



Case Report

Nonconvulsive status epilepticus associated with Alzheimer's disease mimicking symptomatic focal epilepsy following the resection of a frontal parasagittal meningioma

Keisuke Abe¹, Nobutaka Mukae¹, Takato Morioka², Yuhei Sangatsuda¹, Ayumi Sakata³, Satoshi O. Suzuki⁴, Masahiro Mizoguchi¹

¹Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ²Department of Neurosurgery, Harasanshin Hospital, Fukuoka, Japan, ³Department of Clinical Chemistry and Laboratory Medicine, Kyushu University Hospital, Fukuoka, Japan, ⁴Department of Psychiatry, Shourai Hospital, Karatsu, Japan.

E-mail: Keisuke Abe - keisuke.abe23@gmail.com; *Nobutaka Mukae - mukae@ns.med.kyushu-u.ac.jp; Takato Morioka - takato@ns.med.kyushu-u.ac.jp; Yuhei Sangatsuda - y-sangat@med.kyushu-u.ac.jp; Ayumi Sakata - asakata@med.kyushu-u.ac.jp; Satoshi O. Suzuki - sosuzuki@shouraikai.jp; Masahiro Mizoguchi - mmizoguc@ns.med.kyushu-u.ac.jp



*Corresponding author:

Nobutaka Mukae,
Departments of Neurosurgery,
Graduate School of Medical
Sciences, Kyushu University,
Higashi-ku, Fukuoka 812-8582,
Japan.

mukae@ns.med.kyushu-u.ac.jp

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ABSTRACT

Background: Epilepsies are frequent in patients with Alzheimer's disease (AD); however, epilepsies in AD can easily go unrecognized because they usually present as focal impaired awareness seizures or nonconvulsive status epilepticus (NCSE) and can overlap with other symptoms of AD.

Case Description: We performed an epilepsy surgery in a 69-year-old woman with progressive cognitive impairment and consciousness disorder, who was diagnosed with focal NCSE related to the resected meningioma in the right frontal parasagittal region. Intraoperative electrocorticography revealed localized periodic paroxysmal discharges with beta and gamma activities in the neighboring cortex where the meningioma existed. The histopathological diagnosis of AD was first made from the resected epileptogenic cortex.

Conclusion: Even when there is a suspected epileptogenic lesion that could cause focal NCSE, AD should be ruled out in elderly patients with progressive cognitive decline.

Keywords: Alzheimer's disease, Electrocorticography, Hydrocephalus, Meningioma, Nonconvulsive status epilepticus

INTRODUCTION

It is well known that epilepsies are more frequent in patients with Alzheimer's disease (AD) than in those with non-AD dementias. An estimated 10–20% of patients with AD have clinically obvious epilepsies; however, in clinical practice, epilepsies in patients with AD can easily go unrecognized because they can present as focal impaired awareness seizures or nonconvulsive status epilepticus (NCSE) and can overlap with other symptoms of AD.^[1,12]

On the other hand, we often encounter epileptic seizure after brain tumor surgery, which can also present as NCSE. When the patient after brain tumor surgery has developed NCSE and cognitive decline, the AD can be overlooked while the patient had AD as underlying disease. We should be aware of the possibility of underlying AD.

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We performed an epilepsy surgery in elderly patient with progressive cognitive impairment and consciousness disorder, who was initially diagnosed with focal NCSE related to the resected meningioma in the right frontal parasagittal region. The histopathological diagnosis of AD was first made from the resected epileptogenic cortex, confirmed by intraoperative electrocorticography (ECoG). We report the detailed clinical course of this patient.

CASE REPORT

Sixty-nine-year-old woman had been experiencing an 8-month slowly progressive decline in executive functions and language domains, which lead to difficulty in writing, calculating, and activities in daily living. On the Wechsler Adult Intelligence Scale-III, her intelligence quotient (IQ) levels were mildly impaired: verbal IQ = 82, performance IQ = 52, and full scale IQ = 64. Her Hasegawa Dementia Scale-Revised (HDS-R)^[10] score was 29 of 30 points. Magnetic resonance imaging (MRI) demonstrated a large parasagittal meningioma in the right frontal region extending to the left side [Figure 1a]. We presumed that the mild cognitive impairment was attributed to this tumor. Mild atrophy of the cerebrum, including the hippocampus, was noted, but was estimated to be age appropriate [Figure 1b]. She underwent total removal of the tumor (histologically microcystic meningioma) through a right frontal craniotomy, without causing damage to the underlying cortex [Figure 1c and d].

However, postoperatively, her cognitive dysfunction slowly deteriorated rather than improved. Three months postoperatively, she developed dysarthria, gait disturbance, and urinary incontinence and was readmitted. Her HDS-R score dropped to 15 of 30 points. MRI revealed ventriculomegaly and a subdural hematoma on the left side [Figure 1e]. Bilateral hippocampal atrophy was apparent. In particular, the right hippocampus was markedly atrophied, with enlargement of the right inferior horn [Figure 1f]. Periventricular hyperintensity, especially on the right, was also observed. We performed drainage of the subdural hematoma, however, her consciousness level declined to GCS 9 (E2V3M4). Electroencephalography (EEG) revealed repetitive paroxysmal discharges in the right frontal region. With the load of levetiracetam, we performed a ventriculoperitoneal (VP) shunt through the right posterior horn. Postoperatively, her consciousness improved to GCS 11 (E3V4M5) with the disappearance of paroxysmal activities, but her consciousness soon worsened.

Six months after the first craniotomy, she developed a drowsy state. Computed tomography showed progressive ventricular enlargement [Figure 1g and h], and EEG revealed reappearance of repetitive paroxysmal discharges in the right frontal region. Although the ventricular size was controlled by changing the setting pressure of the VP

shunt system [Figure 1i and j], her clinical and EEG findings did not change. Perfusion MRI with arterial spin labeling (ASL) demonstrated a markedly decreased signal in the right cerebral cortex [Figure 1k and l]. Under the diagnosis of symptomatic focal NCSE related to the meningioma resection, various medical treatments, including oral administration of lacosamide and perampnel as well as intravenous fosphenytoin, phenobarbital, and midazolam, were administered; however, her clinical and EEG findings did not significantly improve. Barbiturate coma therapy with thiamylal sodium was administered; however, continuous EEG monitoring demonstrated periodic paroxysmal discharges, especially in the right frontal region [Figure 2a and b]. Thus, epilepsy surgery with intraoperative ECoG recording was indicated.

Through reopening of the right frontal craniotomy [Figure 2c], the frontal convexity was exposed [Figure 2d]. With the effect of the first craniotomy, the arachnoid was thickened and cortical surface was partly brownish. However, an apparent epileptogenic lesion was not noted. ECoG revealed periodic paroxysmal discharges in the neighboring cortex where the meningioma was located [Figure 2e]. The fast-wave activities rode on the descending phase of the major negative component. Beta and gamma activities were determined by time-frequency analysis of these paroxysmal activities [Figure 2f]. The cortex, where the paroxysmal discharges were recorded, was resected.

Postoperatively, her consciousness level improved slightly with the disappearance of paroxysmal activities on EEG, but then worsened. Histologically, in the resected cortex, there were numerous senile plaques [Figure 3a and b], which tested immunopositive for amyloid β [Figure 3c and d] and positive for Congo red and Dylon staining [Figure 3e], as well as phosphorylated tau-immunopositive neurofibrillary tangles (NFTs) and neuropil threads [Figure 3f]. Amyloid β deposition was also observed in some of the meningeal and cortical blood vessels [Figure 3c]. Rarefaction of the white matter was focally prominent [Figure 3a], in which phosphorylated neurofilament immunostaining revealed axonal degeneration. Immunostaining for glial fibrillary acidic protein demonstrated severe gliosis in the white matter and prominent astrocytic reaction against senile plaques in the cortex [Figure 3g]. NeuN immunostaining failed to reveal apparent loss of cortical neurons. The findings indicated AD (corresponding to Braak NFT Stage V)^[2] and associated amyloid β -peptide cerebral angiopathy. While local fibrous thickening of the arachnoid membrane was also noted, other epileptogenic lesions were not observed.

DISCUSSION

Retrospectively, in the present case, mild cognitive impairment as the first symptom was not solely attributed to

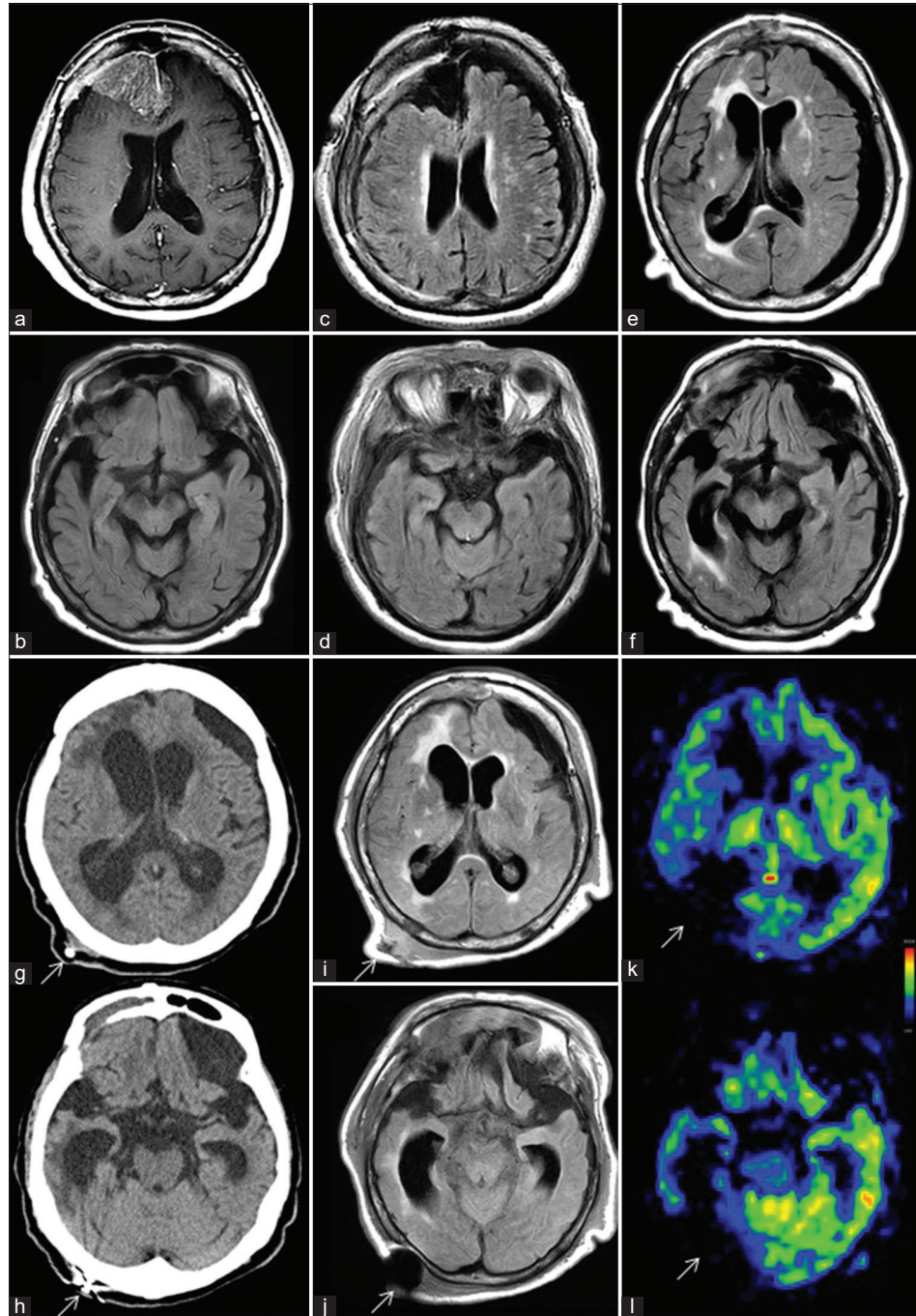


Figure 1: (a and b) Preoperative magnetic resonance (MR) images. (a) T1-weighted MR image with gadolinium-DTPA enhancement demonstrates a large parasagittal meningioma in the right frontal region extending to the left side. (b) On MR image with fluid-attenuated inversion recovery sequence (FLAIR), mild atrophy of the cerebrum including the hippocampus is noted. (c and d) FLAIR images immediately after the surgery confirm the total removal of the meningioma through a right frontal craniotomy, without causing damage to the underlying cortex. (e and f) FLAIR images 3 months postoperatively reveal a subdural hematoma on the left side and marked ventricular enlargement. Bilateral hippocampal atrophy is more evident than that before tumor surgery. In particular, the right hippocampus is markedly atrophied, with marked enlargement of the right inferior horn. Periventricular hyperintensity, especially on the right side, is also observed. (g and h) Computed tomography image 6 months postoperatively shows progressive ventriculomegaly, while the left subdural hematoma is decreased in size. White arrows indicate the ventriculoperitoneal (VP) shunt. (i and j) FLAIR images, after changing the setting pressure of the VP shunt system, show that the ventricular size is well controlled. Atrophy of the cerebrum, including the hippocampus, and periventricular hyperintensity, predominantly on the right side, are apparent. White arrows indicate artifacts caused by the VP shunt system. (k and l) Perfusion MR with arterial spin labeling demonstrates a markedly decreased signal in the right cerebral cortex. White arrows indicate artifacts caused by the VP shunt system.

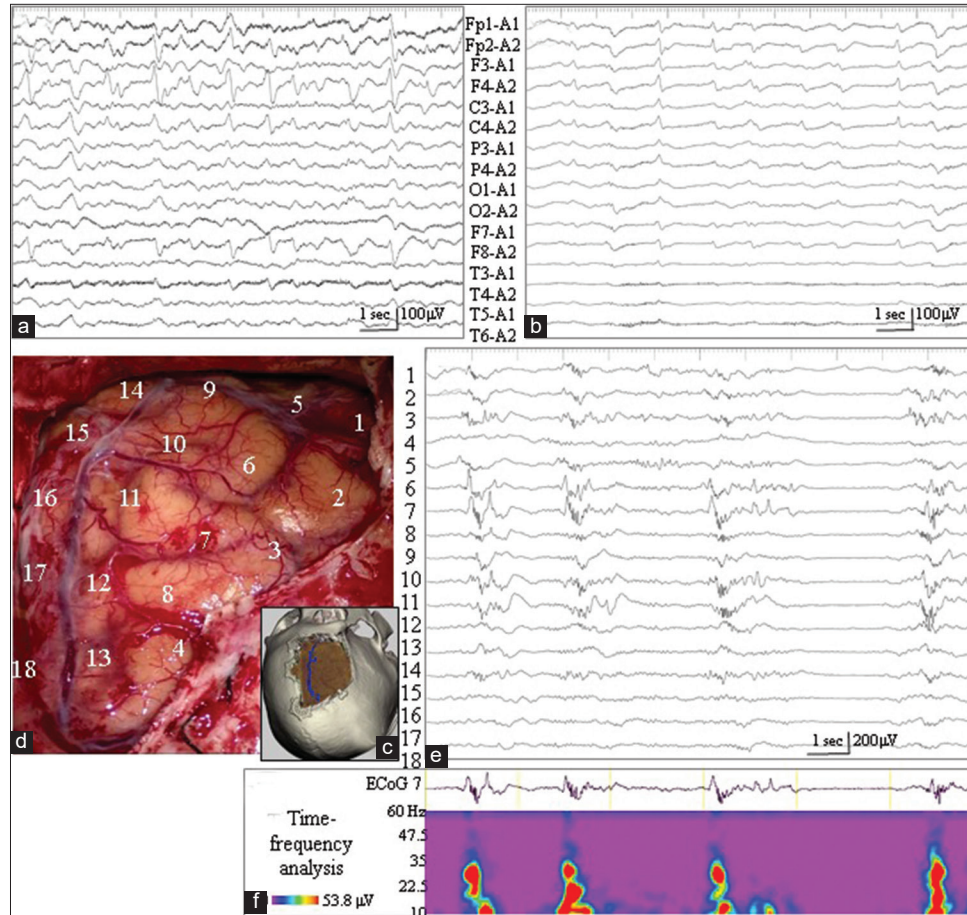


Figure 2: (a) Electroencephalography (EEG) 3 months postoperatively reveals repetitive paroxysmal discharges in the right frontal region (F4 of the International EEG 10–20 System). (b) Continuous EEG monitoring during barbiturate coma therapy, 6 months after tumor removal, demonstrates periodic paroxysmal discharges, especially in the right frontal region. (c–f) Intraoperative findings during epilepsy surgery. (c) Three-dimensional reconstruction of the computed tomography scan demonstrates the extent of the craniotomy. (d) The position and number of the subdural electrodes are placed on the intraoperative photographs, shown in an orientation matched with (c). (e) Intraoperative electrocorticography (ECoG) reveals periodic paroxysmal discharges with the maximal amplitude of electrode No. 7. Fast-wave activities ride on the descending phase of these paroxysmal activities. (f) Beta and gamma activities are determined by time-frequency analysis of the paroxysmal ECoG activities recorded from electrode No. 7.

the right frontal meningioma, but mainly to AD. It has been reported that meningioma is the most common incidental neoplastic finding in patients with AD.^[3] The mild atrophy of the cerebrum and hippocampus before first surgery was estimated as age appropriate but it was underestimated in the presence of compression from the tumor. In the MRI, 3 months after the first operation show bilateral hippocampus atrophy, which first we assumed just as a result from hydrocephalus, may partially resulted from progression of AD. Her clinical course of AD was also modified with the postoperative development of hydrocephalus, chronic subdural hematoma, and NCSE, each of which can also develop cognitive decline.

Many seizure semiologies in AD are typical of medial temporal lobe epilepsy (TLE), and interictal paroxysmal

activities on routine EEG are commonly detected in the temporal or frontotemporal region.^[4,8,11] Although the exact reason why the clinical manifestation of epilepsy in AD is similar to that of TLE is unknown, TLE and AD share several pathological features.^[12] For example, in 101 patients with TLE without dementia who underwent temporal lobectomy, brain samples from 10 patients had more than age appropriate amyloid β plaque accumulation.^[6] Another pathological study also revealed that in 33 patients who underwent surgery for TLE, 94% of the excised temporal samples had hyperphosphorylated tau.^[9]

In the present case, the focus of the paroxysmal activities was localized in the right frontal region related to the meningioma resection. However, localized epileptogenic lesions, such as tumor invasion or surgical scars, were not histologically

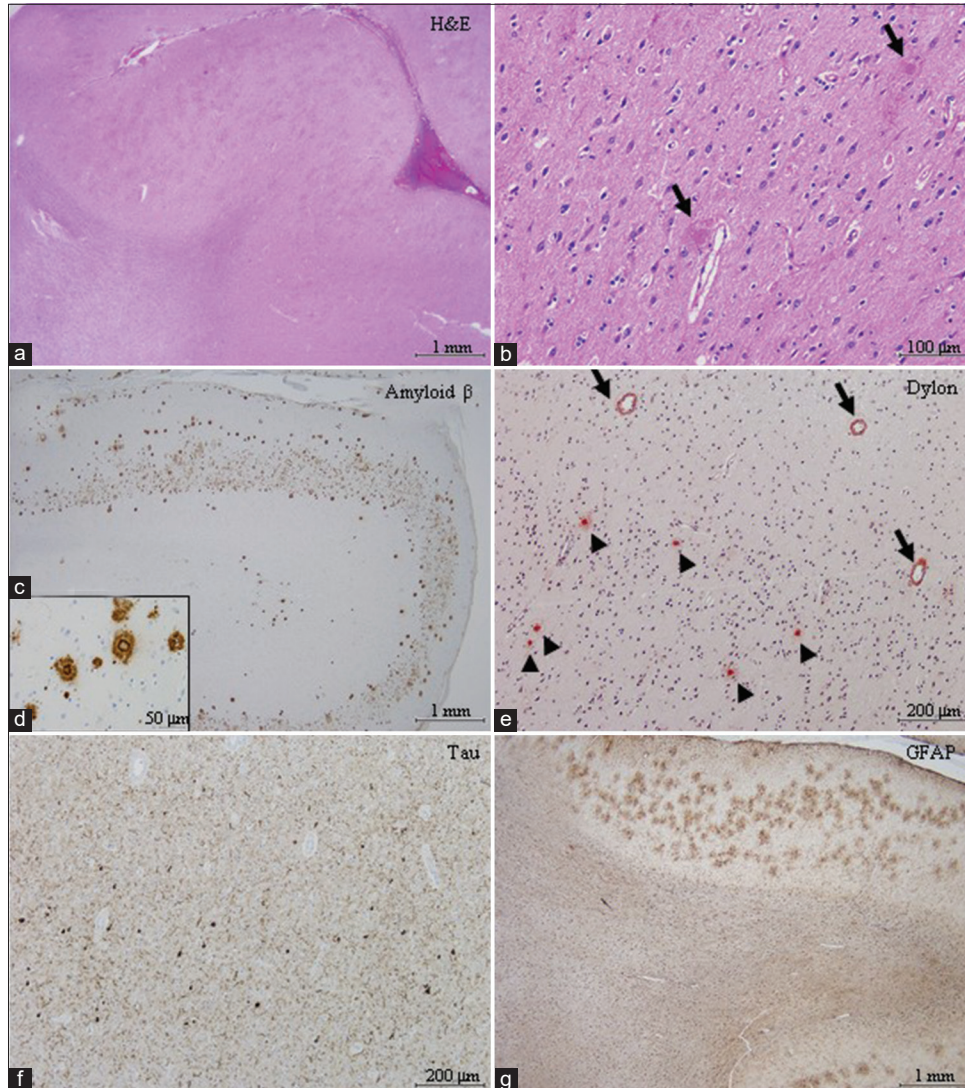


Figure 3: Histopathological findings of the resected paroxysmal foci. (a and b) Numerous senile plaques associated with the amyloid core (black arrows) are noted in the cortex. Rarefaction of white matter was focally prominent. (c and d) Amyloid β immunopositive senile plaques are located mainly in the cortex. Amyloid β deposition is also observed in some of the meningeal and cortical blood vessels. (e) The amyloid core of the senile plaque tested positive for Dylon staining (arrow heads). Amyloid β deposition was also observed in the cortical blood vessels (arrows). (f) Phosphorylated tau immunopositive neurofibrillary tangles and numerous neuropil threads are observed. (g) Immunostaining for glial fibrillary acidic protein demonstrates severe gliosis in the white matter and prominent astrocytic reaction against senile plaques in the cortex.

verified in the resected cortex. Thus, the exact epileptogenic mechanism of this patient was not straightforward and may have been multifactorial. One possible explanation is that, based on the neurophysiological findings, the presence of the meningioma and its surgery-induced AD-associated epilepsy. Since the development of the EEG abnormality exhibited a temporal relationship with that of hydrocephalus, there is a possibility that hydrocephalus was involved as a worsening factor in the development of NCSE. The fact that ventricular enlargement was more prominent on the ipsilateral side to the EEG abnormality may support the second idea.

It is generally accepted that treatment of epilepsy in AD with selective antiepileptic drugs such as levetiracetam and lamotrigine in low doses is usually well tolerated and efficacious.^[12] However, in the present case, various medical treatments, including barbiturate coma therapy, failed to completely control the paroxysmal EEG abnormalities. Thus, epilepsy surgery was indicated.

Intraoperative ECoG demonstrated periodic paroxysmal discharges, which had a waveform similar to that of EEG, in the neighboring cortex where the meningioma existed. A notable ECoG finding was that fast-wave activities rode

on the descending phase of the major negative component. These fast-wave activities were not recorded on EEG, probably due to the smearing effect.^[5] Although these beta and gamma activities could not be categorized as high-frequency oscillations,^[7] as fast oscillations, this finding might indicate that the area was epileptogenic. In fact, no paroxysmal activities were recorded on postoperative EEG, while no significant change in her consciousness level was noted.

Emerging evidence indicates that epilepsy can hasten cognitive decline in patients with AD.^[12] In animal experiments,^[13,14] increased neuronal activity enhances both amyloid β and tau secretion; thus, recurrent epileptic activity in AD could establish a vicious cycle augmenting the aberrant aggregation and spread of these disease-related proteins. Our findings of decreased ASL signal in the ipsilateral cortex to the epileptogenic side might support this idea.

CONCLUSION

Even when a suspected epileptogenic lesion is encountered, which could cause focal NCSE, AD should be ruled out in elderly patients with progressive cognitive decline.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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