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Case report

Cerebral amyloid angiopathy-related inflammation – A case report presenting diagnostic difficulties

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ABSTRACT

We describe an 86-year-old woman with a history of hypertension who presented sudden disturbances of consciousness and left hemiparesis. Brain magnetic resonance imaging (MRI) revealed diffused hyperintensive changes on T2-weighted images localized subcortically in the white matter of both cerebral hemispheres, corresponding to acute vasogenic edema, causing moderate mass effect. Posterior reversible encephalopathy syndrome was initially diagnosed. After implementation of anti-edema intravenous steroid treatment and hypotensive therapy the symptoms began to retire, till the total regression. The successive hospitalizations took place two and eight months later due to the occurrence of seizures, motor deficits and the development of mild cognitive impairment. Brain MRI revealed progression of the white matter changes and diffused subcortical microhemorrhages. Each time pulse steroid therapy was implemented and the symptoms improved significantly after several days. Chronic oral steroid treatment resulted in the stabilization of neurological status. The long-term observation of clinical symptoms, remission after immunosuppressive therapy and white matter changes with subcortical microhemorrhages in brain MRI leaded to the diagnosis of cerebral amyloid angiopathy-related inflammation.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) may be initially suspected when alterations in consciousness and motor deficits occur along with reversible subcortical vasogenic edema on brain magnetic resonance imaging (MRI). The syndrome is typically presented by headache, seizures, visual impairment, focal neurological deficits and mental state changes [1,2]. It is most commonly encountered in association with acute hypertension, preeclampsia or eclampsia, renal

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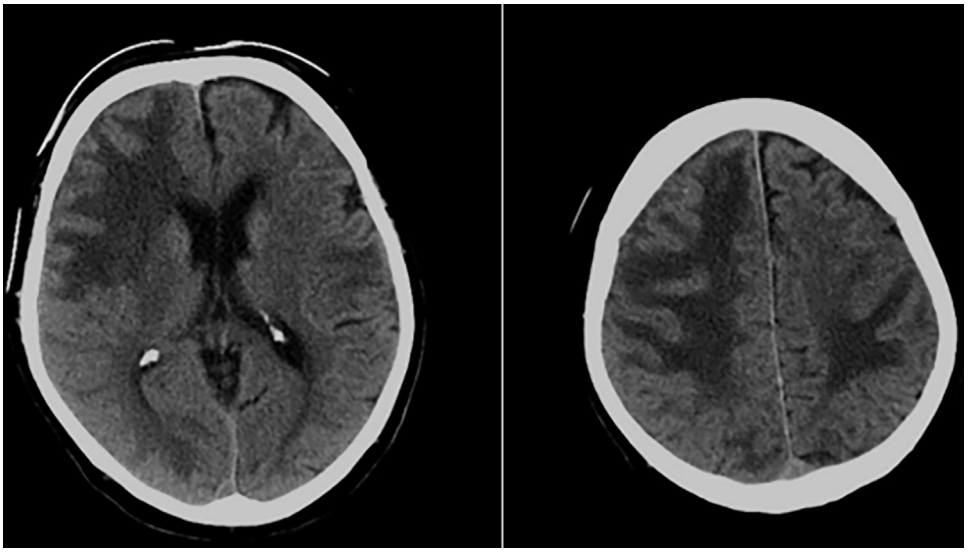

Fig. 1 – Brain CT scan on first admission.

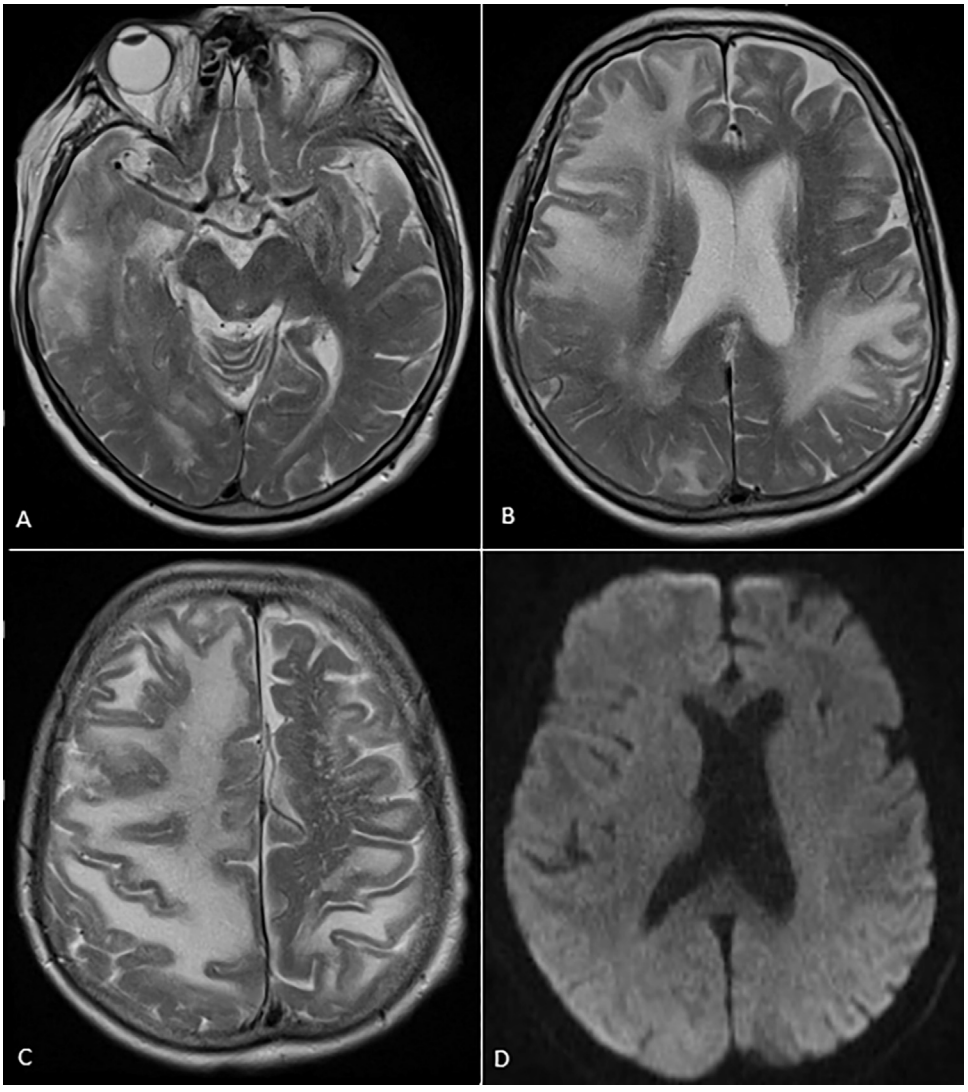

Fig. 2 – First hospitalization – diffused hyperintensive changes on T2-weighted images localized subcortically in the white matter of both cerebral hemispheres (A–C), vasogenic edema in DWI option (D).

disease, sepsis and exposure to immunosuppressive drugs [3]. Brain MRI reveals characteristic hyperintensive changes on T2-weighted and FLAIR images corresponding to the vasogenic edema. They are mainly located in subcortical white matter, less often in cerebral cortex. Classically, the changes are placed in parieto-occipital areas, less commonly in frontal or temporal lobes, basal ganglia, thalamus, mesencephalon, brainstem or cerebellum [1,3]. In most cases the edema is bilateral and symmetric, but can also be unilateral [1].

In the presented case report PRES was initially diagnosed but subsequently differential diagnosis of cerebral amyloid angiopathy-related inflammation (CAA-RI) was considered due to their distinctive clinical presentation and neuroimaging results.

Cerebral amyloid angiopathy (CAA) refers to the deposits of β-amyloid in small and mid-sized arteries and veins of the cerebral cortex and leptomeninges, without associated systemic amyloidosis [4]. Amyloid depositions in the vascular media and adventitia may lead to vessel fragility, rupture and intracerebral hemorrhages, which are frequently recurrent, especially in individuals aged over 55 with normal arterial blood pressure [6]. One of the manifestations of CAA is CAA-RI [5–7]. It is an immune reaction to the deposits of β-amyloid with corresponding inflammatory process. It is presented commonly by seizures, subacute cognitive impairment, headaches and good response to immunosuppressive treatment [6]. Asymmetric T2-weighted or FLAIR hyperintensities in cortex or subcortical white matter with multiple microhemorrhages in brain imaging are characteristic for CAA-RI [6].

Recently, the similarity of CAA-RI and amyloid-related imaging abnormalities (ARIA) reported in Alzheimers's disease (AD) passive immunization therapies was described [8,9]. It was observed that anti-amyloid β (Aβ) autoantibodies in cerebrospinal fluid (CSF) may be produced as a response to β-amyloid immunotherapy trials of AD and that they are also found in CAA-RI [8,9]. Therefore, CAA-RI is considered as a human spontaneous model of drug-induced ARIA [8–10] and thus Aβ autoantibodies in CSF may be a potential biological marker of CAA-RI [10]. Moreover, the prevalence of 80% of APOE ε4 genotype in patients with CAA-RI was described [8–10].

In this study we set out to determine clinical features and characteristic radiologic imaging in an appropriate differential diagnosis between PRES and CAA-RI, in order to avoid the delay of reaching to the correct final diagnosis.

2. Case report

An 86 year-old woman with a history of hypertension was admitted to the Emergency Department due to sudden occurrence of consciousness disturbances and left hemiparesis. At admission arterial blood pressure was 160/80 mmHg. During subsequent days the neurological deficit was escalating – severe disturbances of consciousness and left hemiparesis with Babinski sign on both sides occurred.

Brain computed tomography revealed extensive hypodense changes in the white matter of fronto-parietal region bilaterally with the predominance on the right side (Fig. 1). The traits of moderate cerebral edema were reported. These findings prompted further neuroradiological examinations. The brain MRI with Gadolinum presented diffused hyperintensive changes on T2-weighted images localized subcortically in the white matter of both hemispheres, with the predominance in the parietal lobes and right frontal lobe (Fig. 2). Appearance of the changes in diffusion-weighted

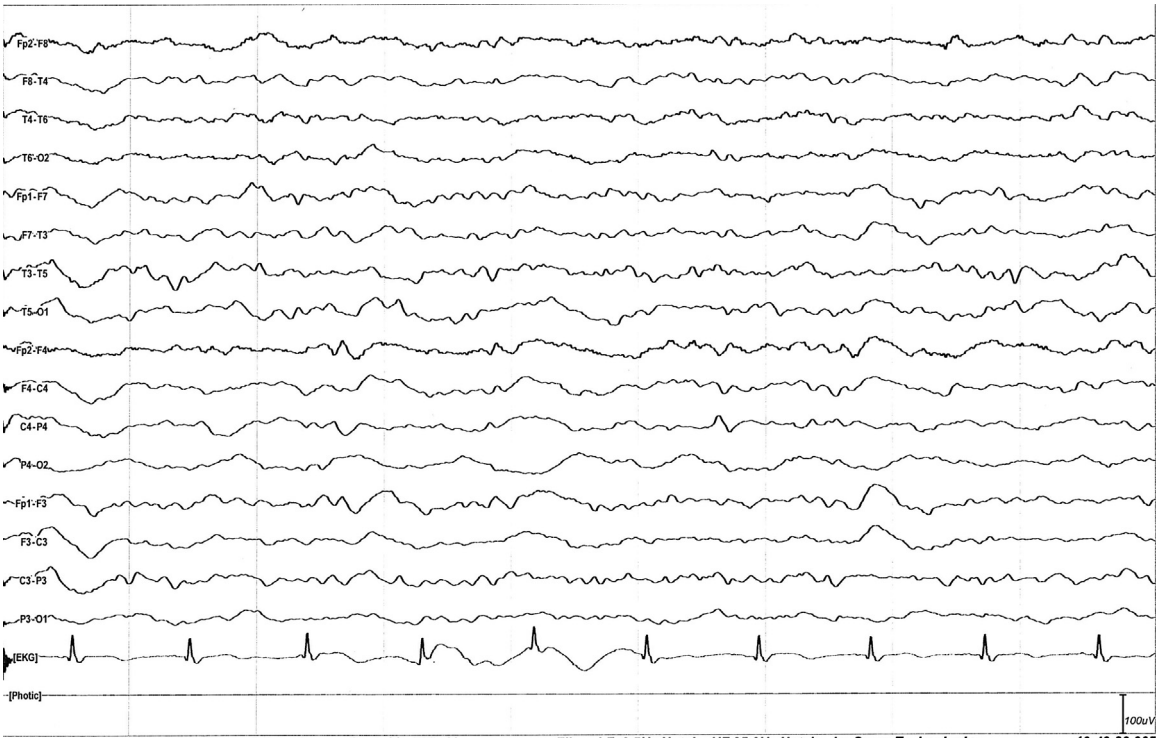

Fig. 3 – EEG on admission during the first hospitalization – severe generalized changes with slowing.

images (DWI) suggested vasogenic edema. Apparent diffusion coefficient (ADC) map did not show areas of restricted diffusion. There was no Gadolinum enhancement. The slight mass effect manifested as a compression of the right lateral ventricle. At that time, susceptibility weighted imaging sequence (SWI) was not assessed. The electroencephalography (EEG) revealed severe generalized changes with slowing (Fig. 3). In CSF there were high protein concentration (90 mg%), cytosis 1.6/μl, 93% of active monocytoid cells with the dominance of CD14 cells, 7% of lymphocytes and few erythrocytes. No cytomegalovirus and herpes virus DNA were found. The presence of JC virus was not tested. According to the neuroimaging findings the diagnosis of PRES or gliomatosis cerebri was suggested. In order to exclude the neoplastic cause the MRI spectroscopy with contrast was performed in which no characteristics of gliomatosis cerebri were found.

The anti-edema treatment by intravenous pulses of dexamethazone was implemented (3 × 4 mg i.v. for five days) with no serious adverse effects. Left hemiparesis and disturbances of consciousness began to retire, till the total regression of the neurological symptoms. Follow-up brain MRI after 16 days revealed less intensified hyperintensive changes on T2-weighted images and no mass effect. EEG two weeks after admission showed less intensified changes than previously. During the hospitalization the arterial blood pressure was normal. No seizures were observed. The patient was discharged home with normal neurological examination.

Two months later the patient presented again to the Emergency Department with acute disturbances of consciousness and left hemiparesis which occurred after an episode of seizures with involuntary urination and defecation. The symptoms lasted for few hours. Brain MRI revealed acute vasogenic edema of right temporal lobe (Fig. 4). Changes on T2-weighted images in frontal and parietal lobes were comparable to those from the previous month. Except them, in the affected brain areas the small, diffuse changes without signal intensi-

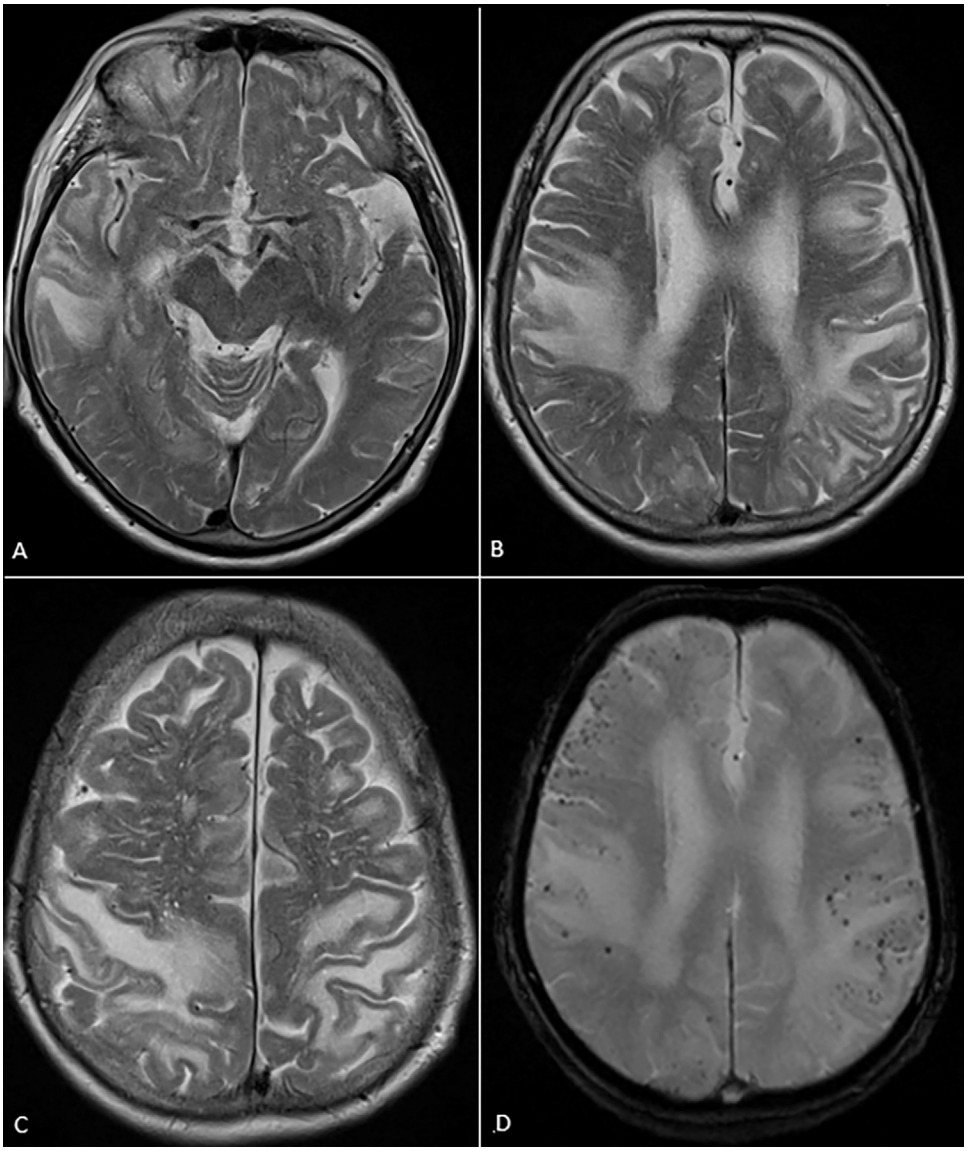

Fig. 4 – Second hospitalization – acute vasogenic edema of right temporal lobe and diffused hyperintensive changes on T2-weighted images (A–C), diffused subcortical microhemorrhages with hemosyderine deposits in SWI option (D).

fication in gradient sequence and SWI were observed. They corresponded to micro-hemorrhagic lesions. There was no Gadolinum enhancement. Obtained images suggested CAA coexisting with persisting white matter hyperintensities after PRES or recurring PRES. EEG on admission revealed generalized slowing with a tendency to synchronization (Fig. 5). As a result, oral levetiracetam 2 × 1 g was started. Follow-up EEG after 10 days presented less intensified changes. After implementation of intravenous pulses of methylprednisolone (1 × 1 g i.v. for five days) with no serious adverse effects, the patient was discharged without any neurological disturbances.

The last, third hospitalization took place eight months later. The patient was found unconscious and with tetraparesis after a seizure attack with involuntary urination and defecation. According to the testimony of the family, during last few months the patient began to present progressive subacute dementia. On admission she presented disturbances of consciousness with no evident motor deficits. The brain MRI revealed large confluent areas of predominantly white matter hyperintense signal on T2-weighted images in both cerebral hemispheres and multiple, scattered, subcortical microhemorrhages with hemosyderine deposits in SWI and a mass effect (Fig. 6). No Gadolinum enhancement was observed. Results of brain MRI images showed a significant progression of changes comparing to previous images. Presence of these findings suggested CAA-RI. EEG showed severe generalized changes with a slight predominance in right hemisphere with slowing (Fig. 7). In CSF examination there were high protein concentration (75 mg%), cytosis 4/μl, 57% of active monocytoid cells, 39% of lymphocytes, 4% of segmented neutrophils, 2 erythrophages and few erythrocytes. In blood and CSF samples, the antibodies which could be responsible for encephalopathy or encephalitis (NMDA, AMPA1, AMPA2, DPPX, LGI1, CASPR2, GABA, JCV-DNA) were not found. The concentrations of inflammatory markers – procalcitonine and CRP – were 0.03 ng/ml and 16.6 mg/l respectively.

The neurological symptoms normalized after intravenous pulses of methylprednisolone (1 × 1 g i.v. for five days, with no serious adverse effects), despite a mild cognitive impairment. The patient was dismissed on oral hydrocortisone 3 × 20 mg and levetiracetam 2 × 1 g. To our best knowledge the patient had no seizures till this moment. The subacute progression of cognitive functions is being observed. The treatment by hydrocortisone 2 × 20 mg is being continued.

3. Discussion

The presented case report shows the diagnostic difficulties in a patient with uncommon and misleading initial presentation of CAA-RI.

During the first hospitalization the largely symmetric cortical and subcortical vasogenic edema in brain MRI and the clinical symptoms which occurred acutely, withdrew completely. Such course strongly suggested PRES. Moreover, the blood pressure on admission and severe generalized changes with slowing in EEG [11] argued in favor of this syndrome.

The second hospitalization, which was caused by a transient hemiparesis after seizure attack, gave us a deeper insight into the etiology of these neurological disturbances. Due to asymmetric acute vasogenic edema of cerebral white matter with numerous microhemorrhages CAA or CAA-RI were suggested, nevertheless, the suggestion of atypical

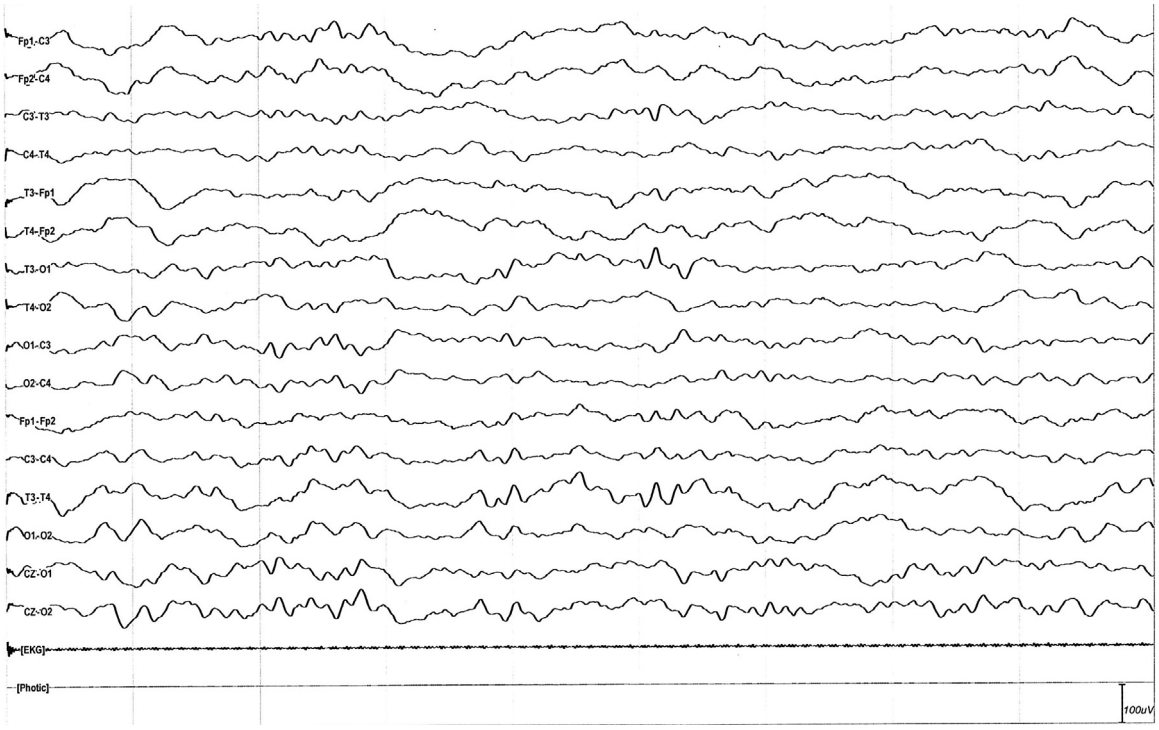

Fig. 5 – EEG on admission during the second hospitalization – generalized slowing with a tendency to synchronization, the changes are more intensified than during the previous EEG.

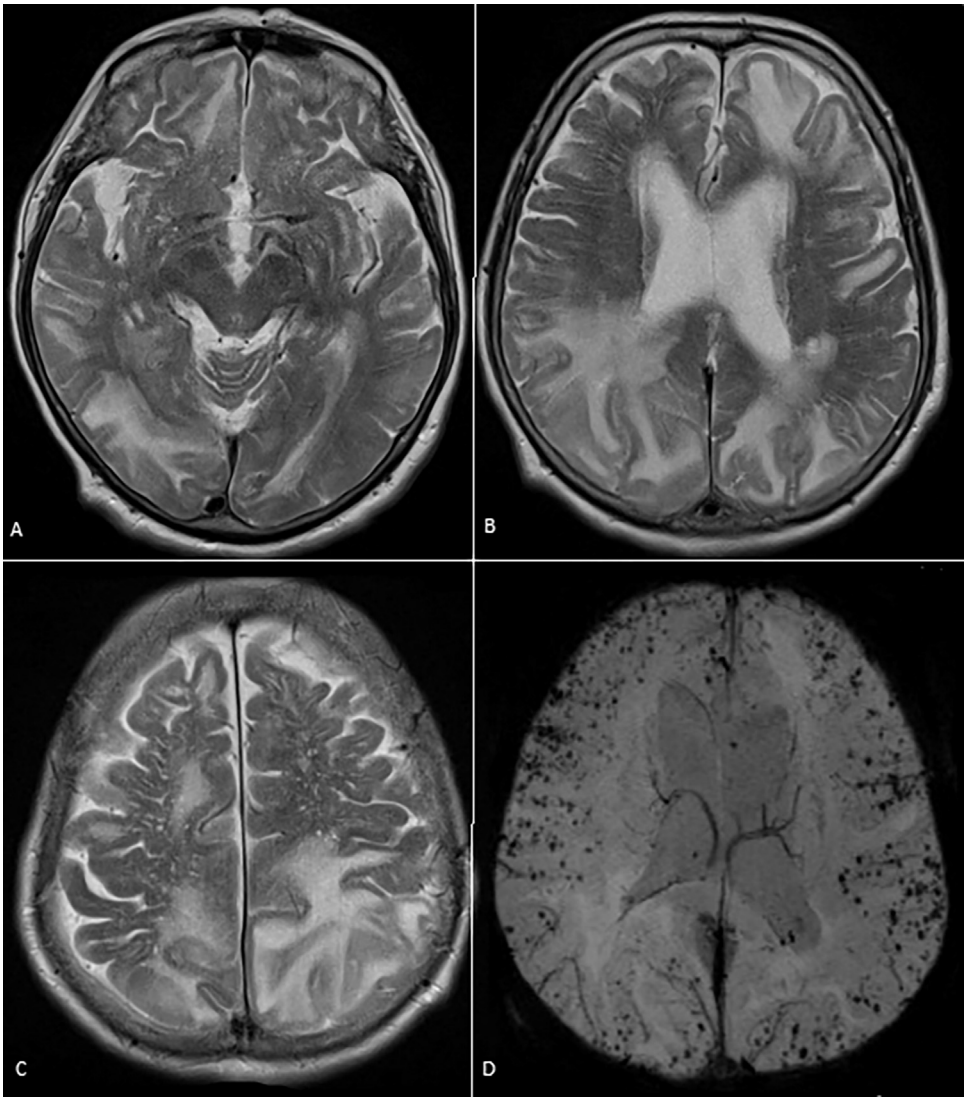

Fig. 6 – Third hospitalization – white matter hyperintense signal on T2-weighted images in both hemispheres (A–C), multiple, scattered, subcortical microhemorrhages with hemosyderine deposits in SWI option (D).

recurring PRES was also present. The asymmetric localization of the white matter hyperintesities was more characteristic for CAA-RI than for PRES, where lesions are most commonly symmetric [3,6]. Although hemorrhages in the affected regions may be observed in both diseases [3] cortical and subcortical microhemmorhages are characteristic for CAA-RI. In addition, the CSF examination which revealed presence of active monocytoid cells, can suggest CAA-RI [12]. Moreover, the moderate hypertension is not a typical risk factor of PRES [3].

The third hospitalization was provoked by similar clinical symptoms as two previous ones, however they lasted longer than before. Brain imaging revealed the significant progression of white matter changes with hemosiderine deposits indicating past microhemorrhages. Developing changes exclude the diagnosis of PRES in this situation and indicate the progression of changes due to recurring CAA-RI. The presence of microhemorrhages with the history of asymmetric white matter changes with good response to immunsupresive therapy and typical clinical presentation indicate strongly CAA-RI [6].

In 2011 Chung et al. [13] proposed diagnostic criteria for definite and probable CAA-RI based on a review of clinical, imaging and biopsy findings. These criteria were recently validated in biopsy-proven cases by Auriel et al. [14] who suggested reliable diagnosis of CAA-RI based on typical clinical features and extensive white matter hyperintensities, without histopathological examination, with good sensitivity and specificity (Table 1). The presented case fulfills the criteria for probable CAA-RI. Nevertheless, even though the reliable diagnosis can be reached using these criteria, still the neuropathological confirmation remains the definitive diagnostic approach to CAA-RI [14].

The treatment of CAA-RI should be implemented without brain biopsy in patients with probable CAA-RI [14]. There are no strict recommendations for the therapy, however the high dose corticosteroids at the beginning and the chronic treatment by immunosuppressive agents or corticosteroids after the clinical and radiological improvement are believed to be the most reasonable [6,10,13,14]. The brain biopsy should be

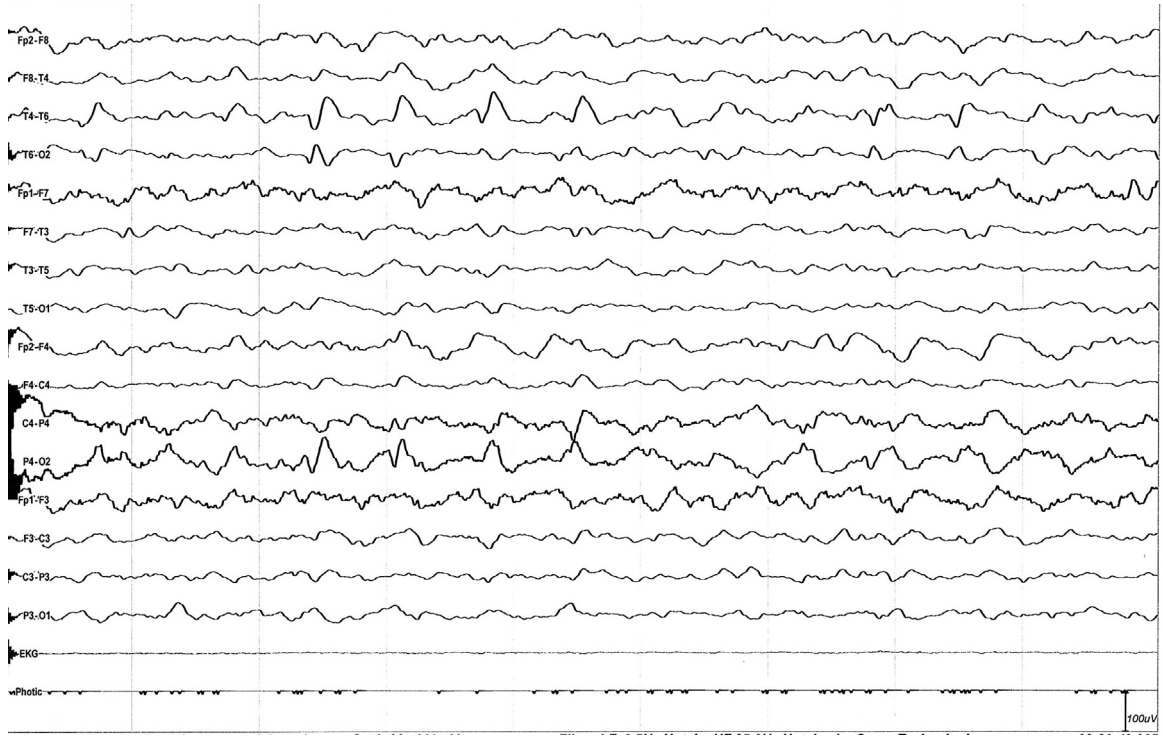

Fig. 7 – EEG on admission during the third hospitalization – severe generalized changes with a slight predominance in right hemisphere (frontal lobe) with intensive slowing.

Table 1 – Diagnostic criteria of CAA-RI, after Auriel et al. [14].

Probable CAA-RI	1. Age ≥40 years. 2. Presence of ≥1 of the following clinical features: headache, decrease on consciousness, behavioral change, or focal neurological signs and seizures, the presentation is not directly attributed to an acute intracranial hemorrhage (ICH). 3. MRI shows unifocal or multifocal white matter lesions that are asymmetric and extend to the immediately subcortical white matter, the asymmetry is not due to past ICH 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrohemorrhages, cerebral microhemorrhages, or cortical superficial siderosis 5. Absence of neoplastic, infectious, or other cause.
Possible CAA-RI	1. Age ≥40 years. 2. Presence of ≥1 of the following clinical features: headache, decrease on consciousness, behavioral change, or focal neurological signs and seizures, the presentation is not directly attributed to an acute intracranial hemorrhage (ICH). 3. MRI shows white matter lesions that extend to the immediately subcortical white matter 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrohemorrhages, cerebral microhemorrhages, or cortical superficial siderosis 5. Absence of neoplastic, infectious, or other cause.

considered in case of a poor response to corticosteroids therapy within 3 weeks [14]. In our case the response to short high-dose corticosteroid therapy was significant and the chronic therapy with hydrocortisone gave the stabilization of the clinical status of the patient, thus further supporting the diagnosis of CAA-RI.

Typically CAA-RI has monophasic pattern, the relapses were reported occasionally [6,15,16]. To our best knowledge, this is a first presentation of a patient who suffered from CAA-RI three times in a short period of time – all previously reported cases depicted one recurrence ranging from 3 months to 8 years after the first episode [16]. The first recurrence of CAA-RI affected different lobe than the initial event, while the second one was observed both in the same and new cerebral regions.

Cerebral microhemorrhages observed in CAA-RI might be seen in various diseases [17]. In our case, having in mind good response to steroid therapy, primary central nervous system vasculitis (PCNSV) should be considered [16]. Confluent hyperintesities in T2-weighted images without the evidence

of infarction are unusual for PCNSV and argue in favor for CAA-RI [16].

Moreover, the flaw of this case report is the fact that anti-Aβ autoantibodies in CSF and APOE ε4 allele were not examined. These findings would make final diagnosis more clear and give more details about the pathogenesis of CAA-RI in this case. What is more, the evaluation of β-amyloid depositions in vessels can be determined using ^{11}C-Pittsburgh Compound B-positron emission tomography (PiB PET) [15]. This examination can be additionally used in the evaluation of the deposits in different brain areas during acute CAA-RI and in case of a relapse. [15].

4. Conclusions

We present a patient with recurrent CAA-RI with clinical improvement after steroid therapy, who was first believed to suffer from PRES. Asymmetric bilateral hyperintensities in T2-weighted images and subcortical/cortical microhemorrhages in SWI in brain MRI were crucial for establishing the suspicion of CAA-RI. To conclude, this rare and under-recognized final diagnosis was reached due to the results of neuroimaging, improvement after immunosuppressive therapy and long-term observation of clinical symptoms.

Conflict of interest

None declared.

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