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Research Article

Novel Hypotheses on the Role of Oligodendrocytes in Neurocysticercosis and their Implications for Drug Development: A Comprehensive Review

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Abstract

Background: Cysticercosis (Ct) is a preventable and curable zoonotic parasitic disease that results from a cestode infection by the pig tapeworm *Taenia solium* (Ts). Neurocysticercosis (NCC) is the term used to describe cysticercus that is located in the brain parenchymal, intraventricular system, Subarachnoid Space (SAS), cerebellum, brainstem, optic nerve, or spinal cord. Less commonly occurring symptoms and signs include headache and epileptic seizures/epilepsy. We are in search for a publication about the function of oligodendrocytes in the pathophysiology of non-communicable cancers (NCCs). We examine this matter and provide some theories on its function and its relevance in the pathophysiology of secondary epilepsy and calcified NCC epileptic episodes.

Method: We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "neurocysticercosis", "Drug Development" "pathogenesis of neurocysticercosis", "comorbidity in NCC" OR "oligodendrocytes" OR "Oligodendrocyte Precursor Cells (OPC/NG2)"; OR "Epileptic Seizures (ES)/Epilepsy (Ep)/NCC" OR "Oligodendrocytes (OLG)/ES/Ep"; OR "calcified NCC/OLG"; OR "OLG Ca^{2+}."

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

Comments and concluding remarks: We have hypothesised on the role played by OLG/OPC/NG2 on the pathogenesis of cysticercus perilesional oedema, the role of OLG/OPC/NG2 on the pathogenesis of ES/Ep and calcified NCC.

Our study identifies multiple potential treatment targets and emphasizes the crucial role that oligodendrocytes play in the pathogenesis of NCC. By concentrating on the processes of oligodendrocyte injury and regeneration, we can create more potent therapies that deal with the parasite infection as well as its neurological effects. A promising area of NCC treatment is the combination of conventional antiparasitic medications with neuroprotective and regenerative treatments.

Keywords: Drug development; Antiepileptic drugs; Oligodendrocytes; Neurocysticercosis; Oligodendrocytes; Oligodendrocyte precursor cell; KG2, Calcified neurocysticercosis; Cellular calcium influx

Introduction

The most common cause of Cysticercosis (Ct), a parasitic disease that can be eradicated and prevented, is a cestode infection caused by the tapeworm *Taenia solium* larvae (Ts). The disease is primarily observed in individuals residing in underdeveloped nations. With the exception of the hair, nails, bone tissue, epidermis, cartilage, and adrenal gland, CT can infect any internal organ in humans or pigs. Neurocysticercosis (NCC) is the term used to describe cysticercus that is located in the cerebral parenchymal, intraventricular system, Subarachnoid Space (SAS), cerebellum, brainstem, optic nerve, or spinal cord. Less frequently occurring symptoms and signs include headache and epileptic seizures/epilepsy [1–5]. Within Intraparenchymal NCC (INCC), Epilepsy (Ep) and Epileptic Seizure Disorder (ESD) are the most prevalent symptoms. As stated in many endemic countries, we conducted over 10 epidemiological studies in rural regions surrounding Mthatha, South Africa, and confirmed that NCC was the primary cause of secondary epilepsy. Antiepileptic Medications (AED) and first-line Antiseizure Medicine (AM) are highly effective in treating EDS and Ep [6–15]. Similarly, the prior premise may be changed if there is no medication available because of COVID-19 limits or for other reasons, such as low compliance and financial constraints.

However, 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 as AED valproic acid and carbamazepine. Levetiracetam is used only in tertiary hospitals and is not available in our rural areas [16-19].

Furthermore, there are significant ramifications for drug development. It may be possible to develop novel medicines that target the pathways involved in oligodendrocyte

damage and repair, so addressing both the parasite infection and the subsequent neurological damage. This would involve creating medications that encourage the growth, differentiation, and myelination of oligodendrocytes, which could help those with the condition perform better cognitively and motorly. In this setting, the fields of parasitology, neurology, and pharmacology combine to provide an ideal environment for novel therapeutic approaches that have the potential to greatly enhance the quality of life for NCC patients.

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 vesicles with an eccentric scolex inside. When these cysts are ingested in undercooked contaminated pork meat, they go to the gut, where scolex evaginates and attaches to the intestinal mucosa wall by 2 crowns of hooks, avoiding being expelled out of the intestine by peristaltic movement. In the gut, one or a maximum of 2 parasites mature into a 2 meters–4 meters length tapeworm, constituted by a neck and 1200 proglottids. Gravid proglottids contain around 600 fertile eggs, each containing an infective embryo (oncosphere), which passes to the environment in faeces 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) where getting clean and safe water is almost impossible, poor sanitation, poor food hygiene, poor educational health, high levels of poverty and free-roaming pigs with access to human faeces-contaminated by Ts eggs the incidence/prevalence is notably high. When the proglottids or eggs are ingested by contaminated water, food or any 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. We also have identified 4 stages of cysticercus in the brain: Parenchymal, vesicular, viable parasite with intact membrane, no-host immunological reaction, and, therefore, no local neuroinflammation. Colloidal: The dying process of the parasite commonly occurs before 5 years of entry. The cyst fluid becomes turbid. Compared with the CSF density, it is the darkest. The damaged membrane leaky oedema surrounds the cyst. In this stage, the neurological manifestations are more evident. Granular nodular: Decrease surrounding perilesional oedema, and the cyst begins to retract, but the enhancement persists. Calcified: No perilesional oedema, all structural characteristic of the cyst disappears, and the remnant material are calcified [20-26].

Recently, we reviewed novel aspects of NCC related to its comorbidity with COVID-19 and HIV, autoimmunity, meningeal lymphatic, glymphatic drainage and the role of activated astrocytes/microcytes in the pathogenesis of NCC clinical manifestations/complications/outcome. As we documented before, activation of microglia and astrocytes is at the centre of NCC neuro-inflammatory pathways either directly or indirectly due to their secretion of pro-inflammatory cytokines, upregulation of BBB disrupting proteinases and formation of an inhibitory glial scar [27]. However, the participation of OLG in the neuro-inflammatory process associated with NCC has yet to be documented; therefore, it is the main aim of this study. We will look at the role of OLG in the pathogenesis of NCC/ES/Ep and its implication on its clinical features, response to treatment and outcome. It has unanimously accepted that OLG is a supporting cell that produces myelin sheaths which facilitate rapid action potential propagation by clustering voltage-gated ion channels into discrete domains and reducing membrane capacitance, enabling saltatory conduction from one Node of Ranvier (NOR) to the next one. Furthermore, a large part of the myelination process is intrinsic to the OLG cell, as oligodendroglia will differentiate and form myelin sheath even in the complete absence of neuronal signals if the structure to be myelinated is above a minimum threshold diameter. Furthermore, myelinating OLG wrap and elongate up to 50 myelin sheaths on neuronal axons, tailoring myelin sheath thickness and modulating conduction velocity according to developmental and activity-dependent neuronal signals [28]. Each myeline sheath layer continues the OLG plasma membrane; a single OLG increases its membrane area by many thousand-fold and grows in thickness and length, extending its innermost layer around and along the axon. The OLG's mechanism to add one membrane over the other is probably related to non-vesicular lipid transport, membrane incorporation of lipoproteins and vesicular membrane trafficking to the cell surface through membrane fusion by SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) complexes, where vesicular SNARE proteins (v-SNAREs) pair with their cognate SNARE partners on the target membrane to trigger exocytosis. How this mechanism can be considered involved in the pathogenesis of perilesional changes in NCC will be discussed later. Other authors reported the upregulation of v-SNARE isoforms VAMP3 and VAMP7 in myelinating OLG and confirmed damaged VAMP3 do not modify the myelinating process, but mislocalization of VAMP7 causes developmental demyelination and highlighted that the required SNARE-mediated exocytosis for myelination remains unknown [29].

In this review, we will focus on Oligodendroglia (OLG) as the most prevalent cell lineage component of the white matter (WM), which includes OLG Precursor Cells (OPCs), immature promyelinating OLG and mature myelinating OLG. As before, the standard myelin sheath allows speedy conduction action potential along axons and provides metabolic support from the OLG cell body to the underlying axon. Recently, we identified the OLG as a typical glial cell that can only produce myelin in the WM. Nevertheless, today, it is generally accepted that OLG, depending on their developmental origin, differentiation

stage, regional and anatomical location, gender, age group, and transcriptome, is morphologically and functionally heterogeneous in healthy people, and this pattern is different in sick persons [30,31]. Moreover, in trying to facilitate normal CNS function, OLG and their precursors are involved in several homeostatic functions, interact with neuron cells, and contribute to preserving the BBB. OLG faces different life cycle stages like origin, migration, and proliferation of OLG Precursor Cells (OPCs). Some authors highlighted their differentiation into mature myelinating OLG, establishing synaptic neuronal contact and proper axon myelination and providing metabolic and trophic support to neuron cells. The OPCs are characterised by displaying a stellate-shaped morphology and extending their processes radially on their cell body. These cells increase gradually in some CNS disorders and are named NG2 glia because of their characteristic expression of the neural-glia antigen 2 markers [32]. Based on the previous information, a research question is arising. What is the role of oligodendrocytes in NCC? Furthermore, how is OLG/OPC involved in the pathogenesis of ES/Ep and Calcified NCC (CNCC)? The principal aid of this review is to answer these interrogations.

Materials and Methods

We searched the medical publications comprehensively, looking for published medical subject heading (MeSH) terms like "neurocysticercosis"; "pathogenesis of neurocysticercosis", "comorbidity in NCC"; OR "oligodendrocytes"; OR "oligodendrocyte precursor cells"; OR "ES/Ep/ESD/NCC" OR "OLG/ES/Ep"; OR "calcified NCC/OLG"; OR "OLG Ca2+". On top of that we also searched at https://www.clinicaltrials.gov/, from the US National Library of Medicine looking for unpublished studies, using the same MeSH terms above mentioned, but applying the filters "entire articles", "full publication", and "abstract", published in Spanish, English, Portuguese or French.

Exclusion and inclusion criteria and screening process

Articles eligible to be included in this study had to meet the following inclusion criteria:

1. Human beings are involved in ethical approval.
2. The entire article should be written in English, Spanish, or Portuguese. Although abstracts written in French were included
3. The central aspects are NCC, ES, ESD, Ep, OLG, OPC, NG2, and Ca^{2+} CNCC.
4. Manuscript published in a peer-reviewed medical journal.
5. Subject focus: Studies must specifically address the role of oligodendrocytes in NCC or explore the implications for drug development targeting oligodendrocyte function.

The mandatory exclusion criteria were:

1. Publication Did Not Refer To Issues Numbered 3.
2. Letters, Medical Hypotheses, Review Articles, Medical Newspaper And All Articles That Did Not Match The Criteria Of An Original Study
3. Conference Proceedings;
4. Clinical Trials With Less Than 15 Patients Per Treatment Arm;
5. Duplicate Articles And Manuscript Written By The Same Author With The Same Data Process;
6. Publication excluding the corresponding authors. All papers were screened no less than twice (blinded).

All manuscripts presenting exclusion criteria were not introduced in the analysis, and a professional analysis discussion solved discrepancies among authors.

Database search: Comprehensive searches were conducted in major scientific databases such as PubMed, Scopus, and Web of Science using keywords like "oligodendrocytes," "neurocysticercosis," "*Taenia solium*", "drug development," and "epilepsy."

By adhering to these criteria and processes, our review aims to provide a thorough and reliable synthesis of current knowledge on the role of oligodendrocytes in NCC and their implications for drug development. This rigorous approach ensures that our findings are based on robust and relevant evidence, contributing valuable insights into potential therapeutic strategies for NCC.

Medical literature searching programmed

We selected case reports, case series, observational cohort studies, systematic reviews and meta-analyses, cross-sectional studies, and clinical trials. During the initial search, we looked for inclusive articles published between January 1, 1990, and December 30, 2022. We searched the following databases: Science Direct, Google Scholar, Medline, Scopus online databases, Scielo, Search of Sciences, BioRxiv, medRxiv and Cochrane Library. All studies were retrieved by utilising MeSH, as before cited. We only included other aspects within the current work scope.

Study and cohort selection

We select prospective/retrospective cohort studies, case-control studies, case reports, case series, review articles, meta-analysis reporting data on listed topics and controlled clinical trials.

Process of data collection

The crucial information has been extracted from each manuscript with Microsoft Excel in a structured coding scheme. The data collected included NCC, clinical features, population size, age distribution, the means used to diagnose NCC, MRI/CT scan studies for NCC, CNCC, ES, Ep, glial cell disorders, Ca^{2+} cortical metabolism and other investigations, if applicable. When there was uncertainty about the interpretation of the information obtained or how it could be used, the authors discussed the situation until they reached a reasonable agreement.

Prospective and retrospective cohort studies: These studies provide valuable longitudinal data on the progression of Neurocysticercosis (NCC) and the role of oligodendrocytes over time. Cohort studies that specifically address the impact of NCC on oligodendrocyte function and the potential for drug interventions were prioritized.

Controlled clinical trials: Clinical trials that investigate the efficacy of drugs targeting oligodendrocytes in the context of NCC were included. These trials provide high-quality evidence on potential therapeutic interventions, their mechanisms, and clinical outcomes.

Synthesis of data

Our study used aggregate data where possible, following some of the PRISMA recommendations.

Quality assessment of included manuscripts

All publications were initially screened for bias using the Jadad scoring system [33]. Trials scoring 3 or greater are considered good-quality trials (Jadad's scores range/from 0 to 5). Therefore, trials with a Jadad score <4 were not selected, while studies with a Jadad score ≥ 4 were excluded for further assessment.

By incorporating diverse study designs and cohorts, our review aims to provide a comprehensive understanding of the role of oligodendrocytes in NCC and explore the potential for developing targeted drug therapies. This approach ensures that our conclusions are based on a broad and diverse evidence base, enhancing the relevance and applicability of our findings.

Results

Study selection

This study aims to update the scientific information released about these issues. Two thousand nine hundred four manuscripts were retrieved from electronic databases until December 30, 2022. After removing irrelevancy and duplicates, 59 manuscripts were taken for full-text screening. No clinical trials on NCC were found. From all selected articles, only 4 publications delivered some information related to ES/Ep or pathogenesis of seizures and OLG disorders, and they were included for review. All selected manuscripts were peer-reviewed, and no one included all inclusion criteria on NCC/ES/Ep/OLG/OPC/NG2/Ca^{2+}. A literature search flow chart is shown below (Figure 1).

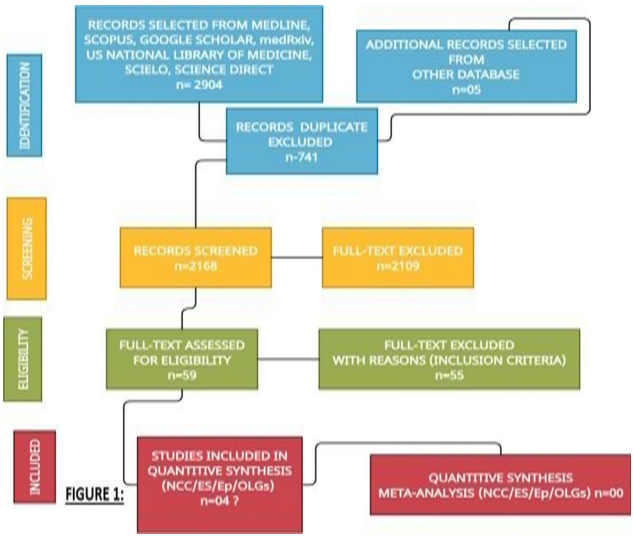

Figure 1: Flow diagram of selected manuscripts

Discussion and Concluding Remarks

The larval form (cysticercus) of the pork tapeworm (*Taenia solium*) life cycle is graphically represented in Figure 2. From time to time, we reported novel clinical features, imagenology findings, management used, and comorbidities (HIV/AIDS/COVID-19) in the medical literature, including some novel immunological aspects [18-20,27].

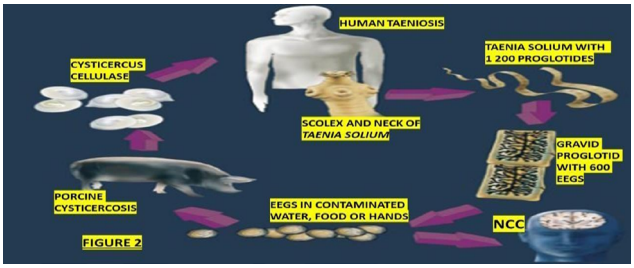

Figure 2: Show the life circle of *Taenia solium* through the primary host (human beings), the intermediate host (pigs) and the way to acquire porcine cysticercosis, human NCC, and taeniosis

The simplified representation of porcine cysticercosis can be seen in Figure 3, where free-range pigs eat human faeces contaminated by eggs and proglottid of *Taenia solium* from a person presenting taeniosis as a final host of *Taenia solium*.

Figure 3: Simplified representation of porcine cysticercosis from the primary/final host (Human beings)

Humans become a final host when they eat undercooked contaminated pork meat from free-range pigs or when people get it from places lacking veterinarian/sanitarian examination. Identifying porcine cysticercosis in the meat is relatively easy, as shown in Figure 4.

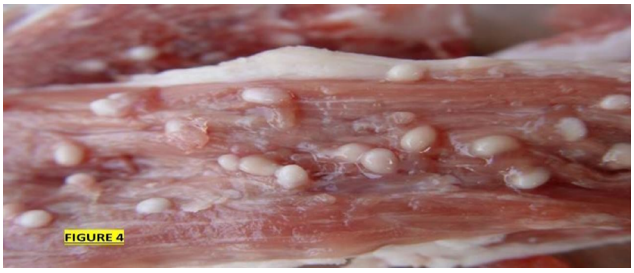

Figure 4: Show a piece of pork meat with multiple cysticerci

Unfortunately, because of poor knowledge of porcine disease, the flavour of the infected meat is not unpleasant, and because hunger is uncontrollable most of the time, some people consume this measly meat. Moreover, in most cysticercosis endemic places, the preferred way to cook the meat is boiling or braaiing because it is the cheapest method. Therefore, if the consumers digest any portion of medium/rare meat containing a single viable cysticercus, they will develop taeniasis. Why the final host develops only 1 or 2 *Taenia solium* despite the number of swallowed eggs, we do not know. We hope gastro parasitologists will shed light on this issue.

The most standard radiological presentation is the Intraparenchymal NCC (INCC), whether in the vesicular/colloid stage or nodular-fibrotic/calcified stage. Figures 5 and 6.

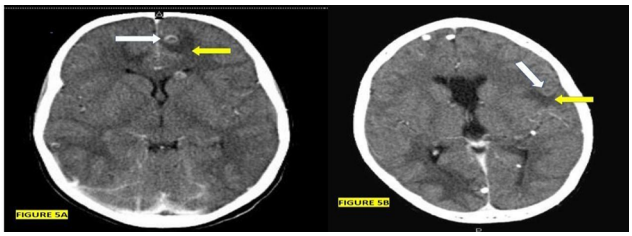

Figure 5: (A) An axial view of a post-contrast CT scan of the brain showing a ring enhancement of cysts with an eccentric scolex (white arrow) and perilesional oedema (yellow arrow); (B) An axial view of a post-contrast CT scan of the brain showing a ring enhancement of cysts with an eccentric scolex (white arrow), perilesional oedema (yellow arrow), and bilateral calcifications

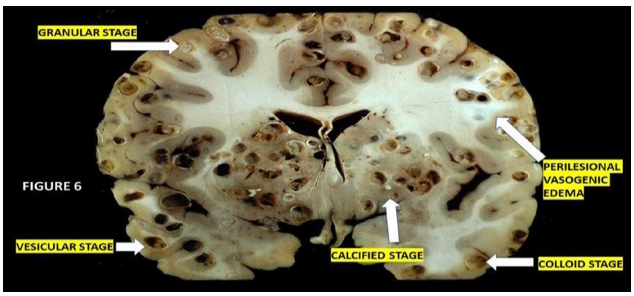

Figure 6: Coronal section of the brain showing all stages of intraparenchymal NCC

Other radiological brain presentations, such as intraventricular and subarachnoid, have been widely reported in our previous publications, but the calcified NCC is undoubtedly the most common (Figure 7).

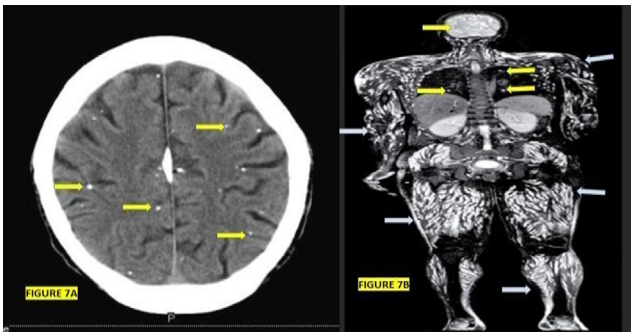

Figure 7: (A) An axial view of a brain CT scan shows bilateral intraparenchymal rounded calcifications (Yellow arrows) measuring between 1 mm and 10 mm with partial calcification of the falx cerebri; (B) Whole body CT scan: Shows tubular-shaped multiple muscular calcifications (Light blue arrows) plus calcifications on the tongue, orbit, heart, lungs, face, pancreas, thyroid, parotid, liver, spleen, kidney, psoas muscle, pharyngeal, and mesenteric lymph node. No calcified cysticercosis in the adrenal glands was observed

After analysing the shape of the calcifications shown in Figure 7, it is easy to identify the geometrical differences. For example, the calcification is parenchymal in the brain, the lungs are round like a circle, and the calcifications in the muscle are tubular. Below, we will deliver a hypothesis to explain why.

Here, we will comment on OLG's role in patients presenting NCC to answer the first research question. An essential property of the CNS is its capacity to change its structure and activity in response to external life events. Moreover, the effects and effectors of CNS plasticity are not addressed to neuronal cells only and include glial cells to provide further fine-tuned circuit function, including experience-dependent regulation of OLG. Therefore, the identified experience-driven oligodendrogenesis and myelination (adaptive myelination) is a relevant and lifelong form of CNS plasticity that must be present around cystic lesions to preserve neuronal function.

Because our brain cells are quite different from the mice, rats, zebrafish, and other preclinical animal cell models, although all scientific results from animal investigations cannot be transferred into the human nervous system's field of research, some acquired knowledge from animal studies can be applied to some investigation's protocol for neurological studies.

Checking the history of medicine, we found that in the 19th century, OLG was first described by Virchow, Deiters, and Camillo Golgi. However, the best description of Microglia (MGL) and OLGs was made by Pio del Rio Hortega (1882–1945) (Figure 8).

Figure 8: (A) Rudolf Ludwig Carl Virchow (October 13, 1821–September 5, 1902) was a German physician, writer, editor, anthropologist, pathologist, prehistorian, biologist, and politician. Known as "the father of modern pathology" and as the founder of social medicine; (B) Otto Friedrich Karl Deiters (November 15, 1834–December 5, 1863) was a German neuroanatomist. He is remembered for his relevant microscopic brain and spinal cord research; (C) Camillo Golgi (July 7, 1843–January 21, 1926) was an Italian biologist and pathologist known for his work on the central nervous system; (D) Pío del Río Hortega (1882–1945) was a Spanish neuroscientist who discovered microglia

In 1921, he was able to differentiate neuroglia into microglia after using his newly developed Golgi-Hortega modified silver carbonate staining methodology on samples of nervous tissues. The recognition of his cell's description was not unanimously accepted by most neuroscientists that year. However, in 1928, the American Canadian neurosurgeon Wilder Penfield supported his theory; soon after, everybody agreed with del Rio Hortega's postulates. His comprehensive overview of OLG and description of 4 types of OLG based on the heterogeneity/morphology of these glial cells have been internationally recognised. During this period, he was the most prominent investigator of the Spanish neurology school, leading the authority on CNS tumours (preceded by Santiago Ramón y Cajal). Based on his observations, Del Rio Hortega reported 3 different types of OLGs according to their location in the CNS as follows:

- Interfascicular OLG when the cells are aligned in rows along the axons
- Perineuronal, when they are located next to the neuronal cell bodies
- Perivascular, around the capillary vessels.

He also delivered another classification of OLG based on their 4 different morphologies type 1, when the cell is elongated by many exemplary processes arising radially towards myelinating axons; type 2, when a polygonal OLG's body has few and thick processes directed longitudinally towards to the axon, type 3 OLGs when they have a large soma and 1 to 4 processes are directed towards to the axon and type 4 when 1 or 2 processes are seen in an elongated OLGs cell body which is only present at the brainstem and spinal cord [32]. These descriptions encourage him to hypothesise on the involvement of OLGs in the process of myelin formation like Schwann cell does in the peripheral nerves. Currently, this classification is not helpful for clinical purposes, but we can use his results in our hypotheses on the role of OLGs in INCC, which will be described below. On top of that, we wish to express our gratitude for his contributions to the current knowledge of OLGs and our most resounding recognition of him as a super extraordinary and poorly recognised neuroscientist.

Dysfunctional OLGs have been implicated in the pathogenesis of Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS), but we do not know how the membrane properties of OLGs participate in their maturation from the OPC stage. However, the interrelationship between neurons and OLG Precursor Cells (OPC) has been well defined, also called NG2, by a dynamic bidirectional signalling (synaptic/extrasynaptic) regulating the beginning of OLG maturation, as seen in Figure 9.

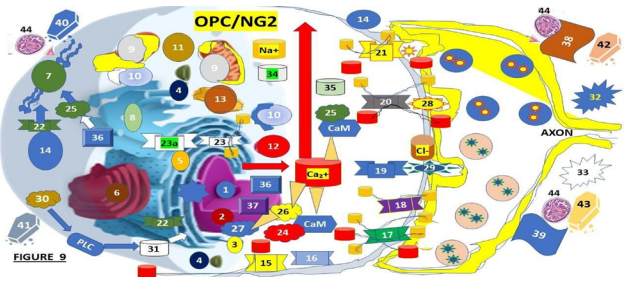

Figure 9: Illustrate most of the components of the neuronal activity-dependent calcium signalling pathways that regulate OPC/NG2 differentiation modified by NCC according to our hypothesis: 1- nucleolus, 2-nucleus, 3-ribosome, 4-vesicle, 5-rough endoplasmic reticulum, 6-golgi apparatus (or, golgi body), 7-cytoskeleton, 8-smooth endoplasmic reticulum, 9-mitochondrion, 10-vacuole, 11-cytosol 12-lysosome, 13-centrosome, 14-cell membrane, 15-VGCa^{2+},16-VGNa^{+}, 17-NI- VGNa^{+}, 18-NCX, 19-GABAAR, 20-NMDAR, 21-CP-AMPAR, 22-IP3R, 23-RyR3, 23a-RyR3 antagonist, 24-calcineurin, 25-CAMKIIβ, 26-ERK1/2, 27-contactin, 28-glutamate receptor, 29-Gamma Amino Butyric Acid (GABA), 30-mGLUR5, 31-IP3 receptor, 32-pro-inflammatory cytokines, 33-chemokines, PLC-phospholipase C, 34-calcium-permeable AMPA receptors, 35-CP-AMPA receptors, 36-CREB, 37-Sox 10, 38-activated astrocytes, 39-activated microglia, 40-meningeal lymphatic vessels, 41-glymphatic system, 42-corpus amora, 43-aquasporin 4, 44-cysticercus cellulosae

As seen here, the OPC/NG2 differentiation is regulated by intracellular signals mediating Ca^{2+} dependent events. This mechanism began by binding Glutamate (GTM) to metabotropic GTM receptors, leading to the activation of phospholipase C (PLC), inducing the release of IP3, which binds to IP3 receptor to release store intracellular Ca^{2+} in the Endoplasmic Reticulum (ER). In this figure, we also highlighted (red arrow) the increased concentration of Ca^{2+} facilitated by the presence of voltage gated Ca^{2+} and Na^{+} channels. This high concentration of Ca^{2+} allows a fast depolarisation of the membrane in response to neuronal activity, as can be proved by other investigators [34].

As shown in Figure 9, OPC/NG2 also contain calcium-permeable AMPA receptors that contribute to synaptic-evoked calcium function modulated by mGluR5 activation at the membrane level.

Differentiation of OPC/NG2 is also facilitated by the presence of NMDA receptors that respond to released GTM and support changes in the expression of the CP-AMPA receptor. On the other hand, by elevating a persistent Na^{+} current through a non-inactivating VGNa channel, the intracellular concentration of Ca^{2+} will increase, and this mechanism facilitates the reversal activity of sodium/calcium exchangers (NCX). The role of calcium induced

Ca^{2+} released from ER deposits *via* Ryanodine Receptor 3 (RyR3) activation in changes of intracellular Ca^{2+} concentration and inhibition (antagonist ryanodine) of OPC/NG2 differentiation is also represented in Figure 9. Ca^{2+} modulates gene expression, and cytoskeletal dynamics are modulated by dependent intracellular signalling pathways beginning from Ca^{2+}-calmodulin binding activation phosphate calcineurin, which dephosphorylates NFAT proteins to stimulate their translocation to the nucleus of OPC/NG2 [34].

Below, we will comment more on Ca^{2+} to better comprehend the coming proposal on calcified NCC's pathogenesis (CNCC). Likewise, it is essential to highlight the role played by transcription factor Sox10 and associated NFAT proteins to relieve reciprocal repression of OPC/NG2 and Nkx2.2 in the OPC/NG2 differentiation mechanism. We also included activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKIIβ, green), by Ca^{2+} which may stabilise the acting cytoskeleton *via* non-kinase catalytic binding as suggested by the same authors [34]. We had considered the consequences of damaged OPC/NG2 secondary to NCC and considered a decreased effect of CaMKIIβ over physiological OLG behaviour through CREB phosphorylation contrary to the standard mechanism. Finally, we have hypothesised that another cause of failure OPC/NG2 differentiation is related to the poor modulation of the kinase function of the extracellular signal-related kinases (ERK1/2), which is fair to phosphorylate cortactin and lack of driving Arp2/3 complex-dependent actin polymerisation. Failure of OPC/NG2 leads to poor remyelination, neuroplasticity, dysfunctional network activity and terminal prognosis, as we might see in massive NCC.

Brief comments on the role of OLG in the pathogenesis of **ES/Ep.**

On top of that, it has been documented that the express maturation markers developed by OLGs can be diminished in voltage-gated potassium (VGK) and sodium channel (VGN) plus loss of tetrodotoxin-sensitive spiking activity by rectifying the VGK and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (switch) composition and N-methyl-D-aspartate which may contribute to the mechanism of exaggerated abnormal hypersynchronic discharge from the brain cortex [30].

Based on this postulation, we have hypothesised that dysfunctional OLG is also involved in the pathogenic mechanism of ES/Ep in patients with INCC. Furthermore, our hypotheses are supported by the presence of satellite OLG at the cerebral cortex next to the neuron cell bodies, which provide metabolic help to the neurons to prevent cellular apoptosis and modulate remyelination [34].

People need to learn the differences between how the activity of satellite OLG and myelinating OLG around the cystic lesion is performed or what happens first. However, we have speculated that both activities happen simultaneously or separately by milliseconds, including the activation of astrocytes, microglia, and cytokine production, which may take longer. Furthermore, many years ago, other authors found diminished I K- and I A-channel expression and differentiation of mouse OLG from OPCs/NG2 related to an increase in inwardly rectifying K^+ (K ir) channel expression, which also serves to support our hypotheses for ES/Ep in NCC. On top of that, It has also been confirmed that K ir4.1 subunit plays a crucial role in OLG development, myelination and setting the Resting Membrane Potential (RMP) of native mature OLG. Unfortunately, there are no specific blockers that can be used to isolate pharmacologically K ir4.1-mediated currents, and the same investigators have observed a hyperpolarisation of the RMP in rodent's OLG, confirming potassium channelopathy in the selected samples and an associated increasing OPC/NG2 proliferation which also support our hypotheses on the participation of dysfunctional OLG in the pathogenesis of ES/Ep in NCC [30]. Another aspect to be considered in the pathogenesis of dysfunctional OLG in patients with NCC is the role played by oxidative stress. Regarding this issue, it has been reported that OPCs/NG2 are more vulnerable than mature OLG in cases presenting hypoxic-ischemic injury in the same scenario of hypoxic/ischemic stroke secondary to NCC vasculitis [35,36]. However, there are no well-designed studies able to prove it because of the limitations of conventional immunohistochemical techniques (fluorescence microscopy) and Nanoscale secondary ion mass spectrometry. Therefore, this issue needs to be appropriately clarified, and we will deliver other hypotheses on the role of OS in the pathogenesis of NCC in our subsequent publication.

It has been well-documented that OLG and OPC/NG2 are: The greatest metabolically active cells in the CNS, supporting the metabolism of the neuronal cells, interacting with other glial cells and the BBB in the inflammatory process caused by insults to the CNS, where NCC is included [37].

The role of pericytes and macrophages will be discussed in a forthcoming publication. The myelin produced by OLG and OPC/NG2 can reduce the capacitance and increase the resistance of the membrane of neurons, allowing the electrical transmission of action potentials along axonal fibres. The minimum axonal diameter required to be myelinated by OLG is 0.2 μm, and the myelination process is mediated by electrical transmission. Nevertheless, myelinisation is regulated by OPC/NG2, astrocytes, microglia, and OLG while inhibiting electrical transmission using voltage-gated Na^+ channel blockers or increasing the extracellular K^+ concentration serves to prevent myelination [37]. In other words, the electrical transmission and the neuron cell membrane activity are mandatory to elicit myelin formation.

Considering that OPC/NG2 glia receive synaptic input *via* glutamatergic and GABAergic activity as has been documented by other authors, its capacity to facilitate voltage-gated sodium (Nav) channel in other cells and downregulate glutamate receptors and Nav during

the process of differentiating myelinating OLG while undifferentiated supporting cells keeps their excitability, we have hypothesised that, on top of the neuropathological changes causes by colloidal NCC in the surrounding areas, this process includes other consequences caused by dysfunctional neuronal activity impedes the expected modulation of migration, proliferation and differentiation of mature NG2 glia, facilitating the production of differentiated OLG without excitability provided by the undifferentiated glial cells [38-41]. Furthermore, based on the results reported by other authors confirming that all neurophysiological activity of the cortical pyramidal cells is modulated by OPC/NG2 glia cells *via* cleavage of N-methyl-D-aspartate (NMDA) and NG2 proteoglycan, influencing alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), including secretion of neuromodulator factors by NG2, we have speculated on the pathogenesis of motor ES secondary to the hypersynchronous discharge of the pyramidal neurons involved in this mechanism which also serve to explain why the ictal activity in INCC is characterised by motor ES while seizures originating in other areas of the cerebral cortex have not ictal expression excepting the insula lobe in anecdotic cases [42-45]. Supporting our hypotheses, we highlighted the contribution of glucose, energy metabolites and lactate from OLG to these neurons through MCT1 at the myelin sheath, apart from the energy metabolites secreted by astrocytes (MCT2) [37]. Injured neuron cells by NCC cannot guide OLG to transfer antioxidant-loaded membrane vesicles (exosomes) and metabolites *via* perineuronal space, which revert into dysfunctional neuronal function leading to chronic brain disorder causing recurrent and unprovoked ES as the most common cause of secondary Ep [1-8].

Although astrocytes and OPC/NG2 have a common source during development, both have different shapes and functions but are connecting to the Nodes of Ranvier (NOR) and synapses on neuron cells in the same manner as we commented before which support their influence on local neurophysiology of the network and dysfunctional cortical neurons leading to motor ES [46,47]. Both also secrete elements that regulate OPC/NG2 glial differentiation. At the same time, those neurons elicit calcium (Ca^{2+}) transient current following glutamate secretion while astrocytes release similar NG2 glia calcium transient *via* adenosine and ATP. However, adenosine works directly on the OPC/NG2 glia, and ATP does it indirectly on astrocytes to produce leukaemia inhibitor factors [48,49]. As we commented recently, the activated astrocytes are always present during the colloid process.

Therefore, we have hypothesised that protoplasmic astrocytes are involved in the mechanism of disruption of BBB leading to local vasogenic oedema commonly seen around the lesions apart from cytokine storm influence astrocyte-induced migration of OPC/NG2 glia [18,19,48]. In contrast, fibrillary astrocytes participate in the healing process and scar formation. Likewise, astrocytes also secrete Platelet-Derived Growth Factor AA (PDGF-AA), favouring proliferation and differentiation of OPC/NG2 glia and soluble factors which, *via* ERK and Akt signalling pathways, protect OPC/NG2 glia from oxidative stress as will be discussed in the forthcoming article [48].

Furthermore, during development, some chemokine receptors (CXCR1, CXCR2) expressed by OLG are targets for astrocytes-secreted CXCL1, which, *via* PDGF-AA signalling mechanism can stimulate OPC/NG2 glia proliferation [37]. However, as we have commented in previous publications, during the dying process of CNS cysticerci and because of released antigens elements from the intracystic fluids, the activated astrocytes lead to a secretion of pro-inflammatory factors commonly expressed in cytokine storm more remarkably seen in associated SARS-COV-2 infection, massive NCC and HIV-AIDS comorbidity which supersede the before-cited protective effect, based on the previous confirmation of OPC/NG2 glial can develop into protoplasmic astrocytes even in the cerebral cortex we have highlighted that cortical brain vasogenic oedema caused by disrupted BBB secondary to local cysticercosis lesion also affect the neuronal metabolism; its mitochondrial ATP production, and dysfunctional Na pump, facilitating the cortical hypersynchronous discharge expressed as ES/Ep [16-19,49]. At the same time, it has been accepted that OLG and OPC/NG2 glia share a close spatial relationship, creating a glial network (glial syncytium-GS) [50]. Another relevant function of OLG is re-distributing K^+ from axons following neuron signs, which is also involved in the mechanism of hypersynchronous discharge seen in NCC [37]. Therefore, we consider that dysfunctional astrocytes (NCC) cannot play their role in the differentiation and myelination of OLG regulated by interaction with integrins and their secreting factors such as gamma-secretase, osteopontin, Ciliary Neurotrophic Factor (CNTF), neuregulin-1, Insulin-Like Growth Factor 1 (IGF-1), Bone Morphogenetic Proteins (BMPs), fibronectin, hyaluronan, Platelet-derived Growth Factor (PDGF), tenascin C, Fibroblast-derived Growth Factor 2 (FGF-2), and Neurotrophin-3 (NT3) involved in the myelination process, which serve to understand why the visual acuity may be affected in optic nerve NCC without direct axonal damaged [51,52]. Despite the number of nerve fibres in the Optic Nerve (ON) being more than one million, only around 1000 arise from the macular region to provide central and colour vision; then, if one OLG can myelinate around 50 ON fibres and one cystic lesion can affect many OLG in the ON, it is mean that many axons going to be affected leading to partial amaurosis secondary to an abnormal electrical saltatory conduction from one NOR to the next along to the ON. On top of that, this process is aggravated by the lack of an effective glymphatic system, meningeal lymphatic vessels, and dysfunctional astrocytes, leading to the malfunctioning of aquaporin 4 and corpora amylacea [53].

Therefore, injured astrocytes caused by NCC can impair remyelination (according to our appreciation), and modulation of OLG and OPC/NG2 glial are also affected by pro-inflammatory and anti-inflammatory elements secreted by active microglia. This mechanism is going to

be discussed in our next article.

We want to highlight that OPC/NG2 glia also support the integrity of BBB *via* TGF-beta signalling, as has been documented by Seo and collaborators [54]. OPC/NG2 protect the permeability of the endothelial tight junction (BBB) by secreting Transforming Growth Factor beta (TGF-β) after binding to TGF-β receptors located in the surface of endothelial cells of BBB by upregulation of the expression of claudin-5 and ZO-1 (tight junction proteins) *via* MAPK/ERK pathways [53]. This scientific results also support our proposal on the mechanism of NCC disrupting the BBB leading to vasogenic oedema in the white and grey matter as it was shown in Figures 5 and 6. Nonetheless, other investigators have documented the role of Fibroblast Growth Factor-2 (FGF-2), Brain-derived Neurotrophic Factors (BDNF), and Vascular Endothelial Growth Factor (VEGF-A) secreted by endothelial cells on the proliferation, migration, and survivability of OPC/NG2 glia through Akt and Src signalling pathways. However, VEGF-A promotes migration (VEGF-receptor 2) but no proliferation, supporting our previous hypotheses [54-56].

Most cysticercus travels by hematogenous route after crossing the small intestine membrane into the CNS, preferably through the carotid circulation, invading the cerebral hemisphere as the top destination. Even in patients presenting massive NCC, the presence of cysticercus in the posterior circulation territory is scanty despite the laminar/turbulent blood flow. However, there is no evidence of cysticercus traverse from the wall of the small intestine to the CNS *via* the gut-brain axis, and it does not make sense, but the effect of gut dysbiosis on the brain deserves special attention, and it will be studied in other forthcoming investigations. Disruption of the BBB favours the entry of cysticercus into the nervous system. However, the absence of BBB at the area postrema does not increase the presence of NCC at the medulla oblongata, which explains why one case presenting Wallenberg syndrome secondary to NCC has been reported in the medical literature [12]. Likewise, any location of NCC in the CNS is associated with local endothelial injury of the BBB at the entry point, leading to perilesional oedema. However, their clinical expressions will depend on the number of cysticerci invading the nervous system, the place of entry, and the host's immune response [1-10].

The role of OLG in local acute inflammatory response caused by NCC. In the vesicular stage of NCC, there is a proper relationship between the larva stage of T. solium and the immune system of the host; in such situations, those people remain free of symptomatology for decades until the parasite dies due to natural causes, antiparasitic drugs, or other reasons [10-19]. The process of dying damage the cysticercus cover allow it to release intracystic antigens causing local neuro-inflammation which trigger the neurophysiological mechanism involved in the protection of the nervous tissue against foreign pathogens and activation of neuroglia to start the healing process. One of the relevant activated glial cells is the phagocytotic microglia in their role in the removal of metabolite waste and secretion of IL-1β, IL-6, TNF-α (pro-inflammatory cytokines), MCP-1, CXCL-1 (chemokines), NADPH oxidase, MPO (reactive oxygen species), and coagulation factors [14-18]. Apart from other necessary functions to alleviate the consequences of reduced perfusion, of oxygen and nutrients, mechanically disrupted BBB, impairment of glymphatic, meningeal lymphatic vessel, AQP4 and Ca dysfunctional response as mentioned previously, and elevated mechanical strain due to tissue displacement by perilesional oedema (Figure 10).

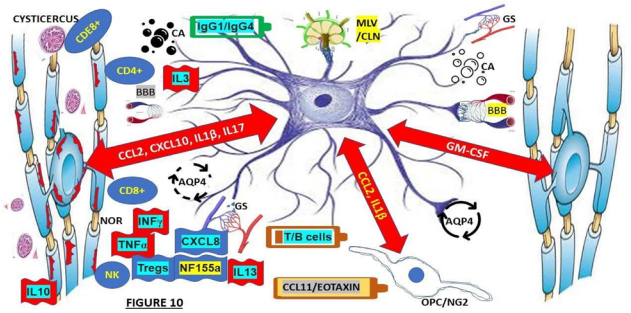

Figure 10: Our proposal is about the graphical representation of the working relationship between healthy myelinating OLG, damaged OLG by NCC, and OPC/NG2 with astrocytes in the presence of pro-inflammatory elements affecting the drainage system of the brain to the cervical lymph nodes leading to the accumulation of metabolite waste

On the other hand, chronic local hypoxia/ischemic stroke caused by NCC vasculitis, mechanical compression caused by giant cysticercus, extensive neuronal injuries due to massive NCC, or damaged vasculature secondary to other comorbidities (HIV/AIDS) promotes angiogenesis and creation of a new vascular network around the perilesional area if the patient survives (Figure 11).

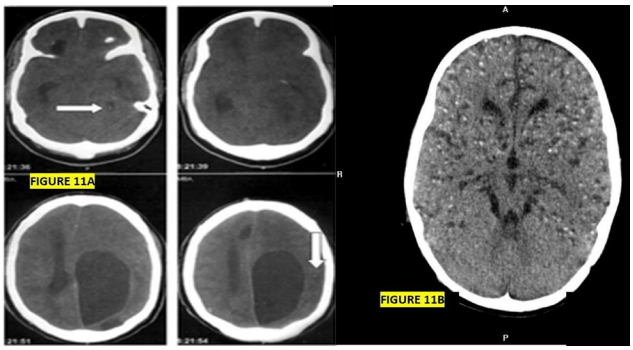

Figure 11: (A) Axial view of CT scan of the brain shows giant occipital lobe cysticercus and other cysticercus in the vesicular stage. This patient presented persistent headache, recurrent generalised motor ES, visual hallucinations, dysnomia, dyslexia, and palinopsia. Occipital lobe syndrome due to giant intraparenchymal NCC; (B) Axial view of CT scan of the brain shows massive NCC in the anterior circulation territory, sparing the vertebra-basilar territory

One way to attenuate glial activation is by modifying the local autoimmune response to cysticerci when it realises cytotoxic elements from the colloid process by administration of anti-inflammatory agents such as dexamethasone and Minocycline (MCy). However, the main impediment to this recommendation is related to the late arrival of patients with NCC to hospitals with

imagenology facilities; in other words, on arrival, almost all patients present cysticercosis at the colloid stage.

Therefore, a prophylactic recommendation should be applied before cysticercus delivers its antigens; it is equal to asymptomatic people who never go to the hospital. Therefore, corticosteroid medication is only indicated as a coadjutant of praziquantel/albendazole to avoid side effects, including ES. In addition, it is known that MCy inhibits Matrix Metalloproteinases (MMPs), which cause tissue inflammation, neurodegeneration, and demyelination simultaneously.

Moreover, anti-IL6, anti-TNF-alpha, and anti-INF gamma can reduce microglia's pro-inflammatory activation. Unfortunately, clinical trials have not been done with NCC patients, probably because it is a neglected disease. Therefore, we have no evidence to suggest being indicated in NCC patients.

Nonetheless, a decreased microglia activation reduces pro-inflammatory insults on OLG, myelin, and OPC/NG2 by reducing the secretion of harmful cytokines, chemokines, and reactive oxygen and nitrogen elements. Another element is astrocyte activating plasma proteins following disruption of the BBB and impairment of waste drainage mechanism (meningeal lymphatic vessel and glymphatic system, AQP4 and CA). Another benefit of favouring neuronal integration and diminished microglia is the oligodendrocyte viability and myelin integrity around the cysticerci lesion. We also hypothesised that minimising the oxidative damage with ROS scavengers, promoting neuronal cell adhesion by extracellular proteins, supporting cells modulating proteins, and any other procedure able to control NG2 glia and oligodendrocyte cell death, differentiation, or myelination should be considered to reach the same goal. On top of that, by introducing a novel therapy with neutralising antibodies against Lingo-1 to modulate OLG, NG2, and myelin protein Nogo-A to improve neuronal growth inhibition, we can regenerate the peri-cystic damaged areas. We based our previous hypothesis on reported clinical trial results obtained in MS cases, but as mentioned, a well-designed clinical trial should be performed to support the prescription [57,58].

Oligodendrocytes and the OPC/NG2 glia are highly susceptible to oxidative stress and excitotoxic lesions, key characteristic events in the NCC reaction to cysticerci invasion, but the issue will be discussed in detail in the forthcoming publication.

The neuron's dependence on this neuroglia for their survivability and physiology prompts the question of their fates during the colloid stage of NCC, where gliosis, other inflammatory response, and its consequences will impair the normal physiological activities of the neuron's cells apart from the associated excitotoxicity during extended glutamate exposure which has been proved a long time ago [59-63]. Notwithstanding, when NCC cause extensive neuronal damage, the prognosis can be fatal because glutamate excitotoxicity highly elevates the production of free radical species in mitochondria due to elevated concentration of Ca^{+} in the intracellular space, as have been proved in other conditions many years ago [64]. Based on this mechanism, patients presenting more than 100 intraparenchymal cysts have the highest mortality rate, as we reported several times before [5,10-12,16-20]. OLG apoptosis strongly contributes to this fatality because kainite and AMPA receptors are activated in either caspase-dependent or independent ways.

Glutamate signalling *via* pro-inflammatory cytokines (TNF-α and IL-1β from activated microglia) and increased glutamate transporters have been documented in other conditions [65,66]. Nevertheless, our previous statement on cell damage/apoptosis also includes the role played by an associated endothelial injury caused by NCC. Apart from the associated perilesional vasogenic oedema shown in Figure 5 (caused by disruption of the BBB), the endothelial damage also secretes cytokines, which largely augment the endothelial permeability, allowing entry of coagulation factors (fibrin), promoting secretion of chemokines CCL2 and CXCL10 *via* CD11b binding of activated microglia and from OLG to astrocytes, which also provoke T cells differentiation directed to myelin antigen-specific Th1 cells through upregulation of IL-12 and macrophages production. The endothelial injury also allows the entry of inflammatory plasma proteins and other harmful elements, causing vasculature infiltration of T cell leukocytes, local neuroinflammation, and demyelination. The role of thrombin (THr-inflammatory factor from an endothelial spill) over fibrin deposit production (fibrinogen) should be considered, too. We believe that a high concentration of Thr in patients with NCC can elicit cell apoptosis, blocking saltatory nerve electrical transmission at the NOR, and suppress ERK1/2 and AKT-mediated brain myelination through activation of Protease-activated Receptor 1 (PAR1) expressed in endothelial cells, neurons, T cells, NG2 and other supporting cells, whilst the low concentration of Thr has a neuroprotective effect mainly on hippocampal neurons and astrocytes according to information reported by other investigators for other conditions [66,67].

In our region, the incidence and prevalence of NCC are decreasing gradually thanks to the support received by the National Government and many people interested in eradicating this parasitic disease. However, in some of the nearest countries, this issue still requires more attention [15]. In memory of those patients, we have hypothesised that reducing the severity of BBB injury and their leakage will provide enormous benefits on the integrity and viability of OLG, NG2 and myelin production (electrical conduction/neuronal signals) at the perilesional areas around the cysticercus because it will also decrease the concentration of cytokines, infiltration of peripheral immune cells plus other reactive species.

We highly emphasise the relevant role of myelinisation at the perilesional cysticercus areas to reinstall the normal neurophysiology of the affected network. However, adding thousands of new cell membranes around the

axons to build/remodel myelin is complicated, and more elements must be considered in this context. Recently, Lam and colleagues from Stanford University introduced novel aspects related to the myelination process. These investigators documented that the before-cited myelination process requires exocytosis, mediated by vesicular SNARE proteins VAMP2/3 and communicated genetic inactivation of VAMP2/3 in myelinating OLG leads to noticeable hypomyelination and premature death. Furthermore, they confirmed that VAMP2/3-mediated exocytosis guides membrane expansion to begin wrapping and substantial myeline sheath elongation by directing vesicle fusion within myelin sheaths and incorporating the necessary axon-myelin adhesion proteins to the inner tongue and paranodes to build the NOR. It is essential to highlight that this is a regulatory nexus (VAMP2/3-mediated exocytosis) indispensable for myelin sheath growth and the formation of NOR for building neural circuitry [68].

We have speculated on the absence of ES due to the hypersynchronous discharge caused by NCC at the brain cortex in some cases, considering the lack of clinical manifestation due to the blocking of the electrical transmission at the level of the CNS paranode region which is a specialised axon-myelin junction next to NOR essential for the propagation of electrical impulses when it happens. These segments of CNS axons can be damaged by the direct effect of cysticercus' antigens and perilesional oedema in the grey/white matter. On top of VAMP2/3-dependent hits and myelin adhesion proteins, there are other elements located at the NOR, such as Myelin-associated Glycoprotein (MAG), Neurofascin-155 (Nfasc-155), and Contactin-1 (Cntn1) which are necessary to establish axon-myelin junctions at paranodes and MAG to maintain axon-myelin interactions at internodes.

Notwithstanding, K.J. Chang et al. (2014) demonstrated other VAMP2/3-dependent hits (intracellular membrane-proximal proteins), such as cytoskeletal scaffolding protein, MBP and Ankyrin-G (AnkG) Cytoskeletal scaffolding protein directly interacts with Nfasc-155 in OLG for paranode assembly [69]. In conclusion, VAMP2/3-mediated exocytosis is a mandatory mechanism of OLG for membrane expansion during myelin sheath formation, myelin plasticity, maintenance, regeneration, and regulation of NOR assembly [68]. The differences between the NOR in the CNS and NOR at the PNS depend on the role played by astrocytes at this level, as we documented recently [70].

Novel hypotheses on Calcified NCC (CNCC)

As has been cited before, the most familiar presentation of NCC is the calcified stage of cysticercus, and based on our experience, a CT scan of the brain is the investigation of choice to confirm it.

Notwithstanding, the presence of multiple and bilateral 1 mm-10 mm calcified lesions on the brain parenchymal are pathognomonic of CNCC, as we reported many times for the past 20 years [1-10,15-20]. However, the shape and pathogenesis of cerebral calcification NCC have yet to be documented. Therefore, now we will comment on the most likely mechanism of CNCC formation based on some knowledge obtained from studies performed in other medical pathologies reported in the medical literature, plus our hypotheses trying to answer our research's questions.

Calcium (Ca^{2+}) signalling is the second central and interrelated well-known mechanism that regulates OLG lineage cells and the myelinating process. According to Paez and Lyons' publication, the known supporting cells have many types of Ca^{2+}-permeable channels and the capacity to release Ca^{2+} from intracellular deposits [71,72]. It has been proved that extracellular elements like adenosine, Glutamate, BDNF or even GABA acting on ion channels, tyrosine kinase or G-protein-coupled receptors modifying the intracellular Ca^{2+} influx, which can modulate several intracellular signalling cascades along with other glial cell process and adaptative myelination, NG2 proliferation, myeline growth and retraction. Its activity-dependent and activity-independent calcium transients allow OLG/NG2 glia to respond quickly to synaptic input through membrane depolarisation, local Ca^{2+} influx, and neuroplasticity [73].

On the other hand, it has been found that changes in intracellular Ca^{2+} signalling modulate OLG function, affecting gene expression, maturation, integration, cytoskeletal dynamics, and axonal support [36]. Other authors have documented group I metabotropic glutamate-receptors (I mGluRs), Ca-permeable AMPA receptors, Ca^{2+}-induced calcium, and Voltage-gated Calcium Channels (VGCCs) released from the Endoplasmic Reticulum (ER) lead the stimulation-induced Ca^{2+} transients in NG2 processes. Apart from ImGluRs, there are other elements such as P2Y purinergic receptors and Gq-coupled protein receptors (muscarinic acetylcholine receptors) promoting the elevation of intracellular calcium by binding to ER IP3 receptors from intracellular ER stores *via* RyR3 receptors, and through phospholipase C-mediated release of Inositol 1,4,5-triphosphate (IP3) [34] (Figure 9). As far as we know, how released intracellular calcium modulates the NG2 behaviour has yet to be studied. However, we have considered that the local inflammatory process caused by colloidal NCC and associated synaptic signals can stimulate the entry of Ca^{2+} into NG2 glia *via* ligand-gated neurotransmitter receptors, VGCCs (as mediators of activity-dependent changes), and other transmembrane proteins.

On the other hand, we also believe that dysfunctional/damaged OLG/NG2 (L-type Ca^{2+} channel Cav1.2) reduce maturation, myelination, and network function at the cortex where cysticercus is more commonly located. Many NCC lesions affecting the whole brain are incompatible with life, as happened to this patient (Figure 6). This figure also illustrates the 4 stages of intra-parenchymal NCC, as before cited.

Here now, we are taking into consideration the confirmation made by other investigators about the significant source of calcium entry in OPC/NG2 related to the calcium-permeable AMPA receptor, which has high levels of mRNA

transcript for Gria2, encodes the calcium permeability-determining AMPA receptor subunit, and modulate NMDA receptors contributing to activity-dependent calcium flux in OPC/NG2 [34]. Based on the previous knowledge, we propose that the process is even more relevant around the neuroinflammation caused by NCC according to our hypotheses. Likewise, the elevated concentration of OPC/NG2 intracellular Ca^{2+} independent of VGCCs is a response of GABAA receptor activity generated by a persistent non-inactivating sodium current (NI-VGNa^{+}) will reverse sodium/calcium exchangers activity. Nonetheless, it has been well documented that NMDA receptors mediate Ca^{2+} accumulation in response to ischemia in myelinating oligodendrocytes by several investigators, and it has also been proved on optic nerve preparation-induced NMDA-mediated Ca^{2+} in OLG, which is remarkably elevated after electrical stimulation [74-77]. Even though some authors rejected this postulated and proposed another mechanism based on dependent proton-gated, calcium-permeable TRPA1 channels, it has been well documented that the Ca^{2+} events in cortical OLG are supported by the mitochondrial activity releasing Ca^{2+} in response to high metabolic requirements of these supporting cells indirectly and by direct neuronal activity [78-81]. Arguably, the cortical neuronal hypersynchronous discharge present in NCC plays a determinant role in the mechanism of OLG Ca^{2+} influx, which serves to understand why Ca^{2+} is imbalanced when the neuronal function is blocked by tetrodotoxin and why internode growth is facilitated by short duration, high-frequency microdomain Ca^{2+} events whilst scanty Ca^{2+} cause retraction of developing myelin sheaths and how Ca^{2+}-dependent regulate cytoskeletal dynamics and the reorganisation of the cytoskeleton and neuron-oligodendroglia interactions on cellular dynamics in OLG [82,83].

Furthermore, Ca^{2+} influx (calcium-permeable AMPA receptors) through quick reorganisation/stabilisation of actin *via* cofilin and cortactin modulates the enlargement of dendrite spines when Long-term Potentiation (LTP) happens together with NMDA receptor-mediated Ca^{2+} transients which establish dendritic spine structure during LTP [84]. Recently, it has been highlighted the role of nuclear factor of activated T-cells (NFAT)/calcineurin nuclear signalling pathway in neuronal activity-induced calcium changes with OLG gene expression and other authors established that lack of NFAT/calcineurin in neural crest cells leads to poor differentiation of Schwann cell and myelination regulated by Ca^{2+}-induced activation of NFATc3/4, its role in activation and infiltration of T-lymphocytes in the brain.

Without a doubt, overexpression/activation of NFAT increases remyelination, and lower expression decreases T lymphocyte activation/infiltration, accelerating remyelination *via* NG2 differentiation. Likewise, calcium/calmodulin-dependent protein kinase type II subunit β (CAMKIIβ) expressed in OLG links neuronal activity-induced Ca^{2+} changes with OLG gene expression [85-88]. On the other hand, neuron-OLG BDNF signalling modulates oligodendrogenesis and myelination [89,90]. Finally, we emphasise the implication of the myelin regulatory factor (Myrf) in preserving mature myelin sheaths, avoiding the progressive degeneration of mature OLG and axonal damage [91]. If axonal signals wholly regulate Myrf has not been proven, the myelin integrity/remodelling relationship with an increased concentration of intracellular Ca^{2+} is internationally accepted. The before-cited relationship drives the beginning of wrapping, acting depolymerisation, and maintenance of active axons if there is no severe damage [92-94].

We also hypothesised on the OLG's capacity to secrete factors able to modify the astrocyte's functions in patients with INCC. Whilst healthy OLG/NG2 physiologically interact with astrocytes, GM-CSF, IL-1β and CCL2 are secreted, supporting beneficial effects from dysfunctional OLG injured by the local harmful action of colloid cysticercus, which can produce a beneficial effect on astrocytes by CCL2 which serves to diminish the local neuroinflammation. At the same time, other released elements like IL-1β and IL-17 exacerbate the inflammatory process, affecting the neuronal function and the network (Figure 9).

In this hypothesis, we also incorporated the role played by the antigens released by cysticercus in the colloid stage and its capacity to activate the non-innate immune cell populations (circulating B and T lymphocytes), including effector memory T-cells, Natural Killer (NK), regulatory T cell (Tregs), CD4+, CDE8+, CD4+/CD8+ T-cells ratio, or central memory T cells. In a previous article, we documented the features of the CNS immunological response according to the nature of the immunologic aggression (antigen). We highlighted the capacity of the CNS/PNS to respond, activating TH1/TH2 cells and providing higher levels of CCL11/Eotaxin, INFγ, TNFα, IL13, CXCL8, CCL2/MCP1, and IL1β, leading to down-regulation of Mp plus the role played by IgG1/IgG4 anti-NF155 antibody, HLA II, T/B cells, and IgG4 NF155+ [73]. We want to introduce novel elements related to the dysfunctional KCNQ2 channels caused by NCC's direct or indirect effect. When it happens, the saltatory electrical transmission is dysregulated, and the intrinsic electrophysiological properties at the Node Of Ranvier (NOR) of the axons disappear, leading to dysfunctional neuronal activity.

On top of that, we added the effect caused by disruption of the two-pore domain potassium (K2P) channels affecting the Aβ-afferent nerves at the NOR, and we speculated that local NCC antigens might trigger an elevated production of contactin 1, autoantibodies against nodal-paranodal proteins such as NF155, contactin-associated protein, and IgG4 as can be seen in other pathologies with associated myelin damage/disorder reported by us [47]. Furthermore, another element contributing to the dysfunctional propagation of the electrical impulses along myelinated axons at the NOR is the presence of astrocytosis, now secondary to the neuroinflammatory process associated with NCC. Previously, we cited the role of OLG at the nodal, paranodal, juxtaparanodal, and internodal axonal segment

regarding the electrical transmission of action potentials through an interchange of ions and the mechanism of NF155+ to naïve T lymphocytes leading to the Tfh2/Th1 differentiation and Tfh2 cells induction of IgG4 regulated by interleukins L3, L10, and L13 [47]. Finally, we want to emphasise that all functional axons are influenced by the Meningeal Lymphatic System (MLS). GL: Glymphatic System (GS), Aquaporin 4 (AQP4), and Corpora Amylacea (CA) from astrocytes.

Therefore, injured astrocytes will affect the drainage of metabolic waste arising from NCC's colloid and fibronodular stage, which explains why death tissues take too long to disappear in imagenology. All the processes mentioned above regarding OLG Ca^{2+} expression serve to understand how the CNS is affected in patients presenting NCC. If there is no extensive brain involvement, all patients will present headache and ES/ES mainly, but in an extensive invasion of the brain, the prognosis will be very poor or even fatal, as shown in Figure 6.

Figures 5-7 show rounded calcifications in both cerebral hemispheres. We have hypothesised the round shape of calcifications located in the CNS compared with the fusiform/tubular shape calcifications seen in the muscle in muscular cysticercosis in Figure 7, as we published before [11]. We have considered that the physical characteristic of the muscular fibres as complex tissue and its mechanical compression over the cysticercus determine its early death and shape parallel to the muscle fibres compared with other soft tissue like lungs and brain where the cysticercus is not compressed due to apparent reasons leading to round shape. Any surrounding soft tissue cannot modify the shape of any calcified material because of its physical consistency.

Therefore, calcification depends on the Parasite Death Tissue (PDT) shape. Our next research question will be why the brain's cleaning system does not remove the PDT at the early stage before becoming a lifelong piece of calcification.

Conclusion

Now, the pathway-specific effects of most of the signalling molecules driving the changes in NG2 intracellular concentration of calcium are still unknown. However, it makes sense to consider that dysfunctional/damaged/apoptotic OLG/NG2 can facilitate an abnormal calcium concentration at the lesion level. Notwithstanding, based on the previously published knowledge, we have hypothesised that NCC affects the normal function of OLG and NG2 due to dysfunctional cortical neuronal activity affecting the modulation of proliferation, differentiation, myelination, and formation of neural circuits and its neurophysiological activity. Therefore, residual accumulated Ca^{+} is expressed as CNCC because of neuronal and glial apoptosis.

Due to globalisation and increasing uncontrolled migration from developing countries to first-world countries gradually increase; therefore, a high number of zoonotic and neglected parasitic diseases will continue invading the developed world. In our opinion, the best scientific way to control and eradicate this problem is by developing the field of neuroparasitology, and other investigations to support, modify or reject our hypotheses should be done shortly.

Declarations

Consent for publication

The authors did not request informed consent because it was unnecessary for this study review.

Availability of data and material

All data supporting this paper are available on reasonable request through the corresponding author.

Declaration of anonymity

The authors of this study certify that they did not mention the names, initials, and other identity issues of any patient in this publication. Therefore, complete anonymity is guaranteed.

Ethical Approval

The Institutional Ethical Committee of WSU/NMAH did not consider this report for additional ethical approval.

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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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Both authors declare that they did not receive any external personal collaboration or financial support able to influence the results written in this manuscript.

Authors Contribution

Study concept and design: LFIV. Data collection from searched literature: HFS and LdeFIV. Data analysis: LdeFIV and HFS. Drafting of the manuscript: HFS and LFIV. Revising the manuscript: HFS. Supervising research and manuscript writing process: HFS and LFIV. Both authors have approved this version for publication.

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