EPILEPSY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "EPILEPSY Newsletter'' which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

- **Investigation of long-term prognosis after stereo-electroencephalography-guided three-dimensional radiofrequency thermocoagulation treatment in patients with mesial temporal lobe epilepsy with hippocampal sclerosis**
- **Determination of 72 hours versus 24 hours of extended video-EEG monitoring for confirming epilepsy diagnosis**
- **Determination of the volume and microstructure of the amygdala in focal epilepsy patients with tonic–clonic seizures, ictal, and post-convulsive central apnea**
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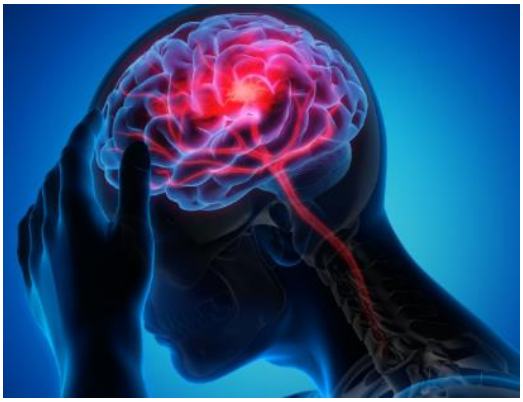
Investigation of long-term prognosis after stereo-electroencephalography-guided three-dimensional radiofrequency thermocoagulation treatment in patients with mesial temporal lobe epilepsy with hippocampal sclerosis

INTRODUCTION



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For patients with MTLE-HS, SEEG-3D RFTC is a potentially effective alternative.

The high prevalence and resistance to medications observed in medial temporal lobe epilepsy-hippocampal sclerosis (MTLE-HS) are a matter of particular concern.[1] In 1950, Penfield and Flanigin introduced anterior temporal lobectomy (ATL) for treating temporal lobe seizures. ATL has been the gold standard for treating mesial temporal lobe epilepsy (mTLE) for more than 50 years, with almost 80% of patients experiencing long-term seizure freedom. However, ATL comes with complications like visual field defects and memory loss, impacting post-procedure quality of life. Approximately 20% of patients experience varying degrees of recurrent seizures. Radiofrequency thermocoagulation (RFTC), first used in 1980, initially showed lower seizure freedom rates than ATL. Advances in imaging and development of frameless robotic systems have greatly improved RFTC. Now, guidance by stereotactic electroencephalography (SEEG), it can target the epileptogenic zone more effectively.[2] So, this study was conducted to examine the extended-term prognosis following stereo-electroencephalography-guided three-dimensional radiofrequency thermocoagulation (SEEG-3D) RFTC treatment in individuals with MTLE-HS.

METHODS

This retrospective study, conducted at a single center, involved 28 patients diagnosed with MTLE-HS. Inclusion criteria comprised of confirmed diagnosis of hippocampal sclerosis, clinically consistent EEG manifestations from the hippocampus, and a minimum postoperative follow-up of 60 months. All patients underwent thorough preoperative assessments, including high-resolution MRI, long-term video scalp EEG monitoring, magnetoencephalography, and positron emission tomography and computed tomography (PET-CT). SEEG-3D RFTC was the chosen treatment. Patients were discharged 2–3 days post-surgery, and postoperative effects were assessed using the Engel classification during a 5-year follow-up.

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RESULTS

After 60 months of SEEG-3D RFTC, 42.86% were Engel class I (combined IA and IB), with 78.57% experiencing over 50% seizure reduction. No permanent neurological deficits were reported during telephonic interviews. At 6 months post-surgery, 72.41% were Engel Ia, and 3.45% were Engel Ib. At 12 months, 51.72% were Engel Ia, and 17.24% were Engel Ib. Kaplan–Meier curves assessed the time to the first seizure (including aura) after surgery (Figure 1), and found that the patients who underwent SEEG-3D RFTC experienced noticeable seizures, including aura seizures, approximately 9–17 months post-surgery. The distribution of Engel class I patients were 79.31% at 3 months, 79.31% at 6 months, 72.41% at 12 months, 67.86% at 18 months, 62.07% at 24 months, 50.00% at 36 months, 42.86% at 48 months, and 42.86% at 60 months.

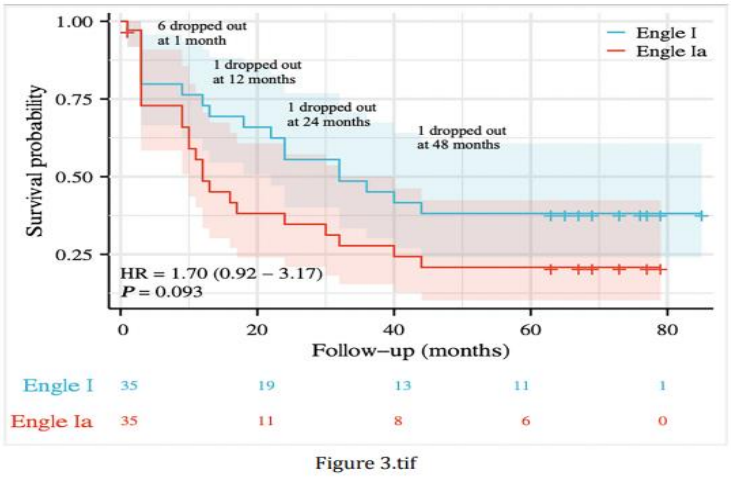

Figure 3.tif

Figure 1. Kaplan-Meier analysis showing the proportion of patients achieving Engel I and Engel Ia outcomes post SEEG 3D-RFTC. The curve considered seven patients lost to follow-up and two undergoing ATL or VNS surgery. It assumed the worst prognosis for those lost (seizure within the first month post-surgery). One patient was excluded due to not meeting inclusion criteria. SEEG - stereotactic electroencephalography-guided three-dimensional radiofrequency thermocoagulation; ATL - anterior temporal lobectomy; VNS - vagus nerve stimulation.

DISCUSSION

The findings indicated that SEEG-3D RFTC was a viable clinical option. In this study, 72.41% of patients achieved Engel class I status at 12 months post-surgery, with 42.86% maintaining this classification after 60 months. In a year, follow-up of 21 patients with HS, 76.2% (16 individuals) were categorized as Engel class I.[3] The treatment effectiveness in the mentioned study aligned with the findings observed 12 months after surgery in this ongoing long-term follow-up, affirming the efficacy of SEEG-3D RFTC in addressing HS. The current study utilized an optimized SEEG protocol with transverse electrodes and a longitudinal electrode placement protocol similar to LiTT, yielding favorable outcomes. In a prior randomized controlled study, it was discovered that SEEG-guided RFTC exhibited significantly lower effectiveness compared to ATL.[4] However in the current study, those designated as Engel I comprised 72.41% of the total at 12 months post-surgery, matching the efficacy of ATL (75.5%).[4]

CONCLUSION

SEEG-3D RFTC stands out as a promising choice for patients with MTLE-HS, given its minimally invasive nature.

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Determination of 72 hours versus 24 hours of extended video-EEG monitoring for confirming epilepsy diagnosis

INTRODUCTION

Episodes with transient loss of consciousness prompt referral to neurology services. Diagnosing epilepsy can be challenging when history, MRI, and EEG offer inconclusive results. Less than 50% of new-onset seizures show MRI abnormalities, and routine EEG may have a low diagnostic yield in focal epilepsies. Achieving certainty may require inpatient continuous 24-h EEG or long-term video-EEG monitoring in epilepsy units. Video-EEG monitoring assess seizure recurrence risk after the first unprovoked seizure, but the optimal monitoring duration for valid diagnostic assumptions remains unclear.[1] A prior investigation addressed this research question in the context of ambulatory long-term EEG but yielded conflicting outcomes. In this study, where 61% of patients were diagnosed with epilepsy, interictal epileptiform discharges (IEDs) were observed in 26.9%, and electrographic seizures were detected in 6% of all participants.[2] Moreover, ambulatory long-term EEG might not be accessible or covered in all clinical settings. So, this study aimed to compare 24 hours with 48, and 72 hours of video-EEG monitoring to confirm epilepsy diagnosis, assessing the time until the first occurrence of epileptic abnormalities (EAs), defined as interictal epileptiform discharges or electrographic seizures.

In patients with FE and unknown epilepsy types, VEM monitoring for up to 72 hours improves the likelihood of discovering EA and enhances the possibility of detecting spontaneous seizures.

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METHODS

In this retrospective study at a single center, 111 patients experiencing paroxysmal, seizure-like events underwent a minimum of 72 hours of video-EEG monitoring. Inclusion criteria comprised continuous recording during admission to the epilepsy monitoring unit (EMU), admission for a conclusive diagnosis after an inconclusive initial workup, confirmation of epilepsy diagnosis upon discharge, and explicit inclusion of individuals on antiseizure medication without meeting International League Against Epilepsy (ILAE) diagnostic criteria for epilepsy. This encompassed cases with normal routine EEG and MRI findings and a singular, unprovoked seizure. VEM recordings were analyzed to pinpoint the exact time of the first occurrence of epileptic abnormalities (EAs). Subgroup analyses were conducted for epilepsy types and treatment status.

RESULTS

Epileptic abnormalities (EAs) were observed in 69.4% (77 out of 111) of the subjects during video-EEG monitoring (VEM). Among these, 71 subjects showed detectable EAs within the initial 24 hours, three subjects between 24 and 48 hours, and another three between 48 and 72 hours. The average time until the first EA was 8.4 hours (standard deviation, SD = 12.5 hours). Notably, EAs were detected after 24 hours of continuous VEM in only 5.4% (6 out of 111) of all subjects. (Figure 1A) In 25 (22.5%) of 111 patients, epileptic abnormalities (EAs) were already observable during the resting EEG on the initial day of video-EEG monitoring (VEM).

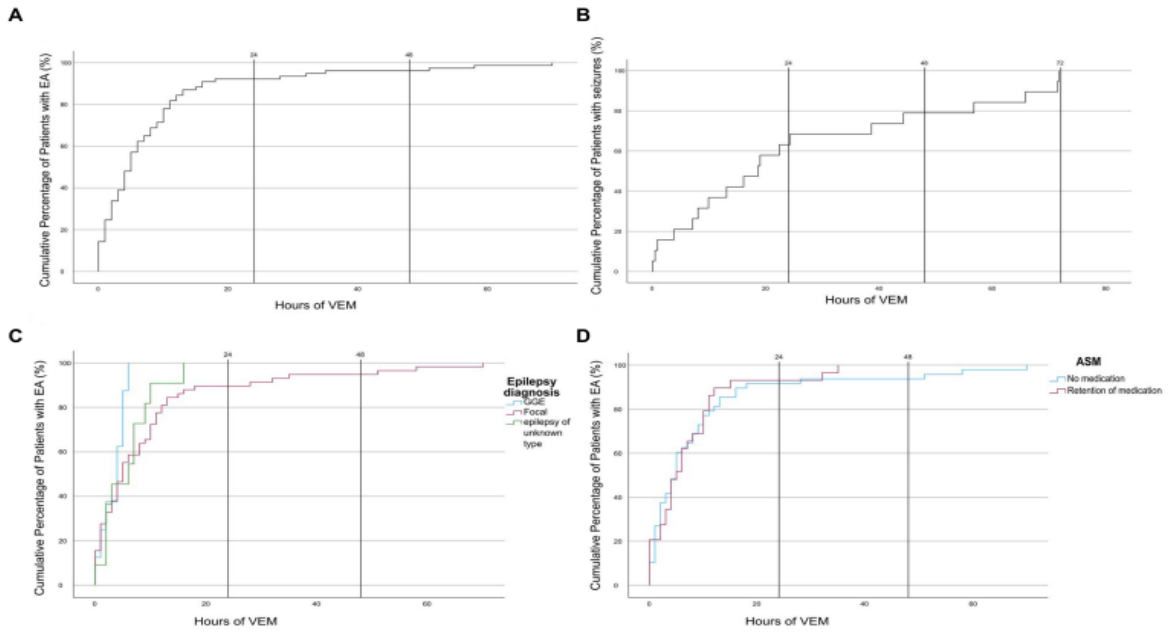

Figure 1. A cumulative time distribution chart with dashed lines at 24 h and 48 h of video-electroencephalogram (VEM) is presented. The chart covers time to the first epileptiform abnormality (EA) (A), time to the first seizure (B), time to the first EA based on epilepsy diagnosis (C), and time to the first EA based on antiseizure medication (ASM) status (D). The abbreviations used include IED (interictal epileptic discharges), EA (epileptiform abnormalities), GGE (genetic generalized epilepsy), and ASM (antiseizure medication)

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34 (30.6%) of 111 patients did not exhibit any EAs during the recording. For genetic generalized epilepsy (GGE), EAs were identified within 24 hours in all cases, averaging 3.4 hours (SD = 2.1). The average time until the first EA in the focal epilepsy (FE) group was 9.6 hours (SD = 14.1), and for patients with an unknown epilepsy type, it was 5.8 hours (SD = 4.7). Group differences were not statistically significant (Z = 1.434, p = 0.488). (Figure 1C) A total of 46 subjects adhered to a consistent antiseizure medication (ASM) regimen, while 65 subjects did not receive ASM treatment. In the former group, the first epileptic abnormality (EA) was identified only after 24 hours in 2 out of 46 subjects, and in the latter group, this occurred in 4 out of 65 subjects. The average time until the first EA for individuals maintaining their medication was 7.2 hours (with a standard deviation of 8.4 hours), and for those without ASM, it was 9.2 hours (with a standard deviation of ±14.5 hours). (Figure 1D) No significant difference was found between patients who were and were not on medication ($U = 692.500$, $Z = -0.037$, $p = 0.971$). Out of 111 subjects, 19 experienced at least one spontaneous electroclinical seizure, with an average time to the first seizure of 25.9 (±24.7) hours. Notably, 68.4% of the seizures occurred within the initial 24 hours, while 31.6% occurred after this period. (Figure 1B)

DISCUSSION

This study identified the benefits associated with VEM extending beyond the 24-hour mark in our group of patients. A significant portion of individuals exhibited epileptic activity exclusively after this 24-hour threshold, particularly those with focal epilepsy or an unspecified epilepsy type.[1] By supporting earlier studies, the author confirmed that interictal epileptiform discharges (IEDs) manifest sooner in genetic generalized epilepsy (GGE) compared to focal epilepsy (FE).[3] Around one-third of unplanned seizures occurred beyond the 24-hour mark of video-electroencephalography monitoring (VEM), despite patients being either on stable antiseizure medication (ASM) or not receiving any ASM.[1] In the another study, it was discovered that 40% of paroxysmal events occurred within the initial day of video-electroencephalography monitoring (VEM), and the average duration of VEM was 6.9 days.[4]

CONCLUSION

Monitoring individuals for 24 hours with video-electroencephalography (VEM) seems effective in identifying epileptic activity (EA) in most cases, a crucial consideration in resource-constrained settings. But extending VEM to 72 hours enhance the likelihood of detecting EA in those with focal epilepsy (FE) and unspecified epilepsy types, as well as capturing spontaneous seizures. The absence of EA during VEM introduced diagnostic uncertainty, suggesting the potential utility of long-term ambulatory monitoring strategies to address this diagnostic gap.

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Determination of the volume and microstructure of the amygdala in focal epilepsy patients with tonic–clonic seizures, ictal, and post-convulsive central apnea

INTRODUCTION

Reduced ODI and NDI in epilepsy patients, particularly in the FBTCS group, together with elevated bilateral amygdala sizes might point to mechanisms that directly affect cardiac and respiratory rhythms, hence increasing the chance of SUDEP.

Sudden Unexpected death in epilepsy (SUDEP) is a primary contributor to premature mortality in individuals with epilepsy, yet the underlying mechanisms of these fatal events are not fully understood. The occurrence of frequent tonic–clonic seizures (TCS) stands out as a significant risk factor. Some investigations examining the prevalence of seizures linked to respiratory issues propose that post-convulsive central apnea (PCCA) could serve as a clinical indicator for SUDEP.[1] Recent studies revealed that postictal central apnea, occurring after tonic–clonic seizures (TCS), a specific risk factor for sudden unexpected death in epilepsy (SUDEP). Structural MRI studies demonstrated changes in cardiorespiratory brain sites among individuals at SUDEP risk, with enlarged limbic structures like amygdala, parahippocampal gyrus, and entorhinal cortex. The amygdala, known for triggering apnea, may exert abnormal influences on cardiac and respiratory structures following a TCS. Critical sites within the cerebellum, thalamus, and brainstem lose volume in epilepsy, potentially contributing to these abnormal influences.[2] So, this study aimed to assess the size and microscopic characteristics of the amygdala, a crucial structure implicated in inducing apnea in individuals with focal epilepsy. The analysis was organized based on the occurrence or absence of focal-to-bilateral tonic–clonic seizures (FBTCS), ictal central apnea (ICA), and post-convulsive central apnea (PCCA).

METHODS

In this prospective study, 73 patients exclusively experiencing focal seizures and 30 with focal-to-bilateral tonic–clonic seizures (FBTCS) recorded during video Electroencephalogram (VEEG) with respiratory monitoring were enrolled during pre-surgical investigations. High-resolution T1-weighted anatomical and multi-shell diffusion images, along with neurite

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orientation dispersion and density imaging (NODDI) metrics, were acquired from all epilepsy patients and 69 healthy controls. Amygdala segmentation was conducted on the T1-weighted images. Initially, the cohort was divided into three groups: healthy controls, a focal-unaware seizure cohort (no recent FBTCS), and an FBTCS cohort with ongoing seizures. Subsequently, both seizure cohorts were further divided based on the presence or absence of ictal central apnea (ICA). Additionally, the FBTCS cohort was analyzed based on the presence or absence of post-convulsive central apnea (PCCA). Amygdala volume and microstructure differences between groups were evaluated using multivariate analysis of covariance (MANCOVA), with age and sex as control variables.

RESULTS

There was a notable enlargement in left amygdala volumes observed in the FBTCpos cohort in comparison to both healthy controls ($p<0.001$) and the focal cohort ($p<0.001$). (Figure 1 A). In the FBTCpos group, right amygdala volumes exhibited a noteworthy increase in comparison to both healthy controls ($p<0.001$) and the focal-only group ($p=0.008$) (Figure 1 B). Healthy controls had the smallest left amygdala volumes, followed by the focal cohort without ictal central apnea (ICA) (Figure 1 C), However, there was no significant difference in left amygdala volumes between healthy controls ($p=1.000$). The FBTCpos cohort without ictal central apnea (ICA) exhibited a noteworthy

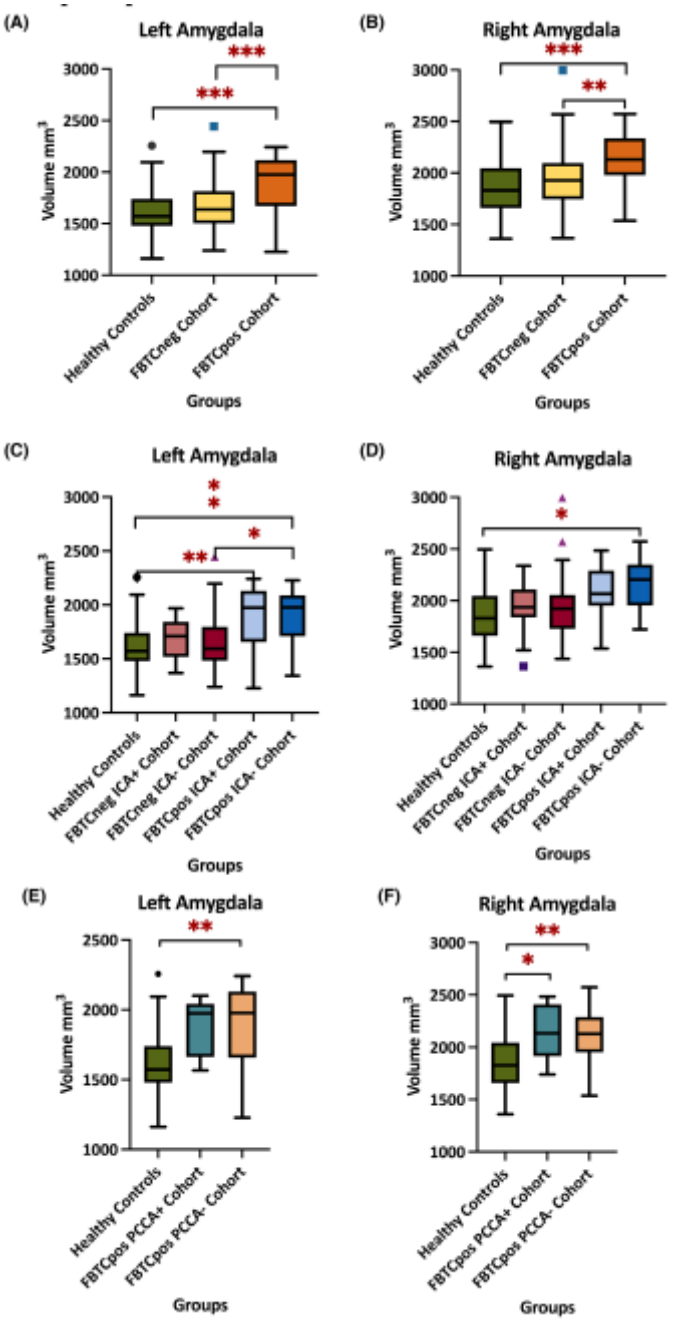

Figure 1. Tukey Box Plots for Amygdala Volume. The whiskers represent the minimum and maximum values, while the line represents the median. A few dots represent the extreme outliers. PCCA was for post-convulsive central apnea; FBTC stands for focal-to-bilateral tonic-clonic; and ICA stands for ictal central apnea. (A) left amygdala volume in millimetres in 172 subjects, broken down into FBTC seizures, FBTCneg cohort, and healthy controls. (B) Right amygdala volume in millimetres (mm3) in 172 subjects split into three groups: FBTCpos, FBTCneg cohort, and healthy controls. (C) further subdivided amygdala volume groups based on whether ICA was present or not. (D) The division of right amygdala volume groups was based on whether ICA was present or not. (E) further subdivided amygdala volume groups based on whether PCCA was present or not. (F) Further division of left amygdala volume groups in association with PCCA

increase in volume compared to controls (p=0.006) and the focal cohort without ICA (p=0.010). Similarly, right amygdala volumes followed a comparable pattern, with the FBTCpos cohort without ICA displaying a significant volume increase compared to healthy controls (p=0.013) (Figure 1 D). The FBTCS cohort, whether with or without ictal central apnea (ICA), exhibited an overall increase in mean amygdala volume compared to controls. In the left amygdala, both the PCCA-FBTCpos cohort and PCCA + FBTCS group demonstrated elevated volumes compared to healthy controls, with statistically significant differences observed only between healthy controls and the FBTCpos group without PCCA (p=0.002). In the right amygdala, both FBTCS groups displayed statistically significant volume increases compared to healthy controls. The FBTCpos ICA-seizure cohort showed higher mean diffusivity (MD) compared to healthy controls (p=0.014), while the FBTCpos PCCA+ seizure cohort exhibited higher fractional anisotropy (FA) than the FBTCpos group (p=0.037). Lower FA values were observed in the FBTCpos PCCA-seizure cohort compared to healthy controls (p=0.008). Neurite density index (NDI) values were significantly lower in both focal and FBTCS groups than in healthy controls, with the FBTCS group showing the greatest decline. ODI was decreased in both focal and FBTCS groups compared to healthy controls, with a significant decline in the left amygdala between the focal seizure cohort and healthy controls (p=0.013). Notably, patients with recorded PCCA exhibited the most substantial bilateral amygdala ODI decrease.

DISCUSSION

According to this study, those with PCCA and FBTCpos have profoundly altered architecture on both sides, with more pronounced alterations on the left, and considerably larger amygdala volumes. Particularly following FBTCS, abnormal cardiorespiratory patterns mediated by the amygdala may be linked to the structural changes shown by NODDI and volume discrepancies. The amygdala's consistent ability to cause apnea was confirmed by Nobis WP et al.[3] Compared to healthy participants, patients with epilepsy had bigger amygdala sizes and lower neurite density indices (NDI); the left amygdala volumes were particularly enlarged. The left side exhibited more microstructural modifications, as shown by NDI differences. These changes were concentrated in the lateral, basal, central, auxiliary basal, and paralaminar amygdala nuclei; bilateral basolateral NDI lowering was also seen. Reduced neurite density in amygdala nuclei that project to downstream circulatory and respiratory regulatory areas was associated with larger amygdala sizes in epileptic individuals. This kind of disturbance in nuclear organisation probably made it harder to regulate respiration and blood pressure.[2]

CONCLUSION

Elevated bilateral amygdala volumes, coupled with reduced ODI and NDI in epilepsy patients, especially the FBTCS group, might indicate processes directly impacting cardiac and respiratory patterns, potentially increasing SUDEP risk. These volume and microstructure changes could stem from various mechanisms, such as local inflammation causing dendritic projections loss or gliosis, or excitotoxicity triggered by excessive external influences on the

amygdala. Recognizing amygdala microstructure alterations could aid in identifying individuals with epilepsy at a heightened risk of SUDEP.

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Case report on Smith-Kingsmore syndrome presented initially with nystagmus

INTRODUCTION

Genetic testing was essential for confirmation, and eye movement irregularities may serve as potential indicators for SKS.

Smith-Kingsmore syndrome (SKS) is an infrequent autosomal dominant disorder, primarily characterized by de novo mutations of MTOR in the majority of cases and, in some instances, germline mosaicism. The exact incidence of SKS was still undetermined, and the clinical presentations of the syndrome were varied.[1] Individuals with SKS exhibit distinctive dysmorphic features such as macrocephaly, frontal bossing, a depressed nasal bridge, and hypertelorism. Those affected by SKS often experience intellectual disability and commonly present with seizures, which may be difficult to manage.[2] In this instance, the reported case highlighted Smith-Kingsmore syndrome, where the initial symptom was observed as nystagmus.

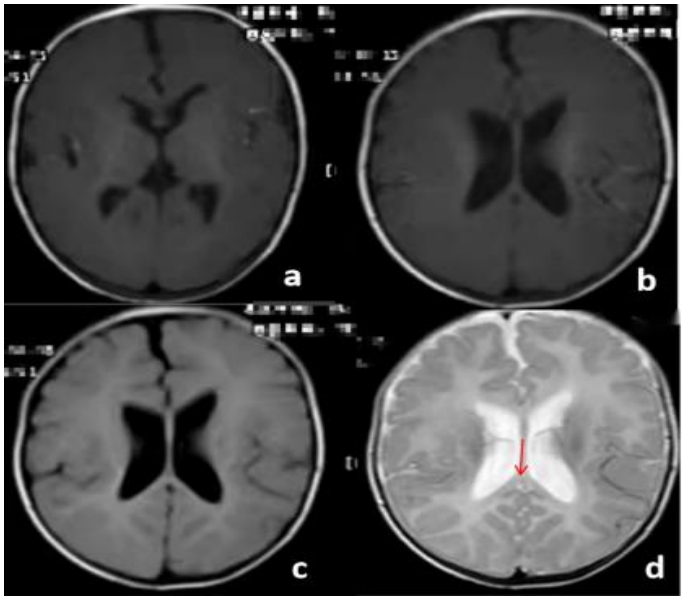

Figure 1. Brain MRI showing dysplasia of the corpus callosum and dilation of the bilateral ventricles (a-d).

CASE PRESENTATION

A 5-month-old girl infant was hospitalized due to presenting symptoms of nystagmus, a 2-month developmental delay, and intermittent convulsions. At approximately 3 months old, she displayed spontaneous isolated horizontal nystagmus occurring 5-6 times a day, each episode lasting 3-5 seconds. The frequency and duration of nystagmus intensified leading up to admission. During nystagmic episodes, her gaze lowered, accompanied by body twitches. In addition, her inability to lift her head at 3 months indicated developmental delay. At 5 months, she measured 67 cm in length, weighed 8.5 kg, and had a head circumference of 42 cm. Physical features included a protruding forehead, a noticeable bregma, a low and broad nose bridge, sloping eye fissure, and a small mandible. Abnormal, mobile limbs, low muscle tone, and negative pathological signs were observed. Skin findings included large areas of pigmentation, mosaic-like depigmentation, and café-au-lait spots. Developmental screening revealed a delay equivalent to 1 month. Brain MRI displayed dysplasia of the corpus callosum and bilateral ventricle dilatation. (Figure 1) Karyotype analysis indicated two X chromosomes (46, XX) with a detected missense mutation. Continuous 6-hour video electroencephalography (VEEG) unveiled abnormal brain activities during awake and sleeping periods, identifying 11 solitary attacks and two clusters of spastic-seizure episodes. A diagnosis of SKS was established through whole-exome sequencing and clinical assessment. Treatment with adrenocorticotropic hormone, methylprednisolone sodium succinate, topiramate, levetiracetam, and zonisamide initially reduced convulsions, but drug resistance ensued. Despite combined antiseizure medications, seizures persisted, albeit with reduced limb movement amplitude compared to pre-treatment levels.

DISCUSSION

This was a case of SKS where nystagmus was the initial symptom. A 5-month-old girl had nystagmus, developmental delay, and intermittent convulsions. Physical exams revealed facial deformity, low-limb muscle tension, extensive pigmentation, mosaic depigmentation, and developmental lag. The diagnosis was SKS.[1] Gordo et al. reviewed clinical characteristics in reported cases, including their four SKS cases. They summarized traits in patients with brain somatic MTOR mutations. Among them, ten had strabismus, three had visual impairment, but none with pathogenic MTOR variants had nystagmus. Nystagmus initiated the parental concern leading to medical attention in this case. Consequently, this instance suggested the importance for primary care providers to broaden their assessments and consider genetic testing for potential SKS confirmation. Nystagmus and other atypical eye movements could serve as sensitive indicators for diagnosing SKS.[3] Nystagmus could also be associated with retinal issues, like the absence of retinal pigment epithelium.[4] MTOR mutations impact the expression of the corresponding protein in the mTOR signaling pathway, leading to varied clinical manifestations. Abnormalities in mTOR pathway genes or activities can induce epileptic brain activity.[5]

CONCLUSION

This report highlighted SKS emphasized nystagmus as the initial sign. Despite extensive EEG and body movement abnormalities, it was the first warning sign leading parents to seek medical attention. Our findings broaden the SKS phenotype spectrum, underscoring the importance of

noting nystagmus during diagnosis. Genetic testing was essential for confirmation, and eye movement irregularities may serve as potential indicators for SKS.

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