Article

The CSHQ-DE Questionnaire Uncovers Relevant Sleep Disorders in Children and Adolescents with Long COVID-19.

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Abstract: Acute SARS-CoV-2 infections in children and adolescents are usually mild. However, they can suffer from ongoing symptoms generally referred as long COVID. Sleep disorders are one of the most frequent complaints in long COVID although precise data are missing. We assessed the sleep behavior of children and adolescents who presented at our outpatient clinic between January 2021 and May 2022 with the Children's Sleep Habits Questionnaire (CSHQ-DE). We compared sleep behavior at three different time points: pre-COVID-19, post-COVID-19 at initial presentation and post-COVID-19 at re-presentation. Data from 45 patients were analyzed. Of those, 64% were female and the median age was 10 years (range 0-18 years). Asymptomatic or mild COVID-19 disease was experienced in 89% of patients, whilst 11% experienced moderate disease. Initial presentation occurred at a median of 20.4 weeks (6 weeks - 14 months) after infection. The CSHQ-DE score increased significantly from pre-COVID-19 (45.82+8.7 points) to post-COVID-19 (49.40+8.3 points; p=<0.01). The score then normalized at re-presentation (46.98+7.8; p=0.1). The greatest changes were seen in the CSHQ-DE subscale score "daytime sleepiness". Our data show that children and adolescents with long COVID often suffer from sleep disturbance. For most children and adolescents these sleep disorders decreased over time without further medical intervention, aside from a basic sleep consultation.

Keywords: long COVID; Post COVID-19 condition; sleep disorders; SARS-CoV-2; Coronavirus; children

1. Introduction

Acute SARS-CoV-2 infection in children and adolescents is usually mild [1]. Similar to adults, children can suffer from ongoing symptoms [2]. This new disease is generally referred as long COVID, Post-COVID-19 condition or Post-COVID-19 syndrome [3]. NICE defines long COVID in children, adolescents and adults as persisting symptoms that develop during or after COVID-19 infection and are present for more than 4 weeks (ongoing COVID-19) or 12 weeks (Post-COVID-19 syndrome) [4]. A slightly different definition exists from WHO which currently only refers to adults [5]. Worsening symptoms in a pre-existing disease as a result of a SARS-CoV-2 infection is also assigned to long COVID according to the German long COVID guideline [64]. Over 200 Symptoms are described and any organ may be affected [6,7,8,9]. The most frequently described complaints are fatigue, respiratory problems, cognitive dysfunction, cardiac symptoms, abdominal pain and sleep disturbances [10,11,12]. Whilst it is known that sleep disorders have a great impact on the quality of life of children and adolescents [13], precise data, especially longitudinal data relating to the effect of long COVID on sleep in children and adolescents are lacking. Adequate care of sick children and adolescents requires a holistic approach in order to

address all aspects of the illness. Therefore we routinely assessed the sleep behavior of children and adolescents who presented to our outpatient long COVID clinic.

2. Materials and Methods

2.1. Cohort Composition

From January 2021 to May 2022 children and adolescents who presented to the interdisciplinary long COVID outpatient clinic of the Children's Hospital of Jena, Germany, were screened for sleeping disorders using the CSHQ-DE. Patients who fulfilled the long COVID diagnostic criteria and consented to the study were included in the study. One hundred and two children and adolescents met this criteria, of which 45 completed the questionnaires, in full, at all three time points and were included in the analysis. The most common reason for exclusion was that the questionnaire was not completed at the time of re-presentation as symptoms had resolved.

2.2. CSHQ-DE

Sleep-related symptoms in patients were assessed using the standardized Children's Sleep Habits Questionnaire (CSHQ-DE) for clinically relevant sleeping issues of school-aged children (4-10 years) [14,15,16]. In this study, the CSHQ-DE was also used to screen sleep disorders of children and adolescents outside of this age range (0-18 years). The questionnaire provides a total score and eight subscale scores which reflect the key sleep domains. The clinical cut-off used for a possible sleep dysfunction was a total score ≥ 41 points. The CSHQ-DE was usually parent-reported, with adolescent patients filling out the questionnaire independently, if able to do so. The CSHQ-DE was completed at three time points: pre-COVID-19 (retrospectively), post-COVID-19 at initial presentation and post-COVID-19 at re-presentation (three months later). Only patients for whom the CSHQ was completed, in its entirety, at all three time points and whose complaints met the diagnostic criteria for long COVID were included in the analysis. All parents gave their written informed consent to their children's participation in the study. The study protocol was approved retrospectively by the local Ethics Committee (Protocol No. 2022-2614_1-BO).

2.3. Further Investigations

A diagnosis of long COVID necessitates that alternative diagnoses are excluded. Additionally, residual organ damage following SARS-CoV-2 infection should be detected. Therefore all children presenting to our long COVID clinic underwent extensive investigations. In addition to a detailed history and physical examination, all patients were investigated with echocardiography, ECG, vital signs (incl. blood pressure), extensive blood and urine tests. Patients who were able to cooperate underwent orthostatic test, exercise test, pulmonary function test, endothelial dysfunction test (Dynamic Vessel Analysis) and a psychosocial review. If indicated, the assessment was supplemented with additional investigations, including sonography, MRI/CT (lung, brain, abdomen, renal, joints), EEG, hand strength measurement and stool pathology.

2.4. Statistical Analysis

Data was analyzed using SPSS 28. Since most of the data was normally distributed, data are presented as mean +/- SD (standard deviation). Groups were analyzed using univariate ANOVA with repeated measures for multiple time points. Multiple measurements were corrected using Bonferroni post-hoc analysis. Multivariate Regression between sleep quality indices and symptoms of long COVID were performed. A p-value <0.05 was considered to indicate statistical significance (2-tailed).

3. Results

Data from 45/102 (44.1%) patients presenting for the first time at the long COVID outpatient clinic between January 2021 and May 2022 were analyzed. Of those, 64% were

female and the median age was 10 years (range 0 to 18 years). Asymptomatic or mild COVID-19 disease was experienced in 89% of patients, whilst 11% experienced moderate disease. The average Body Mass Index (BMI) mean percentile, based on CDC values, was 74% (IQR 39, 89).

Fifteen (33%) of all patients had a current or previous medical issue (Table 1). Six children had more than one current or previous medical issue. The most common disease group was Pulmonary/allergic disease (10/45), with 7 patients (16%) having a history of atopy (asthma/eczema/allergies). Two patients (who were siblings) had cystic fibrosis, two patients had obesity, whilst two patients had a current seizure disorder. One patient with a diagnoses of metabolic syndrome and Rolandic epilepsy was medicated with gabapentin, enalapril and metformin. One patient had absence seizures on nil medications and a further patient had autoimmune hepatitis/ primary sclerosing hepatitis overlap and was managed with prednisone and azathioprine. Of note, nil patients had a diagnosis of obstructive sleep apnea.

Table 1: Patient Characteristics and Medical History

Characteristics	**n**	**Distribution**
n	45	
Age, mean in years	45	10.0 (IQR 8.0, 14.0)
Female gender	45	29 (64%)
BMI percentile mean (based on CDC)	45	74.0 (IQR 39.0, 89.0)
COVID-19 course	45	
asymptomatic		5 (11%)
mild		35 (78%)
moderate		5 (11%)
Medical History		
Pulmonary/allergic disease		10 (22%)
- Cystic Fibrosis		-2
- Asthma/ reactive airways		-3
- Other allergy/ Eczema		-3
- RDS, pneumothorax, allergy		-1
- Recurrent Croup*		-1
Neurological diseases		5 (11%)
- Seizure Disorder		-2
- Migraine		-1
- Developmental delay		-1
- Febrile seizures*		-1
von Willebrand Disease (type 1)		1
Right sided aortic arch*		1
Autoimmune hepatitis, primary sclerosing cholangitis		1
Constipation		1
Obesity		2
Metabolic Syndrome		1
Psychogenic gait disorder, somatization disorder		1
Williamsbeuren Syndrome		1
Prematurity (32 and 34 weeks gestation)		2

** indicates disease which is either resolved at time of infection or is considered a normal variant*

Initial presentation occurred at a median of 20.4 weeks (6 weeks to 14 months) after infection. The assessment was repeated at the scheduled re-presentation 3 months later (mean 14.3 weeks; range 7 weeks to 9 months). At initial presentation 80% of the patients suffered from two or more symptoms (Table 2). The most common symptoms were fatigue/stress intolerance (62%), concentration/learning difficulties (44%), sleep disorders (42%), pulmonary symptoms (38%) and headache (36%).

Table 2. Predominant symptoms at initial presentation.

Symptoms	In total (%)
Fatigue/stress intolerance	30/45 (62%)
Concentration/learning difficulties	20/45 (44%)
Sleep disorders	19/45 (42%)
Pulmonary symptoms	17/45 (38%)
Headache	16/45 (36%)
Gastrointestinal symptoms	14/45 (31%)
Cardiac symptoms	10/45 (22%)
Dizziness	10/45 (22%)
Muscle and joint symptoms	9/45 (20%)
Neurological symptoms	9/45 (20%)
Smell and taste disorders	9/45 (20%)
Hair loss	6/45 (13%)
Skin changes	4/45 (9%)

Table 3: Predominant symptoms at initial presentation – Differentiation by age

Symptoms	**In total (%)**
Fatigue/Stress intolerance	30/45 (62%)
0-5 years	*5/9 (56%)*
6-11 years	*11/18 (61%)*
12-18 years	*12/18 (67%)*
Concentration/learning difficulties	20/45 (44%)
0-5 years	*1/9 (11%)*
6-11 years	*10/18 (56%)*
12-18 years	*9/18 (50%)*
Sleep disorders (reported in medical history)	**19/45 (42%)**
0-5 years	***3/9 (33%)***
6-11 years	***7/18 (39%)***
12-18 years	***9/18 (50%)***
Pulmonary symptoms	17/45 (38%)
0-5 years	*5/9 (55,6%)*
6-11 years	*5/18 (28%)*
12-18 years	*7/18 (39%)*
Headache	16/45 (36%)
0-5 years	*0/9 (0%)*
6-11 years	*8/18 (44%)*
12-18 years	*8/18 (44%)*
Gastrointestinal symptoms	14/45 (31%)
0-5 years	*4/9 (44%)*

6-11 years	*3/18 (17%)*
12-18 years	*7/18 (39%)*
Cardiac symptoms	10/45 (22%)
0-5 years	*0/9 (0%)*
6-11 years	*4/18 (22%)*
12-18 years	*6/18 (33%)*
Dizziness	10/45 (22%)
0-5 years	*2/9 (22%)*
6-11 years	*2/18 (11%)*
12-18 years	*6/18 (33%)*
Muscle and joint symptoms	9/45 (20%)
0-5 years	*2/9 (22%)*
6-11 years	*3/18 (17%)*
12-18 years	*4/18 (22%)*
Neurological symptoms	9/45 (20%)
0-5 years	*2/9 (22%)*
6-11 years	*4/18 (22%)*
12-18 years	*3/18 (17%)*
Smell and taste disorders	9/45 (20%)
0-5 years	*0/9 (0%)*
6-11 years	*2/18 (11%)*
12-18 years	*7/18 (39%)*
Hair loss	6/45 (13%)
0-5 years	*1/9 (11%)*
6-11 years	*1/18 (6%)*
12-18 years	*4/18 (22%)*
Skin changes	4/45 (9%)
0-5 years	*1/9 (11%)*
6-11 years	*3/18 (17%)*
12-18 years	*0/18 (0%)*

On history, 42% of patients reported sleep disorders post-COVID-19. At initial presentation the CSHQ-DE showed that 88.9% suffered from possible sleep dysfunction (total score $\geq$41); however 66.7% already had a possible sleep dysfunction pre-COVID-19. 94.7% of patients who self-reported suffering from sleep disorders post-COVID-19 had a total CSHQ-DE score $\geq$41. Pre-COVID-19 the mean CSHQ-DE score of all 45 assessed patients was 45.82$\pm$8.7 points, increasing significantly to 49.40$\pm$8.3 points (p=<0.01) post-COVID-19. Thereafter, a trend to normalize (46.98$\pm$7.8; p=0.1) was observed at re-presentation (Figure 1). In an age group sub-analysis (Table 3), a statistical difference was shown for the CSHQ scores of the 6-11 (p=0.035) and 12-18 (p=0.007) years age groups. No statistical difference was found for the 0-5 year age group.

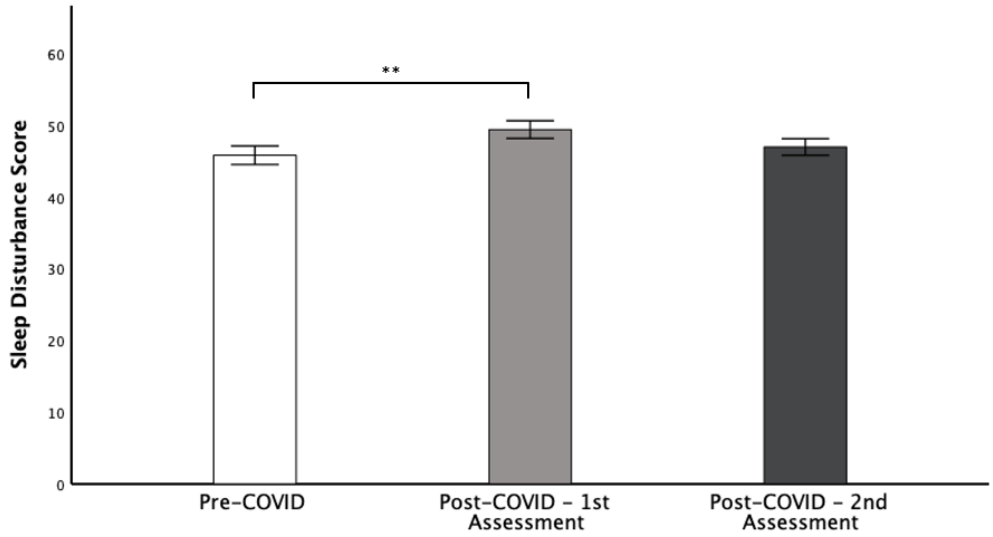

Figure 1. Total CSHQ-DE score pre-COVID-19 vs. post-COVID-19 initial and re-presentation. The sleep disturbance score increased significantly between pre-COVID-19 and 1st Assessment (45.82+8.7 to 49.40+8.3), then decreased following (46.98+7.8). Univariate ANOVA with multiple measurements, post-hoc Bonferroni (**p=<0.01).

Table 3: Subgroup analysis of the CSHQ-DE score differentiated by age group (Two Sided ANOVA (Friedman)

Age group	Total CSHQ-DE			p-value
	Pre-COVID	Post-COVID 1st Assessment	Post-COVID 2nd Assessment	
0-5 years	49.0 (IQR 46.0; 61.0)	55.0 (IQR 53.0; 58.0)	48.0 (IQR 45.0; 53.0)	0.131
6-11 years	**46.5 (IQR 40.0; 52.25)**	**54.0 (IQR 45.0; 56.0)**	**47.0 (IQR 44.0; 55.75)**	**0.035**
12-18 years	**43.0 (IQR 38.25; 44.0)**	**45.0 (IQR 41.0; 46.75)**	**43.5(IQR 40.25; 46.75)**	**0.007**

Of note, the CSHQ-DE subscale score "daytime sleepiness" significantly increased from pre to post-COVID-19 (13±3.0 vs. 14±3.2; p=<0.001) and significantly decreased again at follow-up (13±3.2; p=0.029) (Figure 2). All other subscale scores of CSHQ-DE did not display a change from pre- to post-COVID-19 (Table 4).

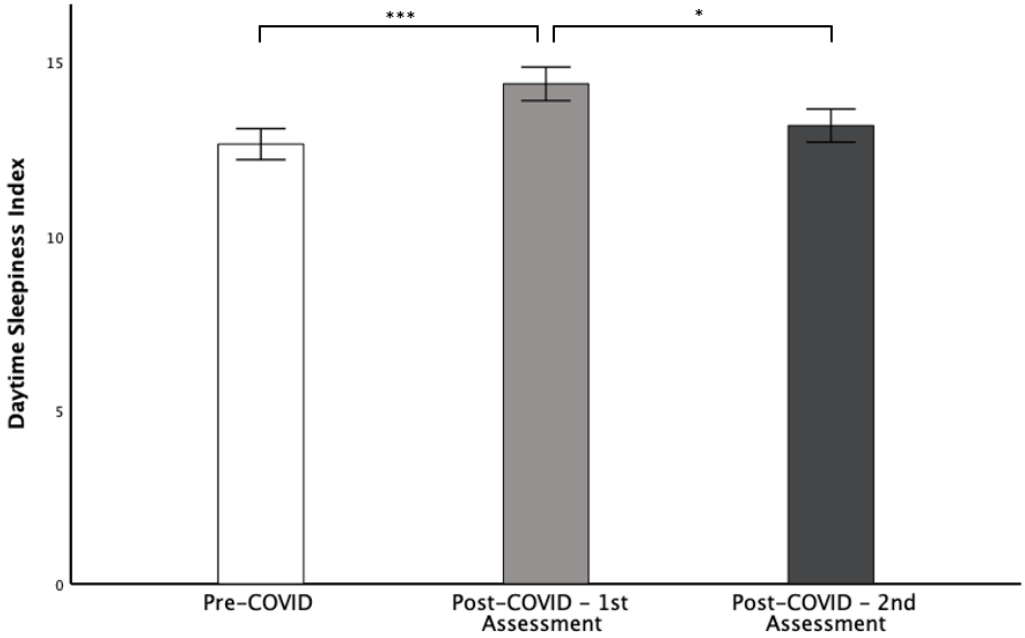

Figure 2. Subscale score "Daytime Sleepiness" pre-COVID-19 vs. post-COVID-19 initial and re-presentation: Significant increase from pre to post-COVID-19 (13±3.0 vs. 14±3.2) and significant decrease at re-presentation (13±3.2). Univariate ANOVA with multiple measurements, post-hoc Bonferroni (*** p=<0.001; *p=0.029).

Table 4. CSHQ-DE Subscales, Mean (SD), ANOVA with multiple measurements, post-hoc Bonferroni.

CSHQ-DE Subscales	Pre-COVID-19	Post-COVID-19 Initial presentation	Post-COVID-19 Re-presentation	p-value
Bedtime resistance	8.2 (±2.7)	8.4 (±2.4)	8.0 (±2.7)	0.495
Sleep Onset Delay	1.8 (±0.9)	2.0 (±0.8)	2.0 (±0.9)	0.239
Sleep Duration	4.1 (±1.3)	4.6 (±1.4)	4.5 (±1.6)	0.150
Sleep Anxiety	5.4 (±2.1)	5.5 (±1.9)	5.3 (±2.2)	0.665
Night Waking	4.0 (±1.6)	4.5 (±1.6)	4.2 (±1.5)	0.130
Parasomnia	9.0 (±2.6)	9.3 (±2.4)	9.1 (±2.4)	0.645
Sleep Disordered Breathing	3.5 (±1.1)	3.5 (±1.0)	3.6 (±1.3)	0.543
Daytime Sleepiness	**12.6 (±3.0)**	**14.4 (±3.2)**	**13.2 (±3.2)**	**<0.001**

Multivariate regression analysis showed no significant effect of the occurrence of fatigue/stress intolerance, neurological, cardiac or pulmonary long COVID symptoms on either the CSHQ-DE score or daytime sleepiness. The presence of a pre-existing medical condition did not affect the risk of developing a sleep disorder after SARS-CoV-2 infection, compared to previously healthy individuals. (Data not shown). Individual comorbidities could not be meaningfully statistically analyzed due to small sample size.

4. Discussion

The presented data shows that sleep disturbances, most notably an increase in daytime sleepiness, occur in children and adolescents with long COVID. As has already been described in adults [17], sleep dysfunction is independent of disease severity. The distribution of symptoms is consistent with other studies of long COVID in children and adolescents, including a female preponderance [3,10,18,19]. The patients underwent a thorough history and diagnostics with the aim of identifying alternative diagnoses which may be responsible for the presenting symptoms. As such, we are confident that the children and adolescents included in this study had long COVID. The study patients has no diagnoses of obstructive sleep apnea, narcolepsy or hypertension (aside from a patient with

previously diagnosed metabolic syndrome). Two patients were taking medication during the study period, which theoretically had an influence on sleep behavior. One patient was on regular gabapentin due to epilepsy, for which the dose remained unchanged from prior to infection and throughout both assessments. In our opinion the gabapentin had no influence on her sleep behavior. The second patient, who had liver disease, commenced prednisolone between initial presentation and re-presentation. Her sleep behavior was markedly improved at re-presentation, however an effect secondary to prednisolone cannot be excluded. For all other patients there were no medications considered causative for sleep disorders. Our results showed a correlation between long COVID and changes in sleep behavior and we assume the disease to be causal. Our study does not provide a pathophysiological explanation for this relationship.

Various pathophysiological causes of sleep disturbances secondary to SARS-CoV-2 infection are discussed in the literature [20,21]. Mechanisms include long-term tissue damage, viral persistence, and chronic inflammation. The production of pro-inflammatory cytokines in the central nervous system, in particular the brainstem, can cause post-viral symptoms [22]. Some cytokines and viral envelope proteins are hypnogenic and have specific effects on both NREM and REM sleep. Certain phases of the infection and the strength of the immune response, may be arousal-inducing and cause sleep disruption [23,24]. A long-term consequence is disturbed sleep-wake cycles [25]. Moreover, it appears that the systemic inflammation triggered by the virus and consecutive activation of inflammatory mediators such as interferons and interleukin-6 can impair neuronal function and cause CNS symptoms [26]. Inflammatory mediators may in turn contribute to the manifestation of autoimmune processes [27]. There is evidence for an underlying autoimmune mechanism as shown by persistently elevated antinuclear antibody (ANA) [28] and G-protein coupled receptor antibody titres [29] in long COVID patients. In this regard, the typically high female proportion in long COVID cohorts after mild disease is consistent with the known female predominance in autoimmunity [30].

Differentiating sleep disturbances, especially daytime sleepiness, from fatigue is difficult. The pathogenesis of fatigue after COVID-19 remains unclear and is currently under investigation. COVID-19 related organ damage as well as psychological disturbances can be related to the development of fatigue [31]. Persisting inflammation or an autoimmune response due to antigen mimicry may also play a role [32]. In addition, nonrestorative sleep is associated with daytime sleepiness, which can contribute to fatigue and cognitive dysfunction. Therefore, sleep disturbance in long COVID overlaps with, and is difficult of differentiate from, fatigue and cognitive dysfunction. This highlights the importance of a differentiated assessment of sleep disturbances versus fatigue, with the aim to guide treatment [33].

Furthermore, it remains difficult to separate infectious sequelae of SARS-CoV-2 from factors relating to the broader pandemic (e.g., lockdowns and school closures). There is a paucity of data relating to lockdown´s and school closure´s effect on screen time, social interaction and exercise, which are known risk factors for poor sleep quality. The effect of the broader pandemic, coupled with changes in electronic device and social media behavior, can induce stress, anxiety and weight gain, which in turn exacerbates sleep dysfunction [34].

Two thirds of our patients already had an abnormal CSHQ-DE score Pre-COVID-19 infection. In adult patients, there is evidence that poor sleep is associated with higher susceptibility to SARS-CoV-2 infection as well as worse clinical outcomes [35,36,37]. It is possible that poor sleep results in delayed resolution of symptoms, however evidence for this in children is lacking

The impact of chronically disturbed sleep on the development of long COVID remains unknown. Sleep deficiency can contribute to cell stress and consecutive neuronal damage [38]. In addition, sleep disorders can induce mild inflammation, causing blood-brain barrier dysfunction, allowing antigens and inflammatory mediators passage into the CNS. In this respect, preexisting sleep disturbances in the context of long COVID could adversely influence the long-term course of COVID-19 disease [33].

Each patient underwent a thorough assessment of their past medical history with 15/45 (33%) found to have a current or resolved medical condition. Once patients with resolved/ clinically non-significant diseases are excluded (marked with * in Table 1), 12/45 (26.7%) patients had an ongoing medical issue. This value is slightly higher than KIGGS data which displayed that the prevalence of chronic disease in 0 to 17 year olds in Germany is 16.2% [65]. Our findings are consistent with recently published data from the USA [66] which shows that children with pre-existing medical conditions have a higher risk of developing long COVID. Our cohort was, however, too small to reliably assess the effects.

As discussed above, it remains difficult to differentiate sleep disorders from daytime fatigue. Regardless of the aetiology, our study shows that this is a relevant problem for children and adolescents following SARS- CoV-2 infection. Only 42% of patients reported sleep difficulties in the medical history at initial presentation, whilst the CSHQ-DE showed that 89% of patients had sleep dysfunction. Given that there is currently no causal therapy for the treatment of long COVID, symptomatic treatment options must be exhausted in all sufferers.

4.1. Treatment Recommendations

Our approach to the treatment of sleep disorders was analogous to the recommended treatment of non-organic sleep disorders by the German guideline [41]. The most important intervention was detailed advice on sleep hygiene (Table 5). A sleep diary should be kept with every attempt at sleep modification in order to monitor the effectiveness of the intervention.

Table 5. Treatment Recommendations for Non-organic Sleep Disorders.

• Regular bedtime as part of a regular daily routine, including weekends (or put to bed only when the child is tired) • Regular daytime sleep at the same time (particularly important in smaller children)
• In the evening avoid bright light, especially in the blue-wave range (LCD screens, mobile phones, tablets, TV, etc.) • Avoidance of media consumption in the evening, especially in the hour before go ing to bed
• Sufficient physical activity during the day
• No exciting or strenuous activities before falling asleep
• Quiet, dark, warm sleeping environment • Sleep environment not associated with other activities (gaming, cell phone, television, homework, punishment, etc.)
• Bedtime rituals depending on age (between 15 and 30 min)
• Eating/drinking: o Introduction of a behavioral pattern in early childhood: being fed during the day and sleeping at night o Avoid excessive amounts of stimulating drinks during the day o Avoid stimulating drinks and sweets a few hours before bedtime o Not responding to child´s intake wishes which only serve to delay sleep o At bedtime avoid hunger and thirst, as well as large meals and significant liquid intake
• Not responding to wishes/demands of the child that only serve to delay sleep
• For older children and adolescents: restrict naps to 20mins and not after 3pm

In cases of severe sleep disorders, pharmacotherapy should be considered. The choice of medication depends on the type of sleep disorder and underlying disease (e.g., depression or panic disorders) [41]. The dose varies greatly between patients and should therefore be implemented carefully. Most of the medications available are prescribed off-label in Germany and can therefore only be used as part of an individual treatment regime.

Throughout our study we initiated pharmacotherapy in only four patients. Melatonin was used in increasing doses in three adolescents over a maximum period of six weeks. A 15-year-old boy and 13-year-old girl with issues relating to sleep initiation, sleep maintenance and daytime tiredness experienced significant improvement after four and six weeks respectively. This improvement persisted even after discontinuation. Additionally a 17-year-old girl with severe sleep initiation issues was treated with melatonin resulting in nil improvement. The fourth child (9-year-old girl) had only mild problems with sleep initiation was treated with Dimentinden (Fenistil) primarily due to recurrent urticaria. Both symptoms improved with the medication.

Our first choice for the treatment of moderate and severe sleep disorders secondary to long COVID is melatonin. Taken regularly for a few weeks, melatonin restores the regular circadian rhythm [42]. It has antioxidant, anti-inflammatory and immunomodulatory properties [43,44] and thus could potentially have a positive effect on the previously discussed mechanisms of long COVID [6,8,45]. Melatonin accumulates in the mitochondria of endothelial cells resulting in beneficial effects on sepsis-induced mitochondrial dysfunction, oxidative stress, and cytokine response [41].

Endothelial dysfunction occurs in acute COVID-19 infection [46,47,4,8,49,50,51,52]. Endothelial dysfunction caused by persistent endotheliitis could explain many of the symptoms of long COVID [53,54,55,56]. Melatonin activates Nuclear factor erythroid-derived 2-like 2 (NRF2) [37]. NRF2 is the primary regulator of the inducible antioxidant response, which attenuates cellular injury in oxidative stress [53]. Melatonin has been explored as a treatment for other viral infections which produce an excessive inflammatory response [54,55,56]. Its use in COVID-19 has also been proposed [57] and is part of several international trials [58].

We were restrictive in the treatment of sleep disorders with medications. Given the potential of melatonin to have a positive effect on many aspects of the discussed pathogenesis of long COVID, coupled with minimal side effects, we are currently considering earlier use. Future studies should focus on melatonin´s effect on clusters of long COVID symptoms and its use independently of sleep disorders.

5. Strengths and Limitations

A strength of our study is the detailed assessment of symptoms which were obtained via a physician led interview and questionnaires. The temporal relationship between SARS-CoV-2 infection and symptoms were assessed in detail. Extensive diagnostics assisted in excluding alternative diagnoses as the cause of the symptoms. Therefore the diagnosis of long COVID was made as accurately as possible according to the currently available criteria.

One limitation of this study was the absence of a control group. Further studies on this topic would benefit from a control to correct for confounders of the broader pandemic and non SARS-CoV-2 viral illnesses. It has been demonstrated in adults that sleep disorders were more prevalent among patients who had recovered from COVID-19 than the non-infected control group [39]. A systematic review from 2022 of the effects of coronavirus disease on sleep in children aged 12 years and younger revealed an increase in sleep duration, sleep latency and daytime sleepiness. Reliable data regarding long-term effects on children's sleep and daytime function is lacking [40]. Another limitation is that the Pre-COVID sleep assessment was conducted retrospectively, which may have resulted in recall bias. Due to the nature of the study, a concurrent assessment was not possible.

Our results were limited by the fact that a large proportion of patients who presented to our long COVID outpatients clinic were not included in the study. The study only included patients whom fulfilled the diagnostic criteria for long COVID, which is highly subjective and lacking in objective measurements, such as biomarkers. We used the same diagnostic criteria which was later published in "Recommendation for standardized medical care for children and adolescents with long COVID" of the German Society for Pediatrics (DGKJ) [11]. Of the 102 who presented to the clinic, only 45 families completed the questionnaire in full at all three time points. The two primary reasons for non-completion were omission of answers to individual questions or, above all, the symptoms has resolved and the parents therefore considered the completion of the questionnaire to be unnecessary. We think the inclusion of the missing questionnaires would have further highlighted the group differences.

Whilst patients were questioned regarding pre-existing medical conditions, they were not routinely screened for all possible organic causes of a sleep disorder. Polysomnography was only performed when the history suggested a central or obstructive respiratory disorder. This was not the case for any of the patients included in this study.

6. Conclusions

Our results suggest that sleep disturbances are common in children with long COVID. Eighty-nine percent of children and adolescents in our study showed abnormalities in sleep behavior when using an objective questionnaire. The increase in the CSHQ-DE score from 45,8 to 49,4 due to the infection was significant. Therefore monitoring of sleep behavior should occur in all patients with long COVID. If sleep disturbance does not improve with counselling, medication should be used. In our opinion, melatonin is the first line medication due to improvements in sleep, good side-effect profile and potential beneficial effects on underlying long COVID pathophysiology.

Author Contributions: Sarah Werner: writing—original draft preparation, investigation, formal analysis, data curation; **Claus Doerfel**: Conceptualization; **Michael Lorenz:** investigation, project administration; **Hans Proquitté**: writing—review and editing, supervision, resources; **Richard Biedermann:** writing—review and editing, formal analysis; **Marius Rasche:** investigation, data curation; **Lars Newman:** writing—review and editing; **Daniel Vilser**: Conceptualization, investigation, writing—review and editing, funding acquisition, project administration.

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Institutional Review Board Statement: The study protocol was conducted in accordance with the Declaration of Helsinki, and retrospectively approved for studies involving humans by Ethics Committee of University Hospital Jena.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: IPD sharing plan: Study protocol and individual participant data underlying the results reported in the article, after deidentification. Documents will be available 3 months after publication for 3 years for investigators submitting a structured application, after approval by a committee. Data will be made available for all types of analyses that produce results in the approved application. Requests should be sent informally to daniel.vilser@med.uni-jena.de. A data agreement must be signed for access to the data.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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