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HYPERSOMNIA DISORDERS (D PLANTE, SECTION EDITOR)

COVID-19 and Central Nervous System Hypersomnias

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Abstract

Purpose of review Central nervous system (CNS) hypersomnias can be triggered by external factors, such as infection or as a response to vaccination. The 2019 coronavirus disease (COVID-19) pandemic, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to a worldwide effort to quickly develop a vaccine to contain the pandemic and reduce morbidity and mortality. This narrative review is focused on the literature published in the past 2 years and provides an update on current knowledge in respect of the triggering of CNS hypersomnias by infection per se*,* vaccination, and circadian rhythm alterations caused by social isolation, lockdown, and quarantine.

Recent findings At present, there is no consensus on the association between hypersomnias and COVID-19 vaccination or infection per se*;* however, the data suggest that there has been an increase in excessive daytime sleepiness due to vaccination, but only for a short duration. Kleine Levin syndrome, hypersomnia, excessive daytime sleepiness, and narcolepsy were aggravated and exacerbated in some case reports in the literature. Both increased and decreased sleep duration and improved and worsened sleep quality were described. In all age groups, delayed sleep time was frequent in studies of patients with hypersomnolence.

Summary The hypothesis that there is a pathophysiological mechanism by which the virus, vaccination, and the effects of quarantine aggravate hypersomnias is discussed in this review.

Keywords COVID-19 · SARS-CoV-2 · Hypersomnia · Narcolepsy · Kleine Levin syndrome, Idiopathic hypersomnia

Introduction

Central nervous system (CNS) hypersomnias are a group of disorders (Box 1) in which the main complaint is usually excessive daytime sleepiness (EDS), which is defined as "the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep, or unintended lapses into drowsiness or sleep" [1]. EDS can be caused by non-restorative sleep during the night; sleep disorders, such as insomnia; and disturbed circadian rhythms and/or disturbed nighttime sleep, and may lead to accidents, reduced work or school performance, social stigmatization (social stigma associated with constant sleepiness, sleep attacks, and cataplexy), and other negative consequences.

BOX 1. Central Nervous System Hypersomnias
- Narcolepsy type 1 [hypocretin deficiency, cataplexy is often present]
- Narcolepsy type 2 [normal hypocretin levels, no cataplexy]
- Idiopathic hypersomnia
- Kleine-Levin syndrome
- Hypersomnia due to a medical disorder
- Hypersomnia due to a medication or substance
- Hypersomnia associated with a psychiatric disorder
- Insufficient sleep syndrome

From the American Academy of Sleep Medicine [1]

As potential neuroimmunological diseases, hypersomnias (narcolepsy, Kleine-Levin syndrome (KLS)) and idiopathic hypersomnia (IH)) can be triggered by external factors, such as upper airway infection, H1N1 influenza, or neuroimmunological response to vaccination [2]. Moreover, the timing of wild-type infection and seasonality are hypothesized to

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be factors contributing to the appearance or worsening of hypersomnias, according to a recent report by the *International Alliance for Biological Standardization* [3].

The COVID-19 pandemic resulted in widespread infection and the administration of an enormous number of vaccinations, which led researchers to consider whether there was a risk of the infection and/or vaccination triggering hypersomnias, as was seen in 1918 during the Spanish flu and in 2010 following H1N1 vaccination [4, 5]. However, the pathophysiological mechanisms through which a virus or vaccination could trigger hypersomnias remain unclear.

The pandemic not only affected the sleep of adults, but also that of children and adolescents; This deserves particular attention, as sleep is crucial in respect of physical and cognitive development in these groups [6]. Most studies about sleep during the COVID-19 pandemic in this population address insomnia, psychological symptoms, and the impact of disrupted sleep–wake schedules [6–8]. Disorders related to initiating and maintaining sleep being more common, and it is estimated that around 16% in a group of Egyptian children experienced EDS during the pandemic [7]. Studies during the COVID-19 pandemic suggested that children's sleep duration increased with a transition to circadian phase delay [6]. Most adolescents naturally shift their sleep to later, highlighting the importance of school start time in respect of avoiding chronic sleep deprivation [9].

The period of the pandemic has been an unprecedented time, with the whole world entering into "quarantine" and/or lockdown; The imposition of new routines resulted in changes in many daily habits and behaviors (including in respect of sleep), including those in respect of mealtimes and working and studying practices. This was accompanied by restrictions on performing outdoor physical activity, reduced face-to-face social contact, and decreased exposure to sunlight [10] and increased exposure to artificial light and screens.

Quarantine had a significant impact on *zeitgebers* (the external clues modulating the circadian system). The circadian system temporally orchestrates physiological processes by using external clues. As the immune system is intrinsically related to circadian biology [11], the production and release of many hormones linked to immunity were affected by the new routines imposed by lockdown and social isolation. This raised several questions, such as whether a "side-effect" of quarantine could be the development or aggravation of hypersomnias, and whether factors such as increased anxiety and depression, changes in sleep–wake cycles, or circadian rhythms could impact hypersomnias. This narrative review focused on the literature published in the past 2 years and provides an update on current evidence in respect of the appearance of central nervous system hypersomnolence (CNSH) and their management, triggered by external factors such as the infection per se, the vaccination, and circadian rhythm alterations during the COVID-19 pandemic.

SARS-COV-2 Infection-Related Hypersomnias

SARS-CoV-2 can result in encephalitis (by direct or immune-mediated action of the virus), resulting in EDS due to lesions in many parts of the CNS such as the hypothalamus, temporal lobes, hippocampus, and brain stem [12–14]. We found two case reports of young adults previously diagnosed with KLS indicating that SARS-CoV-2 infection triggered exacerbated KLS. Regarding the pediatric population, two investigations addressed sleepiness as a potential symptom of SARS-CoV-2 infection in a 5-week-old baby and a male 12-year-old child [12, 13]. In both cases, although being a non-specific symptom, we believe that sleepiness occurred in the context of encephalopathy secondary to systemic inflammation, as suggested in the literature. Lesions in the temporal lobes and hippocampus can trigger KLS like-symptoms, even though the brain pathology of patients with KLS is not clear [14, 15]. In addition, a few reports described elevated levels of titers of glutamic acid decarboxylase 65 (GAD65) and anti-N-methyl-D-aspartate [NMDA] receptor antibodies in cerebrospinal fluid correlating with this KLS relapse [16].

Kleine-Levin Syndrome

A case report of a 24-year-old Croatian man with Kleine-Levin Syndrome (KLS) described how the disease was exacerbated after SARS-CoV-2 infection; he had been diagnosed 2 years earlier, but after treatment with modafinil and risperidone [gradually discontinued], and improved sleep hygiene, he was without symptoms (in 2017). In January 2021, he got COVID-19 with respiratory symptoms, and then started sleeping for more than 18 h a day, felt tired and lethargic, angry, and gained weight due to overeating, a sign he presented before being diagnosed with KLS. Brain MRI showed changes in white matter, including hyperintensive lesions located bilaterally frontally, subcortically, and periventricularly. Modafinil and lithium were introduced as a treatment, and the symptoms were controlled. The authors stated that no causative agent was found in this case except for the SARS-CoV-2 virus, although the mechanism which activated the quiescent disease is unclear [17•].

Another case report described how a 36-year-old American man with a known history of KLS since the age of 14 experienced a relapse secondary to SARS-CoV-2 virus infection, which occurred 2 weeks before developing COVID-19 symptoms. He was treated with intravenous

lorazepam and discharged with melatonin prescriptions due to an initial robust response to these drugs [18•]. Hypoperfusion of the thalamus, temporal and frontal lobes, and basal ganglia in KLS patients is seen during the symptomatic period, indicating perfusion abnormalities [19]. Hypoperfusion of both frontotemporal lobes has been seen in COVID-19 cases, possibly explaining KLS symptoms [20].

COVID-19 Vaccination-Related Hypersomnias

COVID-19 vaccines are an essential instrument to control the pandemic, helping to reduce the devastating economic and social impacts of the disease [21–23]. The COVID-19 pandemic increased the development of novel vaccines, especially viral vector-based DNA and RNA vaccines [2, 24••]. Regulators have sanctioned many vaccines since December 2020, and large-scale immunization programs are ongoing around the world [25].

Many kinds of COVID-19 vaccine received authorization for emergency use [25]. During the pandemic, a higher tolerance of significant risks of vaccination is tolerable due to the enormous morbidity and mortality caused by COVID-19; however, careful monitoring and robust pharmacovigilance in respect of new vaccines are essential. Usually, a vaccine is not expected to be 100% effective nor 100% safe ("no effect, no side effect") but insufficient or excessive responses to infection are not desirable. "A disproportionate response to vaccination in patients susceptible to autoimmunity, such as the "cytokine storm", and adverse events that include acute respiratory distress syndrome, can be fatal [2, 26]." Regulatory agencies in all countries must have adequate surveillance strategies in respect of vaccination. The US FDA Center for Biologics Evaluation and Research published a protocol on "Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring." The European Medicines Agency funded the vACCine COVID-19 monitoring readinESS (ACCESS) project, including the estimation of adverse events of particular interest, such as myocardial infarction, Guillain–Barre syndrome, among other conditions, in their protocol [25, 27••].

In 2010, there was a possible increase in the incidence of narcolepsy following the pandemic influenza A [H1N1] and vaccination with Pandemrix (GlaxoSmithKline, Dresden, Germany) [23, 28]. Reports suggested that the development of narcolepsy could have been triggered by the AS03-adjuvanted H1N1 vaccine in many countries such as Denmark, Finland, and Sweden, reporting an incidence rate ranging from a 1.9 to 14.2 per million p-y [29]. Pandemrix, an AS03-adjuvanted H1N1 vaccine, contributed to a spike in narcoleptic onset among children and young adults, with a 12.7-fold increased risk of narcolepsy diagnosis 8 months after the vaccine [30–32]. Adjuvants are helpful in many kinds of vaccines because some viral strains induce different levels of immunological responses. Adjuvants may stimulate the strongest sub-pathways of the immune system of interest to the immune responses [2]. However, in Quebec, Canada, where Pandemrix was used in the population, there was a lower incidence of the development of narcolepsy [1.5 per million-p-y] compared to previous investigations in respect of the onset of narcolepsy following vaccination with Pandemrix [5]. The reasons or mechanisms for an association between use of the AS03-adjuvant and a higher incidence of narcolepsy remain unclear; however, a correlation between vaccination and the onset of narcolepsy was earlier observed in the 1918 influenza pandemic [4].

Non-adjuvanted H1N1 vaccines have not shown a strong association with increased narcolepsy incidence, and many countries have not reported increases in narcolepsy after AS03-adjuvanted H1N1 vaccination [31, 33]. Potent adjuvants, such as AS03, have been used to develop COVID-19 vaccines that are currently in use. However, the use of AS03 alone was not responsible for the reported increase in narcolepsy—flu infections, independent of vaccination, were also a possible trigger, as described over 100 years ago, as was the case in the 1918 flu pandemic [3, 34]. AS03 stimulated CD4 + T cell responses targeting different H1N1 flu sequences and consequent hypocretin fragments are needed to manifest narcolepsy [2, 35, 36]. Current research suggests that narcolepsy seems to result from an initial CD4 + T cell response that targets H1N1 influenza sequences puzzled by hypocretin fragments, suggesting that a combination of influenza sequences and AS03 was needed for narcolepsy to manifest [35]. Thus, this is a complex subject that demands time, effort, and further investigation into neuroimmunology and sleep to reach a better understanding of the possible mechanisms involved [36, 37].

An extensive study drawing data from 13 databases (126,661,070 people, and 227,043,370 person-years of follow-up) demonstrated that many diseases (e.g., acute myocardial infarction, anaphylaxis, appendicitis, Bell's palsy, deep vein thrombosis, disseminated intravascular coagulation, encephalomyelitis, Guillain–Barre syndrome, stroke, immune thrombocytopenia, myocarditis/pericarditis, narcolepsy, pulmonary embolism, myelitis) were most prevalent after COVID-19 vaccination, depending on age [25]. Some adverse events of particular interest (e.g., myocardial infarction, Guillain–Barre syndrome] increased with age, while others [e.g., anaphylaxis, appendicitis) were more common in young people [25]. This epidemiological investigation

reported deep vein thrombosis, pulmonary embolism, stroke, immune thrombocytopenia, and disseminated intravascular coagulation rates, conditions potentially associated with COVID-19 vaccination, as the SARS-COV-2 virus has been shown to have a possible influence on coagulopathy [25, 38]. Narcolepsy was more common in younger populations, following the pattern observed in previous reports [25, 38].

Relapse of Hypersomnia Due to a Medical Disorder Triggered by the COVID-19 Vaccine

Hypersomnia reappeared in a 19-year-old female patient, possibly related to COVID-19 vaccination with CoronaVac, an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China) [23]. The symptom of excessive daytime sleepiness appeared 10 days after the first vaccination dose. The patient had been previously diagnosed with hypersomnia secondary to infectious mononucleosis at the age of 13 when she had started treatment with methylphenidate and sertraline. Before receiving the vaccine, the patient was asymptomatic and had discontinued the medication 2 months earlier. She presented with excessive sleep duration and sleep attacks [13 h/day] and was diagnosed with hypersomnia and methylphenidate and sertraline were prescribed for treatment, but with an inadequate response [23].

Excessive Daytime Sleepiness After COVID-19 Vaccine

Some studies have shown that over 50% of people have complained of sleepiness after receiving a COVID-19 vaccination [39–41]. It has been suggested that the COVID-19 vaccine could trigger the relapse of secondary hypersomnia with an autoimmune response after vaccination possibly playing a role in the pathogenesis of the condition [23]. However, to the best of our knowledge, there are no immunological findings as yet that support this hypothesis.

COVID-Somnia, the Impact of Home Confinement, and CNS Hypersomnias

COVID-somnia is a term used to describe sleep disorders experienced during the COVID-19 pandemic. They vary from insomnia to hypersomnia, nightmares, and sleep terrors to worsening sleep apnea [42]. The impact of COVID-somnia was felt across the whole world, not only in those who had the disease, but also is some who did not. In those infected, the virus was responsible; it is known that viruses affect sleep, although different infections have different effects on sleep, with some increasing sleep while others reduce it due to their different effects on the immune system [43]. In those not infected, the emotional distress caused by a world pandemic, and the associated anxiety, depression, fear, and stress, which are well known to impair sleep, played important roles in sleep disturbance [10]. In many cases, sleep schedules were changed by the lockdown, leading to a loss of the *zeitgebers*, the time cues that help to entrain circadian clocks [10]. Chronotype, a person's predisposition to sleep at a particular time in a 24-h period, also played an important role in sleep disruption during the pandemic, as the effects of the lockdown affected people's abilities to follow their natural sleep patterns [44]. Studies have shown that in general people tended to present delayed sleep and wake-times during the pandemic, as well as a reduction in sleep duration during the night and increased daytime napping, increased insomnia, and changes to usual circadian rhythms [10, 42].

People with hypersomnias were also affected by COVID-somnia, despite having different sleep needs than the general population and many neurobiological differences in respect of sleep, and during the lockdown. A French online study conducted by Nigam et al. with 225 participants with narcolepsy [types 1, NT1, and 2, NT2] and idiopathic hypersomnia (IH) asked the participants about their sleep habits. Delayed bedtimes and wake times and increased sleep duration during the night were found [45]. Insomnia (symptom) was reported in more than half of the sample during the lockdown, with participants with NT1 being more likely to report insomnia, followed by NT2 and IH. EDS decreased in the whole sample and was associated with increased wellness. Almost one third of the participants reported more minor complaints of fatigue, reduced sleep attacks, and better concentration, despite decreased stimulant usage. Interestingly, most of the participants liked the lockdown, and their sleep benefited from it, being 1 h longer during the lockdown [45]. Participants with IH were more likely to delay bedtime and wake-up than those with NT1 and NT2. Among the participants with NT1, more than half reported diminished or a disappearance of cataplexy, a third reported no changes and slightly less than a fifth reported increased cataplexy. The authors suggested that the reduced levels of sleepiness and decreased social interactions (which could lead to cataplexy attacks) were responsible for the positive changes. Hallucinations decreased for more than a third of the NT1 and NT2 samples and remained unchanged for more than half of the participants in both groups. More than 70% of IH participants reported difficulty getting out of the bed during the lockdown, longer sleeping times, and eveningness-type of chronotype. In the qualitative analysis, the authors stated that there was an increase in nighttime sleep, sleep phase delay, and free napping schedules, and an improvement in wellbeing in patients with NT1, NT2, and IH. The possibility to experience an ultradian rhythm, with multiple sleep episodes and refreshing naps

resulted in reduced sleepiness and in many of the symptoms related to hypersomnia for the majority of individuals. One hypothesis is that during the lockdown, with fewer social and professional activities, they could sleep more for many periods of the day.

Working from home became common during the pandemic, and a study by Postiglione et al. in Italy demonstrated that 50 participants with NT1 working from home experienced increased sleep time and decreased EDS. These participants also experienced an increase in weight gain [46•].

It is worth mentioning that some patients with narcolepsy tend to circadian misalignment, as the loss of *zeitgebers* could result in them having a free-running sleep disorder. Sleep phase delay in patients with narcolepsy [NT1 and NT2] and lack of adaptation to the adversities of the lockdown were found in a previous study by our group. Aguilar et al. noted increased sleep fragmentation, sleepiness, daytime napping, and appetite. Most of the sample of our study found a worsening quality of life and no changes in cataplexy, sleep paralysis, and hallucinations [47•], contrary to Nigam et al. [45]. A significant reduction in antidepressant medication could explain our findings and the financial hardship and unemployment caused by the pandemic in Brazil [47•].

Cultural, social, and economic burden implies psychological distress related to the COVID-19 lockdown. Contrary to the previous study of our group, Italian patients with NT1 showed a decrease in daytime sleepiness [47•] and fragmented sleep during the lockdown, leading to an improvement in narcolepsy symptoms [47•, 48•].

In children and adolescents, an investigation with 765 participants aged 4–16 years conducted by Refay et al. found that 65.6% showed symptoms suggestive of a sleep disorder, as measured by the Sleep Disturbance Scale for Children score (SDSC) [7]. Almost 16% of the children suffered from EDS, with significant positive correlations between SDSC scores and increased screen usage. Children and young adolescents suffered from the sudden withdrawal from social activities, the disruption of everyday lifestyle, greater utilization of social media, and increased screen time. Screen time usage is associated with decreased sleep duration, prolonged initiation of sleep, and sleepiness, due to the content [game histories] and the emission of light that impairs sleep [10].

In Japan, Komada et al. conducted a longitudinal study to identify changes in the subjective sleepiness of pupils during the pandemic using the Pediatric Daytime Sleepiness Scale [49]. They found that EDS decreased in more than half of pupils between January and June 2020 during the lockdown period. A less restrictive school schedule due to COVID-19-related school closure decreased subjective sleepiness in children and was also associated with reducing *social jetlag* (i.e., the time difference between the midpoint of sleep on workdays and on free days). Therefore, parents and caregivers should be instructed that keeping a regular sleep–wake schedule and preventing *social jetlag* are essential factors for improving sleep quality regardless of the age of their children. Similarly, a Canadian qualitative study was conducted with 45 adolescents using one-on-one semi-structured phone interviews to explore pre- and during-pandemic sleep schedules, duration, and sleep characteristics. The authors found significantly decreased daytime sleepiness after the school shut down. The pandemic led to a 2-h shift in the sleep of typically developing adolescents, longer sleep duration, improved sleep quality, and less daytime sleepiness than those experienced under the regular school-time schedule.

The COVID-19 Pandemic and the Pediatric Population with Narcolepsy

The impact of the pandemic on the management of patients with narcolepsy is another subject that is worthy of discussion. Squeakers et al. produced an interesting analysis that teaches important lessons about pediatric narcolepsy [50]. They observed the consequences of lockdown measures on daytime functioning, well-being, and school performance. Adolescents with narcolepsy tended to have decreased attention levels during school shutdown. To overcome this, the authors emphasized the importance of promoting a regular schedule of at-home physical exercise and encouraging flexibility in school start times to allow for increased sleep which could result in a decrease in narcolepsy symptoms.

A study using actigraphy in 18 NT1 children and adolescents under stable pharmacological treatment with sodium oxybate during the first Italian lockdown found that children and adolescents went to bed and woke up later (delayed bedtimes by 75 min during weekdays and about 60 min during the weekend), slept more during the daytime, and napped more frequently. *Social jetlag* decreased by 17 ± 30 min. The study objectively showed that NT1 children and adolescents delayed the sleep phase and slept more during the daytime during the lockdown. However, no difference emerged in estimated sleep duration, nocturnal sleep quality, or sleepiness for these patients [51].

Delaying school start times to decrease sleep deprivation in adolescents has been debated for many years. It is likely that positive consequences could be obtained in healthy children and adolescents and those with NT1. After the lockdown in Canada, following the school shutdown, the school day started at 10:00 [9]. The American Academy of Pediatrics has recommended that junior high and high schools delay school start times to 08:30 or later to prevent insufficient sleep, resulting in daytime dysfunction [52]. The topics previously discussed again highlight the potential importance of school start times.

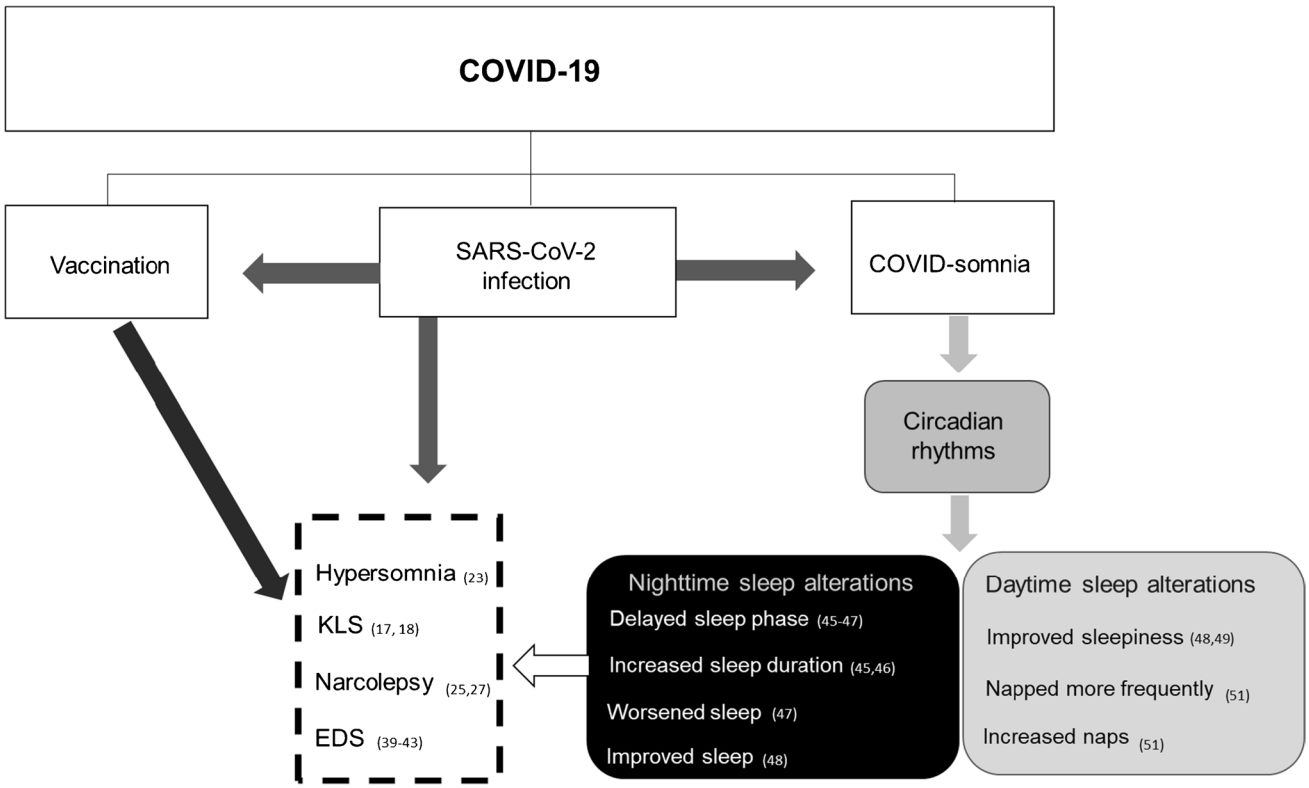

Fig. 1 Interplay between COVD-19 and central disorders of hypersomnolence triggered by external factors. Dark arrows represent the consequences of infection; light gray arrows represent secondary consequences, and measures taken to ameliorate the COVID-19 pandemic; white arrow represents the influence of altered sleep pattern on central disorders of hypersomnolence. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; KLS, Kleine- Levin Syndrome; EDS, excessive daytime sleepiness

It is important to note that a number of the findings of this review have been contradictory (as shown in Fig. 1). Seasonality could explain some of these controversial results. In Italy and France, the lockdown happened in wintertime, and in Brazil, the lockdown occurred in summer. During the wintertime, people tend to stay indoors more with reduced exposure to natural light, while in the summer people spend more time outside with greater light exposure. Seasonality may also have had an impact on behavior and levels of psychological distress and stress during the pandemic.

Conclusion

The data collected showed that in some countries EDS decreased, while in others it increased, which could have impacted levels of anxiety and sleep rhythms and thus the management of hypersomnias. At present, there is no consensus on whether the appearance of hypersomnias can be associated with the COVID-19 vaccine or infection per se. However, some data suggest that there has been an increase in EDS following vaccination, but with only a short-term effect. KLS, IH, and narcolepsy have been shown to be aggravated and exacerbated in some case reports in the literature, and there have been reports of both increased and decreased sleep duration, and also, improved and worsened sleep quality of patients with CHS hypersomnias. In all age groups, delayed sleep time was frequently reported in studies of patients with CNS hypersomnias. Further studies with longer follow-ups are required to elucidate whether there is a long-term association between COVID-19 and CNS hypersomnias.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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