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REVIEW DERLEME

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Vestibular Function in Mild Cognitive Impairment and Alzheimer's Disease: A Narrative Review

Hafif Bilişsel Bozuklukta ve Alzheimer Hastalığında Vestibüler Fonksiyon: Geleneksel Derleme

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ABSTRACT The vestibular system is responsible for gaze stabilization and postural control. Recent studies have shown that vestibular function is related to various cognitive processes, too. These studies have examined the effect of the vestibular system on cognitive functions as a whole. However, it is unclear how different parts of the vestibular system, the semicircular canals and otolith organs, contribute to these processes. Several studies investigating the relationship between vestibular system and cognition have evaluated vestibular function in adults with Alzheimer's disease and mild cognitive impairment. In this review, the current literature evaluating vestibular function in adults with cognitive impairment will be investigated and we will discuss possible causal links between the vestibular and cognitive functions. Electronic databases such as PubMed, Cochrane Library, Science Direct, and Google Scholar were searched using the keywords of "cognition", "cognitive function", "cognitive impairment", "mild cognitive impairment", "Alzheimer's disease", "dementia", "vestibular system", "vestibular function", "vestibular function tests", "vestibular evoked myogenic potentials", "ocular vestibular evoked myogenic potentials", "cervical vestibular evoked myogenic potentials", "video head impulse test", "videonystagmography", "oculomotor tests" and various combinations of these keywords between January 2023 and 2024. After the titles and abstracts of the relevant articles were reviewed by the researchers, the articles related to the research topic were listed and reviewed. Although the findings obtained from the studies using different vestibular tests in Alzheimer's disease and mild cognitive impairment vary, the studies indicate the importance of the vestibular evoked myogenic potentials test in the early diagnosis of Alzheimer's disease. Further studies are needed in which vestibular functions are evaluated in adults with cognitive impairment.

Keywords: Cognition; vestibular function test; Alzheimer's disease; mild cognitive impairment

ÖZET Vestibüler sistem bakış stabilizasyonu ve postüral kontrolün sağlanmasından sorumludur. Son yıllarda yapılan araştırmalar, vestibüler işlevin sadece denge ve postüral kontrolü sürdürmekle değil, aynı zamanda çeşitli bilişsel süreçlerle de ilişkili olduğunu göstermiştir. Bu çalışmalar, vestibüler sistemin bilişsel işlevler üzerindeki etkisini bir bütün olarak ele almıştır. Ancak vestibüler sistemin semisirküler kanallar ve otolit organlar gibi farklı bölümlerinin bu süreçlere nasıl katkıda bulunduğu hâlâ açık değildir. Vestibüler sistem ile biliş arasındaki ilişkiyi araştıran çalışmaların bir kısmında, Alzheimer hastalığı ve hafif bilişsel bozukluğu olan erişkinlerde vestibüler fonksiyon değerlendirilmiştir. Bu derlemede, bilişsel bozukluğu olan erişkinlerde vestibüler işlevi değerlendiren güncel literatür incelenecek ve vestibüler ve bilişsel işlevler arasındaki olası nedensel bağlantılar tartışılacaktır. Ocak 2023-2024 tarihleri arasında PubMed, Cochrane Library, Science Direct ve Google Scholar gibi elektronik veri tabanlarında "biliş", "bilişsel fonksiyon", "bilişsel bozukluk", "hafif bilişsel bozukluk", "Alzheimer hastalığı", "demans", "vestibüler sistem", "vestibüler fonksiyon", "vestibüler fonksiyon testleri", "vestibüler uyarılmış miyojenik potansiyeller", "oküler vestibüler uyarılmış miyojenik potansiyeller", "servikal vestibüler uyarılmış miyojenik potansiyeller", "video head impuls test", "videonistagmografi", "okülomotor testler" anahtar kelimeleri ve bu anahtar kelimelerin çeşitli kombinasyonları kullanılarak arama yapılmıştır. İlgili makalelerin başlıkları ve özetleri araştırmacılar tarafından incelendikten sonra araştırma konusuyla ilgili makaleler listelenerek incelenmiştir. Alzheimer hastalığı ve hafif bilişsel bozuklukta farklı vestibüler testler kullanılarak yapılan çalışmalardan elde edilen bulgular farklılık göstermekle birlikte, çalışmalar Alzheimer hastalığının erken teşhisinde vestibüler uyarılmış miyojenik potansiyeller testinin önemini ortaya koymaktadır. Bilişsel bozukluğu olan erişkinlerde vestibüler fonksiyonların değerlendirildiği ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Biliş; vestibüler fonksiyon testleri; Alzheimer hastalığı; hafif bilişsel bozukluk

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The vestibular system evolved more than 500 million years ago to provide a sense of gravitational verticality in primitive invertebrates. This sensory system, which developed before the visual system, is critical for orientation and mobility.[1] The vestibular system consists of two end organs: the otolith organs (the utricle and saccule) and semicircular canals (SCCs). The utricle and the saccule respond to linear acceleration. It is primarily responsible for the postural control, orientation, and changes in sympathetic arousal to recompense for the shift of the vertical column based on gravity through movements. On the other hand, SCCs respond to angular movements in roll, pitch, and yaw.[2]

Recent studies have shown that vestibular function is related to various cognitive processes, as well as with maintaining postural control and balance.[1,3-16] These studies are evaluating visuospatial ability in various vestibular disorders, dual-task studies of balance and cognitive functions, and studies investigating the relationship between the vestibular system and cognition in individuals with cognitive impairment.[1,3-16] In this review, studies evaluating vestibular function in adults with mild cognitive impairment (MCI) and Alzheimer's disease (AD) will be inspected and possible causal links between the vestibular and cognitive functions will be discussed.

SEARCH PROCEDURE

Electronic databases such as Pubmed (National Library of Medicine, United States), Cochrane Library (John Wiley & Sons, Inc, United States), Science Direct (Elseiver, Netherlands), and GoogleScholar (Alphabet Inc., United States) were searched using the keywords of "cognition", "cognitive function", "cognitive impairment", "mild cognitive impairment", "Alzheimer's disease", "dementia", "vestibular system", "vestibular function", "vestibular function tests", "vestibular evoked myogenic potentials", "ocular vestibular evoked myogenic potentials", "cervical vestibular evoked myogenic potentials", "video head impulse test", "videonystagmography", "oculomotor tests", and various combinations of these keywords between January 2023 and 2024. After the titles and abstracts of the relevant articles were reviewed by the researchers, the articles related to the research topic were listed and reviewed.

VESTIBULAR SYSTEM AND COGNITION

The vestibular system is responsible for the stabilization of the gaze and postural control. This role of the vestibular system is provided by reflex mechanisms.[4,8] The vestibuloocular reflex (VOR) constitute fast compensatory eye movements that keep the image stable on the retina, ensuring clear vision during head movement.[1] Descending connections starting from the vestibular nuclei reach the medulla spinalis and form the vestibulospinal reflex (VSR).[17] The VSR maintains the posture during movement.[1] The vestibular system also sends links to subcortical and cortical structures about the movement and orientation of the head, which are used for high-level cognitive processes such as spatial memory and navigation.[4,8] Even though the largest vestibular projection region is located in the posterior Sylvian region, which includes the temporoparietal and parietal-insular cortex, there is also an important vestibular projection to the medial-temporal cortex, containing the hippocampus and parahippocampal gyrus.[2]

The relationship between the vestibular and cognitive functions is not fully explained, but several potential pathways have been highlighted. Spatial memory centers were thought to be located in the hippocampus and basal ganglia, and important vestibular striatal connections were identified.[9] One of the important areas of vestibular input is the hippocampus.[1,18]

Before the mid-1990s, only a few researchers have hypothesised that vestibular inputs project to the hippocampus and other medial temporal structures.[19-21] In the 1990s, Horii et al. showed changes in acetylcholine release in the hippocampus after electrical stimulation of the vestibular system in rats.[22] These studies were followed by studies showing vestibular effects on the firing of hippocampal place cells, the hippocampal theta electroencephalography rhythm, and the firing of head direction cells in the subiculum.[23-25]

Animal experiments have shown that many nerve cells in the hippocampus carry location memory, and these nerves are activated when the animal passes through familiar places.[26,27] Location memory is found in the granule cells of the dentate gyrus, except for the pyramidal nerves of the hippocampus.

The idea that environmental topography is a cognitive map that constitutes the representation of the nervous system has emerged with the discovery of place cells.[28] Brain imaging studies show that hippocampus is more active during direction finding.[26] In addition to these, the hippocampus also has an important role in finding shortcuts in familiar/known places. Taxi drivers in London undergo rigorous testing before they start working and are asked to know many places and the shortest routes between them. In a study conducted at the University of London College, it was found that the relevant parts of the hippocampus of taxi drivers are larger, and this size increases as the driver's experience increases.[29]

Many pathways transmit the vestibular signal to cerebral cortical centers involved in spatial cognition, as well as to the entorhinal cortex and the hippocampal formation. The outputs from the vestibular nucleus complex are transported via vestibulocortical pathways to various cortical regions, containing the parietal and visual cortices, through the thalamus nuclei. Besides, the vestibulocerebellar-cortical pathway transmits vestibular information to the retrosplenial and parietal and cortices. From there, vestibular information is transmitted to the hippocampus via the entorhinal cortex. Fibers emerging from the vestibular nucleus complex are connected to the dorsal tegmental nucleus, which sends connections to the lateral mammillary nucleus. The information from there is then transmitted to the postsubiculum and anterodorsal thalamic nucleus. Finally, it is thought that vestibular information reaches the hippocampus through the system that includes the supramammillary nucleus, pedunculopontine tegmental nucleus, and medial septum.[30]

The hippocampus performs a critical function in memory, spatial navigation, and cognition. There is a consensus that the hippocampus is necessary for spatial representation of the environment and the ability to remember certain events, or episodic memory. By providing a spatial and temporal framework for relating experiences, the hippocampus creates a "cognitive map" of the world that the organism is experiencing. A cognitive map is a representation of an ambient layout that captures objects in the environment, the position of these objects relative to each other, and how these objects interact throughout a movement.[31]

The hippocampus contains cells that are interconnected both with each other and with other structures. Cells working together in the map of the place and the perception of direction enable the organism to find its way in a particular place. Animals form a snapshot memories remembering events such as where the objects were, where the hunter was last seen. This situation is very important for animals to find food and water and then return to their nests, to be protected from dangers and to continue their lives.[32]

There are three types of cells fired by spatial information; head direction cells, place cells, and grid cells.[17,33] The head direction cell system is a network containing cells that show specific firing in the head direction. By firing the head direction cells, target direction selection and angular orientation are encoded. Production of head direction signals is based on angular head velocity from the vestibular nuclei and occurs in the lateral mammillary nuclei and dorsal tegmental nuclei. These signals reach the dorsal thalamus, postsubiculum, and entorhinal cortex via the mamillothalamic tract. While SCCs are required for signal generation, otolith organs play a role in signal stability. Head direction signals carry vestibular information to higher centers involved in spatial navigation. Disruption in transmission along ascending pathways impairs spatial navigation.[17] Lesion studies in rodents showed that disruption of the head direction cell system impairs parahippocampal grid cell function.[34]

Orientation in the space is coded with ground cell firing.[17] Hippocampal place cells are thought to play an important role in the creation of cognitive maps during spatial navigation and memory.[35]

How we perceive space and our position in space has been an important subject of research.[32] Tolman suggested that there is a map related to the positional environment in human and animal brains and encoded his experiences on this map.[36] O'Keefe and Dostrovsky discovered that there are ground cells in the hippocampus.[28] They found that these cells are activated when the organism reaches certain positions, and they called these cells place cells. These cells are a type of pyramidal neuron, which is usually located in the cornu ammonis (CA)

3 and CA 1 regions of the hippocampus. The information obtained by the brain about the current spatial location is transmitted to these cells. Some of these cells have an increased activity while the organism is in a certain position. When the organism comes to this position again, an increase in activity occurs again. If the organism moves from one location to another, the activity of place cells in another part of the hippocampus increases. Thus, different cells encode different parts of the environment, creating a cognitive map of the environment.[32]

O'Keefe and Conway found that place cells dynamically and continuously update location information in space.[37] Then Hafting et al., discovered grid cells in the entorhinal cortex.[38] With the discovery of grid cells, significant progress has been made in the identification of certain features of neural representations of spatial location.[39] Grid cells create a coordinate system in the brain, providing complete path finding and positioning. Later, boundary cells were discovered that are activated when the animal comes to a boundary, such as a wall or threshold. It has also been shown that there are time cells in the hippocampus. Time cells carry temporal information about past events. Time cells are activated by changes in the range of motion of the organism.[40]

In order for the hippocampus, which receives projections from the vestibular system and many other systems, to record this information and provide spatial positioning, place cells and time cells must work harmoniously. A recent study has investigated whether time cells always remain as time cells or turn into place cells. Although some researchers have suggested that time cells act as place cells when necessary, this issue has not been clarified yet. In addition, current studies on where the necessary information comes from to the ground cells point to the entorhinal cortex.[41]

VESTIBULAR FUNCTION IN PATIENTS WITH AD AND ADULTS WITH MCI

The prevalence of vestibular disorders increases with age. Associated with vestibular dysfunction, symptoms such as oscillopia and imbalance are observed due to disruption of vestibuloocular and vestibulospinal connections. In addition, vestibular dysfunction is a risk factor for cognitive decline, especially in older adults. In this population, along with vestibular dysfunction, cognitive disorders such as attention and spatial memory disorders can also be observed.[12,17] It has been suggested that the imbalance (presbystasis) that occurs in older individuals is associated with degeneration in the vestibulolimbic and vestibulocortical pathways rather than degeneration in inner ear hair cells.[17]

In recent years, studies investigating vestibular functions in patients with AD and adults with MCI have been increasing.[8-16,42,43] In these patients, visuospatial abilities were impaired, processing speed, memory and executive functions were also impaired, and structural changes such as hippocampal volume loss were also revealed.[17]

Wei et al. investigated the relationship of poor spatial cognitive ability with vestibular loss in individuals with MCI and patients with AD. They found that adults with MCI with vestibular loss and AD patients had more errors in spatial cognitive tests than those with normal vestibular function. They divided AD patients into groups according to their performance in the spatial cognitive test as "spatially normal" and "spatially impaired" and found that the prevalence of vestibular loss was significantly higher in spatially impaired AD patients than in spatially normal AD patients. They interpreted these findings as that vestibular loss causes a decrease in spatial cognitive abilities in AD and MCI independent of general cognitive decline, and that a "spatially impaired" subtype of AD can be predicted.[16]

Previc et al. investigated the relationship between vestibular function and topographic memory in their study with individuals aged 70-85 who had MCI and normal scores according to the Montreal Cognitive Assessment Test. As a result of the significant relation, they found between vestibular function and topographic memory, they stated that vestibular loss may contribute to topographic memory impairment in the elderly.[44]

Recent studies investigating vestibular function in patients with AD have used video head impulse test (vHIT) to evaluate the VOR in six SCCs separately at physiological frequencies, and vestibular evoked myogenic potentials (VEMP) tests to evaluate the function of otolith organs (utricle and saccule), superior and inferior vestibular nerve, otolith ocular, and otolith cervical reflexes.[9-11,42,45] In the literature, only one study was found in which oculomotor tests in VNG was used to evaluate the VOR pathways in adults with MCI.[43] A study also evaluated caloric stimulation and visual suppression in patients with AD.[13]

EVALUATION OF VESTIBULAR FUNCTION WITH VHIT IN PATIENTS WITH AD AND ADULTS WITH MCI

Harun et al. evaluated vestibular function with VEMP and vHIT to investigate whether vestibular function is affected in adults aged 55 and over with MCI and, AD patients and compared them with healthy controls in terms of lateral SCC VOR gain. They did not find any significant differences between patients with AD and adults with MCI and the control group in terms of lateral SCC VOR gain.[11]

Wei et al. investigated the relationship between vestibular loss and cognitive impairment by evaluating vestibular function with cervical VEMPs (cVEMP), ocular VEMPs (oVEMP) tests, and vHIT in adults aged 55 and over with MCI, AD, and healthy controls. Lateral SCC VOR gain was lowest in individuals with MCI, followed by AD patients and then controls. While there was a significant difference between individuals with MCI and the control group in terms of lateral SCC VOR gain, no significant difference was found between patients with AD and controls.[42]

Micarelli et al. evaluated vHIT and VOR in individuals aged 55 years and older with MCI or AD with unilateral vestibular dysfunction, and compared vHIT findings with controls aged 55 and over with unilateral vestibular dysfunction. They did not find a difference in terms of lateral SCC VOR gain between adults with MCI, AD, and controls.[12]

EVALUATION OF VESTIBULAR FUNCTION WITH VEMPS IN PATIENTS WITH AD AND ADULTS WITH MCI

In experimental studies of spatial learning and memory, the importance of otoliths has remained relatively unclear due to the difficulty of surgical access to otoliths. The emergence of mutant mice with otolith deficiency made it possible to evaluate the relative contributions of the utricle and saccule to these cognitive processes.[46] Studies suggest that the saccule may play an important role in spatial cognition.[9]

A prominent example of the importance of otolith input for orientation is the “visual reorientation illusions” experienced by astronauts in microgravity. Although astronauts have a intact vestibular system, unlike the patients with vestibular loss, their otoliths cannot detect static excitation in the absence of the gravity. Their perception of up and down is based solely on their internal body-centered references without landmarks and is therefore inaccurate.[34]

Functional magnetic resonance imaging studies of saccular stimulation in humans have shown activation of a large cortical network, containing the temporoparietal junction, intraparietal sulcus, cingulate cortex and paracentral lobule.[9] Electroencephalographic studies show that stimulation of the saccule via sound-stimulated VEMPs activates a similar cortical structures around the temporoparietal junction, including the operculum and insular cortex.[47]

Most of the studies investigating the relationship between otolithic dysfunction and spatial memory in humans have examined the relationship between spatial memory and cVEMP, especially arising from the saccular portion of the otoliths.[45] Some studies have also evaluated oVEMP produced by the utricle.[11,42]

In the studies of Harun et al. and Wei et al., oVEMP and cVEMP tests were used to evaluate the VSR and VOR arcs in patients with AD and adults with MCI.[11,42] While the cVEMP test evaluates the VSR, saccule function, inferior vestibular nerve, vestibular nucleus, vestibulospinal tract and SCM muscle motor neurons, the oVEMP test evaluates the VOR arc, utricle function, superior vestibular nerve, contralateral medial longitudinal fasciculus, and extraocular muscles.[48]

Harun et al. found that the bilateral cVEMP response rate was decreased in AD patients compared to the control group, and there was a decrease in both cVEMP and oVEMP amplitudes. Harun et al. stated that individuals with bilaterally absent cVEMPs had an over three-fold increased odds ratio of AD. No difference was found between individuals with MCI and the control group in terms of vestibular test findings.[11] In the study conducted by Harun et al., the function of SCCs was preserved. In order to explain why otolith function decreases with cognitive impairment while maintaining SCC function, the underlying neural pathways should be considered.

Vestibular afferents transmit vestibular information to the vestibular nuclei, higher-level brain regions, and to spinal cord motor neurons that is related to VSR.[11,49-51] Higher-level brain areas contibutes to the cognitive processing.[51] Harun et al. attributed changes in VEMP responses with cognitive decline and the reason for the VOR not being impaired to anterograde degeneration of projections towards vestibular (especially saccular) upper brain structures, and they hypothesized that this causes deterioration of the VSR.[11] Harun et al. also stated that individuals with cognitive impairment will have losses related to spatial awareness and spatial memory.[11] Wei et al. found that with the increase of cognitive impairment, decrease in the response rate of cVEMP and oVEMP.[42]

In the studies conducted by Harun et al. and Wei et al., the participants consisted of adults aged 55 and over. Studies for VEMP finding normalization in healthy individuals show that VEMP responses are reduced at the age of 60 years and above. Even if the individuals in this age group are otologically or neurologically healthy, 40% response cannot be obtained in cVEMP, while 25% response cannot be obtained in oVEMP.[48] In these studies, it is thought that one of the reasons why some of the participants did not respond in the cVEMP and oVEMP tests is the age-related morphological changes in the vestibular system. It is known that there is 25% loss in hair cells in the utricle and saccule, and approximately 40% loss in hair cells in the SCCs due to aging. Welgampola and Colebatch and Ross et al. reported that the number of otoliths in the saccule decreased.[52,53] In addition, it has been reported that the number of neurons in the vestibular nuclei decreases by 3% every 10 years after the age of 40.[54] Welgampola and Colebatch observed a decrease in click-evoked VEMP responses in the 60s, and in the 70s with galvanic VEMP. They stated that there was degeneration in the peripheral vestibular system before the neural degeneration.[52] Lee et al. attributed the age-related decrease in cVEMP amplitudes to a decrease in cervical muscle contraction.[55]

Birdane et al. investigated whether the VEMP test could be used for diagnostic purposes in the early stage of AD and applied the cVEMP test in adults with MCI, AD, and controls. They obtained a high rate of abnormal cVEMP responses in Alzheimer's patients of different levels. They stated that the VEMP test can be used for diagnostic purposes in the early stage of AD. They obtained a longer mean P13 latency and a significantly lower amplitude in patients with cognitive impairment compared to the control group. They noted that a prolonged P13 latency was associated with cognitive impairment. They also found that there was no significant difference in VEMP amplitude between Alzheimer's patients and individuals with MCI.[10] When the studies on cVEMP and oVEMP are examined, it is seen that the amplitude values are in a wide range. It has been reported that the amount of tonic activity of the sternocleidomastoid muscle, muscle fatigue, position differences, and stimulus intensity may affect the amplitude values.[56]

It is thought that the differences in the literature depend on the type of stimulus, test parameters, factors such as muscle weakness, obesity, age, and the cognitive assessment test scores, duration and stage of the disease of the individuals included in the study group. Another parameter affecting the VEMP response is conductive hearing loss. Although the VSR and VOR arcs are intact, in conductive hearing loss, P13-N23 and N10-P16 waveforms may not be obtained in the air conducted VEMP test due to external and/or middle ear pathology.[57] Birdane et al. excluded patients with conductive hearing loss.[10]

EVALUATION OF VIDEONYSTAGMOGRAPHY TEST RESULTS IN PATIENTS WITH AD AND ADULTS WITH MCI

There is only one study in the literature that uses oculomotor tests in individuals with MCI. Baydan et al. compared the results of oculomotor tests with VNG in individuals with MCI and in healthy controls and found no significant differences between the two groups.[43] Evaluating the eye movement system with oculomotor tests applied in the VNG test system provides information about the central vestibular system located in the cerebellum and brain stem and the ways of their connection.[58]

Nakamagoe et al. evaluated whether there is a difference between healthy older adults and patients with AD in terms of caloric nystagmus and visual suppression test. They found that the suppression rate in Alzheimer's patients was significantly lower than in healthy adults. Except for the suppression rate, nystagmus parameters before and during the visual suppression test were similar in both groups. Based on this, they interpreted that the decrease in the suppression rate in patients with AD may be due to cerebral vestibular cortex disorder rather than accompanying peripheral vestibular disorders.[13]

CONCLUSION

Deterioration of cognitive functions as a result of both aging and neurodegeneration can lead to important geriatric consequences such as falls, injuries due to falls, inability to perform activities of daily living and loss of independence. Treatments and rehabilitation to compensate for vestibular loss are of great importance in reducing functional deficiencies and the risk of falling and even slowing down cognitive decline. Understanding the relationship between vestibular function and cognitive functions is important in terms of early diagnosis, planning and implementation of effective treatments and rehabilitation in these individuals. In addition, considering the effects of age-related cognitive decline on affected individuals and society, there are also important public health implications of the findings obtained from studies in the literature. Although the findings obtained from the studies using different vestibular tests in AD and MCI vary, the studies indicate the importance of the VEMP test in the early diagnosis of Alzheimer's disease. Further studies are needed in which vestibular functions are evaluated with vHIT, VEMP and VNG in adults with cognitive impairment.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Anı Parabakan Polat; **Design:** Anı Parabakan Polat; **Control/Supervision:** Anı Parabakan Polat; **Analysis and/or Interpretation:** Anı Parabakan Polat, Berna Deniz Kuntman; **Literature Review:** Anı Parabakan Polat, Berna Deniz Kuntman; **Writing the Article:** Anı Parabakan Polat, Berna Deniz Kuntman; **Critical Review:** Anı Parabakan Polat, Berna Deniz Kuntman.*

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