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Research Article

The Oxidative Stress in Neurocysticercosis

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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 globalisation and uncontrolled migration. In this study, we look for the role played by OS in the pathogenesis of neurocysticercosis.

Method: We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "neurocysticercosis", "pathogenesis of neurocysticercosis", "NCC/OS," OR "Treatment of NCC/OS.

Results: All selected manuscripts were peer-reviewed, and we did not find publications related to NCC/OS.

Comments and concluding remarks: We hypothesised the role played by OS on the pathogenesis of NCC during the colloid/nodular stage of NCC.

Keywords: Neurocysticercosis; Oxidative stress; Reactive oxygen species; Reactive nitrogen species

List of Abbreviations

(4-PBA) 4-Phenyl Butyric Acid; (6-OHDA) 6-Hydroxydopamine; (8-OHdG) 8-Hydroxydeoxyguanosine; (A1AT) Alpha1-Antitrypsin; (Aβ) Amyloid-Beta; (ABAD) Amyloid Beta-Binding Alcohol Dehydrogenase; (AD) Alzheimer's Disease; (AIF) Apoptosis-Inducing Factor; (ALS) Amyotrophic Lateral Sclerosis; (AMPK) Amp-Activated Protein Kinase; (APP) Amyloid Precursor Protein; (ASC) Apoptosis-Associated Speck-Like Protein containing a Caspase Activation; (ASK1) Apoptotic Signalling Kinase 1, (ATF4) Activating Transcription Factor 4; (AU) Aucubin; (BACE1) Beta Secretase 1; (BAX) Bcl2-Associated X protein; (BBB) Blood-Brain Barrier; (BDNF) Brain-Derived Neurotrophic Factor; (BFA) Brefeldin A; (BID) BH3 Interacting Domain Death Agonist; (BiP) Binding Immunoglobulin Protein; (BITC) Benzyl Isothiocyanate; (BPA) Bisphenol A; (Cd) Cadmium; (CHOP) C/EBP Homologous Protein; (CL) Cardiolipin; (c-FLIP) Cellular FADD-like Interleukin-1β Converting Enzyme Inhibitory Protein; (cIAP1) Cellular Inhibitor of Apoptosis Protein 1; (CNS) Central Nervous System; COX (Cyclooxygenase); CSF (Cerebrospinal Fluid); (Cyt C) Cytochrome c; (DA) Dopaminergic; (DAMP) Damage-Associated Molecular Pattern; (DBM) Dibenzoyl Methane; (DHCR24) 3-Beta-Hydroxysteroid Delta-24-Reductase; (DHM) Dihydromyricetin; (DL-NAT) N-Acetyl-DL-Tryptophan; (DR5) Death Receptor 5; (ADRs) Activated Death Receptors; (eIF2α) Eukaryotic Translation Initiation Factor 2α; (ER) Endoplasmic Reticulum; (ERAD) ER-Associated Degradation; (ER Oxidase 1) Endoplasmic Reticulum Oxidase 1; (FADD) Fas-Associated Death Domain; (GRP78) 78kDa Glucose-Regulated Protein; (GLT-1) Glutamate Transporter-1; (GM-CSF) Granulocyte-Macrophage Colony-Stimulating Factor; (GSH) Glutathione; (GSK-3β) Glycogen Synthase Kinase-3beta; (GSK3) Glycogen Synthase Kinase 3; (H_2O_2) Hydrogen Peroxide; (HD) Huntington's Disease; (HNE) 4-Hydroxy-2-Nominal; (HO•) Hydroxyl Radical; (IL) Interleukin; (IKK) Iκb Kinase; (iNOS) Inducible Nitric Oxide Synthase; (InsP3) Inositol 1,4,5-Trisphosphate; (IMM) Inner Mitochondrial Membrane; (ITR) Inositol Triphosphate Receptor; (IRE1α) Inositol-Requiring Transmembrane Kinase/Endoribonuclease 1α; (IRI) Ischemia-Reperfusion Injury; (AK-STAT) Janus Kinase-Signal Transducer and Activator of Transcription; (JNK) c-Jun N-Terminal Kinase; (KIRA6) Kinase-Inhibiting Rnase Attenuator 6; (L-NAT) N-Acetyl-L-Tryptophan; (LPO) Lipid Peroxidation; (LPS) Lipopolysaccharide; (MDA) Malondialdehyde; (MDM2) Mouse Double Minute 2; (MLK) Mixed Lineage Kinase Domain-Like Protein;

(mHTT) Mutant Huntingtin Protein; (MPP+) 1-Methyl-4-Phenyl-Pyridinium; (MPTP) 1-Methyl-4phenyl1,2,3,6-Tetrahydropyridine; (mPTP) Mitochondrial Permeability Transition Pore; (mSOD1) Mutant Superoxide Dismutase 1; (mtDNA) Mitochondrial DNA; (NAS) N-Acetyl Serotonin; (Nec-1) Necrostatin-1; (NLRP3) NLR Family Pyrin Domain Containing 3; (NMDAR) N-methyl-D-Aspartic Acid or N-Methyl-d-Aspartate Receptor; (NOD) Nucleotide-Binding Oligomerisation Domain; (NOX2) NADPH Oxidase 2; (NLRP3) NOD-Like Receptor Protein 3; (NF-κB) Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; (NFT) Neurofibrillary Tangle; (NLRP3) NLR Family Pyrin domain containing 3; (NOX) NADPH Oxidase; (Nrf2) Nuclear Factor Erythroid 2-related Factor 2; (OMM) Outer Mitochondrial Membrane; (OPTN) Optineurin; (p38 MAPK) p38 Mitogen-Activated Protein Kinase; (PAMP) Pathogen-Associated Molecular Pattern; (PARK7) Parkinsonism Associated Diglycine; (PERK) PKR-Like ER Kinase; (PINK1) PTEN-Induced Putative Kinase 1; (PPAR) Peroxisome Proliferator-Activated Receptor; (PUMA) the p53-Upregulated Modulator of Apoptosis; (RIC) RIPK1-Inhibitory Compound; (RIPK1) Receptor-Interacting Protein Kinase 1; (RIPK3) Receptor-Interacting Protein Kinase 3; (RA) Rosmarinus Acid; (rAAV) Recombinant Adeno-Associated Virus; (REST) Repressor Element 1-Silencing Transcription Factor; (RIDD) Regulated IRE1α-Dependent Decay; (RY) Ryanodine; (RYR) Ryanodine Receptor; (SOD1) Superoxide Dismutase 1; (TAK1) Transforming Growth Factor B-Activated Kinase-1; (TGF-β) Tumour Growth Factor-β; (V TICAM-1) TIR Domain-Containing Adaptor Molecule 1; (TLR) Toll-Like Receptor; (TNF-α) Tumour Necrosis Factor α; (TNFR1) TNF Receptor 1; (TRADD) TNFR-Associated Death Domain; (TRAF2) TNF Receptor-Associated Factor 2; (Trib3) Tribbles Pseudo Kinase 3; (TRIF) Toll/IL-1 Receptor Domain-Containing Adaptor Inducing IFN-β; (TXA2) Thromboxane A2; (TRPM2) Transient Receptor Potential Melastatin-2; (UPR) Unfolded Protein Response; (VAPB) Vesicle-Associated Membrane Protein-Associated Protein B; (VEGF) Vascular Endothelial Growth Factor; (XBP1) X-Box Binding Protein 1; (XIAP) X-Linked Inhibitor of Apoptosis

Introduction

Adult tapeworms develop in the small intestine after ingesting cysticercus from unfreezing/undercooked contaminated pork meat in the human host. When pigs or human beings ingest eggs/proglottids, then, the oncospheres hatch in the gut mucosa and then penetrate the intestinal wall before disseminating to almost all the body except thing membranes, narrow cavities, hair, nail, 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 has 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, including 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]. We performed more than 10 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]. 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 [16-25].

Like human beings, pigs can ingest eggs and develop porcine cysticercosis. Person-to-person transmission is relatively standard and explains how non-eaten pork peoples 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].

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 [26].

In 2006, we commented on the clinical features and other aspects related to Spinal Cord NCC (SCNCC), and recently we commented on the role played by pericytes on the pathogenesis of local neuro-inflammation due to NCC, the healing process and outcome of the SCNCC [27,28].

Oxidative Stress can damage proteins, lipids, nucleic acids, cells, and tissues more commonly seen involved in the pathogenic mechanism of some degenerative disorders (such as PD, AD, and ALS), malignancies, diabetes mellitus, and cardiovascular diseases [29]. Apart from that, the same author reported the role played by non-coding RNAs (ncRNAs) as a critical regulator of gene expression and dynamic function in the onset and development of OS-related diseases and NI and suggested it as a potential target for controlling the before cited pathologies through administration of natural product with high content of antioxidant favouring by their great benefits providing a low level of toxicity, side effect and biological effect on OS and NI such as Tanshinone IIA, Geniposide, Carvacrol/Thymol, Baicalein, Triptolide, Genistein, Solarmargine, Allicin, Oleacein, Curcumin, Resveratrol, aqueous extract or pulp of Açai, and Quercetin plus Canna genus rhizome, *Aronia melanocarpa*, *Zanthoxylum bungeanum*, Fuzi-Xinjiang herb pair, Peppermint, and Gingerol which are high effective against OS and NI-related disorders. Besides that, OS is closely related to AD development and affects

myelin formation and renewal, the neurophysiological function of CV/BBB, and physiological sleep [30].

It has been proven that a few can induce OS, such as drugs, lifestyle choices, air pollutants, radiation, poor diet, environmental chemicals, and genetic aspects leading to an abnormal concentration of FR, weak antioxidant protection, and Mt dysfunction causing tissue degeneration and cell ageing [31].

The principal goal of this study is to answer the following research questions.

What is the role of OS in NCC according to published information? Moreover, based on the information found to lighten the current gaps in our understanding of NCC/OS and elaborate new hypotheses to encourage other colleagues to perform a better investigation of this matter.

Methodology

A systematic search of EMBASE, Medline, Cochrane Library, Scopus, PsycINFO, Global Health, and Health Management Information Consortium was conducted to identify articles published between January 31st, 2003, to January 31st, 2023, followed by hand-searching of relevant journals.

Search strategy for this review

A systematic online search of manuscripts published from January 01st 2000 to January 31st, 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 "I-SNCC," "Mg activation" [MeSH], "Mg/I-SNCC" [MeSH], and Mg/I-NCC/IRI. 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 systematically 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 those full-text written in Spanish, Portuguese, and English-language.

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

Inclusion and exclusion criteria

We also selected randomised controlled trials or quasi-experimental studies published in peer-reviewed journals. However, the studies were excluded if they evaluated interventions for other parasitic infections, other infections, or vascular problems because their etiologies 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 SNCC 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 methodological quality assessment and then verified by HFS.

Data extraction

A data extraction mechanism was developed to extract research data about the setting, study design, demographic profile of patients, methods, measurement tools and 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 synthesised 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 IS/SNCC, IS/INCC, Mg/Mp/I-SNCC/IRI, 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 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 as usual and included only those with Jadad scores ≥ 4 for further assessment.

Results

Literature search

A total of 2973 manuscripts were of sufficient quality to be selected for the first screening. Figure 1, which 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 1226 articles were excluded during the next phase, most of which (n=0) did not show clinical evidence of NCC/OS or did not confirm the diagnosis of NCC by neuroimaging. Finally, no articles were included in this review because they did not afford the role of OS in NCC. From the beginning, all selected studies were peer-reviewed publications, and no one met all inclusion criteria on NCC/OS. Therefore, there has never been a systematic review of the role played by OS in patients presenting NCC. A flow chart for the literature searched is shown below.

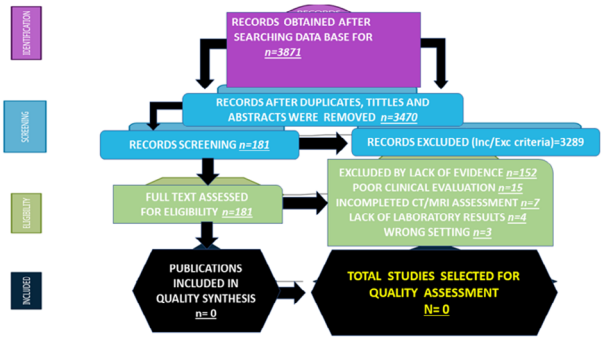

Figure 1: Flow diagram with included publications

Study characteristics

The ethics committee did not consider reviewing this study because it has not included 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%), Africa (12.7%) and European countries (5.7%). Most studies (77.3%) focused on people older than 18 years. The total of publications identified was n=2973; after duplicate removal, n=1747; after full text excluded, n=22; for quality synthesis, n=0; for quality assessment, n=0.

Comments and concluding remarks

Most studies combined case reports, cases-series, only 2 cross-sectional studies, immunological analyses, and medical literature reviews. Those reports probably did not include some affected populations because of the lack of proven diagnostic confirmation. In addition, due to scarce studies in children due to criteria diversity regarding age group, many clinical features, demography, and immune response still need to be identified.

We grouped our series in 4 stages of NCC at the brain parenchymal, named vesicular (stage 1), which is characterised 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 which is characterised 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 characterised 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 [1-29] (Figure 2).

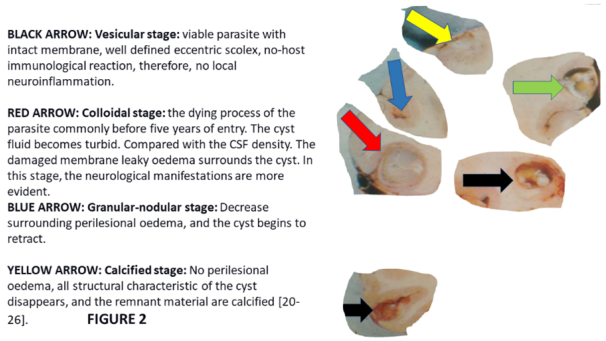

Figure 2: Coronal section of both cerebral hemispheres showing all stages of intraparenchymal NCC

As cited before, AO, like glutathione/vitamins (A, C, and E)/minerals/beta-carotene, can remove/neutralise FR by donating an electron. Some recognised factors contribute to the exaggerated production of FR favouring OS, such as lifestyle, pollution, radiation, and diet. The state of NI and their autoimmune response can trigger OS in patients with NCC, as we reported before [16-19]. However, despite the role of FR (superoxide-SO, hydroxyl radical-HR, nitric

oxide radical-NOR), including ROS and RNS in cases of NCC, plus the role played by MG, Ast, OLG, and PC determine the pathogenesis, types/nature of neurological complications and prognosis of NCC as we also commented before [30].

In this study, we like to highlight some aspects of OS related to NCC with more emphasis on the role of FR. It is well known that electrons surround the atoms' layer (shells), and each layer must be filled with several electrons. When an atom has not a filled shell by electrons, it bonds with another atom to complete its outer shell with the other electron to become stable (Figure 3).

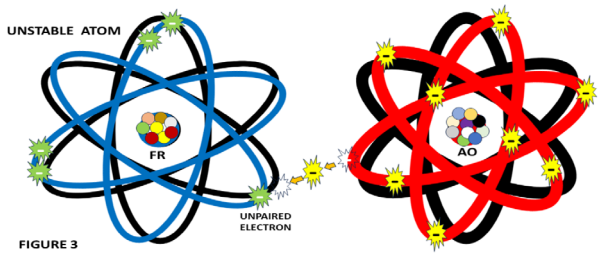

Figure 3: Simplified schematic FR/AO mechanism to create a stable atom

Since 2010 Forman and collaborators have established that cells exposition to hydrogen oxygenated (H_2O_2) triggers the overproduction of OS [31].

Based on previous author's publications and own studies, we hypothesised that the invasion of the CNS by *T. solium* is remarkably associated with OS damage of the NC/Supporting cells at the perilesional cysticerci regions, mainly affecting the OLG/OPC and axons due to oxidative damage to DNA on the expression of mRNA (transcription factors) associated with OLG myelination and OPC differentiation *via* several mechanisms of PCD, the OS damage OLG/OPC, as summarised in Figure 4 [32-34].

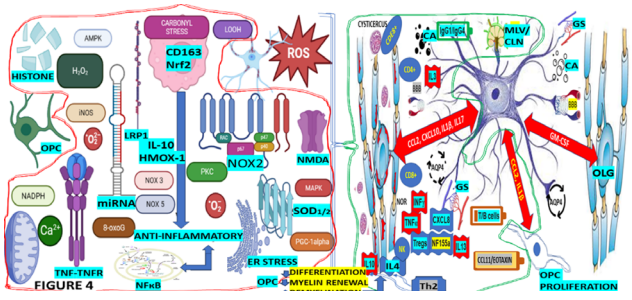

Figure 4: Hypothetical proposal about the main elements involved on the surveillance of the brain by resting mg from vesicular to colloid stage of NCC under OS mechanism. RNS=Reactive nitrogen species are a family of antimicrobial molecules whose main source is Nitric Oxide (NO) and superoxide (O^{2-}). Both are produced through the enzymatic activity of NADPH oxidase and nitric oxide synthase 2 (NOS_2), respectively; ROS=Reactive oxygen species surge from biochemical reactions that occur during respiration and photosynthesis mitochondria in mitochondria, peroxisomes and chloroplasts. It is well known that the mechanism of ATP production in the mitochondria (oxidative phosphorylation) includes the transportation of protons across the inner part of the Mc membrane to oxidation-reduction reactions. Included P2X7, CB2, COX2. During respiration, the Mc convert energy for the NC into a usable form, Adenosine Triphosphate (ATP). The process of ATP production in the Mc, called oxidative phosphorylation, involves the transport of protons (hydrogen ions) across the inner mitochondrial membrane through the electron transport chain. P2X7=P2X purinoceptor 7 (a protein) belongs to the family of purinoceptors for ATP. The receptor is commonly found in the CNS/PNS, Mg/Mp, uterine endometrium, and the retina. Ideally, concentrations of ATP will activate a homotrimer protein cation channel P2X7 receptor. In cases of NCC, we speculated that after a prudential expression time, it complexes with membrane proteins to create a wide pore at the cellular membrane, leading to increased ATP release into the extracellular milieu and PCD. Other authors have established that P2X7 receptors are widely expressed in the CNS Mg, mainly at the level of the hippocampus, amygdala, frontal cortex, and striatum, which are regions involved in neurodegenerative diseases and psychiatric disorders. We have hypothesised that the P2X7 receptor is highly expressed in NCC Mg where mediated CP/PCD, fast and reversible membrane blebbing, multinucleated cell production of exosomes, phosphatidylserine exposure, the release of microparticles formation of nitrogen species and ROS. P2X7r expression also triggers intracellular signalling pathway and binding ATP modify its state and open membrane pore for the entrance of Ca^{2+} plus other cations. In the case of NCC, we speculate that the elevated concentration of intracellular Ca^{2+} ($[Ca^{2+}]i$) activates some kinases (a protein enzyme that increases the speeds of chemical reactions) such as CaMKII, PKC, PI3K, AKT, GSK3, and ERK1/2 lead to inhibition of Ap or elevated genetic transcription of cell survival.

In conclusion, M1 Mg is a proinflammatory cell that serves as the first line of defence of the neuroimmune system arriving at the scene in a few hours after an appropriate stimulation and generating complex responses according to the intensity of the brain injury sending. In mild injury, the M1 sends a "localise me" signal followed by M2 state activation characterised by small cell body-like changes, distal branches, secretion of anti-inflammatory elements, cell tissue regeneration, nerve repair, phagocytic activity, and neuroprotective roles. In cases of intensive lesion/damage, the Mg sends a "swallow me" signal followed by an activated toxic M1, typically characterised by amoeboid modifications characterised by thick protrusions and large and round cell bodies able to remove debris of dying cells, infected cells and exert cytotoxic effects.

Nevertheless, exaggerated M1 activation leads to neuronal dysfunction and cell loss/damage/degeneration. These authors concluded that M1/M2 Mg conduct different activities responding to the inflammatory stages and environmental stimulations. Nucleotide oligomerisation domain receptors, Toll-like receptors, and scavenger receptors recognise the harmful stimulus. An endorsed level of M1 Mg has been reported in response to Lipopolysaccharide (LPS), other bacterial components or signals of CNS infections if IFN-γ is elevated.

Damaged OLG/OPC the by OS

From some years back, it is well known that OLG plays a crucial role in the mechanism of the healthy neural network, providing adequate nourishing of axons, firm structural and functional support of the nervous tissue, plus an accurate movement of neurotransmitter and electrical transmission along the myelin sheaths and keeping the necessary balance among the oxidative reactions with anti-oxidative defences. It is also known that persistent OS affect cellular differentiation and the maintenance of axonal sheath; it can trigger PANp of OPC and increase Ast expression and reactive phenotype [34]. Based on previous author's publications and own studies, we hypothesised that the invasion of the CNS by *T. solium* is remarkably associated with OS damage of the NC/Supporting cells at the perilesional cysticerci regions, mainly affecting the OLG/OPC and axons due to oxidative damage to DNA on the expression of mRNA (transcription factors) associated with OLG myelination and OPC differentiation [32-34].

Since 2008, has been well documented by McTigue and Tripathi that OLG must produce a large amount of myelin-related protein to provide the high-energy demands of myelin output requiring high metabolic rates [34].

Therefore, we speculate that during the colloid/nodular-fibrotic stage of NCC with associated myelin damage due to dysfunctional OLG/OPC could increase sensitivity to OS, leading to elevated toxic byproducts of cellular metabolism production like ROS, RNS, H_2O_2 and consequent lipid peroxidation, DNA damage, and PANptosis of OLG if proper metabolism does not happen as has been reported under different circumstances [35-37]. Based on other reports, we hypothesise that in this stage of NCC, the Mc of OLG/OPC are a target for ROS/RNS interfering with necessary proteins participating in cellular respiration, while other authors documented that OLG/NG2 glia has a small amount of glutathione (AO); therefore, they are more likely to be more damaged by OS than other supporting cells [38,39].

We also hypothesised that in NCC, the OLG/OPC have more capacity for storing an essential amount of ferritin subunits and iron than NC and other supporting cells related to the quantity of oxygen/ATP consumed to produce myelin as has been proposed by other authors under different conditions a long time ago [40]. In previous publications, we considered that NCC's colloid/nodular-fibrotic stage provides a dysfunctional iron metabolism and high ferritin concentration, mainly in patients with NCC associated with COVID-19 [17,18]. We suggest that the dysfunctional state of OLG/OPC is strongly linked to OS, mainly under hypoxic conditions seen in cases with NCC/IRI. The iron accumulated intracellularly induces ER stress, Mc dysfunction, hydroxyl radical formation, DNA, lipid, protein disruption and PANptosis, as was reported by Evans and collaborators but in different pathological conditions [41].

Recently, we reported the presence of a high concentration of ferritin in patients with NCC infected by SARS-CoV2 and commented on the role of OLG in the synthesis of transferrin (iron transport protein) which moves the iron into the NC [17-19].

Considering the postulates reported by Wellman and colleagues in 2018, we hypothesised that IRI associated with I-SNCC due to BBB disruption and increased accumulation of ROS/RNS related to Mg expression contribute to OS and mediate the intensity of NI. On the other hand, we considered that OLG/OPC loss related to OS/ERs/Ap seen in some degenerative diseases like ALS also happens in NCC based on some autoimmune similarities [42]. Therefore, we propose to protect OLG/OPC from ER stress and decrease the production of ROS/RNS to obtain a BBB free of damage diminishing the hypoxia IRI area seen in NCC. The author reported a similar postulate but for another pathological process [43].

Like some cases of neurodegeneration characterised by carbonyl and oxidative stress, which primarily affect OPC plasticity caused by limited antioxidant capacity and high metabolic demand, in cases of NCC in the colloid/nodular-granular stage, similar situations can be seen. Nevertheless, considering the impact caused by the oxidative/carbonyl stress on OPC function, the OPC-targeted therapeutic strategies in NCC/neurodegenerative disorders might be applied [44].

We also considered that OLG/OPC are remarkably exposed to ROS, mainly to $O^{2\bullet-}$ released into the intermembrane space or the Mc matrix in cases infected by *T. solium*, as suggested for other conditions [45]. Notwithstanding, during the colloid/nodular-fibrotic stage, there is an associated Mg polarisation that we commented on in a recent publication, leading to increased enzymatic ROS production in OLG/OPC in response to VLCFA, pro-inflammatory cytokines, oxygen-glucose deprivation, nitric oxidase synthase, NADPH oxidase, neuronal NOS enzymes and increased peroxisomal lipid metabolism, altogether causing a high concentration of cytosolic Ca^{2+}, ROS/RNS, Mc depolarisation and PANptosis [46-48]. On the other hand, we hypothesised that in NCC, NMDA activation triggers the production of protein kinase activating NOX2 and ROS production, as has been reported under different circumstances, being attenuated by the overactivation of glutamate receptors. Acting like buffer organelle for Fe-ions/Ca^{2+} intracellular Mc as a potent regulator of gene transcription, cell growth and protein translation machinery, play a vital role in the perilesional cysticercus linked directly to cell signalling, redox metabolism and PANp after high production of ROS/OS injury as have been reported in other neuroinflammatory/neuroimmnological conditions [48,49]. Based on other reports, we hypothesised that extracellular ROS released by M1 Mg after polarisation and Mp in NCC attack OLG/OPC has been reported happened under other circumstances [50,51]. Furthermore, we also considered that high activity of NOX complexes 1–5 (mainly NOX2) and iNOS are the primary triggers of OS in NCC inflammatory response during the colloid/nodular-fibrotic stage leading to Mg polarisation, high NOX expression, hyper ROS production affecting the maintenance of homeostasis, and increased NI-mediated OS due to weakness of the Nrf2 and AO Transcription Factor Nuclear Erythroid 2-related factor 2 leading to demyelination secondary to OLG/OPC as can be seen graphically in the figure.

All 3 isoforms of Superoxide Dismutase (SOD) are essential for the enzymatic conversion of $O^{2\bullet-}$ to H_2O_2 in the mitochondrial OLG/OPC and extracellular space. We hypothesised that the OLG/OPC development, if affected by OS, lead to poor OPC differentiation and remyelination at the pericystic region with additional intracellular ROS production by NOX_3 and NOX_5 depending on PKC signalling as has been proposed in other conditions [46]. We also speculate that reactive chemicals of OS might damage all major macromolecules, including both DNA damage (nDNA and mtDNA) in NCC with the subsequent dysfunctional OLG/OPC molecular processes, including transcription, replication, mutations or genomic instability, and reduced myelination capacity as was reported by Tse and Herrup in the process of brain ageing [51]. Currently, it is well known that by attacking the sugar residues, adding to their double bonds, or abstracting hydrogen atoms from methyl groups, both mtDNA and nDNA are injured by excessive ROS production (8-oxo-7,8-dihydroguanine [8-

oxoG]), implicating oxidative/carbonyl stress in OLG/OPC modifying its pathological outcome and interfering with all cell activities including Base Excision Repair [BER]), recombinational or Double-Strand Break Repair (DSBR), and Nucleotide Excision Repair [NER] which was reported by Zio and collaborators in 2012 [49].

Unfortunately, we could not have enough evidence to support the hypothesis of the role of histone modification (acetyltransferases, deacetylases) as the most vital link between OPC differentiation and ROS in cases of NCC.

The role of the miRNA system and the OS are closely entwined. Therefore, we hypothesised that in cases where OS deregulate both miRNA activity and biogenesis, leading to cellular stress and increase ROS production during the colloid stage of NCC, it can cause several modifications in the miRNA system like down-and upregulation of specific miRNA (miR-219, miR-138 and miR-338) which target OS-modulating genes, transcription factors, histone modification, and change in DNA methylation which promote OPC proliferation and inhibit it is differentiation [52]. In summary, OS affect the DNA methylation patterns, histone modifications and miRNA system, directly interfering with OPC metabolic process, differentiation and (re)myelination [44]. Taking into consideration author's finding under different conditions, we hypothesised that in cases of the colloid process of NCC, many cellular homeostatic processes and cell differentiation are affected due to severe dysfunctional redox-sensitive Mt in response to oxidative/carbonyl stress causing Mt phospholips membrane injury, dysfunctional enzymes, ETC changes leading to increase ROS (activator of PGC-1α signalling) production and its vicious circle: Damaged Mt produce ROS and ROS cause Mt damage impairing myelination, cell growth and differentiation until this process moves to the next stage (PANp/nodular-fibrotic/calcified) under strict/close MO/Mg surveillance [48,49]. We include in this hypothesis the role of mitogen-activated protein kinase (MAPK), LDL receptor-related protein-1 (LRP1), and AMP-activated protein kinase (AMPK) as potent activators of PGC-1α/Nrf2 after modification of energy level and state of cellular redox. It is graphically represented in the figure. Based on this postulate, we recommended introducing metformin as a therapeutic approach to patients with NCC to improve the OPC capacity of remyelination and demyelinating protection [50].

We hypothesised that the colloid stage of INCC induces a high production of ROS at the Mt level of NC and all supporting cells from Mg polarisation. ROS are oxygen-containing chemical species characterised by reactive properties molecules, FR, and non-radical species plus hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), and hydroxyl radicals ($OH^{\bullet}$), as graphically represented in Figure 5.

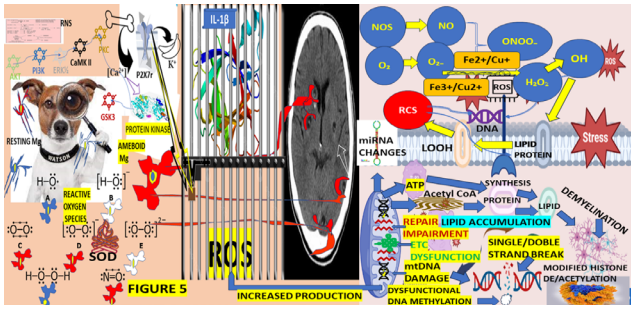

Figure 5: Graphical hypothesis on activation of PANP and PANOP during NCC/colloid/initial nodular-fibrotic stage We have hypothesised that TLRs and innate receptors also sense NCC infection to elaborate/release NFκB-dependent inflammatory cytokines (including the TNF superfamily), as we commented in previous articles, which promote inflammatory signalling through death receptors such as TNFR1, Fas, TRAIL-R, and DR3. Combined death receptors signal and TLRs *via* adaptor proteins like TRADD, FADD, and RIPK1 engage downstream signalling pathways (TAK1 and NF-κB). If TAK1 activity fails, signalling through these receptors leads to PCD *via* RIPK1. We also considered that TAK1-mediated suppression of PANoptosis can be affected by dysfunctional ES mechanism promoting a PANoptosome formation plus a remarkable downstream expression of Ap (CASP3/6/7), Pp (GSDMD), and Np (MLKL) executioners as is illustrated. In this hypothesis, we included the adaptor ASC recruiting and activating caspase 1/8 when inflammasome sensors identify their specific parasitic PAMPs.

In summary, the process of PANp and the formation of PANop happen after stimulated ZBP1, RIP1, RIP3, caspase-1, ASC, NLRP3, FADD and caspase-8 form PANop, mediating PANp. We also hypothesised that Caspase-6 regulates NCC's interaction between RIP3 and ZBP1. To deliver a comprehensive hypothesis about the TLR4 signalling pathways in Mg during NCC, we needed help finding supporting evidence on the molecular mechanism for caspase-8 activation. However, we commented on these issues (TLR4) in previous publications [16-20, 35]. Apart from the before-cited PCD, in this hypothesis, we included Fp: Oxytocic/ferroptosis, another (genetically and biochemically) type of PCD depending on iron's CNS and characterised by the increasing deposit of lipid peroxides. However, this issue will be commented on in detail in forthcoming articles. In this figure, we summarised the participation of ZBP1 (innate sensor of IAV) that triggers NI and PANoptosis and ZBP1 activation interacting with caspase-3/6/7, RIPK3, RIPK1, and caspase-8 to assemble the PANoptosome. We have hypothesised that ZBP1-dependent PANoptosome in cases of NCC also engages NLRP3 inflammasome activation and GSDMD-dependent pyroptosis as is illustrated in this figure, including activation of caspase-8 and we propose that in NCC, the caspase leads to caspase-3-6-7 activation, Ap and cleave GSDMD, while inhibition of caspase-8 cause phosphorylation of MLKL and Np. Because, in NCC, there are simultaneously different pathological processes according to the number of cysticercus, location, stage of the cysticercus, and the local immune response, we proposed that PANp is the predominant PCD for massive NCC with fatal outcome. MicroRNA (miRNA) are small, single-stranded, non-coding RNA molecules containing 21 to 23 nucleotides. Found in plants, animals and some viruses, miRNAs are involved in RNA silencing and post-transcriptional regulation of gene expression. miRNAs base-pair to complementary sequences in mRNA molecules, then gene silence said mRNA molecules by one or more of the following processes. NF-kappa-B1: Can produce a 50 kD protein (DNA binding subunit of the NF-kappa-B protein complex). NFKB is a transcription regulator activated by various intra-and extracellular stimulation by FR, bacterial/viral products, and ultraviolet irradiation. NFKB expression translocate into the nucleus and stimulates gene expression in various biological functions. However, inappropriate activation of NFKB has been associated with several NI disorders. Notwithstanding, persistent inhibition of NFKB leads to inappropriate immune cell development or delayed cell growth. NFKB is a vital regulator of the immediate-early

response to infection (viral). This hypothesis included the failure of UPR: Known as the mechanism of increasing the cellular response to molecular stimulation secondary to an elevated number of receptors on the NC/GC surface). P-elF2α: Phosphorylation of eukaryotic initiation factor-2 alpha leads to inhibition of global translation, keeping energy and in favour of reprogramming of gene activity and signalling pathways to restore protein homeostasis. ATF4: activating transcription of Factor 4 translation which regulates mitochondrial content and morphology; PUMA: p53-upregulated modulator of apoptosis, a pro-apoptotic protein (from the Bcl-2 protein family). In HN, it is encoded by the BBC3 gene. The tumour suppressor p53 regulates the activity of PUMA. p-IRE1α: phosphorylation of inositol requiring protein-1α, an endogenous substrate of endoplasmic reticulum-associated degradation. ASK1: Apoptotic-signalling kinase-1 is a protein kinase of the MAPKKK family. Its primary function is to activate the JNK and p38 MAPK signalling cascade related to NC/GC survival, apoptosis, and differentiation; JNK: c-Jun N-terminal kinase is a family member of protein kinases that plays a crucial role in stress signalling pathways related to gene expression, PCD, neuronal plasticity, regeneration, and regulation of NC senescence, p38 MAPK: p38 mitogen-activated protein kinase is an essential transducer of stress stimuli, which is activated in response to environmental and cellular stresses, including proinflammatory cytokines from Mg polarisation, DNA damage, OS, influencing cellular proliferation, cell cycle progression and PANp. BAX: B cell lymphoma-2 associated X is a protein-coding gene of the Bcl-2 family which induces apoptosis. Cyt C: Cytochrome C is involved in the electron transport chain of Mc, carrying electrons from the inner Mc membrane to another and part of the pathway for the synthesis of ATP. ATF6: Activating transcription of factor 6 has been implicated in the ER stress response pathway because it can activate the expression of GRP78, among other genes. XBP1: X-box binding protein 1 regulates the activity of several target genes involved in ER biogenesis.

Discussion

Brief comments on the role of antioxidants in NCC

The 7 different ways of action AO uses in the human body are represented in Figure 6. Based on the previous postulate, we hypothesised that in NCC, the high ROS level promotes damage of nucleic acids, proteins, carbohydrates, lipid membranes and proteins around the cystic lesion with an associated PANp; we believe that surviving neurons and supporting cells around can protect themselves utilising natural or artificial AO to scavenge ROS to avoid the chain reaction of oxidative damage and the subsequent increase protein aggregation, lipid peroxidation and DNA strand breaks, local upregulation of NI factors/proinflammatory cytokines and additional CNS tissues damage/chronic inflammation. Some authors made similar proposals for different pathological conditions [31].

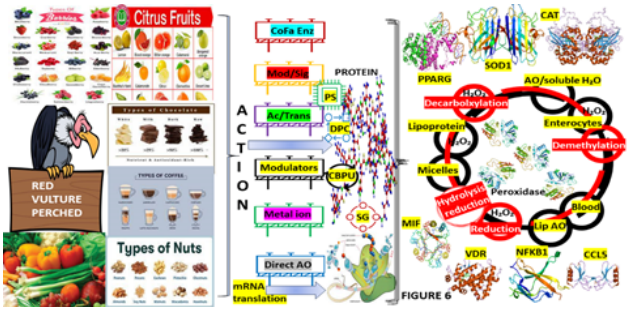

Figure 6: Graphical representation of hypothetical ways of actions of AO in NCC. Food AO can exhibit several modes of action in the body. They are

(i) cofactors of enzymes involved in AO expression,

(ii) modulators of signalling pathways,

(iii) activators of transcriptional factors which induce expression of genes involved in AO expression,

(iv) modulators of proteolytic stability and primary function of bound proteins, secondary and tertiary structure, thermal

(v) metal ion chelators (thus, inhibitors of Fenton reaction) as AO,

(vi) direct AO of oxidised substances,

(vii) participants in other physiological actions.

We hypothesised that food AO in cases of NCC might interact with proteins at four different places:

1. At the Cleft Between Protein Units (CBPU),
2. At the Shallow Surface Groove (SG),
3. At Deep Protein Cavity (DPC), where is low the accessibility of environmental solvent,
4. At the Protein Surface (PS), the charged amino acid residues are remarkably exposed.

Here the elaborated AO/protein complex change the proteolytic/thermal stability of the protein, and proper mRNA translation is required for proper protein targeting, folding, and specificity. We hypothesised that AO in soluble water passes directly to enterocytes by transportation/diffusion. From here, it is translocated to the blood flow while after digestion in the stomach, the lipophilic AO then build up micelles with the bile acid released from the patient's gallbladder, and exogenous lipids move across the epithelial surface of the gut by diffusion. The absorbed micelles are carried out *via* lymph as lipoprotein particles. Then the expiration of the physiological life of AO is excreted through the bile (liver) or the urine (kidneys). While the not absorbed AO in the gut (in white/red) move forward to the ascending colon, where microbial enzymes process it *via* hydrolysis, decarboxylation, reduction, dihydroxylation, and demethylation process creating new derivatives. AO protect NC against OS, mainly lipid components of cell membranes leading to NC/GC integrity and adequate neurotransmission. Hundreds of food AO/plasma proteins complex have a positive impact on the biochemical profile, the body composition, and oxidative and inflammatory gene expression like PPARγ: Peroxisome Proliferator-Activated Receptor gamma, which is able to modulate gene expression on ligand binding, SOD1: Superoxide dismutase, CAT: Catalase is an enzyme which catalyses the decomposition of H_2O_2 to H_2O and O_2., CCL5: chemokine C-C motif ligand 5 is a protein, also named as RANTES (regulated activation, normal T cell expressed and secreted). NFKB1: Nuclear Factor Kappa B Subunit 1 is a protein encoded by the NFKB1 gene, VDR: Vitamin D Receptor (known as the calcitriol receptor) is a component of the nuclear receptor family of transcription factors, MIF: Macrophage Migration Inhibitory Factor, also known as glycosylation-inhibiting Factor (GIF), is a protein encoded by the MIF gene and an important regulator of innate immunity.

Brief comments on other neural cell responses to OS

Under physiological circumstances and the proper concentrations, ROS contribute to tissue repair, the normal function of the neural cells supporting the neural net worth activity, angiogenesis, and cell proliferation keeping the sources of OPC and regulating the long-term potentiation among NC. Therefore, elevated concentration of ROS leads to PCD/PANp, mutagenesis, carcinogenesis, Mc dysfunction and OS, which provide a high metabolic activity of the CNS and augment the number of polyunsaturated lipids in the nervous tissue. Furthermore, the expression of oxidisable neurotransmitters and regenerative potential decreases when the levels of antioxidant enzymes diminish, promoting an elevated sensitivity of the CNS to OS. The neurons from the frontal cortex and CA1 region of the hippocampus have heightened sensitivity and specific vulnerability to OS [31].

We hypothesised that the NC under OS related to the colloid

stage of NCC might respond by producing additional ROS and pro-inflammatory elements, causing cellular dysfunction and PCD in nearby CNS tissue.

Apart from the before cited OLG/OPC, other supporting cells are affected by OS, becoming dysfunctional cells, causing neuronal vulnerability. Even though GC are strong enough to resist OS better than NC, the mechanism of neuron-glia crosstalk (neuron-neuron/glial-glia) will fail because of OS pathology.

Astrocytes (Ast) contributes to extracellular ion homeostasis, regulate the BBB, release neurotrophic factors, and support the structure/function of NC; therefore, as described in NCC in our previous reports, we hypothesised that Ast activation can secrete pro-inflammatory cytokines and ROS simultaneously, causing damage of the tripartite synapse around the cysticercotic lesion [11,12,16-18,20,45,46]. The role of Mg in NCC and IRI has been commented on widely in our previous articles [45,46]. Nevertheless, we hypothesised that, like Ast, the Mg activation also can produce ROS, affect the homeostatic set point, and lead to long-term signal pathway dysregulation in neural/immune cells passing from neuroprotective function (i.e., clearing amyloid plaques) to neurotoxic function by high production of pro-inflammatory elements, and damaging the synaptic pruning and neuroplasticity.

The role of PC/EC in NCC was also documented recently by us [28]. Here, we hypothesised that the OS could damage these particular cells affecting the Neurovascular Unit (NVU), the gene expression in EC, disrupt the TJ if the EC increases the permeability of the BBB (a risk factor for neurodegenerative disorders and NI) plus damage of the clearing system of the brain including the MLV, GS, AQP4 and CA; consequently, it increases the accumulation of amyloid-β within the Dentate Gyrus of the Hippocampus (DGH) and its deleterious effects as is represented in Figure 7 [31].

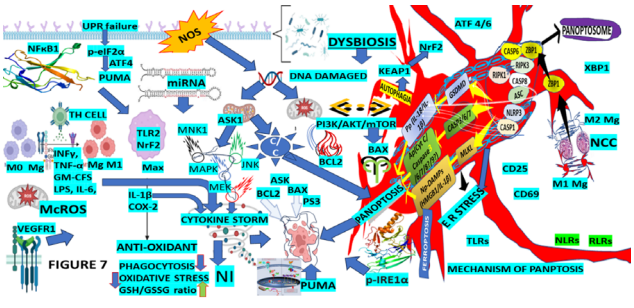

Figure 7: Graphical representation of the role of OS on OLG/OPC. Here, our hypothesis about the graphical representation of the working relationship between healthy myelinating OLG, damaged OLG by NCC, and OPC/NG2 with astrocytes in the presence of proinflammatory elements such as IL-1β, IL-6, TNF-α, 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 two different processes. CD163: Cluster of Differentiation 163 is a protein with a high-affinity scavenger receptor for the Hb-haptoglobin complex. NrF2: The Nclear 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 O2, 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.

The final neuro-element under the OS effect is Neural Progenitor Stem Cell (NPSC) relatively abundant within the DGH. The subventricular area of the anterolateral ventricles plays a crucial role in gliogenesis and neurogenesis under ROS/OS (in physiological conditions) for homeostasis, regeneration, development, repair, and neuroplasticity but under continuous OS, they cause damage to the repairing mechanism, protein dysfunction, and gene expression leading of affected gliogenesis/neurogenesis, loss of progenitor cells and morphological changes and reduced brain size. All factors previously described can be present in CNS NCC. Because we did not find enough evidence after searching the medical literature to elaborate hypotheses, we recommend performing a well-designed investigation looking for clarification about other molecular processes damaged by OS in patients presenting NCC, including lipid peroxidation, reactive species dynamics, and DNA/RNA damage and repair regulated by endogenous AO (SOD, GPs, GR, and Cat) to confirm other aspects of the neuropathology and novel therapeutic approach for NCC.

The animal investigation has identified metabolic changes in ER stress, several transcriptomic, Mt dysfunction, and OS in the brain/SC with OLG loss/demyelination by PANp after chronic high-fat diet consumption [53].

Taking into consideration the previous report, we recommend low-fat diet consumption as a critical modifiable lifestyle factor in patients with NCC to improve the myelin integrity and as a therapeutic metabolic target

for repair mechanism and myelin protection as has been suggested by other authors for different pathological conditions [54].

Unfortunately, we could not find reliable information about the contribution of native/modified OLG-derived Extracellular Vesicles (OLG-EVs) in modulating chronic NI-NCC related to allow us to formulate a new hypothesis. However, we know that in activated Mg, the central role of OLG-EVs is to contribute to the clearing system for removing cytotoxic proteins after the proteotoxic stress supported by the intracellular small Heat Shock Protein B8 (HSPB8), which facilitates autophagy and cell protection from OS. Therefore, the production of HSPB8 might benefit neurons/glial cells in cases presenting chronic NI related to NCC. Notwithstanding, the mechanism of HSPB8 secreted to provide cellular proteostasis remains unknown [55].

Recently, we documented the role of Mg polarisation in I-SNCC/IRI [44]. Now, we hypothesised the capacity of activated M1 in NCC to produce the necessary amount of hydrogen peroxide, superoxide anion, peroxynitrite or nitrogen dioxide to keep the balance between FR/AO. We also speculate on the role of ROS in membrane damage and calcium overload in the brain NCC causing dysfunctional Mt, ATP deficiency with sodium-potassium-ATPase, calcium pump disturbance, ions transportation deficiency and the consequent generation of hypersynchronous discharge of the cortical neurons leading to ES/Ep. In cases of I-SNCC/IRI, we believe that OS reach high expression by activation of enzyme Xanthine Oxidase (XO) followed by hyperuricemia, SOD radical anion and H_2O_2 by hypoxanthine as has been reported in cases of ischemic stroke due to other causes by Zhang, et al. (2017) [56]. Now we hypothesised on the shallow expression of AO (SOD/GSH) in cases of I-SNCC/IRI, facilitating the ROS attack to lipid, proteins, and nucleic acids leading to PANp like the report made by Chamorro in stroke cases of different aetiology [57]. We documented before that I-SNCC/IRI cause neuronal damage of surrounding neurons/GC, which release DAMPs inducing Mg polarisation to M1 high production of proinflammatory elements including IFN-γ activating STAT1 promoting M1 phenotype plus IL-4/IL-13 activating STAT6 promoting Mg polarisation to M2 leading to anti-inflammatory interleukin production [46].

On the other hand, we hypothesised that in I-SNCC/IRI, the expression of TLR/NF-κB signalling pathway and the induction of M1 Mg by IFN-γ produced by T helper 1 cell are strongly associated, and the Mg release ROS from NADPH Oxidase 2 (NOX2) signalling activation as it main pathway. Almost simultaneously, the regulatory part of NOX2 crosses the cell membrane binding to the xanthochroid subunit membrane induced by IFN-γ; this complex associated with Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase activity induces ROS production, causing additional damage to the cysticercus surrounding tissues.

A brief comment on antiepileptic treatment in NCC

Secondary Ep is the most common clinical manifestation of NCC in developing countries. Fortunately, Ep in NCC responds very well to first-line AED and Antiseizure Medication (ASM) [1,3,6-8,17,18,21-24,26]. However, in some uncommon situations, the Ep becomes refractory to those AED, and then the second generation of AED/ASM (SGAED/ASM) should be administered to control ES [25]. However, sometimes when antiparasitic medication is administered to kill the parasite, the frequency of ES increases even SE due to the neuroimmnological response of the dying process of *T. solium* and the creation of new zones of hypersynchronous discharge at the brain cortex leading to neuronal death; therefore, the introduction of SGAED/ASM is highly recommended. Notwithstanding, some medications like gabapentin, topiramate, tiagabine and vigabatrin enhance GABA-ergic neurotransmission, which increases OS markers depending on dose-depending way, while others like levetiracetam and lamotrigine reduce NC oxidation markers. Some authors have proved that benzodiazepines can exert a neuroprotective action after excitotoxic or OS. However, lower doses do not protect the CNS against NC damage, and high doses produce neurodegeneration. The same authors concluded that high doses of SGAED can enhance GABA-ergic neurotransmission and may cause neurodegeneration and OS. Therefore, we hypothesise that SGAED/ASM should not be prescribed in patients presenting NCC in the colloid state to avoid collateral NC damage around the lesion and to determine the accurate concentrations of endogenous AO like SOD, CAT, GPx, and GSH can be used to confirm the intensity of the OS to correct it and avoid the subsequent PANp. In cases of NCC or I-SNCC/IRI with associated OS, VGB must be avoided because of their capacity to induce OS even under normal circumstances. At the same time, GBP and TPM have an oppositive effect activating P13k/Akt/mTOR signalling pathways and reducing the OS.

Brief comments on other infections and oxidative stress

There are some common points between infectious diseases and OS; here, we summarise the most important ones and our hypotheses, comparing their pathophysiology with NCC/OS. The infection caused by Angiostrongylus cantonensis L5 leads an eosinophilic meningitis. These eosinophils use the peroxidative oxidation and (H_2O_2) generated by the dismutation of SOD produced during respiratory bursts for killing helminths. This parasite produces Acan-Gal-1 to promote resistance to OS by reducing fat deposition [58]. Some parasitic diseases can produce histological changes in the liver and gonads of the Clarias gariepinus under OS, causing histological changes in the liver and gonads of the fish by depletion of AO activity and increased lipid peroxidation in their tissues [59]. The Acanthamoeba castellanii bacterial thioredoxin reductase is strongly induced by OS with involve of the glutathione system in a complex redox system [60]. Leishmania parasites mainly invade Mp at the site of infection, which, as a mechanism

of defence, induces an oxidative burst contributing to signalling pathways, NI, autoimmune response, and promoting pathogen removal. Here the FR plays a double role in protecting against invading pathogens from one side and causing NI/tissue damage to the other. Leishmania cause a dysfunctional Mg metabolism inducing SFK signalling and NRF2 pathway activation [61]. The parasitic infection caused by Eimeria has some common points compared with *T. solium* infection regarding reduction levels of SOD, GPx and GSH; however, levels of NO, MDA, pro-inflammatory cytokine expression (TNF-α and IL6), and apoptotic genes (BCL2 and Caspase-3) are significantly elevated [62].

Kim, et al. (2023) reported that omega-class glutathione transferases (GSTOs) are crucial for maintaining viability by protecting the reproductive cell DNA of the helminth, Clonorchis sinensis by changes in the NADPH/NADP+ and GSH/GSSG and molar ratios suppressed the overproduction of ROS [60]. The alteration of CsGSTOs diminishes the GSH/GSSG ratio and reduces PSSG production under high OS [63].

Currently, the most common intestinal protozoal infection worldwide is Giardia duodenalis. This infection triggers OS mainly in immunocompromised children leading to additional body tissue damage secondary to the excessive expression of FR with highly remarkable adverse effects in children under the administration of immunosuppressive drugs [64]. Another similitude between *T. solium* and *T. cruzi* consist of that both utilise L-arginine and O_2 as substrates to induce Nitro Oxide Synthase (iNOS) and Nitro Oxide (NO) in oxido-reductase complex reaction [65]. However, one difference is the low production of ROS/NO and delayed pro-inflammatory response seen in *T. cruzi* compared with *T. solium* parasitic infection. We hypothesised that it is probable due to differences in Mg polarisation. Here, high expression of ROS affects apurinic/apyrimidinic sites making DNA susceptible to OS. Therefore, cardiac biopsies have proved 8-hydroxy-2-deoxyguanosine (8-OHdG) DNA lesions in patients with *T. cruzi* infection.

Nuclear Factor Erythroid 2 Like 2 (NFE2L2) regulates the expression of antioxidant proteins. The binding of NFE2L2 to cis-acting DNA regulatory AO Response Elements (ARE) was significantly decreased and linked to deteriorating concentrations of AO such as hemoxygenase 1, γ-glutamylcysteine synthetase, and glutamate-cysteine ligase modifier subunit in *T. cruzi* infected mice [66]. Recently Rubio-Canalejas and collaborators documented that the synthesis of deoxyribonucleotides which is the necessary monomers for repair and replication is catalysed predominantly by Ribonucleotide Reductases (RNRs). According to their metal cofactors and overall structure, these enzymes are grouped into 3 types (I, II, and III). These authors studied the regulation of RNRs through AlgR under OS. They found that Pseudomonas aeruginosa non-phosphorylated AlgR is closed related to class I and II RNR being mandatory for infection chronicity and to induce RNR activity under OS infectious conditions [67]. Staphylococcus aureus, a member of the Bacillota, is a Gram-positive bacterium, a member of the gut microbiota frequently found on the skin and respiratory tract. Quorum-sensing agr system of *S. aureus* primes gene expression for protection from OS considering agr as a constitutive protective factor.

Nevertheless, increased respiration and aerobic fermentation are caused by agr deletion associated with decreased ATP levels with an accumulation of ROS more in the agr mutant than in wild-type cells and high susceptibility of Δ agr strains to lethal H_2O_2 doses [68]. During infection of host cells, SARS-CoV-2 trigger an imbalance between increased production of FR (ROS) and reduced AO host responses, leading to increased redox stress which contributes to diminishing antiviral host responses and elevated virus-induced NI, autoimmunity, neurovascular dysfunction, multiorgan damage, and PANp related to the crosstalk between NOX, ACE2, and mito-ROS after viral entry apart from downregulation of AO genes like Nrf2 plus an upregulation of OS genes such as myeloperoxidase leading to NI and increased viral replication [69].

In previous articles, we graphically documented the role of ER in patients presenting NCC, now, we hypothesise on the role of ER as an organelle involved in folding and protein maturation with OS and NI together in NCC. We commented before that those toxic aggregates secondary to released antigens during the colloid/nodular-fibrotic stage of *T. solium* NCC, with associated ROS, PAMPs, and DAMPs, and may disrupt the process of protein folding in the lumen of ER leading to ER stress as has been reported by other investigators in patients presenting neurodegenerative disorders [70]. The aggregation of before cited misfolded/unfolded proteins inside the ER lumen of NC and NG led to ER failure in keeping protein homeostasis through ERAD/UPR-dependent NI/PANp, resulting in NC death or ER Ca^{2+} impairment of UPR components vesicular trafficking and dysregulation of some vital sensor proteins such as Inositol-requiring Transmembrane Kinase/Endoribonuclease 1 α (IRE1α), PKR-like ER Kinase (PERK), and Activating Transcription Factor 6 (ATF6) remarkable involved in UPR regulation as have been reported by Ghemrawi, et al. (2020) under different pathological conditions [67].

The same investigators reported that these misfolded proteins might interact with the substrate binding domain of BiP (under ER stress conditions), which is released, dimerised and leads to auto-phosphorylation of PERK, IRE1 α and proteolysis of ATF6 followed by UPR cascade activation to keep homeostasis and avoid overload of proteins inside the lumen of ER [71-73]. We also speculated on the IRE1α participation in some mRNA/miRNA degradation based on previous publications on the role of mRNA/miRNA in the pathogenesis of NCC, now including the 3rd sensor protein of UPR cascades (ATF6) after embedded in the ER membrane and interacting with aggregated proteins being able to release BiP at the lumen of ER and later translocate to the Golgi apparatus leading to proteolysis following by protein homeostasis after inducing

transcription of cleaves ATF6 of XBP1/ER chaperones in intranuclear space. Other authors have confirmed this hypothesis in cancer and neurodegenerative disorders [74].

Brief comments on the mechanism of OS-induced PANp

As mentioned, the nervous cell Mc releases ROS from oxidative phosphorylation as a byproduct under physiological conditions. However, dysfunctional/damaged Mc and increased calcium influx produce an exaggerated amount of ROS/RNS, disrupting the balance of AO and FR generation (ROS/RNS), leading to OS affecting the NC/GC homeostasis because they are highly vulnerable to injured by ROS/RNS and the elevated content of PUFA (arachidonic acid, cardiolipin, and docosahexaenoic acid) making NC/GC highly susceptible to subsequent outcomes and lipid peroxidation. We hypothesized that the colloid stage of NCC allows ROS/RNS to affect the peroxidation/oxidation of macromolecules like specific nucleic acids, protein carbonylation, and lipid peroxidation to Malondialdehyde (MDA). While other authors have proved that ROS allows AIF and Cyt C to be released from the inner Mc membrane of NC/GC and cause PANp.

Considering all said, we hypothesised that despite all changes made in the brain by NCC, the content of redox-active metals (iron and copper) remains elevated, facilitating an essential generation of FR and peroxidation of lipids. On the other hand, Zhao, et al. (2020) proved that Cadmium could induce an NC/GC/Mt ROS production, downregulate x-linked inhibitor of apoptosis (XIAP), and cause neurotoxicity after trespassing the BBB and diminish p53 favouring PCD in mice [71].

We hypothesised that during the colloid stage of NCC with associated increased production of FR from dysfunctional Mc in the NC/NG, the level of oxidation of macromolecules is remarkably high, mainly in patients with low levels of AO such as vitamin E/C, uric acid, catalase, SOD or more critical the AO glutathione (GSH) provoking a substantial diminishing of detoxification of FR (ROS/RNS) in the NC/NG plus decreased clearance of Aβ molecules (increased level of JNK) by GS, AQP4 and CA leading to Ca^{2+} dyshomeostasis (ER) and Ca^{2+} influx in the cytosol, reduced endogenous level of GSH, Cu^{2+}, Zn^{2+}, Fe^{3+}, increase p53, Drp1, PUMA, BAX, 8-OHdG, lipid peroxidation and neurodegeneration/PANp. We speculate that the process in NCC does not cause neurodegeneration due to its short duration and because at the following (end of nodular-fibrotic/calcified stage), healthy Mc arrives in this region *via* nano-tubules from normal nearby NC/NGs. Patients will suffer from PD, AD, ALS, or HD if it has not happened, as other authors think [75].

Brief comments on novel therapeutic approaches

In the near past, we had considered the harmful effect caused by a disruption of gut barrier permeability in patients presenting NCC/COVID-19 due to dysbiosis and secondary brainstem damage. We hypothesised that the associated OS is one of the main contributors to this process caused by gut epithelial cell PANp because of mass secretion of ROS by affected Mc.

A food plant medication (Gastrodia elata polyphenols) from China has been introduced into the arsenal of therapies to approach OS due to its protective action by increasing cell viability, intracellular AO enzymes and reducing lactate dehydrogenase infiltration, decreasing MDA, ROS production, mitochondrial membrane potential, NI and PANp [76]. Recently, Liang and collaborators have proven the efficacy of Baicalin which is an ingredient of Chinese traditional herbal medication with potent anti-cancer, anti-inflammatory and AO properties of protecting intestinal wall against hydrogen peroxide (H_2O_2), avoiding damage of the intestinal porcine enterocytes of neonatal unsuckled piglet (IPEC-J2) by upregulating Claudin1, protein expression of ZO-1, Occludin, and more critical mRNA. Bai therapy impeded H_2O_2- induced ROS, MDA super production, and elevated SOD, CAT, and GSH-PX effects as AO.

Conclusion

Almost all authors generally accept that non-coding RNAs (ncRNAs) can be regulatory or housekeeping non-coding protein genes with transcriptional, post-transcriptional and epigenetic functions represented by various types like snRNA, snoRNA, rTNA, IncRNA, tRNA including short ncRNAs such as miRNA which has been graphically represented in Figure x plus siRNA and piRNAs. We hypothesised that non-coding RNA might act as modulators in response to OS and mediate ROS production, PCD/Cell PANp/NI in cases of NCC, as confirmed in other pathological processes by some investigators.

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' Contribution

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

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