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Clinical implications of cerebral age-related white matter cerebral changes

Synopsis

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Cerebral age-related white matter changes (WMC) designate the changes of the radiological appearance of cerebral white matter, detected either in CT scan or in MRI, of probable vascular aetiology, that are frequently described in elderly people (1,2,3). The clinical significance of those changes has gained attention in the last three decades and remains a controversial issue.

Some demographic and vascular risk factors are associated with higher risk of developing more severe WMC, and among these, mainly aging, hypertension and stroke (2, 3, 4). WMC are more frequent in demented patients (5). White matter changes have been implicated in cognitive decline, gait disturbances, urinary dysfunction, personality changes and depression (6), however contradictory results inhibit the consensus in this topic (7).

Several questions remained unanswered when we started our study, namely concerning long term cognitive implications of WMC in subjects living in full autonomy. Furthermore, no convincing data was available regarding information on the risk of evolution for any type of dementia taking into account the global spectrum of risk factors.

The objectives of this thesis were 1. to study the influence of WMC and vascular risk factors on the neuropsychological performance and on the progression for dementia of non-disabled independent elderly people with WMC; 2. to study the implications of self-perceived memory complaints; 3. to study the meaning of late onset depressive symptoms; and, 4. to clarify if regular physical activity reduces the risk of dementia in elderly subjects with WMC.

Our study was conducted within a large European multicentre collaboration (the LADIS study: 11 European centres: Amsterdam, Copenhagen, Florence – coordinator centre-, Graz, Göteborg, Lisbon, Helsinki, Huddinge, Mannheim, Newcastle-upon-Tyne and Paris), that was designed to assess the role of WMC as an independent predictor of the transition from an autonomous functional status to disability in elderly subjects and the role of WMC progression in this transition (8). The Lisbon center took responsibility of all cognitive evaluation and definition of criteria and monitorization of cognitive diagnosis.

Inclusion criteria for the study were: (i) 65–84 years of age; (ii) changes in WMC on MRI of any degree, according to the scale of Fazekas (9); and (iii) no disability, as determined by the Instrumental Activities of Daily Living scale (IADL) (10). Patients were referred for the study with minor complaints, incidental findings on cranial imaging caused by non-specific events without impact on daily living activities or were otherwise volunteers (8). Subjects were evaluated at baseline and yearly during 3 years with a comprehensive protocol including registry of demographic and vascular risk factors, co-

morbidities, evaluation of depression, quality of life and a neuropsychological battery. Clinical evaluation included the classification of cognitive impairment according to usual clinical criteria (11). MRI was performed at baseline and at 3-year follow-up.

The inclusion of subjects started in July 2001, 639 patients were enrolled (mean age 74.1 years-old, SD 5.0, 55% women, 9.6 years of educational level, SD 3.8). From the initial sample, 89% (568), 78.4% (501), and 75% (480) of the patients were followed up in a clinical visit at months 12, 24 and 36. After a median follow-up period of 2.9 years, information on the transition from full autonomy into disability was available for 633 (99%) patients. Forty-three subjects died (6.7% of study sample) until the third year of follow-up. Fifty-one patients missed the complete cognitive evaluation in any of the follow-up clinical visits. For those 51 patients no cognitive diagnosis was attributed, although vital status and IADL were known in those patients. Considering the cognitive diagnosis performed in the last clinical visit, dementia was diagnosed in 90 patients (Vascular dementia, 54; Alzheimer disease, 22; Alzheimer disease with vascular component, 12; Frontotemporal dementia, 2), and 147 patients had cognitive impairment not dementia (Vascular cognitive impairment non dementia - CIND, 86; mild cognitive impairment - MCI, 61).

Our study showed that:

1. The severity of WMC is related with worse performance on global measures of cognition, executive functions, speed/motor control, and tests of attention, naming and visuoconstructional praxis in elderly subjects living independently. The impact of WMC on neuropsychological performance was present even when controlling for demographic variables (age and education), vascular risk factors and temporal lobe atrophy.
2. WMC severity is a predictor of cognitive impairment (dementia and not dementia) in elderly subjects with WMC, overtime. WMC and stroke predicted vascular dementia but not Alzheimer's dementia, while medial temporal atrophy predicted both Alzheimer's dementia and vascular dementia. Vascular risk factors (diabetes, hypertension and previous stroke) emerged as relevant factors with influence on neuropsychological tests in older people living with full autonomy, independently of WMC severity. After 3 years, diabetes at baseline was the only vascular risk factor that predicted cognitive impairment of any type (dementia and not dementia).
3. Memory complaints are a strong predictor of Alzheimer's disease and Alzheimer's disease with vascular component during the follow-up, independently of depressive symptoms and global cognition status at baseline in older subjects with WMC. To the best of our knowledge this is the first study that approaches implications of memory complaints in independent elderlies with white matter changes. Prediction

of Alzheimer's disease among elderly subjects with evidence of small vessel disease and self-perceived memory complaints was surprisingly high. We think this finding is clinically relevant and it reinforces the importance of memory complaints in the elderly with WMC.

4. Depressive symptoms are associated with worse cognitive performance (in global cognitive measures, executive functions and speed) at baseline and are predictors of further cognitive decline over a 3 year follow-up. These results are in accordance with the hypothesis of vascular depression for late onset depressive symptoms as depressive symptoms could be an expression of vascular damage and not a result of a depressive disorder. It is possible that depressive symptoms and WMC have an additive or synergistic effect for the future development of dementia.
5. Physical activity reduces the risk for progression for cognitive impairment, namely vascular dementia, but not Alzheimer disease among non-disabled elderly people with WMC. Possible explanations for this reduced risk could be through vascular risk factors control, as physical exercise is usually associated to better life-style. Morevoer, physical exercise could improve connectivity and synapse release transmitter. Our data support the view that elderly subjects with vascular risk factors and evidence for vascular cerebral damage benefit from regular physical activity.

Our study has some limitations, mainly related with a sample selection that was not drawn from the community. Participants were selected in outpatient clinics due to the presence of white matter changes. Patients could have minor complaints or could otherwise be volunteers. So we must be cautious in the generalization of our results. The other main limitation is associated with technological evolution, as the study was designed 10 years ago.

However, this study was conducted in the a large heterogeneous population, rigorously assessed with a systematic and comprehensive evaluation, and this sample probably represents the first moment when non-disabled elderly subjects with cerebral white matter changes seek medical attention, and this fact is meaningful for clinical practice. Moreover, despite some missing information in the cognitive evaluation overtime, 99% of the initial sample had information on follow-up data, and follow-up was long enough to have conversion for cognitive impairment and dementia. Moreover, a substantial part of the initial sample was able to repeat MRI.

After our work, we think that there is sufficient evidence to sustain that WMC are not an innocuous finding associated with ageing.

In clinical practice, we deal frequently with elderly subjects that require an appointment due to the detection of cerebral white matter changes. Our data support the fact that WMC are implicated in the evolution for disability and for cognitive impairment. Furthermore, we identified several risk factors that are implicated in the progression for cognitive impairment, such as diabetes and stroke that appear as potential factors for intervention when preventing dementia. Our results emphasize the key role of both vascular risk factor control and physical activity in reducing the risk of cognitive impairment with ageing.

Unfortunately, insufficient information exists concerning the recommendations for the control of the risk factors identified in the elderly in order to prevent dementia. Similarly, there is no recommendation regarding type and intensity of physical activity, influence of other leisure activities and type of intervention in subjects with depressive symptoms in order to be effective when preventing cognitive impairment in subjects with WMC. On the other hand there are still no known drugs specifically designed (or being currently in development) for the prevention of cognitive impairment in small vessel disease, other than those that aim to treat vascular risk factors. One of the clear areas of increasing interest is the impact of diet, risk factors control and physical and leisure activities on cognitive functioning in subjects with white matter changes. These relationships have to be determined by means of interventional studies that should be controlled by imagiological vascular biomarkers. These biomarkers must include sensitive tools for the measure of cerebral WMC as a hallmark of small vessel disease, including novel MRI sequences (diffusion, perfusion and spectroscopy) that allow the visualization of tissue changes in areas of white matter that appear normal using conventional MRI. Additionally, other biomarkers must be taken into account, namely other manifestations of small vessel disease (such as mibrobleeds and lacunes) and atrophy (either regional, including medial temporal lobe atrophy, or global) as potential confounders. Numbers of included subjects must be large enough to allow the control of multiple concomitant factors that can confound the interpretation of results and interfere with the statistical power. Clearly such a study can only be possible in a multicentric setting. Although designing a clinical trial is always limited to the knowledge available at a given time, we are convinced that: 1. any project aiming to study factors that influence cognitive changes in elderly should be controlled for white matter changes; 2. most available sensitive methods for detecting WMC should be used; 3. WMC severity is a potential end-point in cognitive trials.

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