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MULTICOMMODITY OF INTRAVENTRICULAR NEUROCYSTICERCOSIS WITH TWO VIRAL INFECTIOUS. A COMPREHENSIVE REVIEW.

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ABSTRACT

Background: Human herpesviruses (HHV) are double-stranded DNA viruses able to cause a wide range of medical conditions, from vesicular rashes to malignant disorders. This study's primary aim is to review the medical literature related to the comorbidity of HIV/HHV7/intraventricular neurocysticercosis (IVNCC) and formulate some hypotheses about the pathogenesis of these combined diseases.

Method: We searched the medical literature comprehensively, looking for published medical subject heading (MeSH) terms like "IVNCC-HIV-HHV7; OR "Human herpes virus 7", OR "comorbidity HIV/HHV7 disorders"; OR "Pathogenesis of HIV/HHV7/IVNCC", OR HIV/HHV7/cytokine/chemokine".

Results: All selected manuscripts were peer-reviewed, and we did not find publications related to HIV/HHV7/IVNCC

Comments and concluding remarks: This is the first study to address the comorbidity of IVNCC/HIV/HHV7. The authors also proposed some hypotheses related to the pathogenesis of this multimorbidity.

KEYWORDS: Intraventricular NCC, Human immunodeficiency virus (HIV), human herpes virus seven (HHV7), comorbidity HIV/HHV7, pathogenesis HIV/HHV7/IVNCC

INTRODUCTION

Cysticercosis can invade many human anatomy places, except the hair, nails, cartilage, bones, epidermis, membranes, and the adrenal gland. When the cysticerci live in the subarachnoid space (SAS), cerebral parenchymal, intraventricular system, posterior fossa, spinal cord, or optic nerve, then this pathological condition is named neurocysticercosis (NCC), which is a zoonotic, preventable, and curable neuroparasitic disease. NCC is the most common parasitic disease of the CNS, and it is more prevalent in Sub-Saharan Africa, Latin America, and Asia, among other places. Racemose NCC is characterized by the location of the cysticerci in subarachnoid space, Sylvian fissure, anterior interhemispheric fissure, and basal cistern causing mass effect by multiloculated cysts and surrounding neuroinflammatory (NI) response. The typical clinical manifestations of NCC are headache, epileptic seizures (ES) and secondary epilepsy (Sep), among other less frequent symptoms and signs [1-5]. ESD and SEp are more common in intraparenchymal NCC (INCC). Over the past twenty years, we performed many epidemiological investigations in rural areas around Mthatha in South Africa, and we could confirm that NCC is the leading cause of SEp [6-15]. However, the previous statement is modified by the lack of available medication due to COVID-19 restrictions or other reasons, including poor compliance and financial constrictions. Likewise, patients presenting refractory SEp to NCC without other causes were never seen in our region in the past twenty-seven years. The most common ASM used for controlling ES is diazepam, and the AEDs prescribed are valproic acid and carbamazepine [16-19].

On the other hand, humans are the final host for the adult tapeworm *Taenia solium* (Ts), which causes taeniasis. In contrast, humans and pigs can be intermediate hosts carrying the cysticercus (larval form), a fluid-filled cyst with an outer membrane with one eccentric scolex inside. When these cysts are ingested via undercooked measly-contaminated pork meat, they go to the gut, where scolex evaginates and attaches to the gut mucosa wall by two crowns of 25 hook lets, avoiding being expelled out by the peristaltic movement with the faecal material. In the small intestine, the parasites mature into a 2-4 meters length tapeworm, conformed by a neck and 1200 proglottids. Gravid proglottids contain from 600 to 2000 fertile eggs, and each one contains an infective embryo (oncosphere), which passes to the environment with faeces on alternating days. In impoverished countries or poor economic regions inside of advantageous countries (like our country) where poor sanitation, scarce access to safe and clean water, poor food hygiene, low educational level, remarkable poverty, and free-roaming pigs with access to human faeces-contaminated by *Ts* eggs, the incidence/prevalence of cysticercosis were very high in our region. When the proglottids or eggs are ingested through the faecal-oral route or by contaminated food or water, the embryos are released from the egg into the small intestine and pass through the gut mucosa to the blood flow, which carries them to the target tissues, where they are transformed into cysticerci. Like humans, pigs can ingest eggs and develop porcine cysticercosis following a similar mechanism. Stool parasitological examination is insensitive since most NCC patients do not have a viable *Ts* tapeworm in the gut at the time of diagnosis of NCC.

Person-to-person transmission is relatively standard, explaining why non-eaten pork like Muslin can be infected and why the disease may be present in developed countries without free-range pigs [20-25].

Recently, we reviewed novel aspects of NCC related to autoimmunity, glymphatic drainage, and its comorbidity with COVID-19, HIV, and ischemic stroke [26-30]. We also reported the role of activated OLG/OPC/NG2 in the pathogenesis of NCC, plus the clinical manifestations/complications/outcomes of affected people. We also documented the mechanism of activation of microglia (Mg) and astrocytes (as) in the NCC neuroinflammatory pathways either (directly or indirectly) through the upregulation of BBB disrupting proteinases, secretion of proinflammatory cytokines, and formation of an inhibitory glial scar [27].

Intraventricular NCC (IVNCC) is an uncommon type of cysticercosis, resulting in a multiloculated large cyst in the cerebrospinal fluid (CSF) inside the ventricular system [28]. In 2003, we reported twenty-one patients fulfilling the clinical and immunological criteria of IVNCC. Fifty-seven per cent of those patients presented an associated HIV comorbidity and pulmonary tuberculosis. After the CT scan of the brain, eighteen cases had clinical signs of intracranial hypertension and dilatation of the ventricular system. We hypothesized that in HIV patients, the cysticercus lives longer in the vesicular stage compared with non-HIV patients because the parasites are minimally attacked by the immunological system, which is severely depressed; however, the perilesional reaction secondary to excreted/secreted (glutamate) substances released by the parasite has a more intensive effect on the surrounding neurons and supportive cells. Other potentially life-threatening complications, such as ischemic stroke and intraventricular haemorrhage, have also been reported [28]. Summarizing, subarachnoid NCC (SNCC) (Racemose) and IVNCC are uncommon NCC types, leading to a grape-like cluster and multiloculated appearance in the CSF spaces. In SNCC, cysticerci are in different basal cisterns and subarachnoid spaces, leading to multiloculated cystic lesions with an associated space-

occupying lesion mass effect and a surrounding neuroinflammatory (NI) reaction. We reported cases of SNCC/IVNCC with well-documented lesions, mainly in the basal cisterns and Sylvian fissures, some of which were HIV-positive patients associated with COVID-19 or presenting ischemic stroke [28–30].
According to the definition delivered by van den Akker and colleagues in 1996, the coexistence of two or more chronic medical conditions is known as multimorbidity (Mm) [31]. Since last century, it has been well known that the human immunodeficiency virus (HIV) is a species of neurotropic *Lentivirus from* a subgroup of the retrovirus family that preferentially attacks CD4+ T helper lymphocytes, leading to the continued destruction of the immune system to advanced acquired immunodeficiency syndrome (AIDS) and death is not adequately treated in which situation will be a manageable chronic disease. Recently, Sukumaran and Sabin defined the multimorbidity in people living with HIV/AIDS (PLWHA) and found that the most common condition included in multimorbidity publications among PLWHA such as metabolic, chronic infections, respiratory, digestive, cardiovascular, dermatological, malignancy, urogenital, ear/nose/throat, congenital, oral, ophthalmological, and musculoskeletal disorders plus stroke, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, T2DB, sexually transmitted diseases (human papillomavirus, chlamydia, and gonorrhoea), dyslipidaemia, acute myocardial infarction, AIDS-related events (cytomegalovirus, *Pneumocystis* pneumonia, Kaposi's sarcoma), mental health diseases, and neurological conditions (epilepsy, migraines/headaches, and encephalitis) [32]. In previous publications, we reported comorbidities among HIV/AIDS/NCC/COVID-19/PM/MG several times [2, 6, 12-14, 17-19, 30].

In 2021, we commented on the role played by Bacteroidetes and Firmicutes (gut dysbiosis) in the pathogenesis of some neurological disorders through increased expression of the proinflammatory cytokine, macrophage inflammatory protein 1, chemokine, interferon γ, TNFα, and other components from leukocytes infiltration, activated astrocytes/microglial other proinflammatory elements have been included in the pathogenesis of the cytokine realize inflammatory syndrome process causing damage on the cells and blood vessels, and direct endothelial damage caused by dysbiosis leading to increase the permeability of blood-brain barrier [33]

There are three subdivided families of *Herpesviruses* named *Alphaherpesvirinae* (*Alpha-), the most closed Betaherpesvirinae (Beta-),* and *Gammaherpesvirinae. A total of nine species of HHV are displayed across these subfamilies and several genera which have been living in this world from 180/220 million years back, and they have been a* tractable and informative model to investigate virus genome evolution at the level of protein domain rearrangement and gene duplication [34]. These species of HHVs are named *Human alpha herpesvirus one*, also known as herpes simplex virus type 1(HSV-1), *Human alpha herpesvirus two*, also named herpes simplex virus type 2 (HSV-2), *Human alpha herpesvirus three*, better known as varicella-zoster virus (VZV), *Human gammaherpesvirus four* which is best known as Epstein–Barr virus (EBV), *Human betaherpesvirus five* also known as human cytomegalovirus (CMV), *Human betaherpesvirus 6A* like human herpesvirus 6A (HHV-6A), *Human betaherpesvirus 6B* like human herpesvirus 6B (HHV-6B), *Human betaherpesvirus seven* better known as human herpesvirus 7 (HHV-7)), and *Human gammaherpesvirus eight* more commonly named Kaposi's sarcoma herpesvirus (HHV-8) [35]. HHV-6 is a widespread beta-herpesvirus genetically related to CMV and exhibits a broad cell tropism like other HHVs, induces lifelong latent infection in many people corresponding to primary infections, exogenous reinfections or even reactivations in complete asymptomatic persons while may cause lethal disorders mainly in immunocompromised peoples [36].

One exciting aspect recently reported is the interaction of toll-like receptors (TLR) and HHVs. TLRs are a group of single and non-catalytic protein components of the immune system, which is crucial for recognizing structurally conserved molecules released by pathogenic microbes, and thirteen members have been identified up to date. TLRs 1–10 are in the human genome, while TLRs 11–13 occur in mice only. In addition, some authors have demonstrated a remarkable elevation of the TLR2 and TLR4 expression in people carrying HHV-7, and they proved that there is a closed interaction between HHV-6 and HHV-7, being HHV-6 activated by HHV-7 infections [37]

The main aim of this study is to answer the following research questions. 1. How often is the comorbidity of HIV/HHC-7 in patients presenting IVNCC? 2. What is the most likely pathogenesis of IVNCC in PLWHA/HHV-7?

METHODOLOGY

After identifying articles published between January 31st, 2000, and March 30th, 2023, a systematic search of EMBASE, Medline, Cochrane Library, Scopus, PsycINFO, Global Health, Health Management Information Consortium, and CINAHL was conducted, followed by hand-searching relevant journals.

Literature search strategy for this review.

A systematic online search of investigations published from January 01st 2000, to December 31st, 2023, was conducted using the following databases: PubMed/PubMed Central. These databases support the systematic search of many topics in health and healthcare. We screened all papers pertained to the comorbidity of IVNCC, HIV/AIDS/ HHV7 in the primary or secondary health care setting under the search terms "HIV IVNCC," "IVNCC," "HHV7/IVNCC," We selected for review those that were relevant to these issues. For practice guidelines, we reviewed the references of each included manuscript. After this first process, we systematically searched the following electronic library databases)): Cochrane Library, Health Management Information Consortium, Global Health, CINAHL, Web of Science (Clarivate Analytics), EMBASSY, MEDLINE (Ovid), and Scopus (Elsevier). The aim was to select the original research studies related to the before-mentioned search strategy in PLWHA. After a confident peer-review process, the search was restricted to full-text Spanish, Portuguese, and English-language publications.

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

Inclusion and exclusion criteria

We selected randomized controlled trials or quasi-experimental studies published in peer-reviewed journals. The studies were excluded if they evaluated interventions for other types of IVNCC, such as those due to other causes, such as intraventricular obstruction, communicating hydrocephalus, congenital malformations, other types of infections, or vascular problems because their aetiologies differ from HIV/HHV7.

Study selection.

We performed the literature search and scanned all articles by title and abstract. LdeFIV and HFS independently screened articles in full text 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, which HFS verified.

Data extraction

A data extraction mechanism was developed to extract research data about the setting, study design, demographic profile of patients, methods, measurement tools, timing of assessments, and outcomes. 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 conducted the data extraction; the consensus was achieved through discussion among LdeFIV/HFS.

Methods of analysis

Data syntheses were programmed to comprise the narrative analysis and intervention synthesis of selected manuscripts based on the PRISMA methodology.

Extracted data were initially synthesized using textual descriptions to determine the characteristics of the selected studies. 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 that release 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 HIV-NP, HHV7/HIV disorders, 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 analyzed the situation until we arrived at an acceptable agreement.

Data Synthesis

Our study used aggregate data when necessary, following the guidelines of PRISMA.

Quality Assessment of Selected Publications

Initially, all studies were screened for bias using the Jadad scoring system [38]. The Jadad score is commonly used to evaluate the methodological quality of clinical controlled trials. Studies are scored according to three main methodological features of clinical trials: masking, randomization, and accountability of all selected patients, including withdrawals. One point is added for an affirmative answer to each of the first five items, and one point is removed for a positive answer to either of the last two items (for an overall score from 0–5). We included only those clinical trials with Jadad scores≥ 3 for further assessment.

RESULTS

Study selection.

All selected manuscripts were peer-reviewed publications, and no one met all inclusion criteria on HIV/HHV7/PN. Below, A PRISMA flow chart for the literature searched is shown below (Figure 1).

PLACE FOR FIGURE 1

Study characteristics.

Ethics committees approved all publications included in this review, and patient consent was obtained; without this requirement, the pertained data were removed from this study.

Most studies (74.3%) were published in the last three years.

The number of people with HIV ranged from 253 to 49 671 (median 2010, interquartile range [IQR] 963–7503). Most investigations were conducted in the United States of America/Canada (54.1%), followed by the European continent (39.2%). Most studies (89.8%) focused on people older than 18. The total of publications identified was n=3403; after duplicate removal, n=380; after full text excluded, n=29; for quality synthesis, n=09; for quality assessment, n=0.

COMMENTS AND CONCLUDING REMARKS

Nine of the selected publications met the inclusion criteria, but no publication was found for the quality assessment of comorbidity of HIV/HHV7/ IVNCC. There was no heterogeneity in outcome measures, study designs, and intervention components. However, many studies were appraised as moderate/strong in methodological design, but greater rigour is needed for study design and blinding.

Comments on IVNCC.

Neurocysticercosis is the most seen zoonotic parasitic infection of the central nervous system, and the metacestode larva of the pig tapeworm, T. solium, causes it. In the brain, the cysticerci can present as either an extra parenchymal form, as racemose cysts in the basal cisterns, subarachnoid spaces, and within the ventricles or/and a parenchymal form (cysticercus cellulose). The clinical manifestations and therapy of the two forms can be medical, surgical or both accordingly. The associated intracranial hypertension can be due to the mass effect of giant cysts, hydrocephalus, meningitis, and vasculitis [1-30]. NCC it is more prevalent in Africa, Latin America, and Asia and It affects the cerebral hemisphere, brainstem, cerebellum, subarachnoid space, the ventricle system, the optic nerve, and the spinal cord.

In summary, subarachnoid NCC (SNCC) (Racemose) and intraventricular NCC (IVNCC) are uncommon types of NCC, leading to a grape-like cluster and multiloculated appearance in the CSF spaces.
The main locations in the ventricular system are graphically represented in **Figure 2.**

PLACE FPR FIGURE 2

In SNCC, cysticerci are in different basal cisterns and subarachnoid spaces, leading to multiloculated cystic lesions with an associated space-occupying lesion mass effect and a surrounding neuroinflammatory (NI) reaction. We reported cases of SNCC/INCC with well-documented lesions, mainly in the basal cisterns and Sylvian fissures, some of which were HIV-positive patients associated with COVID-19 or presenting ischemic stroke [28-30]. Cysticerci can invade the ventricle system through the choroid plexus, where they can move freely or attach to the ependymal wall tissue. Cysticerci can travel to the cerebral and spinal subarachnoid spaces and the basal cisterns from the ventricle system and become lodged [39]. IVNCC is commonly identified on FLAIR imaging if CSF is suppressed. On post-contrast T1W images, IVNCC appears as an enhancing lobulated cystic lesion with or without associated ventriculitis. On top of that, some obstructive membranes and adhesions can also be found in the ventricles caused by epididymitis [39].
Some authors made a review of the clinical features, therapy and long-term outcomes of 23 patients presenting IVNCC referred to the National Institute of Health over 34 years; the investigators found that 60.9 % of cases were males, 65.2 % of patients had one cysticercus entrapped in the fourth ventricle due to the size of the foramina of Luschka and Magendie and Luschka resulting in hydrocephalus (73.9%), periventricular oedema/ventriculitis (30.4%). Through a suboccipital craniotomy, in 60.9% of cases, cysticercus was removed by cystectomy, and the ventriculoperitoneal shunt treated 43.5%, and 90.9% of patients remained stable without recurrence [40].
The IVNCC may present a rapid progression of neurological worsening with an inferior prognosis, mainly in cases presenting an associated multimorbidity; therefore, a prompt, aggressive intervention must be performed to avoid fatal results [41].
In our series, the predominant clinical features were characterized by moderate/severe generalized headache, sight problems, confusional states, Bruns' syndrome (due to the ball-valve mechanism, the ventricular outflow is blocked), drop attack, sudden positional vertigo secondary to rotatory movements of the head, and rapid recovery from loss of consciousness [28, 42]. However, the reported case suddenly died due to an associated obstructive hydrocephalus, cerebral herniation (brain stem/cingulate lobe) and marked epididymitis, ventriculitis, arachnoiditis, and opportunistic bacterial infection favoured by viral immunosuppression. Other authors have reported the presence of remarkable Bruns syndrome on several occasions [42, 43].
To confirm the presence of hypodense scolex in the ventricular system, other authors have documented the relevant importance of MRI sequences (3D-DRIVE/FIESTA/CISS) and SWI as the best choice for detention and localization of the parasite intraventricularly for better guiding for neuro endoscopic cyst excision [44]. Nonetheless, the IVNCC usually cannot be confidently detected by a conventional CT scan of the head because the cyst looks like iso dense with the CSF and its thin wall; however, the presence of hydrocephalus and intraparenchymal NCC might support the diagnosis. Notwithstanding, other differential diagnoses such as ependymal cyst, choroidal cyst, colloid cyst, arachnoid cyst, and intraventricular epidermoid lesions were ruled out by Ag-ELISA NCC, enzyme-linked electro-immune transfer blot (EITB), NCC antigens in the CSF and the final diagnosis was confirmed by postmortem studies.
Endoscopy procedures are preferable when it is possible to safely remove intraventricular cysts (not adhered to neural/vascular tissue) and to treat hydrocephalus despite some cases needing a VP shunt later [44].
We hypothesized that IVNCC associated with viral infections present the poorest prognosis because cystic degeneration leads to an acute neuroinflammatory response, causing ventriculitis, obstructive

hydrocephalus, and additional opportunistic infection, which is conditioned by the mechanism represented in **Figure 3**

PLACE FOR FIGURE 3.

The neurological sequelae of HIV infection and the HIV-SN are related to the genetic susceptibility of the infected cases that is explained by single nucleotide polymorphisms (SNP) in the mitochondrion and the genetic polymorphisms (GP) due to large deletions, elevated disease susceptibility in different demographics. On the other hand, mitochondrial DNA (mtDNA) has been implicated in the mechanism of idiosyncratic neuropathy related to ART and calcium/calmodulin-dependent protein kinase 2 (CAMK2) has been reported to be associated with an increased risk of developing HIV-SN in patients from South Africa, plus the identification of several haplotypes independent of stavudine exposure [45]. In contrast, other authors determined the complex interplay between HAART, particularly the non-nucleoside reverse transcriptase inhibitors (NNRTI) and the mitochondria, plus the complex pathological effect of protease inhibitors (PI) on the DNA polymerase-gamma (DNA pol-gamma) responsible of several neurological dysfunctions included HIV-SN [46].

HIV/DHSC/DRG microinvasion.

Approximately two weeks after the HIV infection, the CNS monocytes (CD14 + CD16 + cells) are invaded. When they differentiate into macrophages, the virus acts as the trojan horse of HIV, supporting productive HIV replication [47].

We have hypothesized that monocytes from DHSC/DRG express a remarkable level of an HIV-repressor factor and β-catenin favoured by HHV7 infection with macrophage HIV-replication modulated by their phenotype (M1/M-2-like) and CD4dim/CD8bright+ T lymphocytes which migrate into the CNS. Based on the differences between OLG/NG2 of the brain, the BBB/fenestrated CV, the differences between CNS/PNS axonal components, and the differences between the brain/SC clearance system for waste/toxic metabolites, we propose a different pathogenic mechanism for HIV/HHN7 infection at the DHSC/DRG as is graphically illustrated in Figure 2 and 3(FFF). Supporting our hypotheses have been reported a highly enriched blood CD4dimCD8bright T cells in 60% of anti-HIV responses with cytolytic activity, the central mediator of the Wnt/β-catenin pathway, which mediates CD4 expression on mature CD8+ T cells, the increased level of antiapoptotic protein, Bcl-XL, Wnt-rich environment in the brain inducing CD8+ T lymphocyte to become CD4dimCD8bright T cells both in vivo and in vitro which highlight the remarkable role of CD4dimCD8bright T cells in HIV-CNS neuroinvasion. (https://www.nimh.nih.gov/news/research-highlights/2022/t-cells-help-hiv-enter-and-persist-in-the-brain).

Based on previous reports, we have considered that HIV enters neuron cells in the PHSC/PRG using the classically recognized mechanism of binding its gd120 (which determines viral tropism by binding to target-cell receptors) to the CD4 receptor exposing the V3 region of gp120 joining to the chemokine-coreceptors (CCR5, CXCR4) as we represented in Figure 3. Notwithstanding, gp41, which is a transmembrane protein encoded by the envelop gene, mediates fusion between viral and cellular membranes and is involved in the fusion with CD4 membrane to release the viral core and begin the HIV replication cascade from uncoating to integration, to transcription, to reverse transcription, to protein synthesis via DNA/mRNA, to assembly, and budding (see Figure 4). Apart from the previous mechanism, we considered applying the other two mechanisms proposed by Wahl and Al-Harthi [47] for HIV invasion into neurons/glial cells in DHSC/DRG by cell-to-cell direct invasion or by endocytosis, as illustrated in Figure 4. Our proposed hypothesis of cell-to-cell transmission of HIV/Astrocyte DHSC-DRG via CXCR4 chemokine receptor is supported by animal co-cultured live-imaging and three-dimensional electron microscopy studies [48]. Based on other authors' publications [49], we speculate on the endocytic pathway invasion of HIV into the neuron/glial cells in the DHSC/DRG. There are four accepted mechanisms of endocytosis: micropinocytosis, phagocytosis, clathrin-mediated endocytosis, and caveolin-mediated endocytosis, the most ordinary way viruses use [49]. We have hypothesized that HIV/HHV7 use the last two paths to infect neuro/glial cells in the DHSC/DRG, as illustrated in Figure 4. Here, we are refreshing some knowledge on the mentioned elements: Endosomes are well-known intracellular organelles involved in the regulation of the movements of lipids and proteins through the subcellular compartment/spaces of the secretory/endocytic pathway (EP) like vacuoles/lysosomes, trans-Golgi network (TGN), and the Golgi plasma membrane. Lysosomes (Ly) are the last compartment/space of the EP involved in the breakdown into simple compounds of fat, proteins, carbohydrates, cellular metabolic waste, and other macromolecules. Despite their participation in endocytosis, Ly has a high content of active lysosomal hydrolases and lysosomal membrane proteins but no mannose-6-phosphate receptor. During early development, Activating Protein 2 (AP-2), a heterotetrameric clathrin adaptor *complex* multimeric protein, plays pivotal roles in regulating gene expression and works on the membrane of neuron/glial cells to internalize cargo in clathrin-mediated endocytosis (CME), and several intracellular vesicle trafficking pathways how is represented in figure 4. While CME is the major endocytic pathway in humans and other mammalian cell bodies, it is also in charge of transporters and transmembrane receptors for regulating cell surface signalling and remodelling the plasma membrane composition responding to environmental transformation. We speculate that DHSC/DRG's intra-endosome-HIV neurons/glial cells release its content in situ, degrade its acidic pH transform endosome to the lysosome and start the usual replicative cycle as has been proposed by Chauhan and Khandkar for brain's astrocytes (Ac) [49]. At this level of building up new hypotheses of the role of DHSC/DRG/Ac in HIV/HHV7 infection, it is essential to summarize the most crucial information on the role of HIV infection of Ac. The brain's Ac plays a remarkable role in maintaining homeostasis by regulating the level of water, potassium, and sodium ions, feeding process to the neurons through storing glycogen, secreting neurotrophic factors, and modulating the level of neurotransmitters like glutamate (in excess, is neurotoxic), immune functions (cytokines/chemokines), myelination, phagocytosis, neurogenesis, and maintaining the integrity of the BBB. All before-cited functions of the brain's Ac can be dysregulated by HIV infection [50]. In Figure 4, we hypothesized the mechanism of HIV entry into DHSC/DR' ’s Ac from surrounding infected cells independently of CD4. We also speculate on the participation of other receptors to facilitate the cell-to-cell entry of HIV into Ac in DHSC/DRG regions. We believe that galactocerebroside, human mannose receptors (binding to gp120), and orphan chemokine co-receptors are involved in this mechanism based on the report made by other authors under different conditions [47]. DHSC/DRG/Ac are HIV DNA provirus reservoirs in around 3% of billions of brain's Ac [47] induced/reactivated by infections/inflammatory signals.

On the other hand, we also hypothesized on HIV infection of microglia (Mg)/macrophage (Mp) at the DHSC/DRG. Differentiating Mg from Mp in the brain is a stiff challenge because both express the same surface markers (CD45, CD14 and CD68), HIV co-receptor CCR5, and low levels of CD4 [47]. Despite this, we do not know if DHSC/DRG HIV-Mg has high expression of aspartic acid domain-containing protein 1 (SAMHD1), which is a deoxy nucleoside tri phosphohydrolase (dNTPase) with the capacity to restrict HIV infection (by reducing cellular dNTP pools), elevated expression of sterile alpha motif, and histidine, as has been described in the brain and where the infected Mg in a G1-like state leads phosphorylation and inactivation of SAMHD1 by promoting upregulation of cyclin kinase 1 [51]. However, based on the accurately reported information regarding viral protein production (gp120, Vpr, and Tat) by HIV-Mg, the well-known mechanism of releasing proinflammatory cytokines like TFN-α and IL-1β /chemokines, inflammatory mediators like glutamate, ROS (reactive oxygen species), perivascular inflammatory cells, and RNS (reactive nitrogen species) and the consequent Mg/Ac activation. We believe that the neuronal damage in the DHSC/DRG is related to the high concentration of TFN-α, IL-1β, and neurotoxic molecules like L-cysteine and ceramide, as confirmed in the brain by other investigators [52]. We consider a vital problem for eradicating HIV the elimination of permanent reservoirs of latently infected CD4+T cells/neurons/GC because of their role in the HIV reservoir of virus rebound.

There is an association between TNF-α and neuropathic pain in black Southern Africans [31]. However, this condition was not identified in our case. It has been modified by a genetic factor such as gene alteration in a single nucleotide, at allele rs28445017*A (single nucleotide polymorphism), where neuropathic pain is significantly intense compared with those cases with SNP allele rs28445017*G. On top of that, it has been proved that gp120 is the leading HIV-1 agent causing pain in SN-HIV-related [53]. Based on the findings reported by the same authors, we agreed that the interaction of CXCR4/CCR5 on Schwann cells with gp120 protein plus trans-activator of transcription (Tat) release RANTES and the neurons/GC produce TNF-α–mediated neuronal apoptosis and axonal damage/degeneration plus other cytokines which promote the translation of lysosomes toward plasma membrane, increase production of ATP into the extracellular compartment, lysosome exocytosis, Astrocytes/MG activation, and elevation of intraneuronal calcium at the DRG. Based on the results reported by the same group of researchers, we speculate that perhaps other chemokines (CCR2, CCR5, CXCR3) increase their expression apart from CXCR4 Evans CD3+ B lymphocyte in HIV-NP patients, as has been reported by Evans et al. using MRI as a biomarker in HIV-associated PN and Diabetic PN [54].

Brief comments on HHV7

In 1990, Frenkel and collaborators isolated the HHV7 for the first time. *These authors incubated cells under conditions favouring T-lymphocyte activation and identified the virus from CD+4 T lymphocytes from mononuclear peripheral blood cells by electron microscopy analysis. It was the* seventh human herpesvirus identified at that time. The family of *Herpesviridae* is composed of nine different members being an HHV with 7-trans membrane receptor domains more complex and able to infect humans, causing fever, skin rash, diarrhoea, vomiting, febrile seizures, lymphopenia, and acute febrile respiratory diseases, On the other hand, they can contribute to the pathogenesis of multiple disorder*. However,* most of the time, infected people remain asymptomatic [55]. Recently, Zmasek et al. reported three gene duplication events leading in four groups of orthologous genes identified as US27, U51/ORF74, UL33/U12, and US28, releasing a new classification of groups like G-protein UL33/U12_B, G-protein US27_b (*Betaherpesvirinae*), G-protein U51/ORF74_bg (*Betaherpesvirinae/ Gammaherpesvirinae*), and Envelope protein US28_b (*Alphaherpesvirinae)[34]. Seems to be that all mentioned proteins are hijacking human proteins to be used to modulate the host immune system by the HHV acting as chemokine receptors [56]. HHV7* is closely related to HHV-6, and both have a double-stranded DNA genome of approximately 144 kb. *One of the relevant features of DNA-HHV7 is its latency, where the virus remains in a non-replicative state (latent infection) without triggering the* host's immune response by production of viral proteins establishing life-long immunopathological relationships with the human hosts despite some periods of shedding can happen. However, the site of latency remains to be seen. We hypothesized that the immunosuppression caused by the HIV infection failed the host to suppress HHV7 replication, producing clinical manifestations as has been described in other pathological conditions [57]. HHV-7 commonly infects CD4+ T cells and, less often, CD8+ and immature T cells, and some authors have reported cases of pityriasis rosea eruption, conjunctivitis and myelitis caused by HHV7 [57, 58], apart from reported cases presenting skin lesions [59]. Some authors reported that HHV-7 primary infection occurs mainly in children between the ages of 1 and 3 years, and around the age of 5 years, most of those children (90%) were infected with HHV-7 [60].

Our hypotheses on the role of microRNA in HHV7 infection.

It is internationally accepted that gene expression is regulated by single-stranded, noncoding RNAs, which can be highly dysregulated after being exposed to any infection, while many human DNA viruses, including HHV7, encode and activate viral microRNA (miRNA), named as vmiRNA, which can control the viral life cycle changing the host biological pathways. DNA viruses may apply many strategies to avoid being targeted by cellular miRNA (a critical class of biological regulators). It can be dysregulated during HHV infections as evidence of the importance of miRNA in host HHV infection modulating mRNA translation/degradation. Many DNA viruses (most HHVs) encode miRNA in their genomes. An envelope of a bilayer of lipids, glycoproteins, and viral proteins encloses HHV's tegument (a layer of amorphous proteins). Based on the results documented by other investigators [61, 62], we hypothesized that HHV7-vmiRNA can decrease the immune cell activation after infecting neuron/GC at the DHSC/DRG to prevent the elevated production of cytokine (IL-6 and TNF-α) from GC targeting the secretory pathway by miR-US5-1, miR-UL112, miR-US5-2 of HHV7, and inhibiting T-lymphocyte expression and NK cell avoiding NI as has been represented in Figure 3. That scenario might favour a remarkable intensity of associated acute neuroinflammation leading to ventriculitis aggravating the mechanism of obstructive hydrocephalus. We also speculate that miRNA controls HHV7 replication at the DHSC/DRG neurons/GC level by binding to the HHV7 genome and modifying host transcriptome mediated by HHV7. We believe that the functional role of miRNA can be produced by neurons/GC-HHV7 at the DHSC/DRG during its active replication cycle, and the cellular chemokine receptors allow the HHV7 to enter the cell where it releases its genome and the capsid translocate to the nucleus. Most probable during the lytic phase of HHV7 reactivated infection because of HIV infection, it produces miRNA targeting several proteins leading to deregulate neurons/GC signalling, gene expression, cell death, and innate neuroimmune response. We also hypothesized that miRNA would be a target diagnostic element and the therapeutic molecule as a regulator and curative therapy for many diseases.

Another novel aspect we introduced in our hypotheses regarding the pathogenesis of HIV/HHV7/IVNCC is related to TLR. As we commented, they are expressed on the membrane of macrophages, T/B lymphocytes, dendritic cells, and other non-immune cells like endothelial/epithelial cells, cardiomyocytes and even adipocytes [64]. Some are seen on the cell surface, while others (TLR-3,7,8,9) occur intracellularly. Based on the case-control study made by Ma et al. related to the link of TLR and HHV7 in the pathogenesis of pityriasis rosea [58], we hypothesized that increased expression levels of TLR2/4 might happen inside the cell bodies of neurons/GC at the DHSC/DRG of immunosuppressed persons. HHV7 infections and associated cases presenting encephalitis, epileptic seizures, vestibular neuritis, meningoencephalitis, Bell palsy, fatigue, nausea, vomiting, photosensitivity, headache, ataxia, and abnormal level of consciousness from drowsiness to coma have been reported [57, 59, 65] and recently encephalopathy in children [60]. However, as far as we know, this case is the first patient presenting HHV7/HIV-IVNCC.

Brief comments on the interaction between non-neuronal cells and miRNA.

Based on the results reported by Morchio and collaborators [66], we considered that miRNAs could induce changes in other cells, including astrocytes, Schwann cells, microglia, macrophages, and T cells. Therefore, we hypothesized that following the nerve lesion caused by HHV7/HIV infection on the peripheral nerve/DHSC/DRG, local macrophages are activated by released damage-associated expression molecular patterns and pathogen-associated molecular patterns in response to the infection plus elevated expression of neuroimmune cells and vasoactive mediators leading to NI influenced by proinflammatory molecules, nitrous oxide, prostanoids and communicate with neurons through miRNA (containing exosomes). Furthermore, considering the report delivered by Morchio et al., we have hypothesized that myelin sheath lesions caused by HHV7/HIV by dysfunctional Schwann cells (SC) at the Remak bundles and surrounding areas affect the neuronal nourishment and axonal regeneration if miRNA fails its functions. We also speculate that after primary HHV7/HIV lesion, the interactivity between ERBB2/3 on the side of SC and Neuregulin on the side of the axonal membrane causing demyelination of the peripheral nerves followed by proliferation of the SC as has been found in other aetiologies [66].

On top of that, we also believe that nerve growth factor, brain-derived neurotrophic factor, matrix metalloproteinases (MMPs), prostaglandins and cytokines secreted by SC contribute to the aggravating scenario present in HHV7/HIV/INVCC and dysfunctional neuronal gene expression. We also speculated about the role of miRNA soon after brain damage by HHV7/HIV/IVNCC. We considered that the downregulated miR-34 interact with the regulators of oligodendrocytes and oligodendrocytes precursor cell (proliferation/nerve regeneration/chronic pain) Ccnd1 and Notch1, represented in **Figure 4**.

PLACE FOR FIGURE 4

Here, we introduce another proposal for the mechanism of regulatory T cells (Tregs) differentiation under miRNA expression at the level of periventricular tissue, considering that miR-124a and miR-155 are involved in this mechanism as have been proved in cases presenting trigeminal neuralgia, postherpetic neuralgia [66] by modulation of histone deacetylase sirtuin1 (a negative regulator of Foxp3), a modulator of Treg's development. Furthermore, under the mechanism of the regulatory process of miRNA, we also included the CNS-specific macrophage (Mg) and astrocytes activation and cytokine production triggered by CXCR4/CXCR5 (known as CXCL13 receptor) in the eriventricular tissue. All proposed hypotheses in this manuscript must be confirmed by further investigation; unfortunately, it is a rare multimorbidity; therefore, obtaining data from many cases will be almost impossible; in the meantime, we suggest focusing on the capacity to identify therapeutic procedures addressed to miRNA to provide the best benefit of most patients.

DECLARATIONS.

Consent for Publication: We obtained our patient's written informed consent for publication, including laboratory results. All information is fully available for any interested reader by request.

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

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.

Funding: We declare that we have not received financial aid that might influence the results delivered in this manuscript.

Authors' contributions*:* Investigation concept and design: HFS and LFIV. Data collection: HFS and LdeFIV. LdeFIV/HFS analyzed the obtained data and this paper's first and final draft. HFS and LFIV revised and supervised the manuscript. Manuscript writing process: HFS and LFIV. We have approved this version for publication.

Declaration of anonymity: All authors certified that they did not mention this patient's name, initials, and other identity issues. Therefore, a complete anonymity is guaranteed.

Availability of data and material*:* All data used in this study are available from the corresponding author by request.

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ILLUSTRATIONS

FIGURE 1: PRISMA Flow diagram of selected manuscripts.

FIGURE 2: Graphical representation of the lateral view of the ventricular system and in blue an obstructive hydrocephalus, plus locations of the cysticercus inside the system and at the subarachnoid space (Racemose cysticercosis).

FIGURE 3: HIV-gp120 protein-induced demyelination via RANTES. 1.-HIV gp120: Human immunodeficiency virus glycoprotein 120, 2.- CCR4: C-C chemokine receptor 4, 3.-CCR5:C-C chemokine receptor 5, 4.- RANTES: Regulated on activates normal T cell expressed and secreted, 5- TNF-α: Tumor necrosis factor alpha /Chemokine (C-C motif) ligand 5 (also CCL5), is a protein encoded by the *CCL5* gene, 6- Dorsal root ganglion (DRG), 7.- Bipolar cell, 7A-Unipolar cells without dendrites, the 8-Lateral view of the brain, 9.-HHV-7: Human herpes viruses seven, 10.-HIV: Human immunodeficiency virus, 11.-Nucleus, 12.- Blebs, 13.-Golgi apparatus, 14.-Nucleus condensing pyknosis, 15.-Cell shrinkage, 16.-Nucleus fragmenting karyorrhexis, 17.-Apoptotic body, 18.-Phagocyte macrophage/microglia cell, AQP4 (aquaporin four), CA (corpora amylacea), GS(glymphatic system), 19.- Translation of released mitochondria through TNT, 20.-IL-6: Interleukin six, 21.-Endoplasmic reticulum, 22.- Polyribosomes (or polysome or ergosome) is a group of ribosomes bound to an mRNA molecule like "beads" on a "thread", 23.-mitochondrion, 24.-Activated microglia/macrophage, 25.-Messenger ribonucleic acid (mRNA) is a single-stranded RNA molecule necessary for protein production.

FIGURE 4: Representation on the hypotheses on entry mechanism of the HIV/HHV7 into the neurons and supporting cells trough gp120/CD4/chemokine receptors/cell-to-cell/endocytic. 1-HIV-envelope membrane glycoprotein-120 (gp-120), 2-Human immunodeficiency virus (HIV), 3-HIV glycoprotein 41 (GP-41), 4- Chemokine receptor CXCR4, 5- Chemokine receptor CCR5, 6- CD4, 7-Neuron/glial cells from DHSC/DRG, 7A-Astrocytes, 7B-Cell membrane, 8- Endocytic vesicle

(endosome), 9-Lysosome 10-Released nucleocapsid, 11-clathrin which is a large protein involved in the mechanism of formation of a coated pit on the plasma membrane (inner surface) of the neurons/glial cells.12-Transferrin 13-Tf receptor, 14-Lysosomal hydrolase, 15-Mannose-6-phosphate receptor, 16-Activating protein two (AP2), 17-messenger ribonucleic acid (mRNA).

FIGURE 4: Graphical representation of the main elements involved in the surveillance of the brain guided by resting Mg in IVNCC. **RNS=**Reactive nitrogen species, are a family of antimicrobial molecules which main source is nitric oxide (NO) and superoxide ($O_2^{\bullet-}$). Both are produced through the enzymatic activity of NADPH oxidase and nitric oxide synthase 2 (NOS2) respectively, **ROS**= Reactive oxygen species surge from biochemical reactions that occur during respiration and photosynthesis in mitochondria, peroxisomes and chloroplasts. It's well known that mechanism of ATP production in the mitochondria (oxidative phosphorylation), include transport of protons across the inner mitochondrial membrane to oxidation-reduction reactions. Included P2X7, CB2, COX2. During the respiration process the mitochondria convert energy for the cell into a usable form, adenosine triphosphate (ATP). The process of ATP production in the mitochondria, called oxidative phosphorylation, involves the transport of protons (hydrogen ions) across the inner mitochondrial membrane by means of the electron transport chain. **P2X7= P2X purinoceptor 7** is a protein belongs to the family of purinoceptors for ATP. The receptor is commonly found in the CNS/PNS, Mg/Mp, uterine endometrium, and in 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 create a wide pore at the cellular membrane that leads to increased released of ATP 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 hippocampus, amygdala, frontal cortex, and striatum, regions involved in neurodegenerative diseases and psychiatric disorders [82]. We have hypothesized that P2X7 receptor is highly expressed in NCC Mg where mediated CP/PCD, fast and reversible membrane blebbing, multinucleated cell production of exosomes, phosphatidylserine exposure, release of microparticles formation of nitrogen species and ROS.P2X7r expression also triggers intracellular signaling pathway and binding ATP modify its state and open membrane pore for the entrance of Ca^{2+} plus other cations. In case of NCC we speculate that the elevated concentration of intracellular Ca^{2+} ($[Ca^{2+}]_i$) activate some kinases (a protein enzyme that increase speeds of chemical reactions) such as, CaMKII, PKC, PI3K, AKT, GSK3, and ERK1/2 leading to inhibition of Ap or elevate genetic transcription of cell survival. In figure 3, we also included (as part of this hypothesis) the consequences of activation of P2X7r releasing IL-1β/ROS from "jail" and increasing inhibition of GSK3 if the formation of the NLRP3 inflammasome and NF-κB are completed. Finally, we have hypothesized that administrating P2X7 receptor antagonists in patients with massive NCC instead of PZQ/ALB/St may provide some improvement of NI without risk of development of ES/SE and death.

Abbreviations: PKC =Protein kinase C, **CaMKII**= Calcium-calmodulin kinase II, **PI3K**= phosphorylates and activates phosphoinositide 3-kinase, **ERK1/2=** extracellular signal-regulated kinases 1/2, **AKT=**protein kinase B, **GSK3**= Glycogen synthase kinase 3, **FLT1**: *I*s a member of VEGF receptor gene family, encodes a receptor tyrosine kinase which is activated by VEGF-A, VEGF-B, and placental growth factor **ERRB1**: The epidermal growth factor receptor (also known as EGFR; ErbB-1; HER1) is a transmembrane protein receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands, **IL1R**: Interleukin 1 receptor, type I also named as CD121a, is an interleukin receptor. **IL-17**: Interleukin 17 family is a family of pro-inflammatory cystine knot cytokines, produced by a group of T helper cell named as T helper 17 cell, **INFGR1**: Interferon gamma receptor 1 also called as CD119, is a protein encoded by the *IFNGR1* gene, **cPLA2:** cytosolic phospholipase A2, **CCL2:** The chemokine (C-C motif) ligand 2 is also named as monocyte chemoattractant protein 1 (MCP1) and small inducible cytokine A2 and it is a small cytokine that tightly modulates cellular mechanics and thereby recruits memory T cells, monocytes, and dendritic cells to the sites of NI produced by the colloid/nodular stage of NCC according to our hypotheses, **XBP1**: (1) X-box binding protein 1, also called as XBP1, is a transcription factor protein which regulate genes expression to support the immune system and the cellular stress response, **MAFG**: (2)Transcription factor MafG is a bZip Maf transcription factor protein is one of the small Maf proteins, which are basic region and leucine zipper (bZIP)-type transcription factors, **NF-kB:** (3) Nuclear factor kappa-light-chain-enhancer protein of activated B cells control cytokine production, and transcription of DNA, and its involved in cell survival, cellular responses to stimuli such as stress, free radicals, heavy metals, cytokines, ultraviolet irradiation, oxidized LDL, and bacterial/viral antigens and we assumed parasitic antigens too. NF-κB also participate in regulating the immune response to infection, **C3**: Complement component 3, is a protein of the immune system in the blood and plays a remarkable role in the complement system contributing to innate immunity, **NRF2:** (4)The nuclear factor erythroid 2–related factor 2 is a RNA element present in the 5′ UTR of the mRNA encoding the transcription factor Nrf2 and an emerging regulator of cellular resistance to oxidants, **MAT2A**: methionine adenosyl transferase *also known as S*-adenosylmethionine synthetase is an enzyme that creates *S*-adenosylmethionine and is also involved in cell proliferation, gene transcription, and production of secondary metabolites, **AHR**: The aryl hydrocarbon receptor (also known as ahR, AhR, ahr, AH receptor, or dioxin receptor) is a protein transcription factor that regulates gene expression, **BBB**: The blood–brain barrier is a remarkable selective semipermeable border of EC which control that solutes in the brain circulation do not cross into the extracellular fluid of the CNS to protect neurons while allow the entry of the necessary nutrients, **CA**: Corpora amylacea is a small hyaline masses found in the lungs, the nervous system, and the prostate gland, among other organs of the body which increase in advancing age, and its involved in the clearance the metabolite waste in the CNS [39], **AQP-4:** Aquaporin-4, is a water channel protein belongs to the aquaporin family of integral membrane proteins that conduct water through the cell membrane and participate in the clearance system of the brain [39]. **GS:** The glymphatic system oversees waste clearance in the brain of vertebrates modulating the flow of the CSF into the perivascular space mixing the interstitial fluid and parenchymal solutes and exiting down CNS venous perivascular spaces with the capacity to protect the neural network [39]. Unfortunately, we have not evidenced how the clearance system works at the DRG (apart from the fenestrate CV) and at the enteric nervous system (apart from gut/brain axis/CLN) [80], **Pc**: pericytes are only cell located between endothelial cells, astrocytes, and neurons within the neurovascular unit extending their processes along capillaries, pre-capillary arterioles and post-capillary venules. Pc contact with more than 90% of the total vascular length in the cerebral cortex the capillary bed possessing the highest flow resistance within the cerebrovasculature [29], **Mo**: Monocytes are a type of white blood cell which can differentiate into monocyte derived dendritic cells and macrophages. They are part of the innate immune system, can influence the adaptive immune responses and participate in tissue repair mechanism, **NK**: Natural killer cells,(5–20% of all circulating lymphocytes) also named large granular lymphocytes (LGL), are a cytotoxic lymphocyte of the innate immune system belong to the innate lymphoid cells family, **cPLA2**: Cytosolic phospholipase A2 expression is one of the pathways that activates microglia and astrocytes in the brain, **DysMit:** dysfunctional mitochondria, **ER stress**: (7) endoplasmic reticulum stress is a new apoptosis regulatory pathway. **ROS**: Reactive oxygen species, **MMP9:** Matrix-metalloproteinases 9 belongs to the class of matrix metalloproteinases and is secreted as a latent pro-enzyme that requires activation in the extracellular space. The crucial function of MMP is to degrade and later remodel the extracellular matrix. Therefore, MMP-9 has confirmed to be an integral part of several medical conditions where modulation of the ECM is a key step including malignancies, parasitic zoonoses, osteoporosis and fibrosis. This figure also shows an axial view of the CT scan of the head showing signs of bilateral dilatation of the ventricular system and calcified NCC.

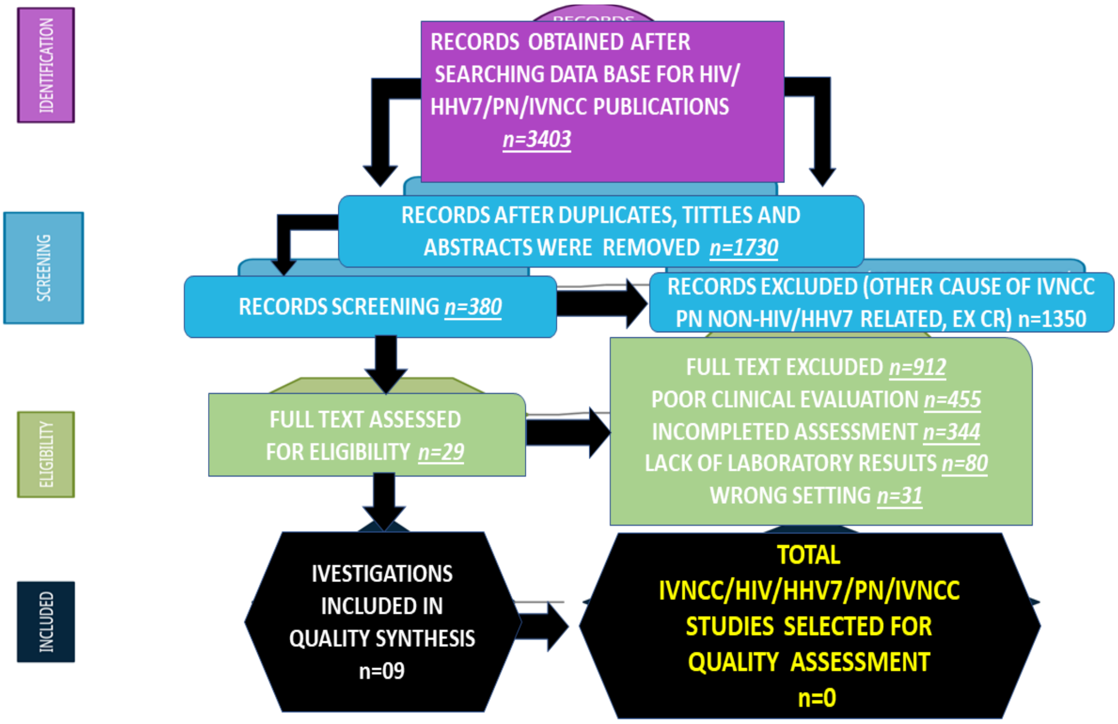

FIGURE 1: Flow diagram of included publications.

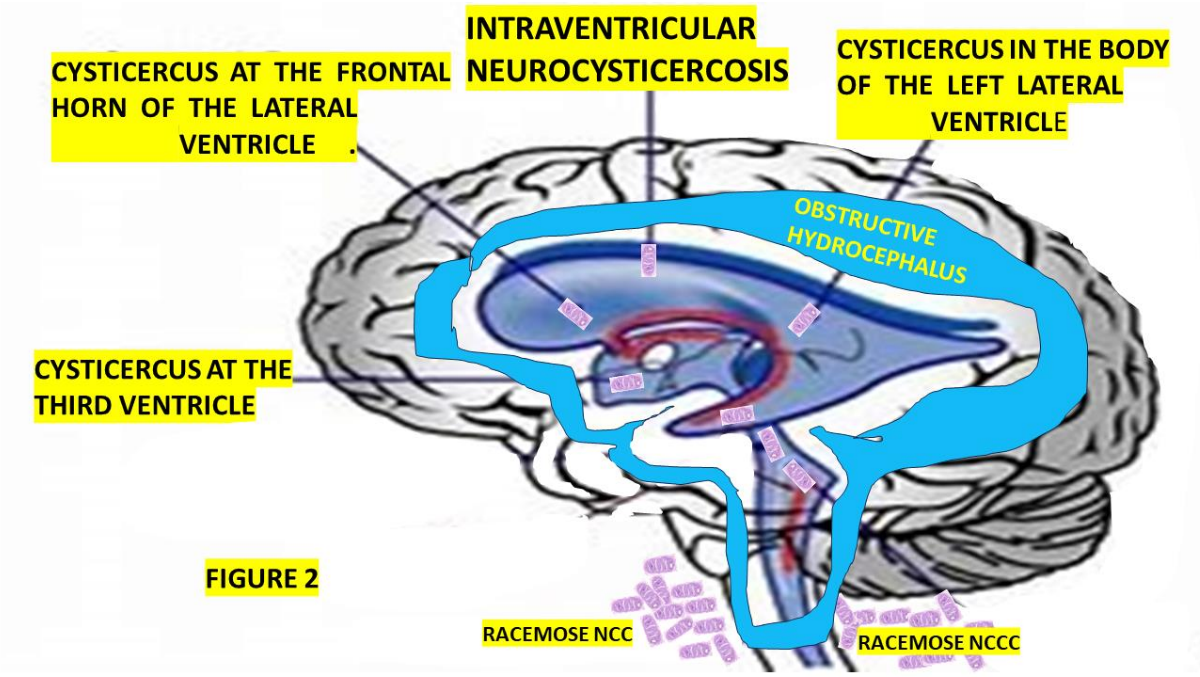

FIGURE 2

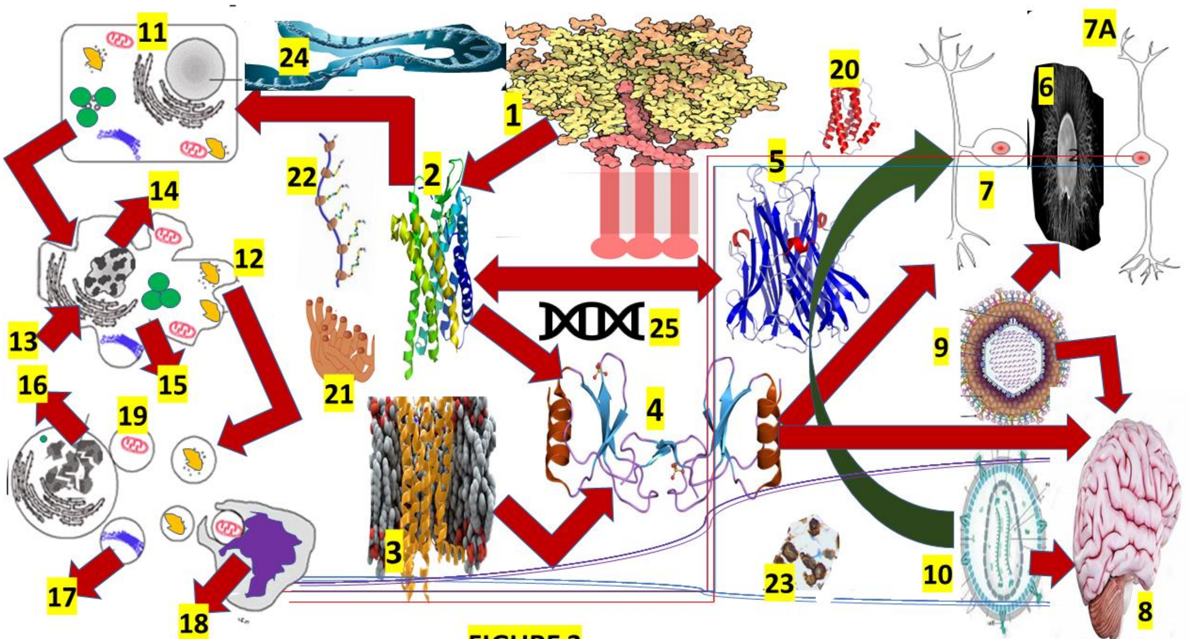

FIGURE 3

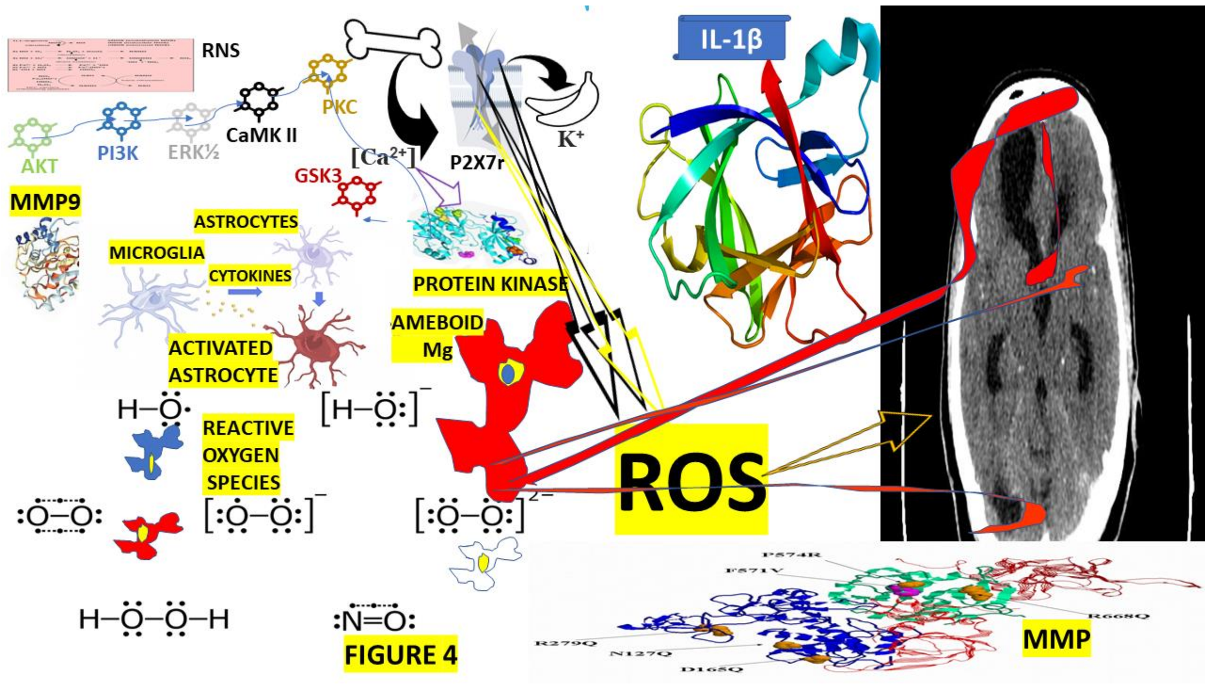
RNS
AKT
PI3K
ERK½
CaMK II
PKC
$[Ca^{2+}]$
P2X7r
K^+
IL-1β
MMP9
GSK3
ASTROCYTES
MICROGLIA
CYTOKINES
PROTEIN KINASE
ACTIVATED ASTROCYTE
AMEBOID Mg
REACTIVE OXYGEN SPECIES
ROS
P574R
F571V
R279Q
N127Q
D165Q
R668Q
MMP

FIGURE 4