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EDITORIAL

Dear Colleagues,

In this issue, I would like to draw your attention to our review article, which is published in both English and Turkish. This article, written by our esteemed colleagues Semai Bek, Mahmut Bilal Çaman, Gülnihal Kutlu, is titled "Journey to 2017 in Seizure Classification Studies and After: What's in the New offer?" tells us the history of epilepsy classifications and draws attention to a new debate opened by the ILAE. Please take the time to evaluate both this review and the ILAE's current proposals and provide feedback by blending them with your own experiences. ILAE will receive feedback until October 16, 2024.

I wish you all a good and productive semester after the summer vacation, which I hope you enjoyed.

S. Naz Yeni, M.D., Prof.
Editor-in-Chief

Journey to 2017 in Seizure Classification Studies and After: What is in the New Offer?

Nöbet Sınıflandırma Çalışmalarında 2017'ye Yolculuk ve Sonrası: Yeni Teklifte Neler Var?

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Abstract

The Turkish Epilepsy Society, the International League Against Epilepsy (ILAE), our close ally, completed the preliminary evaluation of the study range on August 12, 2024. This evaluation included recommendations for updating the role of the "2017 Seizure Classification" (2017 SC) in clinical practice worldwide. Following this study, an update document was presented to us, and we were invited to provide individual opinions by October 16, 2024. In this article, we summarize the pre-2017 stages, the 2017 classification, the findings of the Turkish Epilepsy Society, and the results of an e-mail survey conducted in 2018. This summary aims to enhance the understanding of the subject and revisit the process. Furthermore, we incorporate the forward-looking scientific basis and explanations of the changes made by the ILAE task force, presented in the working group's own words. The final version of the classification, along with the classifier and descriptor tables, has been included in Turkey directly from the original article without altering the terminology used in the 2017 SC. We must consider what new options we propose and whether they will address the shortcomings of the 2017 SC. Together with colleagues from around the globe, we are committed to determining the future direction of this classification.

Keywords: Epilepsy, epileptic seizure, International League Against Epilepsy, electroencephalography, taxonomy

Öz

Türk Epilepsi ile Savaş Derneği olarak yakın bağlantıda olduğumuz International League Against Epilepsy (ILAE), 12 Ağustos 2024 tarihinde "2017 Nöbet Sınıflamasının" (2017 NS) dünyada klinik uygulamadaki yerini değerlendirmek ve güncelleme önerilerinde bulunmak üzere oluşturulan çalışma grubunun ön çalışmalarını bitirdiğini açıklamıştır. Bu çalışma sonucunda güncelleme belgesi bizlere sunulmuş, 16 Ekim 2024 tarihine kadar bireysel görüşlerimiz istenmiştir. Bu yazıda, konuya hakimiyeti yaratmak ve süreci hatırlatmak için nöbet sınıflandırma çalışmalarının 2017 öncesi aşamaları, 2017 sınıflaması, Türk Epilepsi ile Savaş Derneği üyelerinin 2018 yılında yapılan e-posta anket değerlendirmeleri özetlenmiştir. Devamında ILAE çalışma grubunun öngördüğü değişikliklerin akademik zemini ve yapılan değişiklikler gerekçeleri ile beraber çalışma grubunun kendi ağzından maddeler halinde sunulmuştur. Sınıflamanın son hali, sınıflayıcı ve tanımlayıcı tabloları da orijinal yazıdan alınarak 2017 NS'de kullanılan terminolojide değişiklik yapılmayarak Türkçe olarak eklenmiştir. Yeni öneriler bizlere neler getirecek ve 2017 NS'nin eksiklerini giderebilecek mi, tüm dünyadan bizlerin ve meslektaşlarımızın katkıları ile hangi şekli alacağını hep birlikte göreceğiz.

Anahtar Kelimeler: Epilepsi, epileptik nöbet, International League Against Epilepsy, elektroensefalografi, taksonomi

INTRODUCTION

The International League Against Epilepsy (ILAE), with which we are in close contact as the Turkish Epilepsy Society maintains close contact, published a preliminary report from the Executive Committee's working group in its electronic newsletter on August 12, 2024. This group was formed to evaluate the role of the "2017 Seizure Classification" (2017 SC) in clinical practice worldwide and to make updated recommendations. They announced the completion of their studies and presented an updated document to us, requesting our individual opinions by October 16, 2024. What new proposals will be introduced and will they address the shortcomings of the 2017 SC?

Historical Process During the 2017 Seizure Classification

First, we explore the historical journey of the seizure classifications up to the 2017 classification system. Prior to 1964, clinics that pioneered the study of epilepsy worldwide utilized their own classification systems for diagnosis, follow-up, and prognosis determination. In April 1964, the first formal joint classification study was initiated in Marseille, involving 120 participants from the ILAE European group chaired by Gastaut. Representatives from six countries - France, Germany, Sweden, Britain, Spain, and Italy - developed a preliminary classification. This study was subsequently discussed at the Dutch "Meer en Bosch" meeting in May 1964, which included participation from the ILAE Terminology Commission, comprising both American and European representatives, as well as members from the World Federation of Neurology, the International Federation of Societies for Electroencephalography (EEG), and the Clinical Neurophysiology Societies. A classification was established that avoided the introduction of new terminology.[1] According to the clinical type of seizures, they were categorized into five main categories: partial seizures, generalized seizures, unilateral seizures (in children), variable seizures in neonates, and unclassifiable seizures. This classification was presented in this format at the 8th International Neurology Congress in Vienna in 1965.

After the 1965 congress presentation, the classification was developed based on the recommendations of 170 neurologists who were in direct contact with Gastaut, ultimately taking its final form in New York in 1967. It was presented at the 1969 ILAE Congress with minor terminological changes.[2]

After the acceptance of the 1969 classification, the use of objective methods - now referred to as video EEG monitoring - has increased. This technique involves the simultaneous recording of seizures on videotape and EEG data on a split screen for examination. Following a workshop on complex partial seizures in 1975 and a subsequent workshop on generalized epilepsy held in Berlin in 1977, a primary framework for this classification was proposed. A commission established in Florence in 1979 was charged with planning the new classification. The commission's objectives included revising the classification by analyzing video footage, coordinating the classification with other international bodies, promoting its use, and developing standardized terminology. This process continued in Copenhagen in 1980.

In 1981, anatomical relationships, etiology, and age - previously considered to be based on speculative information rather than objective findings - were removed. The second significant change was the distinction between simple and complex partial seizures, determined by whether consciousness is impaired. Although many epileptologist have argued that the definition of "complex" is confusing and suggests "higher cortical integrated dysfunction" rather than simply indicating whether consciousness is preserved, these concerns were not addressed until 2017, nearly half a century later. An attempt was made to clarify these issues in the dictionary published alongside the classification.[3] In the final paragraph of the 1981 revision statement, where this classification was first introduced, it is noted that the "epileptic syndrome classification" will be the next topic the commission will tackle.

Despite its widespread use, the 1989 classification has faced criticism for being trapped in a partial and generalized dichotomy, for the incorrect application of idiopathic, symptomatic, and cryptogenic definitions, and for being perceived as a grouping method rather than a true classification system.

After a considerable period, in 1998, Engel[4] proposed the necessity for a renewal that would be more clinically user-friendly and emphasize clinical features. In 2001, efforts were initiated to standardize ictal semiology. A list was presented under the title of epilepsy syndromes to distinguish these syndromes from epileptic seizure conditions that do not require a diagnosis of epilepsy. Additionally, syndromes that are still evolving were also noted. However, the criteria that the accepted syndromes must meet to be included in this list remain unclear. An exemplary classification was introduced, but the omission of age at onset classification became one of the most significant criticisms.[5] Subsequently, disagreements arose. While Wolf[6] stated, "this is not a classification but a diagnostic regulation," Engel[7] mitigated the criticism by asserting, "the studies will continue with your contributions". Luders et al.[8] remarked, "it has many steps; it is not useful for the center at all levels (semiological classification is easier). Do not confuse dictionary and classification studies. Try it first and then publish it." Berg and Blackstone[9] criticized this approach, stating, "There is no systematic approach; even though the definition of the syndrome is known, it is unclear what criteria are used to classify or categorize it." The scientific purpose of the classification is to be easy to use."

These dissident writers also joined the group, and a core group study was conducted in August 2003, December 2003, and May 2005. Although there has been no change in the definition of the syndrome, a decision was made regarding which features should be evaluated. Although Luders stated that he will continue to work with the group, he has expressed that he does not wish to be listed as an author in the final article.[10] The classification of epileptic syndromes was based on various criteria, including the type of epileptic seizure, age at onset, progressive course, interictal EEG findings, associated interictal signs and symptoms, pathophysiological mechanisms, anatomical relationships, etiological categories, and genetics. Epileptic syndromes were classified using background criteria.[11]

In 2010, the waters appeared to have partially calmed, and although there was no retreat on either side, it seemed that everyone was continuing on their own path. In addition to significant changes in terminology for epilepsy classification (e.g., instead of in the syndromic approach. The report stated that "in forward-looking comments, it is believed that classification studies will evolve into a comprehensive database over time, and as general scientific

MAIN POINTS

- The International League Against Epilepsy announced on August 12, 2024 that the update work for the "2017 Seizure Classification" (2017 SC) has been completed.
- As in the 2017 SC, the main purpose is to create a common language and framework, to provide flexibility, and to prepare a well-defined classification that can be used at every stage, is suitable for research.
- As a result of this work, the update document has been presented to us, and our individual opinions have been requested until October 16, 2024.
- You can access the online form where you can enter your opinions and contributions on the proposed classification at the link https://www.surveymonkey.com/r/FY657FN

progress advances (including epidemiology, electrophysiology, imaging, developmental neurobiology, genomics, computational neuroscience, and neurochemistry), the autocratic approach characterized by simple and rigid rules will diminish. In the 2010 report, the ILAE did not introduce a new classification but rather provided an update that could serve as a foundation for the existing classification system.[12]

Berg[13] stated, "There is still much to be done." The team, which was formed in 2013, developed the new classification in 2017.[14-17] 2017 SC is presented as both a simplified version and an extended version, tailored to different levels of expertise.[18]

2017 Seizure Classification

The first step in classifying seizures is based on their onset. Seizures with an untraceable, unrecorded, or unknown onset are categorized under the subheading "unknown onset. Seizures with monitored and/or recorded onset are further divided into focal onset and generalized onset. Focal-onset seizures refer to those that originate from networks confined to one hemisphere, are clearly defined or have a widespread distribution, and may also arise from subcortical structures. Generalized-onset seizures are characterized by their origin from a single focus that rapidly spreads to bilateral networks.

The next stage in the evaluation of focal-onset seizures is awareness assessment. In practice, if the patient reports being aware of the seizure after the conclusion has been reached, then awareness is considered preserved. The patient's inability to answer questions or follow commands during an examination while the seizure is occurring does not necessarily indicate a lack of awareness. The primary criterion for assessing awareness was the patient's recollection of their experiences during the seizure. Additionally, it is important to determine whether the patient loses awareness at any point during the seizure and, if so, for how long. If awareness is lost, the seizure must be classified as impaired awareness. If a definitive conclusion regarding awareness cannot be reached, this step is bypassed, and the classification process continues.

In focal-onset seizures, it is sufficient to specify whether the seizures have motor or non-motor onset. An explanation of motor and non-motor findings, along with additional information, is provided in the expanded version of the seizure classification. Although it is not classified as a separate seizure type, the term "focal to bilateral tonic-clonic" is used to describe the pattern of seizure activity spread, given its frequent occurrence and significance.

Generalized-onset seizures are categorized into two types: motor and non-motor (absence) seizures. The level of awareness is not a criterion for the classification of generalized-onset seizures. In the most straightforward classification of generalized motor seizures, they can be divided into tonic-clonic seizures and other types of motor seizures. EEG data may be necessary to differentiate absence from focal seizures, particularly when awareness is compromised.

Although terms such as simple partial seizure, complex partial seizure, and secondary generalized tonic-clonic seizure in the 1981 classification have been used for many years, they have been supplanted by more comprehensible and widely accepted terminology in the new classification due to their inherent limitations. This is particularly evident in the case of partial seizures, where the level of awareness is uncertain and a clear distinction cannot be made between simple and complex seizures. Consequently, these seizures were categorized as which has been a significant motivating factor for the development of the new classification. Additionally, tonic, atonic, myoclonic, and epileptic spasms, previously classified solely under generalized seizures in the original classification, can also manifest in focal seizures. As a result, they are now included under focal and generalized-onset seizures in the new classification. Furthermore, seizures that are prevalent but were not addressed in the old classification, such as myoclonic-tonic-clonic seizures, have been incorporated into the new framework.

Widespread adoption of this classification was encouraged, with the expectation that it would become more effective as both positive and negative feedback increased during its use. This continued until an electronic newspaper was published by the ILAE on August 12, 2024.

We examined the historical development of classification studies, the conflicts between various groups, and the significance of the 2017 SC. However, exploring why the 2017 SC was necessary and how it was established is essential. Providing a brief answer to these questions is crucial for gaining a comprehensive understanding of classification studies.

Some seizure types could not be classified, they did not fit into the classification of seizures with no apparent onset, and the definition of consciousness or consciousness did not meet the situation that occurs in seizures other than its classical place in neurological examination. The patient does not lose consciousness during the seizure and does not become a coma as we know it classically; therefore, this situation had to be defined differently. Some confusing terminological terms were used in old classifications; such as psychic, simple partial (completely different from the simple complex distinction in febrile seizures), complex partial (complex is a word that describes confusion as a term, but this is confusing in the definition of seizure), or dyscognitive.

As a result, the 2017 SC was not a completely new classification; rather, it was a restructuring of the 1981 classification, organized in accordance with the International Classification of Diseases.

2024 Proposal

A working group established in 2023 conducted the evaluation in three phases: identifying strengths and weaknesses in the 2017 NS, identifying proposals and updates, and building consensus through an iterative Delphi process to reach a comprehensive conclusion.

A working group consisting of 37 experts was established at the beginning of 2023. Care was taken to ensure that the members were specialists in both adult and pediatric epileptology and represented diverse regions of the world: 7 members from North America, 5 from Latin America, 11 were from Europe, 2 from the Eastern Mediterranean, 9 from Asia and Oceania, and 9 from Africa. Additionally, 4 members of the team that developed the 2017 SC. Meetings were held in April, May, and September 2023.

They conducted a systematic evaluation to identify the strengths and weaknesses of the 2017 SC.[18] They searched the PubMed and Embase databases for research articles, reviews, and commentaries

that assessed the applicability of the 2017 SC. Conference papers were also included in the screening if they provided sufficient information. In total, 41 articles were evaluated.

The 2017 SC examined seizures in 4 main categories and included seizures of unknown onset in its classification, which were considered significant strengths. Although there were varying opinions regarding the "focus to bilateral tonic-clonic seizure," it was still deemed useful. The additional strengths of the present study included the extensive range of common descriptors and the differentiation of focal epileptic spasms.

A vigorous debate has emerged regarding the appropriateness of the term "awareness" to describe seizure semiology.[19-22] For general neurologists, epileptic seizures are included in the differential diagnosis of temporary loss or impairment of consciousness. In contrast, others define consciousness simply as the ability to react and remember. It is frequently reported that patient responsiveness is impaired during history-taking. The ability to respond is often assessed through awareness in epilepsy centers. However, it is not possible to evaluate awareness among children aged four and under.[23] One of the main challenges is that the meanings of awareness and consciousness may be similar or differ across various languages. It is widely accepted that the term is more familiar in the field of neurology.

It was determined that the dichotomous classification of "with or without observable manifestations" was more practical than the definitions of "motor and non-motor".[24] The precise meaning cannot be established. For example, findings are observable in non-motor aphasic seizures.

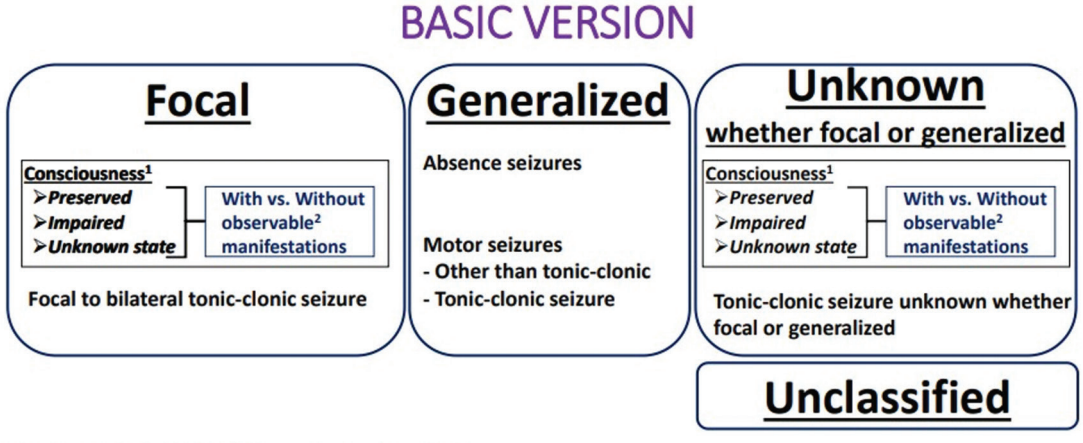
Classifying absence seizures as non-motor seizures in the 2017 SC is misleading. Marked automatism, head tremors, blinking, which can be clearly observed in typical absence seizures, and atonia in atypical absence seizures. Additionally, eyelid myoclonia or myoclonus that can occur in the absence of seizures are also included in this category.

Negative myoclonus, which is distinctly different from asterixis observed in metabolic encephalopathies, was not included in the 2017 SC, although it has been well defined over the years.[25]

Focal onset has been observed in generalized seizures in both human studies and animal models.[26,27] 2017 "generalized onset" in 2017 SC is inaccurate when assessed from this perspective.

As a result, the four primary categories were adhered to. Simple and extended classifications are presented in Figures 1 and 2. Table 1 illustrates the hierarchy of seizure classification taxonomy. "Classifiers" determine the type of seizure and are directly related to diagnosis, treatment decisions, and prognosis. "Descriptors", along with other clinical information, play a crucial role in the overall patient management. Focal seizures originate from networks confined to one hemisphere. These seizures may be distinctly localized or more diffuse and can arise from either cortical or subcortical origins. Each seizure type may have an evident ictal onset and preferred propagation pattern to the opposite hemisphere. Occasionally, more than one network may be responsible for multiple seizure types; however, there is a specific starting point for each type of seizure.

The focal to bilateral tonic seizures are focal seizures that spread to both hemispheres. Along with this, semiological consciousness is impaired, and bilateral tonic-clonic muscle activity occurs. During the clonic phase, there is a notable decrease in the frequency of muscle contractions, and the silent periods between contractions gradually lengthen. In contrast, generalized seizures originate from a specific point and involve cortical or subcortical structures that rapidly integrate into bilaterally spreading networks, although they do not engage the entire cortex. The onset of these seizures may be localized, and they can also present asymmetrically. When insufficient information is available to classify a seizure as either focal or generalized, it can be categorized as "unknown if it started focal or generalized". However, if the clinician is confident that seizures are occurring but lacks adequate information for classification, they should be documented under the "unclassifiable".



1. Operationally defined by *awareness* and *responsiveness*.
2. Observable manifestations are readily recognized by an eyewitness. These may be motor, aphasic, autonomic or other (see Table 2). Impaired consciousness qualifies as an observable manifestation.
Classifiers (seizure types) are shown in black, while descriptors are in blue color.

Figure 1. Basic version of the updated seizure classification

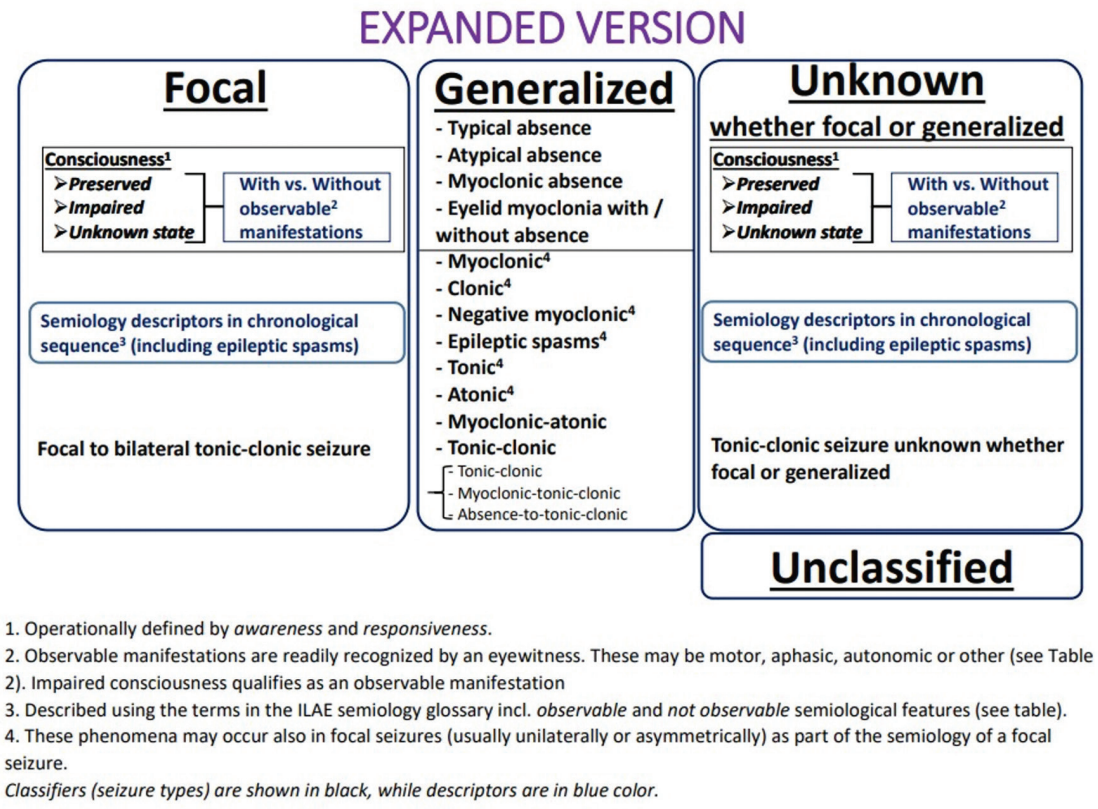


Figure 2. An expanded version of the updated seizure classification

"Consciousness" is primarily defined by an assessment of awareness and responsiveness based on data obtained from the patient's medical history or an examination by healthcare professionals during a seizure. Essentially, it is characterized by the ability to recall the seizure in a manner that the patient and his/her relatives can comprehend, or by the capacity to respond appropriately during the seizure. It is more accurate to evaluate the patient's recollection of the seizure or question their responsiveness during the event than to rely solely on the accounts of the patient and their relatives regarding their consciousness. An inappropriate response, or a response that is ineffective or significantly delayed compared to the interictal period, should also be considered indicative of impaired responsiveness. Patients and their relatives should be informed that the patient's consciousness may be compromised even if the patient's eyes are open and they attempt to engage with their surroundings. The narrative may only encompass information about awareness or responsiveness. Any impairment should be classified as a "seizure with impaired consciousness." It should also be kept in mind that epileptic amnesia, ictal paresis, or ictal sensory aphasia may be the main cause of unresponsiveness.

Descriptors encompass additional characteristics that describe seizures. In the simplified version, the dichotomy is quite clear: with and without observable manifestations. Observable findings refer to signs, apart from voluntary movements, that can be perceived by individuals monitoring the seizure (Table 2). Impairment of consciousness is one such observable finding. In the expanded version, seizures are elaborated on, and chronological semiological features are organized using arrows. For instance, the sequence may be represented as follows: epigastric aura → automatism in the right hand → impairment of responsiveness + impairment of awareness. The features outlined in Table 2 were organized according to the ILAE dictionary.

Generalized seizures in simple classification; they are divided into two main categories: absence seizures and generalized motor seizures. The latter category is further subdivided into tonic-clonic seizures and other types based on distinct motor signs. In the expanded version, all generalized seizures are listed, and "generalized negative myoclonus" has been included in addition to the updates from the 2017 SC.

Epileptic spasms can be classified as generalized, focal, or generalized/focal spasms with an unknown distinction. Although they are presented as separate categories among generalized seizures, the other types are considered semiological features.

Epileptic seizures are categorized under four main headings and subheadings according to the taxonomic hierarchy. While the 2017 SC lists 63 seizure types, the new approach consolidates these into 20 types, allowing for the flexibility to specify additional seizures using descriptors (Table 2). Until the characteristics of a seizure are fully understood, it should be classified as unknown or unclassifiable. This aspect aligns with the 2017 SC.

Table 1. Taxonomic hierarchy of epileptic seizure classification

1. Focal
1.1. Focal preserved consciousness seizure (FPC)
1.1. – 1. With observable manifestations
1.1. – 2. Without observable manifestations
1.1. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
1.2. Focal impaired consciousness seizure (FIC)
1.2. – 1. With additional* observable manifestations
1.2. – 2. Without additional observable manifestations
1.2. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
1.3. Focal unknown state of consciousness seizure (FUSC)
1.3. – 1. With observable manifestations
1.3. – 2. Without observable manifestations
1.3. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
1.4. Focal-to-bilateral tonic-clonic seizure
1.4. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers

2. Generalized
2.1. Absence seizures
2.1.1. Typical absence seizure
2.1.2. Atypical absence seizure
2.1.3. Myoclonic absence seizure
2.1.4. Eyelid myoclonia with/without absence
2.2. Generalized motor seizures
2.2.1. Generalized motor seizures other than tonic-clonic
2.2.1.1. Generalized myoclonic seizure (GM)
2.2.1.2. Generalized clonic seizure
2.2.1.3. Generalized negative myoclonic seizure
2.2.1.4. Generalized epileptic spasm
2.2.1.5. Generalized tonic seizure (GT)
2.2.1.6. Generalized atonic seizure
2.2.1.7. GM-atonic seizure
2.2.2. GT-clonic seizure
2.2.2.1. GT-clonic seizure
2.2.2.2. Myoclonic tonic-clonic seizure
2.2.2.3. Absence-to-tonic-clonic seizure

3. Unknown whether focal or generalized
3.1. Unknown FPC seizure (UPC)
3.1. – 1. With observable manifestations
3.1. – 2. Without observable manifestations
3.1. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
3.2. Unknown FIC seizure (UIC)
3.2. – 1. With additional* observable manifestations
3.2. – 2. Without additional observable manifestations
3.2. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
3.3. FUSC seizure (UUSC)
3.3. – 1. With observable manifestations
3.3. – 2. Without observable manifestations
3.3. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers
3.4. Unknown focal or generalized - tonic-clonic seizure (UTC)
3.4. – 3. Semiology descriptors in chronological sequence: Semiology (glossary**) + Somatotopic modifiers

4. Unclassified

Classifiers are shown in black, and descriptors are shown in blue. The main classes are indicated in bold font, and seizure types are underlined. The hyphen in the numbering separates classifiers (to the left) from descriptors (to the right); the basic version uses descriptors 1 and 2, while the expanded version uses descriptors 3

Table 2. Semiology features

Somatotopic modifiers
Side (left, right, bilateral-symmetric, bilateral-asymmetric) + Body part

1. Elementary motor phenomena
Akinetic
Astatic
Atonics
Clonic
Dystonic
Epileptic nystagmus
Epileptic spasm
Eye blinking
Eye deviation
Gyratory
Head orientation
Ictal paresis
Myoclonic
Myoclonic-atonic
Negative myoclonus
Tonic (focal tonic, chapeau de gendarme, fencing posture)
Tonic-clonic (figure-of-four)
Versive

2. Complex motor phenomena*
Automatisms
- Gestural automaton-distal
- Gestural automatisms-genital
- Gestural automatisms-proximal
- Ictal grasping
- Mimic automatisms (gelastic, dacrystic)
- Oro-alimentary automatisms
- Verbal automatons
- Vocal automatons
Hyperkinetic behavior

3. Sensory phenomena**
Auditory
Body-perception
Illusion
Depersonalization
Gustatory
Olfactory
Somatosensory
- Painful
- Non-painful
Vestibular/dizziness
Visual

4. Cognitive and language phenomena
Aphasia
Dysmnesia
- Amnesia
- Déjà vu/jamais vu/dreamy state/or nostalgia
Forced thinking

5. Autonomic phenomena#
Cardiovascular
- Ictal asystole
- Ictal bradycardia
- Ictal tachycardia
Cutaneous/thermoregulatory
- Flushing
- Piloerection
- Sweating epigastric
Gastrointestinal
- Flatulence
- Hypersalivation
- Nausea, vomiting
- Sialorrhea
- Spitting
Pupillary
- Miosis
- Mydriasis
Respiratory
- Apnea
- Choking
- Hyperventilation
- Hypoventilation Urinary
- Incontinence
- Urinary urge

6. Effective (emotional) phenomena
Anger
Anxiety
Ecstatic/bliss
Fear
Guilt
Mirth
Mystic
Sadness
Sexual

7. Indescribable aura**

Postictal phenomena
Autonomic signs
Blindness (hemianopsia or amaurosis)
Confusion
Headache
Language dysfunction
Nose-wiping
Palinacousis
Paresis (Todd's paresis)
Psychiatric signs
Unresponsiveness

*Observable manifestations; **Not observable manifestations; #Possibly observable manifestations. If phenomena not listed above occur during the seizure, they are added to the free text. Awareness and responsiveness define consciousness and hence are classifiers. All items in this table are defined in the semiological glossary

DISCUSSION

The new classification is, of course, based on the 2017 SC. The necessary changes were implemented based on the clinical experience gained since 2017. In fact, approximately 1 year after the introduction of the new classification, we obtained similar results from a survey conducted via email with members of the Turkish Epilepsy Society prior to the May 2018 National Epilepsy Congress, of which 92% were adult neurologists. Among this group, 16% were specialists and 84% were academicians. Notably, 97% were familiar with the classification, and 73% had used it in their clinical practice. However, only 35% of respondents believed that the 2017 NS could replace the 1981 classification. In contrast, 56% of respondents expressed the opinion that certain modifications should be made before the classification can be deemed sufficient for use. Additionally, 9% of the group felt that the 2017 SC could not replace the old classification, regardless of any changes.

When we asked participants for their contributions and suggestions for changes based on the survey results;

1. The definition of "awareness" may be confusing, while the definition of "consciousness" may be more accurate,

2. Simple, easy, and understandable stories or video recordings are required,

3. It is preferred to use the term complex partial seizure,

4. Typical absence seizures can be divided into simple and complex,

5. The new classification is still unclear and non-didactic and does not address clinical and research problems,

6. It is incorrect to call bilateral generalized tonic-clonic instead of secondary generalization does not fully correspond to each other,

7. This classification drowns in the semiological details of seizures rather than using practical and easy-to-say definitions,

8. It is not easy or usable,

9. Epileptic seizures that start focal and become generalized cannot be well categorized,

10. It was answered that it was incomplete to define epileptic syndromes.

The responses received largely aligned with the findings obtained from the ILAE core group through database analysis. They also indicated that both existing and new changes were implemented based on the results obtained from the database.

As outlined in the 2017 SC, the primary objective is to establish a common language and framework that offers flexibility and provides a well-defined basis applicable at all levels of care, from primary to tertiary, while also being suitable for research purposes. Within this framework of taxonomic rules, four main categories, two subclasses (specifically for generalized seizures), and a total of 20 seizure types were defined. To simplify the classification process, the aim was to avoid the introduction of new terminology and to utilize a common language that was accessible to patients and their families.

Changes made;

1. Removed "onset" from the main 4 groups (based specifically on evidence of focal onset generalized seizures).

2. Classifiers and descriptors were distinguished from each other within the framework of taxonomic rules.

3. The term "awareness" was removed, and the term "consciousness" was employed as a classifier (based on evidence that consciousness functionally defines both awareness and responsiveness).

4. Instead of motor and non-motor dichotomy, "with or without observable findings" was used (it was evaluated that it would be more useful for clinical studies).

5. Seizure semiology was arranged chronologically rather than relying on the first finding to explain the seizure (based on the evidence that it is more accurate to evaluate not only the seizure as the first symptom but also all the findings sequentially, especially during video EEG monitoring follow-ups and surgery preparation).

6. The term non-motor was removed for absence seizures (based on evidence that myoclonic absence and eyelid myoclonus may occur in absence).

7. Negative myoclonus was classified as seizure (it was not in the 2017 SC).

8. In generalized seizures, epileptic spasm was considered a seizure type, whereas focal seizures or seizures of unknown onset were considered part of the seizure semiology.

CONCLUSION

As a result, ILAE proposes the changes outlined in the 2017 SC in its electronic newsletter, which was published on August 12, 2024. This article summarizes the pre-2017 stages of seizure classification studies, the 2017 classification, and the e-mail survey evaluations conducted among members of the Turkish Epilepsy Society in 2018. The aim is to provide a comprehensive understanding of the subject and to remind readers of the process. Subsequently, the academic foundation for the changes proposed by the ILAE working group, based on a review of the database and the justifications for these changes, is presented in the words of the working group. The final version of the classification, along with the classifier and descriptor tables, was extracted from the original article and translated into Turkish without altering the terminology used in the 2017 SC.

As a result of this study, an updated document has been presented to us, and we are requested to submit our individual opinions by October 16, 2024. You can access the online form at the following link: https://www.surveymonkey.com/r/FY657FN. In this form, you can enter your name, e-mail address, title, or competency level, and, in the final box, share your opinions and contributions regarding the proposed classification. Together, we will explore the potential impact of the new proposals and assess whether they can address the shortcomings of the 2017 SC and what form they will take with the contributions from us and our colleagues worldwide.

Ethics

Authorship Contributions

Concept: S.B., M.B.Ç., G.K., Design: S.B., M.B.Ç., G.K., Data Collection or Processing: S.B., M.B.Ç., G.K., Analysis or Interpretation: S.B., M.B.Ç., G.K., Literature Search: S.B., M.B.Ç., G.K., Writing: S.B., M.B.Ç., G.K.

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Derleme / Review

Nöbet Sınıflandırma Çalışmalarında 2017'ye Yolculuk ve Sonrası: Yeni Teklifte Neler Var?

Journey to 2017 in Seizure Classification Studies and After: What is in the New Offer?

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Öz

Türk Epilepsi ile Savaş Derneği olarak yakın bağlantıda olduğumuz International League Against Epilepsy (ILAE), 12 Ağustos 2024 tarihinde "2017 Nöbet Sınıflamasının" (2017 NS) dünyada klinik uygulamadaki yerini değerlendirmek ve güncelleme önerilerinde bulunmak üzere oluşturulan çalışma grubunun ön çalışmalarını bitirdiğini açıklamıştır. Bu çalışma sonucunda güncelleme belgesi bizlere sunulmuş, 16 Ekim 2024 tarihine kadar bireysel görüşlerimiz istenmiştir. Bu yazıda, konuya hakimiyeti yaratmak ve süreci hatırlatmak için nöbet sınıflandırma çalışmalarının 2017 öncesi aşamaları, 2017 sınıflaması, Türk Epilepsi ile Savaş Derneği üyelerinin 2018 yılında yapılan e-posta anket değerlendirmeleri özetlenmiştir. Devamında ILAE çalışma grubunun öngördüğü değişikliklerin akademik zemini ve yapılan değişiklikler gerekçeleri ile beraber çalışma grubunun kendi ağzından maddeler halinde sunulmuştur. Sınıflamanın son hali, sınıflayıcı ve tanımlayıcı tabloları da orijinal yazıdan alınarak 2017 NS'de kullanılan terminolojide değişiklik yapılmayarak Türkçe olarak eklenmiştir. Yeni öneriler bizlere neler getirecek ve 2017 NS'nin eksiklerini giderebilecek mi, tüm dünyadan bizlerin ve meslektaşlarımızın katkıları ile hangi şekli alacağını hep birlikte göreceğiz.

Anahtar Kelimeler: Epilepsi, epileptik nöbet, International League Against Epilepsy, elektroensefalografi, taksonomi

Abstract

The Turkish Epilepsy Society, the International League Against Epilepsy (ILAE), our close ally, completed the preliminary evaluation of the study range on August 12, 2024. This evaluation included recommendations for updating the role of the "2017 Seizure Classification" (2017 SC) in clinical practice worldwide. Following this study, an update document was presented to us, and we were invited to provide individual opinions by October 16, 2024. In this article, we summarize the pre-2017 stages, the 2017 classification, the findings of the Turkish Epilepsy Society, and the results of an e-mail survey conducted in 2018. This summary aims to enhance the understanding of the subject and revisit the process. Furthermore, we incorporate the forward-looking scientific basis and explanations of the changes made by the ILAE task force, presented in the working group's own words. The final version of the classification, along with the classifier and descriptor tables, has been included in Turkey directly from the original article without altering the terminology used in the 2017 SC. We must consider what new options we propose and whether they will address the shortcomings of the 2017 SC. Together with colleagues from around the globe, we are committed to determining the future direction of this classification.

Keywords: Epilepsy, epileptic seizure, International League Against Epilepsy, electroencephalography, taxonomy

GİRİŞ

Türk Epilepsi ile Savaş Derneği olarak yakın bağlantıda olduğumuz International League Against Epilepsy (ILAE), 12 Ağustos 2024 tarihinde yayımladığı elektronik gazetesinde, İcra Komitesi'nin "2017 Nöbet Sınıflamasının" (2017 NS) dünyada klinik uygulamadaki yerini değerlendirmek ve güncelleme önerilerinde bulunmak üzere oluşturulan çalışma grubunun ön çalışmalarını bitirdiğini açıkladı. Bu çalışma sonucunda güncelleme belgesi bizlere sunularak 16 Ekim 2024 tarihine kadar bireysel görüşlerimiz istenmektedir. Yeni öneriler bizlere neler getirecek ve 2017 NS'nin eksiklerini giderebilecek midir?

2017 Nöbet Sınıflaması ile Sonuçlanan Tarihsel Süreç

Öncelikle nöbet sınıflamalarının tarih içerisinde yolculuğundan başlayarak 2017 NS'ye gelelim. 1964 yılından önce dünyada epilepsiye öncülük yapan kliniklerin bir şekilde kendi tanı, takip ve prognoz belirlemelerinde kullandıkları kendi sınıflamaları vardı. 1964 yılının Nisan ayında Marsilya'da Gastaut başkanlığında ILAE Avrupa grubundan 120 kişiyle ilk formal ortak sınıflama çalışmalarına başlandı. Altı ülkenin temsilcileri, Fransa, Almanya, İsveç, İngiltere, İspanya ve İtalya ön bir sınıflama oluşturdular. Bu çalışma Amerika ve Avrupa temsilcilerinden oluşan ILAE Terminoloji Komisyonu, Dünya Nöroloji Federasyonu ve Uluslararası Elektroensefalografi (EEG) ve Klinik Nörofizyoloji Cemiyetleri Federasyonu'nun temsilcilerinin katılımıyla Mayıs 1964'de Hollanda "Meer en Bosch" toplantısında görüşüldü. Yeni terimler oluşturulmaktan kaçınılarak bir sınıflandırma oluşturuldu.[1] Nöbetlerin klinik tipine göre temelde parsiyel nöbetler, jeneralize nöbetler, unilateral nöbetler (çocuklarda), yenidoğanın değişken nöbetleri ve sınıflandırılamayan nöbetler olmak üzere 5 ana başlığa ayrıldı. Bu şekliyle 1965 yılında Viyana'da 8. Uluslararası Nöroloji Kongresi'nde sunuldu.

1965 kongre sunumu sonrası sınıflandırma, 170 nörolog tarafından direkt Gastaut ile temasa geçilerek öneriler doğrultusunda şekilleniyor ve 1967'de New York'da son halini alıyor. Küçük terminolojik değişiklikler ile 1969 ILAE kongresinde sunuluyor.[2]

1969 sınıflamasının kabul görmesi sonrasında manyetik teyp üzerine nöbetlerin video kaydı ve eş zamanlı bölünmüş ekran üzerinde EEG kaydının incelenebildiği ve günümüzde video EEG monitörizasyon olarak tanımlanan objektif yöntemler artmıştır. 1975 yılında kompleks parsiyel nöbetler üzerine bir çalıştay ve takibinde 1977 yılında Berlin'de jeneralize epilepsiler üzerine düzenlenen bir çalıştay sonrasında bu sınıflama ile ilgili ana şema ortaya kondu. 1979 yılında Floransa'da kurulan komisyon yeni sınıflandırmanın planlanması için görevlendirildi. Komisyonun görevleri; video görüntüleri irdelenerek sınıflamanın revize edilmesi, sınıflamayı diğer uluslararası dernekler ile koordine etmek, sınıflamanın kullanımını yaygınlaştırmak, ortak terminolojiyi geliştirmek olarak belirlendi. 1980 yılında Kopenhag'da aynı süreç devam etti.

1981 sınıflamasında objektif bulgulardan ziyade spekülatif bilgiye dayandığı düşünülen anatomik ilişki, etiyoloji ve yaş kaldırıldı. İkinci ana değişiklik ise parsiyel nöbetlerde bilincin bozulup bozulmamasına göre basit ve kompleks ayrımının yapılmasıdır. Birçok epileptolog "kompleks" tanımlamasının kafa karıştırıcı olduğunu, bilincin korunup korunmamasından ziyade "yüksek kortikal bütünleşik fonksiyon bozukluğunu" çağrıştırdığını ifade etmiş olsalar da bu çabaları ancak 2017'de, yarım yüzyıl sonra, kabul görecektir. Sınıflama ile birlikte yayımlanan sözlük ile sorular cevaplanılmaya çalışılmıştır.[3] İlk kez bu sınıflamanın sunulduğu 1981 revizyon açıklamasının son paragrafında "epileptik sendrom sınıflamasının" komisyonun bir sonraki değineceği konu olduğunu belirtiliyor.

1989 sınıflandırması yaygın kullanımına rağmen parsiyel ve jeneralize dikotomisine takılması, idiyopatik-semptomatik-kriptojenik tanımlamalarının yanlış kullanılması, sınıflamadan ziyade bir gruplama yöntemi olarak değerlendirilebileceği için eleştirildi.

Uzun bir aradan sonra 1998 yılında Engel,[4] klinik kullanımı kolay ve klinik özellikleri ön plana çıkartan bir yenileme gerektiğini ortaya koydu. 2001 yılında ise iktal semiyoloji standardizasyonu için kollar sıvandı. Burada epilepsi sendromları başlığı altında liste sunuldu. Bu liste epilepsi sendromları ile epilepsi tanısı alması gerekmeyen epileptik nöbet durumlarını ayırdı. Ayrıca halen gelişmekte olan sendromlar da belirtildi. Ancak kabul görmüş sendromların hangi kriterleri karşılayarak bu listede yer aldığı sorusu yanıtsız kaldı. Örnek bir sınıflama sunulmuş ve başlangıç yaşının sınıflanmamış olması da en önemli eleştirilerden biri olarak yerini aldı.[5] Sonrasında karşılıklı atışmalar başladı. Wolf[6] "bu bir sınıflama değil tanısal düzenlemedir" derken Engel[7] "çalışmalar katkılarınız ile devam edecek" diyerek eleştiriyi yumuşattı. Luders ve ark.[8] ise "çok basamaklı, her seviyede merkez için kullanışlı değil (semiyolojik sınıflama daha kolay), sözlük ile sınıflama çalışmalarını karıştırmayın, önce deneyin sonra yayınlayın" diyerek sert çıkışırken Berg ve Blackstone[9] de "sistematik yaklaşılmadığı, sendrom tanımı bilinse de bunu sınıflarken veya kategorize ederken hangi kriterlerin kullanıldığının bilinmediği … sınıflandırmanın bilimsel amacı kolay kullanılabilir olması ile mümkün" şeklinde eleştiride bulundu.

Bu muhalif yazarlar da gruba katılarak Ağustos 2003, Aralık 2003 ve Mayıs 2005'te toplantı yapılarak bir çekirdek grup çalışması yapılıyor. Sendromun tanımında değişiklik yok ancak hangi özelliklerin değerlendirilmesi gerektiği konusu kararlaştırılıyor. Luders her ne kadar grupta çalışmaya devam edeceğini ifade etse de sonuç yazısında yazar olarak yer almak istemediğini belirtiyor.[10] Epileptik nöbetin tipi, başlangıç yaşı, progresif seyir, interiktal EEG, ilişkili interiktal belirti ve bulgular, patofizyolojik mekanizma, anatomik ilişki, etiyolojik kategori ve genetik zemin kriterleri kullanılarak epileptik sendromlar sınıflandırıldı.[11]

2010 yılında suların kısmen durulduğunu, gerçi iki tarafta da geri çekilme olmamakla beraber sanki herkesin kendi kabülüyle yola devam ediyor gibi göründüğünü görüyoruz. 2010 raporunda bir yandan epilepsi sınıflaması için belirgin terminoloji değişikliklerinin yanında (örneğin; idiyopatik yerine genetik, semptomatik yerine yapısal-metabolik kullanılması gibi) sendromik yaklaşımda da bazı değişiklikler sunuldu. Rapor sonucunda "geleceğe dönük yorumlarda aslında sınıflandırma çalışmalarının zaman içerisinde bir veritabanı haline geleceği, genel bilimsel ilerleme oldukça (epidemiyoloji, elektrofizyoloji, görüntüleme, gelişimsel nörobiyoloji, genomik, kompütasyonel sinirbilim ve nörokimya) basit ve katı kuralları olan otokratik yaklaşımın kaybolacağı düşünülmektedir" diye belirtildi. 2010 raporu ile ILAE yeni bir sınıflama değil ancak mevcut sınıflama sistemine zemin oluşturabilecek güncelleme yapmıştır.[12]

ANA NOKTALAR

- International League Against Epilepsy, 12 Ağustos 2024 tarihinde "2017 Nöbet Sınıflamasının" (2017 NS) güncelleme çalışmalarının tamamlandığını açıklamıştır.
- 2017 NS'de olduğu gibi temel amaç ortak bir dil ve çerçeve oluşturmak, esneklik sağlamak, her aşamada kullanılabilen, araştırmalara uygun, iyi tanımlanan bir sınıflama hazırlamaktır.
- Bu çalışma sonucunda güncelleme belgesi bizlere sunulmuş, 16 Ekim 2024 tarihine kadar bireysel görüşlerimiz istenmiştir.
- https://www.surveymonkey.com/r/FY657FN linkinde teklif edilen sınıflama konusundaki görüş ve katkılarınızı girebileceğiniz çevrimiçi forma ulaşabilirsiniz.

Berg[13] "daha yapılacak çok şey var" dedi ve 2013 yılında oluşturulan ekip 2017 yılında yeni sınıflama ile karşımıza çıktı.[14-17] 2017 NS kullanım uzmanlığına göre basit ve genişletilmiş sürüm olarak sunulmuştur.[18]

2017 Nöbet Sınıflaması

İlk aşama nöbetleri başlangıcına göre ayırmaktır. Başlangıcı izlenemeyen, kaydedilmemiş veya bilinmeyen nöbetler "başlangıcı bilinmeyen" alt başlığında incelenir. Başlangıcı izlenen ve/veya kaydedilen nöbetler ise fokal başlangıçlı veya jeneralize başlangıçlı olarak ayrılmaktadır. Fokal başlangıçlı nöbetler, bir hemisfere sınırlı ağlardan kaynaklanan, net bir şekilde tanımlanan veya yaygın bir dağılım gösteren, subkortikal yapılardan da kaynaklanabilen nöbetleri tanımlamak için kullanılmaktadır. Jeneralize başlangıçlı nöbetler ise aynı odaktan kaynaklanan ve hızla bilateral ağlara yayılan nöbetler için kullanılmalıdır.

Fokal başlangıçlı nöbetlerde sonraki aşama farkındalığın değerlendirilmesidir. Pratik olarak nöbet bittikten sonra hasta o nöbet sırasında farkında olduğunu ifade ediyorsa farkındalık korunmuştur. Hastanın nöbet sırasındaki muayenesinde sorulan sorulara cevap vermemesi veya verilen komutları uygulamaması farkındalığın korunmadığı anlamına gelmemektedir. Temel özellik hastanın nöbet sırasında yaşadıklarını hatırlaması ile ilişkilidir. Dikkat edilecek diğer özellik ise nöbet süresi içerisinde hasta herhangi bir dönem ve ne kadar süre olursa olsun farkındalığı kaybediyorsa, nöbetin mutlaka farkındalığı bozulmuş olarak sınıflandırılmasıdır. Farkındalık konusunda karar verilemiyorsa bu basamak atlanarak sınıflandırmaya devam edilir.

Fokal başlangıçlı nöbetlerde motor veya non-motor başlangıçlı olduğunu belirtmek yeterlidir. Motor ve non-motor bulguların açıklanması ve bilginin zenginleştirilmesi nöbet sınıflamasının genişletilmiş sürümünde yer almaktadır. Ayrı bir nöbet tipi olmamasına rağmen sık görülmesi ve öneminden dolayı "fokalden bilateral tonik kloniğe" geçiş ifadesi nöbet aktivitesinin yayılım paternini belirtmek için kullanılır.

Jeneralize başlangıçlı nöbetler ise motor ve non-motor (absans) olarak ikiye ayrılır. Jeneralize başlangıçlı nöbetlerin sınıflandırılmasında farkındalık derecesi kullanılmaz. Jeneralize motor nöbetleri sınıflandırmanın basit sürümünde sadece tonik-klonik veya diğer motor nöbetler şeklinde sınıflandırmak yeterlidir. Absans nöbetler ile fokal başlangıçlı farkındalığın bozulduğu nöbetlerin ayrımında EEG bilgisi gerekebilir.

1981 sınıflamasında bulunan basit parsiyel nöbet, kompleks parsiyel nöbet, sekonder jeneralize tonik klonik nöbet gibi tanımlamalar yıllarca kullanılmış olmasına rağmen sınırlılıklarının olması nedeniyle yeni sınıflamada yerlerini daha anlaşılır ve yaygın kullanılabilir ifadelere bırakmıştır. Özellikle de parsiyel nöbetlerde farkındalık durumunun bilinmediği durumlarda basit ve kompleks ayrımı yapılamadığı için sınıflandırmanın devam edememesi ve bu nöbetlerin sınıflandırılamayanlar başlığı altına alınması yeni sınıflamanın yapılması için en önemli motivasyon kaynaklarından birisi olmuştur. Eski sınıflamada yalnızca jeneralize nöbetler altında sınıflandırılan tonik, atonik, miyoklonik ve epileptik spazm fokal nöbetlerde de görülebilmesi nedeniyle yeni sınıflamada hem fokal hem jeneralize başlangıçlı nöbetler altında yer almıştır. Miyoklonik-tonik-klonik nöbetler gibi sık görülen ancak eski sınıflamada yer almayan nöbetler yeni sınıflamada kendilerine yer bulmuşlardır.

Kullanıldıkça olumlu ve olumsuz eleştiriler arttıkça yapılacak değişiklikler ile daha da kullanılabilir hale geleceği düşünülen bu sınıflamanın yaygın kullanımı teşvik edilmekteydi. Ta ki ILAE'nin 12 Ağustos 2024 günü yayımladığı elektronik gazeteye kadar…

Sınıflandırma çalışmalarının tarihsel süreci, gruplar arası çekişmeler ve en nihayetinde ortaya çıkan 2017 NS'yi gördük. Ama neden 2017 NS gerekliydi ve nasıl oluşturuldu? Bu soruyu kısaca yanıtlamak sınıflama çalışmalarının anlaşılması açısından önem taşımaktadır.

Bazı nöbet tipleri sınıflandırılamıyordu, başlangıcı görülmeyen nöbetler sınıflamasına oturmuyordu, bilinç veya şuur tanımı nörolojik muayenedeki klasik yeri haricinde nöbetlerde ortaya çıkan durumu karşılamıyordu. Hastanın nöbet sırasında şuuru kapanmıyor, klasik olarak bildiğimiz koma halini almıyor ve dolayısıyla bu durumun farklı bir şekilde tanımlanması gerekiyordu. Eski sınıflamalarda akıl karıştırıcı bazı terminolojik terimler kullanılmaktaydı; psişik, basit parsiyel (febril nöbetlerdeki basit kompleks ayrımından tamamen farklı olarak), kompleks parsiyel (kompleks terim olarak karmaşayı anlatan bir kelimedir ama nöbet tanımında bu akıl karıştırıcı oluyor) veya diskognitif gibi.

2017 NS sonuçta yepyeni bir sınıflama olarak değil ancak 1981 sınıflamasına bir yeniden yapılanma olarak gelmiş ve uluslararası hastalıklar kod sistemi (International Classification of Diseases) ile de uyumlu olarak düzenlenmiştir.

2024 Teklifi

2023 yılında kurulan bir çalışma grubu üç aşamada değerlendirme yaptı: 2017 NS'deki güçlü ve zayıf yönlerin belirlenmesi, teklif ve güncellemeleri belirlemek, geniş kapsamlı bir sonuca ulaşmak için yinelemeli bir Delphi süreciyle fikir birliği oluşturmaktır.

2023 başında 37 uzman ile bir çalışma grubu kuruldu. Hem erişkin hem de pediatrik epileptoloji konusunda uzman ve dünyanın farklı yerlerinden olmalarına özen gösterildi (Kuzey Amerika 7, Latin Amerika 5, Avrupa 11, Doğu Akdeniz 2, Asya Okyanusya 9 ve Afrikadan 9 üye). 2017 NS'yi geliştiren ekipten 4 kişi vardı. Nisan 2023, Mayıs 2023 ve Eylül 2023 toplantıları yapıldı.

2017 NS'nin güçlü ve zayıf yönlerinin belirlenmesi için sistematik bir değerlendirme yaptılar.[18] PubMed ve Embase veritabanlarını 2017 NS'nin uygulanabilirliğini değerlendiren araştırma yazıları, gözden geçirme ve yorum yazılarına göre taradılar. Yeterli bilgi içerdiği takdirde kongre bildirileri de taramaya dahil edildi. Toplam 41 makale değerlendirmeye alındı.

2017 NS'nin nöbetleri 4 ana kategoride incelemesi, başlangıcı bilinmeyen nöbetlerin sınıflamada yer alması güçlü yanları arasında görüldü. "Fokalden bilateral tonik klonik nöbete geçiş" konusunda farklı fikirler vardı ama yine de kullanışlı olduğu değerlendirildi. Ortak tanımlayıcıların fazla olması, fokal epileptik spazmın ayrıştırılması diğer güçlü yanlar arasındaydı.

Nöbet semiyolojisini tanımlamak için "farkındalık" teriminin uygunluğu konusunda güçlü bir tartışma ortaya çıktı.[19-22] Genel nörologlar için epileptik nöbet, bilincin geçici kaybı veya bozulmasında ayırıcı tanıda yer alır. Diğerleri için ise bilinç basitçe tepki verme ve hatırlama yeteneği olarak açıklanır. Hastanın

öyküsünün alınması sırasında yanıt verme yeteneğinin bozulduğu sıklıkla rapor edilir. Yanıt verebilme yeteneği de sıklıkla epilepsi merkezlerinde farkındalık üzerinden değerlendirilir. Dört yaş ve altında ise farkındalığı değerlendirmek pek de mümkün değildir.[23] Esas sıkıntılardan birisi ise farklı lisanlarda farkındalığın ve bilincin karşılığının benzer veya farklı olmasından kaynaklanmaktadır. "Bilinç" teriminin nörolojinin daha aşina olduğu bir terim olduğu kabul edilmektedir.

"Motor ve non-motor" tanımlamalarından ziyade "gözlenebilen bulgularla birlikte olan veya olmayan" şeklinde bir dikotomik kullanımın daha pratik olduğu değerlendirildi.[24] Tam olarak birebir anlam karşılanamamaktadır. Örneğin; non-motor afazik nöbetlerde bulgular gözlenebilirdir.

2017 NS'de absans nöbetlerin non-motor nöbet olarak sınıflandırılması yanıltıcıdır. Tipik absans nöbette net bir şekilde gözlenebilen belirgin otomatizma, baş titremesi, gözlerin kapaklarının kapanıp açılması ve atipik absans nöbetlerde ise atoni görülmektedir. Göz kapağı miyoklonisi veya absans sırasında görülebilen miyokloniler de bu gruptadır.

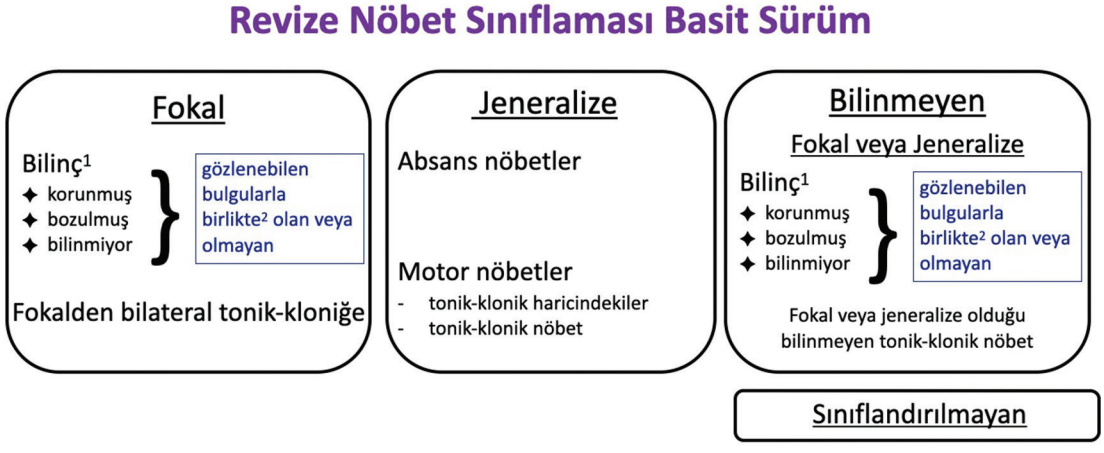
Metabolik ensefalopatilerde gözlenen asteriksten net bir şekilde farklı olan negatif miyoklonus ise yıllar içerisinde çok iyi tanımlanmış olmasına rağmen 2017 NS'de bulunmamaktadır.[25]

Gerek insan çalışmaları gerekse hayvan modellerinde jeneralize nöbetlerde fokal başlangıç gösterilmiştir.[26,27] 2017 NS'de "jeneralize başlangıç" bu açıdan değerlendirildiğinde yanlıştır.

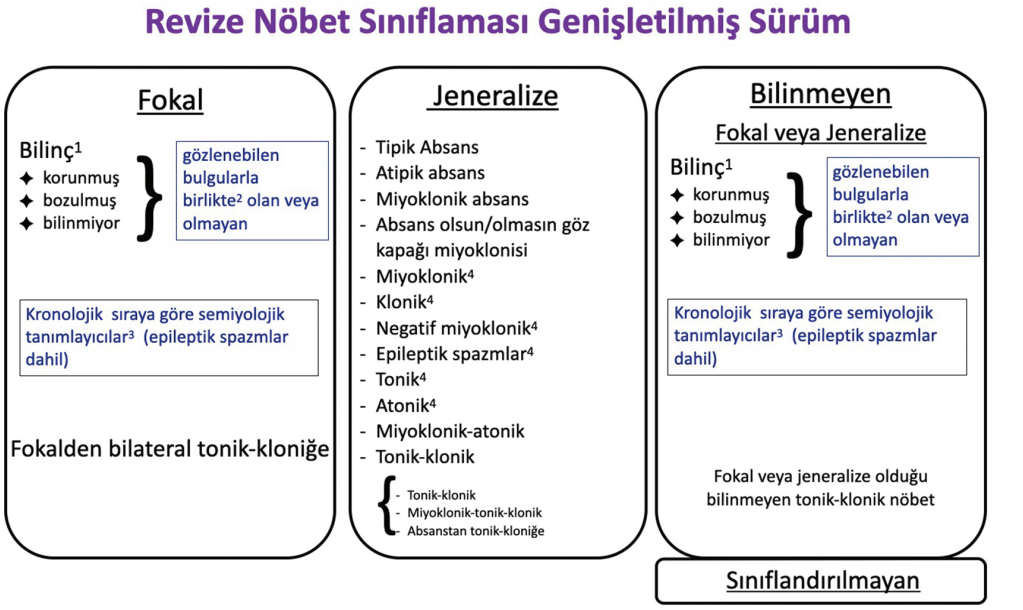
Sonuçta temel 4 ana kategoriye sadık kalındı. Şekil 1 ve 2'de basit ve genişletilmiş sınıflama sunuldu. Tablo 1'de nöbet sınıflamasının taksonomisinin hiyerarşisi gösterildi. "Sınıflayıcılar" nöbet tipini belirler ve direkt tanı, tedavi kararı, prognoz ile ilişkilidir. "Tanımlayıcılar" ise diğer klinik bilgiyle beraber hastanın genel menanjmanında önemlidir. Fokal nöbetler bir hemisfere sınırlı ağlardan kaynaklanır. Belirgin olarak ayrışmış veya daha dağınık olabilir, kortikal veya subkortikal kaynaklı olabilir. Her nöbet tipi için iktal başlangıç belirli ve karşı hemisfere doğru tercih ettiği yayılım paterni belli olabilir. Bazen de birden fazla ağ sorumludur ve birden fazla nöbet tipi ancak her bir tip nöbet için belirli bir başlangıç yeri vardır.

Fokalden bilateral tonik kliniğe geçiş yapan nöbetler her iki hemisfere yayılan fokal nöbetlerdir. Beraberinde semiyolojik olarak bilinç bozulur ve bilateral tonik klonik kas aktivitesi olur. Klonik faz ile kasılma frekansında belirgin azalma olur ve aradaki sessiz dönemler giderek uzar. Jeneralize nöbetler ise aynı noktadan başlayıp bilateral yayılım gösteren ağlara hızla entegre olan kortikal veya subkortikal yapıları içeren ama tüm korteksi içermeyen nöbetlerdir. Nöbet başlangıcı lokalize ve nöbetler de asimetrik görülebilir. Nöbeti fokal veya jeneralize olarak sınıflandıracak yeteri kadar bilgi yoksa "fokal veya jeneralize başladığı bilinmeyen" olarak sınıflandırabiliriz. Ancak klinisyen nöbet olduğundan emin ancak sınıflandırmaya yetecek kadar bilgi sahibi değilse bunları da "sınıflandırılamayan" başlığı altında değerlendirmelidir.

"Bilinç" tıbbi öyküden elde edilen veriye veya nöbet sırasında tıbbi personelin muayenesine göre, pratik olarak farkındalık ve yanıtlılığın değerlendirilmesiyle tanımlanır. Temel olarak hasta ve hasta yakınlarının anlayacağı şekilde nöbeti hatırlamak veya nöbet sırasında doğru yanıt verebilmek olarak tanımlanır. Hasta ve yakınlarına bilinç olarak sormaktansa nöbetin hatırlanması veya nöbet sırasında yanıtlılığın sorgulanması daha doğrudur. Burada uygunsuz yanıt veya interiktal döneme göre cevabın yararsız veya belirgin uzun sürede verilmesi de yanıtlılığın bozulması olarak değerlendirilmelidir. Hasta ve yakınlarına, hastanın gözleri açık olsa ve etrafla ilişkiye girmeye çalışsa dahi bilincin etkilenmiş olabileceği anlatılmalıdır. Öyküde sadece farkındalık veya yanıtlılık konusunda bilgi edinilmiş olabilir. Herhangi birisinin etkilenmesi durumunda "bilincin etkilendiği nöbet" olarak sınıflandırılmalıdır. Epileptik amnezi, iktal parezi veya iktal duyusal afazinin yanıtsızlığın temel nedeni olabileceği de akılda bulundurulmalıdır.



Şekil 1. Revize nöbet sınıflaması, basit sürüm



1. İşlevsel olarak farkındalık ve yanıtlılık olarak tanımlanır
2. Gözlenebilen bulgular gözlemci tarafından izlenmiş. Bunlar motor, afazik, otonomik veya diğer (Tablo 2) şekilde olabilir. Bilinçte bozulma gözlenebilen bulgudur.
3. ILAE semiyoloji sözlüğüne göre açıklandı (bkz tablo).
4. Bu olaylar fokal nöbetin semiyolojisinin bir bölümü olarak fokal nöbetlerde de (genellikle tek taraflı veya asimetrik) olabilir.

Sınıflayıcılar (nöbet tipleri) siyah, tanımlayıcılar mavi renkte verilmiştir.

Şekil 2. Revize nöbet sınıflaması genişletilmiş sürüm

Tanımlayıcılar nöbeti tanımlamakta ek özellikleri içerirler. Basit sürümde dikotomi çok nettir: Gözlenebilen bulguları olan ve olmayan. Gözlenebilen bulgular nöbeti izleyen kişinin çıplak gözle görebildikleri, istemli hareketlerin dışındaki bulgulardır (Tablo 2). Bilincin bozulması gözlenebilen bir bulgudur. Genişletilmiş sürümde nöbetler daha detaylı anlatılır ve kronolojik semiyolojik özellikler oklar ile sıraya sokulur. Örneğin epigastrik aura → sağ elde otomatizma → yanıtlılığın bozulması + farkındalığın bozulması. Tablo 2'de tanımlanan tüm özellikler ILAE sözlüğüne göre düzenlenmiştir.

Basit sınıflamada jeneralize nöbetler; absans ve jeneralize motor nöbetler olarak ayrılmıştır. İkincisi ayrıca belirgin motor bulguya göre tonik-klonik nöbetler ve diğerleri olarak tekrar ayrılmıştır. Genişletilmiş sürümdeyse tüm jeneralize nöbetler listelenmiş ve 2017 NS'ye ilaveten "jeneralize negatif miyoklonus" yerini almıştır.

Epileptik spazm jeneralize, fokal veya jeneralize/fokal ayrımı bilinmeyen olabilir. Jeneralize nöbetler arasında ayrı bir başlık olarak sunulmasına rağmen diğerleri semiyolojik özellik olarak alınmıştır.

Epileptik nöbetler taksonomik hiyerarşiye göre 4 ana başlık sonrası alt başlık ve nöbet tipleri olarak sıralanmıştır. 2017 NS'nin 63 nöbet tipini sıralamasına rağmen yeni yaklaşımda 20 nöbet listelenerek diğer nöbetleri tanımlayıcılar kullanarak belirtmek için esneklik sağlamaktadır (Tablo 2). Bir nöbetin özellikleri tam bilinene kadar bilinmeyen veya sınıflandırılamayan başlığı altında değerlendirmek gerekir. Bu özelliği ile 2017 NS ile benzerlik göstermektedir.

TARTIŞMA

Yeni sınıflandırma elbette ki 2017 NS'nin çatısı üzerine oturmuştur. Gerekli değişiklikler 2017 yılından beri elde edilen klinik tecrübenin üzerine yapılmıştır. Nitekim 2017 yılında yeni sınıflama kullanıma girdikten yaklaşık bir yıl sonra Mayıs 2018 Ulusal Epilepsi Kongresi öncesi Türk Epilepsi ile Savaş Derneği üyelerine mail yoluyla yapılan anket sonuçlarında biz de %92'si erişkin nöroloji uzmanı olan gruptan benzer sonuçlar elde etmiştik. %16'sı uzman ve %84'ü akademisyen olan grubun %97'si sınıflamayı biliyor ve %73'ü de sınıflamayı klinik pratiğinde kullanımına sokmuştu. Bu grubun sadece %35'i 2017 NS'nin 1981 sınıflaması yerine geçebileceğini ve yeterli olduğunu düşünürken; %56'sı bazı değişiklikler yapılması gerektiği ve ancak değişikliklerden sonra sınıflamanın kullanım için yeterli olacağı görüşünü sundular. Grubun %9'u ise 2017 NS'nin üzerinde değişiklik yapılsın ya da yapılmasın eski sınıflamanın yerini alamayacağı görüşünü bildirdi.

Biz de bu anket sonuçlarında katılımcılara katkı ve değişiklik önerilerini sorduğumuzda;

1. "Farkındalık" tanımının akıl karıştırıcı olabileceği ve "bilinç" tanımının daha doğru olabileceği,

2. Basit, kolay, anlaşılır ancak iyi öykü ya da video kayıtları gerektiği,

3. Kompleks parsiyel nöbet teriminin kalmasının tercih edildiği,

4. Tipik absans nöbetlerin basit ve kompleks diye ayrılmasının gerektiği,

Tablo 1. Epileptik nöbet sınıflamasının taksonomik hiyerarşisi

1. Fokal
1.1. Bilincin korunduğu fokal nöbet (BKF)
1.1. – 1. Gözlenebilen bulgularla birlikte
1.1. – 2. Gözlenebilen bulgularla birlikte olmayan
1.1. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
1.2. Bilincin bozulduğu fokal nöbet (BBF)
1.2. – 1. Gözlenebilen ek* bulgularla birlikte
1.2. – 2. Gözlenebilen ek* bulgularla birlikte olmayan
1.2. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
1.3. Bilinç durumunun bilinmediği fokal nöbet (BDBF)
1.3. – 1. Gözlenebilen bulgularla birlikte
1.3. – 2. Gözlenebilen bulgularla birlikte olmayan
1.3. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
1.4. Fokalden bilateral tonik-kloniğe nöbet
1.4. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler

2. Jeneralize
2.1. Absans nöbet
2.1.1. Tipik absans nöbet
2.1.2. Atipik absans nöbet
2.1.3. Miyoklonik absans nöbet
2.1.4. Absans olsun/olmasın göz kapağı miyoklonisi
2.2. Jeneralize motor nöbetler
2.2.1. Jeneralize motor nöbetler – tonik-klonik haricinde
2.2.1.1. Jeneralize miyoklonik (JM) nöbet
2.2.1.2. Jeneralize klonik nöbet
2.2.1.3. Jeneralize negatif miyoklonik nöbet
2.2.1.4. Jeneralize epileptik spazm
2.2.1.5. Jeneralize tonik (JT) nöbet
2.2.1.6. Jeneralize atonik nöbet
2.2.1.7. JM-atonik nöbet
2.2.2. JT-klonik nöbet
2.2.2.1. JT-klonik nöbet
2.2.2.2. Miyoklonik tonik-klonik nöbet
2.2.2.3. Absanstan tonik-kloniğe nöbet

3. Fokal veya jeneralize olduğu bilinmeyen nöbet
3.1. BFK veya jeneralize olduğu bilinmeyen nöbet
3.1. – 1. Gözlenebilen bulgularla birlikte
3.1. – 2. Gözlenebilen bulgularla birlikte olmayan
3.1. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
3.2. BBF veya jeneralize olduğu bilinmeyen nöbet
3.2. – 1. Gözlenebilen ek* bulgularla birlikte
3.2. – 2. Gözlenebilen ek* bulgularla birlikte olmayan
3.2. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
3.3. BDBF veya jeneralize olduğu bilinmeyen nöbet
3.3. – 1. Gözlenebilen bulgularla birlikte
3.3. – 2. Gözlenebilen bulgularla birlikte olmayan
3.3. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler
3.4. Fokal veya jeneralize olduğu bilinmeyen tonik-klonik nöbet
3.4. – 3. Semiyolojik tanımlayıcılar kronolojik sırayla: Semiyoloji (sözlük**) + Somatotopik modifiye ediciler

4. **Sınıflanmayan**

Sınıflayıcılar siyah, tanımlayıcılar maviyle renklendirilmiştir. Ana sınıflar kalın karakterle ve nöbet tipleri ise altı çizili karakterle gösterildi. Numaralandırmada kullanılan ara çizgi (-) solda sınıflayıcı ile sağda tanımlayıcıyı ayırır. Basit sürümde tanımlayıcılar 1 ve 2, genişletilmiş sürümde ise 3 ile numaralandırıldı

Tablo 2. Semiyoloji özellikleri

Somatotopik modifiye ediciler
Taraf (sol, sağ, bilateral-simetril, bilateral-asimetrik) + vücut parçası

1. Elementer motor olay*
Akinetik
Astatik
Atonik
Klonik
Distonik
Epileptik nistagmus
Epileptik spazm
Göz kırpma
Göz deviasyonu
Giratuvar
Baş oryantasyonu
İktal parezi
Miyoklonik
Miyoklonik-atonik
Negatif miyoklonus
Tonik (fokal tonik, jandarma şapkası, eskrimci postürü)
Tonik-klonik (dört işareti)
Versif

2. Kompleks motor olay*
Otomatizma
- Vücut otomatizması-distal
- Vücut otomatizması-genital
- Vücut otomatizması-proksimal
- İktal yakalama
- Mimik otomatizması (jelastik, dakristik)
- Oro-alimenter otomatizma
- Verbal otomatizma
- Vokal otomatizma
Hiperkinetik davranış

3. Duyusal olay**
İşitsel
Vücut-persepsiyon ilüzyonu
Depersonalizasyon
Gustatuvar
Olfaktör
Somatosensöriyel
- Ağrılı
- Ağrısız
Vestibüler/sersemlik hali
Görsel

4. Bilişsel ve lisan olayı#
Afazi
Dismenzi
- Amnezi
- Deja vu/jamais vu/rüya hali/anımsama
Zorlu düşünce

5. Otonomik olay#
Kardiyovasküler
- İktal asistol
- İktal bradikardi
- İktal taşikardi
Kutanöz/termoregülatuvar
- Flashing
- Piloereksiyon
- Terleme
Epigastrik
Gastrointestinal
- Gaz çıkartma
- Hipersalivasyon
- Mide bulantısı/kusma
- Salya akması
- Tükürme
Pupiller
- Miyozis
- Midriazis
Respiratuvar
- Apne
- Öksürme
- Hiperventilasyon
- Hipoventilasyon
Üriner
- İnkontinans
- İdare sıkışma

6. Efektif (emosyonel) olay#
Öfke
Anksiyete
Coşku/keyif
Korku
Suçluluk
Neşe
Mistik
Üzüntü
Seksüel

7. Tanımlanamayan aura**

Postiktal olay
Otonomik bulgular
Körlük (hemianopi veya amaroz)
Konfüzyon
Baş ağrısı
Lisan fonksiyon bozukluğu
Burun silme
Palinakoz
Parezi (Todd paralizisi)
Psikiyatrik bulgular
Yanıtsızlık

*Gözlenebilen bulgular, **gözlenemeyen bulgular, #gözlenmesi mümkün olan bulgular. Yukarıda listelenen olaylar içinde yer almayan bir bulgu gözlemlendiğinde metin olarak eklenir. Farkındalık ve yanıtlılık, bilinci tanımlar ve sınıflayıcılar arasında yer alır. Tabloda tanımlanan tüm maddeler semiyoloji sözlüğünde yer almaktadır

5. Yeni sınıflamanın halen net olmayan, didaktik olmayan, klinik ve araştırmalardaki sorunları çözmeyen bir yapıda olduğu,

6. Sekonder jeneralizasyon yerine bilateral jeneralize tonik klonik denmesinin birbirini tam karşılamadığı,

7. Pratik kolay söylenebilecek tanımlar yerine nöbetlerin semiyolojik detaylarında boğulan bir sınıflama olduğu,

8. Kolay ve kullanılabilir olmadığı,

9. Fokal başlayıp jeneralize olan epileptik nöbetlerin iyi kategorize edilemediği ve

10. Epileptik sendromları tanımlamada eksik olduğu yanıtları verilmişti.

Yukarıda alınan yanıtlar ana hatlarıyla ILAE çekirdek grubunun veritabanı taraması sonucu elde ettiği yanıtlar ile örtüşmektedir. Kendileri de zaten mevcut yeni yapılan değişiklikleri veritabanından elde edilen sonuçlar ışığında yapıldığını ifade etmektedirler.

2017 NS'de olduğu gibi temel amaç ortak bir dil ve çerçeve oluşturmak, esneklik sağlamak, birinci basamaktan üçüncü basamağa kadar her aşamada kullanılabilen, araştırmalara uygun, iyi tanımlanan bir zemin hazırlamaktır. Taksonomik kurallar çerçevesinde 4 ana başlık, iki alt sınıf (jeneralize nöbetlerde) ve toplam 20 nöbet tipi tanımlandı. Sınıflamayı olabildiğince basit kılmak için yeni terim tanımlamaktan kaçınılarak hasta ve hasta yakınları ile de ortak bir dil kullanılması amaçlandı.

Yapılan değişiklikler;

1. Ana 4 gruptan "Başlangıç" ifadesi kaldırıldı (özellikle fokal başlangıçlı jeneralize nöbetlerin olduğu kanıtına dayanılarak).

2. Taksonomik kurallar çerçevesinde sınıflayıcılar ve tanımlayıcılar birbirinden ayrıldı.

3. Sınıflayıcı olarak "farkındalık" ifadesi kaldırılarak "bilinç" terimi kullanıldı (bilincin işlevsel anlamda hem farkındalık hem de yanıtlılığı tanımladığı kanıtına dayanılarak).

4. Motor ve non-motor dikotomisi yerine "gözlenebilen bulgularla birlikte olan veya olmayan" kullanıldı (klinik çalışmalar için daha faydalı olacağı değerlendirildi).

5. Nöbeti açıklamak için ilk bulguya güvenmekten ziyade nöbet semiyolojisinin kronolojik olarak sıralanması sağlandı (sadece nöbetin ilk bulgu değil ama özellikle video EEG monitörizasyon takipleri ve cerrahi hazırlığında tüm bulguların sıralı olarak değerlendirilmesinin daha doğru olduğu kanıtına dayanarak).

6. Absans nöbetler için non-motor ifadesi kaldırıldı (miyoklonik absans ve absansta göz kapağı miyoklonileri olabildiği kanıtına dayanılarak).

7. Negatif miyoklonus nöbet sınıflamasına alındı (2017 NS'de yoktu).

8. Jeneralize nöbetlerde epileptik spazm bir nöbet tipi olarak kabul edilirken fokal nöbetler veya başlangıcı bilinmeyen nöbetlerde nöbet semiyolojisinin bir parçası olarak kabul edildi.

SONUÇ

Sonuç olarak ILAE 12 Ağustos 2024 tarihinde yayımladığı elektronik gazetesinde 2017 NS'de yukarıda sıralanan değişiklikleri teklif etmektedir. Bu yazıda, konuya hakimiyeti yaratmak ve süreci hatırlatmak için nöbet sınıflandırma çalışmalarının 2017 öncesi aşamaları, 2017 sınıflaması, Türk Epilepsi ile Savaş Derneği üyelerinin 2018 yılında yapılan e-posta anket değerlendirmeleri özetlendi. Devamında ILAE çalışma grubunun veritabanı incelemesi sonucu öngördüğü değişikliklerin akademik zemini ve yapılan değişiklikler gerekçeleri ile beraber çalışma grubunun kendi ağzından maddeler halinde sunuldu. Sınıflamanın son hali, sınıflayıcı ve tanımlayıcı tabloları da orijinal yazıdan alınarak 2017 NS'de kullanılan terminolojide değişiklik yapılmayarak Türkçe olarak eklendi.

Bu çalışma sonucunda güncelleme belgesi bizlere sunularak 16 Ekim 2024 tarihine kadar bireysel görüşlerimiz istenmektedir. https://www.surveymonkey.com/r/FY657FN linkinde pratik olarak isminizi, e-posta adresinizi, ünvan veya yetkinlik düzeyinizi ve son kutucukta da teklif edilen sınıflama konusundaki görüş ve katkılarınızı girebileceğiniz çevrimiçi forma ulaşabilirsiniz. Yeni öneriler bizlere neler getirecek ve 2017 NS'nin eksiklerini giderebilecek mi, tüm dünyadan bizlerin ve meslektaşlarımızın katkıları ile hangi şekli alacağını hep birlikte göreceğiz.

Etik

Yazarlık Katkıları

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Relationship Between Cognitive Impairments and Serum Orexin Levels in Epilepsy Patients

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Abstract

Objective: Recent studies on neurodegenerative diseases have indicated that Orexin A plays a role in cognitive impairment. Furthermore, animal studies have demonstrated that Orexin A enhances synaptic plasticity in the hippocampus. The present study aimed to investigate the potential effect of orexin A on cognitive decline in patients with epilepsy.

Methods: This study included patients with epilepsy (patient group), including those with idiopathic generalized epilepsy (IGE subgroup) (n=24) and mesial temporal lobe epilepsy (mTLE subgroup) (n=17), and healthy controls (control group) (n=27), all aged 18-65 years. The Wechsler Memory Scale (WMS) visual memory subtest and Oktem Verbal Memory Processes Test (OVMPT) (15-word Turkish verbal learning memory test) were administered to all participants. Serum Orexin A levels were measured using enzyme-linked immunosorbent assay.

Results: The mean Orexin A level in the control group was 25.84±14.65 pg mL^{-1}, versus 24.57±12.50 pg mL^{-1} in the IGE group and 23.01±12.86 pg mL^{-1} in the mTLE group. There were no significant differences in the Orexin A level between any of the groups/subgroups. Moreover, no significant correlation was observed between the Orexin A level, WMS visual memory subtest, and OVMPT scores.

Conclusion: Our findings showed no association between the Orexin A level and cognitive impairment in patients with epilepsy. Further studies are needed to clarify the complex role of Orexin A in cognitive function.

Keywords: Cognitive, epilepsy, Orexin A

INTRODUCTION

Epilepsy is a chronic disease of the central nervous system (CNS) characterized by a variety of recurrent and unpredictable seizures caused by an imbalance in neuronal electrical activity.[1] Epilepsy is one of the most common neurological diseases in the world, with an estimated prevalence of 6.38 per 1000 person.[2,3] Cognitive impairment is frequently observed in patients with epilepsy and is often characterized by mental slowing, memory disorders, and attention deficit.[4]

Orexin A is synthesized by a cluster of neurons located in the lateral hypothalamus and perifornical area.[5] Orexin neurons are multitasking neurons that regulate several vital body functions, including sleep/awake states, eating behavior, energy homeostasis, reward systems, cognition, and mood.[6]

Animal studies have indicated that the orexinergic system might increase hippocampal neurogenesis, which is known to affect learning and memory positively. These studies revealed that orexin/ataxin-3 transgenic mice lacked long-term social memory and that nasal administration of exogenous Orexin A restored social memory and increased synaptic plasticity in the hippocampus.[7] Orexin A has also been shown to enhance the long-term potentiation (LTP), which plays a critical role in attention and memory.[8] It was reported that local dentate gyrus perfusion with Orexin A in rats under anesthesia increased LTP and strengthened the link between structural and functional hippocampal plasticity. It was also shown in the same study that providing SB-334867, an orexin 1 receptor (Ox1R) antagonist, to the rats blocked the increase in LTP.[9] A study examining the absence of epilepsy and the orexin system in rats showed that rats with epilepsy had decreased levels of orexin receptor type 1 protein (OX1) compared with rats without epilepsy. The authors suggested that the orexin system is involved in the pathophysiology of epilepsy in patients without epilepsy.[10]

Clinical studies have increased with the occurrence of the importance of the role of Orexin A in narcolepsy in neurological diseases. Recently, various studies have been conducted on several neurological diseases, such as Alzheimer's disease, Parkinson's disease, and stroke.[11-15] A previous study revealed that Orexin increased amyloid-β accumulation and prevented amyloid-β degradation in Alzheimer's disease patients, leading to neurodegeneration and cognitive impairment.[13-15] A review study on stroke showed that the Orexin system improved memory by modulating other neurotransmitters after stroke.[12] However, very few studies have investigated the relationship between Orexin A and epilepsy.[16,17] Few studies have focused on the relationship between seizures and Orexin A; however, the results were inconsistent. Only one study examined the relationship between Orexin A and cognitive impairment in epilepsy patients in 2023 and suggested that lower Orexin A levels in epilepsy patients may be associated with cognitive damage.[18]

In this context, this study aimed to determine whether there is a relationship between Orexin A levels and cognitive impairment in patients with epilepsy using the Wechsler memory scale (WMS) visual memory subtest and Oktem Verbal Memory Processes Test (OVMPT) and to contribute to the literature.

METHODS

Study Design

This study was conducted at the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, İzmir, Turkey, between April 2020 and November 2020. The İzmir Tepecik Training and Research Hospital Ethics Committee approved the study protocol, and all procedures were followed according to the ethical standards outlined in the Declaration of Helsinki (decision no: 3, date: 21.02.2020). Written informed consent was obtained from all participants, and the study protocol, potential hazards, and benefits were explained to all participants.

Participants and Seizure Classification

The study included participants aged between 18-65, followed up for mesial temporal lobe epilepsy (mTLE) and idiopathic generalized epilepsy (IGE) and healthy controls who agreed to participate in the study. The patient sample consisted of patients with epilepsy diagnosed according to the clinical epilepsy diagnosis criteria established by the International League Against Epilepsy (ILAE) in 2014 and followed up in the epilepsy outpatient clinic. IGEs, which include the following four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone, were determined according to the ILAE 2017 classification of epilepsies. mTLE was defined as patients with one of the familial mTLE (FmTLE) or mTLE with hippocampal sclerosis syndromes according to the ILAE 2017 epilepsy classification.

MAIN POINTS

- Orexin A is a multitasking neuropeptide that plays a role in several aspects, including sleep/wake states, eating behavior, and energy homeostasis.
- Animal studies have shown that Orexin A can enhance synaptic plasticity in the hippocampus.
- Recent research on neurodegenerative diseases has revealed that Orexin A plays a role in cognitive function.
- Our findings did not indicate a relationship between cognitive impairment and Orexin A levels in patients with epilepsy.

The exclusion criteria for all participants were as follows: diagnosis of dementia or cognitive impairment, comorbid psychiatric disorders, such as anxiety and mood disorders, concomitant CNS diseases, ongoing use of opioids, and CNS stimulants.

Cognitive tests and Orexin A level measurements were performed after the post-ictal period was over in order not to affect the results in patients with frequent seizures.

Assessment of the Seizure-free State, Drug Sensitivity, and Seizure Frequency

Patients' demographic characteristics, other chronic illnesses, and the medications they have been using were recorded. Patients who could not attain long-term seizure-free status despite receiving ≥2 appropriate antiepileptic drugs alone or in combination were defined as drug resistant according to the ILAE 2010 criteria. The patient group was divided into three subgroups according to the frequency of seizures: rare seizures subgroup: <1 seizures per year; sporadic seizures subgroup: 1 to 11 seizures per year; frequent seizures subgroup: 1 to 4 seizures per month. No patient experienced >4 seizures per month.

Orexin A Measurements

Blood samples to measure serum Orexin A levels were collected 10 mL peripheral blood from each participant between 8:00 and 9:00 a.m., according to the diurnal rhythm. Blood samples were centrifuged (2500 g for 15 min) within 1 h of collection and then kept frozen at -80 °C until assay. Blinded researchers determined serum NFL concentrations for clinical diagnosis. Serum Orexin A levels within the 10-1280 pg mL^{-1} range were measured using enzyme-linked immunosorbent assay method. Blood samples were taken from each participant into a clot-activating tube with a gel separator (BD Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm, NJ, USA).

Statistical Analysis

The collected research data were analyzed using the Statistical Package for the Social Sciences 21.0 (Statistical Product and Service Solutions for Windows, version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package and MS Excel 2007 (Microsoft Excel 2007, Microsoft Corporation, Redmond, Washington U.S., retrieved from https://office.microsoft.com/excel) software. The normal distribution characteristics of continuous variables, including age, WMS short- and long-term memory scores, OVMPT immediate memory score, maximum learning number, spontaneous recall, total recall, total learning scores, and Orexin A level, were analyzed using the Shapiro-Wilk test. Additionally, the Kruskal-Wallis non-parametric analysis of variance (ANOVA) was used to compare the WMS STMS and OVMPT immediate memory, maximum learning, 40-min. delayed spontaneous recall, and total recall scores between the groups/subgroups (GE subgroup, TE subgroup, and control group). The Bonferroni correction was applied to the paired comparisons. In cases in which one-

way ANOVA revealed a significant difference, post hoc pairwise comparisons were conducted to identify the group/subgroup that significantly differed from other groups/subgroups. The Mann-Whitney U test was used to compare changes in Oexin A level, WMS short - and long-term memory scores, OVMPT immediate memory, maximum learning, spontaneous recall, and total recall scores in patient and control groups with variables of education level, drug sensitivity, and response to treatment. Spearman's non-parametric correlation analysis determined the correlation between the Orexin A level, WMS short - and long-term memory scores, and OVMPT immediate memory, maximum learning, 40-min delayed spontaneous recall, total recall, and total learning scores. Probability (p) statistics of <0.05 indicated statistical significance.

RESULTS

Baseline Characteristics

The study sample consisted of 41 patients aged 18-65 years diagnosed with epilepsy (patient group) and 27 age- and sex-matched healthy controls (control group). Of the 24 patients with IGE, 16 had tonic-clonic epilepsy or tonic-clonic epilepsy+ absence/myoclonic epilepsy, 5 had pure myoclonic epilepsy, and 3 had pure absence epilepsy. The mean age of the patient and control groups was 35.56±12.05 years (range: 18-60 years), and the mean age of the control group was 36.93±12.44 years (range: 19-58 years). In the patient group, 73.2% (n=30) were female, 26.8% (n=11) were male, 58.5% (n=24) graduated from a primary school or had a lower level of education, and 41.5% (n=17) graduated from a high school or had a higher level of education. In the control group, 51.9% (n=14) were female, 48.1% (n=13) were male, 48.1% (n=13) graduated from a primary school or had a lower level of education, and 51.9% (n=14) graduated from a high school or had a higher level of education (Table 1).

Overall, 24 (58.5%) patients had IGE, 17 (41.5%) had mTLE, 33% had frequent seizures, 67% were treatment-resistant, and ≈50% were on a single medication. Participants' demographic and clinical characteristics are shown in Table 1. The mean age at seizure onset was 16.48±12.06 years, and the mean disease duration was 17.27±12.43 years.

Relationships Among WMS Score, Demographic, and Clinical Characteristics

WMS short and long memory scores were analyzed separately by pairwise comparisons among the three subgroups (mTLE, IGE, and control groups). Pairwise comparisons analysis revealed that the WMS visual memory subtest short-term memory scores (WMS-STMS) were significantly lower in the IGE subgroup than in the control group (p=0.015); there were no statistically significant differences between mTLE-IGE and mTLE-control subgroups (p=1.000 and p=0.090, respectively). The results also revealed that the WMS long-term memory scores (WMS-LTMS) were significantly lower in the GE and TLE subgroups than in the control group (p=0.012 and p=0.026, respectively). Still, there was no statistical difference between the IGE and mTLE subgroups in terms of WMS-LTMS scores (p=1.000). All groups' WMS-LTMS and WMS-STMS scores decreased significantly with age (Spearman's correlation coefficient=-0.257, p=0.034 and Spearman's correlation coefficient=-0.277, p=0.022, respectively).

Table 1. Patients' characteristics

	Patient group [n=41 (%)]	Control group [n=27 (%)]
Age*	35.56±12.05	36.93±12.44
Gender (female/male)	30/11 (73.2/26.8)	14/13 (51.9/48.1)
Level of education (≤primary, ≥high school)	24/17 (58.5/41.5)	13/14 (48.1/51.9)
The type of epilepsy		
Idiopathic generalized epilepsy	24 (58.5)	
Tonic-clonic epilepsy±absence/myoclonic epilepsy	16 (39.0)	
Pure myoclonic epilepsy	5 (12.0)	
Pure-absence epilepsy	3 (7.0)	
Temporal lobe epilepsy	17 (41.5)	
Seizure frequency		
Low	16 (39.0)	
Sporadic	12 (29.3)	
Frequent	13 (31.7)	
AED medication		
Monotherapy	20 (48.7)	
Carbamazepine	3 (7.3)	
Valproate	7 (17.1)	
Lamotrigine	6 (14.6)	
Levetiracetam	3 (7.3)	
Oxcarbazepine	1 (2.4)	
Polytherapy	21 (51.3)	
Response to treatment		
Responsive	16 (39.0)	
Drug-resistant	25 (61.0)	

*Mean±standart deviation.
AED: Antiepileptic drugs

The mean WMS-LTMS and WMS-STMS scores in all groups who graduated from a high school or had a higher education level were higher than those who graduated from a primary school or had a lower education level ($p<0.001$ and $p<0.001$, respectively). The WMS-LTMS and WMS-STMS scores of the patients who received monotherapy were significantly higher than those who received polytherapy in the analysis of all epilepsy patients ($p=0.010$ and $p=0.010$, respectively). Additionally, there was no significant difference between the WMS-LTMS and WMS-STMS median scores between the groups based on treatment response or seizure frequency ($p=0.864$ and $p=0.470$, respectively).

The mean OVMPT immediate memory, maximum learning, 40-min delayed spontaneous recall, total recall, and total learning scores were highest in the control group and lowest in the TLE subgroup ($p=0.045$, $p=0.007$, $p=0.001$, $p<0.001$ and $p<0.001$, respectively). Pairwise comparisons analysis revealed that the OVMPT maximum learning and 40-min delayed spontaneous recall scores were significantly lower in the TLE subgroup than in the control group ($p=0.005$ and $p<0.001$, respectively). There was no significant relationship between immediate memory after OVMPT, frequency of seizures, or number of medications used ($p=0.761$, $p=0.198$, and $p=0.279$, respectively). On the other hand, no significant difference was observed between the OVMPT 40-min delayed spontaneous recall scores and response to treatment and the number of drugs used. Still, a negative correlation was revealed with the frequency of seizures. The OVMPT immediate memory and 40-min delayed spontaneous recall scores decreased significantly with age in all groups ($p=0.002$ and $p=0.003$, respectively).

Relationships Between Orexin A Levels and Demographic and Clinical Characteristics

The mean Orexin A level was 23.92±12.52 pg mL^{-1} in the patient group and 25.84±14.65 pg mL^{-1} in the control group. The mean Orexin A level was 24.57±12.50 pg mL^{-1} in the IGE group and 23.01±12.86 pg mL^{-1} in the mTLE group (Figure 1). The patient and control groups did not exhibit any significant differences in terms of Orexin A levels; moreover, there was no significant difference between the IGE and mTLE subgroups in the Orexin A level ($p=0.721$ and $p=0.771$, respectively). In parallel, triple comparisons did not reveal any significant difference in the Orexin A level between the IGE, mTLE, and control subgroups ($p=0.899$).

There was no significant relationship between Orexin A level and age ($p=0.883$) or level of education ($p=0.464$). Orexin A levels did not significantly differ according to the frequency of seizures, response to treatment, and the number of medications used ($p=0.663$, $p=0.062$, and $p=0.006$, respectively). There was also no significant relationship between the Orexin A level and the WMS-STMS and WMS-LTMS scores, and the OVMPT immediate memory, OVMPT total learning, and 40-min delayed spontaneous recall scores ($p=0.251$, $p=0.629$, $p=0.549$, $p=0.550$, and $p=0.0621$, respectively) (Table 2).

DISCUSSION

This study was conducted to determine the role of Orexin A in cognitive impairment in patients with epilepsy. However, the findings revealed that the orexin A level in patients with epilepsy was not correlated with the OVMPT verbal and WMS visual memory test scores. Therefore, there was no relationship between Orexin A and cognitive damage in patients with epilepsy. Additionally, in our study, no significant difference was found between the Orexin A levels of patients with epilepsy and healthy controls. There is a severe shortage of literature on Orexin A and cognitive damage in patients with epilepsy. A study that explored a scientific question similar to ours reached different conclusions. Li et al.[18] conducted a retrospective study investigating the relationship between Orexin A and cognitive damage in 77 patients with epilepsy and 65 controls. In this study, non-specific screening test MMSE scores were used to detect cognitive damage, and MMSE scores in patients with epilepsy were found to be lower than those in healthy controls. They also found that the Orexin A level was lower in patients with epilepsy than in controls. The multivariate analysis concluded that lower Orexin A levels were an independent risk factor for cognitive impairment in epileptic patients. Further studies are necessary to establish the association between the orexinergic system and cognitive impairment in patients with epilepsy.

On the other hand, clinical studies examining the relationship between epilepsy and Orexin A have primarily focused on the relationship between Orexin A and seizure pathophysiology. One of these studies reported that the CSF Orexin A level measured within 48 hours after the seizure was significantly lower in 21 patients than in the control subjects and that patients with recurrent seizures had the lowest Orexin A levels. Based on these findings, the authors suggested that Orexin A deficiency plays a role in the complex pathophysiology of recurrent generalized tonic-clonic seizures and status epilepticus and may be associated with post-seizure somnolence.[17] A study on paroxysmal sleep disorder biomarkers reported that the serum Orexin A level was lower in epileptic children without seizures than in children with parasomnia; however, the Orexin A level increased after a seizure in children who had seizures during polysomnography. The authors of the said study attributed these findings to an increase in the permeability of the blood-brain barrier during an epileptic attack or to the synthesis of Orexin A during seizures due to neuroprotective/anticonvulsant function.[16] In our study, because of these uncertain results, Orexin A samples were collected after the post-ictal period ended in patients with frequent seizures. Our study did not observe a significant relationship between the Orexin A level and seizure frequency under the given conditions.

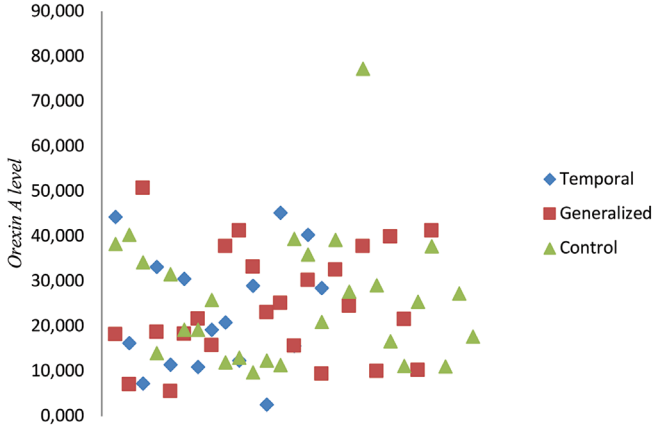

Figure 1. Distribution of Orexin A level by group/subgroup

Table 2. Comparison of Orexin A levels and visual and auditory memory test results among groups/subgroups

	IGE (n=24) Mean±SD Median (IQR)	mTLE (n=17) Mean±SD Median (IQR)	Controls (n=27) Mean±SD Median (IQR)	p value
Orexin A level (pg mL^{-1})	24.57±12.50 pg mL^{-1} 22.38 (20.9)	23.01±12.86 pg/mL^{-1} 20.84 (19.9)	25.84±14.65 pg/mL^{-1} 25.4 (22.9)	0.899
WMS STMS	9.50±3.57 10.0 (5.8)	10.29±2.62 10.0 (5.0)	12.11±1.48 12.0 (3.0)	0.011
WMS LTMS	7.00±3.92 7.0 (6.8)	7.00±2.81 7.0 (5.5)	9.59±2.34 9.0 (3.0)	0.005
OVMPT immediate memory	4.97±1.25 5.0 (1.8)	4.23±1.79 5.0 (2.0)	5.44±1.53 5.0 (1.0)	0.045
OVMPT maximum learning score	14.21±1.38 15.0 (1.0)	13.06±2.13 14.0 (4.0)	14.74±0.59 15.0 (0.0)	0.007
OVMPT 40-min delayed spontaneous recall score	10.58±2.78 10.5 (4.8)	8.35±1.93 9.0 (3.0)	11.59±2.45 12.0 (4.0)	0.001
OVMPT total recall score	13.37±1.81 14.0 (3.0)	11.94±1.39 12.0 (2.0)	14.29±0.99 15.0 (1.0)	<0.001
OVMPT total learning score	115.08±17.33 117.0 (24.5)	95.53±18.45 102.0 (34.5)	122.93±13.5 124.0 (22.0)	<0.001

SD: Standard deviation, IQR: Interquartile range, WMS STMS: Wechsler memory scale short test of mental status, OVMPT: Oktem verbal memory processes test, LTMS: Long-term memory scores, IGE: Idiopathic generalized epilepsy, mTLE: mesial temporal lobe epilepsy

Orexin neurons are predominantly located in the temporal region, and animal studies have revealed that orexin may affect hippocampal neurogenesis. Considering these findings, specific cognitive tests that measure hippocampal function may provide more accurate results than non-specific screening tests. As a matter of fact, in our study, we selected the WMS Visual Memory Subtest and OVMPT, which evaluate hippocampal function. In our study, the OVMPT 40-min delayed spontaneous recall and total recall test scores, which are indicators of long-term verbal memory, were highest in the control group and significantly lower in the mTLE subgroup. In addition, WMS-LTMS scores, which are indicators of long-term visual memory, were substantially lower in the IGE and mTLE subgroups compared with the control group. Memory disorders are expected because TLE originates from the hippocampal and related temporolimbic structures. "Long-term memory" (retrieval of newly learned information) impairment is typically observed in patients with mTLE, and verbal or visual memory impairment is also observed depending on language dominance in the affected temporal hemisphere[19-21] Numerous studies have shown that patients with IGE may have cognitive impairments, such as worsening executive skills, attention deficit, and low general cognitive ability (IQ). However, these studies reported normal functionality in the areas of learning and memory;[22-24] only a few small studies suggested that verbal and visual memory may be affected in patients with IGE.[25-28] The present study revealed that the epilepsy groups (IGE and mTLE) had lower verbal and visual memory scores than the control group. Although our study has a limited sample size, it can be evaluated in line with the literature.

Study Limitations

This study has several limitations. First, the sizes of both the patient and control groups were relatively small and heterogeneous. Second, there is the presence of multiple factors that can affect cognitive test scores, such as epilepsy duration, seizure type, seizure frequency, age at epilepsy onset, use of multiple antiepileptic medications, and side effects, which is also a significant challenge. In our study, half of our patients received monotherapy; the other half received polytherapy. The frequency of seizures differed. These variations may have affected the cognitive function assessment and, consequently, the results. Third, the younger mean age of both the epilepsy patients and control groups may have contributed to the inconclusive results. Last, given that Orexin A affects sleep, autonomic functions, appetite, mood, and the physiological status of patients, the serum Orexin A level might have been affected.

CONCLUSION

Cognitive disorders are common in patients with epilepsy and significantly affect their quality of life. Orexin A, which plays a role in various aspects, such as sleep/awake states, eating behavior, and energy homeostasis, is also believed to be involved in cognitive functions. Animal studies have shown that Orexin A positively affects memory by increasing synaptic plasticity in the hippocampus. Recent research on neurodegenerative diseases has revealed the role of orexin A in neurodegeneration and cognitive impairment. However, studies on Orexin A in patients with epilepsy

are limited, and a clear relationship with cognition has not yet been demonstrated. Our findings showed that the Orexin A level was not associated with verbal or visual memory test scores, indicative of hippocampal function. Therefore, there is no association between Orexin A and cognitive impairment in patients with epilepsy. Further research is required to elucidate the complex role of Orexin A in neurogenesis and epileptogenesis.

Ethics

Ethics Committee Approval: The İzmir Tepecik Training and Research Hospital Ethics Committee approved the study protocol, and all procedures were followed according to the ethical standards outlined in the Declaration of Helsinki (decision no: 3, date: 21.02.2020).

Informed Consent: Written informed consent was obtained from all participants, and the study protocol, potential hazards, and benefits were explained to all participants.

Authorship Contributions

Surgical and Medical Practices: Z.Y., Concept: Z.Y., İ.F.U., Design: İ.F.U., Data Collection or Processing: Z.Y., A.B., Analysis or Interpretation: İ.F.U., A.B., Literature Search: Z.Y., U.Ş., A.S., Writing: Z.Y., İ.F.U., U.Ş.

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Original Article

Self-management, Spousal Support, and Related Factors Among Individuals Diagnosed with Epilepsy

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Abstract

Objective: This study aimed to determine the self-management of epilepsy, spousal support, and related factors in individuals diagnosed with epilepsy. Manage the disease process in individuals diagnosed with epilepsy is crucial in terms of daily functionality and quality of life.

Methods: This descriptive cross-sectional study included 135 individuals diagnosed with epilepsy. Data were collected using a patient information form that included sociodemographic and clinical characteristics and the Epilepsy Self-Management Scale and Spousal Support.

Results: In this study, the mean score of the epilepsy self-management scale was 133.64 (18.40). Education, gender, income level, presence of children, and frequency of seizures were determined as factors affecting epilepsy self-management. No relationship was found between spousal support and epilepsy self-management.

Conclusion: This study makes a significant contribution to the literature in determining factors affecting self-efficacy. Our results revealed the personal characteristics of the patients, especially sociodemographic factors that affect epilepsy self-management.

Keywords: Epilepsy, self-management, spousal support, family health, nursing

INTRODUCTION

Epilepsy is a neurological disease that occurs as a result of the sudden, abnormal, and hypersynchronous discharge of neuron groups located in the cortical and subcortical regions of the central nervous system. Epilepsy usually progresses with recurrent changes in consciousness. In other words, epilepsy is a chronic disease that aims to achieve a high quality of life by keeping seizures under control, which requires significant behavioral and psychosocial adjustments.[1] There are 50 million people diagnosed with epilepsy in the world, and 125,000 of them die each year, with more than 80% of these deaths occurring in low- and middle-income countries.[2] Due to the unpredictable nature of the disease, epilepsy can present many challenges for those affected.[3] In order to adapt to the disease, lifestyle changes and good self-management are required.[4] Self-management refers to the individual's ability to control the negative consequences of the disease, adapt to treatment, and make and manage lifestyle changes to keep her/his health at the highest level, together with the family, society and health worker.[4]

Self-management for epilepsy includes regular use of antiepileptic drugs, minimizing conditions that lead to seizures, taking safety precautions to avoid injury during seizures, regular and adequate rest and nutrition and coping with stress.[4] It is essential to increase patients' and families' coping abilities, develop their self-efficacy, preserve and enhance their skills, meet their information needs, increase self-control over the disease, and improve their quality of life.[5] Nurses can help patients improve epilepsy self-management by teaching them.[5-8] Self-management activities have been reported to reduce seizure frequency, increase seizure control, and improve overall quality of life. Self-management may be linked to higher quality of life and lower depression.[3]

The primary caregivers of married individuals diagnosed with epilepsy are often spouses.[9] Evidence indicates that spousal support may be important for health and life satisfaction.[10] Social relationships, especially close relationships (such as romantic relationships characterized by emotional attachment and support), have been found to significantly affect mental and physical well-being in both healthy people and those with the disease.[11] Married individuals diagnosed with epilepsy have a better quality of life.[12] A dysfunctional family is associated with social anxiety in patients with epilepsy.[13] It has been determined that individuals receiving spousal and physician support are more inclined to accept the disease.[14]

The aim of this study was to determine the level of self-management, status of spousal support received, and sociodemographic factors influencing self-management in patients diagnosed with epilepsy.

METHODS

This descriptive cross-sectional study was conducted after obtaining ethical approval from the İzmir Democracy University Non-interventional Clinical Research Ethics Committee (decision no: 2022/01-07, date: 05.01.2022). This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Institutional permission for the study was obtained from the administration of Kocaeli University Research and Practice Hospital where the study was conducted. Additionally, the principle of volunteerism was adopted in the study, and all participants provided written consent.

The study population included individuals who were over the age of 18, had a spouse/partner, voluntarily agreed to participate in the study, and were diagnosed with epilepsy and seeking care at the Neurology outpatient clinic. The G*Power 3.1.5 program was used to determine the sample size of the study, and the sample size was found to be 135 people, taking into account the values of α=0.05, β=0.95, effect size=0.30 in the study.

In this study, the questionnaire form prepared by the researcher, the epilepsy self-management scale (ESMS) and Spouse Support Scale (SSS) were administered to the participants. The questionnaire includes questions about the socio-demographic characteristics of the participants and the disease. The ESMS was developed by Dilorio et al.[15,16] The Turkish validity and reliability of the scale were examined by Yeni et al.[4] in 2019. The scale, which consists of five subscales evaluating drug treatment, knowledge, safety, seizure, and lifestyle management in patients with epilepsy, is a 5-point Likert scale with 38 items. The scores to be obtained from the scale vary between 38 and 190, and high scores indicate good self-management. According to the internal consistency analysis on the validity and reliability of the scale, the Cronbach's alpha coefficient for the entire scale was determined as 0.740.[4]

Statistical Analysis

The SSS developed by Yıldırım[17] was used to measure the social support of married individuals from their spouses. The results of the analysis show that the scale consists of four dimensions: emotional, financial, and information support, appreciation, and social interest support.[17] The SSS comprises 27 items and is a 3-point Likert type. The total score varied between 27 and 81, with higher scores indicating greater perceived spousal support. While the Cronbach's alpha value was 0.95 in the original form of the SSS, in this study the Cronbach's alpha and McDonald's omega values were found to be 0.96.[17] The data were evaluated using the Statistical Package for Social Sciences package program, and the significance level was accepted as $p<0.05$. Shapiro-Wilk and Kolmogorov-Smirnov tests were used for data conformity with normal distribution, and percentages and means were used for data evaluation. Pearson's correlation analysis was used to investigate the relationship between self-management and spousal support. Student's t-test was used to determine the relationship between sociodemographic factors and the epilepsy self-management and spousal support scale. The Bonferroni test was used for further analysis.

MAIN POINTS

- Epilepsy is an important disease that affects the quality of life of patients and requires long-term treatment and follow-up.
- Self-management significantly affects daily functioning among individuals diagnosed with epilepsy.
- Spousal support is a protective and supportive factor for patients.
- Our results revealed the personal characteristics of the patients, especially sociodemographic factors that affect epilepsy self-management.

RESULTS

Approximately six out of ten participants were women, while approximately four out of ten were at undergraduate or higher education levels. Individuals whose income was equal to their expenses were 54.1%. Two-thirds of the patients had children. The mean age of the patients was 38.21 (13.26) years, and the mean time to diagnosis was 10.63 (8.41) months (Table 1).

Table 2 presents the patients' ESMS, its subdimensions, and mean SSS score. The mean ESMS score of patients was 133.64 (18.40). When we examined the subdimension mean scores of the scale, it is 40.75 (5.79) for drug management, 20.65 (6.75) for information management, 28.79 (3.63) for security management, 22.94±4.68 for seizure management, and 20.49 (5.08) for lifestyle management. The SSS score was 52.88 (14.21).

Table 3 presents the mean scores of the patients from the ESMS according to their sociodemographic characteristics. Compared with women, men's medication score was statistically significantly higher (p=0.035). Significant differences were observed in the total score of the ESMS and its subscales, specifically in the information and seizure domains, based on the educational level of the participants in our study. To identify the group that made the difference, a corrected Bonferroni test was applied.

Table 1. Sociodemographic characteristics of patients (n=135)

Characteristics	n	%
Gender		
Female	82	60.7
Male	53	39.3
Education level		
Primary school or lower education level	37	27.4
Secondary school	45	33.3
High school or higher	53	39.3
Income level		
Income less than expenses	62	45.9
Income equals expenses	73	54.1
The child		
Yes	90	66.7
No	45	33.3
	Mean	**Standart deviation**
Age	38.21	13.26
Mean time to diagnosis (as months)	10.63	8.41

High school graduates had lower epilepsy self-management scale scores than both primary and lower education graduates and individuals with undergraduate and graduate education (p=0.002). High school graduates had lower knowledge management scores than individuals with undergraduate and higher education and individuals with primary education and below (p<0.005). Individuals with undergraduate or higher education scores had higher seizure management scores than high school graduates (p=0.026). Those with a bachelor's degree or higher had higher lifestyle management scores than high school graduates (p=0.001). On the other hand, eta squared (η^2) was examined to determine the effect size of education. The obtained eta squared value was interpreted in accordance with Cohen's (1988) "d" index, which is an effect size measure. Cohen (1988) defined specific cutoff points for interpreting the d index as follows: effect sizes are categorized as "small" at d=0.02, "medium" at d=0.06, and "large" when d=0.14.[18] In this case, considering the eta square value (η^2=0.091) obtained for the education variable, it is seen that the gender variable has a moderate effect on epilepsy self-management. Those whose income was equal to their expenditure received a higher level of knowledge management score than those whose income was less than their expenditure (p=0.0259). Knowledge management and lifestyle management for those who did not have children are at a better level.

There was a statistically significant negative correlation between the number of seizures per year and the ESMS score. Disease self-management scores decreased as the number of seizure increases. Similarly, a negative and statistically significant relationship was found between age and ESMS score. As age increased, the ESMS score of the disease decreased (Table 4).

DISCUSSION

This study was conducted to determine epilepsy self-management, spousal support, and sociodemographic factors affecting patients diagnosed with epilepsy. It is widely accepted that self-management is increasingly important for quality of life, self-efficacy, and self-esteem in patients diagnosed with epilepsy.[19] Self-management interventions in epilepsy help patients manage their daily lives by

Table 2. Mean scores of participants in the epilepsy self-management scale and Spousal Support Scale (n=135)

Scales	Mean±SD	Min-max	Score range
Epilepsy self-management	133.64±18.40	81-181	38-190
Medication	40.75±5.79	23-50	10-50
Information	20.65±6.75	8-37	8-40
Safety	28.79±3.63	18-37	8-40
Seizures	22.94±4.68	6-30	6-30
Lifestyle	20.49±5.08	6-30	6-30
Spouse Support Scale	52.88±14.21	27-79	27-81

SD: Standard deviation, Min-max: Minimum-maximum

Table 3. Comparison of epilepsy self-management scale and Spouse Support Scale levels according to sociodemographic characteristics of the participants (n=135)

	Epilepsy self-management scale	Medication	Information	Safety	Seizure	Lifestyle	Spouse Support Scale
Characteristics	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Gender							
Female	134.28±19.46	39.91±6.19	21.13±7.28	29.06±3.69	23.15±4.95	21.01±4.91	52.85±14.62
Male	132.66±16.78	42.05±4.87	19.90±5.82	28.37±3.52	22.62±4.25	19.69±5.28	52.94±13.71
	p=0.619	**p=0.035**	p=0.304	p=0.287	p=0.518	p=0.143	p=0.972
Education level							
Primary school or lower education (37)	136.70±17.01	40.72±6.03	22.05±6.43	29.45±4.88	23.78±3.31	20.67±4.25	53.94±15.34
Secondary school (45)	125.86±12.81	40.91±4.14	16.46±4.59	28.73±2.85	21.42±3.36	18.33±4.70	54.68±6.71
High school or higher level (53)	138.11±21.32	40.64±6.83	23.22±6.90	28.37±3.17	23.66±6.02	22.20±5.31	50.62±17.63
	p=0.002	p=0.974	**p=0.000**	p=0.380	**p=0.026**	**p=0.001**	p=0.323
	1>2, 3>2		1>2, 3>2		3>2	3>2	
Perceived economic level							
Income less than expenses (62)	131.90±15.87	40.79±5.63	19.25±6.24	29.25±2.96	22.75±4.34	19.83±4.77	53.06±12.48
Income equals expenses (73)	135.12±20.30	40.72±5.95	21.83±6.98	28.39±4.09	23.10±4.97	21.05±5.29	52.73±15.62
	p=0.313	p=0.949	**p=0.025**	p=0.160	p=0.662	p=0.163	p=0.895
The child							
Yes	131.93±17.98	40.74±5.77	19.72±6.55	28.92±3.50	22.80±4.53	19.74±5.12	51.68±12.44
No	137.06±18.97	40.77±5.88	22.51±6.84	28.53±3.50	23.24±5.0	22.0±4.70	55.28±17.13
	p=0.127	p=0.975	**p=0.023**	p=0.560	p=0.605	**p=0.015**	p=0.166

SD: Standard deviation

Table 4. Correlations between the epilepsy self-management scale scores

		Spouse Support Scale	Mean time to diagnosis	Number of seizures in a year	Age
Epilepsy self-management	**r**	-0.57	-0.129	-0.175	-0.186
	p	0.512	0.137	**0.042***	**0.031***

*p<0.001

developing behaviors to manage epilepsy seizures and improve medication and treatment.[20] In this study, the average ESMS score was 133.64 (18.40). Although studies in the literature report scores that are much better than our findings, there are also findings that have lower scores than our findings. Quon et al.[21] found an ESMS score of 71.1 (8.23). An increase in epilepsy self-management skills is associated with an increase in quality of life.[21] In addition, disease management can help improve symptom management, potentially enhancing well-being and reducing seizure frequency in patients.[22]

In this study, the ESMS medication management subscale score was higher in men than in women. Similarly, Adadıoğlu and Oğuz[23] found higher epilepsy self-management scores in men than in women. In another study, it was determined that epilepsy seizure management was better in women than in men.[24] Mohsen and Ahmed[25] found that women with epilepsy had a higher quality of life than men in their study. The ESMS score of patients with epilepsy did not vary by gender.[26,27] Self-management education and support interventions are effective in improving self-efficacy, self-esteem, and quality of life in individuals diagnosed with epilepsy.[19] It is recommended that nurses working in neurology departments prioritize providing these trainings to at-risk groups.

High school graduates have lower ESMS and knowledge management scores than those who have graduated from primary school or below, as well as those with bachelor's degrees or higher. Adadıoğlu and Oğuz[23] found that individuals with higher education levels had better self-management skill scores than those with lower education levels. Individuals with low education levels are associated with an increased risk of depression.[28] In this study, individuals with a bachelor's degree or higher education received higher scores in seizure management and lifestyle management than high school graduates. Low education levels are associated with quality of life.[29] Yildirim and Yildiz[26] determined that the ESMS score did not vary according to educational level of the patients. Epileptic patients with higher education levels also have higher levels of knowledge about their disease.[30] Nurses are healthcare professionals who constantly work together with patients to provide education and care tailored to their needs. Therefore, nurses play a significant role in helping patients understand their condition, adhere to treatment, and adapt their daily lives to the symptoms of the disease.

Those whose income equals their expenses received a higher level of knowledge management score than those with lower income than expenses. Adadıoğlu and Oğuz[23] found that patients with high and middle incomes had better epilepsy self-management skills than those with low levels. Income status has an impact on the ability to manage epilepsy, as with many other diseases. Income status is believed to facilitate access to healthcare services and use of other treatment options, and this outcome may be related to income. In the study, knowledge management and lifestyle management of those who did not have children were at a better level. Having children and spending time with them can reduce patients' time allocated to themselves. It is thought that this outcome may be related to that. Additionally, it is believed that those who have children should receive educational support.

In this study, no statistically significant relationship was found between SSS and ESMS scores. The high score 52.88 (14.21) obtained on the spousal support scale in this study is believed to have affected this result. Adadıoğlu and Oğuz[23] determined in their study that epilepsy self-management was better in patients with high family support scores.[26] A good level of SSS is desirable; however, providing support to spouses at certain intervals is also thought to have a positive effect. Practitioner nurse-physician teams can more effectively implement epilepsy education and screen for psychological disorders.[31] In cases of family issues, it is important to identify at-risk individuals who require support, such as couple therapy or family therapy, and to refer them to an expert. For this purpose, nurses use their observational and communication skills within the clinical setting to provide assistance to patients.

In this study, we found that as the number of seizures increased, the ESMS scores of the patients decreased. This result may be related to the association between seizures and fatigue in patients.[32] In the literature, there have been different findings regarding this result. Adadıoğlu and Oğuz[23] found that the self-management score of epilepsy increased as the number of seizures increased. In a Ugandan study, self-management was associated with improved quality of life and reduced incidence of depression, stigma, and seizures among individuals with epilepsy and a history of adverse health events.[33] Yildirim and Yildiz[26] did not find a relationship between seizure frequency and epilepsy self-management in their studies.

In this study, a statistically significant negative correlation was found between patient age and ESMS score. Yildirim and Yildiz[26] found no correlation between age and the epilepsy self-management score in epilepsy patients. In a study evaluating quality of life in patients with epilepsy, a negative correlation was found between age and quality of life.[34] It has been reported that anxiety levels increase in individuals living with the disease for 16 years or more.[35] It is believed that individuals with aging may experience fatigue, burnout, and a decrease in their ability to manage the disease. This result shows that although patients gain experience as they age, their self-management may decrease. For this reason, follow-up of patients is considered important.

Study Limitations

This study has several limitations. First, because the study design is cross-sectional, it is not possible to evaluate causal or temporal relationships. The study sample was obtained from a single tertiary university hospital. Therefore, it should be taken into account that patients receiving primary care may produce different results.

CONCLUSION

In this study, the ESMS score was found to be at a moderate level in individuals diagnosed with epilepsy, and the medication management scores were found to be better in men. In those with higher education levels, seizure management and lifestyle management were found to be better, while knowledge management was found to be better in those with higher economic status and no children. The study found that spousal support did not have a statistically significant effect on epilepsy self-management. The ESMS score decreased as the age and seizure frequency increased.

Implications

Epilepsy is an important disease that affects the quality of life of patients and requires long-term treatment and follow-up. Self-management significantly affects daily functioning in individuals diagnosed with epilepsy. Spousal support is a protective and supportive factor for patients. Our results revealed the personal characteristics of the patients, especially sociodemographic factors that affect epilepsy self-management. Due to the nature of the disease, the emotional burden of patients can also affect their spouses. From the time of diagnosis, supporting the family and counseling have a positive effect on disease self-management. Family therapists, nurses, and psychologists can support the patient and caregiver by taking an active role in providing spousal support. Health professionals should support the mental aspect of the disease as well as their self-care skills. It is recommended to conduct experimental studies that support spouses. In addition, the conditions of the patient and the family should be evaluated through home visits, and improvements in the patient's self-management skills should be achieved.

Ethics

Ethics Committee Approval: This descriptive cross-sectional study was conducted after obtaining ethical approval from the İzmir Democracy University Non-interventional Clinical Research Ethics Committee (decision no: 2022/01-07, date: 05.01.2022).

Informed Consent: All patients read and approved the enlightened information sheet.

Authorship Contributions

Surgical and Medical Practices: S.D., Y.C.Ö., Concept: S.D., Y.C.Ö., Design: S.D., Data Collection or Processing: S.D., Y.C.Ö., Analysis or Interpretation: S.D., Y.C.Ö., Literature Search: S.D., Y.C.Ö., Writing: S.D., Y.C.Ö.

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Validity and Reliability Study of the Turkish Version of the Subjective Handicap of Epilepsy

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Abstract

Objective: This study aimed to investigate the validity and reliability of the Turkish version of "The Subjective Handicap of Epilepsy (SHE)" questionnaire.

Methods: Upon the permission from the authors of the questionnaire, the English questionnaire was separately translated into Turkish by two neurologists who had a native language of Turkish and who had a valid certificate for English. A single translation was created by combining these two translations by another neurologist specialized in epilepsy. Afterwards, the Turkish translation was translated back to English by two other neurologists, blind to the original questionnaire. Internal consistency of the test was measured by using the Cohen's kappa coefficients. The questionnaire was interpreted in 20 patients and was repeated after 15 days. After the intraclass consistency coefficient between the two evaluations was determined to be positive, it was applied to a total of 252 patients during the study period.

Results: A total of 252 patients (146 women- 57.9%, 106 men- 42.1%) with a mean age of 33.4+11.5 years were included in the study. The mean age of epilepsy onset was 19.0+10.9 years, and the mean disease duration was 14.4+11.2 years. The internal consistency of the scale was found to be highly consistent with Cohen's kappa value of 0.864. The intraclass correlation coefficient value for the test-retest reliability was found to be excellent, with a value of 0.945 for the whole questionnaire ($p<0.001$).

Conclusion: We observed that the Turkish version of the SHE is a valid and reliable assessment for determining disability in epilepsy patients.

Keywords: Epilepsy, disability, validity, reliability, handicap

INTRODUCTION

Epilepsy is a chronic disease of the central nervous system that occurs in the form of attacks and affects people all over the world. Epilepsy is a condition characterized by sudden, recurrent epileptic seizures resulting from abnormal and excessive electrical discharge in cortical neurons. The probability of a person experiencing a single epileptic seizure in their lifetime is 10%. The incidence of epilepsy is 50.4 to 81.7 per 100,000 people per year.[1]

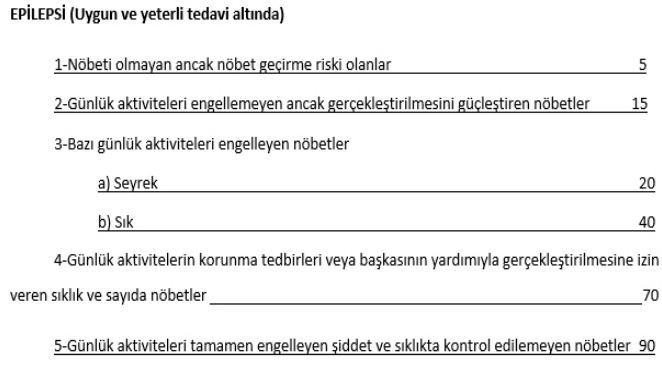
There are approximately 50 million people with epilepsy worldwide, and approximately 30-40% have seizures that are resistant to treatment with anti-seizure medications.[2,3] The International League Against Epilepsy (ILAE) defines resistant epilepsy as a condition in which seizure control cannot be achieved despite the use of two or more appropriately selected, appropriately used and tolerated anti-seizure medications (monotherapy or combination).[4]

Epilepsy, especially in its resistant subtypes, not only disrupts the patient's daily living activities but also creates disability by seriously restricting the person's participation in social and community life.[5] In epilepsy, comorbid conditions, seizure frequency and severity, treatment modality, medication and side effects, socio-economic status and stigmatization are considered to be the most important factors affecting the quality of life of patients.[6] Quality of life in patients is affected by psychosocial factors rather than seizures. Quality of life assessment is frequently preferred to evaluate the effect of epilepsy on the individual. Although quality of life scales are accepted as an indirect measurement of disability, they do not adequately assess the effects of epilepsy on social and community participation.

The World Health Organization defines the concept of disability as "a disadvantaged situation that limits or prevents the fulfillment of one or more roles that are considered normal, depending on age, gender, social and cultural factors, as a result of an impairment or disability".

In our country, the legislation regarding the definition of disability and how health board reports should be submitted is regulated by the 'Regulation on disability assessment for adults' published by the Council of Ministers in the official newspaper dated 20 February 2019 and numbered 30692.[7] In this regulation, the concept of disability refers to 'an individual who is affected by attitudes and environmental conditions that limit his/her full and effective participation in society on equal terms with other individuals due to various levels of loss of physical, mental, spiritual and sensory abilities'.

Today, disability assessments are carried out in accordance with the legislation determined by the Ministry of Health (Figure 1). As a matter of fact, many physicians and researchers are interested in the diagnosis and treatment of epilepsy consider the current disability rating for epilepsy patients as inadequate. When determining disability in patients with epilepsy, not only the frequency of attacks but also other problems that may accompany epilepsy should be considered and these patients should be evaluated in more detail. In 1998, O'Donoghue et al.[8] developed "The Subjective Handicap of Epilepsy (SHE)" scale in English, which is a more comprehensive measurement model based on the disability concept of the World Health Organization. This study aimed to assess the validity and reliability of the Turkish version of the "SHE" questionnaire.


EPİLEPSİ (Uygun ve yeterli tedavi altında)

1-Nöbeti olmayan ancak nöbet geçirme riski olanlar 5

2-Günlük aktiviteleri engellemeyen ancak gerçekleştirilmesini güçleştiren nöbetler 15

3-Bazı günlük aktiviteleri engelleyen nöbetler

a) Seyrek 20

b) Sık 40

4-Günlük aktivitelerin korunma tedbirleri veya başkasının yardımıyla gerçekleştirilmesine izin veren sıklık ve sayıda nöbetler 70

5-Günlük aktiviteleri tamamen engelleyen şiddet ve sıklıkta kontrol edilemeyen nöbetler 90

Figure 1. February 2019, official newspaper, regulation on disability assessment for adults, from the Ministry of Family, Labor, and Social Services and the Ministry of Health, Epilepsy

MAIN POINTS

- The degree of disability in patients with epilepsy is affected not only by the clinical features associated with the disease, the frequency and severity of seizures, but also by psychosocial factors.
- Detailed evaluation of disability in patients with epilepsy is required.
- Turkish version of the Subjective Handicap of Epilepsy is a valid and reliable assessment for determining disability in epilepsy patients.

METHODS

Study Design and Participants

Patients diagnosed with epilepsy who had applied to the Department of Neurology Epilepsy Center for two years were included in the study. The inclusion criteria were (i) definitive diagnosis of epilepsy; (ii) age between 18 and 65 years; and (iii) agreement to participate in the study. Patients with other diseases that could cause disability were not included in the study.

In terms of treatment response, patients were evaluated as treatment responsive if they had been seizure-free within the last 2 years and as treatment unresponsive if not.

The following permission from the authors who created the SHE scales for this study, a Turkish adaptation was made (Appendix 1). This scale, developed by O'Donoghue et al.[8] specifically for health problems related to epilepsy, consists of 32 items under six subheadings. These items are: (i) "Work and activity" (eight items), (ii) "Social and personal" (four items), (iii) "Physical" (four items), (iv) "Self-perception" (five items), (v) "Life satisfaction" (four items) and (vi) "Change" (seven items) subscales. The questionnaire takes approximately 10 minutes. Each item is scored between 1-5 points using the Likert measurement method. After item scores are collected, the subscale score is linearly converted to a scale of 0-100. Low scores indicate poor disability, and high scores indicate reduced disability (Appendix 2). The SHE questionnaire has high internal consistency and reliability. The test-retest reliability of the scale was found to be high, and intraclass correlation coefficients (ICC) were found to be between 0.83 and 0.89.

In our study, the translation-back-translation method was applied to adapt the scale to Turkish. The English questionnaire was translated into Turkish separately by two neurologists who are native Turkish speakers and have English certificates. The two translations were combined into a single translation by a neurologist who specializes in epilepsy. It was then translated back into English by two other neurologists, regardless of the original Turkish translation. The test, translated into Turkish, was applied to a total of 20 patients and repeated 15 days later. The questionnaire, whose question and questionnaire consistency were found to be positive in the analysis of preliminary results, was applied to a total of 252 patients who met the inclusion criteria of the study during the two-year study period.

Statistical Analysis

Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS-version 21.0) were used for statistical evaluation. Nominal

Table 1. Sociodemographic and clinical characteristics of the patients

Demographic and clinical characteristics	Minimum	Maximum	Mean	Standard deviation
Age (years)	18	65	33,4	11.5
Education (years)	0	15	10.6	4.0
Age at epilepsy onset (years)	1	58	19,0	10.9
Duration of epilepsy (years)	1	60	14,4	11.2

data are expressed as numbers and percentages, and numerical data are expressed as mean + standard deviation. Reliability analysis was performed by calculating internal consistency and test-retest reliability. Internal consistency was determined by calculating Cohen's kappa value. Test-retest reliability was performed by calculating the ICC for each question in the SHE test.[9] ICC data were classified as poor (<0.50), fair (between 0.50 and 0.75), good (between 0.75 and 0.90), and excellent (above 0.90).[10] A p value of 0.05 or less was accepted as statistical significance.

Ethical Approval

The study was approved by the İstanbul University Cerrahpaşa-Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (date: 22.05.2019, no.: 77991). Informed consent was obtained from all patients participating in the study.

RESULTS

Of the patients with epilepsy, 146 (57.9%) were female and 106 (42.1%) were male. The mean age of the whole group was calculated as 33.4±11.5 years. The mean educational level of the patients was 10.6+4.0 years. The mean age at epilepsy onset was 19.0±10.9 years and the mean duration of the disease was 14.4±11.2 years (Table 1). Regarding marital status, 50.4% of the patients were single and 44.8% were married. When the treatment response was analysed, it was observed that 64.8% of the patients had not yet achieved a response, while 35.2% had partial and/or complete response to treatment. A total of 129 (50.8%) patients were followed with monotherapy, and 117 patients (46.6%) had polytherapy; only 6 patients (2.6%) were followed without any anti-seizure medication.

Cohen's kappa value for internal consistency was 0.864 for the entire questionnaire. When considered separately for all questions, it ranged between 0.838 and 0.885 [test statistics (F)=7.252; p<0.001].

According to the ICC data analyzed for test-retest reliability, Question 1, "Has epilepsy caused problems at work in the last 6 months?", Question 2, "Have you ever been unable to go to work due to epilepsy in the last 6 months?", Question 6, "Does epilepsy prevent you from doing the type of work you really want to do?", Question 8, "Does epilepsy cause problems in your relationships with your relatives (e.g., your children, relatives)?" Question 9: "Does epilepsy cause problems in your relationships with your friends?", Question 20: "Has epilepsy prevented you from going out for sightseeing or travelling?" was found to be excellent in terms of score agreement (ICC value >0.90). In all other questions, the agreement was evaluated as good (0.75< ICC value <0.90). No question was observed to indicate poor agreement. In the entire questionnaire evaluation, the ICC was 0.945, and the agreement was found to be excellent (p<0.001; Table 2).

Table 2. Intraclass correlation coefficient for each question in the scale

Questions	ICC	ICC (min-max)	F values	p values
1	0.917	0.893-0.935	12.021	<0.001
2	0.911	0.886-0.930	11.198	<0.001
3	0.891	0.861-0.915	9.204	<0.001
4	0.887	0.855-0.912	8.836	<0.001
5	0.873	0.837-0.901	7.853	<0.001
6	0.911	0.887-0.931	11.292	<0.001
7	0.892	0.861-0.916	9.245	<0.001
8	0.912	0.887-0.931	11.351	<0.001
9	0.903	0.876-0.924	10.335	<0.001
10	0.894	0.865-0.918	9.462	<0.001
11	0.898	0.869-0.920	9.763	<0.001
12	0.827	0.779-0.865	5.796	<0.001
13	0.843	0.798-0.877	6.358	<0.001
14	0.862	0.823-0.892	7.232	<0.001
15	0.845	0.802-0.879	6.459	<0.001
16	0.800	0.743-0.844	4.993	<0.001
17	0.867	0.830-0.896	7.532	<0.001
18	0.874	0.839-0.902	7.963	<0.001
19	0.879	0.845-0.906	8.279	<0.001
20	0.908	0.882-0.928	10.845	<0.001
21	0.880	0.847-0.907	8.354	<0.001
22	0.872	0.836-0.900	7.798	<0.001
23	0.885	0.853-0.910	8.698	<0.001
24	0.894	0.865-0.918	9.476	<0.001
25	0.861	0.822-0.891	7.184	<0.001
26	0.772	0.708-0.822	4.393	<0.001
27	0.821	0.770-0.860	5.581	<0.001
28	0.803	0.748-0.846	5.078	<0.001
29	0.847	0.804-0.881	6.535	<0.001
30	0.855	0.815-0.887	6.915	<0.001
31	0.852	0.811-0.885	6.769	<0.001
32	0.864	0.826-0.894	7.372	<0.001
Total	0.945	0.928-0.957	17.926	<0.001

ICC: Intraclass correlation coefficient, min-max: Minimum-maximum

DISCUSSION

With this study, it has been shown that the internal consistency of the Turkish version of the Subjective Handicap of Epilepsy questionnaire, which is called "The Subjective Handicap of Epilepsy, SHE" in English, is significantly compatible with Cohen's

kappa value of 0.862. The reliability coefficient measured by test-retest was found to be excellent with an ICC value of 0.944. Based on these findings, it was concluded that the Turkish version of the SHE questionnaire is a valid and reliable test for the evaluation of disability in patients with epilepsy.

With the current legislation determined in our country, disability due to epilepsy is evaluated only on the basis of seizure frequency and is inadequate. Moreover, accurate assessment of seizure frequency is not always possible due to difficulties in recognizing seizures by the patient's relatives.[11] On the other hand, epilepsy is a disease that affects almost every aspect of patients' lives. Patients with epilepsy experience problems in society not only because of seizures but also because of the negative effects caused by the existence of the epilepsy diagnosis. The fear caused by sudden and unexpected seizures, side effects of the drugs used, cognitive impact due to epilepsy, psychosocial impact, and stigma are the main causes of epilepsy- related disability. In addition, epilepsy becomes a serious social disorder due to difficulties in finding or maintaining a job and problems in obtaining a driver's license.[12] Studies have found that approximately half of epilepsy patients feel stigmatized. Epilepsy is a stigmatized disease worldwide. Although there have been sensitization efforts to reduce stigma among people with epilepsy, there has been limited progress.[13] Even if epilepsy is treated and seizures are controlled, people experience serious problems in society due to stigma.[14] The negative impact of stigma on the quality of life of epilepsy patients is greater than the impact of the disease itself.[15] In a survey conducted with epilepsy patients, it was determined that the diagnosis of epilepsy most frequently evokes a feeling of fear. This fear has been reported as fear of death, fear of having a seizure and accident while driving, fear of having children witness a seizure, fear of being embarrassed in public, and fear of losing one's job.[16] In the same survey, the degree to which epilepsy limits life choices and experiences and the stigma epilepsy imposes were the worst things cited by at least a quarter of respondents, while physical problems associated with epilepsy were among the least mentioned problems.

In addition, in our country's legislation, it is accepted that there is no disability if the disease progresses seizure-free with treatment, and the psychosocial situation due to epilepsy is not evaluated.

More detailed evaluations are needed to better understand the deficiencies of patients with epilepsy, especially in work and social situations. There are limited studies in the literature on quality of life and disability in epilepsy patients. It was thought that it would be appropriate to conduct a Turkish validity and reliability study of the SHE because it evaluates all aspects of epilepsy and has a simple scoring system. O'Donoghue et al.[8] developed the SHE questionnaire, and in their study using this scale, they reported that even patients with a low number of seizures had high disability.[17] In another study, the effect of extratemporal epilepsy surgery on quality of life was evaluated using the SHE questionnaire before and one year after surgery, and it was suggested that it was a reliable test that well revealed the disability associated with epilepsy and its surgery.[18] In a study conducted by Hopker et al.[19] in 2017 with 30 treatment-resistant temporal lobe epilepsy patients, SHE was used as one of the tests used to evaluate the patients' quality of life. Researchers found significant correlations between stigmatization, work and social activity, problems in personal and social areas, and SHE scores, and showed that the SHE questionnaire can be used reliably. In the validation study of the questionnaire conducted in another language, the questionnaire was found to be psychometrically sufficient for both the post-epileptic surgery and drug treatment follow-up groups.[20]

CONCLUSION

It is clear that the effects of epilepsy on the degree of disability and quality of life should be evaluated not only by the clinical features associated with the disease, the frequency and severity of seizures, but also by psychological and social factors. The SHE questionnaire evaluates additional parameters such as psychosocial factors in the assessment of disability/disability degrees of patients with epilepsy and provides much more detailed information than the evaluation made according to the Ministry of Health Legislation. In this respect, it is important that this survey, whose validity, and reliability we have demonstrated, be widely used in our country. As a matter of fact, conducting numerous prospective studies with a higher number of patients and revealing the "real" disability in patients with epilepsy may enable adjustments to be made in the current legislation.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University Cerrahpaşa-Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (date: 22.05.2019, no: 77991).

Informed Consent: Informed consent was obtained from all patients who participated in the study.

Authorship Contributions

Concept: F.K.M., S.N.Y., Design: G.B.Ş., F.K.M., S.N.Y., Data Collection or Processing: E.K.K., G.K., İ.N.C., E.A.C., Ç.Ö., Analysis or Interpretation: G.B.Ş., Literature Search: E.K.K., G.B.Ş., Writing: E.K.K., G.B.Ş.

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Archives of Epilepsy

Original Article

Identification and Resolution of Drug-related Problems Encountered by Individuals with Epilepsy in Nigeria

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Abstract

Objective: Interventions by clinical pharmacists are required to identify and resolve medication-related problems. This study aimed to identify drug-related problems (DRPs) encountered by patients with epilepsy, provide pharmaceutical care (PC) interventions, and evaluate the impact of these clinical interventions.

Methods: A prospective longitudinal study was conducted on 95 patients with epilepsy attending the neurology/medical outpatient clinics of two epilepsy referral centers. During patient clinic visits, the pharmacist collected medication history, reviewed patient medication use, identified DRPs, provided PC services, and collaborated with physicians and patients to resolve identified DRPs. Documentation and classification of identified DRPs, categorization of the pharmacists' interventions, categorization of acceptance of the pharmacist's intervention proposals, and categorization of the status of the DRPs after the interventions were performed using the Pharmaceutical Care Network Europe Classification Scheme for DRPs V8.02.

Results: The total number of DRPs identified by the clinical pharmacists in the study population was 277. Three hundred and seventy-nine interventions were offered by the clinical pharmacists. Approximately 57.04% of the identified DRPs were patient-related, whereas 15.88% were dispensing-related. Approximately 64.12% of the research pharmacist's interventions were at the patient level, whereas 24.01% of these interventions were at the prescriber level. Two hundred and eleven (55.67%) of the clinical pharmacist interventions were accepted and fully implemented. Approximately 61.73% of the identified DRPs were fully resolved.

Conclusion: Most DRPs encountered were resolved following the acceptance of the clinical pharmacist's PC interventions by the patients and attending physicians. This study revealed the huge potential of clinical pharmacists in providing specialized care for patients with epilepsy.

Keywords: Pharmaceutical care, epilepsy, drug-related problems

INTRODUCTION

An estimated 70 million people are reportedly living with epilepsy globally, with approximately 95% of this population living in developing parts of the world. The disease is ranked as the second most frequently encountered neurological condition, with a worldwide prevalence of 5-9 persons per 1,000 population.[1,2]

Anti-seizure medication is the first line of treatment for most epileptic patients with the goal of sustaining a normal lifestyle through absolute seizure control with minimal or no side effects.[3]

The role of pharmacists has evolved over the years to involve a variety of responsibilities, from dispensing medications to patient care, patient counselor, health care educator, and community service to clinical practice. Recommendations by the Joint Commission on Accreditation of Healthcare Organizations state that all prescriptions must be evaluated by pharmacists before dispensing and emphasize that outcomes should be documented as a result of direct patient care by the pharmacist.[4]

In 1990, Hepler and Strand[5] defined pharmaceutical care (PC) as ''the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life''. Medication errors are errors encountered during ordering, transcribing, dispensing, administering, and monitoring in the process of medication use. Interventions by pharmacists are required to identify and

resolve drug-related problems (DRPs). Many of these problems can be prevented by educating healthcare providers about them. These clinical interventions by pharmacists have a positive impact on the healthcare system by enhancing patient care and reducing costs. It is important to ensure that all interventions by the pharmacist are documented. This will help justify pharmacists' services to patients, healthcare administrators and providers, and patient care takers. It also helps to strengthen the profession and its image in thesociety.[4,6]

PC is ideally provided by a clinical pharmacist who is part of a multidisciplinary team that provides care to the patient. Medication reviews are a part of PC interventions to reduce inappropriate prescribing and drug use. This is the process in which a pharmacist reviews the patient, their disease, and drug treatment. PC enables pharmacists to implement interventions designed to reduce inappropriate prescribing and drug use. It also helps identify unmet therapeutic needs.[7]

Reports from previous studies have shown that pharmacists' interventions were essential to improving the health of patients with epilepsy. These reports indicate that pharmacists' interventions can prevent drug therapy problems. However, more studies are needed to highlight the positive impacts of pharmaceutical services on the health of patients with epilepsy.[8]

In Nigeria, evidence of the involvement of pharmacists in the provision of specialized care to patients with epilepsy is lacking. This study aimed to identify DRPs encountered by patients with epilepsy using PC instruments; provide PC interventions to resolve identified DRPs; and determine the status of the DRPs after the implementation of PC interventions.

METHODS

Study Design and Setting

This was a prospective longitudinal study with a 6-month follow up period.

The study sites were the University of Uyo Teaching Hospital in Uyo, Akwa Ibom State, and the University of Calabar Teaching Hospital in Calabar, Cross River State. These selected hospitals are major referral centers for epilepsy management in Southern Nigeria. Patients were recruited from the neurology and medical outpatient clinics of the hospitals.

Study Population

Ninety-five patients diagnosed with epilepsy and receiving treatment for epilepsy at selected hospitals who fulfilled the inclusion criteria were identified and recruited into the study. The Inclusion criteria were patients diagnosed with epilepsy and receiving treatment for epilepsy at the study sites, those who provided written informed consent to participate in the study, and those who expressed willingness to abide by the rules of the study.

The exclusion criteria were patients who were diagnosed with non-epileptic seizures only, those aged less than 16 years, those who expressed willingness to withdraw from the study, those with intellectual disabilities, and those with acute psychiatric illness.

MAIN POINTS

- Involvement of pharmacists in the provision of specialized care to patients with epilepsy are lacking in Nigeria.
- Pharmaceutical care (PC) enables pharmacists to implement interventions to reduce inappropriate drug use.
- This study revealed the great potential of pharmacists in providing specialized care for persons with epilepsy.
- Providing justification for the integration of PC services with other elements of health care for patients with epilepsy.

Pharmaceutical Services

In this study, PC intervention was aimed at identifying and resolving DRPs encountered by patients. The research clinical pharmacist interacted with the physicians and patients during each clinic visit to optimize therapy with anti-seizure medications. PC was provided in a stepwise approach:

Setting priorities for patient care;

Assessing patients' specific educational needs and identifying DRPs;

Developing a comprehensive and achievable PC plan in collaboration with the patient and physician;

Implementation of this plan;

Monitoring and review of the plan from time to time according to the needs of the patient.

During each clinic visit, patients met with the research pharmacist prior to visiting their physician. The research pharmacist collected medication history, identified DRPs, collaborated with the physician and patients to resolve identified problems, answered questions on drug therapy, and encouraged adherence.

The research pharmacist also provided counseling services to the patients during their clinic visits. When necessary, the pharmacist provided relevant recommendations for consideration by the physician when making an overall treatment plan. Patients were also provided with a report diary with the time and date of an appointment following each visit. The patient report diary contains a table for the patients to record the time that they took their anti-seizure drugs and the time that they had a seizure or experienced unusual symptoms. The patients were also requested to document in the diary the name and dose of the anti-seizure medication taken, the frequency of administration, the time each dose was taken, the side effects experienced (if any), and the anti-seizure medication suspected.

Assessment of Pharmaceutical Intervention

The type and incidence of DRPs, as well as the type of intervention provided, the acceptance or rejection of the intervention, and whether the problem was resolved or not were documented using the Pharmaceutical Care Network Europe (PCNE) Classification Scheme for Drug-related Problems version 8.02.

The PCNE classification is used for research into the nature, prevalence, and incidence of DRPs. Moreover, it is used as a process indicator in experimental studies on PC outcomes. This

tool is intended to help healthcare professionals document DRP information during the PC process.

The following official definition of PCNE-DRP is the basis for the classification:

"*A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.[9]

The basic PCNE classification now has 3 primary domains for problems, 8 primary domains for causes and 5 primary domains for Interventions. A section called 'Acceptance of the Intervention Proposals' is added, including 3 domains. However, on a more detailed level there are 7 grouped sub-domains for problems, 35 grouped sub-domains for causes, 16 grouped sub-domains for interventions, and 10 sub-domains for intervention acceptance. These sub-domains can be considered an explanation of the principal domains. A scale is also added to indicate whether or to what extent the problem has been solved, containing 4 primary domains and 7 sub-domains.[9]

Statistical Analysis

Data were analyzed using IBM Statistical Products and Services Solutions (SPSS) for Windows, version 25.0 (IBM Corp, version 25.0 Armonk, NY, USA). Frequencies and proportions were used to summarize the data. The analyzed data were presented using the PCNE classification scheme for DRPs version 8.02.

Ethical Approval

The research protocol was approved by the Health Research Ethics Committees of the University of Uyo Teaching Hospital and University of Calabar Teaching Hospital (reference numbers: UUTH/AD/S/96/VOL.XIV/571 & UCTH/HREC/33/454. Dates: 25: 04: 2016 & 11: 04: 2016 respectively). In addition, informed consent was obtained from the participants prior to their recruitment into the study.

RESULTS

Ninety-five patients with epilepsy were recruited into the study. The sociodemographic and clinical profiles of the patients are presented in Table 1.

Identification and Resolution of Drug-related Problems

The classification and sub-classification of DRPs, categorization and sub-categorization of interventions by the research pharmacist, acceptance of the research pharmacist's intervention proposals, and the categorization of the status of the DRPs after the intervention proposals are presented in Tables 2, 3, 4, and 5, respectively.

The total number of DRPs identified by the research pharmacist among patients with epilepsy was 277. Three hundred and seventy nine (379) interventions were offered by the research pharmacist.

Approximately 57.04% of the identified DRPs were patient-related, whereas 15.88% were dispensing-related. Approximately 64.12% of the research pharmacist's interventions were at the patient level, whereas 24.01% of these interventions were at the prescriber level. Approximately 61.73% of the identified DRPs were fully resolved after implementation of PC interventions.

DISCUSSION

PC involves identifying the medication needs of an individual patient and providing not only the required medicines but also the necessary clinical services before, during, or after treatment to ensure an optimally safe and effective drug therapy.[10] This describes the principal essence of clinical pharmacy, from where it was adopted as a professional practice rather than merely a health science, and provides a way for clinical pharmacists, particularly specialists and subspecialists, to coordinate their clinical work more effectively.[11]

Two hundred and seventy-seven DRPs were identified by the research pharmacist among the patients who participated in the study. Three hundred and seventy-nine intervention proposals were offered by the research pharmacist, while one hundred and sixty-one of the identified DRPs were fully resolved. Although interventions were made at both the prescriber and patient levels, most of the interventions in this study were at the patient level. This is because most of the identified DRPs were patient-related.

Table 1. Socio-demographic/clinical characteristics of patients

Characteristics	Frequency	Percentage
Age (years)		
16-24	29	30.53
25-34	25	26.32
35-44	19	20.0
≥45	22	23.16
Sex		
Male	54	56.84
Female	41	43.16
Educational level		
Primary	11	11.58
Secondary	31	32.63
Tertiary	53	55.79
Marital status		
Single	49	51.58
Married	38	40.0
Widowed	8	8.42
Religion		
Christianity	93	97.89
Islam	2	2.11
Duration of illness		
≤2 years	27	28.42
3-5 years	20	21.05
≥6 years	48	50.53
The type of epilepsy		
Generalized tonic clonic	64	67.37
Focal onset awareness	9	9.47
Impaired awareness	11	11.58
Diverse seizures	8	8.42
Absence seizures	3	3.16

Table 2. Classification and sub-classification of drug-related problems

Primary domain	Causes of DRPs	Total	Domain proportion	Overall proportion
1. Drug selection	Inappropriate drug according to guidelines/formulary	0	-	-
	Inappropriate drug (within the guidelines but not recommended) contra-indicated	0	-	-
	No indication for drug	0	-	-
	Inappropriate combination of drugs or herbal products medication	13	39.39	4.69
	Inappropriate duplication of therapeutic or active groups ingredient	9	27.27	3.24
	No drug treatment in spite of existing indication	11	33.33	3.97
	Too many drugs prescribed for indication	0	-	-
	Sub-total	**33**	**-**	**11.91**
2. Drug form	Inappropriate drug form	0	-	-
	Sub-total	**0**	-	-
3. Dose selection	Drug dose too low	0	-	-
	Drug dose too high	0	-	-
	Dosage regimen not frequent enough	0	-	-
	Too frequent dosage regimen	0	-	-
	Dose timing instructions are incorrect, unclear, or missing	14	100	5.05
	Sub-total	**14**	**-**	**5.05**
4. Treatment duration	Duration of treatment too short	0	-	-
	Duration of treatment too long	0	-	-
	Sub-total	0	-	-
5. Dispensing	Prescribed drug not available	12	27.27	4.33
	Necessary information not provided	17	38.64	6.14
	Wrong drug, strength or dosage advised (OTC)	8	18.18	2.89
	Poor drug or strength dispensed	7	15.91	2.53
	Sub-total	**44**	**-**	**15.88**
6. Drug use process	Inappropriate timing of administration or dosing intervals	0	-	-
	Drug under-administered	0	-	-
	Drug over-administered	0	-	-
	Drug not administered at all	0	-	-
	Wrong drug administered	0	-	-
	Drug administered via wrong route	0	-	-
	Sub-total	**0**	-	-
7. Patient related	Patients use/take less drugs than prescribed or do not take the drug at all	57	36.08	20.58
	Patient uses/takes more drug than prescribed	18	11.39	6.50
	Abuse of drugs (unregulated overuse)	22	13.92	7.94
	The patient uses unnecessary drug	15	9.49	5.42
	Patients take food that interacts	0	-	-
	Patient stores drug inappropriately	31	19.62	11.19
	Inappropriate timing or dosing intervals	15	9.49	5.42
	The patient administers/uses the drug in a wrong way	0	-	-
	Patient unable to use the drug/form as directed	0	-	-
	Sub-total	**158**	**-**	**57.04**
8. Other	No or inappropriate outcome monitoring	28	100	10.11
	Other cause	0	-	-
	No obvious cause	0	-	-
	Sub-total	**28**	-	**10.11**
Total		**277**	-	-

DRPs: Drug-related problems

Table 3. Categorization and sub-categorization of interventions by research pharmacists

Primary domain	Intervention	Total	Domain proportion	Overall proportion
No intervention	No intervention	0	-	-
The prescriber level	The prescriber is informed only	19	20.88	5.01
	Prescriber asked for information	16	17.58	4.22
	Intervention proposed prescribering	27	29.67	7.12
	Intervention discussed with the prescriber	29	31.87	7.65
	Sub-total	**91**	**-**	**24.01**
At the patient level	Patient (drug) counseling	143	58.85	37.73
	Written information provided (only)	0	-	-
	The patient referred to prescriber	18	7.41	4.75
	Spoken to family member/caregiver	82	33.74	21.64
	Sub-total	**243**	**-**	**64.12**
At the drug level	Drug changed	0	-	-
	Dosage changed	0	-	-
	Formulation changed	0	-	-
	Instructions changed	16	35.56	4.22
	Drugs stopped	29	64.44	7.65
	A new drug is started	0	-	-
	Sub-total	**45**	**-**	**11.87**
Other intervention or activity	Other intervention	0	-	-
	Side effects reported to authorities	0	-	-
	Sub-total	0	-	-
Total		**379**	**-**	**-**

Table 4. Categorization of acceptance of research pharmacist's intervention proposals

Primary domain	Implementation of intervention proposals	Total	Domain proportion	Overall proportion
Intervention accepted	Intervention was accepted and fully implemented	211	65.12	55.67
	Intervention accepted implemented	54	16.67	14.25
	Intervention was accepted but not implemented	0	-	-
	Intervention accepted, implementation unknown	59	18.21	15.57
	Sub-total	**324**	**-**	**85.49**
Intervention not accepted	Intervention not accepted: not feasible	0	-	-
	Intervention not accepted: no agreement	7	43.75	1.85
	Intervention not accepted: other reasons	0	-	-
	Intervention not accepted: unknown reason	9	56.25	2.37
	Sub-total	**16**	**-**	**4.22**
Other	Intervention proposed, acceptance unknown	39	100	10.29
	Intervention not proposed	0	-	-
	Sub-total	**39**	**-**	**10.29**
Total		**379**	-	-

Table 5. Categorization of the DRP status after the research pharmacist's intervention proposal

Primary domain	Outcomes of interventions	Total	Proportion
Not known	Problem status is unknown	65	23.47
Solved	The problem has been totally solved	171	61.73
Partially solved	Problem partially solved	22	7.94
Not solved	Problem not solved, lack of cooperation of patient	0	-
	Problem not solved, lack of cooperation among prescriber	0	-
	Problem not solved; intervention not effective	19	6.86
	No need or possibility to solve problem	0	-
Total		**277**	-

All intervention proposals from the research pharmacist to attending physicians that were aimed at resolving identified DRPs were accepted. At the patient level, the research pharmacist's interventions principally consisted of health education, counseling, and psychotherapy. The research pharmacist emphasized medication adherence, drug storage, inappropriate timing or dosing interval, and irrational drug use. Patients were also discouraged from dual health-seeking behavior, i.e., patients combining traditional remedies with conventional pharmacotherapeutic management of epilepsy. Patients were also counseled about the need to undergo prescribed medical laboratory and radiological investigations.

We found that the doses and dosing of anti-seizure medicines prescribed as documented in the prescription sheets and patient case notes were appropriate in a large majority of the cases studied. Furthermore, there were no contraindications to the use of prescribed anti-seizure medicines in the cases studied. This is commendable, but expected, given that the study was conducted in a tertiary health facility with specialized services. However, therapeutic drug monitoring was not performed in any of the cases studied. The measurement and interpretation of serum antiepileptic drug concentrations can be beneficial for the treatment of uncontrollable seizures. Therapeutic drug monitoring enables a more decisive and effective optimization of therapy and disease management.[12] The lack of therapeutic drug monitoring in these facilities, as revealed in this study, may be due to the pervasive problem of the non-availability of the facilities required to conduct such investigations, a problem that appears to be common in resource-poor settings.

Studies have shown that clinical pharmacists can identify, resolve, and prevent clinically significant DRPs.[13] Interventions by the research pharmacist in this study resulted in the resolution of a significant proportion, about sixty-two percent, of the identified DRPs. This finding indicates the efficacy of PC interventions in identifying and resolving DRPs. This finding is in agreement with the results of a previous study in which it was found that PC interventions by pharmacists positively influenced clinical outcomes, including a reduction in the frequency of hospital re-admissions, length of patient stay in the hospital, and halting disease regression.[13]

Pharmacists, through pharmacotherapeutic monitoring, can detect the emergence of health problems and prevent the progression of co-morbidities.[14]

A previous study on the implementation of PC interventions on patients with HIV in primary healthcare found that pharmacist interventions were able to significantly reduce DRPs.[15] Other studies have also suggested that pharmacist interventions can reduce DRPs, particularly problems related to drug safety and adverse reactions.[13,16-20]

Acceptance of the research pharmacist's intervention proposals by prescribers indicates good interprofessional collaboration between physicians and clinical pharmacists. A fundamental requirement for creating collaborative practice systems between pharmacists and other healthcare providers is to appreciate the potential contributions of pharmacists to provide safer and more effective drug therapies for the management of various diseases and the overall good of the larger society.[10] Clinical pharmacists should be involved in the selection of suitable pharmacotherapeutic agents for patients and should actively participate in clinical case discussions.[13,15,17,21] There is a compelling need for pharmacists to review all prescriptions before dispensing to patients. Furthermore, the therapeutic outcomes of direct patient care by pharmacists should be monitored and duly documented.[4]

A review of the available literature by Reis et al.[8] found that pharmacists' interventions were essential to improving the health of patients with epilepsy. These reports indicate that pharmacists' interventions can prevent drug therapy problems and improve adherence and response to anti-seizure medications. These studies also reveal significant achievements recorded by pharmacists and confirm that including pharmacists in the therapeutic team produces effective results for the success of pharmacotherapy and the quality of life of people with epilepsy.

Study Limitations

The researchers could not determine the outcomes of some pharmaceutical interventions during the study. However, the results showed that the interventions were effective in resolving most DRPs.

CONCLUSION

The most frequently encountered DRPs were patient related, which revolved around improper patient counseling and relaying medication information to caregivers rather than patients themselves. Most DRPs encountered were resolved following the acceptance of the pharmacist's PC interventions by the patients and attending physicians. PC interventions are effective in identifying and resolving DRPs.

Ethics

Ethics Committee Approval: The research protocol was approved by the Health Research Ethics Committees of the University of Uyo Teaching Hospital and University of Calabar Teaching Hospital (reference numbers: UUTH/AD/S/96/VOL.XIV/571 & UCTH/HREC/33/454. Date: 25: 04: 2016 & 11: 04: 2016 respectively).

Informed Consent: Informed consent was obtained from the participants prior to their recruitment into the study.

Authorship Contributions

Concept: U.E., Design: U.E., C.M.U., Data Collection or Processing: U.E., N.I., Analysis or Interpretation: U.E., C.M.U., N.I., Literature Search: U.E., C.M.U., N.I., Writing: U.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Differential Diagnosis of Focal Onset Seizure Limb-shaking Transient Ischemic Attaks

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Abstract

Limb-shaking transient ischemic attack (TIA); is an uncontrolled rhythmic or dysrhythmic, temporary, and generally coarse tremor movement of the upper or lower extremities. Since Miller Fisher's first report of limb-shaking TIA associated with internal carotid artery (ICA) stenosis in 1962, this condition has been described regularly. These are characterized by brief, arrhythmic, jagged, or jerky movements of the extremities and are generally misdiagnosed as focal seizures or movement disorders. TIA is usually correlated with negative neurological symptoms; thus, the diagnosis of TIA is typically not considered in patients presenting with episodic abnormal movement disorder. We presented three cases, one of these cases was one with ICA stenosis who benefits from revascularizatıon treatment (internal carotid artery stenting), the second case with ICA stenosis and who does not benefit from revascularization treatment (carotid endarterectomy operation), and the last patient wıthout ICA stenosis. The common feature of all three patients was hypotension. These patients are not as rare as thought, and the etiology of cerebral hypoperfusion should be urgently evaluated.

Keywords: Focal-onset-seizure, seizure-mimics, trans-ischemic attacks

INTRODUCTION

Limb-shaking transient ischemic attacks (TIAs) involve uncontrolled rhythmic or dysrhythmic, temporary, and generally coarse tremor movement of the upper or lower extremities.[1,2] TIAs typically occur with focal neurological deficits, such as reduced sensation, vision loss, or loss of muscle strength, and uncontrolled movement is not normally considered a feature of TIAs. Limb-shaking TIAs, which are frequently mistaken for focal motor seizures, represent a rare form of TIA that causes diagnostic difficulty.[1,3-7] It is vital to correctly diagnose limb-shaking TIAs because they are a sign of serious internal carotid artery (ICA) stenosis, and patients are at high risk of stroke.[6-9] Here, we present three patients with limb-shaking TIAs in light of the literature.

CASE PRESENTATIONS

Case 1

A 79-year-old male patient was examined in the neurology outpatient clinic due to clonic jerks in his left hand. From the patient's anamnesis, it was learned that this symptom had been present for 10 days and had become more frequent in the last 3 days, occurring every day and generally lasting about 10 minutes. During the neurological examination, the patient was conscious and demonstrated full orientation to the person at times. His cranial nerves were intact, his muscle strength was normal, and there were clonic jerks in his left upper extremity. The patient was taking amlodipine (10 mg/day) for hypertension. The patient's blood pressure was 100/60 mmHg. Emergency cranial computed tomography (CT) results were normal with no acute changes. His blood biochemistry and haemogram results were normal, as were his electroencephalography (EEG) results (Figure 1).

The patient was admitted to the neurology ward for further examination and treatment. His course of amlodipine was stopped. During clinical observation, the patient developed weakness in his right upper extremity. Diffusion magnetic resonance imaging (MRI) was performed, and the results showed that acute infarct areas exhibited diffusion restriction in the right precentral and postcentral gyri. In addition, cranial and neck CT angiography revealed critical stenosis in the right ICA. A course of acetylsalicylic acid (300 mg/day) and clopidogrel (75 mg/day) was initiated, and the patient underwent ICA stenting.

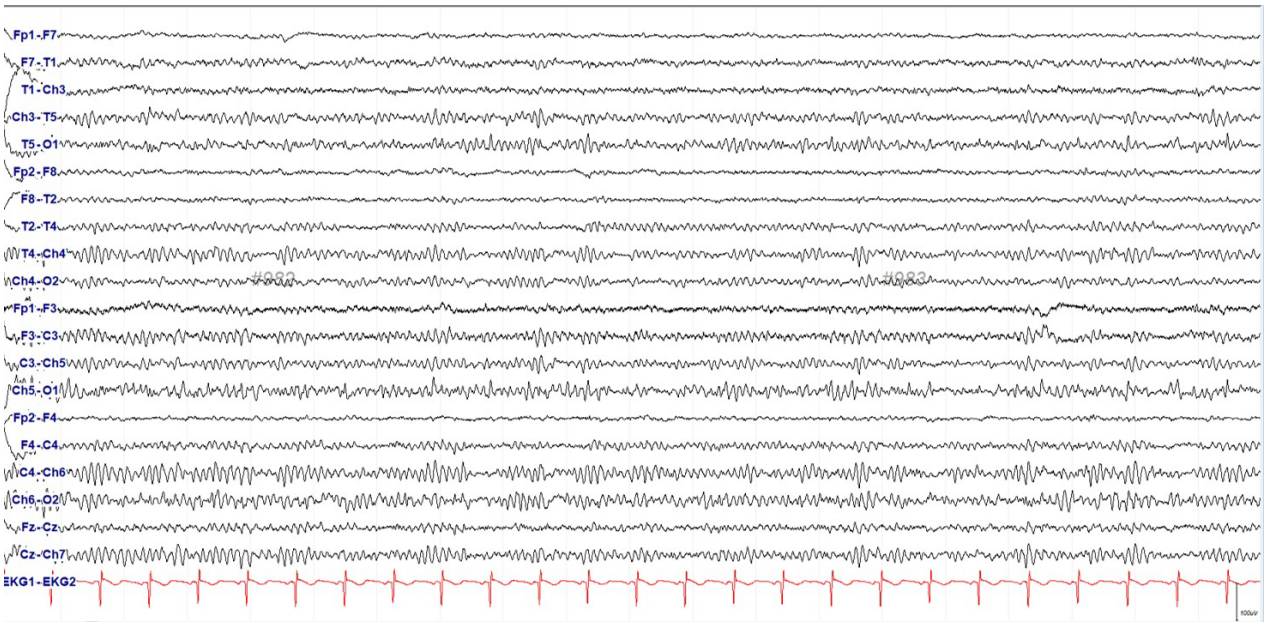

Figure 1. EEG of case 1 showing normal
EEG: Electroencephalography

The patient's involuntary movements regressed. During the neurological examination at discharge, the patient was conscious, oriented, and cooperative. His left nasolabial groove was blurred, and his left upper extremity exhibited plegia. During the 3-month neurology outpatient clinic follow-up, the patient regained muscle strength, and the neurological examination findings were normal.

Case 2

A 61-year-old male patient who complained of jerks in his left hand was examined. These clonic jerks started for 10 days and have become more frequent in the last 3 days, occurring every day and generally lasting about 1 minute. The symptoms were triggered by standing up. During the neurological examination, the patient was conscious and had full orientation to the person at times. His cranial nerves were intact, his muscle strength was normal, and clonic pulsations were detected in the left upper and lower extremities. The patient's medical history indicated that he had been diagnosed with hypertension and was taking amlodipine (10 mg/day) and valsartan (320 mg/day). The patient's blood pressure was 100/60 mmHg. Emergency cranial CT results were normal. The EEG results were normal. The patient was hospitalized for further examination and treatment. Diagnostic cerebral angiography showed an occluded right ICA and a critical stenotic left ICA was critical stenotic (Figure 2). The patient underwent carotid endarterectomy. However, the patient's involuntary movements did not regress after carotid endarterectomy, and he was subsequently admitted to the non-invasive video-EEG monitoring unit. The background EEG activity showed waves in the alpha band of 9-10 Hz and 35-40 µV located parieto-occipitally, and waves in the beta band of 16-18 Hz and 5-10 µV located frontocentrally. No ictal activity was detected during video-EEG. Normal sleep patterns were observed. The 5-6 Hz and 40-45 µV theta waves occasionally produced sparse and scattered localization. The patient had clonic jerks in his left upper and lower extremities while being admitted to the video-EEG monitoring unit, and a diagnosis of limb-shaking TIA was considered. The course of amlodipine and valsartan was stopped. The patient's symptoms subsided 21 days after carotid

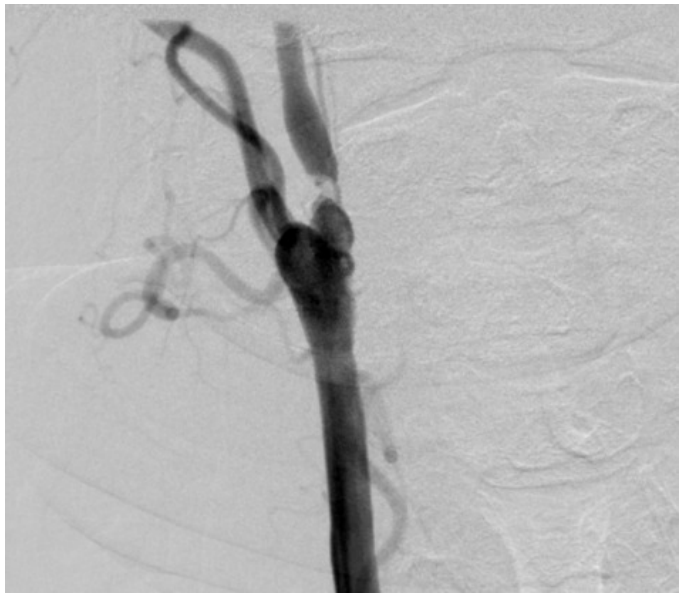

Figure 2. Diagnostic cerebral angiography showing near-complete occlusion of the left internal carotid artery bifurcation

MAIN POINTS

- Limb-shaking transient ischemic attack; is an uncontrolled rhythmic or dysrhythmic, temporary, and generally coarse tremor movement of the upper or lower extremities.
- These are characterized by brief, arrhythmic, jagged, or jerky movements of the extremities and are generally misdiagnosed as focal seizures or movement disorders.
- The common feature of all three patients was hypotension and internal carotid artery stenosis. These patients are not as rare as thought, and the etiology of cerebral hypoperfusion should be urgently evaluated.

endarterectomy. During the 3-month neurology outpatient clinic follow-up, the patient's symptoms did not recur, and the patient had a good clinical outcome.

Case 3

A 77-year-old female patient presented with clonic jerks in her right arm that had been present for the last year and were triggered by sudden postural changes, such as standing or sitting up from a bed. From his medical history, it was learned that he had chronic renal failure and received hemodialysis three times a week. His examination results revealed findings consistent with chronic renal anemia. As the patient's anemia advanced, his symptoms increased; however, they regressed with erythrocyte suspension replacement. Although the patient underwent extensive testing to identify the etiology of his anemia, it could not be determined, and the diagnosis of chronic anemia was confirmed. Widespread chronic ischemic lesions were identified via cranial MRI. Acute infarction was not detected. A plan was developed to conduct vascular evaluation, and the nephrology service was consulted; however, it was deemed inappropriate to perform a contrast examination due to the patient's high creatinine level. The carotid vertebral Doppler, intracranial magnetic resonance angiography, and EEG results were normal. Postural changes and momentary hypotensive attacks triggered the patient's symptoms. The cardiology service was consulted to address both anemia and hypotensive attacks, and the patient's antihypertensive treatment regimen was changed.

The patient's symptoms have regressed as his hypotension and anemia have been controlled. However, when the anemia intensifies and the patient changes his posture, the symptoms occur intermittently, although for a shorter period (Table 1).

DISCUSSION

Since Fisher[10] first reported in 1962 that limb-shaking TIAs are related to ICA stenosis, this condition has been regularly diagnosed. It is characterized by brief, arrhythmic, jagged, or jerky movement of the extremities and is generally misdiagnosed as focal seizures or movement disorders. TIAs are typically correlated with negative neurological symptoms. Thus, the diagnosis of TIA is not usually considered in patients presenting with episodic abnormal movement disorders.[1,4] However, these attacks can be distinguished from seizures by the absence of aura, incontinence and unconsciousness; there are also other important clinical differences, such as the absence of a Jacksonian spread.

In cases of TIA, EEG results are always normal, and anticonvulsants are ineffective. The clinical features of limb-shaking TIAs are as follows: rhythmic or arrhythmic involuntary hyperkinesis that unilaterally affects the hand, arm, leg, or limb; preservation of facial muscles; and greater prominence of upper extremities. An almost universal sign of limb-shaking TIA is the occurrence of symptoms after the patient performs action that theoretically provokes cerebral blood hypoperfusion, such as standing up. There is usually a short delay of a few seconds between standing up and the onset of symptoms.[11] Although EEG-based studies have shown that some patients have a contralateral slow background activity, limb shaking is not associated with TIA.[12] In the first and second cases presented in this paper, critical stenosis was detected in the ICA contralateral to the side of the involuntary movements; however, in the second case, the symptoms did not regress after ICA revascularisation. Although it is known that ischemic stroke is a heterogeneous group of diseases involving many complex mechanisms,[13] it is unknown how cerebral hypoperfusion causes symptoms such as clonic jerks in extremities.

One possibility is that cerebral hypoperfusion affects subcortical motor pathways. Small-vessel disease and normal carotid angiography have also been reported as causes of limb-shaking TIAs.[12] In all three of our cases, the neurological examination results were normal and the modified Rankin scale score was zero during the third month of neurology outpatient clinic follow-up. Unfortunately, the prognosis can be poor for patients with limb-shaking TIA because they have a high risk of stroke. Therefore, it is important to diagnose and treat limb-shaking TIA. Managing low-flow TIAs involves maintaining or improving cerebral blood flow while carefully controlling blood pressure and revascularization. In many cases, symptoms regression has been reported after increasing blood pressure.[2-10] In the second case, although ICA revascularisation was achieved, the limb-shaking TIA symptoms did not regress. However, after the patient's antihypertensive medications were stopped and his blood pressure increased and regulated, his symptoms were resolved.

CONCLUSION

In summary, limb-shaking TIA is a rare form of TIA that must be distinguished and differentiated from conditions such as focal motor seizures. Diagnosis is often accompanied by ICA occlusion, and timely treatment not only eliminates attacks in patients but also reduces the risk of stroke. Limb-shaking TIAs are not as rare as

Table 1. Clinical, radiological and demographic features of patients with limb-shaking trans ischemic attacks

	Case 1	Case 2	Case 3
Age	79	61	77
Sex	Male	Male	Female
Cranial MRI	Normal	Normal	Chronic ischemic lesions, no acute infarction
Cause of limb-shaking transient ischemic attack	ICA stenosis, hypotension	ICA stenosis, hypotension	Anemia of chronic disease, hypotension
Ipsilateral internal carotid artery	Near-occlusion	Near-occlusion	Normal
Contralateral internal carotid artery	Normal	Ocluded	Normal
Routine EEG	Normal	Normal	Normal
Video EEG monitoring	-	Normal	-
Clinical outcome	Good clinical outcome	Good clinical outcome	Good clinical outcome

EEG: Electroencephalography, MRI: Magnetic resonance imaging, ICA: Internal carotid artery

once thought, and patients with these conditions should be urgently evaluated for the etiology of cerebral hypoperfusion.

Ethics

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: B.H., Concept: Y.D., M.B., Design: A.B.D., E.A.D., Data Collection or Processing: Y.D., A.B.D., E.A.D., Analysis or Interpretation: B.H., Literature Search: Y.D., E.A.D., M.B., Writing: Y.D., E.A.D., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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