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CASE REPORT

Exacerbation of restless legs syndrome following amygdalohippocampectomy: A case report

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Abstract

Background: Restless legs syndrome (RLS) is a neurological sensorimotor disorder characterized by an uncontrollable urge to move the legs. In the perioperative period, patients with RLS may experience an acute exacerbation of symptoms. Although studies on the exacerbation of RLS after brain surgery are limited, we present a case wherein symptoms worsened following left amygdalohippocampectomy.

Case Presentation: A 58-year-old woman diagnosed with mesiotemporal lobe epilepsy accompanied by left hippocampal sclerosis underwent a left amygdalohippocampectomy. The patient reported uncomfortable sensations in the lower limbs preoperatively. However, the urge to move her legs was manageable and not distinctly diagnosed with RLS. The symptoms began to deteriorate on the fifth postoperative day primarily affecting the legs and back, with a notable emphasis on the right side. Pramipexole treatment effectively ameliorated these symptoms.

Conclusion: No reports are available highlighting the exacerbation of RLS after amygdalohippocampectomy. Perioperative factors, such as anesthesia and iron deficiency due to hemorrhage, have been proposed as aggravating factors for RLS; however, the asymmetry of RLS, particularly the atypical right-sided exacerbation in this case, makes it unlikely that this was the primary cause. A negative correlation between opioid receptor availability in the amygdala and RLS severity has been reported, suggesting that amygdalohippocampectomy contributes to the exacerbation of RLS symptoms. This case provides valuable insights into the possible involvement of the amygdala in the pathophysiology of RLS and practical considerations for the clinical management of the condition.

KEYWORDS
amygdalohippocampectomy, brain surgery, exacerbation, postoperative complications, restless legs syndrome

BACKGROUND

Restless legs syndrome (RLS) is a neurological sensorimotor disorder characterized by an uncontrollable urge to move the legs.[1] The incidence of RLS in Japan is estimated to be 1%–4%.[2,3] Complications after amygdalohippocampectomy have been reported, including cerebrovascular disorders and memory impairment.[4] However, no reports are available on the exacerbation of RLS after amygdalohippocampectomy. In this study, we present a case in which the symptoms worsened on the fifth day after a left-sided amygdalohippocampectomy, particularly in the lower limbs and back, mainly on the right side. This case will play an important role in elucidating the pathophysiology of RLS.

CASE PRESENTATION

Patient information

A 58-year-old woman diagnosed with mesiotemporal lobe epilepsy and left hippocampal sclerosis underwent a left amygdalohippocampectomy at a university hospital. Epilepsy control with antiepileptic drugs was poor. Figure 1 displays pre- and postoperative resonance images of the patient's head. Before surgery, the patient was prescribed quetiapine 300 mg/day to manage peri-ictal psychiatric symptoms, such as anxiety, agitation, and insomnia. The patient complained of mild discomfort in both lower limbs about an hour after falling asleep. There was no asymmetry in this discomfort, and it did not persist throughout the night, but it often led to difficulty in falling asleep. At that time, RLS had not been definitively diagnosed.

On the fifth postoperative day, the patient experienced a significant exacerbation of uncomfortable sensations and an urge to move, particularly localized on the right side of her back and lower limbs, especially during the night. The patient was not disorientated and, despite feeling drowsy, she engaged in vigorous leg shaking and upper limb movements to relieve the discomfort. The symptoms began around 10:00 p.m., an hour after lights out, and she experienced difficulty falling asleep until approximately 5 a.m. due to restless sensations. Supporting Information S1: Video 1 demonstrates the patient engaging in vigorous leg shaking and upper limb movements to alleviate discomfort, particularly on the right side of her back and lower limbs. Consequently, the patient was referred to a psychiatrist for further evaluation.

The patient had a history of epilepsy since the age of 3 years with normal growth and development. She had no significant medical history, except for epilepsy. She had completed high school and worked as a company employee after graduation. She married at the age of 33 and had two children, both of whom had experienced normal growth and development. Laboratory investigations, including thyroid function tests, revealed no abnormalities. There was no family history of RLS.

Diagnostic assessment

Detailed psychiatric evaluation revealed an uncontrollable urge to move the limbs to relieve discomfort in the legs and back, and reported some relief when the limbs were moved or cooled. Differential diagnoses included abnormal behavior related to nocturnal epilepsy, delirium, and rapid eye movement (REM) sleep behavior disorders. Postoperative electroencephalography revealed no ictal discharge, thereby ruling out nocturnal epilepsy-related behavioral abnormalities. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) and *International Classification of Sleep Disorders*, Third Edition (ICSD-3), nocturnal delirium is characterized by impaired attention (orientation, concentration, maintenance, and ability to focus) and awareness (decreased awareness of surroundings), whereas REM

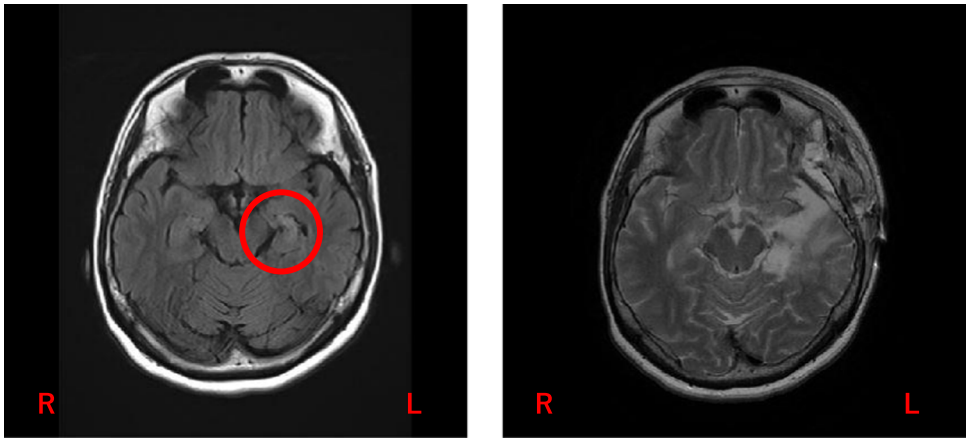

FIGURE 1 Magnetic resonance imaging (MRI) scans of the head before and after amygdalohippocampectomy. The image on the right is an MRI taken 10 days preoperatively, showing the left hippocampal sclerosis. The image on the left, taken 6 days postoperatively, shows the removal of the left hippocampal amygdala.

sleep behavior disorder involves abnormal behavior during sleep. The patient remained awake during the episode, responded appropriately to questions from the nurse, and was aware of her surroundings. Thus, nocturnal delirium and REM sleep behavior disorders were ruled out. Based on the clinical course and symptoms, the patient was diagnosed with RLS exacerbation according to ICSD-3.

Therapeutic interventions

Considering various perioperative factors that may exacerbate RLS, the following interventions were planned: First, considering the potential for quetiapine to worsen RLS, a decision was made to gradually taper and discontinue quetiapine. The dosage, initially at 300 mg, was reduced by 100 mg every 2 days. If no improvement was observed with this intervention, the perioperative decrease in hemoglobin and hematocrit levels (from 12.2 g/dL and 39.4% preoperatively to 9.2 g/dL and 28.8% postoperatively, respectively) and low postoperative ferritin level (26 ng/mL) prompted consideration of postoperative iron deficiency as a potential exacerbating factor for RLS. Consequently, administration of 100 mg/day of sodium ferrous citrate was planned. Moreover, if these interventions did not result in improvement, considering the dynamic changes in the dopamine system associated with surgery, administration of the dopamine agonist pramipexole at 0.125 mg/day was considered. The duration of each intervention was determined as needed through shared decision-making with the patient. The antiepileptic drug (lacosamide 150 mg/day) was not increased or decreased.

Outcomes

All outcomes were assessed before and after intervention. The primary outcome involved the patient's subjective experience of uncomfortable sensation and urge to move specifically focusing on the right side of her back and lower limbs, which were evaluated through interviews conducted by a psychiatrist. Additional outcomes included anticipated side-effects associated with each intervention, such as worsened psychiatric symptoms (e.g., anxiety or depression), nausea, gastrointestinal issues, hypotension, and dizziness. Furthermore, unexpected adverse events were also monitored.

Results and patient perspective

Figure 2 illustrates the patient's clinical course. Four days after discontinuation of quetiapine, the patient continued to experience subjective sensations of discomfort and an urge to move particularly on the right side of her back and lower limbs. Furthermore, despite receiving 100 mg/day of sodium ferrous citrate for 4 consecutive days as the next intervention, no alleviation of the patient's reported discomfort and urge to move was observed. Despite the short observation period of 4 days for assessing the effectiveness of the intervention, the patient desired immediate symptom relief. Hence, the administration of pramipexole at 0.125 mg/day was initiated as the next therapeutic intervention. Notably, the patient experienced an improvement in subjective discomfort and the urge to move on the right side of her back and lower limbs from the first night of administration. The uncomfortable sensation disappeared quickly, and the patient reported that "I slept well." This intervention has been continued for 9 months to date, with sustained effectiveness noted from initiation to the present. The patient reported "no nighttime uncomfortable sensations and a better sleep rhythm" without any observed adverse events since the intervention began. In addition, the patient maintained medication adherence throughout the treatment period.

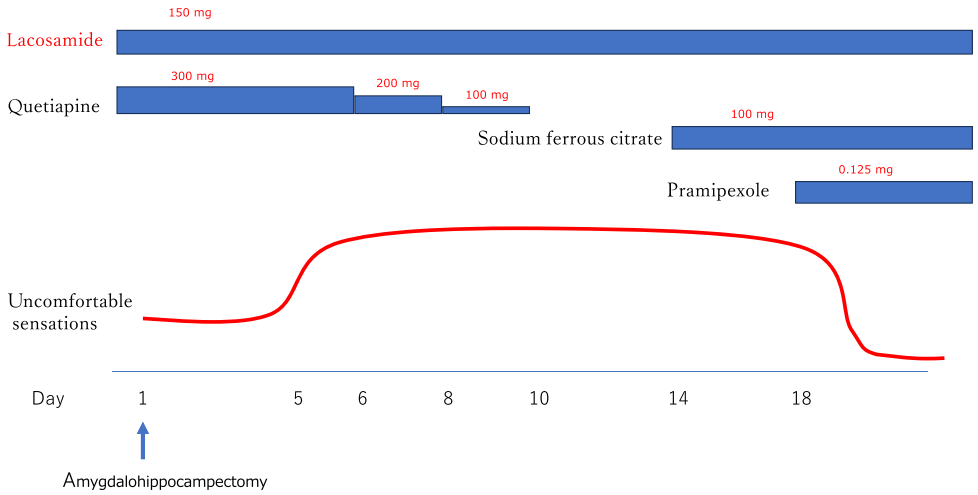

FIGURE 2 Clinical course. On the 5th day after amygdalohippocampectomy, uncomfortable sensations worsened, so quetiapine was gradually discontinued from the 6th day. As the symptoms did not improve, sodium ferrous citrate was added from the 14th day to address iron deficiency, a presumed indirect exacerbating factor. Pramipexole was subsequently added on the 18th day. These interventions resulted in an improvement of symptoms. The antiepileptic drug (lacosamide 150 mg/day) was not increased or decreased.

DISCUSSION

This case highlights the worsening of RLS symptoms, particularly in the right lower extremity and back, on the fifth day after a left-sided amygdalohippocampectomy. One strength of this study is the ability to attribute the exacerbation of RLS to left amygdalohippocampectomy, supported by the treatment course.

Previous studies have revealed that perioperative factors, such as anesthesia and blood loss, exacerbate RLS.[5,6] However, in this case, the exacerbation of RLS observed on postoperative day 5 was inconsistent with the effects of anesthesia. Although the postoperative decrease in hemoglobin and hematocrit levels may suggest the influence of iron deficiency as an exacerbating factor for RLS, given the asymmetric nature of the syndrome, particularly the atypical right-sided exacerbation, iron deficiency was unlikely to be the primary cause in this case. These results strongly suggest that the resection of the left hippocampus or amygdala is the primary cause of RLS exacerbation. Complications after amygdalohippocampal resection have been reported, including cerebrovascular disorders and memory impairment.[4] However, to the best of our knowledge, no reports highlighting RLS exacerbations exist.

Pramipexole treatment effectively alleviated these symptoms. The treatment of RLS is effective with iron supplementation and dopamine agonists.[1] The pathophysiology of RLS suggests dysfunction of the A11 dopaminergic system[7] and decreased iron levels in the cerebrospinal fluid.[1] The effectiveness of pramipexole in this case suggests involvement of the hippocampus and amygdala in the dopaminergic system. Consistent with our findings, Mogavero et al.[8] reported that participants with RLS demonstrated a statistically significant reduction in the volume of the left amygdala, and concluded that dopaminergic pathways from the A11 cell group and structures within the basal ganglia and limbic system may be involved in RLS. Considering that the main causative factor, in this case, may have been the resection of the left hippocampus and amygdala, the observed improvement with pramipexole suggests a complex relationship between the A11 dopaminergic system and the left hippocampus and amygdala.

A study investigating the availability of opioid receptors in the medial nociceptive system, including the amygdala, in patients with RLS identified a negative correlation between the availability of opioid receptors in the amygdala and the severity of RLS.[9] Regarding the hippocampus, studies have demonstrated no significant differences in the subcortical structure and hippocampal volume between patients with RLS and healthy controls.[10] Therefore, the reduced availability of opioid receptors due to the amygdalohippocampectomy may have contributed to the worsening of RLS symptoms in this case.

Limitations of this case include the following: First, polysomnography was not conducted throughout the entire period, so the presence of accompanying sleep disorders, such as periodic limb movement, cannot be ruled out. However, based on the objective assessment by nurses, periodic limb movement, snoring, and apnea were not observed. Second, due to the lack of a pre–post comparison, we could not exclude the impact of postoperative psychological symptoms, such as anxiety and restlessness, on the exacerbation of RLS and the inability to disregard the natural recovery effects over time along with the placebo effects of medication. However, due to close observation by the psychiatric staff immediately after surgery, minimal disturbance was noted in postoperative psychological symptoms. Furthermore, the improvement in symptoms has remained stable since the change in prescription. These factors support the contribution of hippocampal amygdalohippocampectomy in the exacerbation of RLS.

CONCLUSION

This case represents a valuable report on the exacerbation of RLS following amygdalohippocampectomy, suggesting its potential role in amygdala resection. Moreover, this study suggests that the perioperative management of amygdalohippocampectomy should consider the risk of severe exacerbation of RLS. Further research is required to elucidate the pathophysiology of RLS and its relationship with the hippocampus and amygdala.

PUBLISHER NOTE

AUTHOR CONTRIBUTIONS

Sachiko Eguchi: Conceptualization; writing – original draft; writing – review & editing; data curation, investigation. **Saeko Yokotsuka-Ishida**: Supervision, writing – review & editing; writing – original draft. **Yusuke Arai**: Supervision; writing – review & editing; writing – original draft. **Daimei Sasayama**: Supervision; writing – review & editing. **Takugo Maeda**: Supervision; writing – review & editing. **Kohei Kanaya**: Supervision; writing – review & editing. **Tetsuhiro Fukuyama**: Supervision; writing – review & editing. **Kensuke Nomura**: Supervision; writing – review & editing; data curation; investigation; formal analysis. **Shinsuke Washizuka**: Supervision; writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS APPROVAL STATEMENT

This study was conducted according to the principles of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Written informed consent for publication of their clinical details was obtained from the patient.

CLINICAL TRIAL REGISTRATION

N/A

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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