Steroid responsive encephalopathy in cerebral amyloid angiopathy: a case report and review of evidence for immunosuppressive treatment

Raoul P Kloppenborg¹, Edo Richard¹, Marieke ES Sprengers², Dirk Troost³, Piet Eikelenboom¹, Paul J Nederkoorn¹*

Abstract

Cerebral amyloid angiopathy (CAA) is a common but often asymptomatic disease, characterized by deposition of amyloid in cerebral blood vessels. We describe the successful treatment of CAA encephalopathy with dexamethasone in a patient with CAA-related inflammation causing subacute progressive encephalopathy and seizures, which is an increasingly recognized subtype of CAA. The two pathological subtypes of CAA-related inflammation are described and a review of the literature is performed concerning immunosuppressive treatment of CAA-related inflammation with special attention to its pathological subtypes. Immunosuppressive therapy appears to be an appropriate treatment for CAA encephalopathy.

Background

Sporadic cerebral amyloid angiopathy (CAA) is a common but often asymptomatic neuropathological finding, characterized by the deposition of amyloid-β (Aβ) in small and medium-sized cerebral arteries, arterioles and sometimes capillaries of the meninges and brain parenchyma. Its prevalence is strongly associated with increasing age and has been reported to be as high as 57% percent in case series of asymptomatic patients over 60 years of age [1]. CAA is a common finding in patients with Alzheimer’s disease (AD); but many patients with CAA do not develop AD. CAA can lead to lobar haemorrhage in non-hypertensive patients [2]. Other, less often reported clinical manifestations are seizures, transient neurological deficits and dementia other than AD [3]. In addition, more rare presentations have been reported, including space occupying lesions and leukoencephalopathy on magnetic resonance imaging (MRI) [4-6]. The latter is an increasingly recognized syndrome encompassing subacute encephalopathy, headache, seizures or focal neurological symptoms. Upon brain biopsy, an inflammatory process is found in relation to the vascular deposits of Aβ. In contrast to other Aβ-depositing disorders such as AD, immunosuppressive treatment has been reported to ameliorate both clinical and radiological symptoms of CAA encephalopathy, although with variable success [7]. This variability could be explained by the existence of different underlying pathological subtypes. We describe a patient with CAA-leukoencephalopathy, who was treated successfully with dexamethasone. We also performed a literature review concerning the use of immunosuppressive treatment for CAA-related inflammation with special attention to its pathological subtypes.

Case presentation

A 74-year-old man with an unremarkable medical history noted a progressive gait disorder in the months prior to admission. His wife recalled increased sleepiness and loss of initiative. After having seizures the patient was admitted to our hospital. The patient was disoriented in time and did not perform complicated tasks, although this could partly be attributed to apathy. He could not remember the reason for his stay in the hospital. The remaining neurological examination revealed no abnormalities. MRI showed confluent bifrontal white matter lesions and minimal enhancement of the white matter in the right frontal lobe after administration of gadolinium (Figure 1A-D). Routine laboratory measurements were normal. Cerebral spinal fluid examination revealed an elevated protein level (1.78 g/l). No malignant cells were found in the spinal fluid. After diagnostic work-up had excluded a primary tumour elsewhere...
in the body, low grade astrocytoma or gliomatosis cerebri was considered and a stereotactic brain biopsy was performed. Histopathological analysis showed extensive Aβ immunopositivity around smaller and larger blood vessels (Figure 2A, B). No neurofibrillary tangles or amyloid plaques were found in the parenchyma. Reactive gliosis, strong upregulation of microglia and multiple macrophages around the blood vessels in both white and grey matter were present (Figure 2C, D). The findings were compatible with sporadic CAA. After the patient developed progressive apathy, loss of initiative, magnetic gait and hypertonia of the extremities, treatment with dexamethasone (2 × 4 mg/day) was started. There was a remarkable clinical improvement in the following days. The patient became alert, the hypertonia disappeared and he was able to walk with a wheeled walker. After 5 weeks, he was discharged from the hospital with a mild gait disorder. A 3 Tesla MRI three months after admission showed remarkable amelioration of the white matter abnormalities. Gradient echo sequences showed subcortical hypointensities, compatible with multiple microbleeds (figure 1). Dexamethasone treatment was tapered in the months after admission.
Discussion
The clinical picture of CAA-related inflammation includes encephalopathy, seizures and headaches. Extensive vaso-genic edema and/or leukoencephalopathy is visible on MRI, sometimes mimicking space-occupying lesions. Histological examination shows amyloid-laden vessels and the appearance of Aβ in close association with inflammatory cells, implicating Aβ as the potential trigger for the inflammatory response. It remains unclear why only a few CAA patients develop this response. A high percentage of such patients are homozygous for the ε4-allele of the apolipoprotein E gene (APOE ε4/ε4; 76.9% vs 5.1% in non-inflammatory CAA) [6], which is associated with activation of complement and microglia. Additionally, trials of anti-Aβ vaccination in patients with Alzheimer’s disease (AD) induced similar clinical, radiological and pathological inflammation as seen in CAA-related inflammation, suggesting an immune response to Aβ.

Unlike other Aβ-depositing disorders, CAA-associated inflammation appears to derive a beneficial effect from corticosteroid treatment. This effect could be dependent on the pathological subtype of CAA-related inflammation.

Two subtypes of CAA-associated inflammation have been described so far: (i) a non-vasculitic form called perivascular infiltration (PVI), which is characterized by perivascular infiltration of the parenchyma by multinucleated giant cells and (ii) a vasculitic form called transmural (non)-granulomatous angiitis (TGA), which is characterized by inflammation of the vessel wall with the occasional presence of granulomas. Both pathologic forms can co-occur, suggesting at least a partial overlap [8]. The clinical and radiological findings of both variants are remarkably similar. Our case showed reactive gliosis and multiple macrophages around blood vessels in grey and white matter, although no multinucleated cells were seen. This is consistent with reactive edema in encephalopathy and suggests PVI. Although often called CAA-angiitis, the terms CAA-vasculopathy or CAA-encephalopathy are preferred, since these terms do
| Author          | n | Age | Pathology | Radiology | Therapy | Clinical improvement | Radiological improvement | Follow-up | Clinical features | Comments                                                                 |
|-----------------|---|-----|-----------|-----------|---------|----------------------|--------------------------|-----------|------------------|--------------------------------------------------------------------------|
| Ginsberg 1988   | 1 | 73  | TGA       | Confluent | Dx, Pn  | Yes                  | Yes                      | >1 year   | Gait disturbance  |                                                                          |
| Mandybur 1992   | 1 | 62  | TGA       | Mass      | CP, Pn  | Yes                  | Yes                      | Death 8 months | Encephalopathy Focal neurology Hallucinations Remarkable pathological improvement lesions post-mortem compared to initial biopsy |
| Osumi 1995 [4]  | 1 | 59  | ?         | Mass      | CS      | No                   | ?                        | Death 5 months | Focal neurology Headaches Seizures                                     |
| Silbert 1995 [12]| 1 | 74  | ?         | Confluent | Dx      | No                   | No                       | Death 6 weeks | Headache Seizures                                                     |
| Fountain 1996   | 1 | 66  | TGA       | Confluent | CP, Dx, Pn | No               | Partial                 | 20 months | Encephalopathy Headaches Seizures                                     |
| Fountain 1996   | 1 | 69  | TGA       | Confluent | CP, Dx, Pn | Partial           | Partial                 | Death 6 months | Encephalopathy Headaches Seizures Relapse                              |
| Ortiz 1996 [14] | 1 | 68  | PVI       | Mass      | Dx, Pn  | Yes                  | Yes                     | ?                      | Encephalopathy Gait disturbance Headaches Seizures                      |
| Masson 1998 [15]| 1 | 64  | PVI       | Confluent | CP, Pn  | Yes                  | No                      | 15 months  | Encephalopathy Headaches                                              |
| Fountain 1999   | 1 | 71  | PVI, TGA  | Confluent | CP      | Yes                  | Yes                     | 22 months  | Encephalopathy Gait disturbance Headaches Relapse after stop CP        |
| Streichenberger 1999 [17]| 1 | 67 | TGA       | Mass/ Confluent | CS | Yes | Yes | Death 1 month | Headaches Encephalopathy                                      |
| Hoshi 2000 [18] | 1 | 65  | - (after treatment) | Recurrent ICH | Pn | Yes | NA | 6 months | Focal neurology                                                     |
| Schwab 2003 [19]| 1 | 74  | PVI/TGA   | Mass      | Dx, 1m, Pn | Yes | ? | 12 months | Encephalopathy Headaches Seizures                                     |
| Schwab 2003 [19]| 1 | 70  | PVI/TGA   | Mass      | Pn, CP  | Partial               | Yes                     | 18 months  | Encephalopathy Headaches Seizures                                     |
| Oh 2004 [20]    | 1 | 80  | PVI       | Confluent | Dx, Pn  | Yes                  | Yes                     | 8 months   | Encephalopathy Focal Neurology Seizures 1 patient with no therapy excluded |
| Oh 2004 [20]    | 1 | 77  | TGA       | Confluent | Dx, Pn  | Yes                  | Yes                     | 6 weeks    | Encephalopathy Focal Neurology Seizures 1 patient with no therapy excluded |
| Safriel 2004 [5] | 1 | 49  | TGA       | Mass      | Dx, tap 6 weeks | Partial           | 9 months   | Seizures                                                             |
| Scolding 2005   | 7 | 69* | TGA       | Confluent | Pn, Dx, CP | 43% | ? | 58 months* | Encephalopathy Focal Neurology Headaches Seizures 2 patients excluded because of mass resection as therapy |
| Kinnecom 2007 [6] | 12 | 63.2 ± 10 | PVI | Confluent | CS, CP | 83% | 83% | 47 months* | Encephalopathy Headache Seizures 25% relapse, 33% died                |
| McHugh 2007 [9] | 1 | 80  | PVI, TGA  | Confluent | Pn      | Yes                  | Yes                     | 24 months  | Encephalopathy Focal Neurology Seizures                               |
| Machida 2008    | 1 | 69  | PVI       | Confluent | Dx, Pn  | Yes                  | Yes                     | 12 months  | Encephalopathy Focal neurology Relapsing/remitting                     |
and cytotoxic effects of Aβ could be that corticosteroids merely reduce cerebral aphasias or hemianopsias. Encephalopathy is characterised as diffuse cognitive disturbances, somnolence and apathy, focal neurology is characterised as hemiparesis, hemihypesthesia, (non)-granulomatous angiitis although it does not affect initial Aβ deposition [23]. Although the clinical and radiological symptoms are similar in both pathologic variants, immunosuppressive therapy appears to have a slightly less beneficial effect in the vasculitic subtype. Nevertheless, corticosteroid therapy seems to be an appropriate therapy for both. In an elderly patient with a subacute progressive encephalopathy with seizures, CAA-related encephalopathy has to be considered because of the major therapeutic implications.

Conclusions

CAA encephalopathy is an increasingly recognized syndrome that is based upon a vasculitic or non-vasculitic inflammatory reaction to Aβ. Although the clinical and radiological symptoms are similar in both pathologic variants, immunosuppressive therapy appears to have a slightly less beneficial effect in the vasculitic subtype. Nevertheless, corticosteroid therapy seems to be an appropriate therapy for both. In an elderly patient with a subacute progressive encephalopathy with seizures, CAA-related encephalopathy has to be considered because of the major therapeutic implications.

Consent

Written informed consent was obtained from the next of kin of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author details

1 Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands. 2 Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands. 3 Department of Neuropathology, Academic Medical Center, Amsterdam, The Netherlands.

Authors’ contributions

RPK participated in the design of the article, collected and analyzed the data and drafted the manuscript. ER, PE and PJN contributed to the analysis and interpretation of the data. ME3 and DT provided radiological and pathological data respectively. PJN conceived of the case report and coordinated the drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 8 January 2010 Accepted: 9 March 2010 Published: 9 March 2010

References

1. Yamada M, Tsukagoshi H, Otomo E, Hayakawa M: Cerebral amyloid angiopathy in the aged. J Neurol 1987, 234:371-6.
2. Gilbert JJ, Vinters HV: Cerebral amyloid angiopathy: incidence and complications in the aging brain. I. Cerebral hemorrhage. Stroke 1983, 14:915-23.
3. Greenberg SM, Vonsattel JPG, Stakes JW, Gruber M, Finkestein SP: The clinical spectrum of cerebral amyloid angiopathy: Presentations without lobar hemorrhage. Neurology 1993, 43:2073-2079.

Table 1: Studies concerning immunosuppressive treatment of CAA encephalopathy (Continued)

| Study Year | Patients | TGA Type | Corticosteroid | Plasma Protein | Relapse Rate | Treatment Duration | Treatment Outcome |
|------------|----------|----------|----------------|---------------|--------------|-------------------|------------------|
| Salvani 2008 | 8 | 63 | TGA | Confluent, Pn, CP | 75% | 100% | 24 months* | Encephalopathy, Focal Neurology, Headaches | 25% relapse, both after discontinuation of treatment |

CS = corticosteroid (not otherwise specified), CP = Cyclophosphamide, Dx = dexamethasone, Pn = prednisone, PVI = perivascular inflammation, TGA = transmural (non)-granulomatous angiitis

Encephalopathy is characterised as diffuse cognitive disturbances, somnolence and apathy, focal neurology is characterised as hemiparesis, hemihypesthesia, aphasia or hemianopsia.

* calculated mean
4. Osumi KA, Tien RD, Felsberg GJ, Rosenbloom M. Cerebral amyloid angiopathy presenting as a brain mass. Am J Neuroradiol 1995, 16:91-95.
5. Safriel Y, Sze G, Westmark K, Baehring J. MR spectroscopy in the diagnosis of cerebral amyloid angiopathy presenting as a brain tumor. Am J Neuroradiol 2004, 25:1705-8.
6. Kinnekom C, Lev MH, Wendell L, Smith EE, Rosand J, Frosch MP, Greenberg SM. Course of cerebral amyloid angiopathy-related inflammation. Neurology 2007, 68:1411-6.
7. Aisen PS. The potential of anti-inflammatory drugs for the treatment of Alzheimer’s disease. Lancet Neurol 2002, 1:77-84.
8. McHugh JC, Ryan AM, Lynch T, Dempsey E, Stack J, Farrell MA, Kelly P.J. Steroid-responsive recurrent encephalopathy in a patient with cerebral amyloid angiopathy. Cerebrovasc Dis 2007, 23:66-9.
9. Ginsberg L, Geddes J, Valentine A. Amyloid angiopathy and granulomatous angiitis of the central nervous system: a case responding to corticosteroid treatment. J Neurol 1988, 235:438-40.
10. Mandybur TL, Ballo G. Cerebral amyloid angiopathy with granulomatous angiitis ameliorated by steroid-cytoxan treatment. Clin Neuroradiol 1992, 15:241-7.
11. Silbert PL, Bartleson JD, Miller GM, Parisi JE, Goldman MS, Meyer FB. Cortical petechial hemorrhage, leukoencephalopathy, and subacute dementia associated with seizures due to cerebral amyloid angiopathy. Mayo Clin Proc 1995, 70:477-80.
12. Fountain NB, Eberhard DA. Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy: Report of two cases and review of the literature. Neurology 1996, 46:190-197.
13. Ornt G, Reed L. Cerebral amyloid angiopathy presenting as a nonhemorrhagic, infiltrating mass. Neuroradiology 1996, 38:449-52.
14. Masson C, Hénin D, Colombani JM, Dehen H. A case of cerebral giant-cell angiitis associated with cerebral amyloid angiopathy. Favorable evolution with corticosteroid therapy. Rev Neurol (Paris) 1998, 154:695-8.
15. Fountain NB, Lopes MB. Control of primary angiitis of the CNS associated with cerebral amyloid angiopathy by cyclophosphamide alone. Neurology 1999, 52:660-2.
16. Streichenberger N, Girard-Madoux P, Verejan I, Pialat J, Vital C, Kopp N. Giant cell angiitis of the central nervous system with amyloid angiopathy. A case report and review of the literature. On Exp Pathol 1999, 47:311-7.
17. Hoshi K, Yoshida K, Nakamura A, Tada T, Tamaoka A, Ikeda S. Cessation of cerebral hemorrhage recurrence associated with corticosteroid treatment in a patient with cerebral amyloid angiopathy. Amyloid 2000, 7:284-8.
18. Schwab P, Lidov HG, Schwartz RB, Anderson RJ. Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. Arthr Reum 2003, 49:421-227.
19. Oh U, Gupta R, Krakauer JW, Khandji AG, Chin SS, Elkind MS. Reversible leukoencephalopathy associated with cerebral amyloid angiopathy. Neurology 2004, 62:494-7.
20. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, Ellison D, Hilton DA, Williams TL, Mackenzie JM, Xuereb JH, Love S. Anti-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain 2005, 128:500-15.
21. Machida K, Tojo K, Naito Ks, Gono T, Nakata Y, Ikeda S. Cortical petechial hemorrhage, subarachnoid hemorrhage and corticosteroid-responsive leukoencephalopathy in a patient with cerebral amyloid angiopathy. Amyloid 2008, 15:60-4.
22. Salvatari C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J, Meschia JF, Giannini C, Miller DV, Hundley GG. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. Rheumatology 2008, 47:1671-7.
23. Previti ML, Zhang W, van Nostrand WE. Dexamethason diminishes the pro-inflammatory and cytotoxic effects of β-protein in cerebrovascular smooth muscle cells. J Neuroinflammation 2006, 3:18.

Cite this article as: Kloppenborg et al: Steroid responsive encephalopathy in cerebral amyloid angiopathy: a case report and review of evidence for immunosuppressive treatment. Journal of Neuroinflammation 2010 7:18.

doi:10.1186/1742-2094-7-18

Submit your next manuscript to BioMed Central and take full advantage of:
• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit