Case Presentation

An 86-year-old lady requested a visit from her GP following an episode of difficulty forming words and seeing flashing lights in her right eye. There was no facial or limb weakness, swallowing difficulty or headache, and she did not feel systemically unwell. Her son reported that she had been generally tired and less mobile recently. She was known to have difficult to control hypertension and atrial fibrillation, but had been stable on warfarin for many years with no previous vascular events or bleeding episodes. MRI imaging showed a large number of cerebral microbleeds in a lobar distribution, and also 2 small acute subcortical infarcts in the right frontal lobe. The appearances overall were suggestive of cerebral amyloid angiopathy. Her recurrent and stereotyped symptoms were felt to be more in keeping with transient focal neurological events (TFNE) related to cerebral amyloid angiopathy rather than TIAs. However, this left us with a dilemma as to whether to stop or continue warfarin treatment in the light of her acute infarcts and established atrial fibrillation.

MRI scan showed two small areas of restricted diffusion indicating acute infarction on the right posterior frontal lobe, immediately superior to the corpus callosum, and another smaller area in subcortical white matter of the posterior parietal lobe (Figure 1). There were also small well defined foci of susceptibility artefact scattered throughout both cerebral hemispheres, suggestive of cerebral microbleeds (Figures 2-4). The scan appearances overall were consistent with cerebral amyloid angiopathy.

The diagnostic possibilities at this stage included acute infarct or TIA (possibly related to atrial fibrillation), or transient focal neurological events related to her amyloid angiopathy.

Figure 1: Diffusion weighted MRI image showing 2 small acute ischemic strokes.

Keywords: Cerebral amyloid angiopathy; Hypertension; Atrial fibrillation; Transient focal neurological events; Warfarin

Introduction

It is increasingly common to see older patients with multiple intracerebral pathologies which put them at risk of vascular events. Cerebral amyloid angiopathy is an under-recognised cause of transient focal neurological symptoms in the TIA clinic. Appropriate and timely use of MRI imaging can aid the correct diagnosis. This case however also illustrates the difficulty of balancing the risks and benefits of treatment where there is more than one pathology present.

Abstract

An 86-year-old lady was referred to the TIA clinic with recurrent episodes of slurred speech, disorientation and flashing lights in her vision. She was known to have difficult to control hypertension and atrial fibrillation, but had been stable on warfarin for many years with no previous vascular events or bleeding episodes. MRI imaging showed a large number of cerebral microbleeds in a lobar distribution, and also 2 small acute subcortical infarcts in the right frontal lobe. The appearances overall were suggestive of cerebral amyloid angiopathy. Her recurrent and stereotyped symptoms were felt to be more in keeping with transient focal neurological events (TFNE) related to cerebral amyloid angiopathy rather than TIAs. However, this left us with a dilemma as to whether to stop or continue warfarin treatment in the light of her acute infarcts and established atrial fibrillation.
angiopathy (sometimes known as amyloid spells).

transient focal neurological events (TFNE) related to cerebral amyloid angiopathy. We felt that this patient's symptomatic episodes were most likely to be due to hypertensive arteriopathy, but a lobar distribution of CMBs is more strongly associated with CAA.

Cerebral amyloid angiopathy (CAA) is common and probably underdiagnosed. One study found evidence of CAA in 57% of an autopsy series of patients aged 59-101, with the incidence increasing with age [1]. Conclusive evidence can only be obtained from brain biopsy or autopsy demonstrating amyloid deposition in cerebral arterioles. However the Boston criteria, supported by imaging evidence, are widely used to diagnose probable CAA in the absence of biopsy [2]. The central pathology in sporadic CAA is deposition of beta-amyloid protein in the walls of leptomeningeal arteries and arterioles [3]. This is thought to increase the fragility of the vessels and often results in tiny areas of asymptomatic bleeding which are visible on haem-sensitive MRI sequences (T2*, gradient echo or susceptibility weighted MRI). The most significant clinical manifestation is lobar intracerebral haemorrhage, which may be recurrent. CAA also correlates with an increased risk of ischemic stroke, leukoaraiosis, and cognitive decline.

Cerebral microbleeds, as seen in this patient (Figures 3 and 4) are thought to be due to small quantities of blood leaking from a damaged vessel [4]. These are usually controlled by normal haemostasis and so do not generally cause symptoms. Deep microhaemorrhages may be due to hypertensive arteriopathy, but a lobar distribution of CMBs is more strongly associated with CAA.

This patient presented a variety of non-specific symptoms, which were difficult to localize with certainty to one part of the brain. Nevertheless, based on her risk factors and MRI findings, we were able to roughly distinguish between cortical and subcortical etiologies, and propose the likely sites for the transient focal neurological episodes (TFNE), which the patient presented.

We believe that the two acute ischemic strokes seen on MRI-DWI (Figure 1) are most likely related to her atrial fibrillation. Fortunately, these events went unnoticed by the patient, as they did not cause any focal neurology. On the other hand, we propose that her transient focal episodes relate to the variety of amyloid deposits seen throughout the brain. For example, the visual symptoms – flashing, colorful lights – are most likely related to the posterior microbleed sites (Figure 2); the episodes of disorientation and dysarthria could potentially be traced back to the multiple cortical and subcortical amyloid sites (Figures 3 and 4).

Differential diagnosis

Right posterior frontal lobe infarcts TIAs related to AF Transient focal neurological events (TFNE) related to cerebral amyloid angiopathy.

Treatment

There is currently no specific treatment for cerebral amyloid angiopathy. Tight blood pressure control is beneficial in minimising the risk of ICH, so her antihypertensive treatment was increased and early follow up was arranged with her GP. Her long term anticoagulation presented a dilemma, as the risk of ICH associated with anticoagulation in the context of cerebral microbleeds is controversial. Ultimately since she had been stable on warfarin for many years without any bleeding episodes, and she had evidence of recent cortical infarcts on MRI, we decided to continue her anticoagulation.

Outcome and follow-up

She was reviewed in the outpatient clinic 2 months later and was doing well, with no further neurological episodes.

Discussion

Including very brief review of similar published cases (how many similar cases have been published).

The patient was experiencing recurrent stereotyped episodes of neurological symptoms which were not typical of TIA or acute cerebral ischemia, and did not correlate well with the acute infarcts visible on the MRI. TIAs typically cause a transient loss of function that can be localised to one vascular territory. They do not usually cause positive symptoms such as flashing lights or paraesthesiae, which are more typically associated with seizures or migraine.

This lady's events however involved both positive and negative symptoms affecting different territories. Stereotyped episodes involving multiple territories could also be due to migraine. However, it would be unusual for migraine to present for the first time in an 86 year old. Her episodes were briefer than a typical aura and also did not display a typical rate of progression, as all the symptoms were present within a few minutes.

In the light of the MRI findings of multiple cortical microbleeds, we felt that this patient's symptomatic episodes were most likely to be transient focal neurological events (TFNE) related to cerebral amyloid angiopathy (sometimes known as amyloid spells).

Investigations

FBC, ESR, U&E, LFT, cholesterol, coagulation screen ECG, MRI scan.
A retrospective case series in 2013 including a systematic review of published case reports suggested that the incidence of transient focal neurological episodes in patients with diagnosed CAA was 14.5% [5]. In spite of this the diagnosis is not always considered in patients referred to the TIA or stroke clinic with transient symptoms.

A wide variety of clinical syndromes of TFNE have been recognised in patients with CAA.

1. TIA – like TFNE episodes with focal weakness or dysphasia.

2. Migraine-like TFNE episodes with spreading paresthesias or visual symptoms of flashing lights or zig zags.

3. Partial seizure-like episodes with limb shaking.

The mechanism of TFNE in cerebral amyloid angiopathy is not well understood. They have been variously attributed to seizure activity, microbleeds or focal ischemia. However in the review noted above TFNE correlated best with evidence of cortical siderosis, cortical microbleeds or focal subarachnoid haemorrhage, suggesting that they are more likely to be a symptom of haemorrhage than of focal ischemia [5]. In addition although the numbers were small these symptoms seemed to be associated with a relatively high risk of future ICH.

This patient additionally presented us with a therapeutic dilemma as she was already anticoagulated on warfarin for atrial fibrillation. Her CHADS2-Vasc2 score was suggesting an annual risk of embolic stroke of 6.7%, and she had been stable for many years on warfarin. Her HAS-Bled score was suggesting an average risk of a significant bleeding event of 4.1% per year. However the potential additional risks of anticoagulation in the context of CAA and cerebral micro bleeds are not well characterised. Theoretically anticoagulation could increase the risk of one of these microbleeds expanding and resulting in a symptomatic intracerebral haemorrhage.

Conclusion

As yet there have been no prospective studies looking specifically at anticoagulant risk and CMBs. An association between CMBs and ICH on warfarin has been observed [6], but prospective studies of patients with CMBs after ischemic stroke have produced conflicting results [7]. The largest prospective study in an East Asian population found an increased risk of ICH in patients with higher numbers of CMBs [8]. However a later study in Europe found an increased risk of ischemic stroke in patients with CMBs and no clear increase in ICH [9]. The “Clinical Relevance of Microbleeds in Stroke Study” (CROMIS-2) AF arm has been designed specifically to address this important question [10].

Learning Points

1. Transient focal neurological attacks associated with CAA should be considered as a differential diagnosis of TIA especially in older patients.

2. Attacks are often recurrent and stereotyped, but may take the form of positive (migraine-like) or negative (TIA-like) symptoms.

3. MRI with T2* sequences is essential to make the diagnosis, and should be requested in a timely fashion in cases of atypical or recurrent TIA.

4. Antiplatelet agents should be avoided if a diagnosis of CAA with TFNE is suspected as the risk of future haemorrhage appears to be high.

5. A decision on anticoagulation requires careful consideration of the possible risks and benefits to an individual patient.

References


