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Subtype Classification, Pathological Mechanisms and Precision Treatment of Insomnia Disorder

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Abstract. Insomnia disorder (ID) is a highly prevalent sleep disorder worldwide, and unified treatments deliver limited efficacy. This paper systematically reviews the subtype classification, core pathological mechanisms, biomarkers and precision treatment advances of ID. It classifies insomnia based on disease course, etiology and clinical features, elaborates the pathological differences across subtypes from the perspectives of brain network structure, endocrine rhythm and neurotransmitter regulation, sorts out objective classification indicators including neuroimaging, electroencephalogram and peripheral molecules, and lists targeted regimens corresponding to different subtypes, so as to provide references for establishing a more precise diagnosis and treatment system for insomnia subtypes.

Keywords: insomnia disorder, subtype classification, pathological mechanisms of insomnia

1. Introduction

Insomnia disorder (ID) refers to a sleep disorder in which individuals persistently experience sleep problems such as difficulty falling asleep, sleep maintenance difficulties and early awakening despite a suitable sleep environment, and which exerts a significant adverse impact on daytime functioning [1]. Statistics show that around 16.2% of the global population suffers from insomnia, and nearly half of them have severe insomnia [2]. The prevalence rate in females is approximately 1.4 times that in males [3]. ID not only severely reduces patients' quality of life and work efficiency, but also has close associations with mental disorders such as depression, anxiety and cognitive dysfunction, as well as physical diseases including cardiovascular diseases [4], imposing a heavy burden on individuals, families and the social medical system [5]. Since there are remarkable differences in etiology, disease course, clinical manifestations and treatment response among different patients [6], clarifying the subtype-specific pathological mechanisms of ID and building a precise classification and targeted diagnosis-treatment system have become key scientific issues to break through the current clinical bottleneck.

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2. Subtype classification system of insomnia disorder

2.1. Classification by disease course

According to the course of insomnia, ID can be divided into acute and chronic subtypes. The acute insomnia subtype has a disease course of less than 3 months, with acute onset mostly triggered by stressful events, relatively mild sleep structure disturbance, and fast recovery after intervention [7]. Chronic insomnia lasts for more than 6 months, with completely imbalanced sleep rhythm and persistent symptoms. It can only be improved after long-term intervention, and the prognosis of clinical drug treatment is relatively poor [8]. Therefore, dynamic assessment of subtype transformation and etiology changes during follow-up should be the focus of clinical practice.

2.2. Classification by etiology

Based on the etiology of insomnia, it can be categorized into primary and secondary types. Primary insomnia refers to long-term ID caused by no clear physical or mental disease triggers [9], while secondary insomnia refers to ID directly caused by definite primary diseases or other external factors [10]. Primary insomnia includes the physiological hyperarousal subtype, with significantly shortened objective sleep time [11], and the non-physiological hyperarousal subtype, which only has subjective sleep perception errors, namely a deviation between subjective feeling and objective detection [12]. The objective short sleep subtype is associated with cognitive decline and increased risk of cardiovascular diseases [13], while the subjective perception abnormality subtype is related to emotional disorders such as anxiety and depression. Among secondary insomnia, obstructive sleep apnea comorbid with insomnia subtype and depression/anxiety comorbid insomnia subtype are two important categories. Patients with obstructive sleep apnea comorbidity often take insomnia as their chief complaint, so missed diagnosis is common in clinical practice [14]. The main clinical feature of the emotional disorder comorbid type is abnormal emotion regulation, and treatment usually requires simultaneous attention to the synchronous management of emotional disorders and insomnia with combined intervention [15].

2.3. Data-driven subtype classification

Different from traditional empirical classification, data-driven classification is gradually becoming a cutting-edge direction for precise diagnosis and treatment of ID. Based on multi-source clinical data such as electronic health records, data-driven approaches including large language models and machine learning can realize the classification of insomnia subtypes [16, 17]. Researchers use unsupervised clustering and data category analysis to automatically identify groups with similar phenotypes from massive data [18], and adopt supervised learning models such as random forest and gradient boosting tree to achieve precise subtype prediction and external validation [19]. This computer-driven classification mode not only breaks through the subjectivity and one-sidedness of traditional classification, but also provides intelligent support for individualized treatment, showing broad prospects for clinical transformation.

2.4. Limitations and optimization directions of existing subtype classification systems

The current insomnia classification system has many practical problems. Traditional classification relies on patients' subjective self-reports without unified quantitative judgment standards, leading to poor consistency in clinical classification. Polysomnography and imaging tests are cumbersome and

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costly, making it hard to popularize them in daily diagnosis and treatment. Data-driven classification faces problems such as poor data interoperability and algorithms detached from sleep physiological mechanisms, which brings great difficulty to clinical promotion. In response, sleep-related quantitative judgment standards can be established with reference to industry guidelines to reduce human judgment errors. Multi-center clinical studies can also be carried out to expand samples, complete the validation of classification models, clarify the pathological mechanisms of different insomnia subtypes, and accelerate the clinical transformation and application of the classification system.

3. Core pathological mechanisms of insomnia disorder subtypes

3.1. Specificity of brain network function in different insomnia subtypes

Resting-state fMRI studies have confirmed that different insomnia subtypes present differentiated sleep disorders and daytime neurological impairment due to varying abnormal amplitudes of specific brain regions. The attention network of insomnia patients shows pathological hyperfunction: the functional connectivity between the dorsal anterior cingulate cortex and the left dorsolateral prefrontal cortex, superior frontal gyrus and other brain regions is strengthened, and the affective network is over-synchronized, which causes continuous amplification of brain arousal signals and maintains a high arousal state [20]. The neural activity of the medial prefrontal cortex and posterior cingulate cortex in the default mode network is abnormally elevated, so that thinking cannot enter a dormant inhibitory state at rest. The efficiency of descending inhibitory nerve projections from the thalamus to the cerebral cortex is significantly reduced, and cortical excitation is difficult to suppress, eventually resulting in difficulty falling asleep and sleep maintenance disorders [21].

The pathological changes of short-term insomnia are dominated by unilateral localized hyperactivation, mainly manifested as abnormally increased excitability of the left dorsolateral prefrontal cortex and left mediodorsal thalamic nucleus, with impaired unilateral thalamic filtering function and hyperactive unilateral prefrontal-limbic pathway, which mainly causes acute sleep disturbances such as prolonged sleep latency and difficulty falling asleep [22]. Daytime manifestations include transient inattention, without persistent cognitive impairment. The brain regions of chronic insomnia show bilateral extensive inhibitory damage, mainly manifested as continuous down-regulation of metabolic activity in bilateral prefrontal lobes, large-scale inactivation of bilateral thalamocortical arousal inhibitory pathways, and diffuse attenuation of whole-brain prefrontal-parietal functional connectivity. This leads to persistent difficulty falling asleep, fragmented sleep structure, as well as stable daytime cognitive decline and impaired emotion regulation ability [23]. The brain abnormality in psychophysiological insomnia lies in the over-activation of the default network. The local network abnormality of excessive excitation in the posterior cingulate cortex and precuneus does not damage the objective sleep structure, but will keep the self-monitoring circuit hyperactive during sleep, eventually forming the dissociation between subjective insomnia feeling and objective sleep parameters [24].

3.2. Subtype specificity of endocrine disorders

The rhythm disorder of the endocrine system echoes with brain network abnormalities, constituting an important peripheral driving pathway for the pathophysiology of insomnia. Among them, hypothalamic-pituitary-adrenal (HPA) axis dysfunction is the core endocrine pathological change.

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Different insomnia subtypes show obvious differences in endocrine regulatory pathways, hormone secretion rhythms and microbial metabolism.

The physiological hyperarousal subtype is mainly manifested as HPA axis dysfunction, with inverted peak-valley pattern of cortisol circadian rhythm and abnormally elevated nocturnal cortisol secretion. It acts on central arousal nuclei to increase the activity of the locus coeruleus noradrenergic system, forming a positive feedback cycle of endocrine abnormality and central hyperarousal. The hyperactive state of the HPA axis breaks the body's circadian arousal homeostasis, making patients often present the contradictory symptom of coexisting daytime fatigue and nighttime high alertness [25]. The circadian rhythm disorder subtype mainly results from the loss of synchrony between the central pineal gland and suprachiasmatic nucleus rhythm. It is manifested as delayed expression of clock genes (CLOCK, BMAL1, etc.), which not only shifts the peak of melatonin secretion backward, but also inhibits the pulsatile release of pituitary nocturnal growth hormone, and weakens the synchronization effect of light signals on hypothalamic rhythm [26, 27]. The gut-brain axis disorder subtype refers to the imbalance of the gut-brain bidirectional endocrine metabolic pathway. The decreased diversity of gut microbiota directly interferes with the tryptophan metabolism pathway, leading to insufficient peripheral synthesis of serotonin and impaired function of the medial prefrontal cortex and thalamic inhibitory pathway. Reduced intestinal bacterial diversity will lower the synthesis efficiency of 5-hydroxytryptamine and decrease the production of short-chain fatty acids, which reversely up-regulates HPA axis activity through the vagus nerve and humoral pathways, reflecting the triple interactive imbalance of intestinal microecology, endocrine system and central sleep regulation. Patients have disordered sleep rhythm and fragmented nighttime sleep [28, 29].

3.3. Subtype specificity of neurotransmitter imbalance

The imbalance of the neurotransmitter system mediates the dysregulation of the sleep-wake cycle, and is associated with brain network and endocrine abnormalities. In the GABAergic inhibition weakened subtype, GABA synthesis in the brain is insufficient and GABAa receptor function declines, the conduction efficiency of central synaptic inhibition decreases significantly, and nerve excitability remains high, leading to sleep initiation and maintenance disorders. Patients mainly present difficulty falling asleep and frequent nighttime awakenings [30, 31]. The orexin system hyperactive subtype is characterized by excessive activation of the orexin system. Orexin A/B can activate the whole-brain arousal network through OX1R/OX2R receptors, breaking the periodic transition between sleep and wakefulness, and becomes an important neurotransmitter mechanism of intractable insomnia [32, 33]. Patients are often accompanied by excessive daytime alertness and active nighttime brain activity [34]. The 5-hydroxytryptamine rhythm disorder subtype is manifested as imbalanced circadian secretion of 5-hydroxytryptamine in the raphe nuclei, abnormal changes in 5-hydroxytryptamine receptor sensitivity, and impaired conduction of sleep initiation-related nerve signals, resulting in disordered sleep structure, shallow sleep and early morning awakening [27-35]. Moreover, abnormal activation of the dopaminergic system and excessive cognitive arousal in the medial prefrontal cortex not only aggravate sleep onset disorders, but also induce emotional anxiety, forming a pathological cycle of mutual aggravation between insomnia and anxiety [36]. These neurotransmitter abnormalities do not exist in isolation. For example, cortisol secreted by the hyperactive HPA axis can directly enhance the excitability of orexinergic neurons, while weakened GABAergic inhibition will further release the regulation of the orexin system. The endocrine and neurotransmitter pathways are intertwined to jointly maintain the persistent arousal state of the central nervous system [37, 38].

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4. Biomarkers of insomnia disorder subtypes

4.1. Polysomnography (PSG) subtype markers

As the gold standard for sleep disorder detection, PSG can directly capture abnormalities in sleep macrostructure and realize preliminary classification of basic insomnia subtypes. The cortical hyperarousal subtype shows persistently high ORP values, with high-frequency alpha brain waves intruding into the slow-wave sleep period [39]. The sleep maintenance difficulty subtype is manifested as increased detection frequency of CAP cycles and significantly elevated cortical micro-arousal data in N3 sleep stage [40, 41]. For the sleep perception dissociation subtype, all data related to sleep duration and sleep stages fall within the normal range, and only the subjective sleep assessment score is significantly lower [42, 43]. This method provides intuitive values and is suitable for preliminary clinical classification and screening. However, it can only collect nighttime sleep data, lacks reference for daytime arousal-related indicators, and has weak discrimination ability for perception abnormality subtypes.

4.2. Electrophysiological subtype markers

Electroencephalography accurately distinguishes subtypes based on the level and frequency difference of various electrical signal data, and the abnormal manifestations of each indicator are distinct from one another. The persistent hyperarousal subtype has a low proportion of class D microstates and significantly increased electroencephalogram power in beta and gamma bands [39-44]. The emotional cognitive impairment subtype shows no significant inter-group difference in N100, low P300 amplitude and obviously prolonged conduction latency [45]. The sleep perception distortion subtype has low phase coupling between spindles and delta waves, and abnormally elevated theta band power during non-rapid eye movement sleep [46]. Such indicators have excellent sensitivity and can capture subtle changes in neural activity. However, the values are easily disturbed by external factors, and there is no unified reference threshold, making it difficult to achieve large-scale unified application.

4.3. Blood and molecular subtype markers

Peripheral molecular markers distinguish new insomnia subtypes based on the changes of various body fluid indicators, with clear quantitative characteristics of abnormalities. The arousal rhythm shift subtype has significantly higher nocturnal serum cortisol concentration [47]. The metabolic regulation imbalance subtype has low abundance of beneficial intestinal bacteria, and simultaneously decreased detection values of metabolites such as butyric acid and tryptophan [48]. For immune susceptible insomnia, the levels of peripheral inflammatory factors such as IL-6 and TNF-α are high, and the expression levels of glial cell activation-related markers increase significantly [49, 50]. The detection sampling is simple and can complete batch data collection. However, a single indicator fluctuates greatly, and value overlap easily occurs among different subtypes.

4.4. Neuroimaging subtype markers

Neuroimaging classifies subtypes based on data differences such as brain region activity frequency and connection strength, with clear abnormal characteristics of various imaging parameters. The thalamocortical hyperarousal subtype shows significantly up-regulated ALFF local activity in the

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salience network and limbic system, and increased strength of cross-network functional connectivity between brain regions [51]. The rumination load subtype has high global activation level of the default network and abnormally enhanced negative functional connectivity between the striatum and inferior parietal lobule [52]. The chronic structural damage subtype presents structural reduction of gray matter volume in the anterior subregion of the hippocampus and compensatory increase of gray matter volume in the sensorimotor cortex [53]. Imaging data have strong spatial resolution and prominent classification features. However, the detection cost is high, and the interpretation standard for imaging data has not been unified. The above multi-dimensional subtype markers can define the internal pathological subtypes of insomnia to a certain extent, and provide objective classification basis for the implementation of subtype-based precision treatment for ID.

5. Precision treatment of insomnia disorder subtypes

5.1. Traditional treatment methods

For clinical intervention of insomnia, treatment methods can be accurately selected according to different subtypes. Drug treatment has strong targeting: dual orexin receptor antagonists can targetedly improve the sleep state of the physiological hyperarousal subtype [54], and trazodone can effectively regulate the depression-insomnia comorbid subtype [55]. Cognitive behavioral therapy is the first-line intervention, and digital CBT-I is suitable for the sleep maintenance difficulty subtype [56]. At present, various therapies still have limitations such as limited adaptation scope and poor compliance. In the future, a subtype-based combined intervention model can be constructed based on patients' individual pathological characteristics to further improve the overall prognosis effect.

5.2. Emerging treatment methods

The development of emerging treatment technologies provides new intervention options for refractory insomnia subtypes. Repetitive transcranial magnetic stimulation (rTMS) reshapes brain network connection patterns by regulating the excitability of the dorsolateral prefrontal cortex [57]. Metacognitive therapy (MCT) has a significant intervention effect on the cognitive hyperarousal subtype [58]. Probiotic intervention based on the gut-brain axis theory brings new treatment ideas for the circadian rhythm disorder subtype. Supplementing S-adenosylmethionine (SAM)-producing probiotics can regulate the expression of circadian rhythm-related genes and improve abnormal melatonin secretion rhythm by modulating gut microbiota metabolites, realizing targeted intervention for rhythm disorder insomnia from the peripheral mechanism level [48-59].

6. Conclusion

At present, there are still obvious deficiencies in insomnia classification, diagnosis and treatment. On the one hand, classification standards are not unified, making it difficult to achieve accurate distinction. On the other hand, detection costs for imaging and PSG are high, leading to difficulty in popularization and failure to meet the needs of routine screening at the grassroots level. In the future, miniaturized monitoring equipment can be developed combined with AI and wearable technology, which is conducive to real-time long-term monitoring. Easily collectable indicators such as nocturnal cortisol and gut microbiota metabolites can be selected for monitoring. After data aggregation, an auxiliary classification system can be established with AI to gradually unify clinical standard judgment criteria. Focusing on the pathological characteristics of different subtypes, details

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of pathogenesis such as abnormal hyperactivity of prefrontal lobe and thalamic-cingulate gyrus circuits, as well as HPA axis hyperactivity should be refined, and the interactive regulatory rules among central brain regions, endocrine glands and peripheral metabolism should be sorted out. Clinical verification can also be carried out combined with multiple intervention ideas such as probiotics and targeted neurotransmitter regulation, and regimens should be formulated according to the primary pathogenic targets of each subtype, so as to promote the transformation of insomnia treatment from symptomatic sedation to etiological individualized therapy.

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