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Introduction

Vascular dysfunction resulting in deficiency of blood supply into the brain is one of the principal mechanisms of Vascular Dementia (VaD).

The pathogenesis of VaD is related to a thrombotic process with two distinct mechanisms

multiple micro-infarcts¹, associated with a single symptomatic infarct; so called post-stroke dementia-PSD²

microvessel lesions (Sub-cortical VaD or SVaD) which are characterised by fibrin deposition in the microvasculature that promotes ischemia

Sub-cortical VaD although stemming from an ischemic mechanism is associated with the presence of Brain Micro-Bleeds (BMBs), which in turn are implicated into the pathogenesis of Cerebral Amyloid Angiopathy (CAA) and are associated with Cerebrovascular Disease and some of its risk factors such as hypercholesterolemia, hypertension and diabetes³.

VaD could be described as the clinical manifestation of a thrombohaemorrhagic disorder at the level of brain microcirculation

Demented patients most often carry co-morbidities such as cardiovascular disease or atrial fibrillation (AF), for which they commonly receive antithrombotic treatment i.e. antiplatelet drugs or anticoagulant drugs or associations of both.

Elderly patients with VaD suffering from AF and receiving anticoagulant treatment with vitamin K antagonists (VKA) constitute a group of particular interest presenting significant concerns regarding the efficacy and safety of the treatment and its potential impact on the evolution of the VaD.

Particularities of anticoagulant treatment in VaD patients

Elderly patients with VaD receiving treatment with VKA have a low time within therapeutic range of the International Normalized Ratio (INR).⁴

In elderly patients with VaD the adherence to treatment is compromised and results to unstable VKA-induced hypocoagulability or hypercoagulability translated by INR values higher or lower than the recommended therapeutic range.

Failure of VKA treatment to induce the optimum hypocoagulability, results in sustained hypercoagulable state associated with thrombotic risk or significant hypocoagulability resulting in increased risk of intracranial bleeding. Both conditions may induce deterioration of VaD.⁵

Limited data is available in the literature which could help physicians optimise antithrombotic treatment in patients with VaD. This issue is predicted to become more challenging in the near future with increasing use of the new oral anticoagulants (NOAC)

Aim of the study

We performed a literature review, aiming in identifying the role of antiplatelet/anticoagulant treatments in VaD and if their optimisation could have an impact on VaD evolution or prevention.

Methods

A medline research was performed using the terms vascular dementia, antithrombotic, anticoagulant, atrial fibrillation, bleeding, infarcts. Only clinical trials were included in the analysis

Results

Barber et al⁶ assessed biomarkers for plasma and cellular hypercoagulability (fibrinogen, fibrin D-dimer, prothrombin fragment 1+2, thrombin-antithrombin complexes, von Willebrand factor and tissue plasminogen activator) in patients with AF who develop dementia and the effect of treatment with warfarin on the evolution of dementia. Among 218 patients included in the study, 66% were on warfarin treatment and 22% had VaD. Patients with VaD had significantly higher levels of thrombin generation markers as compared to those without VaD. Logistic regression showed a trend towards warfarin use being independently associated with reduced prevalence of dementia (odds ratio 0.52, P = 0.08).

Wozakowska-Kaplon B et al compared 51 patients aged over 65 years with AF and 43 age and sex-matched subjects with sinus rhythm.⁷ This study demonstrated that the presence of AF was associated with lower Mini-Mental State Examination (MMSE) score as compared with subjects with sinus rhythm. Noteworthy, only a small number of AF patients treated with VKAs or ASA were receiving a proper dose of these drugs.

A population-based study by Lopponen M et al, demonstrated that dementia is associated with undermedication of cardiovascular diseases in the elderly.⁹ More specifically, as far as antithrombotics were concerned, 50% of demented patients compared to 86% of non-demented patients with stroke received therapy.

A meta-analysis of the two published randomised trials which assessed the efficacy and safety of treatment with aspirin in patients with Alzheimer's disease versus placebo, concluded that ASA administration increases the risk of intracranial haemorrhage.¹⁰

A cross-sectional population-based study by Vernooij MW et al. investigating the relation between antithrombotic drug use and the presence of cerebral microbleeds, showed that the use of platelet aggregation inhibitors is related to the presence of cerebral microbleeds in non-demented patients over 60 years of age.¹¹

Table I. Summarised data on the use of antithrombotic treatment in patients with dementia included in clinical trials

Study	Antithrombotics in AF pts.	Antithrombotics in Demented AF pts.	Effective VKA anticoagulation in AF pts.	Antithrombotics in Demented Stroke pts.	Antithrombotics in Stroke pts. Without Dementia
Wozakowska-Kaplon B et al	77% (age ~76)	N/A	29%	N/A	N/A
Lopponen M et al	53% (age~80)	45% (age ~84)	N/A	54%	86%

Conclusions

Systematic review of the clinical studies which assessed the relationship between dementia, atrial fibrillation and the influence of antithrombotic treatment to the evolution/severity of dementia leads to the following conclusions:

- The available data is poor and so far published studies are heterogeneous regarding the studied population, the underlying pathologies and the administered antithrombotic treatments
- In patients with AF who receive insufficient anticoagulation with VKA a aggravation of dementia is plausible. However it is unclear if deterioration of dementia is due to the insufficient inhibition of hypercoagulability or to other reasons
- Demented patients do not receive the recommended antithrombotic treatment for the underlying cardiovascular disease or AF. However, from the available data it cannot be established with certainty that dementia is the reason for the under-treatment of these patients
- Even when demented patients receive anticoagulant therapy they are likely to receive it in undertherapeutic levels (patient compliance or lack of correct follow-up?)
- Although dementia seems to be the most possible cause for reduced adherence of patients to treatment, development of adapted strategies for the increase of patients' adherence to antithrombotic treatment is a challenging issue
- Antiplatelet therapy with aspirin conveys a high risk for brain microbleeds and intra-cranial haemorrhage, potentially aggravating instead of preventing dementia

References

- Microinfarct Pathology, Dementia, and Cognitive Systems, Zoe Arvanitakis, Sue E. Leurgans, Lisa L. Barnes, David A. Bennett, and Julie A. Schneider. *Stroke*. 2011; 42: 722-727.
- Poststroke dementia. Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F. *Lancet Neurol*. 2005;4:752-9.
- Brain microbleeds: more evidence, but still a clinical dilemma. Cordonnier C. *Curr Opin Neurol*. 2011;24:69-74.
- Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: a single-center, retrospective, observational study. Jacobs LG, Billett HH, Freeman K, Dinglas C, Jumaquio L. *Am J Geriatr Pharmacother*. 2009;7:159-66.
- Barber M, Tait RC, Scott J, Rumley A, Lowe GDO, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004; 2:1873-8.
- Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost*. 2004;2:1873-8.
- Wozakowska-Kaplon B, Opolski G, Kosior D, Jaskulska-Niedziela E, Maroszyńska-Dmoch E, Włosowicz M. Cognitive disorders in elderly patients with permanent atrial fibrillation. *Kardiol Pol*. 2009;67:487-93.
- Dementia associates with under-medication of cardiovascular diseases in the elderly: a population-based study. *Dement Geriatr Cogn Disord*. 2006;22:132-41.
- Lopponen M, Raiha I, Isoaho R, Vahlberg T, Puolijoki H, Kivela SL. Dementia associates with undermedication of cardiovascular diseases in the elderly: a population-based study. *Dement Geriatr Cogn Disord*. 2006;22:132-41.
- Thoonen H, Richard E, Benthem P, Gray R, van Geloven N, De Haan RJ, Van Gool WA, Nederkoorn PJ. Aspirin in Alzheimer's disease: increased risk of intracerebral hemorrhage: cause for concern? *Stroke*. 2010;41:2690-2.
- Vernooij MW, Haag MD, van der Lugt A, Hofman A, Krestin GP, Stricker BH, Breteler MM. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. *Arch Neurol*. 2009;66:714-20