Histopathology of the Human Brain in Neurocysticercosis

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Abstract

**Background:** Neurocysticercosis (NCC) is a common parasitic disease of the Central Nervous System (CNS) caused by larval stages of *Taenia solium* (TS). It is an important cause of epilepsy, as well as sensory and motor deficits. NCC’s pathology relates to immunological and inflammatory interactions between host and parasite.

**Methods:** In human brain, the larval stage of TS and surrounding nervous tissue were evaluated by immunohistochemistry using anti-CD3, anti-CD20, anti-CD68, Masson’s trichrome, and hematoxylin eosin. Photography registered histological details.

**Results:** The microscopy of NCC’s lesions presents fibrosis, gliosis, perivascular infiltrate, edema, vascular changes, granulomatosis, and calcification. The cyst’s microscopy allows identifying capsule with microvilli and osmotic canaliculi, as well as parasite head with filaments and muscular structures. Immunohistochemistry demonstrates cells responsible for antigen-antibody reactions and wound-repair.

**Conclusion:** Abnormalities in the nervous tissue and parasite characteristics permit diagnosis and explain pathologic mechanisms within NCC’s lesion, particularly chronic inflammation. The protection of neurons recruits chemical mediators, immunological cells (lymphocytes, plasma cells, macrophages) and wound-repair cells (fibroblasts, giant cells, epithelioid cells and glial cells).

**Keywords:** Neurocysticercosis; lymphocytes; plasma cells; fibroblasts; astrocytes; granulomas; fibrosis; gliosis, *Taenia solium*.

**Background**

*Taenia* is the infection caused by the TS in the intestinal tube, where the worm develops into the adult form; whereas, cysticercosis is the infection due to immature stages of TS in extra intestinal tissues.

Metacestodes encompasses developmental stages before the adult form [1]. Metacestodes can penetrate the intestinal mucosa and via bloodstream reach several organs: CNS, eyes, muscle, and skin. Within host's tissues, they grow into fluid-filled bladder worms or cysticerci. Human infection happens by ingesting eggs or metacestodes that can contaminate food or water.

Means of prevention include sanitation, hygiene and inspection of food and water origin.

NCC is a pleomorphic disease because of the diversity of psychiatric and neurologic features, which vary according to the number, size, stage of cysts and parasite-host immunological interaction. They encompass epilepsy, headache, hydrocephalus, intracranial hypertension, motor and sensory deficits, depression, cognitive impairment, and epilepsy.

Diagnosis is based in Epidemiology, clinical presentation and brain imaging. Immunologic assays (Enzyme Linked Immunosorbent Assay, Western blot) are not specific to infection in the CNS [3].

Biopsy of lesions are reserved for times when surgery is necessary (e.g. ocular, spinal cord, 4th ventricle locations); in subcutaneous lesions; or exceptionally; in the brain to conduct differential diagnosis (e.g., suspicion of tumors, abscess, mycosis and tuberculosis).

In the brain, histological alterations are centered on the metacestodes or to the neuronal surrounding tissue. Pathological features related to metacestodes stages emphasize four morphological changes [4].

1) The vesicular stage – in which inflammatory reactions in adjacent tissues are considered absent or imperceptible. The embryo is protected by a thin and translucent membrane that attains the fluid inside the cyst. 2) The vesicular colloidal stage – in which inflammatory reactions start. Vesicular fluid becomes turbid and surrounding tissue edematous. 3) The granular nodular stage – parasite is dead, the capsule and fluid begins to degenerate. 4) The nodular calcified stage – the capsule and the parasite are retracted and calcified. In the literature, consequences of the parasite in the nervous tissue are summarized in pathologic processes such as inflammation, gliosis, fibrosis, necrosis, and interstitial deposits [5].

This work details that, in the cerebral tissue of the host, the inflammatory and immune responses promote four phase of defensive reaction against the parasite.

**Phase I**

Edema and inflammatory infiltrate surrounds blood vessels in the vicinity of the parasite, the site becomes rich with defensive cells responsive to antigens and bioactive molecules.

**Phase II**

Gliosis presents near to the metacestode. Cell proliferation occurs in microglia derived from mesodermal tissue that can become phagocytic, in neuroglia cells as astrocytes, and in oligodendrocytes that form the myelin sheath. Glial and neuronal cells together support surrounding inflammation.

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Phase II

Inflammation elicits cells from connective tissue to develop fibrosis (which are rich in collagen and fibroblasts) and recruits immunological cells to form granulomas (which are composed by giant cells and epithelioid cells) as protective barriers to neural tissue.

Phase IV

Granuloma and fibrosis remains, furthermore necrosis and interstitial deposits are formed in the lesion (necrotic material can be calcified). Vascular changes can develop.

Cells involved in the defensive processes against the metacestodes can be folded in mesenchymal immunological subgroup (lymphocytes T, lymphocytes B, plasma cells, macrophages and eosinophils); mesenchymal epidermal-like subgroup (fibroblast, giant and epithelioid cells); and mesenchymal neuronal subgroup (microglia).

Methodology

The brain tissue of a patient was processed to produce histologic sections of the Cysticercus cellulosae and of the surrounding brain tissue. Samples were preserved at formaldehyde 12%, embedded in paraffin, and cut into micrometers with a thickness of 5 micron. Serial brain sections were stained with hematoxylin and eosin. Masson's trichrome staining was used to study fibrosis. Cellular infiltrates (lymphocytes, plasocytes) and cellular proliferation in the tissue surrounding the cyst (macrophages, epithelioid and giant cells) were differentiated by immunohistochemistry directed to CD3, CD20, CD68 and nervous tissue was marked by glial fibrillary acid protein. Using a microscope at diverse magnifications, the pathologic alterations, and parasite were documented by photography.

Results

Nervous tissue interfaces parasite and perivascular spaces. Debris of the parasite and foreign particles that do not pass the tight junctions between the endothelial cells at the level of blood-brain-barrier can be phagocytized in the perivascular spaces. Fibroblasts and plasma cells proliferate in perivascular space (Figure 1). The beginning of defensive processes, as edema and antibody formation, is identified in the perivasculare space. In the interface between parasite and nervous tissue predominates final processes, as granulomatosis, fibrosis, and calcification.

Edema

Edema is a major sign of inflammations. Vasogenic edema results from increasing permeability of vessels wall; while, in cytotoxic edema the sodium and potassium pump of the cell membrane is impaired, leading to cellular retention of water.

In neurocysticercosis, vasoactive substances released by host's cells are an origin of edema; another possible cause of edema is substances from the cyst, which can have vasoactive or cytotoxic properties.

Gliosis

Gliosis stands for changes of glial cells in response to damage of CNS, when the number of astrocytes increases abnormally due to death of neurons it are called astrogliosis. Astrocytes are the main component of the gliosis in the brain tissue near to neurocysticercosis lesions. Astrogliosis is determined by the expression of glial fibrillary acid protein (GFAP) [6]. GFAP has been identified in astrocytes and their cytoplasmic processes that encompass capillaries. Phagocytosis has been attributed to the astrocytes function; they clean debris, absorbing and digesting it. Microglia cells are present within the lesions; they have also function of phagocytosis. The astrocytes form a matrix with their membrane that fills the surrounding damaged region near to the parasite. Another feature in gliosis is the heterogeneity of cell morphology: astrocytes vary in shape and size (Figures 2 and 3).

Perivascular infiltrate

Perivascular infiltrate is a set of cells between vessels and tissue. The cells found in the specimens of NCC's lesion and located in perivascular spaces are T-cells CD3, B-cells CD20, plasma cells expressing light chains Kappa and Lambda, macrophages CD68.

Lymphocyte T CD3

T lymphocytes are a class of white blood cells originating from thymus, and they have in their membrane the cluster of differentiation (CD) 3 in almost all stages of development. CD3 is required for T-cell activation and consists of a protein complex that contains four distinct chains. These chains associate with the T-cell receptor to generate an activation signal in T lymphocytes [7]. CD3 can be used to distinguish T-cells from B-cells and myeloid neoplasms (lymphomas and leukaemias) [8]. Antigens released by the metacestode activate T-cells CD3. T-cells secrete cytokines as answer to antigens. Cytokines grow more T-cells, attract macrophages, neutrophils and support T-cells to mature and differentiate in T cell helpers or cytotoxic cells. Lymphocytes T CD3 and Lymphocytes B CD20 occur in the perivascular infiltrate near the parasite (Figure 4).

Lymphocyte B CD20

Lymphocytes B are white blood cells, which in mammals mature in the bone marrow. B cells bind to a specific antigen using their B cell receptors on their membrane. The antigen either can be free or introduced by macrophages or dendritic cells. B cells differentiate into a plasma cell that secretes large amounts of antibodies or memory B cells for persistent protection [9]. CD20 is a component of the cell surface that regulates calcium transport across the plasma membrane [10,11]. In B cells, the engagement of CD20 molecules initiates a signal transduction cascade via tyrosine kinases involved in cell adhesion, proliferation, and survival [12-15]. CD20 is a membrane phosphoprotein present on B cells, it is expressed in lymphocytes precursor and mature B cells, but it is not expressed on plasma cells (Figure 5A) [16]. Human CD20 deficiency results in decreased antibody levels against polysaccharides after vaccination, therefore some authors suggest that CD20 enables lymphocyte B activation independent of T-cells. Antigens that activate B cells with the help of T-cells are known as T cell- dependent antigens and include foreign proteins [13]. Antibody production via
Figure 2: Gliosis in NCC. A Astrocyte expressing GFAP with cytoplasmic process encircling a vessel (X400). B Astrocyte expressing GFAP (X400). C Vessels surrounded by GFAP positive astrocytic processes (X400). D Astrocytes (X100).

Figure 3: Barriers in NCC. A Gliosis with astrocytes expressing GFAP close to neurons (X400). B Fibrosis colored in blue by Masson’s trichrome and epithelioid cells in pink (X400). C Gliosis under the layer of fibrosis colored in brown by GFAP immunohistochemistry (X400). D Gliosis in the center, fibrosis in the middle, and epithelioid cells in the interphase with the parasite (GFAP, X100).

Figure 4: Perivascular infiltrate in NCC. A B lymphocytes expressing CD 20 surrounding vessel (endothelial cells and erythrocytes) (X400). B and C CD20 positive B lymphocytes (X100). D CD3 positive T lymphocytes (X100).

Figure 5: Immunological cells in NCC. A B lymphocyte express CD 20, while plasma cells do not express CD 20 (X400). B Plasma cells expressing kappa light chains (X400). C Plasma cells expressing lambda light chains (X400).

T cell- independent antigens may be an alternative route to combat neurocysticercosis, considering that Taenia solium has mechanisms of evasion from the immune system, for instance it can inhibit mitogen-induced proliferation of spleen cells [17].

Plasma cells

Plasma cells secrete antibodies; they are also called plasmocytes and originate from the bone marrow and B cells. After leaving the bone marrow, the B cells internalize an antigen, process it and externalize its fractions to present it to T cell helpers. These T cells bind to the antigen site and cause activation of the B cell [18]. Plasma cells typically result from T cell-dependent activation of B cells; however, they can also result from T cell-independent activation. Independent antigens (e.g. oligosaccharides of the worm) could activate B cells to form plasma cells as an alternative course, once oligosaccharides may participate in the antigenicity of NCC [19]. An evidence of the responsiveness of plasma cells in human brain to antigens of T.S. is the identification of Russel bodies. When a plasmocyte undergoes excess of antibodies it distends endoplasmic reticulum and forms a corpuscle called Russel body [20,21].

Russel bodies, which are eosinophilic inclusions of immunoglobulin, were found in plasmocytes close to the brain lesion of NCC (Figure 1C). Plasma cells with Russel bodies have been reported in the literature, in chronic inflammation and in multiple myeloma [22]. In NCC, their presence suggests that metacestodes of Taenia solium induce a large production of antibodies.

In comparison to malignant plasma cells, which produces monoclonal antibodies, lymphocytes surrounding neurocysticercosis lesions clearly do not have a monoclonal lineage; as demonstrated, they express two types of light chains kappa and lambda (Figures 5B and 5C). Light chains are small polypeptide sub-units; typically an immunoglobulin is composed of two heavy chains and two light chains (kappa and lambda). Monoclonal lineage (e.g., multiple myeloma) has predominantly one type of light chains [23].

Parasite debris elicits a large and prolonged production of antibodies. The massive and continuous production of antibody (presence of Russel bodies within plasmocytes), the intense phagocytic activity (presence of macrophages and giant cells), and the scar formation (coexistence of fibroblasts and epithelioid cells) characterize chronic inflammation, in NCC. Macrophages, epithelioid cells and giant cells Monoblasts originate monocytes, in the bone marrow. Monocytes circulate in the bloodstream for about one to three days and then go into tissues where they differentiate in macrophages [24]. Macrophages main functions are phagocytosis, antigen presentation, and cytokine production. The cells close to the parasite expressing CD 68 were identified as macrophages or their derived cells (giant cells and epithelioid cells). Giant cells were characterized by a mass formed by the union of diverse cells, composed of more than one nucleus per cell, and nuclei are randomly ordinated. Epithelioid cells were detailed by their morphology similar to epithelial cells; they have a pale eosinophilic
cytoplasm and central, ovoid or elongated nuclei (Figure 6). CD68 is a member of the lysosome associated membrane protein that is expressed in macrophages in response to the macrophage-colony stimulating factor (MCF) [25,26]. CD68 is considered a receptor member of the scavenger family. Scavengers clear cellular debris, promote phagocytosis and mediate activation and recruitment of macrophages [27,28]. CD68 is present in lysosomes and endosomes with a smaller proportion in the cell surface of macrophages. The receptor internalizes molecules for enzymatic metabolism [29]. The granulomatous lesions in neurocysticercosis were characterized by the presence of giant cells, epithelioid cells and macrophages. Granulomas have a function of modulators because they control immune response, limit neuronal damage and remove foreign substances. Eosinophils generally are placed between the parasite and the granulomas [30]. Eosinophils have bilobed nuclei and intracytoplasmic granules with affinity for acid dyes. The content of granules mediates parasite defence reactions and is constituted by proteins (major basic protein), lipids (leucotrienes) and cytokines (interleukins-3 and -5). Interleukin-5 was reported as one of the major cytokines present in cerebrospinal fluid (CSF) of patients with active NCC. The eosinophilia present in the CSF of patients with active NCC was understood as being, at least in part, mediated by the interleukin-5 produced by the host [31]. Eosinophils function as mediators because they control immune response, limit neuronal damage and remove foreign substances. Eosinophils are toxic to both parasite and host tissues [32-34].

Fibroblastic barrier

Fibroblastic cells and collagen fibrils are found in the vicinity of NCC lesions. Fibrosis fills gaps in the tissue which are previously displaced or harmed by the mass effect of the cyst (Figure 3). The origin of fibroblastic cells is potentially in the subarachnoid trabeclae. In normal histology of the brain, the subarachnoid trabeculae contain groups of fibroblastic cells arranged together with collagen fibrils [35]. By perforating the arachnoid involving the vessels, the larva will also displace fibroblastic cells towards the nervous tissue. Once in the nervous tissue, fibroblastic cells remain among collagen fibers, and proliferate by stimuli of chemical messengers (e.g. fibroblast growth factor). At the capillary diameter, endothelial cells interact with astrocyte cell projections and the blood brain-barrier is established without the presence of fibroblastic cells [36]. Considering dimensions, the larva would reach nervous tissue by disrupting blood vessel walls before the level of small arteries (19 micrometers) [37], small arteries are surrounded by arachnoid fibroblasts [38]. It should be recalled that the capillary size, averaged from various geometrically different zones in human cerebral cortex, was estimated at 6.47 micrometers in diameter [39], whereas Taenia solium oncospheres measured 32 micrometers, before hatching the embryo [40]. Such physical magnitudes reinforce the idea that the parasite disrupts vessels recovered by subarachnoid trabeculae and carries fibroblastic cells into the nervous tissue. In addition, fibroblastic cells migrate to the site of chronic inflammation by chemical attraction.

Calcifications

Calcifications relate to the death of cyst cell components. There are two main groups of cell components; one encompasses tissues of the parasite body, and the other tissues of the capsule (Figure 7). Cells from the capsule can grow even if the parasite is dead. Cysticercus cellulosae is the living larva of Taenia solium, it is composed by a capsule that protects the head of the parasite (scolex) which shows hooklets and adhesive structures (suckers). Cysticercus racemose is the dead larva of Taenia solium, with active proliferation of the capsule. The presence of calcifications and loss of the typical microvilli in the cell surface indicate capsule degeneration. Calcifications are the main characteristic of the parasitic lesions in the final stage (Figure 8). However, inflammation around calcifications may be reactivated either by remaining debris or living cells of the capsule [41].

Vascular alteration: arteritis and angiogenesis

The literature broadly refers to arteritis in patients with neurocysticercosis [42-45]. The creation of new blood vessels is angiogenesis, which was described in rat models of NCC close to fibrotic tissue and its neuronal interface [46]. Evidence of an increasing number of blood vessels was also found in pig models of NCC [47]. Angiogenesis was related to the active glial scar formation and collagen deposition, in human nervous tissue close to granulomas of NCC, according to the literature [48]. It is know that endothelial cells and fibroblasts stimulate angiogenesis in animal models of spinal injury [49]; and that glial scar stimulates revascularization [50]; those findings support that angiogenesis may follow...
glioisis and fibrosis in human NCC.

Discussion

The bioactive messengers produced by the host are determinants of histological alterations; however, the substances from the parasite elicit and may exacerbate those messengers.

Glial fibrillary acidic protein

The glial fibrillary acidic protein (GFAP) allows astrocytes to produce cytoskeletal structures and project pseudopodia [51]. Enhancement of GFAP in astrocytes and their cytoplasmic processes were observed in areas of gliosis close to the metacestode (Figure 2). Sustaining histological findings, literature documents that GFAP protein was detected in cerebrospinal fluid of patients with NCC [52].

Interferon gamma

Lymphocytes and granulomas are present in NCC alterations (Figures 4 and 6); they produce interferon gamma (IFG) which can trigger astrocytes proliferation and gliosis.

The following experiments together suggest that IFG elicits gliosis due to NCC.

Human IFG was a potent mitogen for human astrocytes cultivated in vitro, and IFG induced gliosis in mouse brain [53]. Furthermore, IFG was present in NCC granulomas prepared in mice, in high frequency (11 of 12 granulomas) [54].

Tumor necrosis factor alpha

Although tumor necrosis factor alpha (TNF-a) occurs in the cerebrospinal fluid of NCC patients, its amount did not differ from controls [55], and was detected infrequently [56]. It is produced primarily by macrophages, as well as by fibroblasts, neurons, lymphoid and endothelial cells [57]. A possible role of TNF-a in gliosis due to NCC must be considered; because, TNF-a can stimulate cytotoxicity and increase inflammation in nervous tissue [58]; and TNF-a activates glial cells and promotes gliosis [59].

Eotaxin and interleukins

Histological specimens of this study illustrated the antibody-producing cells and their precursor B cells being attracted to and maturing in the site of the lesion (Figure 5). Several mediators are elevated in the CSF of NCC patients, e.g. eotaxin, interleukin-5 and interleukin-6. The first is an eosinophil chemotactic protein; interleukin-5 stimulates B cells to grow and secrete immunoglobulin [59]. Interleukine-6 induces the maturation of B cells into plasma cells [60]; reactive gliosis is a consequence of interleukin-6 expression in the brain of transgenic mice [61]. Those mediators interact to perform perivascular infiltrate and may produce gliosis in NCC lesions.

Antigen-antibody complex

The variability of immunoglobulin synthesis supports the concept of multiple antigens from the parasite interacting with diverse antibodies from the host, this is indicated in the histological finding by plasmocytes kappa and lambda positive (Figure 5). Additionally, in animal experiments, the complex light chain and the corresponding antigen increased intracellular calcium on murine dorsal root ganglion [62]; this suggests that not only the entire antibody-antigen complex can interfere with neuronal tissue surrounding the neurocysticercosis lesions, but also that the complex light chain and antigen can do the same.

Collagen

Collagen is an abundant component of the extracellular matrix that blocks cysticercosis invasion into neighboring brain tissue (Figure 3). In cultures of murine astrocytes, collagen did not proliferate astrocytes [63], supporting the concept of fibrosis as a protective barrier in favor of the neuronal tissue, which would form gliosis secondary to a permissive interaction between parasite and immunological cells.

Fibroblast Growth Factors

Fibroblasts among collagen fibers proliferate in a protective layer of fibrosis against the parasite, and are found close to vessels (Figures 1 and 3).

Basic Fibroblast Growth Factor (BFGF) is a potent mitogen and chemotactic factor for endothelial cells and fibroblasts, it increases after neuronal damage [64,65]. BFGF also regulates neuronal cells' proliferation and differentiation during brain maturation [66]. Fibroblast Growth Factors (acid or basic) are more potent angiogenic factors than the vascular endothelial growth factor (VEGF) or the platelet-derived growth factor [67]. Considering that fibroblast growth factors are involved in angiogenesis, wound healing, and embryonic development, they may repair damages of the infection, once BFGF is associated with endothelial cells adjacent to cysticerci [48].

Vascular Endothelial Growth Factor

Vascular Endothelial Growth Factor is a protein whose function is to create new blood vessels during the embryonic development (vasculogenesis) or new blood vessels after injury (angiogenesis).

Levels of VEGF were detected higher than controls in sera from untreated patients with neurocysticercosis [68]. Hypoxia is considered an inductor of VEGF which stimulates angiogenesis [69], as well as axonal growth [70]. Macrophages and neutrophils have been implicated in angiogenesis. Macrophages may induce the development of a vascular circuit in tumors via several angiogenic growth factors including VEGF [71]. Neutrophils would promote angiogenesis in dysplasias and tumors via VEGF activation [72]. Suggesting that NCC lesions could demand supplementary blood vessels, considering that the density of cells near to the granulomas (Figure 6) could produce an environment similar to those in tumors, in terms of cell agglomerate and hypoxia.

Conclusions

The main histological alterations in neurocysticercosis are edema, perivascular infiltrate, gliosis, fibrosis, granulomatosis and calcification. In order to protect neurons, defenses recruit mesenchymal cells from...
blood (neutrophils, eosinophils, lymphocytes, plasma cells), in the
interstitium (macrophages, epitheloid cells, fibroblasts), and in the
nervous tissue (microglia, astrocytes). A long presence of parasitic
debris leads to an environment with a high density of cellular elements
(peri-vascular infiltrate and granulomas), where anoxia and angiogenesis
may occur. A trans-regulation among cells and parasitic aggressors is
mediated by chemical messengers such as GFAP, IFG, TNF-a, eotaxin,
interleukins, antigen-antibody complex and collagen, BFGF, MCF, and
VEGF. Granulomatous lesions and fibrosis signal chronic inflammatory
reaction in NCC. Calculifications typically represent the final stage of
NCC; however, the presence of calcium deposits does not mean the
absence of host-parasite interaction.

Competing Interests
The author declares that there are no competing interests.

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