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Research Article

Obstructive Sleep Apnea Syndrome and Neurocysticercosis: A Comprehensive Review

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Abstract

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

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

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

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

Keywords: Neurocysticercosis; Obstructive sleep apnea; Obstructive sleep apnea syndrome; Ischemic stroke; Epilepsy; Cardiac complications

List of Abbreviations

(AF) Atrial Fibrillation; (AHI) Apnea Hypopnea Index; (AI) Apnea Index; (APAP) Auto-Titrating Positive Airway Pressure; (ARI) Arousal Index; (BMI) Body Mass Index; (BP) Blood Pressure; (CAD) Coronary Artery Disease; (CHF) Congestive Heart Failure; (CI) Confidence Interval; (CPAP) Continuous Positive Airway Pressure; (CRP) C-Reactive Protein; (CSA) Central Sleep Apnea; (CT) Computerized Tomography; (EEG) Electroencephalogram; (HNS) Hypoglossal Nerve Stimulation; (HRV) Heart Rate Variability; (MI) Myocardial Infarction; (NREM) Non-Rapid Eye Movement; (OSA) Obstructive Sleep Apnea; (OSAS) Obstructive Sleep Apnea Syndrome; (PAP) Positive Airway Pressure; (Pcrit) Upper Airway Critical Closing Pressure; (POSA) Positional Obstructive Sleep Apnea; (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-analyses; (QOL) Quality of Life; (RLS) Restless Leg Syndrome; (SAQLI) Sleep Apnea Quality of Life Index; (SBP) Systolic Blood Pressure; (SD) Standard Deviation; (UA) Upper Airway

Introduction

Obstructive Sleep Apnea (OSA) is a disorder typically characterised by recurrent obstruction of the Upper Airway (UA) during sleeping time, causing Intermittent Hypoxia (IH) and Sleep Fragmentation (SF). OSA is usually associated with remarkable daytime sleepiness impairing the Quality of Life (QOL) and increases the incidence/prevalence of Central Nervous System (CNS) and neuropsychiatric disorders, including cognitive decline, memory impairment, depression, and inattention. Furthermore, OSA leads to cardiovascular and cerebrovascular morbidity, including arterial hypertension, coronary disease, cardiac failure, and Ischemic Stroke (IS). The global prevalence of OSA is calculated to be 1 billion among adults aged 30 years–69 years and is seemingly increasing, creating a sizeable socioeconomic burden worldwide [1]. As a unanimous consensus, OSA is a multifaceted and complex disorder characterised by many symptoms, signs, and comorbidities [2].

In 1965, Henry Gastaut, et al. and Jung R, et al. (1965) described OSA for the first time as a nocturnal manifestation of Pickwick syndrome [3]. Continuous Positive Airway Pressure (CPAP) therapy, introduced in 1981 by Sullivan

and collaborators, was recommended as the best treatment modalities for OSA [4,5].

OSA is highly prevalent among cases presenting HTA, DM, cardiac disease (arrhythmias-AF, heart failure with reduced ejection fraction, and acute coronary syndrome), and stroke [2].

The new classification of severity of OSA is based on the frequency of events per hour as follows: None <5, mild OSA from ≥ 5 to <15, moderate OSA ≥ 15 to <30 and severe OSA ≥ 30. Wong and colleagues have established that females have apnea of shorter duration and less desaturation than males, but ageing is associated with a higher rate of cardiac failure and death [6].

To suspect the diagnosis of OSA Syndrome (OSAS), the patient must make a complaint of sleep-related breathing disturbances such as snoring, gasping, snorting or breathing pauses plus fatigue that happens despite good enough opportunities to sleep in the absence of other explanatory medical conditions, excessive daytime sleepiness, or ≥ 5 more episodes of obstructive respiratory events per hour of sleep. Nevertheless, patients presenting ≥ 15 episodes/h of Apnea-Hypopnea Index (AHI) can be included in OSAS [7].

Some consequences of OSAS can be seen related to the frequency of respiratory events such as Arterial Hypertension (HTA) and stroke in a dose-dependent fashion [8].

The guidelines for OSAS therapy proposed by Patil and associates are based on the presence or absence of clinical features, the AHI, and associated comorbidities [9].

The frequency of OSAS increases exponentially in sleep supine position versus lateral position, favouring by the BMI, neck circumference, lateral pharyngeal wall volume and the measurement of the posterior airway space [10,11].

Excessive daytime sleepiness is more frequently present in non-REM-related OSA than REM-related OSA and depression syndrome together, which profoundly affect the Quality of Life (QOL) of affected patients [1].

Other authors reported the substantial criteria to differentiate OSA from Upper Airway Resistance Syndrome (UARS), which is characterised by an airway collapse during sleep leading to respiratory effort-related arousal, which is >10s sequences of breaths with a gradual increase of respiratory effort or flattening of the flow signal during the inspiration plus worse daytime sleepiness, with lower BMI, less weight gain, less N1 and N2 sleep during PSG study, plus the elevated frequency of insomnia, difficulty concentrating, cognitive problems, depression, irritable bowel and poor psychomotor performance that do not meet the established criteria of OSA, despite the UARS and OSA sharing similar pathophysiology [1,12-16].

In America, the prevalence of OSA has been estimated to range between 0.15% and 0.4% in people beyond the age of 18 years old [17,18]. This prevalence may increase to 10%-20% in obese people [19,20]. However, other authors reported the general prevalence of OSA is 24% in males and 9% in females if an alternative definition of hypopnea (≥ 4% oxygen desaturation) is used. Notwithstanding, other levels of prevalence can be reported according to the parameter implemented in the calculation, such as age, AHI ≥ 5, excessive daytime sleepiness, craniofacial anatomy/reduced size of the mandible, gender (males and post-menopause females are almost equal), race/ethnicity data, MBI ≥ 40 among men aged 50 years–70 years, genetic factors, Oxygen Desaturation Index (ODI), family history of OSA, specific structural abnormalities, and regional prevalence data including residential factors/neighbourhood features, greater pollution/ambient air quality [1].

Regarding cysticercosis, we would like to highly that mature tapeworms develop in the gut after ingesting cysticercus from unfreezing/undercooked contaminated pork meat by the human host. When pigs or humans ingest eggs/proglottids, the oncospheres hatch in the small intestinal epithelium and penetrate the intestinal wall and the cysticercus disseminate to almost all over the body excepting membranes, narrow cavities, hair, nails, adrenal gland, bone tissues, or cartilage. When the parasite penetrates the brain tissue, ventricular system, subarachnoid space, optic nerves or the spinal cord to form cysticerci, it is called neurocysticercosis [21-25].

Cysticercosis (Ct) is a preventable neglected zoonosis secondary to a parasitic infection by the larva form of the pork tapeworm Taenia solium (Ts), commonly seen in persons from developing countries. Cysticercosis can infest most organs in human beings and pig populations. The most common clinical manifestations of NCC are headache and Epileptic Seizures (ES)/Epilepsy (Ep), mainly in the intraparenchymal form [21-25].

We made more than ten epidemiological investigations in rural areas around Mthatha (South Africa), concluding that NCC is the main cause of secondary epilepsy. All ES and Ep respond very well to Antiseizure Medication (ASM) and Antiepileptic Drugs (AED) [26-35]. Likewise, lack of available antiepileptic medication, financial constrictions and poor compliance were the common causes of Status Epilepticus (SE). Despite this, patients presenting refractory Ep due to NCC were never seen in our region for the past 2 decades [26-35]. The commonly used ASM is benzodiazepine, and the commonest AED are valproic acid and carbamazepine. Levetiracetam (Keppra) is unavailable in rural areas [36-39].

Humans are the final host for taeniasis. However, humans and pigs can be intermediate hosts if they carry on the cysticerci (larval form). When these cysts are ingested *via* undercooked contaminated pork meat, they go to the gut, where scolex evaginates. They are attached to the intestinal mucosa wall by 2 crowns of hooks. At the gut, one or a maximum of 2 parasites mature are developed [40-42].

Recently, we published some novel aspects of NCC associated with COVID-19, HIV, autoimmunity, and the role activated OLG/OPC/NG2 plays in the pathogenesis

of NCC and its lymphatic drainage. As we documented before, the activation of Microglia (Mg) and Astrocytes (As) are intensely involved in the pathogenesis of NCC [43-47].

We also reported the clinical features of Spinal Cord NCC (SCNCC), and recently, we commented on the role played by Rouget cells/pericytes in the pathogenesis of local NI, the healing process, and the outcome of the NCC [48].

The main aims of this study are to evaluate the association between OSAS and stroke in NCC from reported cases in the available medical literature, to describe any novel clinical features of patients with OSAS/NCC presenting IS/ES/Ep, and to answer the following research question:

1. How often has this comorbidity been reported in the medical literature?
2. What is the most accepted OSAS/NCC pathogenesis?

Material and Methods

Search strategy

We used a novel search strategy for the selected databases, registers, and websites, including filters and limits. We investigated it using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Database retrieval and data extraction were performed independently by 2 authors. Subject headings and text words were searched in electronic databases such as Scopus, Central PubMed, Web of Science, Medline (Ovid), and EMBASE. We searched the medical publications comprehensively, looking for published Medical Subject Heading (MeSH) terms like", "pathogenesis of OSA/NCC", "comorbidity OSAS/NCC", or "Management of OSA" OR" OSAS/NCC/Ep/ES" OR "NCC/OSAS/Cerebrovascular diseases".

We also checked https://www.clinicaltrials.gov/, from the USUS 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, or Portuguese.

The reported incidence and prognosis of NCC/OSAS in the medical literature were searched. Weighted Mean Differences (WMDs) with referent 95% Confidence Intervals (CIs) and pooled Odds Ratios (ORs) with 95% CIs were assessed to explore the risk factors of OSAS/NCC/IS/Ep. The references of selected manuscripts and relevant reviews were also screened, and additional reports were looked for.

Eligibility criteria

Separately, all researchers assessed each publication by screening the title and abstract and, in most cases, reading the full text. Studies were included if they indicated concern about it.

We only included papers published in Spanish, English, or Portuguese. The authors chose the paper with the best calculated and larger sample size when overlapping cohorts were observed. Letters to Editors, editorials, and conference abstracts were excluded.

Data collection and risk of bias assessment

We planned to extract the study location, study design, year of publication, sample size, demographic features, confirmation of diagnosis, management of patients, potential risk factors, and prognosis from the selected studies. To evaluate the quality of the manuscript, we used the Newcastle Ottawa Scale (NOS) scoring ≥ 7 as the criteria for high-quality research. All disagreements were resolved through scientific discussion until we reached a unanimous final consensus.

Statistical analysis

Our protocol establishes that the statistics analysis for this study is performed using Review Manager version 5.4 from Cochrane Collaboration, Oxford, United Kingdon. Notwithstanding, we converted to mean and Standard Deviation (SD) all continuous variables presented by median (quartile) or median (range) according to the reported formula. In a few reports, we Weighted Mean Differences (WMDs) with corresponding 95% CIs and pooled ORs with 95% CIs were calculated using the Mantel–Haenszel fixed-effects when risk factors were identified in more than one research. In the absence of heterogeneity, the random effect was chosen.

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 involved in ethical approval.
2. The whole article should be written in English, Spanish, or Portuguese.
3. The central aspects are NCC, OSAS, and the pathogenesis of OSAS/NCC
4. The manuscript was published in a peer-reviewed medical journal.

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 at least twice (blinded).

All manuscripts presenting exclusion criteria were not introduced, and a professional analysis discussion solved

discrepancies among authors.

Medical literature searching programmed

We selected case reports, case series, observational cohort studies, systematic reviews and meta-analyses, cross-sectional studies, Randomised Controlled Trials (RCTs), and published guidelines were first identified to provide the most relevant Level of Evidence (LOE) if available. Appropriate investigations were displayed in a standardised format, with the quality of each study graded using the Oxford LOE (LOE Level 1a–5). During this search, we looked for articles published between January 1, X, and December 31, 2023. We searched the following databases: Scopus, Central PubMed, Web of Science, Medline (Ovid), and EMBASE. We include articles from other databases such as Google Scholar, online databases, Scielo, BioRxiv, medRxiv and Cochrane Library. All studies were retrieved by utilising MeSH, as previously cited.

Study selection

We select prospective/retrospective cohort studies, clinical trials, case-control studies, case reports, case series, review articles, meta-analysis reporting data on listed topics and controlled clinical trials. Three studies that meet the inclusion criteria were excluded because the authors did not provide proof of confirmation of associated comorbidity. A flow diagram shows the number of search and selection process results from the total identified studies in the review.

Process of data collection

Authors independently extracted crucial information from each manuscript using Microsoft Excel and a structured coding scheme. The data collected included clinical features, population size, age distribution, and the means used to diagnose CT scan of the head studies for NCC, and clinical assessment for OSAS, and other investigations considered to confirm the diagnosis of OSAS.

Synthesis of data

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

Quality assessment of included manuscripts

We used the modified Jadad scoring system to assess the bias and blinding outcomes. All authors independently assessed each study with the same automation tools for risk of bias using the Jadad scoring system (based on randomization-2, double-blinding-2, and a description of dropout rate-1), [17]. Trials scoring 3 or greater are considered good-quality trials (Jadad's scores range/from 0 to 5). Therefore, trials with a Jadad score <3 were excluded.

Results

Study selection

This review aims to update the scientific information released about these issues. 2095 manuscripts were retrieved from electronic databases until December 31, 2023. After removing irrelevancy and duplicates, 308 papers were taken for full-text screening, and finally, 6 studies reporting outcomes of interest were included for review. All selected manuscripts were peer-reviewed, but no publication including NCC/OSAS/Ep/IS were found. A flow chart from the literature search is shown in Figure 1.

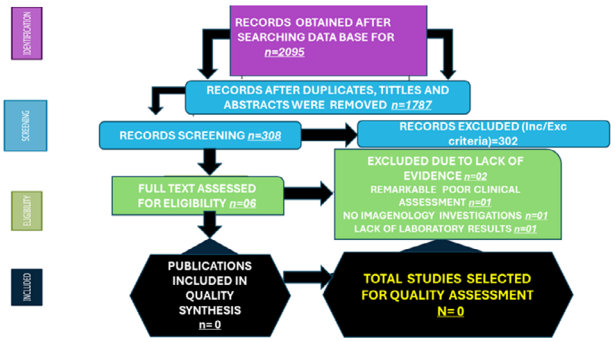

Figure 1: Flow diagram with included publications

Study and subject characteristics

Among the 6 studies, Japan conducted the most studies (n=2), followed by Korea, China, India, and Canada (n=1 each). The methodological quality of 6 studies used was assessed using NOS, and all studies were generally considered of medium-to-high quality. Still, no report about the comorbidity of OSAS/NCC was reported.

Patient-specific variables

Six studies investigated IS risk factors in patients with OSAS. Combining the results of 2 studies, we observed that age at OSA diagnosis was not associated with NCC. No heterogeneity was identified between studies (I2=0%, p=0.53). No correlation was observed between age at NCC diagnosis and OSAS. The pooled analysis suggested that the male sex was associated with an increased risk of OSAS/IS (OR: 1.68, 95% CI: 1.17–2.23), whereas no heterogeneity was observed between studies (I2=0%, p=0.72).

OSA/NCC-specific variables

In 6 studies designed to investigate risk factors for IS/OSAS, no significant differences were observed between NREM and REM groups. We did not perform a meta-analysis because the criteria for positivity varied across studies.

Discussion

The correlation between NCC and OSAS was not investigated before. Therefore, based on the found publications regarding NCC/OSAS/ES/Ep/IS we do elaborate some hypotheses to bring more light into the pathogenesis of this comorbidity to answer one of the research questions.

Some cohort investigations have found severe OSA to be associated with remarkably elevated odds of incident arterial hypertension, ischemic stroke, and cardiovascular fatal outcomes [49]. We hypothesised that ischemic stroke might increase in patients presenting INCC or SANCC and associated OSA due to high activation of the sympathetic system, a pro-inflammatory state caused by cyclic

hypoxemia, negative intrathoracic pressure, arousal, and closure of the upper airway as has been proposed by the same author under different circumstances [49].

Patients presenting IS have a 60%-70% risk of having OSA, and we speculated that the incidence/prevalence of TIA/IS is several times increased in patients with OSA and SANCC, as we will comment below [50].

Intermittent Hypoxia (IH) is one of the consequences of OSAS, causing recurrent cycles of hypoxia/normoxia to the cell bodies, leading to increased ROS production from Mitochondrial (Mt) damage, superoxide production, activated inflammatory cells from one side and on the other side, diminished antioxidant capacity promoting Oxidative Stress (OS) which has been reported in NCC before by us but now it's aggravated by OSAS [51]. Therefore, IH provokes OS in cases presenting OSAS, and this condition promotes the production of pro-inflammatory cytokines, resulting in systemic Neuroinflammation (NI) with increased endothelial cell adhesion molecules, hypercoagulability, and sympathetic and vagal activation. The sympathetic expression triggers the renin-angiotensin-aldosterone system, leading to an elevated concentration of angiotensin II and aldosterone in the blood flow.

In the case of NCC, the elevated production of ROS at the Mt is interconnected with the P13K cascade, MAPK pathways, and c-Jun N-terminal kinase, inducing multiple nuclear transcription factor expression, as we published recently [51]. The most relevant one is the nuclear factor kappa B (NF-κB), which has been well documented in OSAS apart from other adhesion molecules, proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8), and adipokines [52,53] and on top of that, upregulated AP-1 also participate in the pathogenesis of systemic inflammation in OSAS [54].

Biddlestone, et al. (2015) established that IH is intensely involved in the mechanism of OSAS [54]. Recently, we documented the role played by an essential organelle for protein synthesis, secretion, cell homeostasis and lipid biosynthesis named Endoplasmic Reticulum (ER) stress in the NCC OS [55,56]. We hypothesised that homeostasis is disrupted in cases of NCC/OSAS. The increased concentration of unfolded and misfolded proteins activates the ER stress, triggering the unfolded protein response under the regulation of protein glucose-regulated protein BiP/GRP78, as has been reported by Xu, et al. in cases of chronic IH under similar circumstances [55]. On the other hand, accelerated separation of BiP and GRP78 under severe/prolonged ER stress might activate Protein Kinase-Like Kinase (PERK) inositol and Transcription Factor 6 (ATF6), accelerate CHOP protein and mediate Programmed Cell Death (PCD) and Regulated Cell Death (RCD).

Brief comments on epigenetics changes in NCC/OSAS

The epigenetic mechanism has been reported as related to the development of OSAS, OS, sympathetic hyperexpression, low-grade NI, and chronic obstructive pulmonary diseases [56].

The role played by noncoding RNA such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in the pathogenesis of PANoptosis and Mg expression in cases of NCC was reported recently by us (Role of Mg and PANp). However, even before (2018) it was documented the interrelationship between miRNA and IH/induced apoptosis by Liu, et al. while other authors have reported that miR-207 downregulation and miR-26b-5p upregulation are involved in IH-induced cognitive impairment by cleaved caspase-3 expression, increasing Bax and reducing Bcl-2 expression in the hippocampus [57-59]. Based on these findings, we hypothesised that the management of OSAS could soon be monitored through miRNA assessment.

On the other hand, LncRNAs, which are composed of RNA strands longer than 200 nucleotides not translated into proteins, can regulate gene expression through several mechanisms, including chromatin modification, posttranscriptional regulation, and transcriptional activation or repression, and some of them downregulate/upregulate expression can be activated by quantitative reverse transcription PCR. The role played by the lncRNA in the pathogenesis of OSAS and consequently reducing pulmonary arterial hypertension promotes type 2 diabetes, aortic endothelial dysfunction, PCD/RCD, systemic NI, metabolic dysregulation, dysautonomia, OS, atherosclerosis, decline cognitive activities including executive function, memory, and comprehension, insomnia, mood disturbances, excessive daytime sleepiness, intense neuronal injury the CA1 hippocampal region, and other cardio-cerebrovascular disorders [60-62].

Recently, we discussed the role played by gut microbiota in patients with NCC and their influence on the brainstem trough *via* the gut-brain pathway, changes in the intestinal metabolites and neurohormones production, intestinal barrier, increased production of ROS/OS, sympathetic activation, and systemic inflammation [63,64]. Now, we hypothesise that OSA can lead to dysbiosis *via* IH, favouring cardiovascular disorders, metabolic diseases, malignancies, reproductive disturbances, and stroke, according to the studies made by Renjun and collaborators [60].

Epidemiological investigations have reported a close association between OSAS and increased risks of neurological disorders [65,66].

Apart from the previously cited associate disorders to OSAS, the same authors have reported hypertension, cancer, non-alcoholic fatty liver disease, immunological disorders, insulin resistance, glucose metabolism, and kidney disease [62]. Our proposal for the mechanism of OSAS is graphically represented in Figure 2.

Despite the lack of evidence to support a clear-cut mechanism of airway collapse, some functional and anatomical factors have been taken into consideration, such as Pharyngeal critical closing pressure (Pcrit), decreased respiratory arousal threshold, upper airway dilator muscle activity, and increased loops gain [67].

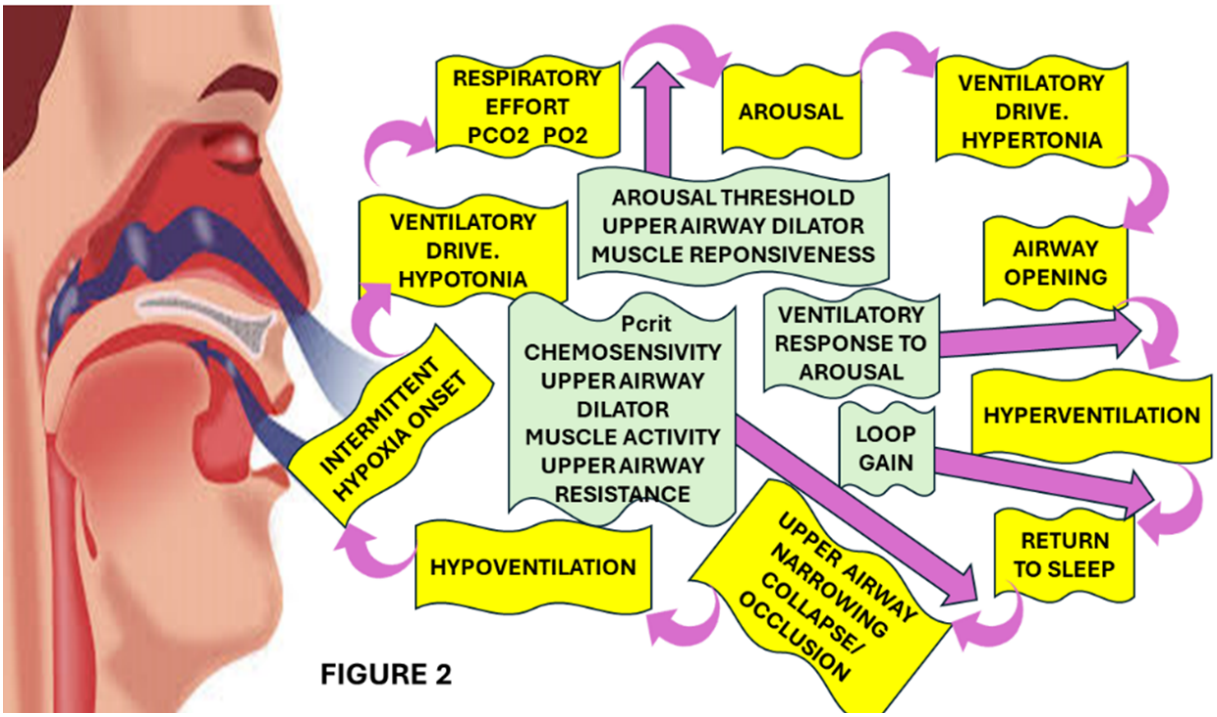

Figure 2: Mechanisms influencing upper airway collapse in the pathogenesis of OSAS and the interplay between various factors. The reduction in upper airway volume caused by obesity or craniofacial structural abnormalities and soft tissue changes is an important factor in upper airway collapse. All OSAS patients have different degrees of upper airway anatomical structure injury. A nocturnal rostral fluid shift is defined as fluid accumulated in the legs during the daytime, redistributing to the upper part of the body upon lying down at night, causing an increase in peripheral pressure. In addition, most patients have mucosal oedema, and the mechanism is not clear. Furthermore, several mechanisms associated with a low respiratory arousal threshold, poor pharyngeal neuromuscular muscle responsiveness, high loop gain, and high passive Pcrit may involve OSAS. When awake, neuronal activity ensures that the muscles of the dilated throat are activated, thereby preventing collapse. When this muscle loses activation during Rapid Eye Movement (REM) sleep (chemosensitivity, central respiratory neurons, and ventilatory drive), the airway may collapse. Schematic representation of multiple pathological factors interacting to promote cyclical OSAS pathogenesis. In addition, these mechanisms might represent therapeutic targets. In the treatment section of this article, we introduce targeted therapies for different mechanisms

In Figure 2, we represented graphically our hypotheses on the UA collapse in patients presenting OSAS, including the interrelationship between different factors.

OSAS in NCC and dysbiosis

Under normal circumstances, the beneficial relationship between human beings and their gut microbiota is reciprocal because the host provides the necessary nutrients to more than 100 trillion microbiotas, while some of them support and maintain the host immunome response, give nutrients to the host, and secure a barrier against invading pathogenic elements [68,69].

Some of the Bacteria play a crucial role in carbohydrate and fibre fermentation, which produce Short-Chain Fatty Acids (SCFAs)-acetate-propionate-butyrate which can pass through the BBB into the neuro site, affecting the growth, development, function and maturation of Mg, enhancing the immunity and immune defence of the CNS and leading to the more important source of energy and nutrition for colonic epithelium. Nonetheless, butyrate may provide neuroprotection by reducing microglial activation as well [70-73].

However, we hypothesise that the most critical microbiotas involved in the mechanism of OSAS in patients presenting NCC are some species of Firm known as Desulfovibrio (Des) and Prevotella (Pre), followed by Lachnospiraceae and Paraprevotella which can disrupt the histological integrity of the gut barrier favouring the IH as we graphically represented in Figure 3 as have been reported by other investigators [73,74].

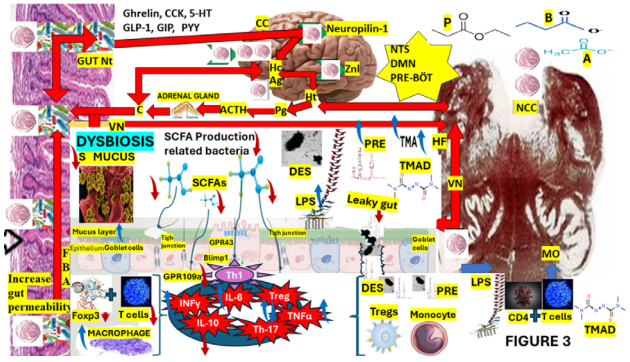

Figure 3: Graphical representation of pathogenesis of brainstem dysfunction, role of microbiome/immune system, subarachnoid neurocysticercosis, gut neuroendocrine activity, gut neurotransmitter, ischemic stroke/gut microbiota, micro thrombosis. A: Acetate. ACE-2: angiotensin-converting enzyme 2. ACTH: adrenocorticotrophic hormone. Ag: amygdala. B: butyrate. C: Cortisol. CC: Cerebral Cortex. CCK: Cholecystokinin. DMN: Dorsal Motor Nucleus Vagus. GIP-1: Gastric Inhibitory Peptide 1. GLP-1: Glucagon-Like Peptide 1. GUT Nt: Gut Neurotransmitter. HFe: Hyperferritinemia. Hc: Hippocampus. Ht: Hypothalamus. IS: Ischemic Stroke. Li: Liver. L: Lungs. Mthr: Micro Thrombosis. MLN: Mesenteric Lymph Nodes. MO: Medulla Oblongata. NCC: Neurocysticercosis. NTS: Nucleus Tractus Solitarious. P: Propionate. PYY: Peptide YY (peptide tyrosine). Pg: Pituitary Gland. PRE-BÖTC; pre Bötinger complex. S: Spleen. VN: Vagal Nerve. Znl: Zonulin. 5-HT:5 Hydroxy Tryptamine.OSAS-induced low-grade systemic inflammation by mediating gut dysbiosis. The increased F/B ratio is a

hallmark of gut microbiota dysbiosis, which is mainly characterized by a decrease in SCFA production-related bacteria and an increase in harmful bacteria. Decreased mucus secretion and mucin synthesis by dermal goblet cells disrupt the integrity of the intestinal barrier. The intestinal epithelium is dysfunctional due to inadequate nutrition, manifesting as reduced mucus production, decreased mucin secretion, and disrupted intestinal barrier integrity. Increased abundances of Prevotella and Desulfovibrio produce lipopolysaccharide and promote the degradation of mucin, increasing intestinal permeability and leading to a "leaky gut", which triggers an intrinsic and adaptive immune response that induces low-grade inflammation in the body. Prevotella converts nutrients containing TMA into TMAO, which promotes inflammation

As we mentioned, the Firm/Bact ratio is a hallmark of gut dysbiosis in NCC/COVID-19 cases, leading to brainstem dysfunction based on IH exposure models [66]. It has been accepted that gut components are generally hypoxic as a general concern. Some investigators have calculated a gradient of O_2 around 150 μm-200 μm close to the intestinal epithelium membrane, which can affect the microbiota metabolism *via* IH [75]. Notwithstanding, we hypothesised that in the case of NCC with OSA presenting IH, a periodic hypoxia/reoxygenation parameter in arterial blood is expected to find and the prolonged duration of hypoxia leads to predominate surveillance of gut anaerobes microorganisms as can be seen in animal investigations under different circumstances [76,77].

Nevertheless, IH exposure modulates changes in the number of aerobic elements and their increment. Therefore, dysbiosis can be a consequence of a modified Fir/Bac ratio due to increased quantities of anaerobic elements favouring by sleep fragmentation and its implications, including arousal, elevated sympathetic expression and catecholamines plus increased growth of Firm and decreased Bact as has been documented in animal investigations [78].

Nonetheless, we speculate that in the absence of NCC/OSAS, the average balance between Firm/Bact supports the necessary regulatory process to keep the cell balance between Th17/Treg and SCFAs *via* epigenetic process can trigger the differentiation and proliferation of Treg while in the presence of NCC/OSAS, the consequent imbalance between Th17/Treg is combined with the increase production of proinflammatory cytokine contributing to the development of several pathologic processes; it is supported by the confirmation of increases number of Th17 cells and the remarkably elevated cell ration of Th17/Treg in cases presenting OSAS [79].

On top of that, augmented adrenergic stimulation of enteric neurons modulates the peristaltic movements and ion transportation, leading to changes in the microbiota composition plus damage to the integrity of the gut epithelial membrane through IH/ischemia-reperfusion injury present in cases with NCC and predominance of Desu/Prev [60,80]. On the other hand, the sulphate delivered by mucin degradation by Prev and cleared by Desu also augments the permeability of the gut mucosa, increases plasma gut fatty acid-binding protein/ischemic gut mucosa, reduces levels of butyrate/acetate, leading to dysfunctional epithelial membrane, "leaky gut", and nutritional disorders.

We also hypothesised that SCFAs production is strongly linked to the reduction of the bacterial population in cases of comorbidity of NCC and OSAS because of the crucial role SCFAs played in the mechanism of secure intestinal integrity. In Figure 3, we also represent butyrate as the most critical source of nutrition and energy for enterocytes, enhancing the tight junction protein activity, increasing transepithelial resistance, and preventing intestinal permeability and its integrity. Butyrate also acts on G-protein-coupled receptor 43 on the epithelial gut, leading to secretion of IL-10 as an anti-inflammatory cytokine, decreasing the inflammatory response of Th cells and stimulating the production of T helper 1 cells (highly differentiated ones) and mTOR, which can upregulate B lymphocyte-induce maturation protein-1. GPR109A is also activated by butyrate, which induces Treg and T-cell differentiation via GPR109A expression, producing IL-10, which enhances the anti-inflammatory response from colonic macrophages and dendritic cells. Butyrate can downregulate the Histone Deacetylase (HDAC) expression of T lymphocytes to regulate immune response [81,82].

Another author documented that butyrate therapy of naïve T cells might accelerate histone H3 acetylation levels in the regions of fork head Box p3 gene, promote naïve CD4+ T cells to change into Treg, which diminishes the remarkable immune response caused by Th1/Th17 cells through central IL10 secretion [83]. We also included propionate because both help to protect the gut epithelial cells through induction of mucin glycoproteins as a vital component of the mucus layer separating the lumen from the colonocytes as has been previously postulated by other investigators [84].

Besides the before-cited process, acetates have a remarkable influence on mucus secretion and the differentiation of the gut epithelial goblet cells. At the same time, other authors highlight the role of that mucus in improving the immune defence capacity of enterocytes by increasing their tight junction. This process inhibits the capacity of bacteria and LPS to pass from the gut into the systemic circulation [85]. We also agreed the SCFAs are hormone signalling molecules able to lead regulation of the immune mechanism in both ways *via* host metabolism's receptors, which increases the phosphorylation of ribosomal protein S6 (a target of the mTOR pathway) inducing the acetylation of p70 S6 Kinase (S6K), phosphorylation of S6, and promoting the secretion of IL-10, IFN-γ, the differentiation of IL-17, and CD4+ T cells and based on the studies published by Rosenzweig, et al. we hypothesised that in cases with NCC/OSAS, the central structural lesions in the CNS are located in gray matter in the prefrontal cortex, thalamus, parietal cortex, anterior cingulate cortex, hippocampus, cerebellum, and Para hippocampal gyrus [86,87].

It is internationally accepted that the CNS (mainly the brain) require more oxygen and energy consumption than the other systems, being more highly sensitive to hypoxia than other organs. Therefore, the IH resulting from the combination of NCC and OSAS causes remarkable dysfunction due to structural neuronal damage of the

CNS through dysfunctional Mt and OS overexpression, leading to programmed/regulated hippocampal cell death in response to Mg polarisation, proinflammatory cytokines, NK-κB, CRP, and cyclooxygenase-2 levels (Figure 4).

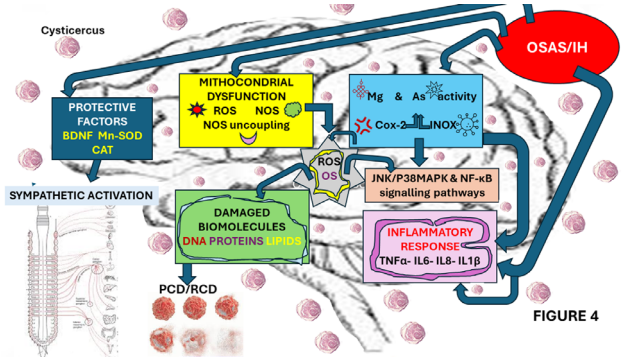

Figure 4: Neurocognitive dysfunction-proposed interactions between neurological disorders and other pathological processes induced by OSAS/IH-induced elevated ROS levels. OSAS/IH upregulates the expression of ROS in the brain, and the inhibitory effect of protective neurotrophic factors on ROS is weakened, which further leads to an increase in ROS. The macromolecular substances in injured nerve cells cause nerve cell death and activate inflammation-related signaling pathways to release inflammatory factors. Sympathetic nerve activation by OSAS/IH could cause cognitive impairment independently of other mechanisms. In addition, OSAS/IH can directly activate microglia and astrocytes and promote the release of inflammatory cytokines in the central nervous system. Excessive neuroinflammatory responses could, in turn, promote the activation of glial cells, resulting in synaptic damage and loss, neuronal necrosis, and apoptosis and ultimately leading to exaggerated neurocognitive dysfunction. BDNF brain-derived neurotrophic factor, Mn-SOD superoxide dismutase, CAT catalase, COX-2 cyclooxygenase-2, iNOS inducible nitric oxide synthase

As we reported recently, Mg expression in cases with NCC is accompanied by a high concentration of COX-2 and inducible nitric oxidases synthase, which leads to elevated ROS production/OS, triggering the NF-κB signalling pathway, JNK (a member of MAPK family) followed by hippocampal injury and cognitive decline [52]. We hypothesised that another member of the MAPK, the p38MAPK could be significantly increased in cases of NCC/OSAS when the IH is remarkably present causing NF-κB signalling pathway hyperexpression, releasing proinflammatory cytokines, mainly IL-1β, IL-6, IL-8, INFγ, and TNF-α, plus adhesion molecules, ROS/OS, neuronal brain injuries, PCD/RCD including Cuproferropanoptosis (CrFePANp) [88].

We highlighted before that during NCC/Mg polarisation, excitatory neurotransmitters such as glutamate are secreted from the colloid stage of the cysticercus and Mg expression [52]. Therefore, we now speculate that in cases of NCC/OSAS, the concentration of perilesional glutamate is even higher, promoting excitotoxicity-induced cerebral neuronal dysfunction and PCD/RCD, which can be supported by the results published by Macey et al. at the insular cortex in OSA [89].

Brief comments on therapy of OSAS in patients presenting NCC

The medical and surgical therapy of NCC has been described many times before by us, and no new therapies have been found during the current review of the medical literature [21-47]. However, new therapies of OSAS addressed to improve Quality of Life (QOL), decrease the number of complications, and reduce the mortality rate has been introduced during the present decade including medical devices such as continuous positive airway pressure, oral appliances such as lower jaw protrusion splint, hypoglossal nerve stimulation for better seizure control (if appropriate), other intra-oral neuromuscular stimulation device, Vagal Nerves Stimulations (VNS) therapy with output current at night less than 1.25 mA and/or the ON time at night less than 30 sec, and to apply deep brain stimulation of the anterior nucleus of the thalamus; pharmacological therapy; behavioural managements and surgical approaches conducted by maxillo-facial and ENT surgeons, neurosurgeons and general surgeons among others [89].

Medical devices can contribute to a better performance of the Ascending Reticular Formation Activating System (ARAS) and vegetative activities related to OSAS, which are more severely affected in cases with NCC/COVID-19 due to brainstem dysfunction with crucial involvement of the Mesencephalic Trigeminal Nucleus (MTN) and its relevant role in the pathophysiology of OSAS as reported Andrisani last year [90]. MTN is the unique anatomical structure in the entire nervous system that remains expressed during the whole seeping process. We hypothesised that MTN reacts to the preoptic hypothalamic GABA release by liberated glutamate from NCC/Mg polarisation expressing NC/GC in the ARAS (parabrachial nucleus), leading to OSAS even without any airway obstruction (central SASA) but associated with a lack of neurotransmitters as has been reported by Andrisani et al. under different circumstances [90]. Now, it's important to highlight that Central Sleep Apnea (CSA) is a result of missing one, two or more breathing cycles while asleep due to a failure of the respiratory centre to provide the signal to inspiration caused by a dysfunction of the pre-Bötzinger complex at the medulla oblongata [91]. Noted that this disturbance is more intense in patients with an associated long COVID-19, as we reported before [63].

Disturbance of GABAergic or glutamatergic neurotransmission leads to remarkable neurological disorders, including neuropsychiatric, neurodegeneration and sleep disorders [92,93].

The excitatory neurotransmitter glutamate is present in many places along the CNS and is involved in maintaining synaptic plasticity. Somewhat, such as in memory consolidation and learning process neurophysiological activities, and in pathological conditions like NCC/OSAS, it is considered a neurotoxin, causing neurodegeneration and neurovascular disorders, as we hypothesised.

Brief comment on the association of OSAS and Ischemic Stroke (IS)

There is progressive accumulating evidence suggesting a link between OSA and Atrial Fibrillation (AF) [94]. On the

other hand, it is well known that IH induces a metabolic derangement that causes OS and chronic inflammation, increasing the frequency of AF [95].

OSA promote an autonomic imbalance with an elevated tone and sympathetic expression, conditioning an ideal scenario for the development of cardiac arrhythmia, in particular AF [96]. AFAF is the most frequent aetiology of cardioembolic stroke, being approximately 15%–30% of all ISIS, and it is strongly associated with OSA.

Based on the previous medical report, we hypothesised that both conditions are highly associated with ISIS, which has been partially supported by another author [97]. To support it, other authors concluded that OSA and AF are highly prevalent but not associated with IS, indicating that they may not share a common pathogenic link in determining stroke. However, OSA acts as an independent risk factor for IS, promoting stroke through multifactorial and complex mechanisms and is not directly associated with AF [98-101]. However, OSA can damage endothelial cells and brain parenchymal worsening outcomes following IS, and male patients are 2 times more likely to develop IS, probably due to more intense oxygen desaturation, higher susceptibility to OS, and greater frequency of more severe airway obstruction [102,103]. Furthermore, the disruption of the sleep cycle reduces the capacity of brain tissue repair and augments the risk of post-stroke depression, leading to poor outcomes [104,105].

Regarding arterial hypertension, it has been documented that the enhancement of the carotid body chemoreflex leads to sustained sympathetic hyperactivity during the daytime in OSA cases, increasing blood pressure [106].

The role played by Rouget cells/pericytes in cases of NCC leading to local vasoconstriction has been well documented recently by us [107]. This condition can worsen when IH is associated with NCC because IH diminish the concentration of nitric oxide, leading to endothelial dysfunction, which increases vasoconstriction [108].

In 2023, some authors documented that there is probably no aetiological relationship between cerebrovascular diseases and OSA [109]. Notwithstanding, most investigators have considered that OSA is an independent risk factor for incident stroke, including its subtypes like large vessel stroke, minor vessel stroke, lacunar/macular stroke, cardioembolic stroke and intraparenchymal haemorrhage [110-114].

Brief comments on NCC/OSAS/Epileptic Seizures (ESES)/Epilepsy (Ep)

The presence of ES/Ep as the most typical clinical manifestation of NCC has been documented by us many times before; therefore, it's not necessary to discuss it again, but the relationship between NCC/ES/Ep and OSAS is a novel aspect, and they deserve to be documented below [21-49].

It's well known that sleep and ES/Ep are interrelated in both directions, and some ES/Ep and its EEG manifestations only happen during sleeping times, mainly during Non-Rapid Eye Movements (NREM-N3). On the other hand, some ES and Antiseizure Medication (ASM) disrupt the neurophysiological structure of the sleep mechanism, and sleep disturbances can affect the ES/Ep control also based on the medical experiences about better control of ES/Ep in patients able to sleep at least 8 hours during the night typically and the opposite way of better quality and quantity of sleep under better control of ES/Ep [115].

People undergo all stages of sleep several times during sleep/wake-up. The sleep cycle has at least 3 stages: N1 (lasting several minutes with predominant theta brain waves and alpha rhythm), stage N2 (with predominant theta activity and sleep spindles and k-complexes), and N3 (more than 20% of delta activity) and REM sleep stage (ranging from 10 minutes to 60 minutes with increments with each cycle all over the night) [116].

In epileptic patients receiving antidepressants, poly-pharmacological therapy or ASM may present disruption of the sleep architecture. Therefore, the management of ES/Ep must be done individually considering the effects of the AED/ASM, high level of risk, comorbidities, amount and stage of the cysticerci, antiparasitic medication used and associated restless legs syndrome, which will increase disease burden [117].

Finally, we hypothesised that in patients presenting NCC/OSAS/Ep, the impact on health-associated conditions, frequency of ES, and prognosis is more significant compared with other groups, including severity of sleep-wake disorders, cognitive declines, drug resistance epilepsy, QOL, cardiovascular and cerebrovascular diseases which is supported by publications made by other authors although under different conditions nonrelated to NCC [117]. Among the previously cited complications, we highlight the incidence of cardiac complications due to recurrent ES in NCC/OSAS. In these cases, we hypothesised that the leading cause is the autonomic dysfunction of the heart created by ASMs, ES-related effects and some epileptic disorders affecting the structural integrity of the cardiovascular system leading to cardiac arrhythmias, ventricular fibrillation, acute coronary syndrome, sudden cardiac death [117].

Other AEDs, such as primidone, phenobarbital, carbamazepine, and phenytoin, can accelerate the atherosclerotic process through the hepatic cytochrome P450 system Surges et al. established in 2021 that epileptic patients have a 2-3-fold higher chance of developing premature death compared with the general population, with 15% of them related to SCD or acute coronary syndrome [62,118]. We speculated that the rate is even higher in patients presenting NCC/OSAS based on reasons before cited.

Although we never use VNS as an alternative therapeutic procedure to control ES due to NCC, it may be necessary in some cases with NCC/OSAS. Therefore, we would like to emphasise that VNS has a cardioprotective effect and

compensates/reverses epilepsy-related heart dysfunction secondary to reduced T-wave alternant levels, episodes of ventricular tachycardia, and improved baroreflex sensitivity, as has been documented [118].

Conclusion

As far as we know, it is the first study correlating NCC and OSAS, and forthcoming well-designed and confident investigations must confirm all hypotheses delivered here.

Declarations

Consent for publication

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

Declaration of anonymity

The authors of this study certify that they did not mention any person's identity issues in this article. Therefore, complete anonymity is guaranteed.

Availability of data and material

The data supporting this study are publicly available on reasonable request from the corresponding author.

Ethical Approval

This manuscript did not require ethical approval.

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Competing Interest

The authors certified that they made this review without any issue able to construe a potential conflict of interest.

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Contributors

Study concept and design: LFIV and HFS. Data collection: LdeF IV and HFS. Data analysis: LdeFIV and HFS. Drafting of the manuscript: HFS and LFIV. Revising the manuscript: HFS. Supervising research and manuscript writing process: LDFIV and HFS. Both authors have approved the publication of this article.

Acquisition of data or analysis and interpretation of data: LIV. Drafting this paper/critically revising the manuscript for important intellectual content: LIV, HFS. All authors are the guarantors, and because they have contributed equally to this work, they share their first authorship.

References

1. H.G. Jeong, T. Kim, J.E. Hong, H.J. Kim, S.Y. Yun, et al. Automated deep neural network analysis of lateral cephalogram data can aid in detecting obstructive sleep apnea, J Clin Sleep Med, 19(2023):327–337.
2. J.L. Chang, A.N. Goldberg, J.A. Alt, A. Mohammed, L. Ashbrook, et al. International consensus statement on obstructive sleep apnea, Int Forum Allergy Rhinol, 13(2023):1061–1482.
3. R. Jung, W. Kuhlo, Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome, Prog Brain Res, 18(1965):140–159.
4. C.E. Sullivan, M. Berthon-Jones, F.G. Issa, L. Eves, Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares, Lancet, 1(1981):862–865.
5. C.H.J. Won, M. Reid, T. Sofer, A. Azarbarzin, S. Purcell, et al. Sex differences in obstructive sleep apnea phenotypes, the multi-ethnic study of atherosclerosis, Sleep, 43(2020):zsz274.
6. G.Q. Roca, S. Redline, B. Claggett, N. Bello, C.M. Ballantyne, et al. Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort the atherosclerosis risk in communities-sleep heart health study, Circulation, 132(2015):1329–1337.
7. R.K. Malhotra, D.B. Kirsch, D.A. Kristo, E.J. Olson, R.N. Aurora, et al. Polysomnography for obstructive sleep apnea should include arousal-based scoring: An American academy of sleep medicine position statement, J Clin Sleep Med, 14(2018):1245–1247.
8. S. Redline, G. Yenokyan, D.J. Gottlieb, Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. Am J Respir Crit Care Med, 182(2010):269–277.
9. S.P. Patil, I.A. Ayappa, S.M. Caples, R.J. Kimoff, S.R. Patel, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: An American academy of sleep medicine clinical practice guideline, J Clin Sleep Med, 15(2019):335–343.
10. A. Oksenberg, E. Arons, H. Radwan, D.S. Silverberg, Positional vs nonpositional obstructive sleep apnea patients–anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data, Chest, 112(1997):629–639.
11. O. Sunnergren, A. Broström, E. Svanborg, Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea, Sleep Breath, 17(2013):173–179.
12. C. Guilleminault, R. Stoohs, T. Shiomi, C. Kushida, I. Schnittger, Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension, Chest, 109(1996):901–908.
13. N.J. Douglas, Upper airway resistance syndrome is not a distinct syndrome, Am J Resp Crit Care,

161(2000):1413–1415.

14. Medicine AAoS, AASM manual for the scoring of sleep and associated events, 2020.
15. A.R. Gold, F. Dipalo, M.S. Gold, D. O'Hearn, The symptoms and signs of upper airway resistance syndrome: A link to the functional somatic syndromes, Chest, 123(2003):87–95.
16. S.J. So, H.J. Lee, S.G. Kang, C.H. Cho, H.K. Yoon, et al. A comparison of personality characteristics and psychiatric symptomatology between upper airway resistance syndrome and obstructive sleep apnea syndrome, Psychiatry Investig, 12(2015):183–189.
17. A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials, 17(1996):1–12.
18. J.F. Masa, J.L. Pépin, J.C. Borel, B. Mokhlesi, P.B. Murphy, et al. Obesity hypoventilation syndrome, Eur Respir Rev, 28(2019):180097.
19. J.S. Balachandran, J.F. Masa, B. Mokhlesi, Obesity hypoventilation syndrome epidemiology and diagnosis, Sleep Med Clin, 9(2014):341–347.
20. A.S. BaHammam, Prevalence, clinical characteristics, and predictors of obesity hypoventilation syndrome in a large sample of Saudi patients with obstructive sleep apnea, Saudi Med J, 36(2015):181–189.
21. H.F. Sibat, L.F.I. Valdes, Pseudo seizures and epilepsy in neurocysticercosis, Electron J Biomed, 2(2003):79-87.
22. H.F. Sibat, M.D.I.V. LdeF, Vascular dementia type binswanger's disease in patients with active neurocysticercosis, Rev Electron Biomed, 1(2003):32-42.
23. F.S.H.I.V. LdeF, Insular neurocysticercosis: Our finding and review of the medical literature, Inte J Neurol, 5(2006):2.
24. H.F. Sibat, L.D. Cowan, H. Carabin, I. Targonska, M.A. Anwary, et al. Accuracy of serological testing for the diagnosis of prevalent neurocysticercosis in outpatients with epilepsy, Eastern Cape Province, South Africa, PLoS Negl Trop Dis, 3(2009):e562.
25. H.F. Sibat, I.V. LdeF, J. More-Rodriguez, Parasitic zoonoses of the brain: Another challenger, Inte J of Neurol, 12(2009):9-14.
26. H.F. Sibat, I.V. LdeF, Treatment of epilepsy secondary to neurocysticercosis, Novel Treat Epilepsy InTech, 2011.
27. H.F. Sibat, L.F.I. Valdés, Clinical features of epilepsy secondary to neurocysticercosis at the insular lobe, Novel Asp Epilepsy InTech, 2011.
28. H.F. Sibat, Epilepsy secondary to parasitic zoonoses of the brain, Novel Asp Epilepsy InTech, 2011.
29. H.F. Sibat, M. Salazar-Campos, L. Ibanez-Valdes, Cysticercosis of the extraocular muscles: Our experience and review of the medical literature, Internet J Neurology, 14(2001):1.
30. H.F. Sibat, L.F.I. Valdes, Introduction to cysticercosis and its historical background, InTech, 2013.
31. H.F. Sibat, L.F.I. Valdes, What is a low frequency of the disseminated cysticercosis suggests that neurocysticercosis is going to disappear? InTech, 2013.
32. H.F. Sibat, L.F. Valdes, Uncommon clinical manifestations of cysticercosis, InTech, 2013.
33. L.F.I. Valdes, H.F. Sibat, Psychogenic nonepileptic seizures in patients living with neurocysticercosis, InTech open, 2018.
34. L.F.I. Valdes, H.F. Sibat, Subarachnoid cysticercosis and ischemic stroke in epileptic patients, InTech open, 2018.
35. E.V. Noormahomed, N. Nhancupe, J. Mufume, R.T. Schooley, H.F. Sibat, et al. Neurocysticercosis in epileptic children: An overlooked condition in Mozambique, challenges in diagnosis, EC Microbiology 17(2021):49-56.
36. H.F. Sibat, Racemose neurocysticercosis long COVID and brainstem dysfunction: A case report and systematic review, Clin Schizophr Relat Psychoses, 15S(2021).
37. H.F. Sibat, Neurocysticercosis, epilepsy, COVID-19 and a novel hypothesis: Cases series and systematic review, Clin Schizophr Relat Psychoses, 15(2021).
38. H.F. Sibat, People living with HIV and neurocysticercosis presenting Covid-19: A systematic review and crosstalk proposals, Clin Schizophr Relat Psychoses, 15(2021).
39. H.F. Sibat, L.F.I. Valdes, Novel hypotheses on the role of oligodendrocytes in neurocysticercosis: Comprehensive review, Clin Schizophr Relat Psychoses, 17(2023).
40. H.F. Sibat, Comorbidity of neurocysticercosis, HIV, cerebellar atrophy and SARS-CoV-2: Case report and systematic review, Clin Schizophr Relat Psychoses, 15(2022).
41. A.H. Del Rio-Romero, H.F. Sibat, Prevalence of epilepsy and general knowledge about neurocysticiercosis at Nkalukeni Village, South Africa, Int J Neurology, 3(2004).
42. H.F. Sibat, A.H. Del Rio-Romero, Neuroepidemiological survey for epilepsy and knowledge about neurocysticiercosis at Ngqwala Location, South Africa, Int J Neurol, 3(2005):11-16.
43. H.F. Sibat, A. Del Rio-Romero, L. Ibanez-Valdes, Prevalence of epilepsy and general knowledge about

neurocysticercosis at Ngangelizwe Location, South Africa, Int J Neurol, 4(2005):23-37.

44. A. Del Rio, H.F. Sibat, Epidemiological survey about socio-economic characteristic of Mpindweni Location, South Africa, Int J Neurol, 4(2005):18-26.
45. H.F. Sibat, L.F.I. Valdes, Refractory epilepsy in neurocysticercosis, Int J Neurol, 5(2006):1-6.
46. L.F.I. Valdes, H.F. Sibat, Meningeal lymphatic vessels and glymphatic system in neurocysticercosis: A systematic review and novel hypotheses, Clin Schizophr Relat Psychoses, 17(2023).
47. L.F.I. Valdes, H.F. Sibat, Co-morbidity of spinal cord neurocysticercosis and tuberculosis in a HIV-positive patient, Int J Neurol, 7(2007):5-10.
48. H.F. Sibat, L.F.I. Valdes, The role of pericytes in neurocysticercosis: Comprehensive review and novel hypotheses, Clin Schizophr Relat Psychoses, 2013.
49. K.G. Johnson, D.C. Johnson, Frequency of sleep apnea in stroke and TIA patients: A meta-analysis, J Clin Sleep Med, 6(2010):131–137.
50. H.F. Sibat, L.F. Valdés, Novel hypotheses on the role of microglia and panoptosis in neurocysticercosis, Clin Schizophr Relat Psychoses, 17(2023).
51. W.J. Lee, C.S. Wu, H. Lin, I.T. Lee, C.M. Wu, et al. Visfatin-induced expression of inflammatory mediators in human endothelial cells through the NF-kappaB pathway, Int J Obes, 33(2009):465–472.
52. L.P. Israel, D. Benharoch, J. Gopas, A.D. Goldbart, A pro-inflammatory role for nuclear factor kappa B in childhood obstructive sleep apnea syndrome, Sleep, 36(2013):1947–1955.
53. L. Lavie, Obstructive sleep apnoea syndrome–an oxidative stress disorder, Sleep Med Rev, 7(2003):35–51.
54. J. Biddlestone, D. Bandarra, S. Rocha, The role of hypoxia in inflammatory disease (review), Int J Mol Med, 35(2015):859–869.
55. L.H. Xu, H. Xie, Z.H. Shi, L.D. Du, Y.K. Wing, et al. Critical role of endoplasmic reticulum stress in chronic intermittent hypoxia-induced deficits in synaptic plasticity and long-term memory, Antioxid Redox Signal, 23(2015):695–710.
56. D.D. Zong, R.Y. Ouyang, P. Chen, Epigenetic mechanisms in chronic obstructive pulmonary disease, Eur Rev Med Pharm Sci, 19(2015):844–856.
57. K.X. Liu, G.P. Chen, P.L. Lin, J.C. Huang, X. Lin, et al. Detection and analysis of apoptosis and autophagy-related miRNAs of mouse vascular endothelial cells in chronic intermittent hypoxia model, Life Sci, 193(2018):194–199.
58. H. Gao, Z. Han, S. Huang, R. Bai, X. Ge, et al. Intermittent hypoxia caused cognitive dysfunction relate to miRNAs dysregulation in hippocampus, Behav Brain Res, 335(2017):80–87.
59. R. Lv, X. Liu, Y. Zhang, N. Dong, X. Wang, et al. Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome, Signal Transduct Target Ther, 8(2023):218.
60. P. Du, J. Wang, Y. Han, J. Feng, Blocking the LncRNA MALAT1/miR-224-5p/NLRP3 axis inhibits the hippocampal inflammatory response in T2DM with OSA, Front Cell Neurosci, 14(2020):97.
61. H. Ding, J. Huang, D. Wu, J. Zhao, J. Huang, et al. Silencing of the long non-coding RNA MEG3 suppresses the apoptosis of aortic endothelial cells in mice with chronic intermittent hypoxia *via* downregulation of HIF-1α by competitively binding to microRNA-135a, J Thorac Dis, 12(2020):1903–1916.
62. F.S. Humberto, Bilateral putaminal haemorrhage and blindness in times of the coronavirus pandemic and dysbiosis: Case report and literature review, Clin Schizophr Relat Psychoses, 15S(2021).
63. R. Lv, S. Nie, Z. Liu, Y. Guo, Y. Zhang, et al. Dysfunction in automatic processing of emotional facial expressions in patients with obstructive sleep apnea syndrome: An event-related potential study, Nat Sci Sleep, 12(2020):637–647.
64. G.L. Dunietz, R.D. Chervin, J.F. Burke, A.S. Conceicao, T.J. Braley, Obstructive sleep apnea treatment and dementia risk in older adults, Sleep, 44(2021):zsab076.
65. D.J. Eckert, D.P. White, A.S. Jordan, A. Malhotra, A. Wellman, Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets, Am J Respir Crit Care Med, 188(2013):996–1004.
66. B.A. Duerkop, S. Vaishnava, L.V. Hooper, Immune responses to the microbiota at the intestinal mucosal surface, Immunity, 31(2009):368–376.
67. C.R. Tiffany, A.J. Bäumler, Dysbiosis: From fiction to function, Am J Physiol Gastrointest Liver Physiol, 317(2019):G602–G608.
68. M.G. Dominguez-Bello, M.J. Blaser, R.E. Ley, R. Knight, Development of the human gastrointestinal microbiota and insights from high-throughput sequencing, Gastroenterology, 140(2011):1713–1719.
69. R.B. Canani, M. Di Costanzo, L. Leone, M. Pedata, R. Meli, et al. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases, World J Gastroenterol, 17(2011):1519–1528.
70. M.A.R. Vinolo, H.G. Rodrigues, R.T. Nachbar, R. Curi, Regulation of inflammation by short chain fatty acids, Nutrients, 3(2011):858–876.
71. R. Berni Canani, M. Di Costanzo, L. Leone, The epigenetic effects of butyrate: Potential therapeutic implications for clinical practice, Clin Epigenetics,

4(2012):4.

72. I. Moreno-Indias, M. Torres, J.M. Montserrat, L. Sanchez-Alcoholado, F. Cardona, et al. Intermittent hypoxia alters gut microbiota diversity in a mouse model of sleep apnoea, Eur Respir J, 45(2015):1055–1065.
73. D. Mariat, O. Firmesse, F. Levenez, V.D. Guimarães, H. Sokol, et al. The firmicutes/bacteroidetes ratio of the human microbiota changes with age, BMC Microbiol, 9(2009):123.
74. L. Albenberg, T.V. Esipova, C.P. Judge, K. Bittinger, J. Chen, et al. Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota, Gastroenterology, 147(2014):1055–1063.
75. V.A. Poroyko, Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice, Sci Rep, 6(2016):35405.
76. J. Ye, H. Liu, P. Li, Z. Chen, G. Zhang, et al. CD4(+) T-lymphocyte subsets in nonobese children with obstructive sleep apnea syndrome, Pediatr Res, 78(2015):165–173.
77. H.F. Sibat, L.F. Valdés, New hypotheses on the role of microglia in ischemic reperfusion injury secondary to neurocysticercosis and a comprehensive review, Clin Schizophr Relat Psychoses, 2023.
78. N. Singh, A. Gurav, S. Sivaprakasam, E. Brady, R. Padia, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis, Immunity, 40(2014):128–139.
79. J.R. Davie, Inhibition of histone deacetylase activity by butyrate, J Nutr, 133(2003):2485S–2493S.
80. M. Sun, W. Wu, L. Chen, W. Yang, X. Huang, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis, Nat Commun, 9(2018):3555.
81. N. Burger-van Paassen, A. Vincent, PJ Puiman, M. van Der Sluis, J. Bouma, The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: Implications for epithelial protection, Biochem J, 420(2009):211–219.
82. L. Wrzosek, S. Miquel, M.L. Noordine, S. Bouet, M.J. Chevalier-Curt, et al. *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent, BMC Biol, 11(2013):61.
83. B.T. Layden, A.R. Angueira, M. Brodsky, V. Durai, W.L. Lowe, Short chain fatty acids and their receptors: New metabolic targets, Transl Res, 161(2013):131–140.
84. M. Luu, A. Visekruna, Short-chain fatty acids: Bacterial messengers modulating the immunometabolism of T cells, Eur J Immunol, 49(2019):842–848.
85. V. Brahmakshatriya, Y. Kuang, P. Devarajan, J. Xia, W. Zhang, et al. IL-6 production by TLR-activated APC broadly enhances aged cognate CD4 helper and B cell antibody responses in vivo, J Immunol, 198(2017):2819–2833.
86. I. Rosenzweig, M. Glasser, D. Polsek, Sleep apnoea and the brain: A complex relationship, Lancet Respir Med, 3(2015):404–414.
87. M.N. Garcia, H.F. Sibat, L.F.I. Valdes, Our Hypotheses about the role of cuproferropanoptosis in neurocysticercosis and a comprehensive review, J Drug Alc Res, 12(2023).
88. P.M. Macey, M.K. Sarma, R. Nagarajan, R. Aysola, J.M. Siegel, et al. Obstructive sleep apnea is associated with low GABA and high glutamate in the insular cortex, J Sleep Res, 25(2016):390–394.
89. A. Domínguez-Mayoral, C. Gutiérrez, J. Sánchez-Gómez, S. Pérez-Sánchez, N. Fouz, et al. Benefits in quality of life following an obstructive sleep apnea screening and treatment program in patients with acute ischemic stroke, Rev Neurol, 76(2023):117–125.
90. A. Giovanni, A. Giorgia, Sleep apnea pathophysiology, Sleep Breath, 27(2023): 2111–2122.
91. S. Javaheri, M.S. Badr, Central sleep apnea: Pathophysiologic classification, Sleep, 46(2023):zsac113.
92. P. Kaczmarski, M. Sochal, D. Strzelecki, P. Białasiewicz, A. Gabryelska, Influence of glutamatergic and GABAergic neurotransmission on obstructive sleep apnea, Front Neurosci, 17(2023):1213971.
93. V. Brunetti, E. Testani, A. Losurdo, C. Vollono, A. Broccolini, et al. Association of obstructive sleep apnea and atrial fibrillation in acute ischemic stroke: A cross-sectional study, J Pers Med, 13(2023):527.
94. R. Kanagala, N.S. Murali, P.A. Friedman, N.M. Ammash, B.J. Gersh, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation, Circulation, 107(2003):2589–2594.
95. A. Arboix, J. Alioc, Cardioembolic stroke: Clinical features, specific cardiac disorders and prognosis, Curr Cardiol Rev, 6(2010):150–161.
96. M.C. Lipford, K.D. Flemming, A.D. Calvin, J. Mandrekar, R.D. Brown Jr, et al. Associations between cardioembolic stroke and obstructive sleep apnea, Sleep, 38(2015):1699–1705.
97. R. Munoz, J. Duran-Cantolla, E. Martínez-Vila, J. Gallego, R. Rubio, et al. Severe sleep apnea and risk of ischemic stroke in the elderly, Stroke, 37(2006):2317–2321.
98. C.Y. Chen, C.H. Ho, C.L. Chen, C.C. Yu, Nocturnal

desaturation is associated with atrial fibrillation in patients with ischemic stroke and obstructive sleep apnea, J Clin Sleep Med, 13(2017):729–735.

99. S.G. Schütz, L.D. Lisabeth, F. Shafie-Khorassani, E. Case, B.N. Sanchez, et al. Clinical phenotypes of obstructive sleep apnea after ischemic stroke: A cluster analysis, Sleep Med, 60(2019):178–181.

100. L. Grote, J. Hedner, J.H. Peter, Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension, J Hypertens, 18(2000):679–685.

101. A.S. Gami, G. Pressman, S.M. Caples, R. Kanagala, J.J. Gard, et al. Association of atrial fibrillation and obstructive sleep apnea, Circulation, 110(2004):364–367.

102. A.N. Devenish, T. Nisar, A. Criswell, D. McCane, D. Thao, et al. Sex differences in 90-day functional outcomes for acute ischemic stroke patients with obstructive sleep apnea, Cureus, 15(2023):e39652.

103. H.K. Yaggi, J. Concato, W.N. Kernan, J.H. Lichtman, L.M. Brass, et al. Obstructive sleep apnea as a risk factor for stroke and death, Engl J Med, 353(2005):2034–2041.

104. S.B. Duss, A. Seiler, M.H. Schmidt, M. Pace, A. Adamantidis, et al. The role of sleep in recovery following ischemic stroke: A review of human and animal data, Neurobiol Sleep Circadian Rhythms, 2(2017):94–105.

105. C. Li, Y. Liu, P. Xu, Q. Fan, P. Gong, et al. Association between obstructive sleep apnea and risk of post-stroke depression: A hospital-based study in ischemic stroke patients, J Stroke Cerebrovasc Dis, 29(2020):104876.

106. N.R. Prabhakar, Y.J. Peng, J. Nanduri, Hypoxia-inducible factors and obstructive sleep apnea, J Clin Invest, 130(2020):5042–5051.

107. L.F.I. Valdes, The Role of rouget cells in neurocysticercosis, J Drug Alc Res, 13(2024).

108. S. Jelic, M. Padeletti, S.M. Kawut, C. Higgins, S.M. Canfield, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea, Circulation, 117(2008):2270–2278.

109. P. Li, Z. Dong, W. Chen, G. Yang, Causal relations between obstructive Sleep apnea and stroke: A mendelian randomization study, Nat Sci Sleep, 15(2023):257–266.

110. Y.K. Loke, J.W. Brown, C.S. Kwok, A. Niruban, P.K. Myint, Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis, Circ Cardiovasc Qual Outcomes, 5(2012):720–728.

111. J.Y. Dong, Y.H. Zhang, L.Q. Qin, Obstructive sleep apnea and cardiovascular risk: Meta-analysis of prospective cohort studies, Atherosclerosis, 229(2013):489–495.

112. M. Li, W.S. Hou, X.W. Zhang, Z.Y. Tang, Obstructive sleep apnea and risk of stroke: A meta-analysis of prospective studies, Int J Cardiol, 172(2014):466–469.

113. J. Kim, Y. Kim, K.I. Yang, D. Kim, S.A. Kim, The relationship between sleep disturbance and functional status in mild stroke patients, Ann Rehabil Med, 39(2015):545–52.

114. P. Mattaliano, C. Lombardi, D. Sangalli, A. Faini, B. Corrà, et al. Impact of obstructive sleep apnea on cardiac organ damage in patients with acute ischemic stroke, J Hypertens, 36(2018):1351–9.

115. T. Hoang-Anh, Q. Duong-Minh, N. Nguyen-Thi-Y, S. Duong-Quy, Study of the obstructive sleep apnea syndrome in cerebral infarction patients, Front Neurol, 14(2023):1132014.

116. Y. Krutoshinskaya, K. Coulehan, G. Pushchinska, R. Spiegel, The reciprocal relationship between sleep and epilepsy, J Pers Med, 14(2024):118.

117. J. Peltola, R. Surges, B. Voges, T.J. von Oertzen, Expert opinion on diagnosis and management of epilepsy-associated comorbidities, Epilepsia Open, 9(2024):15–32.

118. R. Surges, S. Shmuely, C. Dietze, P. Ryvlin, R.D. Thijs, Identifying patients with epilepsy at high risk of cardiac death: Signs, risk factors and initial management of high risk of cardiac death, Epileptic Disord, 23(2021):17–39.