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Brief Report

Amelioration of COVID-19 comorbid depressions via interleukin 6 with agomelatine

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Abstract: Background: Existing research has found that the Spike 2 protein of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) is homogenous to the gp41 protein of the Human Immunodeficiency Virus-1. Postmortem SARS-CoV-2 patients are reported to exhibit microglial activation and expression of interleukin (IL)-1β and IL-6, corroborating with the other in vitro observations. **Methods:** The translational research draws upon the phenomena from metacognition in dreams to achieve the therapeutic solution conception on Coronavirus Disease 2019 (COVID-19) vaccination-induced central nervous system (CNS) cytokine expression. **Results:** Partial milestones have been achieved with cognitive-behavioral therapy in combination with agomelatine and γ-aminobutyric acid stimulation physical therapy, and the direct evidence suggests that the temporal amelioration was contributed by interleukin 6 inhibition with Agomelatine's mechanism of action. The photic and nonphotic treatment designs have progressed in the clinical trials by the evidence-based medicine method. **Conclusions:** The conservation of the circadian CNS function is the main direction for the purpose of the study design progress, and the case study for the participant with Asperger's Syndrome indicates the correlation of migraine in autism spectrum disorder with interferon-λ.

Keywords: cognitive impairment; progressive memory decline; sleep and dreams; major depression disorder; synaptic vesicles

1. Introduction

Existing evidence from the literature research supports the hypothesis that the psychophysiological modulation role of metacognition in wakefulness and sleep may be involved with the thalamus. The suprachiasmatic nuclei (SCN) located in the anterior part of the hypothalamus oscillate the circadian rhythm and the thalamus' functions during slow-wave sleep (SWS), via the synaptic vesicles on an electrically multidirectional basis, which is not yet elucidated [1–3]. The centromedial thalamus (CMT) neurons, as found by Gent et al. [3], promote sleep recovery by brain-wide propagation of slow waves, and are phase-advanced to behavioral/sleep-wake transitions that are dependent on a dorsal thalamic relay to the active (UP) state. Complementarily, the nonphotic afferent projections to SCN, which both direct melatonin synthesis and receive melatonin feedback, promote melatonin secretion and spindle formation on and afterward nonrapid eye movement (NREM) sleep, i.e., SWS, by thalamic function [2,4]. The neuropsychiatric evidence implies that metacognitive phenomena in dreams may be involved with both the active metacognition remains and the spindle repairment-related reflective metacognition formation after NREM sleep, from dorsolateral prefrontal cortex deactivation in rapid eye movement sleep and onwards [2,5–8]. The research, for now, does not

progress to how the competitive chemophysiological dynamics during the metacognitive involvement in SWS influence the Gateway Process and aging after waking up [9–11].

Both the neuroimmune axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis associated with the aforementioned psychophysiological process can be influenced by the proinflammatory cytokine interleukin (IL)-6. Rohleder et al. [12] reviewed the pleiotropic effects of increased IL-6 as messenger molecules that exacerbate aging in the context of affective inflammatory disease, and Vgontzas et al. [13] and Hong et al. [14] found that elevated secretion of IL-6 is negatively correlated with sleep quality and that sleep deprivation increases daytime IL-6 secretion for a down-spiral cycle by days. Furthermore, Jin et al. [15] explained how increased levels of cytokines such as IL-1β and IL-6 can lead to mood disorders by the reductions in brain-derived neurotrophic factor. Soung et al. [16] exhibited that microglial activation and expression of IL-1β and IL-6 are critical to the etiology of SARS-CoV-2 infection in the central nervous system (CNS) by type III (λ) interferon (IFN) [17].

The clinical trial has utilized the mechanism of action of Agomelatine and γ-aminobutyric acid (GABA) stimulation physical therapy with ultra-low frequency transcranial magnetic stimulation, accompanied by the concomitant medicines of beta blocker and angiotensin receptor-neprilysin inhibitor. The mechanism of action of the anti-anhedonic Agomelatine effects in treating major depressive disorder (MDD) is found to be achieved by pleiotropy IL-6 signaling blockage and level modulation [18], and Valsartan reduces brain natriuretic peptide and norepinephrine over time [19]. The GABA stimulation physical therapy compensates for the IL-1β's inhibition impacts on GABA-A receptor [20,21]. The significance of the work is the evidence-based medicine clinical trial approach to the temporal amelioration of COVID-19 vaccination-induced CNS cytokine expression that is commonly observed as COVID-19 comorbidity in MDD, shaping a working hypothesis in further modulations of IFN-λ with the IL-6 factor in the etiology of the whole and/or partial SARS-CoV-2 virus infection [16].

2. Methods

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are applied to corroborate with the psychological assessments of the neurodivergent case with Asperger's Syndrome.

A conservative treatment with equivalence test between selective serotonin reuptake inhibitors (SSRIs) and Agomelatine is adopted. The initial 1-month exposure to Sertraline Hydrochloride is orally administered with 50 mg per day, and while it is increased to 100 mg per day in the second month, Escitalopram is introduced with 5 mg per day orally administered and increased to 10 mg per day after two weeks. So is Duloxetine in the second month from its initial 20 mg per night dosage to 40 mg per night. Agomelatine is introduced in the third month with 25 mg per night, and with a 5-day transition, Duloxetine is reduced to 20 mg per night for another 12 days. On the second day of Duloxetine withdrawal, Agomelatine is increased to 50 mg per night, which is sustained for approximately one month

until reduction to 25 mg per night. Olanzapine is introduced by the end of the sixth month administered orally with 5 mg per night, increased to 10 mg per night on the eleventh month with a 4-day transition of 7.5 mg per night.

On the ninth month, Agomelatine is withdrawn and Sertraline is increased to 150 mg per day. In the eleventh month, the concomitant therapy Clopidogrel Bisulfate (75 mg per day) and Escitalopram are withdrawn, and GABA stimulation, electrical brain stimulation, and electroencephalogram biofeedback sessions are introduced for 6 days. The main concomitant therapies Sacubitril Valsartan Sodium (100 mg per night) stopped one week after the sessions and Metoprolol (95 mg per day) stopped two weeks after the sessions. While Agomelatine is reintroduced by the end of the eleventh month, the Sertraline dosage is reduced to 100 mg per day for 6 days, 50 mg per day for 3 days, and is withdrawn at the middle of the twelfth month. Olanzapine is also gradually withdrawn in the twelfth month.

Methylphenidate is introduced one month after at the middle of the thirteenth month with 18 mg per day for 11 days, and Sertraline is reintroduced with 100 mg per day for 13 days before Bupropion treatment of 150 mg per day at the middle of the fourteenth month. Bupropion treatment stops at the end of the first week of the sixteenth month, and by the end of the month, Methylphenidate is reintroduced with 18 mg per day.

Cognitive-behavioral therapy (CBT) is conducted from the second month on for six months with one session per week.

3. Results

MRI in **Figure 1** shows several ischemic foci on the frontal lobe of the participant, and some asymmetric features of the brain structure can be further seen with MRA in **Figure 2**.

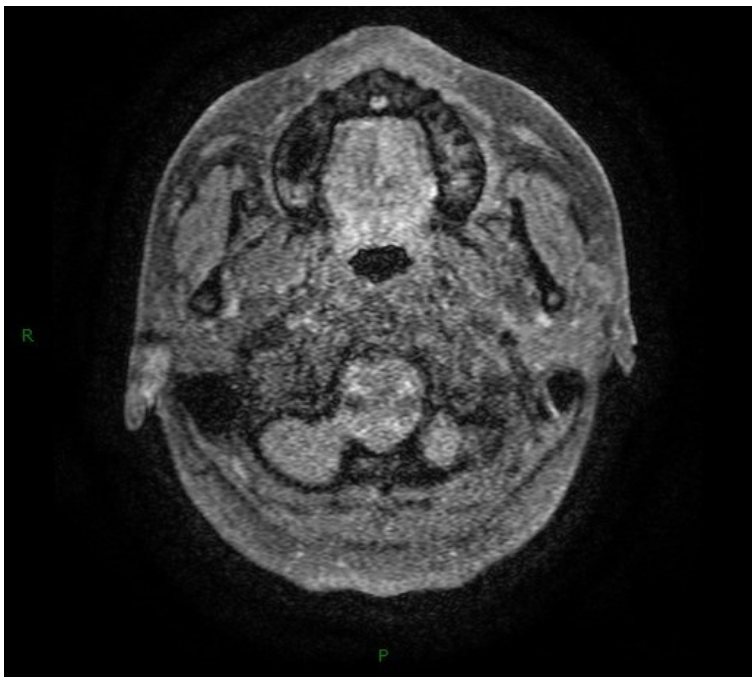

Figure 1. MRI shows the slightly asymmetric brain structure of the case with some ischemic foci on the frontal lobe.

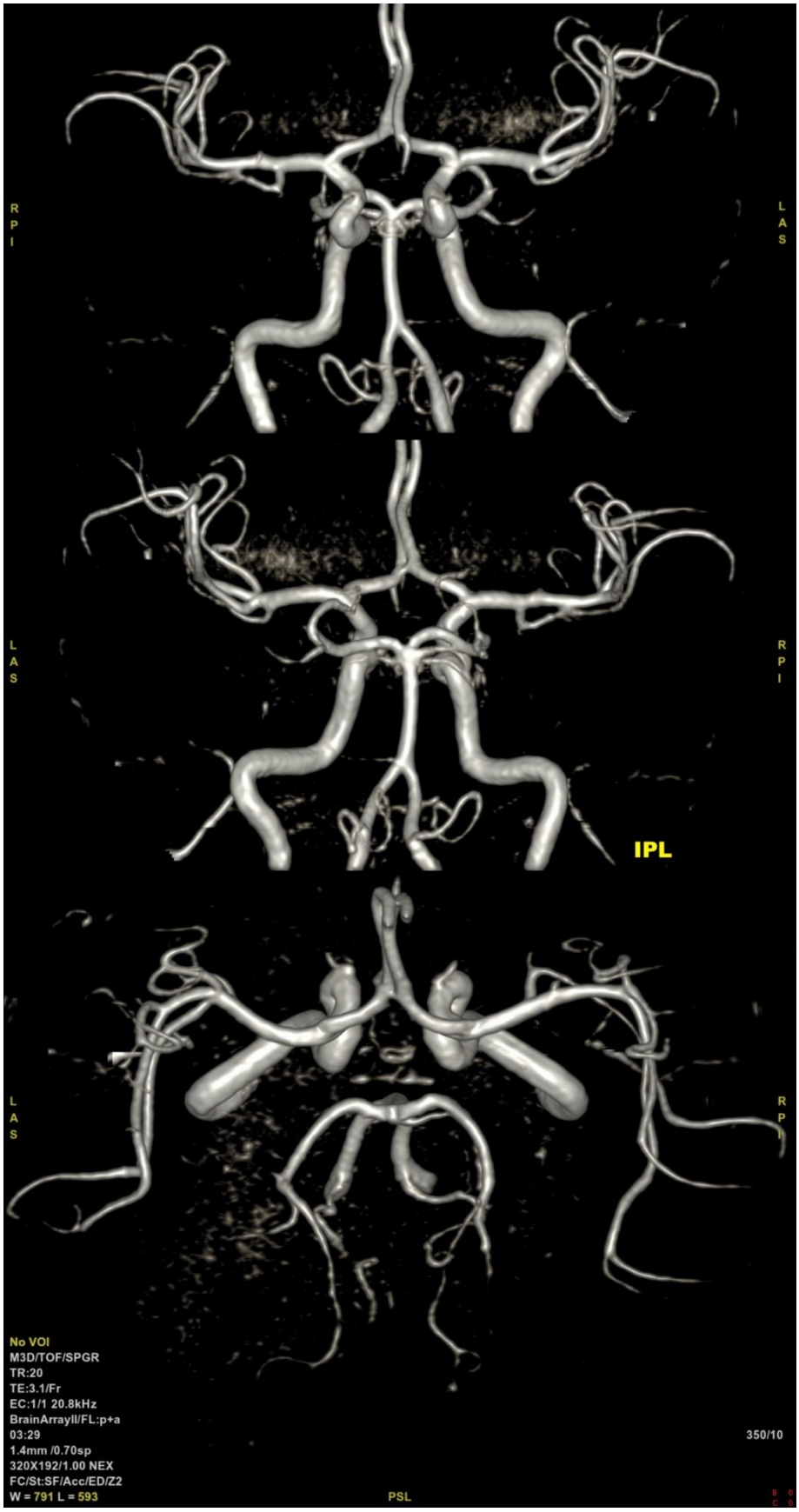

Figure 2. MRA shows the confounding variables of the brain structure regarding cerebrovascular diversity apart from the vagus nerve in ASD cases.

The participant responded positively to the subtypes of SSRIs, and the participant reported more outdoor activities after exposure to Agomelatine, apart from reduced cigarette consumptions. The initial interventions substantially reduced the migraine-like nerve pain on the left side of the participant ever since being treated for hypertension and tachycardia, symptoms of which emerged one-and-a-half years after full COVID-19 vaccination. Hypertension and tachycardia symptoms ceased with the two-month follow-up after GABA stimulation, but the nerve pain remained. Tachycardia rarely occurred in the following adjustments.

In the equivalence test, after one-and-a-half months' withdrawal from Agomelatine, the participant experienced a 30-second-to-one-minute epilepsy-like event around 9 or 10 o'clock, with one hand clenching and the other open and shaking. No other typical epilepsy symptoms are reported to be present. While the reintroduction of Agomelatine was equivalent to the higher doses of Sertraline in treating MDD, the former showed superiority in alleviating autism spectrum disorder (ASD) symptoms and the latter showed superiority in relieving euphoric anxiety from the participant's report. Furthermore, Agomelatine substantially regulated the shifts between insomnia and hypersomnia in the case.

The initial exposure to Methylphenidate amplified the euphoric anxiety symptom and insomnia, whereas the transitional Bupropion treatment ameliorated the side effects for the second exposure to Methylphenidate.

The migraine-like nerve pain is reported to be ameliorated but not utterly disappeared.

4. Discussion

Even though wider consensus has been reached on the COVID-19 vaccination comorbidity of hypertension and tachycardia, the concurrent symptom of migraine-like nerve pain upon treatment is never reported. From the review of Vetri [22], there is a high correlation between anxiety and migraine in ASD cases, and some can be life-long. It is indecisive, however, that the case can be otherwise. Neither Agomelatine nor SSRIs alone exercised satisfactory effects on the pain management, whereby Agomelatine may indirectly increase dopaminergic availabilities and modulate neuropathic pain possibly through the protection of the heart and aorta from lipopolysaccharide (LPS)-induced cardiovascular toxicity [23,24]. Evidence of the indirect increase in dopaminergic availabilities is enhanced by the participant's second exposure to Methylphenidate with positive complement. There is the possibility that the concurrence of comorbidity is associated with the polarization changes during cardiac intervention that influenced microglia's polarization phenotype and activation status, however, no further evidence in the particularity of the ASD case is present apart from the structural brain [25].

The concomitant therapies' combination with GABA stimulation effectively cured the hypertension symptom without Agomelatine, and the prior epilepsy-like event after Agomelatine withdrawal implies that the nerve pain might be associated with the neuroimmune axis but not the HPA axis. Higher levels of IFN-λ are associated with depressive symptoms following sleep disturbance, and extended release of IFN-λ in the nervous system during immunological and infectious

conditions may trigger demyelinating disorders and cause disturbances in brain function [26,27]. The hypothesis supports the rare recurrences of tachycardia, and puts the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) synapses into focus [27].

The metacognition phenomenon of dreams evidences the innate circadian regenerative neurological mechanism. From the mechanisms of action of the currently used antiseizure drugs, the mixed Valproate and presynaptic Gabapentin are adopted for the further study design by circadian pharmacological adaptation. The separated use has been tested and neither has shown lasting effects. Gabapentin, however, has been reported to be slightly superior in the nerve pain control. Further testing has been adopting Sodium Valproate for pre-sleep release and Gabapentin for post-sleep inhibition in preservation for the SCN and CMT effects during sleep and thalamic functional stress release during wakefulness, and Olanzapine is occasionally adapted for histamine control [28].

5. Conclusions

From the occurrence and treatment process of the participant's migraine-like nerve pain, it can be concluded that IFN-λ is correlated with the association between ASD and migraine. The circadian treatment with Agomelatine functions with IL-6 regulation, and the metacognition phenomenon involved in the phases of sleep suggests the possible conceptual framework for sleep medication in psychiatry.

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Data availability statement: The individual participant data can be accessed on Zenodo with the DOI: 10.5281/zenodo.13309060.

Trial registration: The clinical trials involved in the translational research is registered on ClinicalTrials.gov with the National Clinical Trial numbers NCT05930912 and NCT06357104.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of S for Science (protocol codes SARSCoV01 approved on December 22, 2022, SARSCoV02 approved on April 30, 2023, and ASD-Psy-000 approved on May 31, 2023). Informed consent of the participant is obtained and the anonymized form can be accessed via the URLs: https://cdn.clinicaltrials.gov/large-docs/12/NCT05930912/Prot_SAP_ICF_000.pdf and https://cdn.clinicaltrials.gov/large-docs/04/NCT06357104/Prot_ICF_000.pdf.

Conflict of interest: The author declares no conflict of interest.

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