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REVIEW ARTICLE

Classification and Treatment of Sleep Disorders by Clinical Syndrome, Anatomic Localization and Pathophysiology

A Robert Spitzer

[1] Mackinac Neurology

* brainee@icloud.com

ABSTRACT

The treatment of sleep disorders is problematic because the diagnoses consist of an array of unrelated terms, there is little knowledge or link to disease processes, and progression from the patient presentation to effective therapy is not systematic. The purpose of this paper is to provide a coherent framework for understanding sleep disorders, based on anatomy and pathophysiology.

A classification of sleep disorders based on classical neurological diagnosis is presented. First, the diagnostic process in classical, clinical neurology is reviewed. In this traditional approach, diagnoses are not inferred directly from symptoms. Rather, symptoms are used to identify putative anatomic localizations, and pathophysiological mechanisms. Diagnoses are inferred as a second step from the localizations and mechanisms of disease. Subsequently, testing may be applied as necessary, using a probabilistic interpretation to guide treatment. Treatment for diseases classified in this manner is more likely to be successful. In addition, be generating alternative hypotheses during this process, if initial treatments are not successful, alternative approaches may be considered.

The anatomy and physiology of sleep disorders is briefly reviewed. The process of diagnosis is then presented, starting with specific symptoms, including insomnia, hypersomnia, limb movement disorders, fatigue and pain syndromes. Groups of symptoms, as syndromes, are considered. By relating the symptoms to the localizations and pathophysiology, a more ordered approach to management is presented. The distinction of etiology from diagnosis is discussed. Etiologies that have resolved are typically not treatable.

Prior research on fibromyalgia is summarized, including possible anatomic and pathophysiological substrates, and underlying sleep disorders. Other forms of fatigue are contrasted, with implications for different treatments.

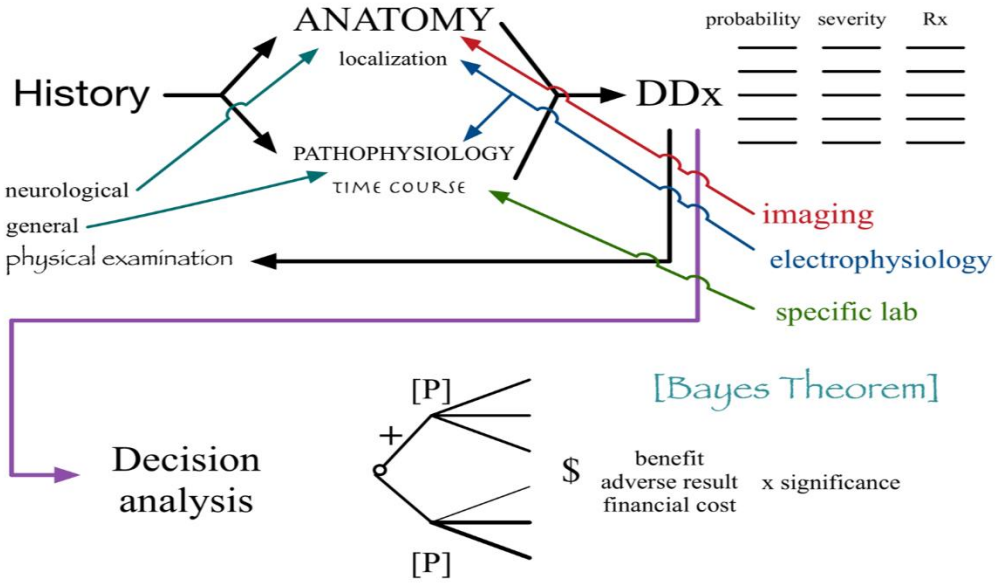
Introduction

The goal of medical care is to provide treatment to patients. Patients are seeking relief of symptoms. In those cases, where relief is not possible, a prognosis and closure regarding treatment is needed. The role of diagnosis (with its many, various definitions) is merely a step in the process of treatment. In sleep disorders, there is extensive literature on neuroanatomy and neurophysiology regarding the underlying mechanisms of sleep. But in the clinical practice of sleep medicine, classification of everything other than sleep apnea is problematic, not directly related to the knowledge of underlying physiology, and often treatment is unsuccessful. In many cases, this leads to an assignment of a psychiatric diagnosis.

This paper addresses the issue by proposing a different organization to diagnosis of sleep disorders, based on a classical neurological approach emphasizing anatomic localization and underling physiology. This paper provides an overview and approach, but does not comprise a detailed review of the subject. References provided illustrate selected concepts.

Background: an overview of classical neurological diagnosis

The diagnostic process involves several steps from patient presentation to the end points of treatment and diagnosis. Patients report symptoms at presentation. Individual symptoms do not directly indicate diagnosis or treatment, but must be interpreted by the clinician. In classical neurological diagnosis, symptoms alone are not directly used to make a diagnosis or guide treatment. Figure 1 shows the steps involved in neurological diagnosis and treatment.



History, anatomy and physiology

In the first step, careful elucidation of symptoms suggests anatomical localization. A symptom of word finding difficulty, or expressive aphasia, by itself simply suggests that the disease process is affecting the left lateral frontal lobe. Parasthesiae in a territory of a single peripheral nerve suggests pathology along the territory of that nerve. Other symptoms, such as gait imbalance, have more than one possible localization. Additional details such as staggering vs. shuffling gait may suggest a more precise localization of the symptom, and allow possible localization to be narrowed down.

An important skill in history taking is interpretation of the reported symptoms. Many patients describe symptoms vaguely. For example, blurred vision on the left could be monocular, or it could imply a hemifield localization. Patients may report not having excessive daytime sleepiness, and then report taking naps for falling asleep while driving. Patients may deny snoring or mood changes, but family members may report those symptoms. Thus, reports from patients and others must have a probability or uncertainty involved. Even facial expressions, educational level and other factors must be considered. Computerized questionnaires are prone to very inaccurate history taking. While taking the history, the clinician is interpreting the reported symptoms in terms of possible anatomic localization.

While considering the history, at the same time the pathophysiological mechanisms that might be responsible are considered. This is usually based on time course. For example, a patient with the abrupt, sudden onset of aphasia might have had a vascular event. The same symptom (and localization) with a slow, gradual onset might represent a tumor, and an even slower onset might represent a neurodegenerative process. Recurrent processes are different than monophasic processes. Recurring visual symptoms lasting 30 minutes might reflect migraine. Recurring altered consciousness might reflect seizures or sleep attacks, or cerebrovascular stenosis.

In assessing the time course, the uncertainty of patient reports must be considered. Some patients will report symptoms as "a long time" and "not very long". Or, in the course of the interview, the patient may report the symptoms variously as a week, months or years, sometimes changing their description within a single visit.

Formulation of individual diagnoses

As a subsequent analysis step (figure 1), individual diagnoses are considered as a juncture of localizations and pathophysiology. Some combinations will result in a short list. As mentioned, some symptoms such as gait abnormality might result in a longer list. In the figure, note the role of the physical (neurological) examination. The examination does not yield single diagnoses. Instead, it tends to support or refute certain localizations, which allows the list to be refined. A patient with foot drop and abnormal corticospinal findings (increased reflexes, positive Babinski reflex) may have a cervical cord or cerebral lesion, whereas a foot drop with decreased tone, loss of reflexes and sensation in the territory of a peripheral nerve suggests a distal localization. Associated findings on exam may alter the localization. For example, the finding of a visual field cut might suggest a central process in a case where originally the consideration was a peripheral process, such as ocular pathology.

Sorting the differential diagnosis

At this point, the list of diagnoses must be sorted. The traditional method is to sort the list by probability. However, the entire list can also be sorted in order of seriousness (danger to the patient), or treatability. A severe headache may be likely to be a migraine, but subarachnoid hemorrhage is more dangerous, even when less likely. A dementia due to Alzheimer's may be more likely, but NPH is more treatable. Each criterion for sorting the list is independent useful.

Clinical decision analysis

At this point, next steps are considered. In certain cases, treatment based on clinical considerations alone is sufficient. For example, a young woman with years of recurrent characteristic headaches with auras, with a family history or migraine, and headaches triggered by menses and alcohol, would often merit initial treatment for migraine on clinical grounds alone without diagnostic testing. However, in some cases, further investigation is warranted.

Diagnostic testing

Testing in neurological cases does not usually establish a single diagnosis (figure 1), though in some cases it can give a very small list of remaining possibilities. Imaging gives us mostly anatomical information, and some suggestion of pathophysiology. Blood and CSF testing gives specific physiological information. Clinical neurophysiology gives elements of anatomic information, and elements of physiology.

Testing should be aimed at clarifying the anatomic and physiological information that will alter the probabilities of key diagnoses. All assessment, clinical and laboratory, is based on probabilities,

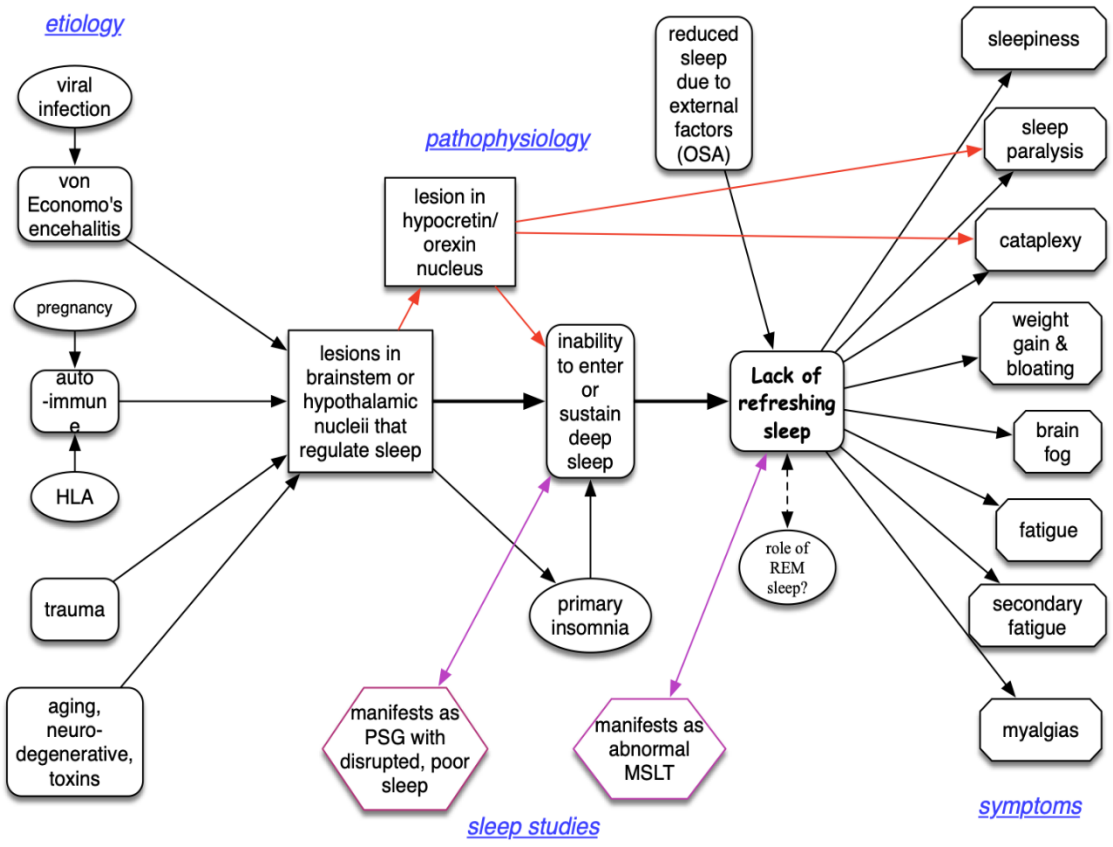
the bedside application of Bayes' Theorem and clinical decision analysis.

Multiple hypotheses about anatomy, physiology, and diagnoses are considered by this approach. If subsequent data conflicts with the first assessment, or treatment response is suboptimal, revisiting the diagnostic schema will point toward alternatives that can be explored. This avoids getting stuck in a diagnostic-therapeutic blind alley.

Confusion often results from the variable use of the word "diagnosis"itself. This term is used to refer at times to etiology. pathology or pathophysiology, syndromes comprising symptoms or other mingled features of the case, physical findings or test results, or other definitions. These variable uses of this term can lead to confusion. Which diagnosis do we seek? Ultimately, the goal of treatment is to help the patient get better. The diagnosis is merely a tool toward that goal. Alternately, diagnosis use is to establish prognosis, or establish why treatment is failing or not available.

Sleep disorders organize by classical neurological diagnostic methods

Figure 2 illustrates a method for re-classifying sleep disorders. Many syndromes that are a combination of symptoms, sleep studies, lab tests, and medication treatments, may produce classifications that can be vague and variable, or alternatively extremely and excessively rigid. Alternatively, Figure 2 is organized according to the classical diagnostic process as described previously.



Disease states: left-to-right analysis

In figure 2, conditions are caused by underlying etiologies, as listed in the leftmost column. These etiologies then cause abnormalities in various anatomic structures, and cause various physiological disturbances in sleep function, shown in the center of the diagram. For the majority of the conditions and patients, the pathway progresses through a disruption that prevents refreshing sleep, or alterations in wakefulness or dreaming. Disrupted sleep produces a constellation of symptoms that are reported by the patient, and cause them to seek medical attention. These are listed in the column on the right. Following this schema leads to a more logical, coherent understanding of sleep disorders.

Clinical diagnosis: right-to-left analysis

Patients present with symptoms, which are shown on the right of the diagram. The physician therefore performs an analysis process that proceeds "in reverse", from right to left. There may be single or multiple presenting symptoms. As mentioned above, often symptoms reported by patients are difficult to interpret. In a large number of cases, patients present with symptoms, and do not recognize or perceive the underlying sleep problem. They is especially true if the condition has been progressive, and present for years before becoming intolerable. Many patients even deny sleep issues. A careful review of symptoms may reveal many other symptoms that were not initially reported.

Some examples of symptoms that are misinterpreted may include: • "I don't have a sleep problem. I just don't-can't sleep." • "I am not sleepy during the day. But I am afraid to drive because I have unexpectedly fallen asleep behind the wheel, or had numerous accidents I can't explain" • "I think I have dementia. My brain is foggy all day long" • "I was told I have pseudo seizures, the tests are negative. But I blank out frequently" • "I am not sleepy, I am just fatigued all day long, or I have physical weakness" • "I suddenly fall or lose my strength for no reason, I fail to the ground for no reason" • "I thought waking up at night with paralysis, or terrible dreams, was NORMAL" • "I didn't want to say anything about my dreams because I was afraid to be called crazy" • "I was told having crazy dreams means PTSD, which is causing all my (psychiatric) sleep problems". The clinician must listen to the patient and recognize symptoms that might be pointing to an underlying sleep problem.

Certain groups of patients with disrupted sleep report a consistent group of symptoms. A constellation of symptoms represents a clinical syndrome. There are many examples of clinical syndromes based on symptoms and signs. Migraine is such syndrome. Parkinsonism may be such syndrome, and a subset to patients with Parkinsonism may have Parkinson's disease. A primary symptom of sleep disorders is excessive daytime sleepiness. Note that patients may however use words like "fatigue". Some may deny sleepiness but report taking frequent naps. Others may deny sleepiness, but they have an extreme, irresistible sleep urge during the day, often fall asleep for a few minutes, cannot stay asleep, and are unrefreshed. They interpret extreme sleep urge with inability to sustain sleep as "not sleepiness". The entire group of symptoms has many features that are reported by patients with narcolepsy. Thus, I have labeled this a 'narcoleptiform syndrome', meaning a clinical syndrome with symptoms and features like narcolepsy, but it may be of more than one localization or etiology. An orexin nucleus abnormality is one localization that produces symptoms of this syndrome, but other abnormalities in the sleep regulatory system produce sleep-related symptoms. Like any other syndrome, some patients may lack certain features, have only some of the clinical features. A single symptom being present or absent does not rule in or rule out the syndrome, nor rule out any specific underlying disease process.

We now have much better access to technology to record sleep patterns. Recordings with "Fitbit" or similar actigraphy devices can show multiple irregular sleep patterns. [1] Analysis of large data sets shows that there are subtypes in this objectively-recorded data. One key observation of this actigraphy data shows that sleep disruption is not "by definition" psychogenic. A real, disrupted sleep physiology is present. For example, one small portion represents unrecognized sleep phase circadian rhythm disturbances, which is not psychogenic.

Cataplexy is often under-reported and may even be a presenting symptom. It can possibly occur in other disorders other than narcolepsy. Similarly, "hallucinations" or vivid dreams are often under-reported. Note that in a significant percentage of

patients with OSA, narcolepsy and other disrupted sleep disorders, refractory weight gain is a frequent problem that does not respond until the sleep disorder is treated. Restoration of deep sleep is necessary to allow weight loss. The literature linking weight and diet with sleep is extensive. Patients who fail gastric bypass may have an underlying sleep disorder.

Brain fog and cognitive issues are frequently reported with disrupted sleep. But the presentation may also include a sensation of fatigue not perceived as sleepiness. Sometimes the sensation is a post-exertional fatigue. In data presented as an abstract [2,3], a very high percentage of patients presenting with reports of severe "neuromuscular weakness" in whom very extensive workup for other central, peripheral neurological and metabolic disorders were completely negative, significant insomnia-hypersomnia disorders were found.

The symptoms and syndrome are used to formulate hypotheses about anatomy and physiology, as shown in Figure 1.

Anatomy of sleep regulation

There are numerous references that outline and summarize the various centers in the brain that regulate sleep. This paper is not intended as a complete review of the literature on this topic. One excellent summary of the anatomy of sleep regulation is provided in a listed reference. [4]

The circadian rhythm strongly influences sleep-wake cycles. Components of this regulatory system includes the pineal, the suprachiasmatic nucleus, and blue-light detecting receptors in the eyes, projections of the pathway to the hypothalamus. Projections from this system control other centers that are directly involved in sleep regulation. Variations in circadian rhythm are well recognized, and well demonstrated in species other than humans, as well. The biology and genetic basis of circadian rhythm is increasingly understood. Specific mutations are know to be associated with prolonged, shortened and irregular sleep phase. These are hard-wired circuits.

REM-NREM sleep is regulated by brainstem nuclei, including nucleus reticular pontis oralis, laterodorsal, pedunculopontine, dorsal raphe nucleii, and locus ceruleus. Incidentally, none of those are orexin nuclei. In addition, areas of the brain involved in dreaming include the amygdala, cingulate gyrus, and other cortical areas. The issue of defining sleep disorders solely by the presence of sleep onset REM (SOREM) on an MSLT is dubious.

Recent studies [5] show that pathways involved in dreaming involve acetylcholine (not orexin) and vivid dreams may be triggered by medications that enhance cholinergic transmission. Also note that acetylcholine is a critical transmitter in the activating centers that originate in the brainstem.

Even in pathways involving orexin, the regulation is complex, and involves centers and pathways other than the orexin nucleus itself. [6]

The primary center of the brain that induces and maintains sleep is the VLPO. It is the only nucleus in the brain that has this function. It has projections that control many of the activating systems in the brain, including the orexin nucleus. In fact, studies of the anatomy by von Economo showed not only an area of damage in the brainstem that caused encephalitis lethargic, but a nearby lesion that caused intractable insomnia. With only one such system in the brain, there is no "back-up" in case of injury or malfunction of this nucleus.

Insomnia

Insomnia is a symptom. The term may refer to many variation of the symptom, and is not precise. Merely listing the times it occurs, such as at sleep onset, or with early awakening, does not clarify the approach to the patient. Lack of effective understanding and treatment has resulted in a large percentage or majority of insomnia patients being labeled as "psychogenic". There is even a diagnostic label (ICD-10 code) for this.

In fact, considering the regulation of sleep anatomically and physiologically, there are multiple possible anatomic and physiologic subtypes of insomnia. Note the nuclei involved in sleep regulation in the prior reference. A potentially devastating form of insomnia would occur with damage to the VLPO. We have many studies addressing the role of the orexin nucleus. but this is not the only nucleus or pathway that can disrupt sleep when damaged. We simply do not have enough data on VLPO lesions. A damaged VLPO may eliminate the ability to enter or sustain sleep, which is a very commonly reported symptom.

Other pathways that could be involved are hyperactivity pathways, often dopaminergic. These pathways are known to underly ADD/ADHD, which is frequently accompanied by insomnia. Dopamine agonists may cause sleepiness as a side effect. The nucleus basalts of Meynert is an activating center. Abnormalities of this nucleus, which is in the frontal lobes, could give rise to sleep-wake disorders. Similarly, there are other recognized brainstem nuclei that are involved in sleep wake regulation.

In addition, the complex regulation of circadian rhythm may be disrupted anatomically or physiologically. Genetic factors underlying certain circadian patterns are now well recognized.

None of the above pathways are psychogenic. Our tools to diagnose them are limited. Treatment would very well depend on which pathway, which physiology, which biochemistry is involved. Findings of disrupted sleep on a PSG does not mean the problem is psychogenic. In fact, disrupted, poor sleep is often the root physiological cause of symptoms reported by patients.

Figure 2 clearly separates the symptoms, anatomy and physiology, from etiology. The etiology of a sleep disorder could be genetic, autoimmune, infectious, vascular, degenerative, demyelinating, or traumatic. By the time a patient presents with symptoms, the original etiology is often gone or may be untreatable. Like many other conditions in medicine, we must treat the end results of the original etiology, which requires treatment of the symptoms.

Hypersomnia

A very similar analysis to that of insomnia applies to hypersomnia. Similar anatomic considerations apply. Damage to activating nuclei may cause hypersomnia. However, it is also important to realize that hypersomnia due to insomnia, or disrupted sleep, is frequent. A simple example of that is obstructive sleep apnea. The daytime hypersomnolence is not due to respiratory issues. It is due to severe sleep deprivation, often with complete loss deep sleep. When deep sleep is restored with CPAP, the somnolence is often resolved.

Note that the use of sodium oxybate to treat hypersomnia underscores this physiological link. If hypersomnia were only due to daytime activation issues, sodium oxybate would have no daytime benefit. Yet the various hypersomnia conditions treated by sodium oxybate (including refractory narcolepsy and cataplexy) show that the problem is being addressed by correcting a deficiency of deep sleep. Note that the primary treatment indicated and effective for cataplexy, sodium oxybate, in fact acts by increasing deep stage III restorative sleep, and does not affect REM pathways.

The best objective measure of hypersomnia is arguably the MSLT. It is strange that there are many disorders that can disrupt sleep, cause lack of slow wave sleep even when lighter sleep is present, yet current guidelines do not allow the use of MSLT when insomnia is present. It is precisely in these cases of insomnia-hypersomnia syndrome that an MSLT may be critical to objectively determine the degree of daytime sleepiness. This is particularly true considering how often the symptoms reported by the patients are difficult to interpret, as discussed elsewhere. In cases where the MSLT shows extreme sleepiness with very short sleep onset, it is in fact paradoxical to find insomnia on the PSG. An extremely sleepy patient should be sleeping deeply and well during the night.

Just as with insomnia, the symptom of hypersomnia is not specific to any single etiology.

Nocturnal movements: insomnia, PLMS, RBD

Disorders of excessive nocturnal movement are usually classified descriptively. However, anatomically and physiologically, there are some clear recognizable subtypes that have relevant anatomic and physiological significance.

The symptom may be reported by the patient, or noted as a finding on a polysomnogram. One critical distinction that often is not recorded, is whether the patient is awake or asleep during the movements. Many patients with insomnia or poor sleep, or frequent awakenings, or alpha-delta sleep, or lack of delta sleep, may have increased movements. Often they will clearly state, "I am uncomfortable, I can't sleep well, I move around trying to get comfortable". This is different that movements occurring during deeper stages of sleep, which represent true periodic limb movements of sleep. The physiology is different.

The response of patients to dopamine agonists suggest an anatomic-physiological imbalance

between wake and sleep mechanisms, including pathways that are related to arousal, hyperactivity, and sleep. Patients with true movements during deep sleep often respond to dopaminergic medications. This implies a problem in a pathway that suppresses movement during normal sleep. Dopaminergic agents do not control movements during REM sleep, REM Sleep Behavior Disorder, which implies a different anatomy and physiology of RBD compared to PLMS. In patients with RBD, they will act out vivid dreams, while remaining asleep. A different pathway seems to be damaged. This pathway that suppresses movement during REM sleep, responds to treatment with melatonin or clonazepam. We can see that the pharmacology and phenomenology are pointing to different anatomic pathways with different physiology.

Those patients with restlessness and movement due to inability to enter deep sleep, do not have disruption in those pathways. Dopaminergic medications and melatonin do not work. Instead, the primary problem is an inability to enter or sustain deep sleep, representing a different anatomy and physiology. As discussed with insomnia, in fact several different underlying mechanisms may be present in different patients. The treatment would be to treat the pathway causing inability to obtain deep sleep.

Etiology

None of the above discussion addressed etiology. In Figure 2, it is seen that individual etiologies may be linked to various different anatomic structures, and different symptoms. Conversely, any particular anatomical localization may be affected by several different possible etiologies.

An example that is evolving recently is the syndrome of "Long COVID". Multiple neurological syndromes are being described, which often include fatigue or brain fog, among others. In the peripheral nervous system alone, acute polyradiculoneuropathy, and ongoing neuropathy of several types are being seen [7]. In the central nervous system, a fatigue syndrome is still under investigation. There is evidence in some cases of persisting viral infection, while in other cases there are persisting inflammation and autoimmune mechanisms. Thus, in the left column of figure 2, a single viral disease, which may trigger immune mechanisms, is the etiology. This one mechanism produces different anatomic localizations, pathophysiology, and symptoms. This paper does not provide a review of this literature, which is evolving very rapidly.

As another example of the distinction between a symptom, anatomy and etiology, a reference [8] is provided that lists five different "diseases" (types of pathology) that may lead to the phenotype of primary progressive aphasia. Aphasia has localizing value. Time of progression is important to consider the mechanism of the disease. Slow, chronic progression often implies a neurodegenerative process. But then, different specific etiologies may produce conditions with the same localization and time course.

In many of the cases presenting with symptoms of sleep disorders or fatigue, in the right column of figure 2, the original etiology may be long gone. However, what remains is the underlying anatomical, structural damage, and pathophysiological abnormalities. One of the first examples of a structural disorder of sleep, as described by von Economo, [4] provides a clear illustration of this fact. When it is no longer possible to treat or cure the etiology, to become necessary to treat the pathophysiology and symptoms.

Fibromyalgia

The genesis for this work began with a study of fibromyalgia, which is reported in two papers [9,10]. These patients are notoriously difficult to treat. Diagnostic criteria for fibromyalgia consist of various clinical syndromes, based on symptoms. The syndrome of Chronic Fatigue Syndrome is essentially indistinguishable from fibromyalgia.

In studying these patients [10], most of whom had been thoroughly evaluated for other causes, each case was re-analyzed starting with a history. It was noted that when the symptoms of pain were excluded, almost every patient was describing many of sleep related symptoms. As a group, the symptoms had many features of narcolepsy. Results of 118 patients analyzed retrospectively showed that only 30% were originally referred for fibromyalgia or chronic fatigue. 80% of cases were female.

Therefore, whenever possible, all patients were tested with an HLA marker associated with narcolepsy, and a complete polysomnogram and multiple sleep latency test. If significant sleep

apnea was found, it was treated, and the patient re-evaluated.

80% of the patients had MSLT results showing significant hypersomnia. A smaller percentage had features trending toward, or even supporting the diagnosis of narcolepsy. 43% were found to have HLA markers that can be associated with narcolepsy, compared to worldwide prevalence of about 8% ($p<0.0001$). This was later confirmed by another investigator, who showed that HLA DQB1*0602 was associated with a spectrum of findings related to narcolepsy.

Based on these results, these patients, who had failed numerous other treatments, were treated with sodium oxybate [9]. Of those who started it, 55% remained on it long term. Others quit mostly because of side effects, or cost. Sixty percent (60%) had relief of pain, 75% had relief of fatigue. More recent studies confirm these results, particularly with an approved indication for idiopathic hypersomnia.

Similar findings have generally been also confirmed in multiple other studies by others. This includes several double-blind, placebo-controlled studies of sodium oxybate for fibromyalgia. A sleep disorder in these patients, usually consisting of poor or alpha-delta nocturnal sleep, had been noted previously on polysomnography. MSLT findings had not been studied before, and a repeat study to confirm the MSLT finding in fibromyalgia patients has not been performed.

In a series published by the author as an abstract, [2,3] 99 patients with referral for unexplained neuromuscular weakness were evaluated (average duration of symptoms 12 years). Eight cases had MS, but also were found to have sleep disorders. An abnormal MSLT was seen in 70%. Twenty percent had 2 SOREM, and 42% had one SOREM. Eighty three percent (83%) of those treated with sodium oxybate had relief of neuromuscular weakness.

Neuromuscular weakness can be a symptom of profound sleep disturbance, and respond to treatment. Sleep studies should be considered when all other causes of neuromuscular weakness have been excluded or treated.

Those studies were the impetus that led to the re-evaluation of sleep disorders, using objective data, and re-evaluating the anatomy and pathophysiology. Extending these observations to other sleep disorders, for example nocturnal movement disorders, has led to this more complete reclassification based on anatomy and pathophysiology. It has been important to separate out etiology. A lot of emphasis on etiology has generally led to negative results and interferes with the symptomatic treatment of these patients. Therefore, it has become apparent that the classification shown in figure 2, separating etiology, anatomy, physiology, and symptoms is necessary.

Summary

Classification of sleep disorders has been problematic. This has led to issues with clinical diagnosis, and with proper treatment. Other than sleep apnea, current treatment of sleep disorders is often ineffective or of limited effectiveness.

Other than sleep apnea, all sleep disorders are neurological. Presented here is a different approach to the classification of sleep disorders, based on a classical neurological approach. Instead of arbitrary diagnoses, the approach proceeds through steps involving symptoms (which are classified into symptomatic syndromes), and then proceeds to anatomic localization, pathways and physiology. Etiology is completely separated in the analysis process.

By concentrating the syndromic classification of sleep disorders, the analysis is more easily applied to clinical cases. Groups of symptoms that are reported by patients with sleep disorders often include insomnia, hypersomnia, fatigue, daytime sleepiness, muscular weakness, confusion or thought dysfunction. Starting with those major groups of symptoms, other associated symptoms may be added to further refine the clinical picture. Patients will often present with one of those symptoms as a chief complaint or "headline", but further review will often clarify the entire picture. Associated symptoms such as dream disturbances, fragmented sleep, weight gain, cataplexy, sleep paralysis, nocturnal movements and others may not initially be reported by patients. At this initial stage, a specific diagnosis should not yet be determined.

In some cases, further exploration may not reveal a precise anatomy or pathophysiology. This situation is not unique to sleep medicine. For example, migraine is a clinical syndrome. Sometimes, treatment of symptoms alone is necessary,

particularly if a significant underlying disease is not unidentified.

As is true in other fields of medicine, underlying diseases often need to be considered, particularly conditions that are not sleep disorders. For example, fatigue or weakness might be due to an endocrine dysfunction or neuromuscular disease, as well as others. Analysis of sleep disorders generally proceeds when other such conditions are excluded or treated.

The clinical analysis should next consider various hypothetical localizations and pathways. Individualized treatment addresses specific pathways, anatomy and physiology that are thought to be disrupted. A hypocretin disorder is one such hypothesis. As described above, other hypotheses then need to be considered. In this manner, the failure to treat successfully based on one hypothesis then allows alternatives to be explored. Testing can be selected and interpreted more appropriately in terms of anatomy and physiology, rather than single diagnoses.

While underlying diseases need to be treated, the exact etiology of most sleep disorders is obscure, or often gone by the time the patient presents with symptoms.

Conclusion

A novel approach to classification and treatment of sleep disorders, based on a separation of symptoms and syndromes, anatomy and physiology is presented. Each stage of analysis should be clearly separated.

Optimally, anatomic and physiologic hypotheses will lead to specific, effective treatments. Considering multiple possibilities in each case, for each clinical syndrome, allows more treatments to be explored, and accepted or rejected based on results for the patient. Since the specific localizations and pathways are often at present estimated clinically, each clinical syndrome presentation may lead to different treatments for different patients. This may yield positive results for more patients. For now, the success of symptomatic treatment needs to be judged clinically. In the interim, symptomatic treatment is key, just as the treatment of diabetes involves insulin and other medications, while after a century of research, mechanisms and etiology are still being studied.

Formulating hypotheses regarding sleep disorders based on multiple possible pathways and localization will be able to consider more and new theories regarding sleep disorders. At this time, the etiology of sleep disorders is usually not apparent or treatable at presentation, but considering different pathways will allow improved genetic analysis to be incorporated into future research. For example, genetic differences in circadian rhythm regulation and dopaminergic pathways are already being studied.