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Research Article

Neuropsychiatric Manifestations of Neurocysticercosis: A Comprehensive Review

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Abstract

Background: Cysticercosis (Ct) is a preventable and eradicable zoonotic parasitic disease secondary to an infection caused by the larva form of pig tapeworm *Taenia solium* (Ts), usually seen in people living in developing countries. However, the number of carriers in developed countries increases gradually due to globalization and uncontrolled migration. In this study, we look for information related with the pathogenesis of neuropsychiatric manifestation in patients with neurocysticercosis (NPNCC).

Method: We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "neurocysticercosis," "pathophysiology of NPNCC," "immunology of NPNCC" OR "dysfunctional mitochondria in NPNCC" "dysbiosis in NPNCC."

Results: All selected manuscripts were peer-reviewed, and we did not find publications related to pathophysiology of NPNCC.

Comments and concluding remarks: We hypothesized the role-played dysfunctional mitochondria, neuroinflammation, dysbiosis on the pathogenesis of NPNCC.

Keywords: Neurocysticercosis; Physiopathology of neuropsychiatric manifestations; Schizophrenia; Bipolar disorder; Cytokine storm; Neuroinflammation; Microbiome

Introduction

An adult tapeworm is developed in the small intestine of the human definitive host after ingesting *Taenia solium* cysticercus from unfreezing/undercooked contaminated pork meat. When pigs or human beings ingest eggs/proglottids, the oncospheres hatch in the gut mucosa and penetrate the intestinal wall before disseminating to almost all the body except thing membranes, narrow cavities, hair, nails, cartilage, bone tissues or the adrenal gland. When the parasite invades the brain parenchymal, ventricular system, subarachnoid space, spinal cord, or optic nerves to form cysticerci, it is named neurocysticercosis.

Cysticercosis (Ct) is a preventable neglected zoonosis but eradicable parasitic disease secondary to a cestode infection by the larva form of the pork tapeworm *Taenia solium* (Ts), most often seen in people living in developing countries. Ct can infest any internal organ in humans and pigs, excluding the hair, nails, bone tissue, epidermis, cartilage, and the adrenal gland. When the cysticercus is in the cerebral parenchymal, intraventricular system, Subarachnoid Space (SAS), cerebellum, brainstem, optic nerve, or spinal cord, then it is best known as Neurocysticercosis (NCC), and the often-clinical manifestations are headache and epileptic seizures/epilepsy among other less frequent symptoms and signs [1-5]. Epileptic Seizure (ES) disorder and Epilepsy (Ep) are the most common symptoms of Intraparenchymal NCC (INCC). We performed more than ten epidemiological investigations in rural areas around Mthatha (South Africa), confirming that NCC is the leading cause of secondary epilepsy. All ES and Ep respond very well to first line Antiseizure Medication (ASM) and Antiepileptic Drugs (AED) [6-15]. Likewise, lack of available AED due to COVID-19 restrictions or other reasons, including financial constrictions and poor compliance, leads to Status Epilepticus (SE) complications. Despite this, patients presenting refractory epilepsy secondary to NCC without other causes were never seen in our region in the past 25 years. The most used ASM are benzodiazepine, and the commonest AED are valproic acid and carbamazepine. Levetiracetam is used only in tertiary hospitals and is not available in our rural areas [16-19].

As mentioned before, humans are the final host for the adult tapeworm (taeniasis), whereas humans and pigs can be intermediate hosts carrying the cysticercus (larval form), a cyst-fluid-filled membrane vesicle with an eccentric scolex inside. When these cysts are ingested by undercooked contaminated pork meat, they go to the gut, where scolex evaginates, and are attached to the intestinal mucosa wall by 2

crowns of hooks, avoiding being expelled out of the intestine by peristaltic movement. At the gut, one or a maximum of 2 parasites mature into a 2 m–4 m length tapeworm, constituted by a scolex, neck and 1200 proglottids. Gravid proglottids contain between 600 to 2000 fertile eggs, which pass into the soil after defecation on alternating days if the person is not constipated or has diarrhoea. In impoverished countries or economically poor regions inside of advantageous countries (like our area), access to clean and safe water is not possible and predominates poor sanitation, poor food/personal hygiene, poor educational health, high level of poverty, and free-roaming pigs with access to human faeces contaminated by Ts eggs, the incidence/prevalence of NCC is notably high.

When the proglottids or eggs are ingested by contaminated water, food or *via* the faecal-oral route, the embryos are released from the egg into the gut and pass through the gut mucosa to the blood flow, which carries them to the target tissues, where they are transformed into cysticerci. Like human beings, pigs can ingest eggs and develop porcine cysticercosis. Person-to-person transmission is relatively standard and explains how non-eaten pork people are infected and why the disease is present in developed countries without free-range pigs and even in places where the 4 stages of cysticercus in the brain parenchymal have been identified [12].

Recently, we reviewed several novel aspects of NCC associated with COVID-19 and HIV, the autoimmunity, meningeal lymphatic, glymphatic drainage, and the role of activated OLG/OPC/NG2 in the pathogenesis of NCC clinical manifestations/complications/outcome. As we documented before, activation of microglia and astrocytes is at the centre of NCC neuroinflammatory pathways either directly or indirectly due to their secretion of proinflammatory cytokines, upregulation of BBB disrupting proteinases and formation of an inhibitory glial scar [20-27].

Recently, we commented on the role played by Oligodendrocytes (OLG), Microglia (Mg), Pericytes (Pc), Oxidative stress (OS), pro/anti-inflammatory cytokines/chemokines, among other autoimmune elements, on the pathogenesis of NCC [18,28-41]. However, we never investigated the neuropsychiatric manifestations seen in patients with NCC. In 1947, Brotto reported that psychotic disorders were present in more than 15% of cases with NCC [39]. In 2004, Mishra and Swain reported that frontal lobe lesions due to NCC may lead to disinhibition, irritability, mania-like symptoms, impaired judgement, and personality changes [40]. Two years back, Batra et al., (2021) documented that temporal lobe injury caused by NCC may be associated with mania in 2.6% of patients infected by *T solium*/NCC and reported a case presenting bipolar disorder [41,42].

The most everyday Neuropsychiatric Manifestations of NCC (NPNCC) reported worldwide are depression, mania, reversible cognitive decline, schizophrenia, personality changes, and visual hallucinations depending on the location of the pericystic lesion apart from other neurobehavioral disorder related to the medical/surgical approach of NCC and its comorbidities seen in up to 15% of reported cases [43].

Other authors found that 8.6% of British soldiers with NCC returning from India in 1960 presented psychiatric manifestations such as affective disorders, schizophrenia, and hysteria [El-Khady], and 18.4% of cases with NCC presented chronic psychiatric disorders in Venezuela [44]. Other publications regarding the NPNCC reported the clinical features/imagenology findings/treatment of cognitive declines, reversible dementia, acute psychosis, and the pathogenesis of the NPNCC [45-53].

Last year, Ahmed and collaborators reported a patient presenting NPNCC characterized by psychosis. After reviewing the medical literature, they found 21 similar cases (13 males and 8 females) with lesions affecting the right cerebral hemisphere (60%) without pathognomonic neuroimaging findings and explanations for the pathophysiology of NPNCC [54,55].

Recently, it has been established that Mt is the only organelle that contains its genome (mtDNA) encoding elements of the Electron Transport Chain (ETC), several investigators have been working with profound dedication to elucidate the relationship between Dysfunctional Mitochondrial (DMt) and NP manifestations and the critical role played by Mt in both disorders and normal health conditions have been reported taking into account that the functions of Mt are not limited to produce the necessary energy (ATP) to support almost all metabolic functions apart from calcium/iron homeostasis plus production of hormones, neurotransmitters, lipid biogenesis, Ca^{2+} clearance, iron-sulfur (Fe-S) clustering and Ap. The most critical components of the Mt are the Inner (IMM) and Outer Mt Membranes (OMM) separated by Inter-Membrane Space (IMS). Normal Mt function needs, fission events (GTPase dynamin-1-like protein), and fusion (mitofusin ½ optic atrophy-1) between individual organelles must be modulated. On the other hand, ETC has 4 different complexes components (I, II, III and IV), cytochrome C and coenzyme Q. It is also well known that some complexes (I, II and IV) can generate a proton gradient through IMM used by ATO synthase to produce ATP which is known as Oxidative Phosphorylation (OXPHOS)/Mt encodes 13 polypeptides while ROS is produced as byproducts. As we commented in a previous publication, hyperproduction of ROS leads to protein/lipids oxidation/Aph/Ap/Np/NI, which has been supported by other authors [36,37]. It has been proved that more than 1,500 types of Mt proteins participate in mtDNA maintenance, dynamics, bioenergetics, import of protein inside the organelle, and ion channel functions [56].

Most of the ATP used by cell metabolism all over the human body is produced by Mts, which are affected in depressed patients confirmed with MR spectroscopy and represented by abnormal levels of N-acetyl-aspartate, Adenosine Diphosphate (ADP), Phosphocreatine (PCr), and ATP [55].

The frontal pole is the most evolutionary advanced and largest cytoarchitectonic region of the human cerebral

cortex (Brodman area 10, BA10). Compared with adjoining areas, BA10 has more dendritic spines and extensive connections, mainly with areas of higher-order association (high level of input integration). In adult persons presenting BP/SCHIZ, reduced BA10 grey matter thickness, reduced BA10 cortical surfaces area, heightened BA10 resting-state activity and dysfunctional connectivity to sensory/association areas/subcortical regions/dysfunctional neurotransmitter-related genes/abnormal pattern of blood flow (downregulated HTR2B), disturbed dopamine function (DRD2-3-4), nominal decrease of Catechol-O-Methyltransferase (COMT) enzymes, reduced Somatostatin (SST) expressed in GABAergic interneurons, increased Gephryin (a postsynaptic scaffolding protein), upregulation of glial fibrillary acidic protein (an intermediate filament), astrocyte expression (excitotoxicity), increase intracellular calcium signaling, nominal elevation of Glutamate Metabotropic Receptor 5 (GRM5), increased Monoamine Oxidase B (MAOB), and upregulated Mt GABA transaminase have been reported [57].

Recently, other authors described an imbalance in the ratio and dysfunctional stage of regulatory T cells (Tregs), T helper (Th) 1-2-17 cells (T cell-mediated immunity disorder) and intracellular signaling, hormone production, and microbiomes in patients presenting BD with episodes of major depression, mania or hypomania seen in more than 1% of the general population worldwide [56].

On the other hand, other investigators have established that the prime source of NC/GC energy is Mitochondrial (Mt), which are highly dynamic organelles in charge of Ca^{2+} homeostasis, regulated CD, and forming a network with the capacity to span throughout the cytosol and to be involved in the pathophysiology of depression which is characterized by alteration in the NC/GC neurotransmission, metabolism, and neuroplasticity [57].

The central aid of this review is to answer the following research question: What is the current knowledge about the pathogenesis of the Neuropsychiatry Manifestations in Neurocysticercosis (NPNCC)?

Methodology

Looking to answer the previous research question, we performed a comprehensive search of EMBASE, Medline, Cochrane Library, Scopus, PsycINFO, Global Health, and Health Management Information Consortium to identify articles published between January 31, 2003, and July 31, 2023, followed by hand-searching of relevant journals.

Search strategy for this review

A systematic online search of manuscripts published from January 01, 2000 to July 31, 2023, was conducted using the selected databases. Two different searches were launched to cover the IS associated with I-SNCC infection and how Mg works in this pathological process. Therefore, we screened all publications related to the issues under the search terms "psychiatry in NCC," "psychosis and NCC" [MeSH], "bipolar disorder and NCC" [MeSH], "pathophysiology of NPNCC" [MeSH], "mitochondrial disorder and NPNCC" [MeSH]. Then, we identified all studies that were relevant to these issues. Additionally, we carefully checked the references/bibliography/citations of each included manuscript. Later, we widely searched: Global Health, CINAHL, Cochrane Library, Health Management Information Consortium, Web of Science (Clarivate Analytics), EMBASSY, MEDLINE (Ovid), and Scopus (Elsevier). The predominant intention was to select the original research studies related to our search strategy. Following an accurate, confident peer-review process, we selected full-text written in Spanish, Portuguese, and English.

As previously cited, all papers were retrieved using MeSH, and we only included aspects within the current work scope.

Inclusion and exclusion criteria

We also selected randomized controlled trials or quasi-experimental studies published in peer-reviewed journals related to the search strategy. However, some studies were excluded if they evaluated interventions for other parasitic infections, other infections, or vascular problems because their aetiologies differ from *T solium* infection. In addition, the review was also limited to studies involving adult patients and published in Spanish, Portuguese, or English. Documents reporting confidence (classified as an absence of significant biases) and original data on IS associated with NPNCC were eligible for inclusion.

Conference proceedings, textbooks and published abstracts were excluded because of a lack of information on the methodology used. Case series with less than 20 participants, review papers without original data and letters to the editor or editorial without an original date were rejected.

Study selection

We performed the literature search and scanned all articles by title and abstract. LdeFIV and HFS independently screened articles for eligibility. It was followed by a discussion to establish consensus on which studies were included, mainly when there was ambiguity.

Quality appraisal

Four areas of study quality were assessed: Selection bias, study design, health status, blinding process, reasons for dropouts or withdrawals, and data collection methods. In addition, LdeFIV independently carried out a methodology quality assessment and then verified by HFS/TD.

Data extraction

A data extraction mechanism was developed to extract research data about the setting, study design, demographic profile of patients, methods, measurement tools, timing of assessments, and outcomes. The screening process was performed using an Excel® spreadsheet (Microsoft Corp., Redmond, WA). In addition, crucial information was extracted from either the primary article or an earlier published manuscript on the intervention for secondary data analysis studies. LdeFIV and HFS conducted the data extraction independently; the consensus was achieved through discussion among the authors.

Methods of analysis

Extracted data were initially synthesized using textual descriptions to determine the characteristics of the selected studies, and then they were grouped, clustered, and presented in tabular form.

Study and cohort selection

We select prospective and retrospective case reports, cross-sectional studies, cohort studies, case-control studies, case series, reviews, controlled clinical trials, and meta-analyses releasing data on inclusion criteria.

Data collection process

The selected information is extracted from each manuscript with Microsoft Excel in a structured coding scheme. The data collected included NPNCC, Mt/NPNCC, Mt/RCD/OS/NPNCC, clinical features, population size, age distribution, and the investigations used to confirm the final diagnosis when applicable. In cases where there was uncertainty regarding the interpretation of the selected data or how it could be used, we analysed the situation until we arrived at a mutual agreement. Some corresponding authors of selected primary studies were contacted by email when the reviewed article contained unclear or missing information on the study design or their reported results.

Data synthesis and analysis

In some publications, we used Cochran's Q test to assess homogeneity across studies, and the I2 index to summarise the total variability in proportion due to between-study variation was omitted. Our study used aggregate data when necessary.

Quality Assessment of Selected Publications

Initially, all studies were screened for bias using the Jadad scoring system mainly applied to assess the methodological quality of controlled trials (randomization, masking, accountability-withdrawals) Moreover, included only those with Jadad scores ≥ 4 for further assessment [58].

Results

Literature search

A total of 3871 manuscripts were of sufficient quality to be selected for the first screening. Figure 1 shows the number of articles selected in each database and included in the level of bibliographic research and the main reasons for exclusions. During the screening phase, nearly three-quarters of the manuscripts were excluded. An additional rest of the articles were excluded during the next phase, all of which (n=0) did not show clinical evidence of the pathophysiology of NPNCC analysis or did not confirm the diagnosis of NCC by neuroimaging. Therefore, no articles were included in this review because they did not afford the pathophysiology of NPNCC. From the beginning, all selected studies were peer-reviewed publications, and no one met all inclusion criteria on NPNCC. Therefore, there has never been a systematic review of pathophysiology in patients presenting NPNCC. A flow chart for the literature searched is shown below.

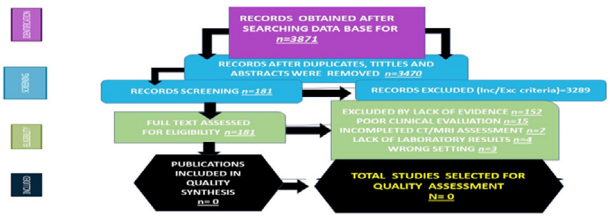

Figure 1: Flow diagram of included articles

Study characteristics

The ethics committee did not consider reviewing this study because it did not include bioethical implications. Most studies (79.1%) were published in the last 4 years. In South Africa, 49.44% of the population was HIV-positive, and 59.2 % were female. Most investigations were conducted in the United States of America/Canada (42.1%), followed by Asia (39.5%), European countries (12.7%), and Africa [5.7]. Most studies (77.3%) focused on people older than 18 years. The total of publications identified was n=3871; after duplicate removal, n=181; after full text excluded, n=0; for quality synthesis, n=0; for quality assessment, n=0.

Comments

We grouped our series of cases with NCC in 4 stages at the brain parenchymal, named: vesicular (stage 1), which is characterized by a translucent wall with transparent fluid and a viable invaginated scolex with intact membrane, no-host immunological reaction; therefore, no neuroinflammation (NI) around the cysts. Colloidal (stage 2): Here, we see the dying process of the parasite commonly before 5 years of entry, characterized by a cyst with a thick wall, turbid fluid, and a degenerating scolex inducing a host inflammatory response. Here, the intra-cystic fluid becomes turbid compared with the CSF density. The damaged membrane leaky liquid antigens damage the BBB, leading to vasogenic oedema surrounding the cyst. In this stage, the neurological manifestations are more evident due to the direct/indirect effects of the released parasite's antigen. Granular/nodular (stage 3): Decrease surrounding perilesional oedema, and the cyst begins to retract, but the enhancement persists and is characterized by a cyst with a thicker wall, degenerated scolex, and little associated inflammatory response Calcified (stage 4): In some cases, perilesional oedema can be present, all structural characteristic of the cyst disappears, and the remnant material is transformed into a coarse calcified nodule (Figure 2) [1-29].

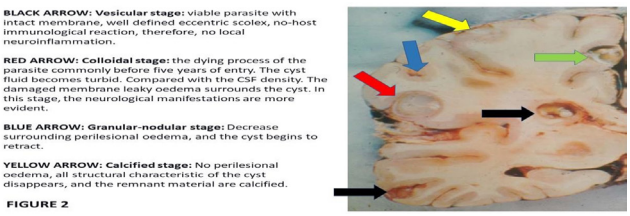

Figure 2: Coronal section of the cerebral hemispheres showing all stages of intraparenchymal NCC

We hypothesized that in cases with NCC/BD, the T lymphocytes subset (Th1,2,17 and Tregs) changes promote alterations in cytokines/chemokines production, which can explain why IL-6 levels are high, Th1 chemokine receptor-5 is downloaded, Interferon-gamma (INF-γ) is reduced, and Th2 (marker IL-4) is upregulated in patients with BD reported by Chen et al., (2023) [59]. Therefore, we assumed that Th1/Th2 shift in NPNCC typified as BD. Based on the knowledge that the relationship among Tregs and Th17 regulates the withe matter microstructure of main tracts in the prefrontal-occipital, temporal-frontal-occipital, and interhemispheric connections which are extremely important for emotional and cognitive brain function, we hypothesized that that brain injury on the areas caused by the colloid/nodular-fibrotic stage of the *T solium* NCC may initiate the process to further developed NPNCC including BD. As we commented in previous publications, the NI process caused by proinflammatory cytokines/chemokines elements also causes a reverse effect, leading to increased production of the same elements, causing direct damage of the BBB with the consequent bidirectional passage of inflammatory elements and additional pericystic surrounding NC/GC damage impacting the local network connections/synaptic transmission/NC-GC survival leading to memory/learning impairment.

We also hypothesized on the role played by a brain-derived neurotrophic factor (BDNF as neurotropic producer) in neuroplasticity/neuro-regeneration/regular NC-GC function/impaired CD4+ T-cell activity, which reduces BDNF expression in the CNS may promote NPNCC as have been reported by other authors in cases presenting BD although under different circumstances [59]. Based on the well-known role of cytotoxic T cells (CD8+ cells) in the immunomodulatory cellular immunity seen in NCC killing perilesional injured cells, we hypothesized that CD8+ T lymphocytes are closely related to NPNCC presenting as BD. Other investigations have revealed that the affected Mitogen-Activated Protein Kinase (MAPK) signaling can be associated with mood disorders and plenty of cellular processes like proliferation, differentiation, activation and Ap contributing to the neuroimmune disorder reported in BD since 2007 by Raman et al., (2007) [60]. We hypothesized that the 3 primary cascades of MAPK known as C-Jun amino-terminal protein kinase/stress-activated protein kinase (JNK), Extracellular Signal-Regulated Protein Kinase (ERK) and p38 are involved in the pathophysiology of NPNCC mainly in cases presenting BD which characterized by low JNK levels in lymphocytes, phosphorylated p38 and ERK1/2 enzymes and increase concentration of p-ERK (phosphorylated protein) in CD4+ and CD8+ T cells contributing to the immune/inflammatory imbalance reported in cases with BD [59].

Modifications in the NF-κB reported in NCC in previous publications [19,29,36-38] have been associated with BD affecting the HPA axis/stress/neurogenesis responding to several stimulations and phosphorylation of p65 subunit (p-p65) and T cells expression [61,62].

Based on the involvement of the two-way communication *via* gut microbiotas-brain axis in the NC-GC/functions/development/regulation/ageing and cognitive activities, we hypothesized that dysbiosis caused by an imbalance in the gut microecology (Bacteroides-Prevotella group/Enterobacter spp) might cause immune disturbances represented by T-cell ratio event leading to NPNCC as has been reported in some cases of BD although different environment and supported by many animal investigations proven the interrelationship between immunity/cognitive functions/behaviour and microbiome [63,64].

Based on our previous reviews on the role of OS in NCC and the increased level of LP biomarkers like malondialdehyde, inflammatory cytokines, dysfunctional autoimmune response, and pro-atherogenic lipid profile seen in those cases, we hypothesized that they are also involved in the pathogenesis of NPNCC which can be supported by the postulates that establish the close relationship between BD and autoimmune disorders such as SLE, MS, RA, psoriasis, and inflammatory bowel disease [65]. Considering that patients with BD are more likely to get infectious diseases, including hepatitis B/C and HIV, we hypothesized that cases presenting NPNCC may have a more intense dysfunctional immune response than the general population, including T-cell defects [66-71].

Brief comments on depression/mitochondrial/neuroinflammation and NCC

Some authors have established that in the brain of patients with depression are damaged Mt membrane proteins, lipids, NI, impaired expression of Mt-related genes, OS, disruption of ETC, and Ap [58]. We hypothesized that the earlier parameters are present in cases presenting NPNCC plus PANp due to dysfunctional Mt-derived ATP/Na+-K+-ATPase activity. We also speculate that NPNCC characterized by depression is closely related to disruption of the HPA axis in control of stress as a consequence of disturbance of monoamines (serotonin/norepinephrine/dopamine) and Monoamine Oxidase (MAO) [72-74] and decreased hippocampal neurogenesis, neuroplasticity, alterations of limbic system (hippocampus, amygdala and basal ganglia), dorsomedial thalamus, prefrontal/cingulate/orbital frontal cortex, insula and dysfunctional Mt plus a reduced level of Mt AO enzymes (manganese dismutase) leading to depression which have been proved by neuroimaging (MR/PET scan) studies (Figure 3) [58].

Here, our hypothesis about the graphical representation of the working relationship between healthy myelinating OLG, damaged OLG by NCC, and OPC/NG2 with astrocytes in the presence of proinflammatory elements such as IL-1β, IL-6, TNF-α, MCP-1, CXCL-1, and NADPH under the influence of ROS affecting the drainage system (Glymphatic (GS), Aquaporin 4(AQP4), and (CA) Corpora Amora) of the brain to the cervical lymph nodes leading to the accumulation of metabolite waste. The most relevant elements involved in this process are Histone, a protein that provides chromosome with the necessary structural

support. The intranuclear DNA wraps around the histone complex leading to a compact shape. AMPK: AMP-activated protein kinase is an enzyme involved in the mechanism of cellular energy homeostasis. When cellular energy is low, it activates fatty acid uptake/glucose and oxidation. NOS: Nitric oxide synthases are enzymes catalysing nitric oxide production from L-arginine. NADPH: Nicotinamide adenine dinucleotide phosphate is a vital electron donor in all organisms, diminishing the redox balance and the power for anabolic reactions. 8-oxoG: 8-Oxoguanine is the most common DNA lesion due to ROS. miRNA: MicroRNA is a class of non-coding RNAs which act regulating gene expression by binding target mRNA to prevent protein production by one of 2 different processes. CD163: Cluster of differentiation 163 is a protein with a high-affinity scavenger receptor for the Hb-haptoglobin complex. NrF2: The Nuclear Factor erythroid 2-related Factor 2 is a transcription factor, an essential leucine zipper protein that regulates the activity of AO proteins to protect the body against OS. LRP1, is a low-density lipoprotein receptor-related protein 1 (protein-receptor of the plasma membrane involved in receptor-mediated endocytosis.

HMOX-1: Heme oxygenase 1 is a gene that encodes for the enzyme heme oxygenase 1 and mediates the first step of heme catabolism. SOD: Superoxide dismutase is an enzyme that catalyses the dismutation of the superoxide (O^{-2}) radical into ordinary molecular O_2 and H_2O_2. It is produced as a byproduct of O_2 metabolism. Lack of regulation causes many types of cell damage. NOX: NADPH oxidases are plasma membrane-associated enzymes in many types of cells mainly involved in the catalyse production of SOD1-electron reduction of O_2, using NADPH as the electron donor. PKC: Protein kinase C is a family member of protein kinase enzymes which participate in controlling the actions of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acids. NMDA: N-methyl-d-aspartic acid or N-methyl-d-aspartate is an amino acid-specific agonist at the NMDA receptor, mimicking the action of glutamate. This neurotransmitter acts at that receptor. MAPK: Mitogen-activated protein kinase is a type of protein kinase-specific to threonine, and serine is involved in addressing the cellular responses to osmotic stress, heat shock, mitogens, and proinflammatory cytokines. MAPK also regulate gene expression, proliferation, mitosis, cell survival, differentiation, and apoptosis. PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha is a protein playing a crucial role in differentiating humans from apes as a master regulator of Mc biogenesis, and it is also the primary regulator of liver gluconeogenesis. LP: Lipid peroxidase is one of the most remarkable features of regulated cell death program which is created after a series of biochemical reactions of FR where it attacks lipids containing carbon-carbon double bond mainly Polysaturated Fatty Acids (PUFA) and hyperproduction of FR (•OH) caused by excess of ferrous iron leading to LP which destroy the fluidity/integrity of the lipid bilayer cell membrane causing cell injury/damage/death.

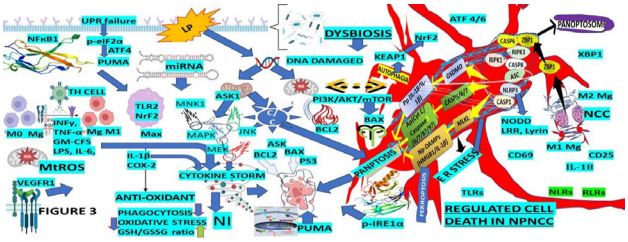

Figure 3: Graphical hypothesis of elements involved in the mechanism of microglia polarization, dysfunctional mitochondria, cytokine storm, PANptosis, and dysbiosis in cases presenting NPNCC

In previous publications [19,29,36-38], we commented on the role of Mt in Ca^{2+} signaling as buffers, modulators, and sensors of Ca^{2+} intracellular levels in NCC, including the remarkable impact on NC/GC excitability, energy production, Mt swelling/depolarization, IMM remodelling, release cytochrome c, activation of caspases inhibition of OXPHOS and PCD, the uptake/overload of Ca^{2+} inside the Mt in cases of NCC. Based on that information, we now hypothesize that the dysregulation of Mt Ca^{2+} homeostasis should be involved in the pathophysiology of NPNCC supported by the reported role of Cacna1c as a candidate risk gene for many neuropsychiatric disorders, considering that Cacna1c encodes the pore-forming α1C subunit of the L-type Ca^{2+} channel (CaV1.2), which is the major L-type voltage-gated calcium channel in the CNS. Therefore, perturbation in Ca^{2+} homeostasis/CaV1.2 signaling can cause depressive phenotypes [70].

Recently, Kathuria and collaborators found differences between Mt function in cerebral organoids in patients with SCZ with deficits in ATP production and basal oxygen consumption rate compared with cases of BD where these deficits were not found but higher expression of ion binding and transport regulation and lower number of contact points between Mt and ER in cortical neurons compared with patients with SCZ [72]. Notwithstanding, we did not find confident evidence to formulate our hypothesis about the predominant features, including the composition of vasculature and the transcriptomic pattern of cerebral organoids/gene expression in cases with NCC.

We documented the relationship between NI and NCC many times before [16-20,32-34]. However, we never commented on the role of NI in NPNCC, even though it is not a piece of novel information that NI is a necessary process involved in depression based on the investigator's report about the dysregulation of both adaptive and innate immune systems in depressed patients [73]. Therefore, we hypothesized that in cases of NPNCC high levels of circulating pro-inflammatory cytokines/chemokines and low levels of anti-inflammatory cytokines/chemokines are present, which is supported by reports on high expression of cytokines interleukin (IL)-2, 1β, IL-6, interferon-γ, and tumour necrosis factor-α (TNF-α) are confirmed in depressed patients [74-76]. Another relevant aspect is that TNF-α impairs the Mt oxidative metabolism, leading to increased production of Mt ROS in animal studies and inhibiting the ETC complex IV activity, diminishing the Mt membrane potential and consequently the ATP produc-

tion [58]. Therefore, we hypothesized this mechanism is part of the pathogenesis of NPNCC, particularly in case of depression or BD/NCC with affected mtDNA expression, OXPHOS, OS leading to NI/RCD, decreased neurogenesis/network NC/GC transmission at the cortical level plus striatum and hippocampus as we before cited.

In summary, we hypothesized that previously reported discoveries allow us to postulate that dysfunctional Mt and NPNCC are interconnected due to dysregulation of the energy metabolism, OS/RCD/dysregulate Ca^{+} homeostasis/dysfunctional electro neurophysiology/and effect of genetic variants as has been proposed by other authors in other different situations [58,77,78]. Based on the report made by Ma et al., (2023) on platelet Mt as a robust immune meditator in neurological disorders, an independent indicator of psychosis and associated with increased nitric oxide levels, dysfunctional Mt membrane potential abnormal citrate synthase activity/ETS complex and p-selectin expression in platelet of depressed cases, we hypothesized that similar process happens in cases of NPNCC [79]. We also speculate that at the marginal region of the pericystic of the colloid-nodular-fibrotic stage of *T solium* NCC, some NC/GC can receive platelet Mt transplantation through extracellular vesicles or nanotubes to keep the metabolic homeostasis, the stress signaling and the necessary local immune response to avoid the expansion of the damage to the near tissues by replaced exogenous healthy Mt from surrounding platelets as have been reported in other neuropathological conditions [79].

Brief comments on the role of microbiome in NPNCC

We hypothesized another link between NPNCC and microbiome. The role of dysbiosis in NCC was reported before, mainly in cases with associated SARS-CoV 2 infections. However, even in cases free of comorbidity, the broken balances between Firmicutes/Bacteroides play a crucial role in the pathogenesis of NCC complications/outcome [18,33]. Therefore, the gut microbiota plays a vital role through the bi-directional interaction between the intestine and the brain, and this co-evolution has proved to have affected the mental/physical health in response to dysbalanced in the gut microbiota composition, as was reported by other investigators [80]. Based on the publication, as mentioned earlier, we hypothesized that dysbiosis is strongly associated with NPNCC. In Figure 4, we summarized this hypothesis.

Brief comment on hormesis and NPNCC

Hormesis (Hm) is a novel phenomenon reported recently related to the maintenance of Mt health in all living organisms throughout the evolutionary conserved adaptive responses to nutritional/environmental/voluntary challenges looking for better tolerance to toxic/stress factors, also known as hermetic/mitohormetic strategies at Mt levels and the elements able to produce hermetic response are named hormetins. Hm is a consequence of an upregulation of stress gene response leading to the production of protective elements and an expression of the longevity-related process [81].

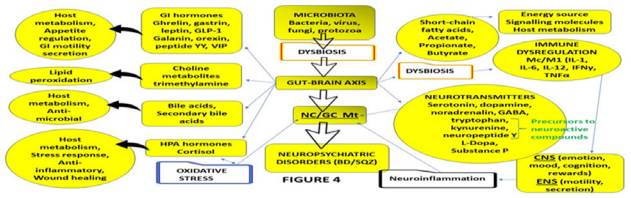

Figure 4: Schematic diagram on the relationship between microbiome/dysbiosis and pathophysiology of NPNCC and all elements involved according to our hypothesis

Unfortunately, we do not have enough evidence to prove whether the Mt stress response to NCC is characterized by the induction of specific Heat Shock Protein (HSP) genes leading to Mt Unfolded Protein Response (UPRmt). We are unsure if the HSP induces mitophagy as part of PANp/Mt transplantation. However, we suspect that HSP, if it is present, will be involved in the immunological response, proteome homeostasis, cell cycle regulation, protein translocation, accompanying protein movement across NC/GC membrane, selecting/repairing damaged proteins in remarkable proximity to the nucleus, plasma membrane, cytosol, and modulation of Mt proteostasis. In Figure 5, we summarized our hypothesis about the pathophysiology of the NPCC.

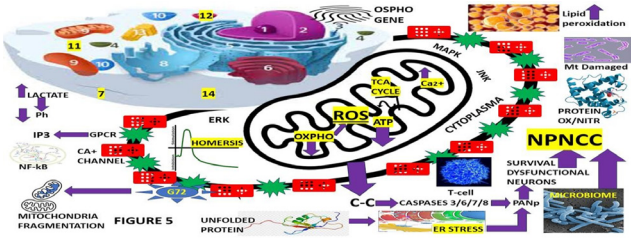

Figure 5: Our graphical hypothesis about all elements involved in the mechanism of production of the NPNCC from dysfunctional Mts and calcium homeostasis supported by dysbiosis, endoplasmic reticulum stress and homersis

Elements included: 1-nucleolus, 2-nucleus, 3-ribosomes, 4-vesicle, 5-rough endoplasmic reticulum, 6-Golgi apparatus, 7-cytoskeleton, 8-smooth endoplasmic reticulum, 9-mitochondrion, 10-vacuole, 11-cytosol (fluids contains organelles; with which comprises cytoplasm), 12 centrosomes, 13-cell membrane, NK-κB: Nuclear factor kappa B, MAPK: Nitogen-activated protein kinase, ROS: Reactive oxygen species, GPCR: G protein-coupled receptor, IP3: Inositol trisphosphate, JNK: c-Jun N-terminal kinases.

Nonetheless, knowing the pathophysiology of the colloid/nodular-fibrotic stage of *T solium* NCC, we hypothesized that Hm might induce a response to HSP (if it happens) through transcription factor/kinases stimulation as has been proposed by Nunn et al., (2020) under different circumstances [82].

Conclusion

Finally, we hypothesized that Mt dynamics/health in NC/GC can be affected by failure of the cytoprotective molecules in response to migration/binding to target genes of some proteins such as nuclear factor kappa B, PPAR,

HIF1, NRF1-2 promoting the transcription of TFAM and PGC-1α response facilitating the occurrence of NPNCC. As far as we know, no similar review has been reported in the medical literature to date. Confidence results from forthcoming well-designed research will support or reject our hypotheses.

Declarations

Consent for Publication

We did not request written informed consent because, for this study, it was unnecessary.

Declaration of anonymity

All authors certified that they did not mention any patient's name, initials, or other identity issues. Therefore, complete anonymity is guaranteed.

Availability of data and material

All data supporting this study are available on request from the corresponding author.

Ethical Approval

The WSU/NMAH Ethical Committee did not request ethical approval for this study.

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Competing Interest

The authors declare that they performed this study without any commercial, financial, or otherwise relationships able to construe a potential conflict of interest.

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Authors' Contributions

Study design: TD, HFS and LFIV. Data collection from searched literature: HFS and LdeFIV. LdeFIV/HFS/TD analysed the obtained data plus this paper's first and final draft. HFS and LFIV revised the manuscript, and HFS/TD supervised it. The manuscript writing process: HFS/TD and LFIV. Both authors have approved this version for publication.

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