Biochimica et Biophysica Acta xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Diagnosis and treatment of vascular damage in dementia☆

Geert Jan Biessels *

Department of Neurology, Brain Center Rudolf Magnus, University Medical Center, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 24 September 2015
Received in revised form 17 November 2015
Accepted 18 November 2015
Available online xxxx

Keywords:
Vascular cognitive impairment
Vascular dementia
Diagnostic criteria
Small vessel disease
Magnetic resonance imaging
Stroke

ABSTRACT

This paper provides an overview of cognitive impairment due to vascular brain damage, which is referred to as vascular cognitive impairment (VCI). Over the past decades, we have seen marked progress in detecting VCI, both through maturation of diagnostic concepts and through advances in brain imaging, especially MRI. Yet in daily practice, it is often challenging to establish the diagnosis, particularly in patients where there is no evident temporal relation between a cerebrovascular event and cognitive dysfunction. Because vascular damage is such a common cause of cognitive dysfunction, it provides an obvious target for treatment. In patients whose cognitive dysfunction follows directly after a stroke, the etiological classification of this stroke will direct treatment. In many patients however, VCI develops due to so-called "silent vascular damage," without evident cerebrovascular events. In these patients, small vessel diseases (SVDs) are the most common cause. Yet no SVD-specific treatments currently exist, which is due to incomplete understanding of the pathophysiology. This review addresses developments in this field. It offers a framework to translate diagnostic criteria to daily practice, addresses treatment, and highlights some future perspectives. This article is part of a Special Issue titled "Vascular Contributions to Cognitive Impairment and Dementia," edited by M. Paul Murphy, Roderick A. Corriveau, and Donna M. Wilcock.

1. Introduction

Vascular brain damage is an important, common, and potentially treatable cause of dementia and milder forms of cognitive dysfunction. In this paper, I will refer to cognitive dysfunction due to vascular damage with the term "vascular cognitive impairment" (VCI). The first sections address the evolution of diagnostic criteria over the past decades. Next, a framework will be offered through which these diagnostic criteria can be translated to daily practice. The final sections deal with treatment, with a focus on treatment after the diagnosis VCI. There is clearly also an important potential in targeting vascular disease to prevent cognitive decline and dementia at the population level [1,2]. For this topic, the reader is referred to other recent comprehensive reviews [3,4].

2. Diagnosis

2.1. Diagnostic criteria

Different diagnostic criteria that have been proposed for cognitive impairment or dementia due to vascular damage in essence all consist of the same three core elements: establish (1) acquired cognitive impairment, (2) vascular damage in the brain, and (3) a causal link between the two. In case of an acute symptomatic stroke that induces acute cognitive dysfunction, all of these criteria are clearly met and the diagnosis cognitive impairment due to vascular damage is readily made. When the development of cognitive dysfunction does not have a clear temporal relationship to an acute stroke, it can be more difficult to establish vascular damage as a cause. Different diagnostic criteria have dealt with this latter issue by earmarking cognitive and non-cognitive symptoms that are suggestive for vascular damage and by defining minimal "thresholds" for the burden of vascular damage on brain imaging as "cause" of cognitive dysfunction.

The first formal diagnostic criteria for vascular dementia (VaD) that came into common use were put forward in the early 1980s and 1990s [5–7]. While often developed for research purposes, these criteria also became widely used in clinical practice. A typical example are the VaD criteria, devised in 1991 at a workshop convened by the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) [5]. These NINDS-AIREN criteria operationalized the first core element of the diagnosis – i.e., establish acquired cognitive impairment – as "a diagnosis of dementia, requiring the presence of a decline in memory and intellectual abilities that causes impaired functioning in daily living" [5]. This definition, which was also part of other criteria for VaD established in that same period [6,7], was criticized later on because it was largely based on clinical features of Alzheimer's disease [8–10]. It was noted that requirement of the presence of memory impairment

☆ This article is part of a Special Issue titled "Vascular Contributions to Cognitive Impairment and Dementia," edited by M. Paul Murphy, Roderick A. Corriveau, and Donna M. Wilcock.

* Corresponding author at: Department of Neurology, University Medical Center, G03.232, PO Box 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: g.j.biessels@umcutrecht.nl.

http://dx.doi.org/10.1016/j.bbadis.2015.11.009
0925-4439/

was unsuitable to capture cognitive impairment due to vascular damage, which can involve multiple other cognitive domains [8]. Moreover, it was recognized that many patients with acquired cognitive impairment due to vascular damage still have relatively preserved daily functioning and thus by definition do not meet criteria for dementia [8]. It was also put forward that vascular damage often co-occurs with other etiologies. Combined with these other etiologies, the presence of vascular disease clearly contributes to the probability that a patient manifests dementia [11,12]. Hence, also in the context of other etiologies, vascular disease should be regarded as a cause and contributor to cognitive dysfunction. By excluding patients without dementia and memory deficits and by focusing on patients in whom vascular damage was considered to be the "exclusive cause," the early VaD criteria thus did not identify a substantial proportion of individuals with cognitive decline and dementia due to vascular damage.

In light of these considerations, criteria to identify cognitive decline due to vascular damage that were put forward from the 90s onwards tended to be more "inclusive" and also considered milder stages of cognitive impairment and mixed pathologies. The term vascular cognitive impairment (VCI) was introduced to refer to all forms of mild to severe cognitive impairment associated with and presumed to be caused by cerebrovascular disease [8,9,13]. The term covers the whole spectrum of cognitive dysfunction, from mild impairment to more severe disturbances meeting dementia criteria, and any vascular etiology, regardless of the mechanism (e.g., cardioembolic, atherosclerotic, ischemic, hemorrhagic, or genetic) [9]. VCI is thus an umbrella term that encompasses all forms of cognitive dysfunction associated with and presumed to be caused by vascular brain damage. The downside of the all-inclusive concept of VCI is that it provides little, if any, indication on nature and severity of cognitive symptoms and underlying etiologies and therefore provides limited information as a diagnostic label in individual patients.

Over the past years, there have been efforts to operationalize the concept of VCI into diagnostic criteria for research and also daily care. The criteria for vascular cognitive impairment from the American Heart Association/American Stroke Association [13] and the criteria for vascular cognitive disorders (VCD) from the VasCog society [14] are recent examples (text Boxes 1 and 2, respectively). Both criteria operationalize acquired cognitive impairment, as (A) acquired dementia, i.e., substantial cognitive decline from a previous level of performance on one or more [14] or two or more [13] cognitive domains (not necessarily involving memory) severe enough to interfere with functional independence, or (B) acquired mild cognitive impairment (MCI), i.e., substantial cognitive decline from a previous level of performance on one or more cognitive domains but with preserved functional independence. The VasCog criteria provide cutoffs for test performance for MCI, which should typically be in the range between 1 and 2 SDs below appropriate norms [14]. Regarding the second diagnostic element, the presence of vascular damage in the brain, both VCI criteria require imaging evidence of vascular brain lesions. The VasCog criteria make specific recommendations on the burden of vascular damage that should be present in the form of one or more large vessel infarcts, strategically placed single infarcts, multiple lacunar infarcts, extensive and confluent white matter lesions, or a strategically placed intracerebral hemorrhage [14]. The AHA/ASA criteria just state that there should be imaging evidence of cerebrovascular disease [13]. Regarding the third diagnostic element, establishing a causal link between cognitive impairment and cerebrovascular disease, the AHA/ASA criteria provide two levels of certainty, "probable" and "possible." For probable VaD or vascular MCI, there should be a clear temporal relationship between a vascular event (e.g., clinical stroke) and the onset of cognitive deficits, or a clear relationship in the severity and profile of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease on brain imaging. Moreover, there should be no evidence of a concomitant neurodegenerative disorder [13]. Possible VaD or vascular MCI is diagnosed when there is cognitive impairment and imaging evidence of cerebrovascular disease but no clear relationship (temporal, severity, or cognitive profile) between the two or when there are concomitant other conditions (in particular neurodegenerative diseases) that may affect cognition (see Box 1). The VasCog criteria specify that when there is substantial evidence of a concomitant neurodegenerative disorder, this precludes the diagnosis mild or major vascular cognitive disorder (see Box 2).

Diagnostic criteria for cognitive dysfunction attributed to vascular damage are likely to show further evolution over time, although the three core diagnostic elements are likely to persist. There is clear benefit in operational diagnostic criteria that are ideally accurate, sensitive, and reproducible. Such criteria are important for research, but of course also in daily care where they help to classify symptoms, attribute them to a certain etiology, guide treatment and provide prognostic information.

Box 1

Core elements of the criteria for Vascular Cognitive Impairment from the American Heart Association/American Stroke Association (2011) [13].

- The term VCI characterizes all forms of cognitive deficits from vascular dementia (VaD) to MCI of vascular origin (VaMCI).
- The criteria do not apply to subjects with a current drug or alcohol abuse and to subjects with delirium.

Dementia or MCI

1. The diagnosis should be based on a decline in cognitive function from a previous level and a deficit in performance in at least two cognitive domains for dementia, one for MCI. For the diagnosis of dementia, the deficits should be are severe enough to affect the subject's activities of daily living.
2. The diagnosis must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.

Probable VaD or probable VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease and

a. There is a clear temporal relationship between a vascular event (e.g., clinical stroke) and onset of cognitive deficits, or
b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g., as in CADASIL).
c. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaD or possible VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease but

a. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (e.g., silent infarcts, subcortical small vessel disease) and the cognitive impairment.
b. There is insufficient information for the diagnosis of VaD (e.g., clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available; aphasia precludes proper cognitive assessment).
c. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, including other neurodegenerative disorders

See the original paper for full definitions [13]. Abbreviations: VCI, vascular cognitive impairment; VaD, vascular dementia; MCI, mild cognitive impairment; VaMCI, vascular mild cognitive impairment; and CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Please cite this article as: G.J. Biessels, Diagnosis and treatment of vascular damage in dementia, Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbadis.2015.11.009