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Investigation of the relationship between sleep disorders, infection-related gastrointestinal diseases and organ dysfunction

Observational Study

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Abstract

The recommendation of the Robert Koch Institute in 2004 to conduct studies on the pathogenetic significance of intestinal Candida colonisation for sleep disorders has remained widely unheeded in medical research. The present study therefore follows the recommended approach and investigates the possible role of infections (especially Candida spec.) and mixed infections (especially Candida spec. and Helicobacter pylori) as well as organ dysfunctions possibly caused by them in connection with sleep disorders.

166 patients with chronic sleep disorders were examined on the basis of a comprehensive medical history and combined diagnostics (serology, microbiology, ECG, ultrasound of the kidneys, spleen, liver, gall bladder, pancreas, gastrointestinal, thyroid, vessels, prostate, Douglas space, ovaries, uterus, lymph nodes). Digestive disorders were found in 92 percent of the patients and organ dysfunctions in 70 percent (kidneys, spleen, liver, gall bladder and heart were observed in particular), infections and mixed infections in 79 percent.

The results show that sleep disorders often occur with infections and organ dysfunctions. Thus, if the treatment of infections leads to an improvement in sleep, antimicrobial therapy of neglected or unrecognised infections and the potential organ dysfunctions associated with them may be an alternative to often unsustainable treatments.

Keywords: Sleep disorders, infections, organ dysfunction

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1 Introduction

The role of infections (especially Candida spec.) and mixed infections (especially Candida spec. and Helicobacter pylori) as well as organ dysfunctions caused by them in the aetiology of sleep disorders has been little studied so far. As a rule, neither the diagnosis nor the therapy of infections in connection with sleep disorders are taken into account (1).

This is also shown by the S3 guideline "Non-restorative sleep/sleep disorders" of the German Society for Sleep Research and Sleep Medicine (DGSM) (2). There, infections as a cause or contributory cause of sleep disorders are only mentioned in general terms, namely in connection with fatigue and states of exhaustion (2: 11), with viral infections of the CNS in lethal familial insomnia (2: 25), in hypersomnia (2: 38), especially in recurrent hypersomnia in Kleine-Levin syndrome (2: 92), in sleep apnoea in infancy as possible triggering factors (2: 136).

No special attention is paid to the possible connection between infections with pathogenic yeasts and sleep disorders in the S3 guideline ("Sleep/Sleep disorders"). This suggests that in investigations of the possible connection between sleep and immunity to infections with pathogenic yeasts, this is not taken into account due to a lack of studies and only viruses, bacteria and parasites are given focus. (3) Similar to infections, the S3 guideline ("Sleep/Sleep disorders") does not systematically consider organ dysfunctions and their role in causing sleep disorders. Although organ dysfunctions are discussed in the context of differential diagnostic delimitations (for example, in the case of enuresis nocturna (4)), an interaction with infections and disorders is not considered, and a connection with disorders of the immune system is only hinted at (4: 38). Only in the context of Kleine-Levin syndrome is an autoimmune basis suspected (4: 92).

Even a recommendation by the Robert Koch Institute in 2004 on the pathogenetic significance of intestinal Candida colonisation (5) has hardly initiated any studies since then that could help to remedy this loophole. However, a study desideratum is explicitly formulated in the RKI recommendations: "As always, when the data availability is unsatisfactory, this leaves room for speculation. Such a situation, which is unsatisfactory for patients as well as for the treating physicians, can only be defused by careful studies and the associated growth in knowledge." (5: 596) This reference has so far remained unconsidered with regard to the correlation of sleep disorders and infections and organ dysfunctions.

The task of the present study was, in order to motivate both further studies and the consideration of infections in the therapy of subacute and chronic sleep disorders (insomnia) (6), to carefully document the infections in the affected persons by means of laboratory diagnostics and, as far as possible, to record their organ dysfunctions by means of laboratory analysis, sonography and ECG. The methods used for laboratory analysis close the existing gap in general medicine of highly precise material collection and evaluation according to evaluated criteria.

In the present study, organ dysfunctions are physical processes and organ changes that prevent organs from performing their function without restriction. These restrictions and changes (e.g. in the case of renal insufficiency) become visible through laboratory parameters and sonographic examination, but can also be determined in complementary medicine through tongue or pulse diagnostics (7).

For the distinction between acute, subacute and chronic sleep disorders, please see the discussion of the results of the procedure and the present study in section 5.

2 Effects of infections on sleep

The restorative and regulating properties of sleep are a body of empirical knowledge that is now also scientifically recognised. (8, 9) The influence of sleep on the immune system has been investigated more intensively in recent years. Several studies have shown, for example, that complete sleep deprivation and REM (rapid eye movement) sleep deprivation can influence components of the immune system, such as the proportion of cell subpopulations (e.g. CD4+, CD8+ and NK) and cytokine levels (e.g. IFN-g, TNF-α and IL-1) (10, 11, 12). Conversely, sleep patterns are also altered during the immune response, suggesting that sleep and immune response are linked by bidirectional communication (3). Sleep is not only a physiological state in which activity and alertness decrease, but a vital process that regulates various physiological functions (13, 14).

Interactions between brain activity and the immune system thus also affect sleep. There is now evidence that the expression of molecules such as neurotransmitters, hormones and cytokines is modulated during sleep. Human studies have described changes in serum levels of some of these components during sleep. More specifically, the secretion of IL-1β, IL-10, IL-12 and TNF-α by monocytes and dendritic cells reaches peak levels during sleep, independent of circadian rhythms. This behaviour seems to be directly related to sleep, because when the rhythmicity of these cytokines is disturbed, the changes in expression drop (15, 16). Blood levels of monocytes, T cells and NK cells follow a clear circadian rhythm in relation to the sleep-wake rhythm (10). Neuroendocrine mediators such as prolactin, cortisol and norepinephrine also exhibit circadian rhythms, but their secretion pattern is more closely tied to the sleep-wake cycle, and all of these substances modulate the immune response (17).

Conversely, certain cytokines influence sleep, such as IL1β, which prolongs the duration of non-REM sleep. This effect is reversed when IL-1β antagonists are administered (18, 19, 20). Administration of the cytokines TNF-α and IFN-α has the same effect as IL-1β (21, 22, 23). The hypothalamus, hippocampus and brainstem harbour immunoreactive neurons for IL-1β and TNF-α and their receptors. These neurons are differentially distributed in different brain regions such as the choroid plexus, the hippocampus, the hypothalamus and the cortex. These regions may be involved in the regulation of sleep. In addition, IL-1β has effects on the serotonergic system and controls sleep at different levels (24, 25, 26).

Due to such interaction between components of the immune system and the mechanisms that control sleep, it is also possible to characterise changes that occur during sleep when an immune response to a pathogen is initiated. Several infectious diseases are associated with sleep disorders. Pathogens such as Candida albicans and Helicobacter pylori cause sleep disorders when they affect the respiratory (27) and endocrine (28, 29) systems and the digestive system (30, 31) (Note 1).

Therefore, the question of what role pathogenic yeasts and bacteria play in the correlation of sleep disorders and inflammatory events through effect-enhancing interaction is of particular interest. The correlation of obstructive sleep apnoea and periodontitis exemplifies how infections with Candida albicans and Prevotella melaninogenica amplify effects (33).

An in vitro study also demonstrated that the InlJ protein of Porphyromona gingivalis and the hyphal protein Als3 of Candida albicans facilitate adhesion between the two microorganisms and cause significant changes in gene expression of P. gingivalis that increase the pathogenic potential of these bacteria (34). Another study showed the promotion of the growth of anaerobic bacteria by C. albicans biofilms, which deprive oxygen and create a hypoxic microenvironment (35).

It is certainly worthwhile to carry out further studies in this regard. In the present observational study, the association between infections with pathogenic yeasts and bacteria, digestive and sleep disorders, which has not been paid attention to in the field of human medicine, was observed specifically; such associations could be demonstrated in animals (36, 37).

The present observational study is related to an investigation of the development of chronic sleep disorders as a result of cumulative and combined organ dysfunction arising from infection-related overload of the spleen and, subsequently, the kidneys (Note 2). However, it is the task of a meta-analysis to determine such interactions (38), causal chains and causal cycles (39: Fig. 1) by comparing and evaluating studies of traditional Chinese medicine and western modern medicine (Note 3).

3 Material and methods

3.1 Patients

From August 2018 to April 2022, 166 patients from the patient collective of the MVZ Ärztehaus Mitte were included in the studies.
The duration of the sleep disorders of the patients at the start of the study was in part quite remarkable. It was between 1 and 5 years in 73 patients, between 6 and 10 years in 50 patients and 43 patients reported having suffered from sleep disorders for more than 10 years.

3.2 Diagnostics

The observation of the patients was done by evaluating serological and microbiological laboratory analytics, ultrasound examinations and ECG recording. Serology, ultrasound and ECG were conducted using standard technical equipment. The microbiological material collection and the evaluation of the material were carried out with special care. Sleep disorders of the patients were reported in the course of complaint treatment of the patients in the ongoing medical practice. A detailed medical history was taken to record the sleep disorders (Note 4).

The material for microbiological diagnostics was obtained by carefully taking mouth swabs and stool samples according to Normamed standards. The examination for yeast fungi was carried out in three stool samples collected on different days. First, stool samples were placed on Sabouraud-2 % glucose agar spiked with chloramphenicol and gentamycin (SABGC agar) and incubated at 30 °C for up to seven days. As soon as growth of yeast-like fungi was visible, the differential diagnosis was carried out. This was based on comparison of the same isolate on SABGC-(24 - 48 h at 30 °C) rice-(24 - 48 h at room temperature) and Brilliance™Candida agar (24 - 48 h at 30 °C). The yeast was identified on the one hand by the RapID™ Yeast Plus System (Remel Inc., San Diego, CA, USA), the Analytical Profile Index API® 20 C Aux (bioMérieux, Marcy l'Etoile, France) or the ID 32 C (bioMérieux, Marcy l'Etoile, France) from the incubated SABGC-plate. Secondly, the colour change on the Brilliance™Candida agar and the micromorphology on the rice agar" were assessed.

Furthermore, stool sample was plated on blood-free Karmali, S.S. and Yersinia selective culture media and enriched in selenite-lactose broth for XLD agar to test for the following diarrhoeal pathogens: Campylobacter, Shigella, Yersinia and Salmonella. Incubation and further procedures were implemented according to the guidelines of the German Society for Hygiene and Microbiology (40). If a pathogen was suspected, differential diagnosis and determination of resistance was carried out using API® Campy (bioMérieux, Marcy l'Etoile, France), API® 20 E (bioMérieux, Marcy l'Etoile, France) and the MicroScan identification system (Beckman Coulter, Brea, CA, USA).

All full and selective culture media listed here were purchased from Thermo Fisher Scientific Oxoid Deutschland GmbH (Wesel, Germany).
Testing for worm eggs was performed using the sedimentation method of ParasiTrap® Fix Separ® ECO (Biosepar GmbH, Simbach am Inn, Germany).
RIDASCREEN® Entamoeba, Cryptosporidium, Giardia (R-Biopharm AG, Darmstadt, Germany) was used for the diagnosis of protozoa in stool. Enzyme-linked immunosorbent assays were performed according to the manufacturer's instructions. Microplates were evaluated using the Sunrise™ Absorbance Microplate Reader and the corresponding software (Tecan Group Ltd., Männedorf, Switzerland).

Fecal occult blood was tested for using the iFOB Collector Kit, the Test Kit, the associated Control Kit (Eurolyser Diagnostica GmbH, Salzburg, Austria). The quantitative immunoturbidimetric determination was then performed with the CUBE-S system (Eurolyser Diagnostica GmbH, Salzburg, Austria).

4 Results

Digestive symptoms were present in 92 percent of the 166 patients with sleep disorders, infections in 79 percent and organ dysfunction in 70 percent (see Fig. 1). In 77 percent of the patients with sleep disorders, the pattern of digestive symptoms was striking to severe (Note 5).

Infections with pathogenic yeasts were found in 70 percent of the patients in the study, infections with H. pylori in 24 percent, and mixed infections in 17 percent (see Fig. 2).

The observations of only the sonographic examinations in correlation with sleep disorders already showed that 45 patients (27 percent) had obvious liver dysfunctions and 33 (20 percent) kidney dysfunctions.

The observations made in these examinations in combination with TCM examinations (cf. figs. 3 and 4) (38) revealed even higher proportions of organ dysfunctions in correlation with sleep disorders (cf. fig. 3), especially in the kidneys, liver and spleen) (Note 6).

Many of the patients exhibited multiple organ dysfunctions that occurred in combination (cf. Fig. 4) (38).

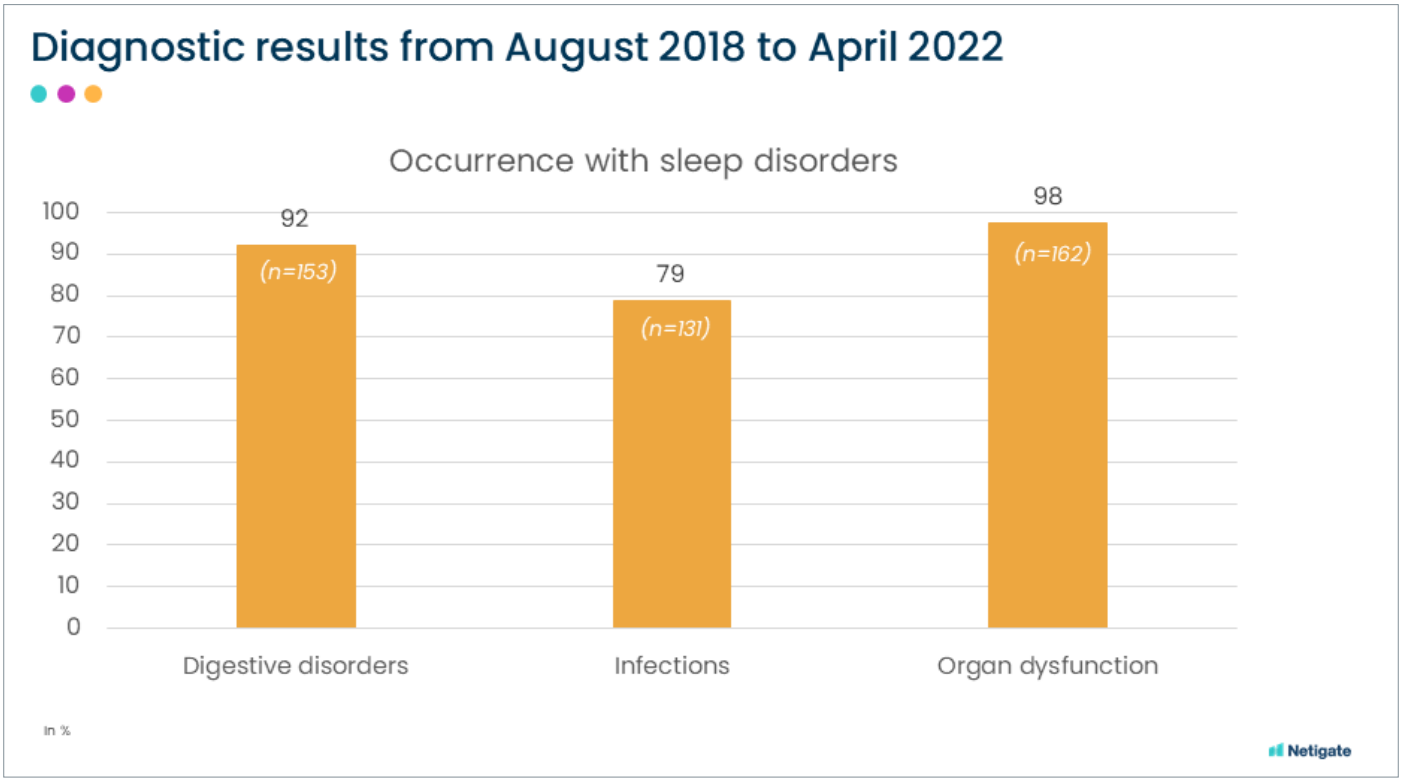

Fig. 1 Occurrence of digestive disorders, infections and organ dysfunction in sleep disorders

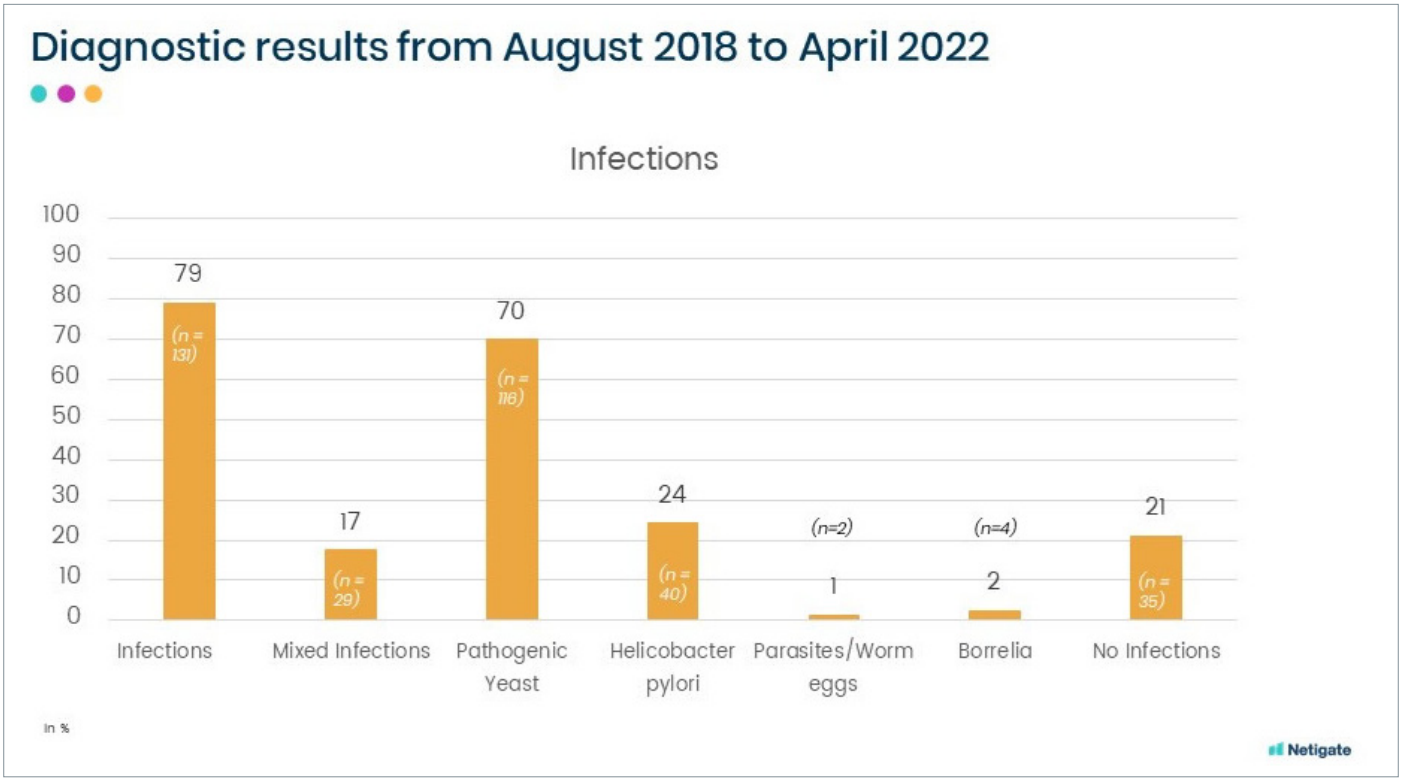

Fig. 2 Type of infections

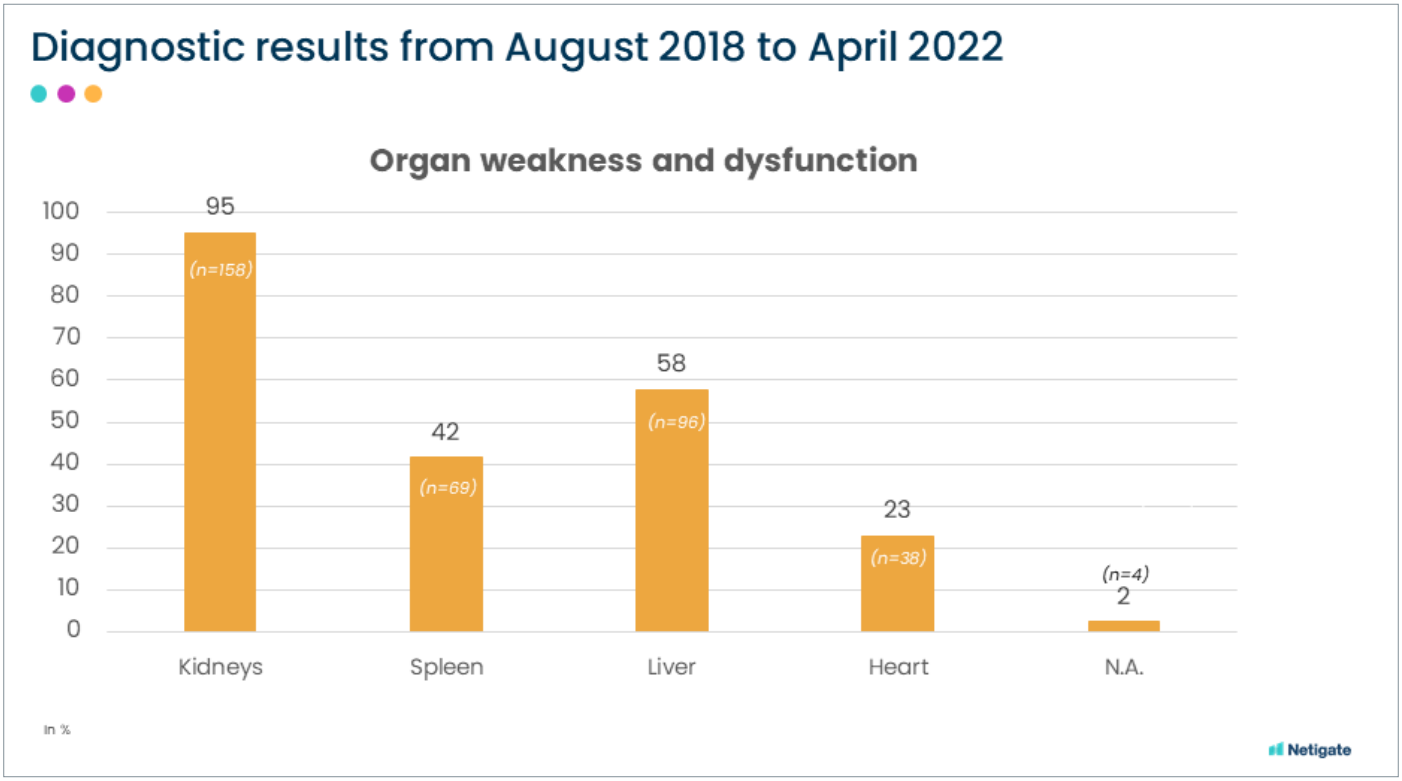

Fig. 3 Frequency of organ dysfunction found in the observed patients of the study by sonographic, laboratory, and TCM examinations (graphic with permission from Bei Wang).

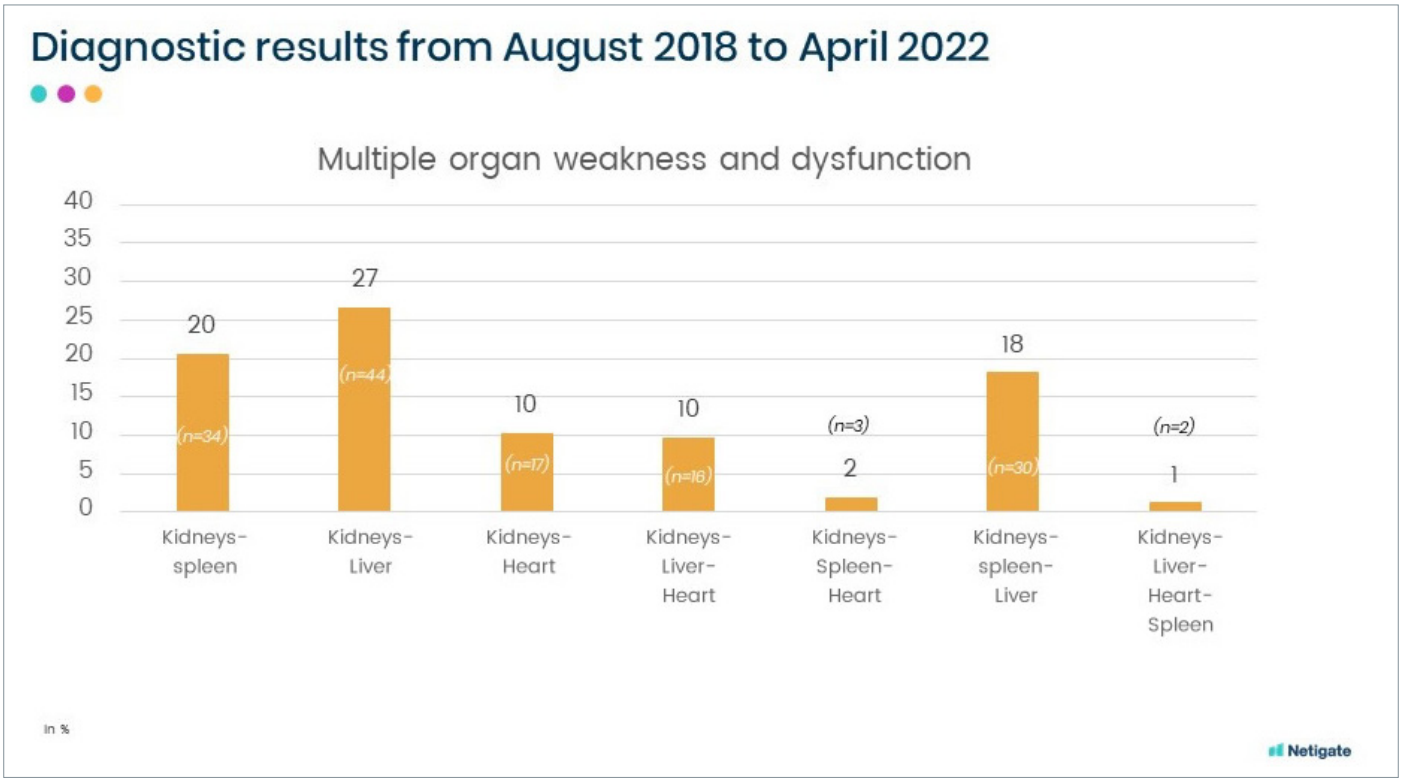

Fig. 4 Frequency of multiple organ dysfunction found in the observed patients of the study by TCM examinations (graphic with permission from Bei Wang)

5 Discussion

In medical practice, sleep disorders are widely isolated and diagnosed and treated in the context of psychological or social conditions. Therapy is often limited to prescribing sleeping pills, determining sleep behaviour in sleep labs and recommending mechanical sleep aids, recommending relaxation exercises such as meditation, behavioural changes against obesity and lack of exercise, reducing psychological stress, and even psychotherapy. All these measures can be supportive, perhaps at least temporarily - or even in the longer term if the cause is well established.

However, if one observes patient histories with long to very long chronic sleep disorders (all patients observed in the study had already suffered from sleep disorders for more than a year and up to more than ten years), then one finds physical causes that are not taken into account and unfortunately do not receive any attention in the medical discourses. After all, the above-mentioned recommended measures were often indicated without bringing about a lasting improvement. In many cases, side effects and problematic addictive behaviour occur with long-term use of the medication. In this respect, it seems worthwhile to consider possible chains of causation, which have so far been given little or no consideration in medical practice.

There are no uniform definitions of what is considered a “chronic” sleep disorder in the medical discourses. Quantifying attempts range from statements such as three times a week for one month or refer to disorders of more than six months. There is a broad consensus that quantifying determinations are ultimately not helpful, but that the subjective sleep experience and perception of the patient should be the yardstick for sleep disorders: Most people know from their own experience the amount of sleep they need to be refreshed and well-rested (41).

As a rule, however, a sleep disorder (insomnia) is considered “chronic” if people do not find sleep recovery over a longer period of time (more than six months, even despite attempts at therapy) and feel that their quality of life and performance is permanently impaired as a result. This cannot be objectified, but it shows the perception of an objective event underlying the disorders. Sleep disorders are considered “acute” if they occur for a short period of time (up to about four weeks) due to causal factors that can often be identified, such as disturbances caused by noise, an injury, a family conflict, etc. (42). Sleep disorders that develop insidiously and over a period of six months are considered “subacute”.

An interdisciplinary and cross-medical view of sleep disorders in the general medical and specialist medical, laboratory medical, microbiological and complementary medical synopsis shows in the present observational study that sleep disorders are very often connected with hidden infections, the organ dysfunctions possibly caused by them, as well as disorders of the immune system. The cause research is complex here, since it can be assumed that interaction Thus, the thesis can be derived from the observations carried out here that (mixed) infections (especially with pathogenic yeasts of the species Candida) and bacteria (especially Helicobacter pylori) and parasites are often correlated with sleep disorders. The present observational study takes a first step by observing the correlation. Monitoring the treatment success of infections and organ dysfunctions can further clarify the causation hypothesis in a next step.

The results of the present study show that sleep disorders do often occur with infections and organ dysfunctions. Therefore, if their treatment leads to a significant improvement in sleep, the therapy of infections and the organ dysfunctions that may be caused by them, which have not been taken into account so far, can be an alternative to treatments that do not have a lasting effect.

The aim of the present study is to motivate both further studies and the consideration of infections in the therapy of chronic sleep disorders (insomnia) in those affected by documenting the infections via laboratory diagnostics and the organ dysfunctions recorded by laboratory analysis, sonography and ECG. The demonstration of the diagnostic results of TCM observed in a parallel study is intended to promote the interdisciplinary exchange between specialist and complementary medicine for the diagnosis and treatment of sleep disorders and organ dysfunctions. Current studies show how, despite the differences in the recording systems, mutual complementation of the procedures is both possible and scientifically justified. One example among many is a study on chronic kidney disease published in 2022, especially because of the importance of renal dysfunction in connection with sleep disorders (7).

6 Summary

The present study investigated the role of infections (especially Candida spec.) and mixed infections (especially Candida spec. and Helicobacter pylori) as well as the organ dysfunctions (especially kidney, liver, gall bladder and spleen dysfunctions) possibly caused by these in connection with sleep disorders. 166 patients were examined on the basis of a comprehensive medical history and combined diagnostics (serology, microbiology, ECG, ultrasound). Digestive disorders were found in 92 percent of the patients, infections and mixed infections in 79 percent. The results show that sleep disorders can be associated with infections and organ dysfunctions rather frequently. The question of whether infections and associated digestive and organ dysfunctions interact to cause sleep disorders can only be determined by monitoring treatment outcomes and further studies.

With regard to therapy, the patients observed in this diagnostic study were examined in parallel with complementary medicine. Pulse and tongue diagnostics of TCM were perceived by the patients as complementary to general and specialist medical and laboratory diagnostic methods. These and the subsequent conventional and complementary medical treatment of the patients were not the subject of the present study. The evaluation of the results of the monitoring of treatment successes (43) in the context of the diagnostic studies must therefore be left to meta-analytical assessments.

Notes

Note 1 Some pathogens infect the CNS and cause sleep disorders due to systemic diseases and due to the immune response triggered against the infection or due to direct effects of the pathogen (32). Such systemic diseases were not the subject of the present observational study.

Note 2 In the lingo of Traditional Chinese Medicine: The cause of the sleep disorders would then often be a spleen-kidney-yin weakness, which then also leads to liver and heart weaknesses in the form of a causal chain, at the end of which there are chronic sleep disorders (38).

Note 3 cf. (39: Fig. 1). on the spectrum of clinical manifestations in APECED patients, features organ-specific autoimmune manifestations observed with varying frequency in patients with APECED. Although this study focuses especially on the effects of loss-of-function mutations in the autoimmune regulatory gene (AIRE), the systemic extent of the correlation with Candida infections is evident. If it could now be shown in a treatment monitoring that the eradications of pathogenic yeasts and the treatment of organ functions cause an improvement in sleep, then meta-analyses and further studies are a desideratum that discuss and investigate bi- or multi-directional causalities in sleep disorders.

Note 4 A standard questionnaire was filled out by the respondents via the Netigate survey programme and was also used outside the study to monitor the success of the treatment.

Note 5 In standardised case histories, the patients were also asked about their assessments of subjectively perceived severity of symptoms using ten-point scales.

Note 6 Western medicine lacks a refined diagnostic technique for the precise determination of organ dysfunctions that may be relevant for sleep disorders. The use of ultrasound and serological laboratory analysis results in a view of the organ condition and values, which can be supplemented by, for example, the inclusion of pulse diagnostics of traditional Chinese medicine. In this respect, the results collected on organ dysfunctions reveal an evaluation of complex information (cf. 38). On this topic, please refer to the results of a parallel observational study in complementary medicine with the same patient collective that was observed in the present study.

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