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The Current Status and Potential Mechanism of Sleepiness: Narcolepsy

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Abstract. In modern society, narcolepsy had been a threat to the world for a long time. Due to the high societal pressure, narcolepsy is more and more common to be detected. Patients with narcolepsy report excessive daytime sleepiness, which can lead to serious consequences in the future if left untreated. Narcolepsy typically manifests in adolescence.[1] According to incomplete statistics, in 2017 there is a total of more than 140 million people that were confirmed that they were suffering from Narcolepsy cautiously. Narcolepsy has five main symptoms, which are clear to be diagnosed: excessive daytime sleep attack sometimes cataplexy and hypnagogic hallucinations, but the most common symptoms are sleep paralysis and nocturnal sleep. Some main causes, treatments, and solutions are also important to be understood. The paper aims at providing information about this serious brain condition and the potential solutions if individuals are under attack.

Keywords: Narcolepsy, sleepiness.

1. Introduction

An odd mixture of sleepiness and wakefulness is a common symptom of narcolepsy, which causes chronic sleepiness. The brain condition disorder narcolepsy is characterized by REM (rapid eye movement) and sleep. In addition to overtime sleeping during the daytime, an irresistible type of sleep attack, cataplexy (loss of muscle tones suddenly on both sides), are characteristics of this disorder, such as cognitive defects, and sometimes sleep paralysis. The disorder is also characterized by fragmented sleep, automatic behaviour, memory loss, loss of concentration, and unclear vision. To incomplete statistics, around 10% of patients who suffers from Narcolepsy exhibit all four components of the tetrad concurrently, and symptoms and intensity vary over time. Since Narcolepsy is a relatively dangerous condition, it is extremely critical to learn about it. Understanding what you should do if you suspect you are being attacked is also imperative.[2] REM sleep behaviour disorder, nocturnal eating disorder, and obstructive sleep apnea syndrome often coexist with it.

2. The Symptoms Of Narcolepsy And How Is It Dangerous

There are several symptoms associated with narcolepsy, but there are five most common ones. During the day, excessive sleepiness or sleep attacks occur, where individuals fall asleep suddenly without warning and notice, and the duration varies from person to person. The individual feels paralyzed and

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is unable to speak or move. This can last for a few seconds or a few minutes and can be quite disturbing. Individuals who experience sleep paralysis may hallucinate vivid waking dreams, which can cause intense anxiety and feelings of fear. When individuals are falling asleep, hypnogogic hallucinations occur. They are common and not considered as causality for concern. They're manifested as images of models, shapes, or flashing lights. This disappearance of the tone, while a person is not sleeping, causes weakness and skeletal muscle regulation. Nocturnal sleep means the sleep schedule is messed up because patients are not able to regulate a healthy sleep schedule, this might be because you had been unhealthy, so your brain is also used to it.

3. Main causes and mechanism

For individuals to completely help from this serious long-term brain condition, it's important to understand the causes of the complaint. According to a recent study by professional neuroscientists, this common and deadly habitual neurological complaint has four main reasons. One of the main causes, as well as the most common causes for wakefulness, is the lack of hypocretins. Hypocretin, an important neurochemical locates in the brain helps to regulate insomnia sleep. Hypocretins situations are low in those who witness cataplexy. The decreased hypocretin is caused by the autonomous system dampening the cells that are responsible for a generation or the enzymes that activate it, and it will stop the brain from regulating the sleep schedule normally. Precisely what leads to the drop in hypocretin-generating cells in the central nervous system is unclear, but it is suggested as an autoimmune response. Researchers in Switzerland claimed in 2010 that wakefulness generates proteins against lineage 2, while hypocretin is also made by the same region of the brain that produces dopamine. As a result, hypocretin is depleted, which makes the brain less capable of regulating sleep cycles. The terrain can also spark wakefulness. poison exposures can lead to numerous negative issues, including wakefulness. Particulate by-products may beget inordinate vulnerable responses and toxins to brain cells if there's poor ventilation and no particular defensive outfit (PPE). When individuals aren't in a great ventilation terrain, it's possible to have brain cells and neuron transmitters damaged, which will beget multiple types of serious brain conditions, including Narcolepsy. A person's family history is not a factor in narcolepsy. Narcolepsy is usually sporadic in nature, which means it does not run-in families. Approximately one in ten cases have been reported to run in families; however, there is no clear pattern of inheritance. Generally, Narcolepsy is determined by environment and individuality rather than genetics, so it is rare to inherit the trait.

4. Treatments for the narcolepsy

The treatment of narcolepsy is mainly drug and behavioural therapy [3]. The medications include three aspects: The psychoactive agents are often used as a treatment of excessive daytime sleepiness; some antidepressants such as SSRIs and SNRIs can improve the symptoms of cataplexy, and sedatives and hypnotics for nocturnal sleep disorders. Although behavioural therapy intervention still lacks clinical research evidence, it is considered as important as medications and has practical value.

4.1 Psychoactive agents

The most used drug to treat daytime sleepiness is modafinil, which is also known as a stimulant. The pharmacological impacts of modafinil in the brain mainly include three aspects[4]: low affinity blocked the reuptake of protein by DAT(dopamine transporter), and this can enhance dopamine neurotransmission in the central-cortical-limbic system; it can improve the choland glutamic nerve excitatory activities in the cerebral cortex and brain stem by enhancing the synchronization of thalamic-cortical electrical activity; it can increase the hypothalamic secretin-dependent histamine neurotransmission in the thalamic nodular papilla nucleus. So, this turned out that modafinil was effective in the long-term control of daytime sleepiness. However, the mechanism of modafinil is still undetermined, but it is speculated that it may selectively activate the hypothalamus part that produces wakefulness [5]. For instance, headache usually occurs three weeks after taking the drug, especially in cases where the dose is increased too fast. As a result, these symptoms can be alleviated by slowly and gradually increasing the dose. Blood pressure should be monitored during the use of modafinil, as the

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drug may cause an increase in blood pressure. Modafinil was approved by American Food and Drug Administration (FDA) in the end of the last century. Used to treat narcolepsy, shift work disorder, and residual sleepiness in sleep apnea syndrome. FDA lists modafinil as a four-class drug [6], which indicates that modafinil has the possibility of abuse and physiological and psychological dependence.

4.2 Antidepressants

These drugs are mainly used as a treatment for cataplexy and other accompanying symptoms of narcolepsy. If cataplexy's frequency is infrequent or cataplexy's symptom is mild, there is no need to have a treatment. When cataplexy happens frequently, and it is seriously affecting the lives of patients, he/she needs medication.

The recommended antidepressants for the treatment of cataplexy are reboxetine, venlafaxine, clomipramine, and nortriptyline, which can also be used in combination [7]. For instance, tricyclic antidepressant (TCA) is an effective treatment for cataplexy, sleep paralysis, and hypnagogic hallucinations. But it will cause plenty of side effects, such as constipation, blurred vision, etc. So, TCA is not the best choice in the treatment of narcolepsy. Compared with tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) [8] like fluoxetine has lower efficacy but fewer side effect, and it is generally preferred. Other antidepressants called serotonin and norepinephrine reuptake inhibitors (SNRIs) also have a significant anti-cataplexy effect such as venlafaxine, which is a reuptake inhibitor of 5-HT (serotonin), NE, and dopamine. The half-life of venlafaxine is about 5 hours and requires 2-3 doses per day. Therefore, venlafaxine is more suitable for the treatment of daytime cataplexy.

4.3 Sedative-hypnotic drug

Sodium oxybate was first used in the clinic as an induction of anesthesia. Unlike other anesthetics and sleep inducers, sodium oxybate induces slow-wave sleep and rapid eye movement sleep [3]. Many clinical studies have confirmed that sodium oxybate can improve a variety of symptoms of narcolepsy, including nocturnal sleep disorders.

4.4 Behavioural therapy intervention

There are four aspects: having a healthy living schedule, which can help maintain a routine; having a good sleep habit [9], for instance, scheduling short naps at regular intervals during the day and avoiding staying up late at night, which can improve the sleeping quality; keep a healthy diet, the patients should avoid overeating and eating too many foods that affect sleep, such as nicotine and alcohol; do daily exercise, which can help to keep awake during the day and also promotes the sleep quality at night.

5. Limitations and future outlooks

Although narcolepsy has been demonstrated to be affected by a selective loss of hypothalamic secretory neurons, some of its medications are still limited, and the mechanism of some drugs, such as modafinil, is still undetermined, this may also affect the treatment of narcolepsy. In addition, the research found that central stimulants traditionally used to treat narcolepsy, like amphetamine, dextroamphetamine or so, are limited in clinical use because of their drug resistance and addiction. And, narcolepsy is a long-term disease, the symptoms of this disease may change with age, physical condition, or more, which will complicate the medications, so there is a lack of effective drugs that can completely cure narcolepsy [10].

In earlier times, narcolepsy has long been a serious misdiagnosis and mistreatment, it results in some patients with symptoms appearing years before the correct diagnosis and treatment. With the deepening of the pathological mechanism of narcolepsy, plenty of studies have focused on the hypothalamic secretory neurons in the ventrolateral hypothalamic, and an early diagnosis of narcosis is expected to be realized. And early treatment is of great significance to help patients improve their symptoms, and the earlier they get treatment, the sooner they can return to normal life.

Some pathological studies have confirmed that the specific loss of hypothalamic secretory neurons in narcolepsy with the symptom of cataplexy is as high as 95% [11]. As an important neurotransmitter

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that regulates the sleep and wake cycle, hypothalamic secretin is the core site of narcolepsy. Therefore, restoring hypothalamic secretin signalling should be a very targeted therapy.

Orexin-related drug development and use for treatment may also become a significant point in future research due to the lack of hypocretin (orexin) is one of the main causes of narcolepsy. According to research, gene therapy for narcolepsy is suggested to be achieved by orexin neuron transplantation or stem cell transplantation [12]. In addition, exogenous orexin or orexin receptor agonists have a great potential value in the treatment of this disease.

Orexin plays a central role in the pathogenesis of narcolepsy, which opens a new space for basic theoretical research. Orexin turned out to be the key regulator of the sleep cycle because it can form synaptic connections in the central nervous system, which ultimately affects the circadian cycle. In the future, people will devote themselves to studying the relationship between neurotransmitters in the central nervous system and the sleep-wake cycle, to further elucidate the pathogenesis of narcolepsy.

6. Conclusion

The serious Brain condition Narcolepsy is one of the most dangerous diseases that will affect an individual's life in many ways. The most significant cause of Narcolepsy is hypocretin deficiency, which is a neurochemical that controls wakefulness. The environmental trigger is also an important factor. Poor ventilation may increase the risk when being exposed to particulate by-products that trigger the immune system. However, inheritors are not an important factor, so family history is not a possible cause. The treatment of narcolepsy is mainly about two aspects. The first one is drug treatment, which can be divided into three groups due to the different effects of the medications, the other one is behavioural therapy which is often used as adjuvant therapy and prevention of narcolepsy. In the future, some treatments for orexin may become the focus of future treatment of narcolepsy, since all recent research by scientists has found that orexin neurons are likely to be key mediators of the sleep cycle. The deeper people understand Narcolepsy, the more likely this serious brain condition will be completely solved. It is believed that narcolepsy will no longer pose a threat to human health in the near future.

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