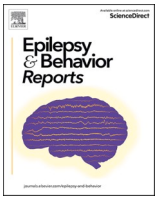
Epilepsy & Behavior Reports 27 (2024) 100701

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr



Hidden cases of epilepsy in cognitive impairment clinics: Exploring the use of a portable device for simplified electroencephalography testing

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ARTICLE INFO

Keywords:
Dementia
EEG
Epilepsy
Temporal lobe epilepsy

ABSTRACT

Late-onset epilepsy, particularly focal impaired awareness seizures, often present without convulsions and can cause memory impairment. This can lead patients to initially seek consultation at memory clinics, potentially delaying referral to epilepsy specialists. We report on three patients, aged 40s to 70s, admitted for cognitive evaluation who were finally diagnosed with epileptic seizures as the underlying cause of their symptoms. Notably, all initially presented to local clinics with symptoms suggesting cognitive impairment. Despite initial diagnostic uncertainty, all patients exhibited epileptic activity on electroencephalography (EEG) and responded positively to antiepileptic drugs, suggesting epileptic mechanisms were involved in their symptoms. Both traditional clinical EEG systems and newly developed, one-minute portable EEG devices were used in their evaluations. The portable device, medically approved in Japan, successfully captured sharp-waves like activities with the same durations, amplitudes, and shapes as traditional devices. This highlights its potential to improve epilepsy diagnosis and future screening due to its portability and ease of use. Implementing portable EEG devices could promote timely and appropriate treatment, preventing misdiagnosis of neurological conditions.

1. Introduction

Epilepsy prevalence follows a U-shaped curve, with peaks in childhood and old age, and a decreased prevalence during adolescence and adulthood [1]. In elderly patients, the most common seizure type is the focal impaired awareness seizure [2], which is often nonconvulsive [3] and challenging to diagnose [4]. Since symptoms can include memory impairment [5], including autobiographical amnesia and accelerated long-term forgetting (as described later), these patients may be referred to dementia clinics instead of epilepsy specialists. In epilepsy management, clinical symptoms often raise suspicion, leading to the use of electroencephalography (EEG) for diagnostic confirmation. However, if an EEG is not performed in the absence of typical clinical symptoms, there is a substantial risk that the patient will be misdiagnosed with a dementia-related disorder [5]. However, routine EEG is rarely performed in outpatient clinics for cognitive complaints.

Here, we present a series of patients admitted for detailed cognitive evaluation who were finally diagnosed with epileptic mechanisms as the underlying cause of their symptoms. This case series highlights the potential of using simple, portable EEG devices for diagnosing epilepsy.

2. Case presentations

First, we provided details about the EEG test utilized in this report, followed by a discussion of the cases.

3. Overview of the EEG test used in this article

Clinical EEG data were collected using a digital 19-channel scalp EEG device (EEG-1200, NihonKoden, Tokyo, Japan) with the International

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https://doi.org/10.1016/j.ebr.2024.100701
Received 8 June 2024; Received in revised form 16 July 2024; Accepted 27 July 2024
Available online 28 July 2024

10–20 electrode placement. The data were acquired with a linked-ears reference and sampled at 500 Hz.

For portable EEG measurements, we employed a patch-type device named "HARU-1" (Supplementary Figure S1). This device consisted of a wireless sensing unit and disposable electrode sheets applied to the subjects' foreheads. HARU-1 has received medical approval from Japan's Pharmaceuticals and Medical Devices Agency and has been demonstrated to capture EEG data according to the same standards as traditional clinical EEG examinations (Certification Number: 302 AFBZX00079000, Class II, EEG). The device records three-channel EEG signals referenced to the left ear at a sampling rate of 250 Hz. This EEG patch offers rapid deployment (approximately one minute) by simply adhering it to the forehead, even allowing for self-application with a mirror. Additionally, it facilitated measurements in various settings, including hospitals, outpatient clinics, and even patients' homes, without requiring hair washing. These disposable electrodes are easily removed after use.

In this study, we analyzed two-minutes-EEG data recorded during rest with eyes closed, measured using this device. Additionally, the device is very light and comfortable to wear, making it possible to record continuous data for up to six hours from the subjects. Furthermore, it has been demonstrated that the data from this device can aid in the diagnosis of neuropsychiatric disorders [6,7], suggesting the robustness of data collection using this device.

3.1. Case A: Male in his 60s

One year before he visited our department, the patient began experiencing occasional episodes of misplaced or lost objects. Concerned about his cognitive decline, his wife accompanied him to a local clinic. He was subsequently referred to our department for further investigation.

A cognitive evaluation revealed a score of 28 on the Mini-Mental State Examination (MMSE) and 8.6 points on the Alzheimer's Disease Assessment Scale-Cognitive Subscale Japanese version (ADAS-J cog). The MMSE [8] is scored on a 30-point scale, with higher scores indicating better cognitive function. The MMSE is often used to screen for cognitive impairment, including orientation, memory, attention and other cognitive functions. The ADAS-cog [9] is a comprehensive tool used to evaluate the severity of cognitive symptoms of Alzheimer's disease (AD). The ADAS-Cog is scored on a 70-point scale, with higher scores indicating greater cognitive impairment. This scale assesses cognitive functions designed to evaluate memory functions, language functions, and other cognitive abilities.

During a detailed interview conducted in our department, his wife reported his episodes of impaired awareness accompanied by oral automatism roughly every six months. Notably, even when presented with photographs from a trip he took two years prior (used to assess autobiographical memory), he displayed no sense of familiarity, suggesting possible autobiographical amnesia (AbA) [5].

Cerebrospinal fluid analysis revealed no elevated cell count or protein levels, and none of Alzheimer's disease (AD)-related biomarker changes (amyloid beta and phosphorylated tau). Brain magnetic resonance imaging (MRI) performed by a certified radiologist confirmed no significant cerebral lesions. EEG identified intermittent sharp waves in both anterior temporal regions (Fig. 1). Notably, the portable EEG device also detected similar sharp-wave like activities (Fig. 2). Following treatment with lacosamide (LCM), his epileptic seizures, impaired awareness, and oral automatisms were effectively controlled with no recurrence. His memory impairment had improved to the extent that it no longer seriously interfered with his daily life, much to his family's relief. This case maintained a good condition at the one-year follow-up.

3.2. Case B: Male in his 40s

Two years before he visited the department, the patient began experiencing difficulty managing unfamiliar work tasks. One year later, he developed memory lapses related to his work and sought consultation at a local clinic for cognitive dysfunction.

Encephalitis was initially suspected. Subsequently, another hospital performed EEG testing, leading to a suspicion of temporal lobe epilepsy (TLE). Based on this diagnosis, he was referred to our hospital's neurosurgical department. Upon evaluation by a neurosurgery specialist at our hospital, obvious symptoms indicative of encephalitis were not observed. However, notable memory impairment was present, raising suspicion of a dementia-related disease, leading to the patient's referral to our department. Concerned about his worsening symptoms, the patient's family moved in with him at that time. They witnessed nightly

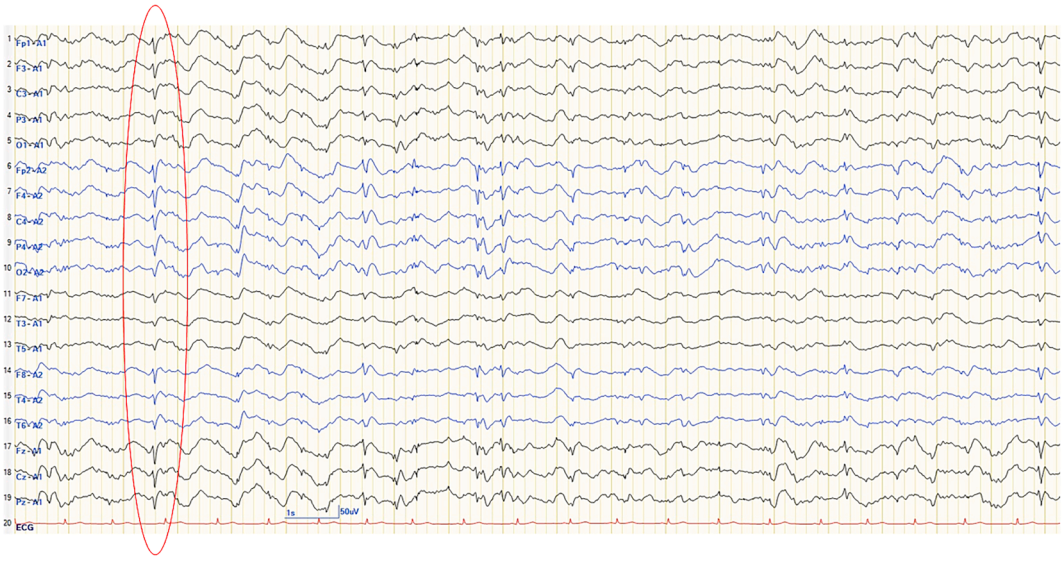

Fig. 1. Clinical EEG with 19 channels of bilateral ears' reference. The area circled in red showed negative sharp waves, which were dominant in the right hemisphere but were also observed in the left hemisphere, and it could be seen that these activities spread to the electrodes in the frontal region. These sharp waves were thought to reflect electrical activation of the ear. These epileptogenic activities varied in appearance depending on the electrodes, but were estimated to last about 100–150 ms and hold amplitude of 50——80 μV. The sharp wave component had a steeper fall in the first half than a rise in the second half. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

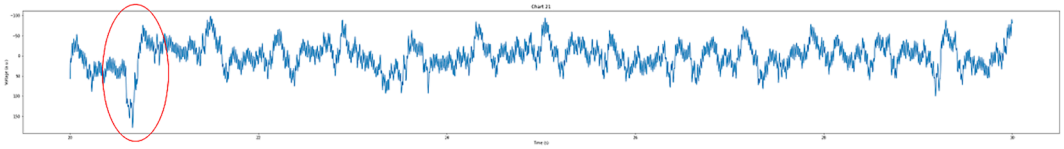

Fig. 2. Portable EEG activity with the left ear's reference. The figure showed EEG activity in 10 s. The area circled in red showed the negative sharp-wave like activity, and the duration and amplitude were estimated to be about 150 ms and 70–100 μV. The sharp wave component had a steeper fall in the first half than a rise in the second half. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

episodes characterized by vocalizations, foaming at the mouth, and aimless standing. These episodes were followed by periods of confusion and slow recovery.

Then, an epileptogenic mechanism was suspected to underlie his clinical symptoms, prompting the introduction of LCM. Following the initiation of LCM treatment, the nocturnal vocalizations almost completely resolved. He then underwent an inpatient cognitive evaluation at our department.

Notably, he had changed jobs multiple times in his 20s and 30s, but exhibited no memory of these past jobs, possibly due to AbA [5]. Cerebrospinal fluid analysis revealed no elevated cell count or protein levels and none of AD-related biomarker changes. A brain MRI performed by a certified radiologist confirmed no significant cerebral lesions. Intermittent sharp waves in both anterior temporal regions were observed on the traditional EEG (Supplementary Figure S2) and sharp-wave like activities on the portable EEG device (Supplementary Figure S3). His memory function improved significantly after LCM treatment, allowing him to return to a normal life without limitations. This case maintained a good condition at the one-year follow-up.

3.3. Case C: Male in his 70s

Approximately one year before presentation at our department, the patient began experiencing occasional episodes of misplaced objects, forgetting recent events from the previous day, and difficulty performing his work. Due to concerns about cognitive decline, his family brought him to a local clinic for evaluation. He was subsequently admitted to our department for further examination.

Cognitive testing revealed scores of 30 on the MMSE and 7.7 points on the ADAS-J cog. During the routine inpatient evaluation at our department, EEG testing was performed. This revealed the presence of epileptogenic activity, as detailed below. While he could recall undergoing a social event memory test a few hours prior, he had no recollection of it four days later, suggestive of possible accelerated long-term forgetting (ALF) [5].

Cerebrospinal fluid analysis revealed no elevated cell count or protein levels and none of AD-related biomarker changes. A brain MRI performed by a certified radiologist confirmed no significant cerebral lesions. Intermittent sharp waves in both anterior temporal regions were observed on the EEG (Supplementary Figure S4). The portable EEG device also detected similar sharp-wave like activities (Supplementary Figure S5). His memory impairment significantly improved after treatment with LCM, allowing him to return to a normal life. This case maintained a good condition at the one-year follow-up.

4. Discussion

This article describes patients admitted to our department for detailed cognitive evaluation whose symptoms were finally diagnosed with epileptic mechanisms as the underlying cause of their symptoms. This case series reaffirmed the critical importance of conducting EEG tests in conjunction with detailed clinical interviews to avoid missing opportunities for appropriate treatment.

The cases in this study appeared to have cognitive dysfunction due to AD, but in all three cases, no changes were observed in the cerebrospinal fluid of AD-related biomarkers. Therefore, while the symptoms might initially suggest the coexistence of AD, it was concluded that this was not the case.

All patients exhibited EEG abnormalities and responded positively to antiepileptic drugs, suggesting epileptic mechanisms as the underlying cause of their symptoms. Sharp waves were predominantly observed in the temporal regions, a finding suggestive of TLE if epilepsy is confirmed. Temporal lobes are the most common source of focal seizures [10]. Patients with TLE typically experience behavioral arrests, including oral and manual automatisms, and varying degrees of impaired awareness with postictal confusion [11]. However, elderly patients with TLE may exhibit less frequent impaired awareness or convulsive seizures leading to falls [12]. Additionally, oral and manual automatisms may be less common in this population [12]. In our case series, only Case A displayed impaired awareness during seizures accompanied by oral automatisms, a symptom typically associated with TLE. As aforementioned, elderly patients with TLE often presents with mild symptoms and impaired awareness. Patients may not retain memories of seizures, leading to misdiagnosis as dementia-related symptoms.

In addition, these patients exhibited epileptogenic activity predominantly in the temporal region, alongside symptoms suggestive of characteristic memory impairments like AbA and ALF. AbA refers to the loss of memories for all or part of one's past life. This often becomes apparent when reviewing family photos or reminiscing about memories with friends and family, and is particularly evident in "experiential" or "autonomous" recollections of salient personal events [5]. ALF refers to an excessively rapid loss of memory for information that appears to have been acquired and stored normally during standard testing intervals of approximately 30 min [5]. Their pathophysiological condition could be associated with the syndrome of transient epileptic amnesia (TEA), which is associated with some cases of TLE. Zeman *et al.* [13] reported clinical features of TEA and transient amnesia with an epileptic origin. Patients with TEA often exhibit memory problems, including ALF and AbA [5], which aligns with our findings. However, since the age of onset and seizure patterns in case B were atypical for TEA, careful consideration was required to determine whether his memory symptoms should be included in the concept of AbA.

Case C lacked witnessed seizures, which would not meet the strictest definition of epilepsy [14]. Case C exemplifies a situation where the opportunity for appropriate treatment could have been delayed if electroencephalogram (EEG) testing had not been performed. This case reaffirms the importance of EEG testing and highlights its critical role in timely and accurate diagnosis. Recent literature describes cases with TEA-like symptoms but without seizures, categorized as TEA complex syndromes [15]. Case C potentially falls within this category. Otherwise, in case C, it is possible that, as in case B, minor symptoms could have been detected through close family observation. EEG recordings provided objective evidence of epileptiform activity, enhancing diagnostic accuracy. They identified localized potential focus and facilitated detailed patient interviews, helping detect subtle seizure signs from family-reported information.

Next, the memory disorders suspected in these cases were not detected by standardized tests, and we hoped that a future challenge could establish standardized tests with a clear consensus on how to detect these memory disorders.

EEG confirmation of epileptogenic activity in all cases allowed for

appropriate treatment. Notably, the portable device likely captured the same epileptiform activity observed with traditional clinical EEG. Although the clinical EEG displayed reduced amplitude in frontal regions, sharp waves extended to those with the ear reference. This suggests the portable device using an ear reference should capture the same signals.

The portable device in this study exhibited frontal EEG activity referenced on the left ear, susceptible to artifacts like electromyography or eye movements. This limits the definitive identification of captured activities as epileptogenic. In addition, although the interval between clinical EEG and HARU-1 recordings was within a week, simultaneous recordings were not conducted due to concerns about potential impacts on the clinical EEG assessment, requiring caution when interpreting the results. However, the portable device captured sharp-wave like activities with durations, amplitudes, and shapes remarkably similar to those captured by clinical EEG. More cases are needed to definitively validate this device for epilepsy detection. Future confirmation of its effectiveness could revolutionize epilepsy screening. This portability allows for measurements anytime and anywhere, without specialized equipment, potentially preventing missed diagnoses. This approach had the potential to detect epilepsy, a treatable condition, and was thought to have important clinical applications especially for the non-neurological clinicians without specialized EEG equipment.

5. Conclusion

This case series reports on patients admitted for cognitive evaluation whose symptoms were finally attributed to epileptic mechanisms. The findings highlight the critical importance of combining EEG tests with detailed clinical interviews to ensure accurate diagnosis and appropriate treatment. Notably, a portable device successfully captured epileptiform activity similar to traditional clinical EEG. This finding suggests promise for utilizing such devices in future epilepsy screening programs.

CRediT authorship contribution statement

Masahiro Hata: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Yuto Satake:** Writing – review & editing, Data curation. **Yuki Miyazaki:** Writing – review & editing, Visualization, Software. **Hisaki Omori:** Writing – review & editing. **Atsuya Hirashima:** Writing – review & editing. **Hideki Kanemoto:** Writing – review & editing, Supervision, Data curation. **Kenji Yoshiyama:** Writing – review & editing. **Shun Takahashi:** Writing – review & editing, Supervision. **Manabu Ikeda:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the staff of the biochemistry and neuropsychology laboratories who collected the specimens and performed clinical tests.

Funding

This study was financially supported by PGV, Inc. Tokyo, Japan. The funding agency was not involved in the research, interpretation of findings, or preparation of the manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Osaka University Hospital (approval number: 20312). Before enrollment, all participants provided a complete description of the research procedure and provided written informed consent.

Author contributions

MH was responsible for the conceptualization, design, and drafting of the manuscript. YS, YM, HO, AH, HK, YS, and MI were responsible for data collection and contributed to data interpretation. All the authors provided critical feedback on the analysis and manuscript. All the authors have read and approved the final version of the manuscript.

Availability of data and materials

All data generated or analyzed in this study are available from the corresponding author upon reasonable request and after additional ethical approval regarding data provision to individual institutions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100701.

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