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Vascular risk factors and cognitive disorders

Facteurs de risque vasculaires et cognition

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ABSTRACT

Delaying the onset of dementia by just a few years could have a major impact on the prevalence of the disease at the population level. Vascular risk factors are modifiable and may offer an important opportunity for preventive approaches. Several studies have shown that diabetes, hypertension, obesity, and smoking are associated with an increased risk of cognitive decline and dementia, but other groups have not observed such a relation. Positive associations were observed mainly in studies where risk factors were assessed in midlife, suggesting that age is an important modulator in the relation between vascular risk factors and cognition. The population attributable risk of dementia is particularly high for hypertension. Associations of vascular risk factors with cognitive decline and dementia are probably mediated largely by cerebrovascular disease, including both stroke and covert vascular brain injury, which can have additive or synergistic effects with coexisting neurodegenerative lesions. To date, randomized trials have not convincingly demonstrated that treating vascular risk factors is associated with a reduction in cognitive decline or dementia risk. Of eight randomized trials testing the effect of antihypertensive agents on dementia risk, only one was positive, and another in a subgroup of individuals with recurrent stroke. In most trials, cognition and dementia were secondary outcomes, follow-up was short and treatment was initiated at an older age. No effect on cognitive decline or dementia could be demonstrated for statins and intensive glycemic control. Future areas of investigation could include differential class effects of antihypertensive drugs on cognitive outcomes and identification of high risk individuals as target population for clinical trials initiated in midlife.

RÉSUMÉ

Retarder la survenue de la démence de quelques années seulement aurait un impact majeur sur la prévalence de cette maladie à l'échelle de la population. Les facteurs de risque vasculaires sont modifiables et pourraient constituer une cible importante pour des

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stratégies de prévention. Plusieurs études ont montré que le diabète, l'hypertension, l'obésité, et le tabac étaient associés à un risque accru de déclin cognitif et démence, mais d'autres études n'ont pas pu mettre en évidence de telles associations. Des associations significatives étaient observées principalement dans des études où les facteurs de risque vasculaires étaient évalués à un âge moyen, suggérant un effet modulateur important de l'âge dans la relation entre facteurs de risque vasculaires et cognition. Le risque attribuable de démence est particulièrement élevé pour l'hypertension artérielle. L'association des facteurs de risque vasculaires avec le déclin cognitif et la démence est probablement médiée principalement par la pathologie cérébrovasculaire, incluant à la fois les accidents vasculaires cérébraux et les lésions cérébrovasculaires « silencieuses », qui peuvent avoir des effets additifs voire synergiques avec des lésions neurodégénératives coexistantes. À ce jour, les essais thérapeutiques randomisés n'ont pas démontré de façon convaincante que traiter les facteurs de risque vasculaires était associé à un ralentissement du déclin cognitif et une réduction du risque de démence. Parmi huit essais thérapeutiques randomisés testant l'effet de traitements antihypertenseurs sur le risque de démence, seul un était positif ; un autre essai était positif dans un sous-groupe d'individus avec récidive d'accident vasculaire cérébral. Dans la plupart des essais, la cognition et la démence n'étaient que des critères de jugement secondaires, le suivi était court et le traitement était initié à un âge avancé. Aucun bénéfice des statines ou d'un contrôle glycémique intensif n'a pu être démontré sur le déclin cognitif et la démence. De futurs axes de recherche pourraient inclure les effets différentiels de certaines classes d'antihypertenseurs sur la cognition ainsi que l'identification d'individus à haut risque comme population cible pour des essais thérapeutiques initiés dans des populations d'âge moyen.

With expanding longevity, the number of dementia cases is increasing worldwide and is expected to triple over the next 40 years. Delaying the onset of this disease by just a few years could have a major impact on the prevalence of dementia at the population level (Barnes and Yaffe, 2011). To date, no effective mechanism-based preventive strategies are available for dementia. Vascular risk factors are modifiable and, given the strong relationship between cerebrovascular disease and dementia, they may offer an important opportunity for preventive approaches. Gathering evidence for associations between vascular risk factors and dementia and evaluating the impact of interventions modifying vascular risk factor exposure on cognitive decline and dementia is therefore of paramount importance.

1. Contribution of cerebrovascular disease to cognitive impairment and dementia

The importance of cerebrovascular disease for cognitive impairment and dementia is now widely recognized (Viswanathan et al., 2009; Gorelick et al., 2011). Vascular cognitive impairment and dementia can occur after one of more strokes (ischemic or hemorrhagic) or in the presence of silent infarcts or diffuse subcortical cerebrovascular disease (Gorelick et al., 2011). It is referred to as ''pure'' in the absence of Alzheimer disease (AD) pathology or positive biomarkers for the latter (e.g. positron emission tomography, cerebrospinal fluid amyloid β or tau protein) (Gorelick et al., 2011). However, the vascular contribution to cognitive disorders reaches far beyond the concept of pure vascular cognitive decline (Viswanathan et al., 2009). Indeed, cognitive impairment and dementia is a continuum ranging from patients with pure vascular dementia to patients with pure AD and including a large majority of patients with contributions from both Alzheimer and vascular pathologies (Viswanathan et al., 2009). Accordingly, neuropathological correlates of cognitive impairment in late-life are most often a mix of AD pathology (amyloid plaques and neurofibrillary tangles) and microvascular brain damage. Moreover, in patients with AD, if cerebrovascular disease is present concomitantly, less AD pathology is needed to express the dementia syndrome. This may be due to additive or even synergistic effects of cerebrovascular damage and neurodegenerative processes (Snowdon et al., 1997; Petrovitch et al., 2005).

2. Association of vascular risk factors with cognition in observational studies

Several studies have shown that diabetes, hypertension, obesity, and smoking are associated with an increased risk of dementia (Kivipelto et al., 2005; Whitmer et al., 2005; Anstey et al., 2007), but other groups did not observe such a relation (Kloppenborg et al., 2008; Barnes and Yaffe, 2011). Overall, positive associations were observed mainly in studies where risk factors were assessed in midlife, especially for blood pressure and obesity, while most negative studies targeted older populations (Kloppenborg et al., 2008; Barnes and Yaffe, 2011). In the ARIC study, the impact of vascular risk factors on dementia was assessed in different age groups and at different time points within the same cohort, demonstrating that age is an important modulator, associations being stronger in individuals aged less than 60 years when the vascular risk factors were assessed (Alonso et al., 2009). There are several possible explanations for these age-dependent effects.