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Cognitive functioning in patients with carotid artery occlusion; a systematic review

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ABSTRACT

Introduction: Patients with complete occlusion of the internal carotid artery (CAO) are vulnerable to cerebral hypoperfusion. Since cerebral hypoperfusion is associated with accelerated cognitive decline, patients with CAO may have an increased risk of cognitive impairment. We aimed to assess the prevalence and profile of cognitive impairment in patients with CAO and to explore the relation between hemodynamic impairment and cognitive functioning.

Methods: We systematically searched Medline and EMBASE for studies including patients with symptomatic or asymptomatic CAO subjected to cognitive testing that were published between 1980 and 2017. We did not include patients with carotid stenosis. We obtained data on type of study, patient characteristics, cerebral imaging and neuropsychological testing. In addition, we extracted data on potential causes of systemic hemodynamic impairment and the presence and stage of cerebral hemodynamic impairment. We assessed methodological quality of included studies with the Newcastle-Ottawa Scale.

Results: We found eight studies comprising 244 patients (mean age 61 years, 76% male, 93% symptomatic CAO). The proportion of patients with cognitive impairment ranged from 54 to 71% in four studies; in the other four studies patients with CAO performed worse on cognitive testing than controls, but results were not quantified. Impairment was reported in all cognitive domains. We found no data on the association between systemic hemodynamic impairment and cognitive functioning. Studies that assessed whether cerebral hemodynamic impairment was associated with cognitive functioning showed conflicting results.

Conclusion: In patients with CAO, cognitive impairment is present in about half to two-thirds of patients and is not restricted to specific cognitive domains. The effect of systemic and cerebral hemodynamic impairment on cognitive functioning in patients with CAO deserves further study.

1. Introduction

Carotid artery occlusion (CAO) can be found in nine to 15% of patients who present with transient ischemic attacks (TIAs) or ischemic stroke [1,2]. Asymptomatic CAO is increasingly diagnosed as an accidental finding during radiological work-up, but reliable information about its prevalence is lacking [3]. The most common site for occlusion is at the origin of the internal carotid artery in the neck, and the most common etiology is atherosclerosis [1,2]. Both symptomatic and asymptomatic patients with CAO have an increased risk of ipsilateral stroke, which can be caused by either thrombo-embolism or cerebral hemodynamic impairment [1–4].

Patients with CAO also have an increased risk of cognitive impairment [5]. This may be the result of white-matter lesions or strategically located ischemia, but it may also be caused by cerebral hemodynamic impairment without structural changes in the brain [5,6]. In the general population, cerebral hypoperfusion has been associated with accelerated cognitive decline and an increased risk of dementia [7]. Cerebral hypoperfusion can be the result of severe steno-occlusive disease of the cerebropetal arteries but may also be caused by systemic hemodynamic impairment such as heart failure or hypotension [8].

Patients with CAO are more vulnerable to cerebral hypoperfusion than patients with carotid artery stenosis [7]. Several systematic reviews have assessed the impact of carotid artery stenosis on cognitive

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functioning with variable results, but information about the impact of a complete occlusion of the internal carotid artery on cognitive functioning is lacking [5,9,10]. The aim of this systematic review was to assess the presence, severity, nature and course of cognitive impairment in patients with both symptomatic and asymptomatic CAO. Furthermore, we explored the relationship between both systemic and cerebral hemodynamic impairment and cognitive functioning.

2. Methods

2.1. Study identification

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11]. We searched Medline and EMBASE from January 1980 to November 2017 for studies on cognitive functioning in patients with CAO. Different combinations of the following search terms were used: 'carotid artery occlusion', 'carotid occlusion', 'carotid stenosis', 'carotid artery stenosis' or 'carotid artery diseases' AND 'cognition', 'neurocognitive', 'intelligence', 'psycho', 'executive', 'cognitive', 'mental', 'memory' or 'dementia'. No limits were set for languages. We checked reference lists of retrieved articles and of review articles for further relevant publications. We continued this method of cross-checking until no further publications were found.

2.2. Study selection

We selected studies that reported on cognitive functioning in at least five patients with complete occlusion of the extracranial internal carotid artery (either on group level or individual patient data). Exclusion criteria were: 1) studies that focused on cognitive changes after revascularization without description of preoperative findings; 2) studies that focused on CAO caused by moyamoya disease or syndrome; and 3) studies that used cognitive impairment (i.e. Alzheimer disease, vascular dementia) as an inclusion criterion. If authors reported data on patients with carotid artery stenosis as a group in which more than five patients with CAO or a contralateral CAO were included, we contacted the principal investigators for individual data of patients with CAO. We also contacted the principal investigators for additional neuropsychological data, data on baseline characteristics, comorbidities and hemodynamic parameters if needed. In case of overlap of patient groups in studies reported by the same authors, we excluded the overlapping patient group or selected the study with the largest sample size or most detailed neuropsychological data. The first author (E.A.O.) performed the literature search, did the title and abstract screening and reviewed all potentially eligible studies on the basis of full text.

2.3. Data extraction

Three authors (E.A.O. all studies, C.J.M.K. and E.v.d.B., each half of the studies) independently extracted data from selected papers using standardized forms; disagreement was resolved by consensus. We extracted the following information: year of publication; country of origin; study design; mid-year of cohort; in- and exclusion criteria; size of the study population; number of patients with CAO; age; sex; level of education; ethnicity; (transient) neurological deficit; asymptomatic or symptomatic (based on author's criteria), further specified as (hemodynamic) cerebral or retinal TIA, minor or major stroke; time interval between most recent ischemic episode and neuropsychological assessment; side of CAO; vascular risk factors. With respect to cerebral imaging we assessed the following parameters: Computed Tomography or Magnetic Resonance Imaging; number of infarcts; presence of atrophy, presence of white matter lesions. For neuropsychological assessments we collected information on: raw or standardized (z-) scores of cognitive tests; proportion of patients with cognitive impairment overall and per cognitive domain based on author's criteria (mostly defined as performance below the 5th percentile compared to normative data). With respect to systemic hemodynamic impairment we assessed the following parameters: hypotension, fluctuating blood pressure; heart failure and presence of atherosclerotic disease in other cerebropetal arteries. With respect to cerebral hemodynamic impairment we collected information on modality of assessment and on the presence of hemodynamic impairment, either stage I or II [12].

Methodological quality was assessed using the 9-point Newcastle Ottawa Scale, which uses a "point" system to rate the quality of studies based on three aspects: (1) selection of participants (maximum points = 4); (2) comparability of study groups (maximum = 2), in our case CAO group versus control group; and (3) outcome of interest (maximum = 3), in our case assessment of cognitive functioning [13].

2.4. Data analysis

Since the studies varied widely with respect to patient characteristics and methodology, we did not perform meta-analysis, but reviewed and analyzed the data descriptively.

3. Results

3.1. Literature search and study selection

We identified 1096 articles of which 889 articles were excluded after assessment of title and abstract. After reading the full text of the remaining 207 articles, we excluded 182 articles because they did not meet our inclusion criteria. The most common reason for exclusion was that studies included also patients with carotid artery stenosis and that it was impossible to analyze patients with CAO separately. We contacted authors of 20 studies [14–34] and we received additional data from four authors [14,23,26,29]. We excluded one study because of overlap of patient groups reported by the same authors [35]. Eventually, we included eight studies with a total of 244 patients (mean age 61 years, 76% male) (Fig. 1) [14,23,26,29,36–39]. Supporting information Table 1 lists the inclusion and exclusion criteria of the included studies.

3.2. Study design and quality

All eight studies had a prospective design. Four were cross-sectional [26,29,36,37] and four longitudinal [14,23,38,39]. Three of the longitudinal studies addressed the outcome after surgery or stenting [14,23,38]. Two studies had a control group comprising 119 healthy controls, consisting of spouses and siblings of the patients who were similar in sex, mean age and median educational level [37,39]. Two studies included < 10 patients with CAO [14,26]. Three studies received quality scores of nine out of nine [36,37,39], two of eight out of nine [26,29], one of seven out of nine [14] and two studies received quality scores of six out of nine (Supporting information Table 2) [23,38].

3.3. Study characteristics

Patient characteristics of individual studies are summarized in Table 1. Demographic features varied substantially between the studies. Seventy-six percent of patients and 30% of controls were male. Level of education was reported in only four studies [36–39]. Six studies assessed the presence of vascular risk factors [14,23,26,37–39]. In five studies, results were adjusted for age, sex, education level, history of previous stroke or presence of depression [23,29,36,37,39]. From the total of 244 included patients, 59% had had a stroke, 34% a cerebral or retinal TIA and 7% were asymptomatic. Four studies described the diagnostic criteria for ischemic symptoms in detail [29,36,37,39]. The time interval between the most recent ischemic episode and neuropsychological assessment was mentioned in four studies and varied