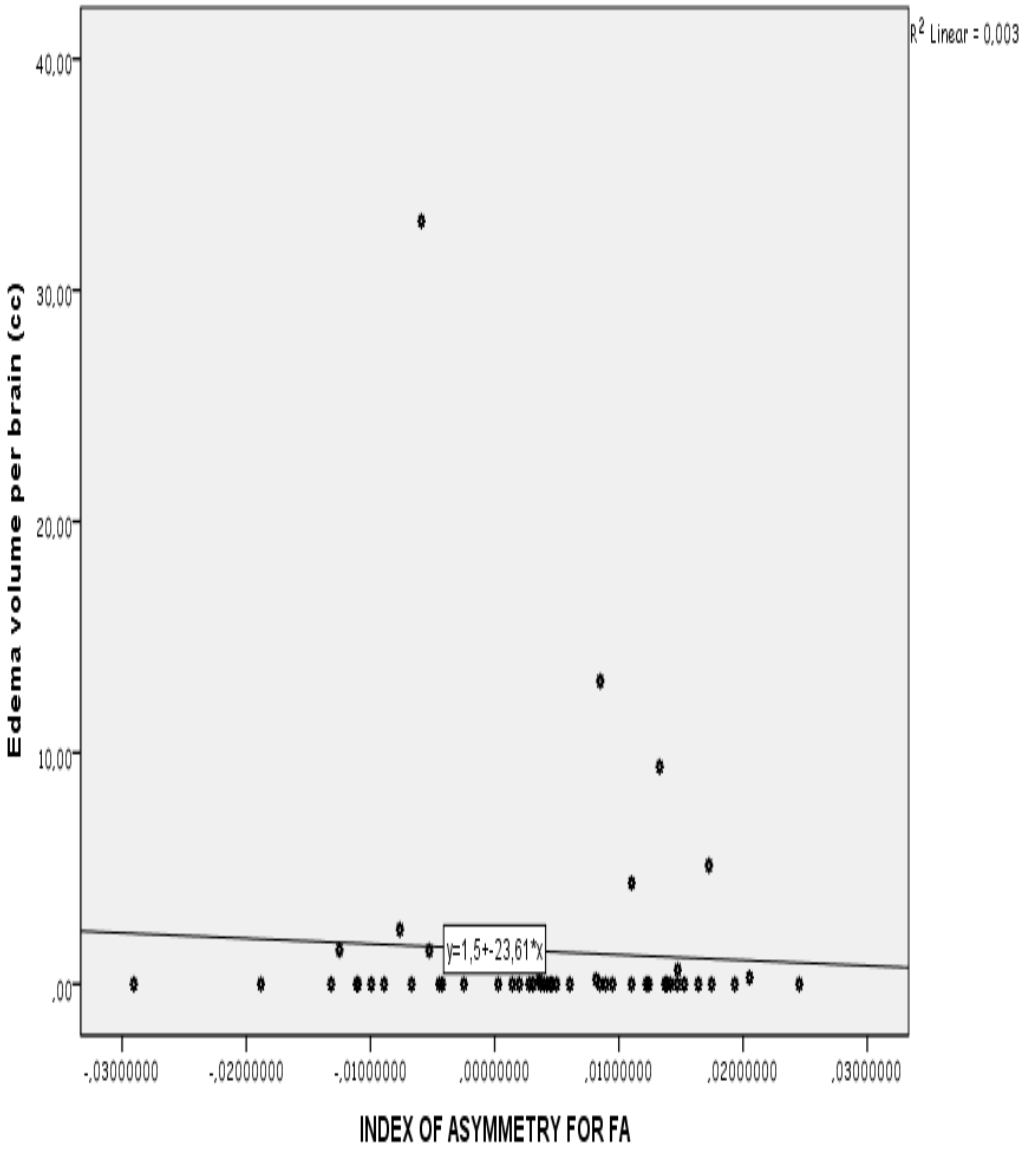

Figure 15: Scatterplot for Edema Volume and Index of Asymmetry for FA.

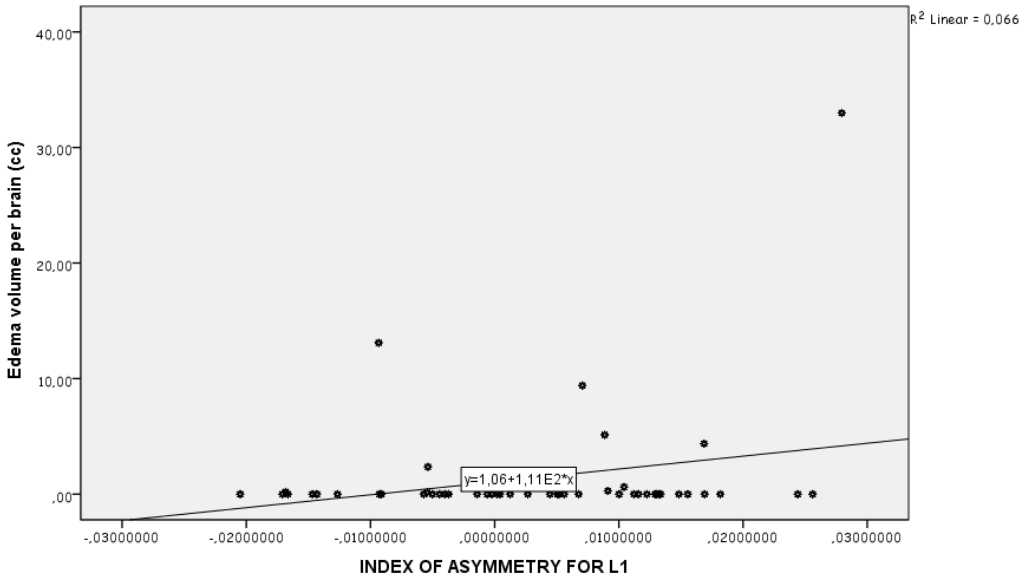

Figure 16: Scatterplot for Edema Volume and Index of Asymmetry for L1.

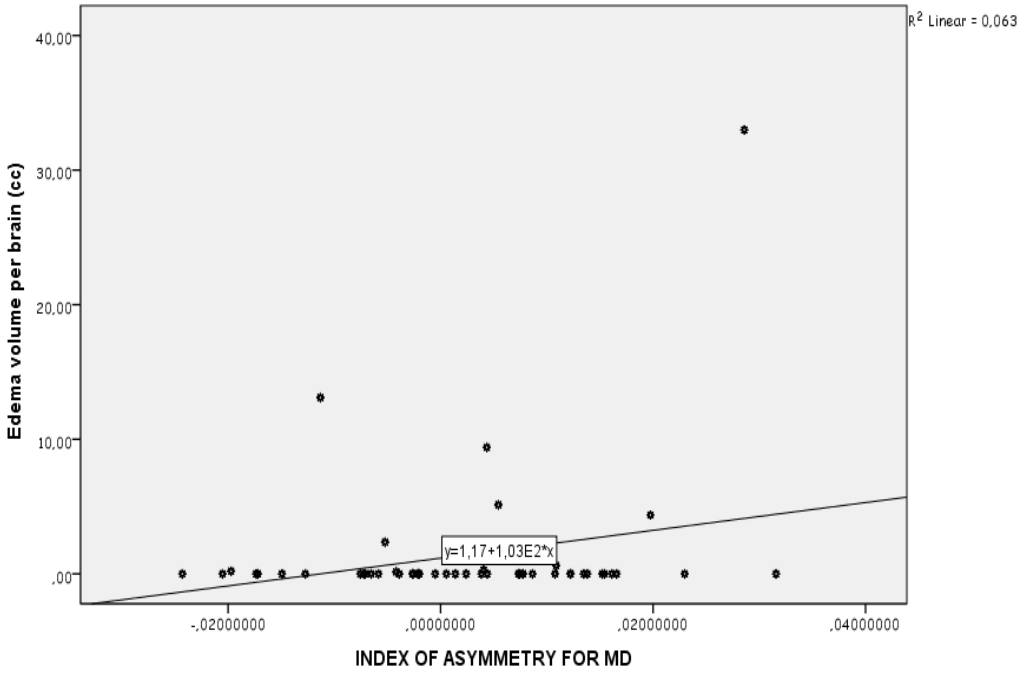

Figure 17: Scatterplot for Edema Volume and Index of Asymmetry for MD.

5.4.7 The t test for ROIs in the lesion site

We calculated differences of DTI metrics between sides considering the ROIs: a) within the lesion, b) nervous tissue nearby the lesion volume 1, 2 and 3. The ROIs surrounding the lesion derived from the volume of lesion expanded one, two or three times. The differences between sides of the DTI variables FA, L1 and MD were computed as index of asymmetry. The t tests at α=0.05 and confidence interval 95% were used to examine differences in the index of asymmetry between groups with and without seizures, considering the ROIs over the lesion and over the nervous tissue nearby. There were no significant differences between the groups with and without seizures for the asymmetry ratios using the parameters DTI (FA, L1 and MD) regarding the areas inside and around the lesions while compared with symmetrical contralateral areas (**Tables 13** to **16**).

Table 13: Independent t-test between groups for DTI metrics intra-lesion.

Asymmetry of DTI metrics of ROIs over lesions		FA INTRA	L1 INTRA	MD INTRA
Levene's Test for Equality of Variances	F	1.260	1.420	3.807
	Sig.	0.267	0.239	0.057
t-test for Equality of Means	t	0.449	-1.667	-1.690
	df	49	49	49
	Sig. (2-tailed)	0.655	0.102	0.097
	Mean Difference*	19.46121696	-35.3594526	-40.0049824
	Std. Error Difference*	43.32182143	21.21469140	23.67680280
	95% Confidence Interval of the Difference* Lower	-67.59724261	-77.9919711	-87.5852990
	Upper	106.51967652	7.27306587	7.57533414

* (Mean Difference, Std. Error Difference, 95% Confidence Interval Difference X 1000)

Table 14: Independent t-test between groups for DTI metrics expansion V1.

Asymmetry of DTI metrics of ROIs surrounding lesions. ROIs were expanded 1X lesion volume.			FA Vol 1	L1 Vol 1	MD Vol 1
Levene's Test for Equality of Variances	F		0.327	2.477	5.075
	Sig.		0.570	0.122	0.029
t-test for Equality of Means	t		-0.101	-1.579	-1.95
	df		49	49	39,44
	Sig. (2-tailed)		0.920	0.121	0.06
	Mean Difference*		-3.15328433	-29.2436635	-30
	Std. Error Difference*		31.32490019	18.51649989	20
	95% Confidence Interval of the Difference*	Lower	-66.1030280	-66.4539631	-60
		Upper	59.79645940	7.96663616	.00

* (Mean Difference, Std. Error Difference, 95% Confidence Interval Difference X 1000)

Table 15: Independent t-test between groups for DTI metrics expansion V2.

Asymmetry of DTI metrics of ROIs surrounding lesions. ROIs were expanded 2X lesion volume.			FA Vol 2	L1 Vol 2	MD Vol 2
Levene's Test for Equality of Variances	F		0.845	3.370	5.989
	Sig.		0.362	0.072	0.018
t-test for Equality of Means	t		-0.288	-1.707	-2.04
	df		49	49	46.71
	Sig. (2-tailed)		0.775	0.094	0.05
	Mean Difference*		-7.48658021	-28.2672241	-30
	Std. Error Difference*		25.98932535	16.56208835	10
	95% Confidence Interval of the Difference*	Lower	-59.7140848	-61.5499867	-50
		Upper	44.74092444	5.01553849	.00

* (Mean Difference, Std. Error Difference, 95% Confidence Interval Difference X 1000)

Table 16: Independent t-test between groups for DTI metrics expansion V3.

Asymmetry of DTI metrics of ROIs surrounding lesions. ROIs were expanded 3X lesion volume.			FA Vol 3	L1 Vol 3	MD Vol 3
Levene's Test for Equality of Variances	F		2.640	4.028	6.391
	Sig.		0.111	0.050	0.015
t-test for Equality of Means	t		-0.460	-1.670	-1,84
	df		49	49	47.52
	Sig. (2-tailed)		0.647	0.101	0.07
	Mean Difference*		-11.3308054	-25.1995432	-20
	Std. Error Difference*		24.60666415	15.08778882	10
	95% Confidence Interval of the Difference*	Lower	-60.7797484	-55.5195900	-50
		Upper	38.11813749	5.12050360	.00

* (Mean Difference, Std. Error Difference, 95% Confidence Interval Difference X 1000)

5.4.8 The effect of age and gender were for each DTI variable

The effect of age and gender were computed for the DTI variables FA, L1 and MD. The analysis of variance (ANOVA) of DTI parameters by gender and age did not reveal statistical differences between DTI variables and gender or age (**Table 17**).

Table 17: ANOVA of DTI parameters by gender and age.

	FA			L1			MD		
	Age	Gender	Age*Gender	Age	Gender	Age*Gender	Age	Gender	Age*Gender
Type III Sum of Squares	0.00	0.00	0.001	0.001	8.86E-6	2.177E-5	0.001	3.66E-5	5.932E-5
Df	2	1	2	2	1	2	2	1	2
Mean Square	6.36E-5	0.000	0.000	0.000	8.86E-6	1.088E-5	0.000	3.66E-5	2.966E-5
F	0.514	2.069	2.129	2.564	0.066	0.081	2.669	0.252	0.204
Sig.	0.601	0.157	0.131	0.088	0.798	0.922	0.080	0.618	0.816
Partial Eta Squared	0.022	0.044	0.086	0.102	0.001	0.004	0.106	0.006	0.009
Noncent. Parameter	1.029	2.069	4.257	5.127	0.066	0.163	5.337	0.252	0.408
Observed Power [b]	0.129	0.291	0.414	0.486	0.057	0.062	0.503	0.078	0.080

5.4.9 The relationship between lesions and nervous tissue

The percentage of lesions located exclusively in white matter were 11.76% (n.6), exclusively in grey matter were 50.98% (n.26), and there were 37.25% (n.19) lesions positioned in both grey and white matter (**Fig**. **18**).

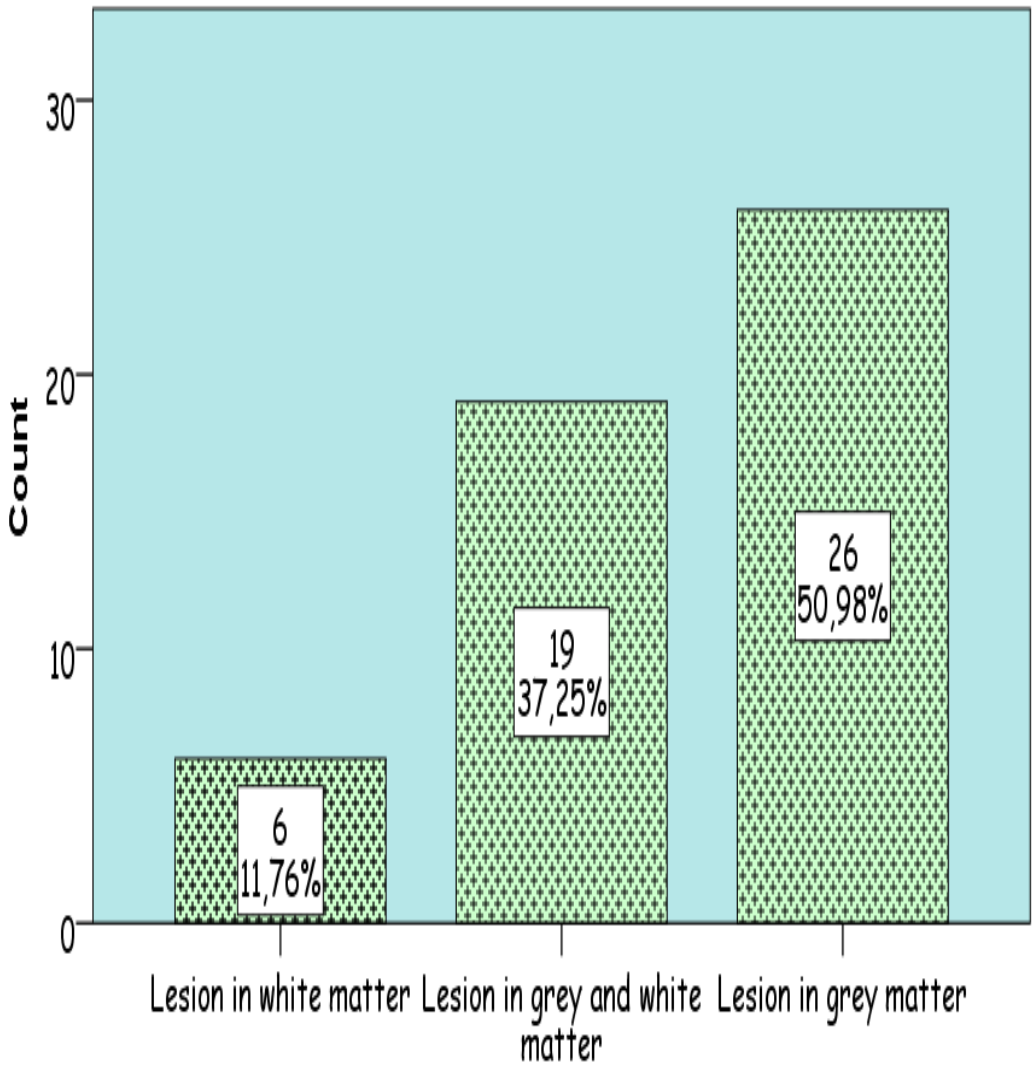

Figure 18: Relationship between single lesions and grey or white matter.

5.4.10 The classes of the characteristics of lesions

The percentage of lesions in class I were 0%, in class II were 17.65% (n.9), in class III were 62.75% (n.32), and in class IV were 19.61% (n.10) (**Fig. 19**).

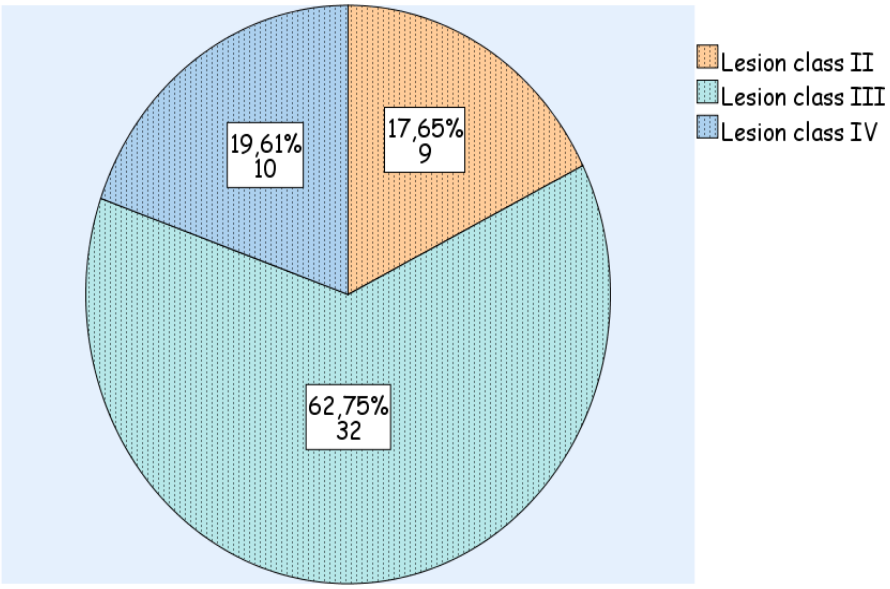

Figure 19: Chart of percentages of single lesions per classes.

5.5 Conclusions

In the first study, the site of a single lesion of neurocysticercosis, the nervous tissue nearby lesion, and the hemispheres were compared with symmetrical areas in the opposite side, through the DTI parameters (FA, L1 and MD) calculated by an index of asymmetry.

The parameters of DTI are useful to further our understanding of neurocysticercosis lesions as agents able to affect the brain hemispheres, particularly in the context of seizures. In the cerebral hemispheres with a single neurocysticercosis lesion, we found that the asymmetry indexes for DTI parameters (FA, L1 and MD) were higher in the brains of patients with seizure in the last 15 days, compared to the group without seizures.

In the site of the single lesion, and nervous tissue nearby the lesion, we did not find statistical differences in the asymmetry indexes for DTI parameters (FA, L1 and MD) between individuals with or without seizures in the last 15 days. We justify that only 11.76% of the lesions were located exclusively within the white matter. It must be noted that parameters of DTI apply to studies of white matter changes. It is important to clarify that neurocysticercosis cysts are usually located at the transition between gray and white matter, where the small diameters of blood vessels may obstruct the passage of larvae in the bloodstream.

This experimental model reinforces the concept that an impact on large hemispherical areas is more likely to produce seizures than changes in small areas. A possible understanding is that neurocysticercosis and seizures asymmetrically affect large myelinated pathways in patients with single lesion in the last 15 days. Even though changes in L1 and MD are associated with demyelination and axonal injury, in this experimental model is speculative to infer which microscopic changes caused the asymmetries.

The data suggest that asymmetries in the parameters L1 and MD correspond to changes in the white matter of the hemisphere affected by the neurocysticercosis lesion and that such changes can reduce the opposition to the passage of electric currents facilitating the occurrence of seizures. This speculation, in accordance to the concept of dielectric model of epileptogenesis, may reinforce the idea of low resistance by changes in the myelin sheath as probable origin of seizures.

The literature describes chronic inflammation in the site and surrounding tissue of the neurocysticercosis lesions. The main alterations are edema, fibrosis, granulomatosis and calcification. It seems reasonable that inflammatory processes affect also large parts of the cerebral hemisphere, considering the common observation that the edema around the cyst diffuses and can reach the middle cerebral line. The inflammation may remain in the white matter of the hemisphere affected by the neurocysticercosis lesion, after the resolution of edema.

In this study, there were no correlations between the asymmetry ratios of MD and L1 and the volume of edema. The sample had edema in 12 patients; the mean volume of edema per patient was 5.95 cc (computing the 12 subjects), with wide variations in volume between individuals. Additionally, 84.32% of patients had lesions with inflammatory characteristics that we identified as being subsequent to the onset of edema. We therefore conclude that the asymmetry changes are not due to the presence of edema.

The lesions were classified into four classes of distinct characteristics. Considering that most lesions were in phases III and IV, we infer that the changes in the asymmetry indexes of L1 and MD occurred in the late phases of the inflammatory response. In class I interface parasite-neuronal tissue is unchanged and in class II edema is present, the increasing vascular permeability suggests the beginning of the inflammation. Otherwise, the characteristics of class III and IV suggest later inflammation. In class III edema is absent, lesion had rough contour, the tissue surrounding has heterogeneity in image gradients. In class IV there are double gradient intra-lesion.

The perspective clarifies that brain inflammation associated with seizures in neurocysticercosis is not restricted to phases characterized by increasing vascular permeability (that is identified by the presence of edema). We purpose that after edema, the inflammation progresses and extends along the white matter tracts and that is associated with seizures.

Complementary studies not restricted to variables DTI parameters (FA, L1, and MD), have the potential to explore the effect of the lesions in the cortical layers, in the context of seizures.

C H A P T E R

6

- STUDY 2

6.1 Hypothesis 2

Pathological brain changes result in seizure by two mechanisms that facilitate the movement of electrons: a) decreasing the resistance of the medium, b) increasing the density of charges (or electrical capacitance), i.e., the ratio between the number of charges and the supporter area.

The electron density can be normally high in brain structures with reverberation circuits (e.g. hippocampus) and in areas with increased number and sizes of neurons (e.g. motor cortex).

We hypothesized that neurocysticercosis lesions may damage grey matter under certain conditions that turn more prone the expression of seizures, such as anatomical location of the lesions and characteristics of the brain-lesion interface.

The damage to the gray matter, in accordance to the concept of dielectric model of epileptogenesis, it may increase the electron density in the reverberation circuits and in the high electrical capacitance areas.

The hypothesis 2 contemplates changes in grey matter.

6.2 Study 2 design

We studied neuroimaging of 92 brain lesions in 64 patients under treatment for neurocysticercosis, 71 lesions were in patients with seizures and 21 lesions were in patients without seizures.

We looked for frequencies of lesions according to anatomical references (brain hemispheres, brain lobes, gyrus, and brain arteries).

Additionally, we measured the distance of the lesions from the cortical surface and compared this measurement between the group with seizures and the group without seizures. The lesions were visualized on MRI-T2 in three directions (anterior-posterior, superior-inferior and lateral-medial), and the distances between the lesions and the brain surface were measured in terms of millimeters in all three axes (**Fig. 20**). Furthermore, characteristics of the brain-lesion interface and volume of brain affected by the disease were estimated to check differences between the groups. The characteristics studied were the contours of the lesions that can be smooth or rough, the presence of parasite's head, the peri-lesion gradient, the intra-lesion double gradient, and the enhancement of the nourishing vessel (*vasa nutricia*). The MRI-T2 and DTI technique allow identification of the edema, which has similar intensity to the cerebrospinal fluid. The RMI-T2 also shows: the contours of the lesions that can be smooth or rough, the presence parasite's head (scolex) identified by the characteristic shape of eccentric point inside the cyst, and the enhancement of the nourishing vessel (*vasa nutricia*).

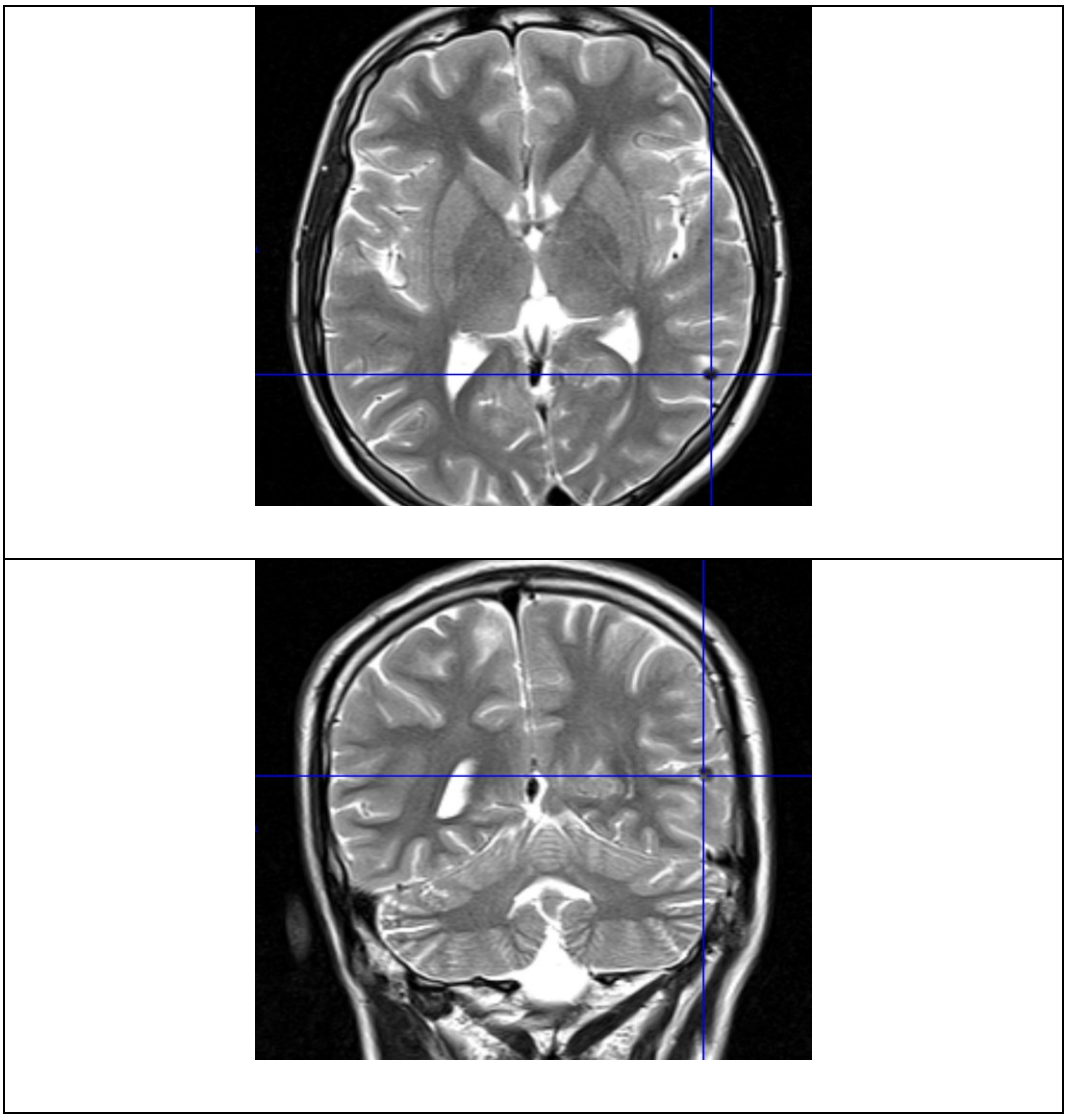

Figure 20: Cortical distance measured in three dimensions.

The SWI-phase technique distinguishes the presence of mineral deposits which are identified as a double gradient intra-lesion in the phase component of SWI.

The SWI-magnitude demonstrated the peri-lesion gradients, that are heterogeneous intensity gradients around some lesions, which give them the appearance of shading.

The characteristics of the brain-lesion interfaces were grouped into four classes.

- In class I the interface boundary of the parasite and neuronal tissue are unchanged, that is, the boundary is smooth, edema is absent.
- In class II edema is present.
- In class III edema is absent, lesion had rough contour, the tissue surrounding has heterogeneity in image gradients.
- In class IV there are double gradient intra-lesion.

We measured parameters of FA, AD, and MD, over regions of interest (ROIs), which were drawn in the entire volume of each lesion. The DTI metrics were extracted from maps normalized to assure same size and orientation among brain scans. The measurement of the lesion volume was assessed in cubic centimeters, before normalization.

6.3 Statistical Analysis

The statistical analysis in the second study used the SPSS statistical software. The descriptive analysis applied tables, circle and bar charts to demonstrate fre-

quencies of occurrence in terms of percentage of lesions among the total number of cases and between groups (with and without seizures). We computed the frequency of lesions among anatomical references as percentages. Additionally, histograms were constructed to compare frequencies between groups as to cortical distance.

Analysis of variance was applied to compare means and variance differences among multiple groups (classes of the brain-lesion interface characteristics), the tests were settle at α=0.05 and confidence interval 95%. The plot of means illustrated the differences among groups graphically. The Scheffé *post hoc* test specifically clarified which groups were different from each other.

Binary logistic regression was also performed to certify the effect of five characteristics of the brain-lesion interface on the likelihood that patient have seizure.

6.4 Results and discussions

6.4.1 Demographics

The experimental condition divided all participants (n.64) in two groups. The first group was patients with seizures in the last 15 days (n. 48), and the second group was patients without seizures in the last 15 days (n.16). Among all lesions (n.92), 71 were in patients with seizures and 21 were in patients without seizures. That means in the group with seizures there were 77% of lesions and in

the group without seizures there were 23% of lesions. The average was 1.44 lesions per patient for all subjects (minimum 1 and maximum 4 lesions).

For the female participants the number of lesions were 46, and for the male participants the number of lesions were 46. That means each gender there were 50% of lesions. The average lesions was 1.58 (46 lesions in 29 patients) in the female group and it was 1.31 (46 lesions in 35 individuals) in the male group.

The age of patients ranged from 5 to 58 years old (mean 25.5 and standard deviation 14.26). Half of the participants (n. 32) were between the ages 5 to 21 years and half were between the ages 22 to 58 years. That means each age group there were 50% of lesions. The average lesions per patient was 1.46 in the younger group and it was 1.40 in the older group. The *presence of seizures* organized by gender, age and experimental condition is illustrated in **Table 18**; in **Table 19** *number of lesions* is displayed in relation to gender, age and experimental condition.

Table 18: Presence of Seizures by gender, age and experimental condition.

		Presence of Seizures		
		Without Seizure	With Seizure	Total
Age	Up to 21 years old	9	23	32
	More than 21 years old	7	25	32
Gender	Male	6	29	35
	Female	10	19	29
Total		16	48	64

Table 19: Number of lesions by gender, age and experimental condition.

		Ratio		
		Number of Lesions	Number of Individuals	Total Means
Age	Up to 21 years old	47	32	1,46
	More than 21 years old	45	32	1,40
Gender	Male	46	35	1,31
	Female	46	29	1,58
Total		92	64	1,43

6.4.2 Frequencies of lesion locations according to brain hemispheres and arteries

In the study about frequencies of lesion locations according to brain hemisphere, we found a higher frequency (55%) of the lesions in the left brain hemisphere when compared to the (45%) implantations in the right cerebral hemisphere (**Fig. 21**). The predominance in the left brain hemisphere was 10% higher, than the opposite site. Lesions were more frequent in the left hemisphere, despite gender and age group, considering that the number of lesions per gender were identical, and only one lesion was more frequent in the group of younger patients.

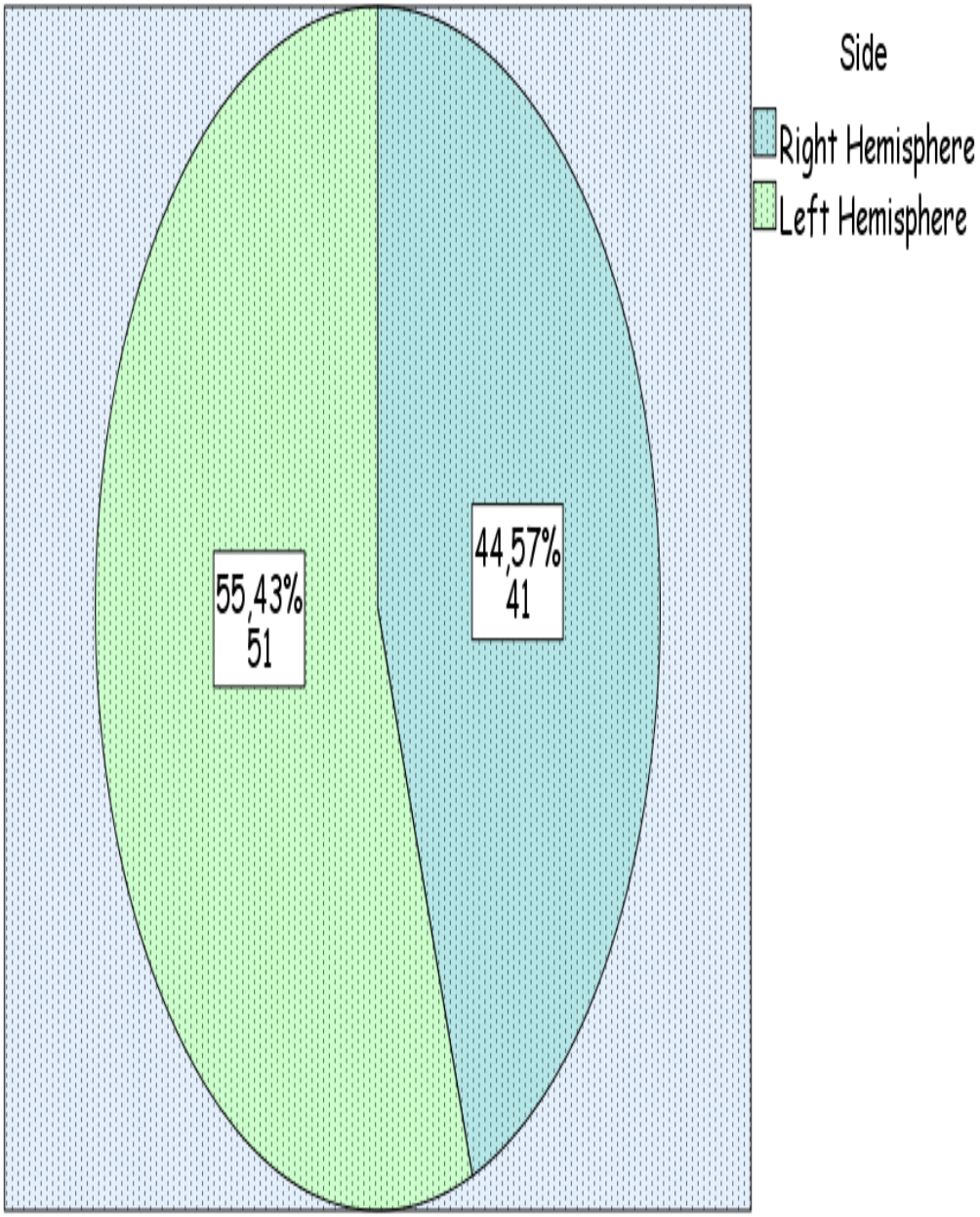

Figure 21: Frequencies of lesion locations according to brain hemispheres.

The brain areas supplied by the middle cerebral artery (MCA) showed a higher proportion of deployments (40.22%, n. 37) compared to: posterior cerebral artery (34.78%, n.32), anterior cerebral artery (23.91%, n. 22), and anterior choroidal artery (1.09%, n.1) (**Fig. 22**).

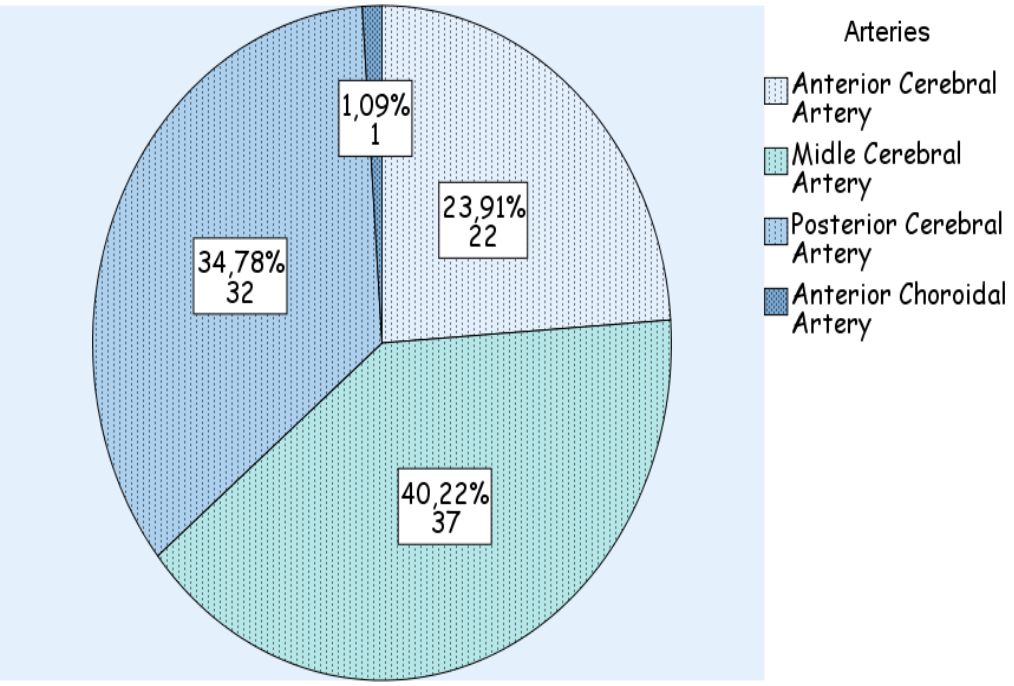

Figure 22: Frequencies of lesion locations according to brain arteries.

The middle cerebral artery is the larger of the terminal branches that arises from the internal carotid artery, which is a continuation almost straight of the aorta particularly at the left side. Such anatomical features can be responsible for more incidence of neurocysticercosis lesions at left and in the areas supplied by the MCA. The MCA receives more abnormal particles circulating in the blood (i.e., emboli) that results in increasing cerebrovascular diseases affecting territories supplied by the MCA (Caplan 2016). Considering that the larvae of the parasite transit through the blood as do other emboli, we observed coherence among the most frequent locals of parasite deployment and the most frequent sites of arterial embolization.

Emboli are also more frequent in the left hemisphere, according to the literature (Hedna et al. 2013). These findings favor the concept that the hematogenous

spread of the parasite follows anatomical standards established by other diseases that have embolic origins.

According to Miranda (2010), there is cohesion between different authors that the left hemisphere as well as cortical layers receive more blood supply than the right hemisphere and the white matter, respectively. There is cohesion between different authors that the left hemisphere receives a cerebral blood flow (CBF) higher than the right one. The CBF is the blood measured volume (mL) per 100 g of brain tissue, per minute. The overage CBF is approximately 60 ml / 100 g / min, which is 15% of the output brain. The left cerebrum has the CBF of 66 (+/- 4) to 56 (+/- 4) at rest, the right cerebrum has the CBF of 62 (+/- 2) to 55 (+/- 3) at rest.

The cerebral cortex receives greater flow compared to white matter. The CBF in the gray matter is 82 ml / 100g / min and in the white matter is 23 ml / 100g / min (Sourbron, 2009).

6.4.3 Frequencies of lesion locations according to the brain lobes

The frontal lobe had a higher number of lesions 36.96% (n. 34), followed by: parietal lobe with 23.91% (n.22), temporal lobe with 22.83 % (n. 21), and occipital lobe with 15.22%. Only one lesion (1.09%) were located in the diencephalon, specifically in the thalamus. The thalamic deployment for neurocysticercosis lesions is rare, according to the literature (**Fig. 23**).

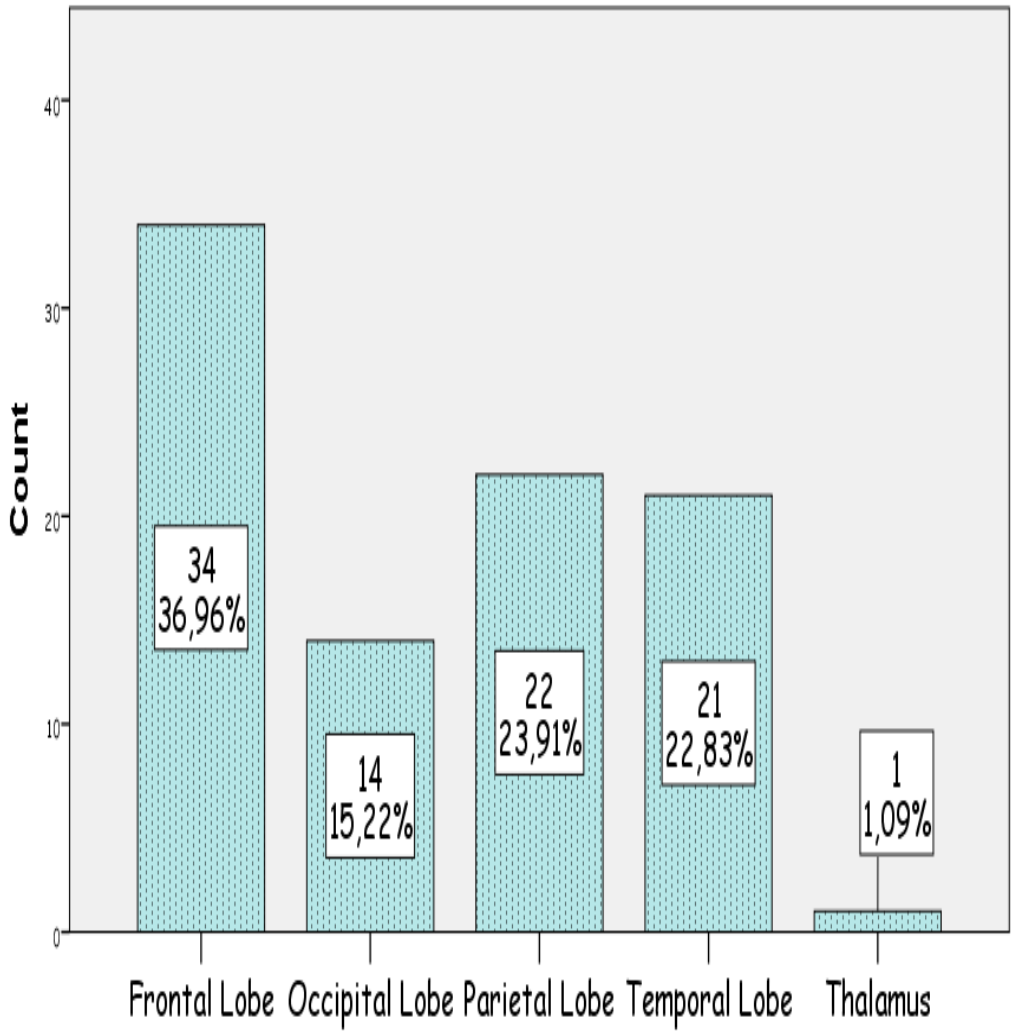

Figure 23: Frequencies of lesion locations according to the brain lobes.

The diencephalon has a lower volume (and lower blood volume) compared to the telencephalon that explains the rarity of thalamic location. The highest frontal lobe location and the lowest occipital lobe location propose that the frequency of lesions increases according to the cortical volume. Human neocortex volume is bigger in the frontal lobe and smaller in the occipital lobe, as following: frontal lobe 41%, temporal lobe 22%, parietal lobe 19%, occipital lobe

18%. (Kennedy et al. 1998). These findings support the idea that neurocysticercosis lesions are more frequently located in lobes with bigger neocortical mantle.

6.4.4 Frequencies of lesion in the grey and white matter

We counted the frequency of lesions regarding to their locations in gray and white matter. The lesions located in the gray matter were 48.91%, in the white matter were 10.87%, and 40.22% of the lesions were affecting both gray and white matter. The simultaneous involvement of white and gray matter can be attributed to the size of the cysts, since the average lesion size was 271.20 mm3 and half of the lesions exceeded 160 mm3. Such dimensions difficult as the lesion to be restricted in the cortical mantle, for which the average thickness is about 2 to 4 millimeters (**Fig. 24**). These data suggest that the lesions elect the transition between grey and white matter as frequent site for location, and reach the vicinity in the white matter after growing. It should be recalled that the grey matter has greater cerebral blood flow than the white matter, the more the blood flow the more lesion implantations.

The literature reports that the peculiar location of the neurocysticercosis lesions in the gray-white matter zone relates to the size of the larvae and diameter of cortical arteries.

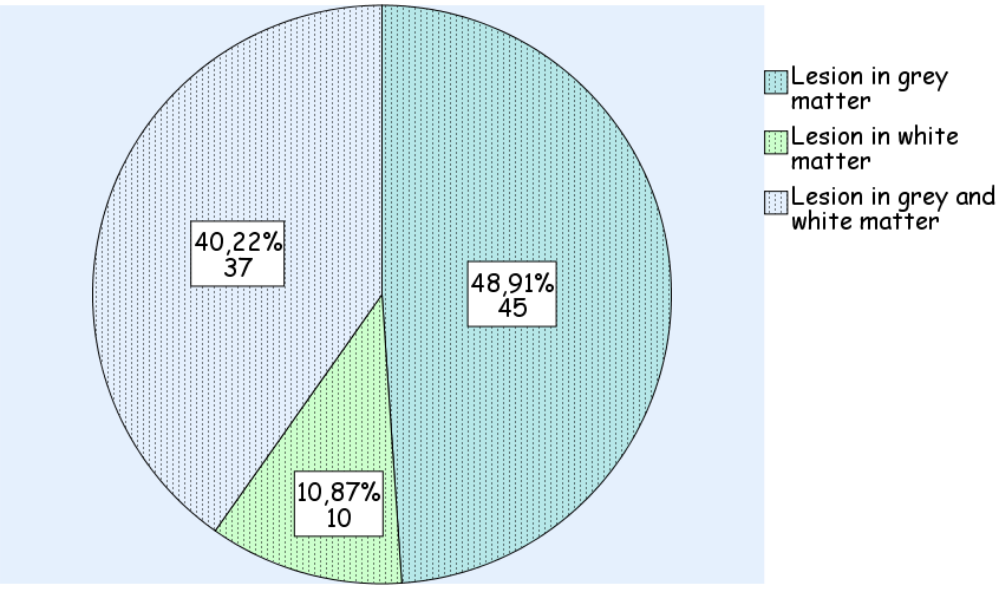

Figure 24: Frequencies of lesion locations relative to grey matter.

Thomas et al. (1989) suggested that the live parasitic larva measuring about 20 µm in diameter stops in the brain blood stream when it encountered a physical narrowing of the vascular lumen at the point of gray-matter transition. Small arteries close to the grey matter have about 18 µm in diameter.

6.4.5 Proximity of lesions to the gray matter relates to seizures

We analyzed differences between the group with seizures and without seizures considering the distance of the lesion from the cortical mantle. Lesions close to 4mm from the cortical surface are more frequent in the group with seizures. The lesions were visualized on MRI-T2 in three directions (anterior-posterior, superior-inferior and lateral-medial), and the distances between the lesions and the

brain surface were measured in terms of millimeters in all three axes. The lesions where one of the three axes was not visible were not included in the analysis. In the group with seizures, 21 lesions were included, and in the group without seizures had 17 inclusions. The average of the three distances was compared between the groups with and without seizures in a histogram. The histogram (**Fig. 25**) shows that in the group with seizures there are more lesions in contact with the cortical mantle, i.e. close to 4 mm from the brain surface. The histogram displays a frequency at least 30 times higher in the group with seizure for lesions up to 4 mm from the cortical surface.

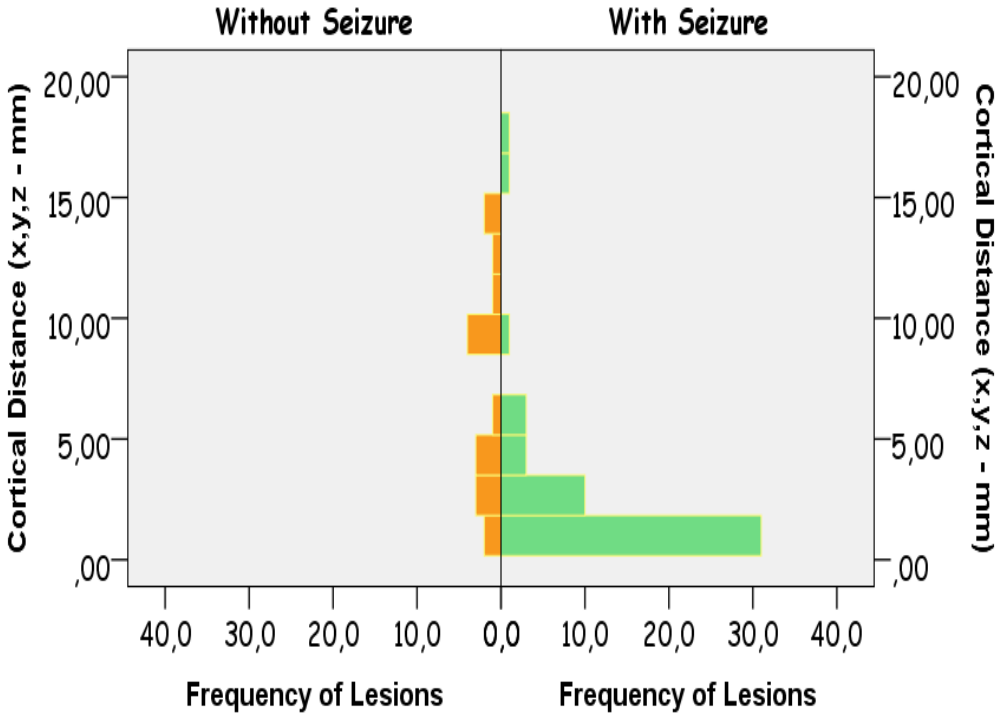

Figure 25: The histogram of cortical distances from lesions.

6.4.6 Comparison of lesions location in brain gyri between groups

The lesions located in precentral gyri, hippocampus plus vicinities were present only in the group with seizures. The locations of the lesions in cortical gyri were compared between the groups with and without seizures in the last 15 days (**Fig. 26**). In the group with seizures, a peak of higher frequencies (32 lesions, 42.25%) occurred between two locations: precentral gyrus and hippocampus plus nearby. The precentral gyrus had the maximum number of lesions (14 lesions, 30.95%). The locations in the hippocampi, in the parahippocampal gyri plus vicinities in the medial temporal gyrus and inferior temporal gyrus grouped 8 lesions (11.27%). The other lesions were distributed among the 20 remaining locations. In the group without seizures there were not peaks of higher frequencies, the lesions were scattered among 10 areas (**Fig. 27**).

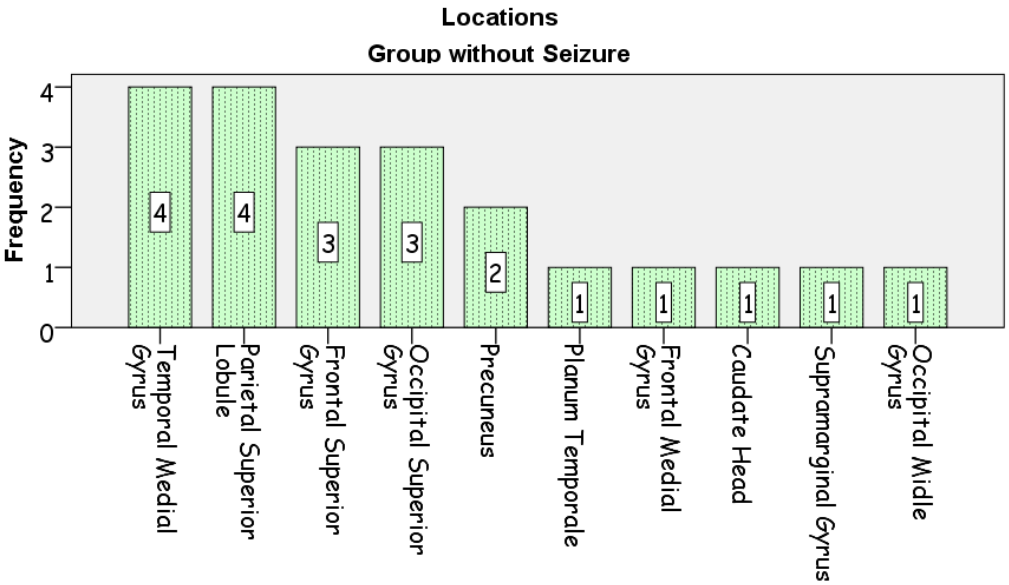

Figure 26: Locations in the group without seizures.

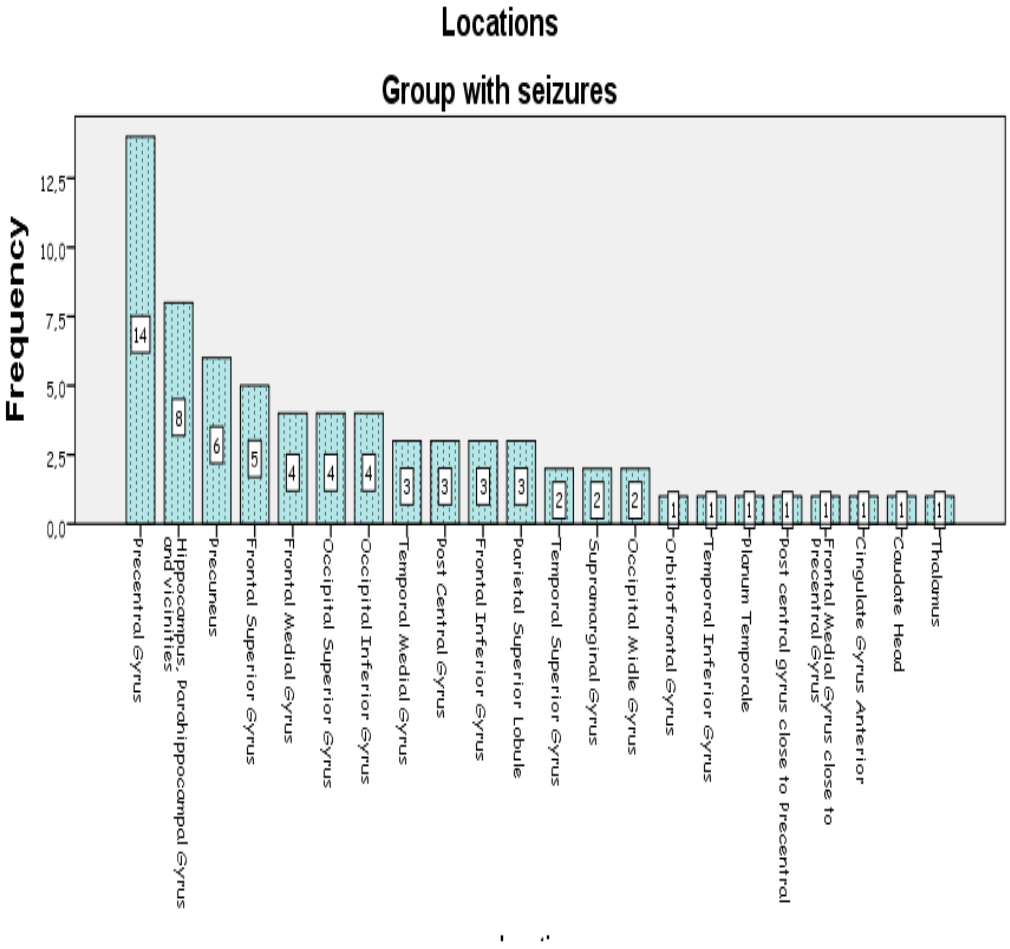

Figure 27: Locations in the group with seizures.

6.4.7 Comparison of lesions characteristics between groups

The characteristics of the brain-lesion interface in MRI-T2, DTI and SWI were tabulated considering the occurrence of edema, roughness on the boundary, ec-centric dot intra-lesion , intra-lesion double gradient, peri-lesion gradient, and *vasa nutricia*.

The characteristics of the brain-lesion interface were grouped into four classes.

Class I, which stands for the absence of changes in the lesion and surrounding nervous tissue (absent from this clinical sample).

Class II the most common feature was edema with 43.75% of occurrence, followed by eccentric dot with 38.46% of occurrence.

Class III the most common feature was the peri-lesion gradient with 33.33% occurrence followed by rough contour with 31.81%, and vasa nutricia with 15.15% of occurrence.

Class IV the most common aspect was the intra-lesion double gradient with 36.11% of occurrence.

We hypothesized that the characteristics of the lesions could predict incidence of seizures. To evaluate this hypothesis, we estimated probabilities by binary logistic regression. We calculated the probabilities of presence or absence of seizures, in relation to the presence or absence of the lesion features: rough contour, peri-lesion gradient, intra-lesion double gradient, eccentric dot, and *vasa nutricia*.

Binary logistic regression was performed to certify the effect of five characteristics (contour rough, peri-lesion gradient, intra-lesion double gradient, eccentric dot, and *vasa nutricia*) on the likelihood that patients exhibit seizures. The analysis found 33,4% (Nagelkerke R^2) of the variance in seizure and correctly classified 84.8 % of cases. The peri-lesion gradient (p=0,003) added significantly to the model of prediction. However, all other characteristics did not add signifi-

cantly to the model: contour rough (p=0,126), intra-lesion double gradient (p=0,332), eccentric dot (p=0,108), and vasa nutricia (p=0,718).

The odds of having seizure was 0,158 times lower for lesions with peri-lesion gradient as opposed to without peri-lesion gradient on this sample, considering the mentioned characteristics together (**Table 20**).

Table 20: Logistic regression of lesion characteristics.

	B	S.E.	Wald	df	Sig.	Exp(B)
Gradient peri-lesion	-1.843	0.611	9.089	1	0.003	0.158
Contour	0.996	0.650	2.345	1	0.126	2.706
Double gradient intra-lesion	-0.608	0.627	0.941	1	0.332	0.544
Vasa Nutricia	0.327	0.905	0.130	1	0.718	1.386
Eccentric dot	1.790	1.113	2.586	1	0.108	5.990
Constant	1.607	0.503	10.189	1	0.001	4.988

The set of lesion characteristics displayed sensitivity of 94%, specificity of 52%, accuracy of 1.17, positive predictive value of 87% and negative predictive value of 73%. The model were sensible to predict seizure, but it had intermediate specificity (**Table 21**).

Table 21: Sensitivity and specificity of the peri-lesion gradient.

		Predicted		
		Presence of Seizures		
Observed		Without Seizure	With Seizure	Percentage Correct
Presence of Seizures	Without Seizure	11	10	52,4
	With Seizure	4	67	94,4
Overall Percentage				84,8

The results of the binary logistic regression analysis demonstrated that the absence of peri-lesion gradients is associated with a higher probability of seizures. The presence of peri-lesion gradients may correspond to the formation of cells barriers around the lesions (i.e. granulomatosis and fibrosis), considering the comparison of lesion volume, DTI and SWI parameters across the lesion classes. The barriers of fibrosis and granulomatosis may have a protective effect against seizures by isolating the lesions from the nervous tissue.

6.4.8 Comparison of lesion volume, DTI, SWI and lesions classes

Analysis of variance was performed to evaluate statistical differences between the DTI and SWI metrics across the three classes. The metrics evaluated within the lesion (ROIs contemplated the entire lesion volume) the values of FA, L1, MD, RD, Magnitude and Phase.

There was a statistically significant difference between classes II and IV with respect to the DTI – FA and the SWI – Phase.

The values of FA increased from class II to IV, while the metrics of Phase decreased from class II to IV (**Figs. 28** and **29**). The increasing of FA is consistent with the increment of lesion volume (**Fig. 30**).

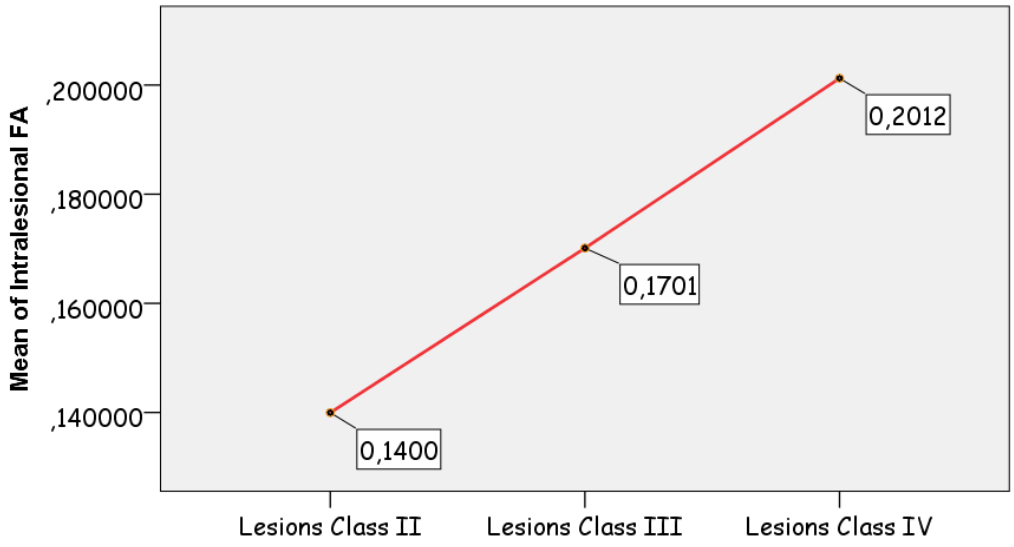

Figure 28: FA increased from class II to IV.

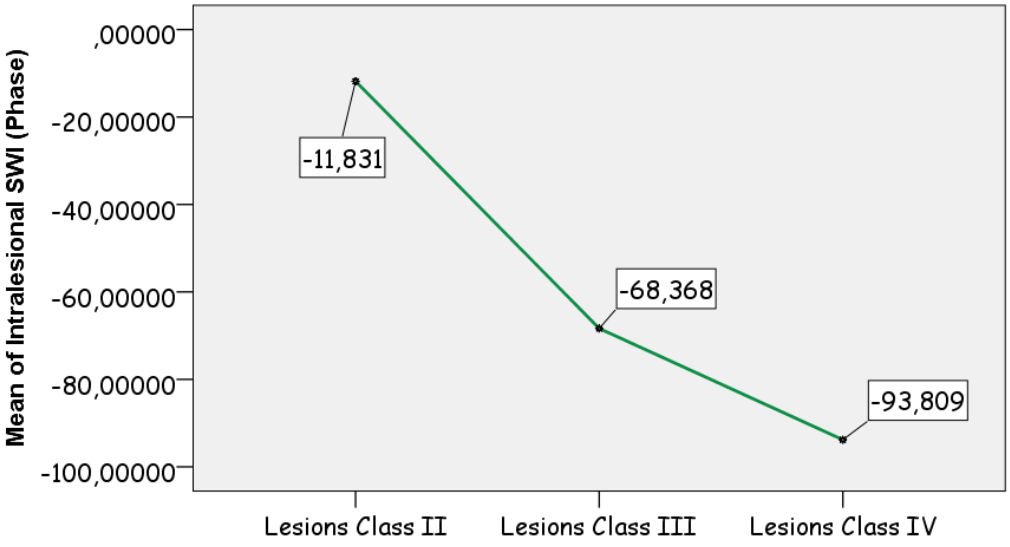

Figure 29: Phase decreased from class II to IV.

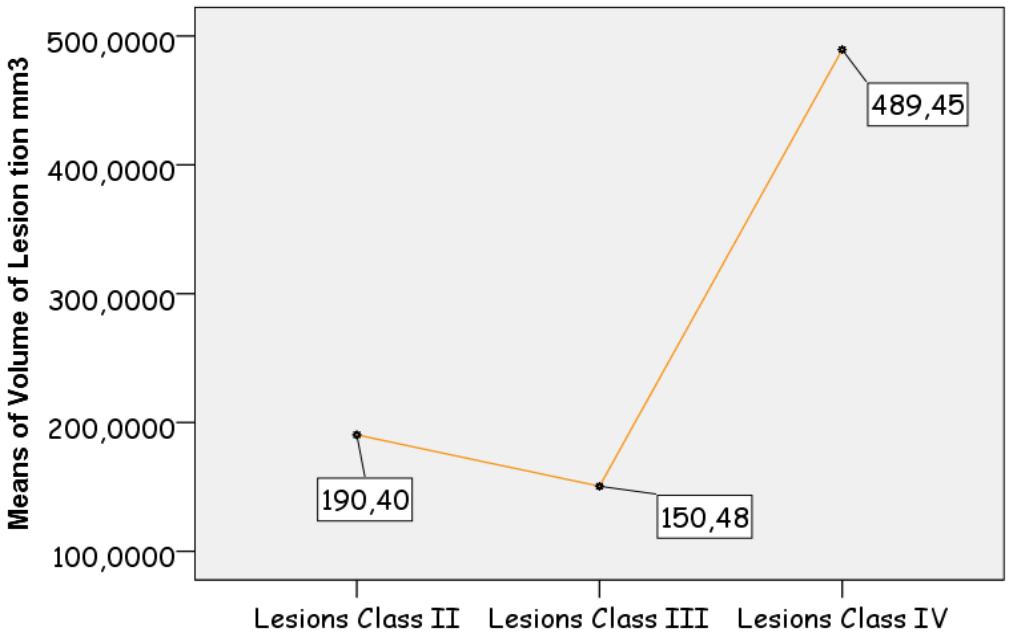

Figure 30: Volume of lesions increased in class II and IV.

According to the literature, increase in FA is related to cell density accretion (Beppu et al. 2003), which suggests that FA was sensitive to cell aggregation (granulomatosis) in the lesion. It must be noted that this sample did not include giant cysts, and that lesion expansion is limited to the inflammatory process, e.g., macrophage and fibroblast proliferation.

The DTI- Phase differentiated class IV from II, which suggests that the Phase was sensible to the mineral deposits in class IV.

For DTI - FA statistically significant difference among classes ANOVA results were as follows: (F = 7.021, df = 2, p = 0.001, partial Eta squared = 0.136,

Table 22: ANOVA for DTI, SWI, and Volume among classes.

	DTI				SWI		Vol.
	FA	L1	MD	RD	MG	PH	(cc)
Type III Sum of Squares	0.041	5.472E-8	1.210E-7	1.695E-7	8081,420	67972.011	2244862.083
df	2	2	2	2	2	2	2
Mean Square	0.020	2.736E-8	6.049E-8	8.475E-8	4040.710	33986.006	1122431.042
F	7.021	0.902	2.120	2.865	1.991	5.612	17.822
Sig.	0.001	0.410	0.126	0.062	0.143	0.005	0.000
Partial Eta Squared	0.136	0.020	0.045	0.060	0.043	0.112	0.286
Noncent. Parameter	14.041	1.803	4.240	5.730	3.982	11.224	35.645
Observed Power[a]	0.920	0.201	0.425	0.548	0.402	0.847	1.000

[a] alpha = 0.05

observed power = 0.920) and for SWI – Phase (F = 5.612, df = 2, p = 0.005, partial Eta squared = 0.112, observed power = 0.847). Scheffé post hoc tests re-

vealed that the mean differences at the 0.05 level between the classes II and IV were statistically significantly for DTI – FA (Mean Difference = -0.06127, standard error = 0.01695, p = 0.002) and for SWI- Phase (Mean Difference = -81.9775, standard error = 24.47565, p = 0.005) (**Table 22**).

6.4.9 Comparison of lesion volumes between groups

The brain volume impacted by the lesions was measured by adding the volume of all neurocysticercosis lesions plus the volume of brain edema in each subject.

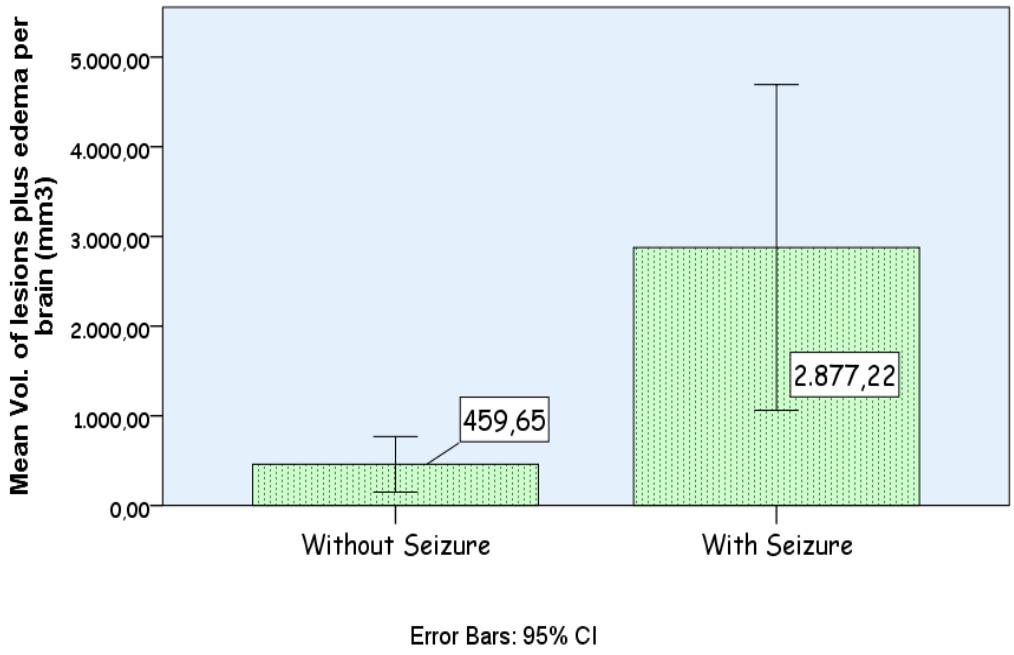

Figure 31: Volume of brain impacted by the parasitosis between groups.

The mean volume of brain impacted was 2877.22 cc for the group with seizures and it was 459.65 cc for the group without seizure (**Fig**. **31**). The data demon-

strates a higher impact over the brain integrity in the group of patients with seizures, considering the sum of the volume of all neurocysticercosis lesions per subject, as well as volume of brain edema. This measurement did not reflect subtle changes that may not be detected by visual inspection of images.

6.5 Conclusions

We found a higher frequency of the lesions in the left-brain hemisphere and in the brain areas supplied by the middle cerebral artery. We proposed that the sites of the lesion implantations follow anatomical patterns of diseases caused by emboli. The results of the analysis of frequencies of lesions according to the brain lobes, hemispheres, arteries and relationship with grey matter support that idea the regions of higher grey matter volume and blood supply manifest a higher frequency of neurocysticercosis implantations. Furthermore, the lesions are closer to the cortical surface in the group with seizures compared to the group without seizures. The lesions reflect the transition between grey and white matter as more frequent site of implantation. Thus, damage close to the cortical mantle was expressed more frequently in the group with seizures. Additionally, the group with seizures had a peak occurrence of lesions located in the precentral gyri, hippocampus and vicinities.

The characteristics of the lesions can be grouped in four classes. The most frequent characteristics in each class are: in the class II edema, in class III peri-lesion gradient, and in the class IV mineral deposits. Lesions without double gradient peri-lesion had increased odds for seizures.

The DTI and SWI parameters measured proved to be useful to differentiate the three classes, the FA increases while the Phase decreases from class II to IV. Increasing FA is consistent with the augmentation of lesion volume, suggesting that FA is a sensitive parameter for cell aggregation (e.g. macrophages and fibroblasts) in the lesion. A lower index of Phase occurs in class IV when mineral deposits are formed in the lesion. The presence of a double gradient seems to correspond to the migration of macrophages and fibroblast towards to the lesion, such barriers around the lesion are proposed to have a protective effect against seizures.

The group with seizures expressed frequent damage to the cortical mantle, especially in the precental gyri and areas close to hippocampus. Additionally, the absence of peri-lesion gradient (which may correspond to defensive barriers against the lesion) is more prone to occur in the group with seizures.

Underlying the alteration in the cortex, the measurement of the brain volume impacted by the lesions and edema were six times higher in the group with seizures.

Considering the context of seizures due to the NCC lesions the brain can be affected in the cortical mantle and in the white matter. In the cortex, damages usually compromise areas more prone to seizures (e.g. hippocampi). In the white matter, the damages affect a large brain volume that usually is reflected by inflammatory process in the hemisphere.

C H A P T E R

7

CONCLUSIONS

7.1 The answers to the research questions

We considered seizures as result of repetitive discharges of neurons, which encompasses two main systems related to the movement of electrical charges. One relies on the cortical layer in which most discharges appear to be triggered. The other relies on the white matter tracts where the charges are transmitted throughout the brain.

The two-system model provides useful theories in our attempt to understand seizures associated to neurocysticercosis lesions. The first system points to the cortex in terms of location of lesions and number, and the second points to the white matter in terms of extension of brain damage. Both addressed the main research questions:

I. What are the frequencies of location, size and number of the neurocysticercosis lesions comparing the groups of patients with and without seizures?

The frequencies of locations are higher in the left hemisphere and in the territories supplied by the middle cerebral artery, such a pattern is associated with the

observation that the larvae disseminate to the brain as emboli. The more the cortical surface (e.g., frontal lobe) and blood supply (e.g. grey matter) the more the number of lesions. Locations in precentral gyri, hippocampi, parahippocampal gyri, and vicinities were most prominent in the group with seizures. The volume of brain impacted to the neurocysticercosis (i.e. sum of lesions volume and brain edema) is higher in the group with seizures.

II. Are there differences between groups with seizure or without seizure, considering the distance from cortical surface and the layer where the lesions were settled (grey matter, white matter or both)?

The most frequent sites of implantation are close to the grey matter, this finding is related to the size of the larvae which stop the transit through the blood stream when find a narrow arterial diameter at the point of the grey-matter transition. The proximity of lesions to the cortical mantle was related to the occurrence of seizure, considering that in the group with seizures the lesions were closer to the cortex than the group without seizures.

III. How to characterize the brain-lesion interface by SWI, DTI, and MRI-T2 considering the inflammatory process derived from host-parasite interaction?

The use of neuroimaging techniques allowed us to identify lesions characteristics. The RMI-T2 revealed the contours of the lesions that can be smooth or rough, the presence parasite's head (scolex) identified by the characteristic shape of eccentric point inside the cyst, and the enhancement of the nourishing vessel (*vasa nutricia*). The SWI-phase technique distinguishes the presence of mineral deposits which are identified as a double gradient intra-lesion in the phase component of SWI. The SWI-magnitude demonstrated the peri-lesion gradients, that are heterogeneous intensity gradients around some lesions, which give them the appearance of shading. The characteristics of the lesions can be grouped in four classes. The most frequent characteristics in each class are: in the class II edema, in class III peri-lesion gradient, and in the class IV mineral deposits. The DTI and SWI parameters are useful to differentiate the three classes, the FA increases while the Phase decreases from class II to IV. The increasing FA is consistent with the augmentation of lesion volume, suggesting that FA is a sensible parameter for cell aggregation (e.g. macrophages and fibroblasts) in the lesion. The lower index of Phase happens in the class IV when mineral deposits are formed in the lesion. The presence of double gradient seems to correspond to the migration of macrophages and fibroblast towards to the lesion.

III. Are the characteristics in the brain-lesion interface related to the presence or absence of seizures?

The odds of having seizures are higher in the lesions without a peri-lesion double gradient. Considering that the formation of granulomatosis (i.e. proliferation of

macrophages) and fibrosis (i.e. proliferation of fibroblasts) around the lesion produce a barrier between nervous tissue and the parasite, it is assumed that such cell migration have a protective effect against seizures.

The peri-lesion double gradient may correspond to the defensive cell migration towards the lesion, and would represent the host's defensive mechanisms to isolate the lesion from the nervous tissue.

The higher risk of seizures in the absence of peri-lesion gradients may correspond to the lack of the host's defense in the isolation of the lesion.

V. Are there alterations in DTI in the whole brain or in the local site of implantation related to the presence of seizures?

We found that the patients with seizures in the last fifteen days and neurocysticercosis single lesion had higher asymmetry for AD and MD in the brain hemispheres, when compared to the group without seizures.

We did not find any statistical difference for the index of asymmetry in DTI parameters between groups, when compared the punctual site of lesion implantation and the surrounding nervous tissue with the symmetrical area in the contralateral side.

These findings support the idea that inflammatory processes of the neurocysticercosis lesions can affect large part of the brain hemisphere, especially in the context of recent seizure.

7.2 The limitations of the current study and prospective researches

Neuroimaging studies may be useful for increasing our understanding of neurocysticercosis lesions as agents able to affect brain hemisphere functions, particularly in the context of seizures.

The experimental models presented in this study did not intend to establish neuroimaging criteria for prognosis of seizures in patients with neurocysticercosis. The main goal was to understand mechanisms related to seizures in the context of neurocysticercosis.

The usual presentations of neurocysticercosis are the multiple lesions, which would hinder comparisons between hemispheres for clinical purposes, except when all lesions are located on the same side.

Future studies may confirm (or refute) the importance of the peri-lesion gradient in the context of seizures and may clarify assumptions like the role of peri-lesion gradient in the defensive cells proliferations; as well as, possibly the proposed associations between the *vasa nutricia* and perivascular infiltration and neovascularization.

The immune system has the potential to reduce the neurocysticercosis lesions to an innocuous scar tissue, even if the lesion are in strategic sites like hippocampus or precentral gyrus. Follow up studies may reveal SWI-phase as a useful tool on this direction. Electrophysiological tests are accurate methods to diagnosis of seizures, such tests can compare asymmetries of electrical activity in small areas

of the cerebral hemispheres. The standard method for diagnosis of epileptic foci is the measurement of electrical voltage over the scalp, which reflects brain waves produced on the cortex and deep structures. The disruption of the normal amplitude and frequencies of brain waves are generally identified in the epileptic foci by the presence of higher amplitudes and faster frequencies. The graphics of such discharges produce sharp waves, spike waves, spike-and-slow-wave complexes or multiple spike-and-slow-wave complexes.

One model for studies of electrical asymmetry in small brain areas creates montages between three electrodes. The triangular montage allows us to measure differences of voltage between electrodes placed ahead, back and beside the point of study, as well as in the symmetrical contralateral point. The references on the scalp electrodes can cover many cortical areas, exceptionally deep locations need electrodes on nasal mucosa. The discharges have higher amplitude close to the point of burst, and they have an inverted voltage (upside-down pattern) comparing the shapes ahead and back to the point of the bursts. This technique can be useful in circumstances of multiple lesions, to evaluate if small brain areas surrounding the lesions have asymmetrical voltages and frequencies (compatible with epileptic waves).

Another model for studies of electrical asymmetry between hemispheres consists in place one electrode on the vertex of the skull and compare voltages between several symmetrical electrodes placed over standard points on the skull at frontal, parietal, temporal, and occipital areas. This technique can be useful to single lesions, to check asymmetrical voltages in large brain areas.

We did not incorporate any detailed electrophysiological analysis in this study. This is an area for development – future electrophysiological studies maybe useful for developing the concepts and findings of this thesis in relation to clinical translation of our results. Neuroimaging methods are limited by cost and access (location) limitations, whereas standard electrophysiological techniques and equipment are widely available globally.

The proposal arising from the DTI measurements, concerning asymmetric indices of MD and RD in large brain areas could be corroborated by findings in electrophysiological studies. Such an approach can provide accurate measure asymmetric voltages between hemispheres. Furthermore, neurophysiological techniques can find asymmetry in small areas related to lesions close to grey matter.

The assumption that peri-lesion gradient is related to cell proliferation (fibroblasts, macrophages and epithelioid cells) requires further studies, which can be achieved by the use of radioisotopes and neuroimaging. Positron emission tomography scans with macrophage tracers has been carried out in neurologic diseases (Banati et al. 2000) and other medical conditions. The macrophages and their derived cells (giant cells and epithelioid cells) are identified by the expression of CD 68. For advanced experimental designs, the tracer ^{11}C-(R)-PK11195, which binds to receptors on macrophages, and is correlated with CD68 staining of macrophages (Van Der Laken et al. 2008) seems to be a promising tool for detecting barriers around the lesions.

The *vasa nutricia,* described as an enhancement of the vessel that nourishes the lesion, may become better characterized by studies of the role of angiogenesis in

the NCC lesions. Angiogenesis is the creation of new blood vessels, which generally follow an injury. Angiogenesis is associated with active glial scar formation and collagen deposition, in human nervous tissue close to granulomas of NCC (Alvarez et al. 2002). This has been described in rat models of NCC close to fibrotic tissue and its neuronal interface (Verastegui et al. 2015). Evidence of an increasing number of blood vessels was also found in pig models of NCC (Sikasunge et al. 2009). The *vasa nutricia* presents as a vessel enhanced, tortuous, sometimes with an abnormal ramified ending. These features resemble a fibrotic vessel intending to create new blood supply in the injury. The observation of this type of vessel in larger neuroimaging samples may help to understand the role of new vessels formation in the recovering of nervous tissue from the parasitic lesion.

The current perspective tends to classify each lesion in isolation; this perspective differs in the present study as we evaluated the volumes of lesions plus nervous tissue characteristics affected by edema. This contribution is valuable because it highlights the importance of considering the set of lesions affecting the entire brain, rather than each lesion in isolation; and it should be considered in future experimental designs related to the evaluation of lesion calcification.

The metrics of SWI, particularly Phase, are usually applied over one lesion to assess if the lesion has mineral deposits, which would give to this specific lesion the assumption of inactivity or final inflammatory stage. Future studies should consider to assess the SWI Phase over the entire volume of each lesion and compute the sum of all lesion per brain. The sum of the measurement of DTI – Phase

in all lesions in each brain may inform the inactivity of the diseases, rather than the inactivity of an isolated lesion.

Prospective cohort studies may well identify the shift between initial inflammatory stage to final inactive stage. The follow up may demonstrate that the volume of lesions plus edema tend to decrease, while the sum of mineral deposits tend to increase. The shift from the edematous phase to the calcified phase may be characterized by the sum of the lesion and edema volume (assessed by MRI – T2) compared with the sum of the metrics of the SWI – Phase in all lesions together. The data collected from such a cohort over time could be used to understand the initial or "baseline" characteristics of mineral deposits during the period when the seizures are expressed and after seizures resolution. The analysis of data gathered in this thesis work demonstrates that the volume of lesion plus edema were at least six times higher in the group with recent seizures. However, we were not able to compute the SWI-Phase in each brain at the final stage of the disease because the experimental design was not a prospective cohort study.

Despite these limitations, new insights arose from the results about seizures associated with NCC lesions. This work highlights the need for a comprehensive approach of an innovative field of research.

We expect to collaborate further in an attempt to advance our understanding of one of the most common causes of seizures in the world, neurocysticercosis.

E N D N O T E S

8

8.1 Supplementary Information about Epidemiology

A map of the endemicity of *Taenia Solium* in the World is available on the website: http://www.who.int/taeniasis/Endemicity_Taenia_Solium_2015.jpg?ua=1

A map of the Human Development Index worldwide is available on the website:

http://hdr.undp.org/en/countries

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