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Inflammatory cerebral amyloid angiopathy with poor outcome – case report

Zapalna postać angiopatii amyloidowej o ciężkim przebiegu. Opis przypadku

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Abstract

The article presents a clinical case of a 62-year-old patient diagnosed with inflammatory amyloid angiopathy after extensive diagnostic imaging and based on the characteristic radiological picture. Inflammatory amyloid angiopathy is a rare condition with intermediate features between the classic form of amyloid angiopathy and primary central nervous system angiitis. Multiple characteristic features suggesting the diagnosis may be seen on brain magnetic resonance imaging. There are no laboratory markers of the disease. Knowledge of this disease is important as it allows for a quick diagnosis and initiation of appropriate treatment. The response to treatment varies, with full symptom resolution in some patients, and resistance to treatment in others, such as the patient described in this case report.

Keywords: CCA, ICCA, CAA-ri, ABRA, cerebral microbleeds

Streszczenie

W artykule opisano przypadek kliniczny 62-letniego pacjenta, u którego po przeprowadzeniu szerokiej diagnostyki różnicowej rozpoznano zapalną postać angiopatii amyloidowej. Zapalna postać angiopatii amyloidowej jest rzadką postacią angiopatii amyloidowej. Choroba wykazuje cechy pośrednie pomiędzy klasyczną postacią angiopatii amyloidowej oraz pierwotnym zapaleniem naczyń ośrodkowego układu nerwowego. W rezonansie magnetycznym głowy można stwierdzić szereg charakterystycznych cech sugerujących rozpoznanie. Nie istnieją żadne swoistne laboratoryjne markery choroby. Znajomość tej jednostki chorobowej w dalszym ciągu jest dosyć niska, co prowadzi do opóźnienia postawienia prawidłowej diagnozy i włączenia odpowiedniego leczenia. Przebieg choroby jest ciężki do przewidzenia, część pacjentów wykazuje doskonałą odpowiedź na leczenie sterydami, inni zaś są oporni na leczenie immunosupresyjne.

Słowa kluczowe: CCA, ICCA, CAA-ri, ABRA, mikrokrwawienia mózgowe

CASE REPORT

A 62-year-old man was admitted to the Department of Neurology due to headaches and dizziness with balance disorders, disorientation in time and space, and difficulties with speaking and making voluntary movements for 2 weeks. For the past 3 days, the patient's family members also observed deterioration of cognitive functions and logical communication, psychomotor restlessness, periodic uncoordinated limb movements, periodic visual hallucinations and behavioural disorders in the form of laughter inappropriate to the situation.

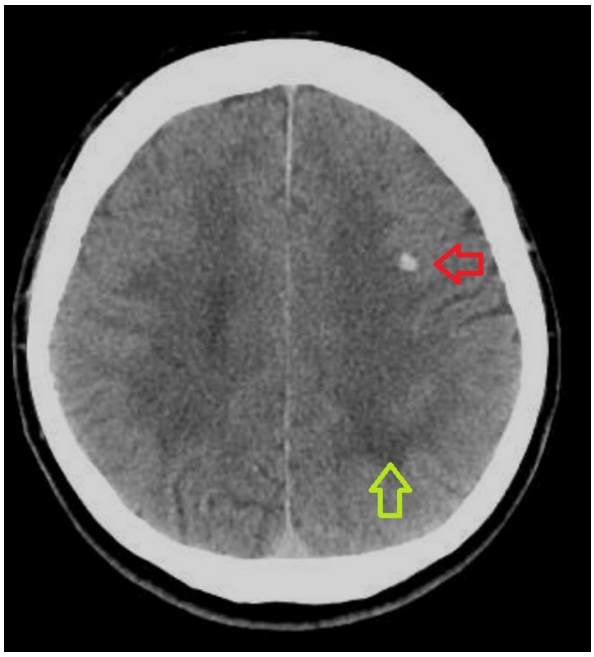

Fig. 1. CT image of the head; a red arrow indicates a haemorrhagic focus in the cortical/subcortical area of the left frontal lobe, a green arrow indicates an area of hypodensity in the left parietal lobe

The patient was treated for hypertension and had COVID-19 two months earlier.

Neurological examination on admission revealed the following symptoms: sensory aphasia, difficult logical contact, partial global disorientation, periodically pathological, laughter inappropriate to the situation, ideomotor apraxia, involuntary (choreatic) movements of the limbs and head, positive Parinaud's sign, unsteady Romberg's test, gait disturbances.

A computed tomography (CT) scan of the head revealed a haemorrhage at the cortical/subcortical border in the left frontal lobe and an area of subcortical hypodensity in the left parietal lobe (Fig. 1). The diagnosis was extended to include magnetic resonance imaging (MRI) of the head, which showed small haemorrhagic foci at the border of the cortex and white matter of the left frontal lobe supraventricularly (Fig. 2) and in the area of the posterior part of the right insula. The gradient echo sequence (GRE) showed multiple further cerebral microbleeds (CMBs) in the frontal and parietal lobes and single ones in the occipital and temporal lobes (Fig. 3). In the vicinity of these foci in the brain tissue there were areas of moderately increased T2 and FLAIR signal, with local oedema, and the administration of a contrast agent resulted in a clear enhancement of the arachnoid mater in the grooves of the gyri of the frontal and parietal lobes on the fornix (Fig. 2). Moreover, white matter hyperintensities (WMHs) were scattered in the white matter of the brain.

Angio-CT showed no abnormalities. The lung X-ray was normal. SARS-CoV-2 infection was excluded based on polymerase chain reaction (PCR) testing. Laboratory tests revealed a positive titre of IgG and IgM anti-SARS-CoV-2 antibodies and increased D-dimers. A lumbar puncture was performed, obtaining xanthochromic cerebrospinal fluid with a high protein level (254.7 mg/dL with a normal value of 45 mg/dL), pleocytosis 4 cells/μL. An extended differential diagnosis was performed, including systemic connective tissue diseases, systemic vasculitis, and neuroinfections.

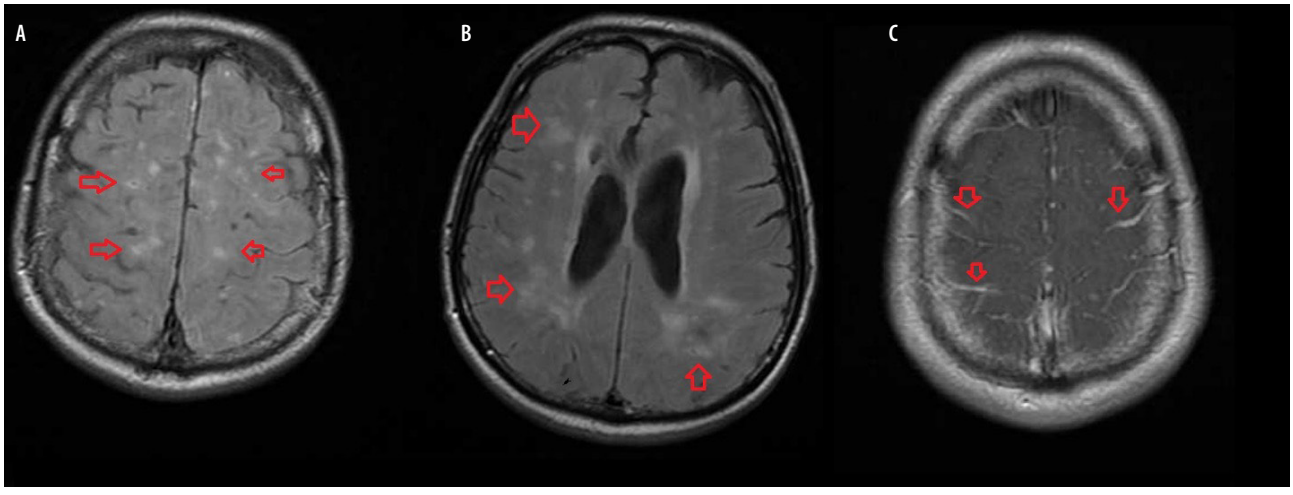

Fig. 2. MRI of the head. **A, B.** *T2/FLAIR images – the arrows indicate scattered WMHs with local vasogenic oedema, distributed asymmetrically;* **C.** *post-contrast T1 images – arrows mark contrast enhancement of the pia mater and arachnoid mater*

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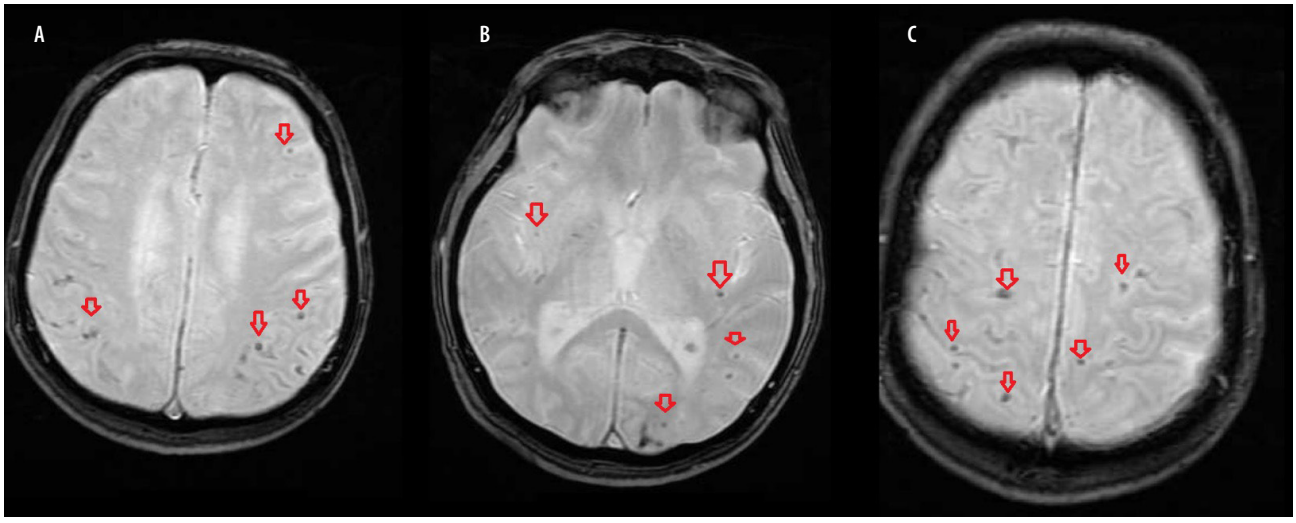

Fig. 3. MRI of the head, GRE sequence. Numerous, scattered CMBs are visible, located mainly in the cortical/subcortical area of both cerebral hemispheres

The treatment included intravenous (IV) infusions of methylprednisolone at a dose of 1,000 mg for 5 days but no improvement in the clinical condition was achieved. During hospitalisation, the patient showed high psychomotor agitation and aggressive behaviour, which were managed ad hoc with benzodiazepines and neuroleptics. Due to the lack of improvement after corticosteroids, intravenous immunoglobulin therapy (IVIg) was administered at a dose of 0.4 mg/kg body weight for 5 days – the patient developed transient renal failure and periodically had fever during the infusions. There was still no improvement in the clinical condition after 5 days. Unfortunately, no brain biopsy was performed because the patient did not give informed consent to the procedure, and cooperation with him was significantly difficult due to psychomotor agitation and impaired consciousness.

In the differential diagnosis, diseases associated with central nervous system vasculitis were taken into account. Ultimately, based on the entire clinical picture, additional tests and the 2016 diagnostic criteria (Tab. 1) (Auriel et al., 2016), probable inflammatory cerebral amyloid angiopathy (ICCA) with poor response to treatment was diagnosed. The patient was transferred to a long-term care facility. His further fate remains unknown.

DISCUSSION

Inflammatory cerebral amyloid angiopathy was first described by Reid and Maloney in 1974. Similarly to classic cerebral amyloid angiopathy (CAA), beta-amyloid (Aβ) is deposited in the walls of the vessels of the cerebral cortex, the pia and arachnoid mater (organ-limited amyloidosis); however, unlike CAA, there is an inflammatory infiltrate, most likely directed against Aβ (autoagression) (Salvarani et al., 2008, 2016). Brain biopsy is the gold standard for reaching a define diagnosis (Kinnecom et al., 2007).

Based on histopathological images, two subtypes of ICCA have been distinguished:

Diagnostic category	Criteria
Probable	1. Age ≥40 years 2. Presence of one or more of the following clinical features: headache, decreased consciousness, behavioural change, or focal neurological signs and seizures; not directly attributable to an acute ICH 3. MRI reveals unifocal or mwultifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to previous ICH 4. Presence of one or more of the following corticosubcortical haemorrhagic lesions: cerebral microbleed, cerebral microbleed, or cortical superficial siderosis 5. Absence of neoplastic, infectious, or other causes
Possible	1. Age ≥40 years 2. Presence of one or more of the following clinical features: headache, decreased consciousness, behavioural change, or focal neurological signs and seizures; not directly attributable to an acute ICH 3. MRI reveals unifocal or multifocal WMH lesions (corticosubcortical or deep) that extend to the immediately subcortical white matter 4. Presence of one or more of the following corticosubcortical haemorrhagic lesions: cerebral microbleed, cerebral microbleed, or cortical superficial siderosis 5. Absence of neoplastic, infectious, or other causes

Tab. 1. Diagnostic criteria for inflammatory cerebral amyloid angiopathy (Auriel et al., 2016)

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a. cerebral amyloid angiopathy-related inflammation (CAA-ri) – when the inflammation is located perivascularly, without vascular wall involvement;
b. amyloid β-related angiitis (ABRA) – when the inflammatory process involves the vascular wall, leading to its destruction (Castro Caldas et al., 2015; Cenina et al., 2015, Kirshner and Bradshaw, 2015).

The available literature may contain some nosological problems and inconsistencies, as some authors use the terms ICCA/ABRA/CAA-ri interchangeably. This article uses the most general term – ICCA.

ICCA can be considered as an intermediate form between CCA and primary angiitis of the central nervous system (PACNS). The average age at ICCA onset is 67 years, which is later than PACNS (45–55 years) and earlier than CCA (77 years). In the course of ICCA and PACNS, the vessels of the spinal cord are involved, which distinguishes them from CCA. The presence of Aβ deposits is a common feature of CCA and ICCA, while the presence of an inflammatory infiltrate composed mainly of T cells and macrophages is a common presentation in ICCA and PACNS.

Currently, homozygosity for the APOE-ε4 allele which is present in almost 75% patients with ICCA and only in 4–5% patients with CCA is the only confirmed risk factor for ICCA (de Souza and Tasker, 2023; Wu et al, 2021).

ICCA symptoms often have an acute or subacute onset. The most common clinical symptoms are encephalopathy with disturbances of consciousness (75%) and sometimes focal symptoms (46–58%), headache (22–41%), epileptic seizures (33%), cognitive disorders (often present several months before diagnosis). Involuntary movements, visual hallucinations (14%), aphasia (14–26%), and ataxia (7%) are less common. Unlike CCA, the presence of intracerebral haemorrhage (ICH) is not typical for ICCA. Stroke-like episodes can be detected in approximately 46% of patients, but foci of restricted water diffusion in MRI, consistent with ischemic strokes, are rare (unlike PACNS). In about 15% patients with ICCA mass-like lesions (amyloidoma) can be seen – in these cases biopsy is required to differentiate ICCA from a neoplastic process (Chu et al., 2016; Moussaddy et al., 2015; de Souza and Tasker, 2023).

MRI is the imaging method of choice; it reveals a number of characteristic features:

- asymmetrically distributed white matter hyperintensities (WMH) in T2/FLAIR images, sometimes confluent, with local vasogenic oedema that may cause a slight mass effect, located mainly in the area of the cortical-subcortical junction;
- CMBs detected in GRE or SWI sequences;
- leptomeningeal enhancement in about 30–50% cases (Corovic et al., 2018; Danve et al., 2014; Moosavi et al., 2016).

Digital subtraction angiography (DSA) does not reveal any abnormalities because the disease mainly affects small vessels. Computed tomography of the head sometimes reveals single subcortical hypodense lesions with a mass effect or CMBs.

An analysis of the cerebrospinal fluid shows increased protein levels in over 80% of cases, and pleocytosis with predominance of lymphocytes in 44%. Oligoclonal bands are typically absent (de Souza and Tasker, 2023; Wu et al., 2021).

A definite diagnosis requires a brain biopsy and histopathological evaluation (gold standard). Over the years, "non-invasive" diagnostic criteria have been developed allowing for a "probable" or "possible" diagnosis based only on the clinical and radiological picture. The currently applicable criteria date back to 2016 (Auriel et al., 2016).

The differential diagnosis includes all diseases that may involve cerebral vasculitis, including: PACNS, posterior reversible encephalopathy syndrome, intravascular lymphoma, neuroinfections, systemic connective tissue disorders, systemic vasculitis associated with antineutrophil cytoplasmic antibodies (Chung et al., 2011; Raghavan et al., 2016; Savoiardo et al., 2010).

Treatment includes high doses of intravenous glucocorticoids (methylprednisolone 1,000 mg for 3–5 consecutive days) followed by oral continuation and gradual dose reduction over several weeks. Sometimes it is necessary to use additional immunosuppressants such as azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil (Kinnecom et al., 2007; Piazza et al., 2013). There are case reports showing good response to IVIg (Cenina et al., 2015).

The course of the disease varies and is difficult to predict. Some patients (approx. 55%) show a good response to corticosteroids, with a gradual improvement in the clinical condition, leading to complete clinical and radiological regression. Others are resistant to treatment, leading to permanent disability and sometimes death (Miller-Thomas et al., 2016; Theodorou et al., 2023).

CONCLUSIONS

Inflammatory cerebral amyloid angiopathy is a rare disease, but potentially curable in at least some cases. Most neurologists are well aware of CAA, but the knowledge of ICCA is still relatively low. This article aims to present the clinical and radiological picture of ICCA because making an accurate diagnosis allows for the implementation of appropriate treatment and improves the patient's prognosis. In the presented case, the patient's clinical condition did not improve after high doses of methylprednisolone and after a course of IVIg treatment. Multiple CMBs and WMHs in head MRI indicate that the disease can develop in an insidious and clinically silent manner over a long period of time.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication

Author contributions

Original concept of study: DD. Collection, recording and/or compilation of data: DD. Analysis and interpretation of data: DD, KD. Writing of manuscript: DD. Critical review of manuscript: DD, KD. Final approval of manuscript: DD, KD.

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