Demyelination in experimental intraventricular neurocysticercosis

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ABSTRACT
Neurocysticercosis (NCC) is classified as a neglected tropical disease, which affects mainly Latin America and Africa in spite of some reports in North America and Europe. NCC represents the cause of up to 30% of the reported cases of epilepsy in endemic countries. The NCC injuries present direct relation to the development stage, location, and number of parasites as well as to the host immune response. This study aimed the characterization of the inflammatory response and tissue injuries by means of the analyses of the periventricular and parenchymatous demyelination through the experimental intraventricular NCC infection. Therefore, BALB/c mice were submitted to experimental NCC inoculation with Taenia crassiceps cysticerci. Their brains were removed at 7, 30, 60, and 90 days after the inoculation (DAI), and analyzed after staining with hematoxylin and eosin (HE), Luxol Fast Blue, and Nissl. It was possible to observe ventriculomegaly, inflammatory infiltration composed by polymorphonuclear and mononuclear cells, and foamy macrophages. The presence of inflammatory cells was associated with neurodegeneration detected by the areas with demyelination observed initially in the periventricular area and lately in the parenchyma. In conclusion, the presence of cysticerci and the consequent inflammation were able to promote initial periventricular demyelination followed by parenchymatous demyelination as the infection progressed.

Keywords: neurocysticercosis; periventricular demyelination; parenchymal demyelination; Taenia crassiceps.

RESUMO
A neurocisticercose (NCC) é classificada como uma doença tropical negligenciada que afeta principalmente a América Latina e a África, apesar de alguns relatos na América do Norte e na Europa. A NCC é responsável por cerca de 30% dos casos de epilepsia em países endêmicos. Estas lesões parecem ter estreita relação com o estádio de desenvolvimento, com a localização e o número de parasitas, bem como a resposta imune do hospedeiro. O presente estudo objetivou caracterizar a resposta de células inflamatórias e as lesões teciduais pela análise da desmielinização periventricular e parenquimatosa ao longo da infecção experimental de NCC intraventricular. Para tanto, camundongos BALB/c foram submetidos a NCC experimental através da inoculação de cisticercos de Taenia crassiceps. O encéfalo foi retirado aos 7, 30, 60 e 90 dias após inoculação (DAI) e analisado após coloração por Hematoxilina e Eosina (HE), Luxol Fast Blue e Nissl. Observou-se ventriculomegalgia, processo de infiltração inflamatório composto por células polimorfonucleares, mononucleares e macrófagos espumosos. A presença de células inflamatórias foi associada com neurodegeneração, observada pelas áreas de desmielinização que foram inicialmente periventricular e mais tardiamente no parênquima. Em conclusão, observa-se que a presença dos cisticercos e a inflamação foram capazes de promover desmielinização periventricular inicial e parenquimatosa conforme houve progressão tardia da infecção.

Palavras-chave: neurocisticercose; desmielinização periventricular; desmielinização parenquimal; Taenia crassiceps.

Amongst the tropical neglected diseases, neurocysticercosis (NCC) emerges as a parasitic public health infection in regions where pigs roam freely, with clandestine slaughtering and deficient basic sanitation. NCC afflicts around 2.5 to 8.3 million people including symptomatic and asymptomatic cases throughout the world. Its prevalence is related to
socio-economic cultural factors such as eating and hygienic habits and pig farming in developing countries. On the other hand, the increase in the immigrant population from endemic areas in developed countries is accounted responsible for the expansion in the NCC cases.

The cysticerci promote an influx of inflammatory cells that vary according to the encephalic location of the parasite and to the time of infection starting from the moment they penetrate into the central nervous system. When it reaches the ventricles, an obstruction of the cerebrospinal fluid may occur leading to hydrocephaly, intracranial hypertension, ventricular dilatation, headache, inflammatory reactions, epilepsy, cerebral vascular accident, and radicular compression, presenting or not fibrosis.

Experimental models have been useful in the understanding of the complex host-parasite interaction of NCC. Up to the moment, there are five experimental models used in NCC studies: *Mesocestoides corti* in BALB/c mice, *Taenia crassiceps* in both BALB/c and C57BL/6 mice, and inoculation of *T. solium* active oncospheres in rats and piglets.

The aggregation of parasites and inflammatory cells in extraparenchymal regions, inducing an initial Th1 immune response followed by a Th2 one leading to the final destruction of the parasites in a late stage of the infection, has been reported. It has been suggested that the parasites induce a balance with the initial immune response, which is lost due to the shift of the immune profile throughout the infection time leading to the destruction of the parasite. The role of the foamy macrophages is controversial. However, it is believed that they are responsible for the phagocytosis of the destroyed cell membranes, accumulating cholesterol within their cytoplasm, which gives their aspect of foam.

The idiopathic demyelinating inflammatory diseases of the CNS constitute a heterogenous group of injuries, which differ in their clinic course, pathology, and immunopathogenesis. In spite of the wide variety of differences between these diseases, what they present in common is the inflammation and varied axonal loss. They may occur in two distinct phases: an initial one characterized by the inflammatory process and a latter one with a progressive neurodegeneration. It has been suggested that the oxidative stress generated by the inflammation may be the cause or at least play an auxiliary role in the pathogenesis of the main neurodegenerative diseases. The demyelination may be induced by soluble factors produced by the inflammatory cells, which diffuse through the parenchyma in a direct form or through the microglia activation.

Demyelination is widely studied in patients and in experimental models of Multiple Sclerosis (MS), which is an inflammatory demyelinating disease of the CNS and causes synaptic alterations in the hippocampus. It is also described the dual role of nitric oxide (NO) leading to the diffuse regional atrophy of the brain. These characteristics in the axonal pathology were experimentally reproduced showing a heterogenous pathogenesis and that the cortical demyelination occurs precociously.

Amongst the literature, there are several hypothesis trying to explain the relation between inflammation and demyelination in several neurodegenerative diseases, but not in a parasitic one. Therefore, the aim of this study was to describe the influence of the parasite in the periventricular and parenchymatous demyelination throughout the infection period using the intracranial inoculation of *T. crassiceps* cysticerci, i.e., experimental NCC.

**METHODS**

**Experimental design**

This study was approved by the Ethics Committee in Animal Use from the Federal University of Goiás (CEUA/UFU), protocol number 010/11.

The NCC experimental infection was performed using female BALB/c mice from 8 to 12 weeks old (n=40). The use of female mice is indicated because estradiol and progesterone stimulate reproduction and infectivity of the cysticerci. Initial stage *T. crassiceps* cysticerci were removed from one intraperitoneal infected mouse, washed twice with PBS for posterior intracranial inoculation.

The mice were anesthetized (0.01 mL/g of 2% Xilazine and 10% Ketamine); afterwards, the tricotomy of the superior region of the head was performed in order to expose the cranial surface. A longitudinal incision was performed in the skin and subcutaneous tissue, which allowed the visualization of the bone junctions and the bregma point. The cranial perforation was performed with a micromotor (LB100-Beltect) and diamond drill (44.5 × 2 mm) according to the stereotaxic coordinates antero-posterior =−2.0 and lateral =+3.0. Three cysticerci were inoculated in each animal with a 1 mL syringe with an adapted 25G needle (2 mm length) which enabled to reach the brain ventricles. After the surgical procedures, the incisions were closed with acrylic resin and sutured. The inoculation of 10 µl of physiologic solution (NaCl 0.9%) was inoculated in the control animals. No animal died after the intracranial inoculation.

The euthanasia of the animals was performed at 7, 30, 60, and 90 days after the inoculation (DAI) through cervical dislocation. The brains were removed for the histopathologic analysis. Each experimental day was evaluated with five infected animals and five control ones.

**Histopathologic analysis**

The removed brains were fixed in 10% buffered formalin for 24 hours, processed for inclusion in paraffin, sliced in 5 µm width, and stained with hematoxylin and eosin (HE). Three serial cuts with 50-µm spacing were performed from each animal.
The pathologic processes analyzed in the brain tissues were: ventriculomegaly, polymorphonuclear cells inflammatory infiltration (PMN), mononuclear cells inflammatory infiltration (MN), foamy macrophages, meningitis, ependimitis, microgliosis (increase in the glial cellularity, especially astrocytic and microglial), and injuries in granular cells (components of the hippocampus). These pathologic processes were classified in a semi-quantitative form as follows: absent, discrete with up to 25% of area commitment, moderate with 26 to 50% of area commitment, and accentuated with more than 50% of area commitment\(^8\). The ventriculomegaly was analyzed in a semi-quantitative form using the same parameters described above, but using as comparison the contra-lateral non-infected ventricle from the same animal\(^9\).

**Demyelination and axonal injurie analyzes**

The demyelination was evaluated through the Luxol Fast Blue staining technique. The Nissl staining was performed in order to verify the axonal disorganization or injury in demyelinated areas. The demyelination was evaluated in a qualitative and semi-quantitative form according to the following criteria:

- **Location** - periventricular or parenchymatous.
- **Intensity** - restricted to the periventricular demyelination cases: absent (score 0), discrete (demyelination sites, score 1), moderate (demyelinating areas up to 50% of the periventricular area, score 2), and accentuated (demyelinating areas greater than 50% of the periventricular area, score 3).
- **Distribution** - restricted to the parenchymatous demyelinating areas: focal or diffuse. The axonal disorganization was evaluated according to the fibers disposition, lamellar or irradiated, in a descriptive form.

**Statistical analysis**

The statistical analysis was performed with the Sigma Stat 3.5 software. All variables were tested as to normal distribution and homogenous variation. The pathologic processes were evaluated through the Mann-Whitney test and Student’s t-test, according to the parametric and non-parametric distribution. The demyelination was evaluated through mean and mean standard error. The differences were considered significant when \(p \leq 0.05\).

**RESULTS**

All mice from the infected groups presented the cysticerci located within one of the lateral ventricles inducing inflammation, expansion of the ventricular cavity, and, in some cases, deviation of the brain midline. All results obtained after the analyses are described in Table 1 and illustrated in Figures 1, 2, and 3.

At 7 DAI, the control group presented MN inflammatory infiltration, microgliosis, and dispersion of the hippocampus cells. In the infected group, it was also observed the presence of MN inflammatory infiltration, but with greater intensity. There was no periventricular nor parenchymatous demyelination in both groups, control and infected. However, the infected group presented axonal disorientation in a parenchymatous inflammation site (Table 1, Figure 1).

At 30 DAI, the alterations observed in the infected group were greater when compared to the ones observed in the control group. It was possible to detect ventriculomegaly in different intensities, mixed moderate inflammatory infiltration, discrete presence of foamy macrophages, discrete meningitis, ependimitis, and hippocampus injury. In the control group, it was possible to observe MN inflammatory infiltration, discrete meningitis, ependimitis, and injury in the hippocampus. In the infected group, the demyelination was discrete in 100% of the analyzed animals and only 40% of them presented focal parenchymal demyelination. In addition, one infected animal presented axonal disorganization in a parenchymatous inflammatory focus at 30 DAI (Table 1, Figures 1 and 3).

At 60 DAI, the mice from the control group presented MN inflammatory infiltration, discrete ependimitis, and hippocampus injury, while the infected mice presented ventriculomegaly of the lateral ventricle, mixed profile of inflammatory infiltration, discrete presence of foamy macrophages, ependimitis, and injury in the hippocampus cells. In the infected group, the periventricular demyelination was present in 80% of the animals. The parenchymal demyelination in CA2 and CA3 hippocampus areas was observed in 20% of the cases in a focal form (Table 1, Figure 3).

At 90 DAI, the infected mice presented discrete intensity of foamy macrophages and microgliosis, ventriculomegaly, mixed profile of inflammatory infiltration, ependimitis, and varied intensity of alterations in the hippocampus cells, while in the control group it was possible to observe discrete intensity of mixed inflammatory infiltration and hippocampus alterations. The periventricular demyelination was observed in 40% of the analyzed animals and 80% of them presented focal parenchymal demyelination (Table 1, Figures 1 and 3).

**DISCUSSION**

The present study used the NCC experimental model of female BALB/c mice intracranially inoculated with initial stage *T. crassiceps* cysticerci. This parasite is the most used as *T. solium* experimental model as they belong to the same genus, presenting antigenic and epitope similarities. They are very rare in human infections, which make its handling very safe. In addition, its capability of asexual reproduction through budding provides a great source of biological material\(^29\).
In the initial phase of the infection, it was possible to observe an influx of inflammatory cells. These cells belonging to the glial group of cells are responsible for the normal functioning of the CNS and are able to communicate between themselves, as well as with neurons and vascular cells. Bernardinelli et al. described that glial cells participate in the maintenance of neurons in homeostasis and when there are alterations, they release Ca\(^{++}\) leading to neuron 

**Table 1 Analysis of the general pathologic processes in the brain of female BALB/c mice intracranially inoculated with Taenia crassiceps cysticerci.**

| Microscopic alterations | DAI | Control group (n=5) median (min-max) | Infected group (n=5) median (min-max) | p-value |
|-------------------------|-----|-------------------------------------|--------------------------------------|---------|
| Ventriculomegaly        |     | 7 0 (0-0)                            | 0 (0-0)                              | 1.000   |
|                         |     | 30 0 (0-0)                           | 3 (1-3)                              | 0.008   |
|                         |     | 60 0 (0-0)                           | 1 (0-3)                              | 0.151   |
|                         |     | 90 0 (0-0)                           | 2 (1-3)                              | 0.008   |
| PMN inflammatory infiltration |   | 7 0 (0-0)                            | 0 (0-0)                              | 1.000   |
|                         |     | 30 0 (0-0)                           | 1 (1-2)                              | 0.008   |
|                         |     | 60 0 (0-0)                           | 0 (0-1)                              | 0.690   |
|                         |     | 90 0 (0-1)                           | 1 (0-2)                              | 0.310   |
| MN inflammatory infiltration |  | 7 1 (1-1)                            | 0 (0-2)                              | 0.690   |
|                         |     | 30 1 (0-1)                           | 2 (2-2)                              | 0.008   |
|                         |     | 60 0 (0-1)                           | 1 (0-2)                              | 0.151   |
|                         |     | 90 0 (0-1)                           | 2 (1-3)                              | 0.008   |
| Foamy macrophages       |     | 7 0 (0-0)                            | 0 (0-0)                              | 1.000   |
|                         |     | 30 0 (0-0)                           | 1 (1-1)                              | 0.008   |
|                         |     | 60 0 (0-0)                           | 0 (0-1)                              | 0.310   |
|                         |     | 90 0 (0-0)                           | 1 (0-1)                              | 0.032   |
|                         |     | 7 0 (0-0)                            | 0 (0-0)                              | 1.000   |
| Meningitis              |     | 30 0 (0-1)                           | 0 (0-1)                              | 0.690   |
|                         |     | 60 0 (0-0)                           | 0 (0-0)                              | 1.000   |
|                         |     | 90 0 (0-0)                           | 1 (0-1)                              | 0.008   |
|                         |     | 7 0 (0-0)                            | 0 (0-0)                              | 1.000   |
| Ependimitis             |     | 30 0 (0-1)                           | 1 (0-2)                              | 0.222   |
|                         |     | 60 0 (0-1)                           | 0 (0-1)                              | 0.690   |
|                         |     | 90 0 (0-0)                           | 1 (0-2)                              | 0.032   |
|                         |     | 7 0 (0-1)                            | 0 (0-0)                              | 0.690   |
| Microglosis             |     | 30 0 (0-0)                           | 0 (0-0)                              | 1.000   |
|                         |     | 60 0 (0-0)                           | 0 (0-0)                              | 1.000   |
|                         |     | 90 0 (0-0)                           | 0 (0-1)                              | 0.690   |
|                         |     | 7 2 (1-2)                            | 1 (1-1)                              | 0.151   |
| Hippocampus injury CA2 and CA3 areas |  | 30 0 (0-2)                           | 2 (1-3)                              | 0.095   |
|                         |     | 60 1 (0-2)                           | 2 (2-3)                              | 0.032   |
|                         |     | 90 1 (1-2)                           | 2 (1-3)                              | 0.548   |

DAI: days after the inoculation; PMN: polymorphonuclear cells; MN: mononuclear cells; CA: Cornu Ammonis; bold: statistical difference performed by the Mann-Whitney test.
death through deficiency in glucose uptake and catabolism. Our results corroborate with this description because it was possible to observe glial cell alterations in both groups, control and infected, probably due to the reception of stimuli, which provoked morphology changes, and acquisition of new phagocytic effector functions capable of inducing

Figure 1. Photomicrograph of the brain of mice infected with *Taenia crassiceps* cysticerci and control groups, intracranially inoculated with saline physiologic solution (NaCl 0.9%). (A) microgliosis (insert) in control group 7 days after the inoculation (DAI), scale 100 µm. (B) presence of cysticercus (arrow) surrounded by inflammatory process in the ventricle, 30 DAI, scale: 100 µm. (C) presence of foamy macrophages (arrow) in infected animals 90 DAI, scale 20 µm. (D) ventriculomegaly and presence of cysticercus (arrow), 90 DAI, scale: 10 µm. Staining: H&E.

Figure 2. Comparison of the intensity of periventricular and parenchymatous demyelination in *Taenia crassiceps* intracranially infected mice and the control group inoculated with saline physiologic solution (NaCl 0.9%). The results are expressed in mean and mean standard error of the scores as follows: absent — score 0; discrete — score 1; moderate — score 2; accentuated — score 3. *: statistical difference. CT: control group, INF: infected group, DAI: days after the inoculation.
inflammation and contributing to the disease pathogenesis. Matos-Silva et al. observed that at 7 days of neuro-infection with *T. crassiceps* in BALB/c mice it was possible to observe gliosis, edema, hyperemia, ependimitis, perivasculitis, and inflammatory infiltration of polymorphonuclear cells and mononuclear cells, all in discrete intensity. Additionally, the analysis of another experimental model of neurocysticercosis using *Mesocestoides corti* in BALB/c mice indicated that after
two days of infection it is possible to detect an inflammatory infiltration of macrophages, neutrophils, γδ T cells, and NK cells in the cerebral parenchyma. In addition, the presence of parasite’s antigens throughout the parenchyma lead to disseminated encephalitis.

At 30 DAI, the cysticerci presence within the ventricles, leading to ventriculomegaly and ependymitis, was probably the cause of the local inflammatory process, allowing the influx of mixed profile of inflammatory cells. Among these cells, it was possible to observe foamy macrophages, which accumulate cholesterol, and its esters derived from cell debris and the parasite itself. The inclusion of lipids bodies in immune cells has been recognized as fundamental, as they are important organelles responsible for lipids metabolism, trafficking, and signaling. They present the enzymatic arsenal associated to conversion of arachidonic acid into eicosanoids. They are also responsible for the production of cytokines such as Interleukin-1 (IL-1), IL-6, IL-8, IL-12, IL-10, tumoral necrosis factor-alpha (TNF-α), and transforming growth factor beta (TGF-β) In addition, gliosis has been linked to the presence of foamy macrophages in infections and inflammatory diseases of the central nervous system.

After the implantation of the parasite in the CNS, several mechanisms are initially observed such as the blocking and inhibition of complement activation through tasiatin and paramyosin, degradation of immunoglobulins, altering cytokine production, i.e., decreasing IL-1 and IL2, and increasing IL-10 and IL-4. Therefore, it is possible to observe the inhibition of the Th1 immune profile which is replaced by Th2 . The parasite’s tegument is composed by glycoconjugates with high antigenic variability, enabling the immune evasion because they are dynamically responsive to the alterations in the hosts microenvironment, favoring the presence of alternatively activated macrophages (AAMo or M2), which enable the parasite’s proliferation. At this point, the parasite has established the ideal survival environment, which is seen in our results in the latter phase of the infection, during which it was possible to observe a predominance of MN cells in the inflammatory infiltration, characteristic of the Th2 profile.

Helminths are uncappable of lipid synthesis and therefore must acquire it exogenously. After the lipid absorption, it is incorporated into the parasite’s tegument and cell membranes. The lipidic corpuscles within macrophages are related to several inflammatory conditions and may function as storage sites and for the synthesis of inflammatory mediators. On the other hand, the first line of defense against microorganism composed by PMN cells are attracted to the infection site and produce chemokines when activated, attracting other immune cells. This local inflammation may have been the cause of the periventricular and parenchymatous demyelination observed in our results. This is in accordance to the literature reports that show that inflammatory mechanism and the oxidative stress generated by the inflammation are the cause or an auxiliary factor in the pathogenesis of the main neurodegenerative diseases. However, this is the first description of this pathogenic effect in the NCC process.

Most of the cases of demyelination observed in our results were focal and parenchymatous, while only 40% were periventricular. These results corroborate with other studies, which reported that demyelination might be a consequence of a local inflammatory process. This is the first description of this process in experimental NCC. Lin et al. confirmed the destruction of the myelin sheath induced by a local inflammatory process related to the presence of a parasite, Angiostrongylus cantonensis. Also, the maintenance of the NCC inflammatory process has direct relation to the increase in the expression of VEGF (vascular endothelial growth factor), which facilitates the influx of immune cells.

The role of the inflammatory cells in the tissue injury has been studied in several other diseases. However, this role in the neuroinflammation and demyelination in NCC is still an enigma. The experimental models for NCC have contributed to unveil part of this process. Cardona et al. have described the initial immune response and the predominance of the Th1 profile with Ty6 (gamma delta) lymphocytes. Other authors described the inflammatory profile composed by mononuclear cells, T lymphocytes, plasmyocytes, macrophages, and eosinophils at late stages of the infection. These data corroborate with our results, in which was also possible to observer MN cell inflammatory infiltration at a later stage of infection. One of the probable causes of the demyelination observed after 30 DAI is the presence of Ty6 lymphocytes throughout the experimental infection, which induced an increase in the pro-inflammatory cytokines production and greater local cellular immune response.

An experimental study described the infection of mice with Trichobilharzia regent (Schistosomatidae) and the histologic and immunohistochemical consequences of this infection. The authors described the axon injuries and demyelination to mechanical injury caused by the parasite’s migration through the nervous tissue and not to the host’s immune response, while the experimental neurological infection with Angiostrongylus cantonensis (Strongyliida) induces the release of inflammatory mediators, leading to intracerebral myelin breakdown, and increase in myelin proteins in the cerebrospinal fluid.

The proper understanding of the neuroinflammation / neurodegeneration / demyelination cycle may help in the treatment of several neurodegenerative diseases, improving the clinical symptoms caused by the neuronal loss. The mechanism by which the immune response reacts to several different stimuli is still being clarified. The study and understanding of the multiple factors of the teniasis/cystercerosis complex and the role of inflammatory cells in CNS may help in its treatment, improving symptoms related to neuron injury.
In our study, little alterations were observed in histopathologic analyzes of the control groups. The surgical procedure promoted the brain blood barrier (BBB), allowing the initial influx of inflammatory cells leading to the hippocampus alterations observed in the late phase of infection. When the BBB integrity is lost, there is an overflow of molecules and cells, which may help to understand some of the mechanisms involved in the cell activation in NCC.

In conclusion, the experimental model of NCC used in this study was able to demonstrate ventriculomegaly and periventricular demyelination at 30 DAI, probably due to the inflammatory process. In the late phase of the infection, it was possible to observe the chronic inflammatory process and the mass effect causing ventricle distension, ependimitis, meningitis, and glial and hippocampus alterations. This is the first description of par enchymatous demyelination in an experimental model of NCC.

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