COVID-19 Anosmia and Lacunar Stroke.

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Research Article

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Abstract

Background: Despite the worldwide COVID-19 vaccination programme, there is not enough information to predict when the current pandemic will end, and new variants of SARS-CoV-2 are travelling worldwide, leading to the new variability of clinical manifestation, complications and increasing fatal outcomes. Many publications on COVID-anosmia and asymptomatic COVID-stroke have been released, and plenty of studies on novel therapeutic approach have been published. Here we report an atypical case, our findings from review the medical literature, and comment on the treatment modalities.

Material and Method: EMBASE, Medline, Scopus online databases, Google Scholar, Science Direct, WHO database, Scielo, LILACS, BIREME, and Cochrane library to identify articles evaluating anosmia*, COVID-19 anosmia*, aetiology of anosmia*, lacunar infarct*, treatment of IS*, and COVID-19 acute stroke* from January 1, 2010, to March 30, 2021.

Results: We found 2454 publications related to these topics. After removing duplicate articles, considering the title and abstracts, screening full text, PCR positives, symptomatic patients, and manuscript written in other languages, only six matches all the selected parameters, but from this group, none one presented COVID anosmia/PCR negative/ No respiratory disturbances/presence of IgG/ lacune larger than 15 mm (macunes).

Case presentation: A 17-years-old male came to the medical outpatient clinic complaining of loss of smell without other symptomatology. The PCR test for SARS-Cov-2 done was negative, and then he did not receive COVID-19 treatment. Four weeks later patient back to the hospital because of no improvement and was admitted to the hospital neurology ward. Apart from anosmia, examination of other systems shows unremarkable findings. We did an extensive serological and CSF work-up to exclude almost all causes of anosmia. Brain MRI confirmed focal oval cyst space with CSF signal measuring 17 mm in the external capsule in the left basal ganglia region like a lacune (macune) from a previous vascular insult.

Comments and final remarks: After an extensive literature review of published manuscript related to these topics, we did not find a report like our case, which presented COVID-19 anosmia/ without respiratory symptomatology/silent macune stroke/PCR negative with positive antibodies, apart from the systematic review of published articles related to these issues. We also included an updated list of anosmia aetiology and the recommended treatments for LS published in the medical literature.

Background

Despite the massive COVID-19 vaccination programme, there is not enough information to predict when the current pandemic will end. While new variants are travelling worldwide, leading to the variability of clinical manifestation, complications, outcomes, and fatalities, many investigators continue looking to solve most of the problem seen in daily medical practice.

One of the common complaints in COVID-19 patients is an olfactory disturbance. Many articles relate to the olfactory system dysfunction due to viral infections have been published before the current pandemic. Therefore, it's well known that some virus leads local congestion, inflammation (rhinosinusitis, coryzal symptoms) and even direct damage of the olfactory epithelium (OE) like SARS-CoV2 [1] usually at the early stage of the infection [2]. This pathophysiology has been described before the previous pandemic caused by SARS CoV2 [3, 4].

The association between SARS-CoV2 and anosmia is quite common, and some authors have suggested several pathogeneses for the occurrence of symptoms in COVID-19 presentations like post viral anosmia syndrome, direct damage of olfactory sensory neurons, cytokine storm, olfactory cleft syndrome, and damage of the olfactory perception centre in the brain [5–6].

Almost all neurotropic viruses can move from the OE to the central nervous system (CNS), causing local immune responses and viral replication in the nonneuronal cells leading to olfactory receptor's damage [7, 8].

Although coronavirus and anosmia's neuroimmunology remains unknown, some authors suggest that future investigation on anosmia would lead us to confirm coronavirus's pathogenesis in the CNS [2, 7–9]. Nevertheless, the high prevalence of anosmia in COVID-19 patients confirmed the hypotheses of SARS-CoV2 is a symptom of COVID-19 infection in mild or moderate cases [5, 9–17].

As before-mentioned, coronaviruses can route to the CNS via the olfactory nerve (ON), mainly through OE neurons' axons connected to the brain and nonneuronal cells in the olfactory bulb (OB).

When the virus reaches the brain, it binds with the angiotensin-converting enzyme 2 (ACE2) cell surface receptor, which has a different expression level along to the nervous system. ACE2 mediates the virus' entry into the host cell with the aid of a cell-surface enzyme -transmembrane protease serine 2 (TMPRSS2), which drives the cleavage of the new coronavirus' spike protein. The new coronavirus (SARS-CoV-2) can then bind these olfactory cells and infect OSNs despite its low expression of ACE2. Some authors reported that ACE2 had a lower expression and narrower distribution than TMPRSS2. The same authors confirmed the highest expression of TMPRSS2 and ACE2 in goblet cells and ciliated cells. Others published that TMPRSS2 and ACE2 were present all over the mouse's olfactory mucosa in rats, mainly in horizontal basal cells and Bowman's gland cells, but ACE2 is not found in purified OSNs [2]. In the before-mentioned contradictory findings on ACE2 and TMPRSS2, gene expression relates to the proteins involved in the cell entry of coronaviruses; the genes are expressed by types of nonneuronal, and neurons located in the OE (more in sustentacular cells/horizontal basal cells) with not an exclusion of OSNs [2]. Another relevant component of the OB is the pericytes which play roles in the inflammatory responses, regulation of the blood pressure, and maintenance of the blood-brain barrier (BBB).

The small infarct on distal small penetrating branches of larger cerebral arteries (LCA) as cavitated end-products has been describing as "lacunes" (French word: cavity) since the 1800s [18]. Currently, up to 20–30% of acute ischemic infarcts (IS) are lacunar strokes (LS) [19, 20]. Comparing the size of infarct from

large vessel occlusion with those from small vessel disease, in the last group, the size of the lesion is smaller, and this is the commonest presentation (37%) [21–23]

Lacunar syndromes are a group of clinical manifestations from lacunar infarctions. Lacunar infarction is a small subcortical lesion with a diameter less than 15 mm, most commonly around the Circle of Willis. These branches of LCA, known as small penetrating arteries (SPA), arise at sharp angles. Therefore, they are prone to constriction and occlusion, mainly in the Circle of Willis (CW) middle cerebral artery (MCA) and the basilar artery (BA) territories. The term “macunes” is reserved for LS above 15 mm in diameter [24, 25].

Many aetiological mechanisms have been delivered as the aetiology of lacunar infarction. The usual aetiology of small LS (between 3 mm and 7 mm) is lipohyalinosis of the small PA feeding deep anatomical structures. Another cause is micro-atheroma formation at the origin of PA from large cerebral arteries (MCA, BA, CW). The incidence of LS is increasing gradually in younger cases [26].

Recently published studies confirmed that eleven million patients develop silent stroke (in the USA alone) annually, and most cases are secondary to cerebral small vessel disease (CVD) [27].

One mandatory criterion to define the LS is the absence of associate abnormal higher cerebral activities like altered level of consciousness, epileptic seizures, visual field defect, agnosia, apraxia, aphasia, memory impairment, and absence of cardiac embolism, and vascular stenosis (< 50%) in an ipsilateral proximal vessel. Some authors recommend careful interpretations of these criteria to avoid misdiagnosis [28]. Almost all LS are secondary to intrinsic disease of the small PA [18]. There are three-stage in the progression of this pathological process. Phase 1: lipohyalinosis on the basal ganglia. Phase 2: lipohyalinosis of the deep white matter. Phase 3: lipohyalinosis of the brainstem [29]. The two primary pathogenic mechanisms of cSVD are: blood-brain-barrier lesion and endothelial dysfunction (ED) refers to angiogenesis, fibrinolysis/coagulation, regulation of vessel tone, and inflammation [30]. This ED shifts several functions leading to proinflammation, vasoconstriction, proliferation, autoregulation, and pro coagulation [30].

The BBB (basement membranes, associated perivascular spaces, tight junctions joining endothelial cells, pericytes, glia limitans, and astrocyte feeding process) plays an essential role in LS's vascular pathology. BBB is degraded by arterial hypertension, which causes damages to the smooth muscle cells secondary to plasma protein deposition in the wall's artery and local oedema, mainly at the WM [31].

Apart from age, race, smoking, sedentarism, thrombophilia, hypertension, Diabetes Mellitus, and atherosclerosis, other relevant risk factors have been reported in the medical literature [32–36]; some of their therapeutic approaches will be discussed below.

Serum alkaline phosphatase [32, 37] and elevated serum levels of C-reactive protein associated with silent LS were reported as well [38]. High levels of soluble vascular cadherin adhesion molecule-1 pro-inflammatory biomarkers and thrombin anti-thrombin have been found after LS [39]. Other potential

biomarkers like plasma panel for lipids (free fatty acid, phosphatidylethanolamine, glucosylceramide, and triacylglycerol) are specific (97%) for LS [40].

Other authors reported low levels of plasma omega 3-polyunsaturated fatty acids in patients presenting LS [41]. Elevated brain-specific proteins (myelin essential protein), focal adhesion proteins (integrin alpha-IIb, talin-1, and filamin-A) and coagulation cascade proteins (fibrinogen alpha chain, fibrinogen beta chain) using quantitative proteomics of microvesicle enriched plasma were confirmed in LS' patients too [42]. Other investigators suggest that cSVD is a component of systemic disease [43], family history of vascular disease [44], and genetic basis [45–48] of these processes. Among the major diseases are Fabry's disease, CADASIL, CARASIL [49], *COL4A1*-related cSVD [50], autosomal dominant retinal vasculopathy with cerebral leukodystrophy [51].

The deletion genotype for angiotensin-converting enzyme and the GG genotype of lu298Asp *eNOS* polymorphism has been explicitly associated with LS [52, 53] and *apolipoprotein E* gene as well [54]. Nevertheless, several genome-wide association studies (GWAS) reported several cases with an associated isolate and multiple LS [55–61].

Apart from reporting a clinical case, this study aims to answer two research questions like 1.- How often is reported in the medical literature the combination of COVID anosmia/Macune stroke/PCR negative/positive antibodies. 2.- What is the most recommended treatment for LS?

Material And Method

Apart from the medical case reported below, we extensively reviewed the available medical literature to answer the previous research question about the number of publications like our case report, aetiology, and treatment.

Literature search strategy

We utilized the PRISMA (Preferred Reporting Items for Systemic review and Meta-Analysis) statement and the PRISMA checklist for the literature review. We suggest searching from January 1, 2010, up to March 30, 2021. We included all studies (case reports, case series, and observational cohort studies) that reported anosmia, LS, COVID-19 during the initial search. Additionally, we reviewed the following databases: EMBASE, Medline, Scopus online databases, Google Scholar, Science Direct, WHO database, Scielo, LILACS, BIREME, and Cochrane library identify articles evaluating anosmia*, COVID-19 anosmia*, and lacunar infarct*. We searched all items about "lacunar stroke* OR COVID-19 stroke* OR macunes* OR neurological manifestations of COVID-19* OR Neuro-COVID-19* OR COVID-stroke* OR COVID-19 LS* where * is the PubMed wildcard for all word ending or beginning. We did not include other neurological issues beyond the scope of the current work.

Study and cohort selection

We select all publications (case reports, case series, clinical trials, and observational cohort studies) reporting Neuro-covid, Covid-anosmia, LS, macunes, Covid-stroke, anosmia, COVID-anosmia, treatment of LS, treatment of COVID-stroke written in English, Spanish, and Portuguese.

Results

Between January 1, 2018, and March 30, 2021, our literature search yielded 2454 publications. After removing duplicate articles, we retained 989 unique records. Considering the title and abstracts, we kept 488 items; then, after screening full text, we removed 187 publications reporting PCR positive, other causes of anosmia, plus other 34 no well-investigated cases. After all, they were asymptomatic patients; 18 publications were removed because the manuscript was written in other languages, and the other 12 due to lack of information about positive antibodies. Therefore, only six matches all the selected parameters, but from this group, none one presenting with COVID anosmia/PCR negative/ No respiratory disturbances/presence of IgG/ lacune larger than 15 mm (macunes). See Appendix A: The flow diagram of included reports.

Case Presentation

A 17-years-old male came to Nelson Mandela Academic Hospital (NMAH) in South Africa complaining of losing smell for four weeks without other symptomatology. His past medical history revealed a story of anosmia without fever, upper respiratory or COVID-19 symptoms and signs. At that time, he denied symptoms or clinical signs such as difficulty walking, difficulty speaking, clumsiness of a hand or arm, visual disturbances, sudden numbness, weakness or paralysis of the face, arm, leg, foot, toes, or any other neurological symptoms. The PCR test for SARS-Cov-2 was negative, and the patient received symptomatic treatment. One month later patient attends the neurology-out-patient because of lack of improvement, and he was admitted to the NMAH neurology ward for further investigations.

On examination, we found him normal BMI, with pink mucosal membranes, anicteric, and afebrile. Her vital signs were normal BP: 120/82 mmHg. The patient was fully conscious and well orientated. No cranial nerve abnormalities except bilateral inability to identify any smell, no meningeal signs; His motor examination revealed the power of 5/5 in all limbs (proximally and distally), with normal tone and deep/superficial reflexes. No sensory deficits. Examination of other systems shows unremarkable findings.

We did an extensive serological and CSF work-up to exclude almost all causes of anosmia, and laboratory results can be seen in Table 1.

TABLE 1

White cell count	6.3 x 10 ⁹ /L	3.9-12,6 x 10 ⁹ /L
Hb	12.4 g/dL	12-15g/dl
Platelets	289 x 10 ⁹ /L	186-454/L
Sodium	143 mmol/L	136 – 145mmol/L
Potassium	4.8 mmol/L	3.5-5.1mmol/L
Chloride	102mmol/L	98-105mmol/L
Urea	5.7 mmol/L	2.1-7.1mmol/L
Creatinine	74 µmol/L	48-90µmol/L
Calcium	2.4 mmol/L,	2.15 - 2.5mmol/L
Magnesium	0.91 mmol/L,	0.63-1.05mmol/L
Phosphate	0.86 mmol/L	0.78-1.42mmol/L
C-reactive protein	6 mg/L	<10mg/L
Erythrocyte sedimentation rate	9.8 mm/hr	0-10mm/hr
Total protein	70 g/L	60 – 78g/L
Total Bilirubin	6 umol/L	5-21umol/L
Alkaline phosphatase	88 U/L	42-98U/L
Aspartate transaminase	42 U/L	13-35U/L
Alanine transaminase	24 U/L	7-35U/L
Total cholesterol	3,9 mmol/L	<4,5mmol/L
HbA1C	4.9 %	<7%
INR	1	1
D-dimer	0.12 mg/L	0.00-0.25mg/L
Rheumatoid factor	17 IU/L	<20 IU/L
Vitamin B12	130 pmol/L	145-569 pmol/L

Folate acid	30,5 nmol/L	
Thyroid stimulating hormone	1.07 Miu/L	0.27-4.2Miu/l
Anticardiolipin antibody	negative	
Protein S	79 IU/dL	55-123IU/dl
Protein C	111 IU/dl	70-130IU/dL
Angiotensin-converting enzyme	226 IU/L	8-53IU/L
Anticardiolipin antibody	negative	
Anti-streptolysin O titre	103 IU/ml	<200IU/L
Toxoplasmosis Gondi IgG antibody	Negative	
Cytomegalovirus IgG antibody	Negative	
Rubella IgG antibody	Negative	
Rubella IgM antibody	Negative	
Cytomegalovirus IgM antibody	Negative	
Ferritin	403 ng/mL	12 to 300 ng/mL
D-dimer	0.97ug/ml	<0.50mg/l (ug/ml=mg/l)
C3	1.0 g/L	0.9 -1.8g/L
C4	0.3 g/L	0.1-0.4g/L
Anti-nuclear antibody	Negative	
Anti-double strand DNA antibody	Negative	
CD4	1069 cells/uL	
Viral load	<21 copies.ml	
Anti-RNP antibody	Negative	
POC COVID-19 antibody tests	Positive	
CSF (herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, JC virus, ADA, NCC antigens, cryptococcal, toxoplasmosis, VDRL).	Negative	

Lumbar punction: opening pressure: 15.1 cm of H2O. CSF: Poly: 0, Lymph: 2, Glucose: 4.9. Protein: 0.34, and normal lactate level

The patient underwent MR imaging which was performed using a 3-Tesla MR imaging system (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany), included T1- and T2- weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DWI) with apparent diffusion coefficient (ADC), susceptibility-weighted imaging (SWI) sequences.

MRI brain: Axial: FLAIR, SWAN, DW/ADC, and T1WI pre-and post-contrast. Coronal T2WI. Axial SWI. DWI/ADC Sagittal T1WI pre-and post-contrast.

Brain findings: Focal oval cyst space with CSF signal measuring more than 15 mm in the external capsule in the left basal ganglia region like a macune from a previous vascular insult. (*See Figure 1a/b and 2a/b*).

PLACE FOR FIGURE 1 AND 2

Cardiac ultrasound and ECG showed no abnormalities. The patient received the following treatment:

- Vitamin B12 supplementation (1000 µg IM daily)
- Aspirin (75 mg daily)
- Simvastatin (20 mg daily)
- Pyridoxine (50 mg daily)
- Thiamine (100 mg daily)

COMMENTS AND FINAL REMARKS

We could not identify similar cases from the literature review when we tried to answer the first research question. However, we believe some unreported cases may exist, or perhaps we made a mistake in the procedure used to select the published material. Therefore, we do not conclude our uncommon presentation has not been published before. However, we do not expect to find similar reports because the epidemiological condition of this region, including the presence of a new variant of SARS-CoV-2 known as 20H/501.V2 or B.1.351, discovered here (Eastern Cape Province of South Africa) in October 2020. This variant has multiple mutations in the spike protein, including K417N, E484K, N501Y (www.virological.org). The presence of different variants of the virus-like B.1.17 (UK), P.1 (Brazil), and B.1.351(South Africa) could explain differences between COVID-19 cases from one country to another.

On the other hand, the incidence of COVID-19 cases continues increasing in different countries worldwide, including rare presentations and different prevalence like a remarkable difference in the prevalence of anosmia seen in Italy (88%) and China (5%) [62]. Day M. et al. [63] informed that four-fifths of patients with confirmed COVID-19 by laboratory tests are asymptomatic, which support our previous hypotheses.

We did an extensive work-up for anosmia aetiologies (**Figure 3**).

PLACE FOR FIGURE 3

The first clinical discussion was quite tricky because the patient's PCR result came back negative, then we looked for causes of anosmia not related to COVID-19. However, we always keep in mind a high suspicion on COVID-19 based on our epidemiological condition, including the new variant of SARS-CoV-2 as before mentioned, and later we confirmed positive SARS-CoV-2 antibodies in our case.

Another essential aspect considered is the expression of ACE2 on the CNS to understand clinical features' variability. ACE2 expression in the CNS differs from one region to another and seems to be higher in the substantia nigra, but we could not find in the medical literature a unanimous agreement about the olfactory pathway ACE2 expression. Some authors [2] refers that changes in water/ion balance are secondary to inflammatory response at the OE and nonneuronal cells due to the high ACE2 expression causing anosmia like our case. We graphically show in figure 3 how fast immune response of the OE mediated by cytokine storm also help to decrease spreading the virus to the mouth and respiratory system, which explain lack of ageusia and pulmonary manifestations in our patient. Coincidentally, Butowt and Bilinska recommend the OE tissue biopsy to confirm the early stage of SARS-CoV-2 infection [6]. In another study, Bilinska and collaborators found a higher expression of ACE2 in the murine OE than in the alveolar epithelium, which supports why our patient did not make a complaint of respiratory disturbance and the previous recommendation of performing early confirmation of SARS-CoV-2 at the OE (sustentacular cells) [64].

Only a few COVID-19 patients presenting stroke without classic clinical manifestations of SARS-CoV-2 infections have been reported in the medical literature [65]. Our case presented only one symptom of COVID-19 (anosmia) without clinical manifestations of LS being another uncommon type of presentation.

As we before-mentioned, due to the presence of anosmia and our local epidemiological conditions, we screened SARS-CoV-2 by PCR, but it came back negative; therefore, our patient did not receive COVID-19 therapy. Because COVID stroke cases can present an absence of neurological manifestation, the screening of SARS-CoV-2 should be done in pandemic times [65].

PCR negative is common in COVID-19, and the proportion of clinical manifestation is also quite different between PCR-confirmed cases and PCR negative patients. In 512 patients studied by Schuler et al., the frequency of anosmia was 70% ($p < 0.001$) in PCR-confirmed compared with PCR-negative [66]. Mao et al. [13], describing his autopsy findings, reported that most of the CSF studies were negative for COVID-19 RNA as well.

Treatments that may help resolve anosmia caused by nasal irritation include [decongestants](#),

[antihistamines](#), [steroid nasal sprays](#), antibiotics for bacterial infections, reducing exposure to nasal irritants and allergens, [cessation of smoking](#). People with anosmia also present a lost interest in food and eating, leading to malnutrition and weight loss. Therefore, patients with a partial loss of their sense of smell recommend adding concentrated flavouring agents to food to improve their enjoyment and take

vitamin supplements. There is no specific treatment for anosmia caused by SARS-CoV-2 infection apart from the treatment for COVID-19.

Despite a massive vaccination against coronavirus worldwide, we could not find enough information to predict when the current covid-19 pandemic will end. In all patients presenting anosmia as an isolated symptom, after excluding nasal obstruction and flu secretions, the swelling of the OE due to SARS-CoV-2 infection is the commonest aetiology during the COVID pandemic.

We reviewed the therapeutic approach of LS, trying to answer our second research question, then we look for a published therapeutic approach to LS. There are no significant differences between acute therapy of LS and acute IS (AIS), and the contraindications for thrombolytic treatment are the same. A summary of LS's updated therapeutic approach based on the literature review can be seen in **Figure 4**.

PLACE FOR FIGURE 4

Stuttering LS results from altered hemodynamic of SPV sometimes preceded by recurrent TIAs (capsular warning syndrome) [67,68], and several therapeutic approaches performed in the large, randomized cohort have proven no efficacy [69]. However, Marsh et al. [70] and Hawkes et al. [71] recommend acutely loading clopidogrel for this type of LS if IV alteplase (4.5-h window) is not an option.

Thrombolysis is the best choice for acute LS treatment, and some clinical trials (including the original NINDS trial) have confirmed it [72-76] because tPA recanalizes these blood vessels improving cerebral perfusion. However, other authors report a lack of replication of these favourable results and neurological deterioration following IV rTPA [77], unsustainable improvement [78] or no differences between usual favourable outcome without treatment and rTPA's treated patients [79].

Antiplatelet therapy is advisable for LS when patients do not qualify for intra-arterial therapy or tPA, as shown in Figure 4. The best known is aspirin which inhibits cyclooxygenase, decreasing thromboxane A2 production leading to remarkable APA activity. In our daily practice, a low dosage of aspirin is not associated with subdural haematoma or ICH, and it has been confirmed by other authors [80-82].

Other platelet aggregation inhibitors have been recommended for the treatment of acute ischemic stroke (AIS), including LS and secondary stroke prevention such as clopidogrel (thienopyridine), dipyridamole (adenosine deaminase, and phosphodiesterase inhibitor) [83,84]. Other authors suggest ticlopidine (thienopyridine agent) which is APA by irreversible binds to the P2Y₁₂ADP receptor. Ticlopidine can reduce LS's risk, providing more benefits than aspirin in selected groups [85-90], but it can cause neutropenia as a significant side effect. Therefore, it is not recommended as a first-line APA. Fortunately, clopidogrel has a similar pharmacological action, and it is not associated with neutropenia [69].

Cilostazol is a phosphodiesterase III inhibitor with good vasodilatation properties, which has shown an annual decreased risk of LS by 2.3% in Japan [91], less risk to develop IPH than aspirin [92, 93], plus other benefits like diminishing the pulsatility index and improvement of functional outcomes in cases with silent LS [94-96]. It is not recommended because it causes headache in 10% of consumers [97,98], and its

benefits have been not proven in western countries [99]. Moreover, cilostazol can be used for secondary prevention of LS in cases with aspirin resistance to tolerate headaches if present [100, 101].

Ticagrelor binds to the P2Y₁₂ ADP receptor on platelets but reversibly with more ICH risk than clopidogrel and aspirin [102-104].

Anticoagulation in LS is not recommended excepting rare cases presenting a solid indication of anticoagulant without other therapeutic choices (Figure 4) [105].

Since 1982 has been established that anticoagulation cause microhaemorrhage and erythrocytes extravasation in lipohyalinosis-related IS [106]. Therefore, heparin has no indication in the management of acute LS and secondary prevention is contraindicated.

Management of hyperlipidemia and Statins are considered to control extensive vessel atherosclerosis secondary to hypercholesterolemia, but hyperlipidemia is not accepted as a risk factor for LS and cSVD by several authors [107-112]. It has been demonstrated that statins decrease the incidence and mortality of IS by the reduction of LDL [113-117]. Other investigators reported an incremented ICH risk in patients presenting LS and cSVD taking statins despite the reduction in IS recurrence [118,119].

Serotonin reuptake inhibition can be used as part of therapy for LS. The use of selective serotonin reuptake inhibitors (SSRIs) has shown benefits in post-stroke patients [120,121]. Other studies have confirmed SSRIs' efficacy on motor recovery of AIS trials [122-127]. As reported on antiplatelet and statins therapy, some investigators reported an elevated ICH risk in patients treated with SSRIs [128-134]. Probable, other clinical trials using large populations of LS cases should be performed to deliver conclusions.

Blood pressure control (BPC) is justified because of the double risk for LS seen in hypertensive patients [135] with large vessel occlusion [136] and stuttering LS [137].

Augmentation of CBF, such as increasing the circulation based on human albumin infusions (HAI), can improve the outcome of LS have been suggested by some authors [138-141]. In summary, strict BPC is safe and beneficial in the treatment of LS [135,142-144] and on top of that, other authors reported less frequency of ICH [145-147] while HAI is not always a beneficial procedure and can be complicated by pulmonary oedema [148].

Diabetes management and glycaemic control are included in the current guidelines of treatment patients with AIS [72,149]; however, there is scarce information on better outcome in AIS patients receiving hyperglycaemia therapy [150,151]. Diabetes mellitus is a significant risk factor in LS patients [152-154], leading to a poor prognosis [155]. It has been proven that pioglitazone (45 mg/day) can decrease cerebrovascular events after AIS, plus other diabetes complications and improve secondary stroke prevention [156-158].

Neural repair and experimental agents for neuroprotection are novel therapeutical procedures that protect the ischemic nervous tissue before being necrotic material, replacing missing tissues and promoting plasticity. These two new elements have proven their efficacy in the first few hours after the AIS and few weeks to months after AIS happened [159]. The interactions between astrocytes, microglia, endothelial cells, smooth muscle cells and neurons is known as the neurovascular unit (NvU), which participate in maintaining energy metabolism, synapses, BBB, CBF, and regulating neurotransmitters [69]. Therefore, keeping NvU in healthy conditions is essential for the best function of the CNS. One of the most assessed neuroprotective agents is the NMDA receptors antagonist, which reduces excitotoxicity in AIS [69]. Other agents able to reduce NMDA-mediated injury is NA-1[160] and IV magnesium sulphate due to its pleiotropic effect, and several preliminary clinical trials have shown promising results [161-164]. Another one is ACE2-Ang-(1-7) used in LVS patients with good efficacy [165-169]. However, good results obtained in animal models cannot be replicated in humans because of fundamental CNS differences. For example, the percentage of water in the white matter (WM) in humans is 50%, while most rodent brains contain only 15%, determining differences in WM ischemia [170]. Another difference is regarding major CBF in grey matter (GM) compare with WM, which has fewer collateral networks [171].

On top of that, WM is more prompt to be damaged in AIS than WM because of their differences in the intracellular calcium and cell death programme [172-176]. Currently, the oligovascular unit (OvU) terminology is preferable for those AIS affecting mainly the WM [177]. Apart from the before-mentioned neuroprotective strategies, other authors propose to include neurogenesis, axonal sprouting, gliogenesis, and neuronal excitability as new targets for augmenting neuron cells repair [159]. These agents' main goal is to work by stabilizing the BBB, modulating glial scarring, preventing axonal degeneration, and repair the OvU [177-179].

As has been proved, AIS on the WM stimulate endogenous repair programs involving oligodendrocyte precursor glial cells [180], which multiply, migrate, and transform into myelinating oligodendrocytes [181,182]. This process's final event is the glial scar formation, which blocks oligodendrocytes' capacity to myelinate new axons and inhibit axonal growth by ephrin ligands, neurite outgrowth inhibitor and chondroitin proteoglycans [183].

Among these agents able to augment neural repair, cerebrolysin is one of more recommended by medical researchers (figure 4) when it is appropriately administered [184] enhancing motor improvement [185,186].

As can be observed in **figure 4**, other author dot does not recommend using drugs that increase excitatory AMPA glutamatergic signalling or decrease the tonic inhibitory GABA signalling because they can amplify the size of the infarcted area if given two to five days after AIS [159].

In summary, we report an uncommon presentation of COVID-19 anosmia/ without respiratory symptomatology/silent macune stroke/PCR negative with positive antibodies. We included a systematic review of published articles related to these issues; we also included an updated list of anosmia aetiology and the treatment recommended for LS published in the medical literature.

Abbreviations

ACE2-Angiotensive converting enzyme two.

ADC- Apparent diffusion coefficient

AIS- Acute ischemic stroke

APA- Anti-platelet aggregation/agent

BBB- The blood-brain barrier

BPC- Blood pressure control

CBF-Cerebral brain flow

CMV – Cytomegalovirus

COVID-19- Coronavirus disease-19

CSF - Cerebro Spinal Fluid

CT – Computed Tomography

DWI-Diffusion-weighted

EBV – Epstein-Barr Virus

FLAIR- Fluid-attenuated inversion recovery

FT4 – Thyroxine

GABA-Gamma aminobutyric acid

GM- Grey matter

HAI- Human albumin infusions

Hb – Haemoglobin

HSV – Herpes Simplex Virus

ICH- Intracerebral haemorrhage

IPH- Intraparenchymal haemorrhage

JCV – John Cunningham Virus

LDL- Low-density lipoprotein

MCS -Microscopy, Culture, Sensitivity

MRI – Magnetic Resonance Imaging

NMACH - Nelson Mandela Academic Central Hospital

NvU- Neurovascular unit

OE- Olfactory endothelium

OvU- Oligovascular unit

PCR- Polymerase-chain-reaction

POC-Point-of-care

SARS-Cov-2- Severe acute respiratory syndrome coronavirus-2

SSRIs- Selective serotonin reuptake inhibitors

SWI-Susceptibility-weighted imaging

RT-PCR or “PCR”- Reverse transcriptase-polymerase chain reaction

TMPRSS2-Transmembrane protease serine 2

TSH – Thyroid Stimulating Hormone

U/E – Urea and Electrolytes

VDRL – Venereal Disease Research Lab Test

VL- Viral load

VZV- Varicella-Zoster virus

WM- White matter

WSU-Walter Sisulu University

Declarations

Ethical issue and consent to publish: We got the written permission from our patient and parents, and they agreed to include all patient’s information for publication purposes. We certify that we did not disclose any identity issues of this patient in this publication, and we guarantee the patient’s anonymity.

Availability of data:Data used in this study are available on reasonable request from the corresponding author.

Competing interest:All authors: reported no conflicts of interest.

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Author's contribution: Both authors made equal contribution to the elaboration of this manuscript. HFS searched Medline by PubMed, Google Scholar, Science Direct, Scopus, and LdeFIV searched Embase, Scielo, LILACS, BIREME, Cochrane library and WHO database. Both authors collected all patient's information and planning this report; LdeFIV wrote the first draft. HFS wrote the final draft. All authors reviewed the final manuscript, made changes, and agreed to publications.

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Figures

Figure 1

MRI brain: Axial: FLAIR, SWAN, DW/ADC, and T1WI pre-and post-contrast. 1a-DWI: diffusion-weighted imaging shows hyperintensity in the left external capsule

Figure 2

Coronal T2WI. Axial SWI. DWI/ADC Sagittal T1W1 pre-and post-contrast. Hypointense fluid-attenuated inversion recovery. Focal oval cyst space with CSF signal measuring 17 mm in the external capsule in the left basal ganglia region like a lacune (macune) from a previous vascular insult.

Figure 3

Update list of causes of anosmia reported in the medical literature.

Figure 4

List of treatment for LS published in the medical literature up to date.

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