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Letter to the Editor

Evolving trends in cerebral amyloid angiopathy research themes: Insights from medical subject heading analysis

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Dear Editor,

Sporadic cerebral amyloid angiopathy (CAA) is a largely untreatable cerebral small vessel disease [1]. It is now an increasingly recognized cause of lobar intracerebral haemorrhage and possible contributor to cognitive dysfunction in the elderly, including Alzheimer's disease [2,3]. However, CAA has a broader impact on cerebrovascular function culminating in both ischaemic and haemorrhagic parenchymal brain injuries [4], even in asymptomatic older individuals. The pathological hallmark of CAA is progressive amyloid-β deposition in the media and adventitia of small arteries and capillaries of the leptomeninges and cerebral cortex [2,5]. Given our aging population, CAA represents an impending public health problem. Consequently, there is an enormous interest in research aiming to improve the diagnosis, treatment, and management of patients with CAA.

We have recently suggested that mapping the landscape of CAA research over time can provide new insights on understanding how this field is evolving and on elucidating various aspects of its development [6]. Building on our previous work on the topic, in this study we systematically identified CAA-related articles from PubMed, and we made use of the medical subject headings (MeSH) terminology data, to investigate publication rates by research theme over time. Categorization by MeSH has the advantage of having been uniformly applied over many years by PubMed annotators to indicate whether a given paper has a given category as a major topic.

1. Methods

We systematically harvested CAA-related publications (without language restriction) and their associated MeSH terms from the National Center for Biotechnology Information's PubMed using a combination of search terms: “amyloid angiopathy” or “congophilic angiopathy” or “dyshoric angiopathy” or “dysphoric angiopathy”. The search covered the period from 1950 to 2015.

Since most MeSH terms are used too infrequently to identify meaningful trends: (a) we focussed on the top 18 most frequently used terms in the CAA literature [6] and selected those that were generic and could define clinical relevant themes; and (b) to examine further areas not captured in the top MeSH terms we pre-defined and used additional MeSH categories selected *ad hoc* (including antithrombotics, ischaemic features of the disease and SAH/cSS). MeSH terms had to be used at least once per year on average to select them for further analysis. Where appropriate we compiled several MeSH subclassifications pertinent to the definition of the same CAA-related theme. For example, if an article is annotated with ‘dementia’ or ‘cognitive impairment’ or ‘neuropsychological testing’ as major headings, it suggests that the research being reported falls into the dementia/cognitive impairment theme.

2. Statistical analysis

Linear regression was used to investigate the change in MeSH-defined themes in CAA research on a year-by-year basis, between 1990 and 2014 (the depended variables were the different research themes and the independed the years — per 1 year increase). We specifically focussed on this period because it provided sufficient data size and a fairly even representation of themes. Publication counts under each theme were divided by the total number of CAA articles for each year. In all analyses we assessed whether linear regression was appropriate by examining the fitted values and the residuals. Linear regression analyses were carried out using STATA (Version 12.1, StataCorp.).

3. Results and discussion

A total of 2153 unique papers directly or indirectly related to CAA were published from 1990 through 2014 in PubMed. Using MeSH-based categories we have identified and explored the following major clinically-relevant themes in the field of CAA research across all articles (Fig. 1): antithrombotic drugs, MRI, neuropathological aspects (including capillary CAA and tangles), cognitive impairment/dementia, intracerebral haemorrhage, subarachnoid haemorrhage/cortical superficial siderosis and other themes (including Alzheimer disease, hypertension and CAA-related ischaemic features).

Most notable over the last 15 years has been an emphasis in MR imaging which has increased our ability to detect and define the consequences of CAA in routine clinical practice, which has coincided with dilemmas regarding the safety of antithrombotic drugs in these patients (Fig. 1A). Not surprising there was also a growing focus in studies investigating subarachnoid haemorrhage/cortical superficial siderosis (Fig. 1B), which are new promising markers of the disease. At the same time, there has been a modest increase in neuropathological studies with major themes being dementia/cognitive impairment, but a decreased or stable, but low, focus on other neuropathological findings (*e.g.* tangles and capillary CAA, Fig. 1C). Moreover, there has been no increase in the frequency of studies investigating other important aspects of CAA, including the exact role of CAA in the context of Alzheimer's disease, the role of hypertension and ischaemic aspects, all deserving further research. Although stable over the last 15 years, the focus on CAA in Alzheimer's disease has been intense, as revealed by

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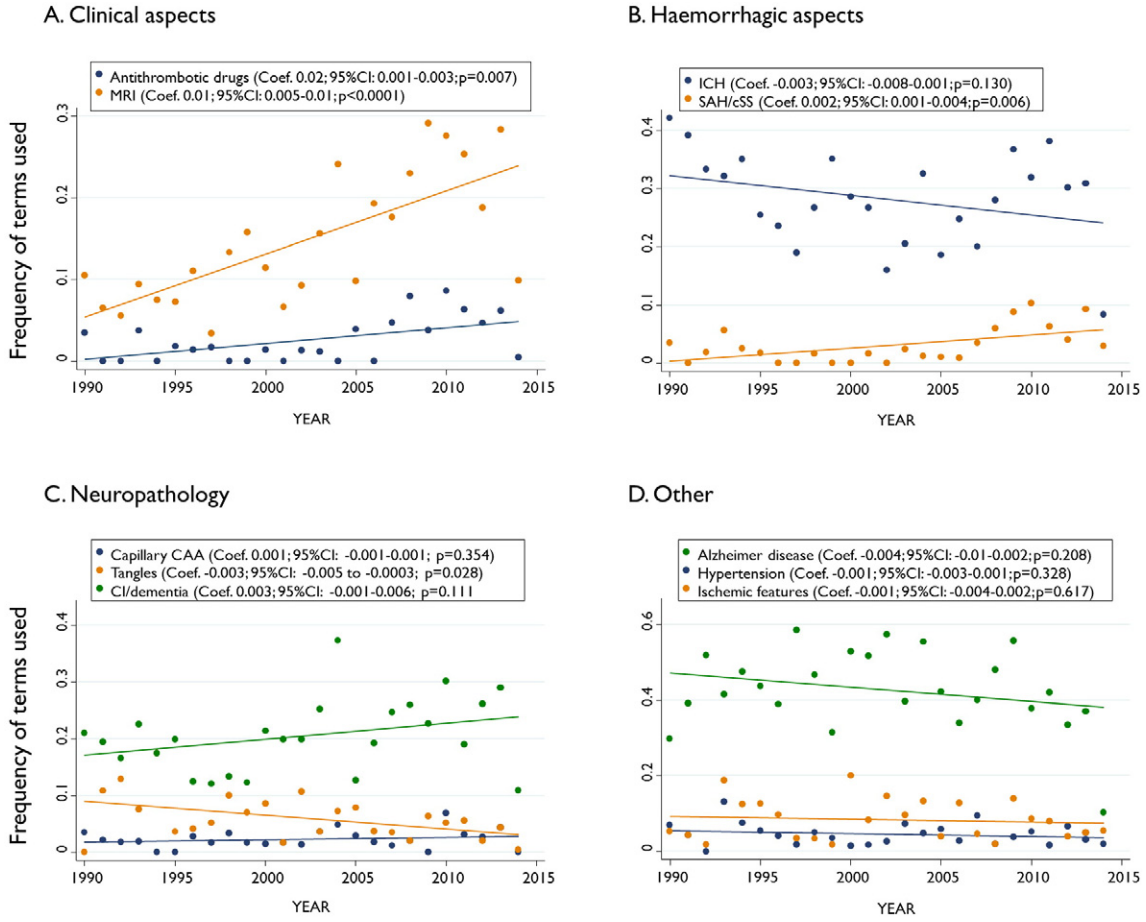

Fig. 1. Changing frequency of publications in the CAA field based on MeSH categories themes between 1990 and 2014. Year-by-year data were fitted into linear regression models.

the high frequency of MeSH terms used. By contrast, hypertension and ischaemic features seem to historically enjoy less attention, perhaps because of CAA being traditionally thought as more hemorrhagic disorder, not accounted for by hypertension of other vascular risk factors. Of note, this notion is now changing in favor of the concept of mixed small vessel disease [7].

Our study might contribute in systematically assessing the rapidly developing field of CAA research using bibliometric analytic tools, by revealing trends in major clinically relevant themes and providing methods and baseline measures to monitor areas in which scientific advances are likely to create new diagnostic and therapeutic opportunities.

Authors and their individual contributions to the manuscript

Statistical analysis was conducted by Dr. Min Song and Dr. Andreas Charidimou.

A. Charidimou: study concept and design, data interpretation, write up, critical revisions.

M. Song: data collection and analysis, write up, critical revisions.

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