Sleep Disorders as Early Biomarkers of Neurological Diseases

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Abstract

Sleep disorders are increasingly recognized as important indicators of early pathophysiological changes in various neurological diseases. Their clinical significance extends beyond their effects on daytime functioning and quality of life, as alterations in sleep architecture, duration, and regulation may precede the onset of characteristic neurological symptoms. Conversely, disturbed sleep may adversely affect the course of the underlying disease, reflecting a complex bidirectional relationship between sleep and neurological pathology. One of the most compelling examples of the prodromal significance of sleep disturbances is isolated REM sleep behavior disorder (iRBD), which is strongly associated with the development of α-synucleinopathies. Patients with polysomnography-confirmed iRBD have an increased risk of developing Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Longitudinal studies have demonstrated an annual phenoconversion rate of approximately 6%, with more than 70% of patients developing clinically manifest neurodegenerative disease over 12 years of follow-up. Furthermore, symptoms suggestive of RBD are approximately seven times more prevalent in patients with Parkinson's disease than in control populations, further supporting their association with neurodegenerative processes. Combining iRBD with olfactory dysfunction, autonomic symptoms, subtle motor abnormalities, and additional neurophysiological or neuroimaging markers may improve individual risk stratification. The relationship between sleep alterations and the preclinical stages of Alzheimer's disease is of particular interest. Pathological amyloid-β accumulation begins approximately 15–20 years before the onset of cognitive symptoms, and changes in sleep quality and architecture associated with amyloid pathology may already emerge during this period. Reduced slow-wave sleep, frequent nocturnal awakenings, and circadian rhythm disruption are associated with altered metabolism and accumulation of amyloid-β and tau proteins. Sleep disturbances are thought to impair physiological mechanisms responsible for clearing metabolic waste products from the central nervous system, while neurodegenerative changes may further disrupt neural networks involved in sleep regulation. Epidemiological evidence links shorter sleep duration to an increased risk of dementia and obstructive sleep apnea (OSA) to a higher incidence of certain neurodegenerative disorders. Although sleep-related parameters currently lack sufficient specificity for use as independent diagnostic biomarkers, they may provide

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valuable complementary information for risk assessment and monitoring of preclinical changes.

The clinical relevance of sleep disturbances extends beyond neurodegenerative diseases. In cerebrovascular disorders, OSA is a common comorbidity associated with increased vascular risk and poorer functional recovery following stroke. In patients with multiple sclerosis, insomnia, sleep-disordered breathing, and restless legs syndrome may substantially contribute to fatigue, excessive daytime sleepiness, and impaired quality of life. Their potential association with disease activity remains an area of ongoing investigation. In amyotrophic lateral sclerosis (ALS), early recognition of nocturnal hypoventilation is particularly important, as sleep-related respiratory abnormalities may precede clinically apparent daytime respiratory insufficiency. Recent research also suggests that alterations in sleep microarchitecture, particularly reduced sleep spindle density and disturbances in slow oscillatory activity, may be detected in the earliest stages of ALS and even in presymptomatic carriers of pathogenic mutations. These findings suggest early involvement of thalamocortical networks and highlight the potential of quantitative EEG measures as early biomarkers of the disease. Sleep also plays a particularly important role in epilepsy, where physiological changes in neuronal synchronization during NREM sleep facilitate interictal epileptiform activity. Sleep deprivation and fragmentation may increase seizure susceptibility, while seizures themselves, antiseizure medications, and comorbid sleep disorders further alter sleep continuity and architecture. Early identification and appropriate management of these disturbances are important components of comprehensive epilepsy care. Contemporary research is increasingly focusing on objective sleep-related measures, including polysomnographic parameters, circadian patterns, and quantitative characteristics of sleep spindles and slow-wave activity. Although their diagnostic specificity remains limited, integrating these measures with clinical, neuroimaging, genetic, and molecular biomarkers may improve the early detection of neurological diseases and monitoring of disease progression. Systematic sleep assessment should therefore assume a more prominent role in routine neurological practice, not only to address associated symptoms but also to facilitate earlier identification of individuals at increased neurological risk.

Keywords: sleep disorders; early biomarkers; neurodegeneration; isolated REM sleep behavior disorder; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis

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Poremećaji spavanja kao rani biomarkeri neuroloških bolesti

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Sažetak

Poremećaji spavanja sve se češće prepoznaju kao važni pokazatelji ranih patofizioloških promjena u različitim neurološkim bolestima. Njihova klinička važnost nadilazi uobičajene posljedice na dnevno funkcioniranje i kvalitetu života jer određene promjene arhitekture, trajanja i regulacije spavanja mogu prethoditi pojavi karakterističnih neuroloških simptoma. Istodobno, poremećeno spavanje može nepovoljno utjecati na tijek osnovne bolesti, stvarajući složen dvosmjerni odnos između spavanja i neurološke patologije. Jedan od najuvjerljivijih primjera prodromalne vrijednosti poremećaja spavanja predstavlja izolirani poremećaj ponašanja u REM spavanju (iRBD), koji je snažno povezan s razvojem α-sinukleinopatija. Bolesnici s polisomnografski potvrđenim iRBD-om imaju povećan rizik od razvoja Parkinsonove bolesti, demencije s Lewyjevim tjelešcima i multiple sistemske atrofije. Longitudinalna istraživanja pokazuju godišnju stopu fenokonverzije od približno 6 %, pri čemu tijekom dvanaestogodišnjeg praćenja više od 70 % bolesnika razvije klinički manifestnu neurodegenerativnu bolest. Dodatno, simptomi koji upućuju na RBD približno su sedam puta učestaliji u bolesnika s Parkinsonovom bolešću nego u kontrolnoj populaciji, što dodatno potvrđuje njihovu povezanost s neurodegenerativnim procesima. Kombiniranje iRBD-a s poremećajem njuha, autonomnim simptomima, diskretnim motoričkim odstupanjima i dodatnim neurofiziološkim ili neuroradiološkim pokazateljima može omogućiti precizniju procjenu individualnog rizika. Posebno je zanimljiva povezanost promjena spavanja s pretkliničkim stadijima Alzheimerove bolesti. Patološko nakupljanje amiloida-β započinje približno 15–20 godina prije pojave kognitivnih simptoma, a već se u tom razdoblju mogu pojaviti promjene kvalitete i arhitekture spavanja povezane s amiloidnom patologijom. Smanjena zastupljenost sporovalnog spavanja, učestala noćna buđenja i poremećaji cirkadijanog ritma povezani su s promijenjenim metabolizmom i nakupljanjem amiloida-β i tau-proteina. Pretpostavlja se da poremećaji spavanja mogu smanjiti učinkovitost fizioloških mehanizama uklanjanja metaboličkih otpadnih produkata iz središnjega živčanog sustava, dok neurodegenerativne promjene dodatno narušavaju funkciju neuronskih mreža uključenih u regulaciju spavanja. Epidemiološki podaci povezuju kraće trajanje spavanja s povećanim rizikom od demencije, a opstruktivnu apneju u spavanju (OSA) s većom učestalošću pojedinih neurodegenerativnih bolesti. Iako parametri spavanja zasad nisu dovoljno specifični za samostalnu dijagnostičku primjenu, mogli bi imati značajnu dopunsku vrijednost u procjeni rizika i praćenju pretkliničkih promjena. Klinička važnost poremećaja spavanja prepoznaje se i izvan područja neurodegenerativnih bolesti. U cerebrovaskularnoj patologiji OSA predstavlja

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čest komorbiditet, povezan s povećanim vaskularnim rizikom i nepovoljnijim funkcionalnim oporavkom nakon moždanog udara. U bolesnika s multiplom sklerozom nesanica, poremećaji disanja tijekom spavanja i sindrom nemirnih nogu mogu značajno pridonijeti umoru, prekomjernoj dnevnoj pospanosti i smanjenju kvalitete života. Njihova moguća povezanost s aktivnošću bolesti predmet je daljnjih istraživanja. U amiotrofičnoj lateralnoj sklerozi (ALS) rano prepoznavanje noćne hipoventilacije osobito je važno jer se respiratorni poremećaji tijekom spavanja mogu pojaviti prije razvoja klinički očite dnevne respiratorne insuficijencije. Novija istraživanja dodatno upućuju na to da se promjene mikroarhitekture spavanja, osobito smanjena gustoća vretena spavanja i poremećaji sporih oscilacija, mogu otkriti već u najranijim stadijima ALS-a, pa čak i u presimptomatskih nositelja patogenih mutacija. Takvi nalazi upućuju na rano zahvaćanje talamokortikalnih mreža i otvaraju mogućnost primjene kvantitativnih EEG pokazatelja kao potencijalnih ranih biomarkera bolesti. Spavanje ima posebno značenje i u epilepsiji, gdje fiziološke promjene neuronske sinkronizacije tijekom NREM spavanja pogoduju pojavi interiktalne epileptiformne aktivnosti. Deprivacija i fragmentacija spavanja mogu povećati podložnost epileptičkim napadajima, dok sami napadaji, antiseizurni lijekovi i pridruženi poremećaji spavanja dodatno mijenjaju kontinuitet i arhitekturu spavanja. Pravodobno prepoznavanje i odgovarajuće liječenje tih poremećaja važan je dio sveobuhvatne skrbi za osobe s epilepsijom. Suvremena istraživanja sve više usmjeravaju pozornost na objektivne pokazatelje spavanja, uključujući polisomnografske parametre, cirkadijane obrasce te kvantitativne značajke vretena spavanja i sporovalne aktivnosti. Iako je njihova dijagnostička specifičnost još ograničena, povezivanje tih pokazatelja s kliničkim, neuroradiološkim, genetskim i molekularnim biomarkerima moglo bi unaprijediti rano otkrivanje neuroloških bolesti i praćenje njihove progresije. Sustavna procjena spavanja stoga bi trebala imati važnije mjesto u svakodnevnoj neurološkoj praksi, ne samo radi liječenja pridruženih simptoma nego i zbog mogućnosti ranijeg prepoznavanja osoba s povećanim neurološkim rizikom.

Ključne riječi: poremećaji spavanja; rani biomarkeri; neurodegeneracija; izolirani poremećaj ponašanja u REM spavanju; Alzheimerova bolest; Parkinsonova bolest; amiotrofična lateralna skleroza

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