REALISING THE POTENTIAL OF COHORT STUDIES TO DETERMINE THE VASCULAR CONTRIBUTION TO NEURODEGENERATION

Report of a JPND Working Group on Longitudinal Cohorts

October, 2015

JPND research

EU Joint Programme – Neurodegenerative Disease Research

This document is the final report from one of ten working groups commissioned by the EU Joint programme – Neurodegenerative Disease Research (JPND) in 2014 through a peer-reviewed call for proposals. The working groups were established to address methodological challenges preventing current population- and disease-based cohorts being further exploited for ND research. All ten reports are listed below and are available to download on the JPND website by clicking on the website link at the bottom of this page:

- **HD-READy (High-Dimensional Research in Alzheimer's Disease)**
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- **Harmonization and innovation of cognitive, behavioural and functional assessment in neurodegenerative dementias**
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- **NETCALS (Network of Cohort Assessment in ALS)**
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- **21st Century EURODEM**
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- **Multi-centre cohort-studies in Lewy-body dementia: Challenges in harmonizing different clinical and biomarker protocols**
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- **Developing a methodological framework for trials in presymptomatic neurodegenerative disease – the Presymtomatic Neurodegeneration Initiative (PreNI)**
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- **BioLoC-PD: Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's disease**
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- **Dementia Outcome Measures: charting new territory**
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- **Body fluid biobanking of longitudinal cohorts in neurodegenerative diseases**
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- **Realising the potential of cohort studies to determine the vascular contribution to neurodegeneration**
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JPND Website link: http://www.neurodegenerationresearch.eu/initiatives/jpnd-alignment-actions/longitudinal-cohorts/

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Summary

The aims of this JPND working group were:

- To create a central catalogue of cohort studies relevant to vascular contributions to neurodegeneration.
- To establish a data-sharing platform for meta-analyses, to assess markers of pre-symptomatic disease, identify sensitive outcomes for future cohorts and trials, test feasibility of combining data from different cohorts, and to harmonise image and data processing.

Achievements include:

- ✓ We surveyed hospital-based, population cohorts and clinical trials in Europe, the Americas, and the Asia Pacific Region to assess the availability of data on subject demographic characteristics, medical, imaging, genetics, biomarkers, cognition and longitudinal assessments that would be relevant to determining vascular contributions to neurodegeneration.
- ✓ At a workshop in Munich, January 2015, we discussed priorities for research into vascular disease, planned and initiated exemplar projects, identified our main recommendations, and planned a main publication. A publication documenting gaps in understanding of vascular mechanisms of neurodegeneration, the persisting gulf between research into dementia and research into vascular disease, work required to bridge these gaps and existing relevant data to inform these analyses, will be submitted for publication in July 2015.
- ✓ The Working Group members have also influenced funder discussions about research priorities in the UK, the USA and the Asia Pacific Region, influenced ongoing national projects in the Europe, North America and the Asia Pacific Region to include assessments of vascular disease, and Working Group members have initiated at least five new projects as a result of this effort.

Introduction

Neurodegeneration is a multifactorial process to which vascular disease, notably intrinsic cerebral small vessel disease (SVD) both adds pathology and may accelerate the clinical expression and pathological burden of neurodegenerative processes. However, to date, this vascular contribution has been largely overlooked: 45% of

all dementias are due wholly or in part due to vascular disease, yet most attention is directed to Alzheimer's disease (AD).

Research on the effects of vascular disease on neurodegeneration is hampered by imprecise data on long-term event rates, the interplay of vascular and neurodegenerative risk factors and pathologies, failure to collect vascular-relevant data systematically in population, hospital studies and trials, failure to adapt cognitive and related functional assessments for use in patients with vascular disease, and failure to collect vascular-relevant data (risk factors, imaging sequences, targeted cognitive tests, biomarkers, etc.) in studies of Alzheimer's and other dementias.

Context

Our guidelines apply to all studies of dementia, all studies of other presentations of neurodegeneration, and all studies of patients presenting with stroke or other clinical manifestations of brain vascular disease, and subjects in studies of asymptomatic brain vascular disease (e.g. in ageing). They apply in observational studies (cross-sectional and longitudinal) and randomised clinical trials.

Terminology

Small vessel disease (SVD) refers to an intrinsic disorder of the penetrating micro-vessels (arterioles, capillaries, venules) that supply the brain parenchyma and which causes cognitive decline, gait and balance disorders, mood disorders, has several imaging manifestations that are visible in ‚clinically-silent' disease, and increases the risk of stroke, dementia, and death several-fold.

White matter hyperintensities, lacunes, cerebral microbleeds, cerebral atrophy, perivascular spaces, and microinfarcts are several imaging and pathology manifestations of this condition. A detailed terminology for imaging SVD features was published as a result of an earlier JPND-funded (Centres of Excellence in Neurodegeneration, COEN) initiative by our group.

Cerebrovascular disease, including SVD, typically affects executive function and processing speed in addition to memory. Alzheimer's disease is a common disorder which typically presents with memory loss, but which also results in physical and multi-system failure at late stages. Other forms of dementia, including frontotemporal dementia and Lewy body dementia, are less common. Rare, monogenic forms of small vessel disease include CADASIL, CARASIL, and Col4-A deficiencies, all of which cause vascular dementia and stroke.

Methods

We established an online survey in SurveyMonkey which recorded details of cohort studies, clinical trials, population and other studies, including information on patient or subject characteristics, risk factors, presenting condition, use of cognitive and physical testing, neuroimaging, other physiological tests, storage of blood or genetic material, long-term follow-up outcome assessed, and availability of data for sharing. The survey was piloted by the Working Group members and ran live from 15 Nov 2014 to 31 May 2015. The survey was circulated to the Working Group and their contacts, PIs of population studies, hospital studies and clinical trials. An interim analysis was performed in January 2015.

The Working Group met in Munich at the Siemens Foundation in January 2015, and reviewed the results of the survey. Working Group members proposed analyses which could be undertaken with the shared data and

established small working groups. A draft publication describing the survey and steps required to bridge the gap between vascular disease and neurodegeneration was planned. Since the workshop, small groups have prepared sections of text, including on population studies, hospital post-stroke cohorts, memory clinic cohorts, clinical trials, gait and balance clinics, summarised evidence on the dynamic aspects of microvascular disease on the brain, prepared advice on cognitive assessments appropriate to vascular disease, on implications of new ICD-11 disease codes for better capturing vascular effects on the brain, and summarised new cohort studies and opportunities in Europe, North America, and the Asia Pacific Region.

AGREED GUIDELINES

Worldwide, nearly 36 million people are estimated to be living with dementia and this is expected to triple by 2050. Cerebrovascular disease is thought to cause up to 45% of all dementias alone or in conjunction with Alzheimer's disease. Many studies have demonstrated that cognitive impairment and dementia are both common and under-recognised after stroke,1 and cognitive deficits are amongst the most feared symptoms for patients with vascular diseases and their caregivers.2 The commonest vascular cause of dementia is now recognised to be cerebral small vessel disease (SVD),3 which may present without stroke, adds pathology and accelerates neurodegenerative processes. Despite being a target for public health intervention in many countries, little is known about the magnitude, causes or potential treatments for these vascular contributions to dementia. The concept of vascular cognitive impairment was introduced in 1994.4 However, most attention in dementia research is still directed to Alzheimer's disease, with the vascular contribution largely being overlooked.

The survey ran from 15 Nov 2014 to 31 May 2015 and is still being analysed. It is not intended to capture all relevant studies but to at least be representative of a sample from the perspective of vascular disease. The following is an approximation of the information captured. Data on a total of 87 studies, including 112,519 subjects (612,519 including UK Biobank) were collected. The sample size ranged from 50 to 15,000 (excluding UK Biobank). 10% were cross-sectional and 90% longitudinal. Many studies were ongoing, either still recruiting or still performing long term follow-up. The longest duration of follow-up so far was about nine years. Thirty-three studies were based in mainland Europe, 25 in the UK, 17 in North America and 12 in the Asia Pacific Region (Japan, Korea, China, Singapore, Australia). The main types of studies overlapped to some extent, but in general there were population cohorts, hospital-based stroke clinics, hospital-based cognition clinics, and randomised clinical trials (which were under-represented). None focused exclusively on gait and balance problems. These studies were enriched for vascular disease, but included studies of healthy ageing and other neurodegenerative disorders.

Many of these cohorts do not appear in the JPND Report of 123 cohort studies,5 nor did they overlap by more than 20% with other recent initiatives, e.g. Cohort Studies of Memory in an International Consortium, COSMIC,6 the Virtual International Stroke Trials Archive (VISTA) Cognition7, or the Optimising the Analysis of Stroke Trials-Cognition (OA-Cog) Initiative which now includes 27 stroke trials of 70,000 patients. This lack of overlap provides some indication of a) the gap in information about vascular disease in neurodegeneration when viewed from 'traditional' neurodegenerative perspectives and b) the amount of data available for sharing and meta-analyses if it could be brought together efficiently and effectively.

The following is a summary of the main points that the Group established during the preparation and analysis of the online survey, in debate at the Workshop, or during work on pre-specified sub-topics after the Workshop. The Group is preparing a complete summary of the data captured in the survey for publication. The following is separated into subsections on general principles and specific assessments, eg of cognition, physical function, imaging, the dynamic nature of cerebrovascular disease, and areas where new research is needed.

General points:

- Studies of neurodegeneration and dementia should recognise that vascular disease plays an important role, either as a primary disorder or by increasing damage secondary to other pathology like Alzheimer's pathology.
- Secondary neurodegeneration due to stroke and other insults is an important contributor to accumulating structural brain damage and its effects on functional neuronal networks.
- Studies of neurodegeneration and vascular disease should recognise the intimate relationship between vascular and neurodegenerative pathology: vascular pathology is an integral part of the pathological spectrum of Alzheimer's disease and vascular lesions may induce secondary neurodegeneration.

Integrated approaches are needed:

Vascular neurodegenerative disorders present to many different types of clinics because of their multiple manifestations. Traditionally, these clinics have operated separately, without integration, therefore overlooking the multifaceted effects of vascular disease on cognition, psychiatric symptoms and physical function. It is important to recognise that these different presentations are all underpinned by a common vascular disorder and so clinical practice, as well as research, should account for this by comprehensive assessment (risk factors, clinical, cognitive, imaging, physical function), analysis, and care.

Vascular disease is a dynamic and far-reaching process:

Vascular disease, and in particular SVD, is a dynamic process (Figure). Apparently small lesions which may precipitate clinical presentations have remote effects on other parts of the brain which increase dysfunction. Small lesions are also evidence of a global brain disease and should be treated as global rather than dismissed as being only small, trivial lesions.

Always assess vascular risk factors, disease burden and outcomes in studies of neurodegeneration:

All studies of neurodegeneration and dementia (observational or clinical trials) should routinely assess common vascular risk factors using standardised, validated methods: blood pressure, blood lipids, blood glucose as an absolute minimum. History of vascular disease including cerebrovascular, peripheral vascular, myocardial ischaemic, valvular or rhythm disorders as well as lifestyle factors such as smoking and exercise, occupation, and diet should be routine, and can be assessed usefully in 'light touch' approaches.

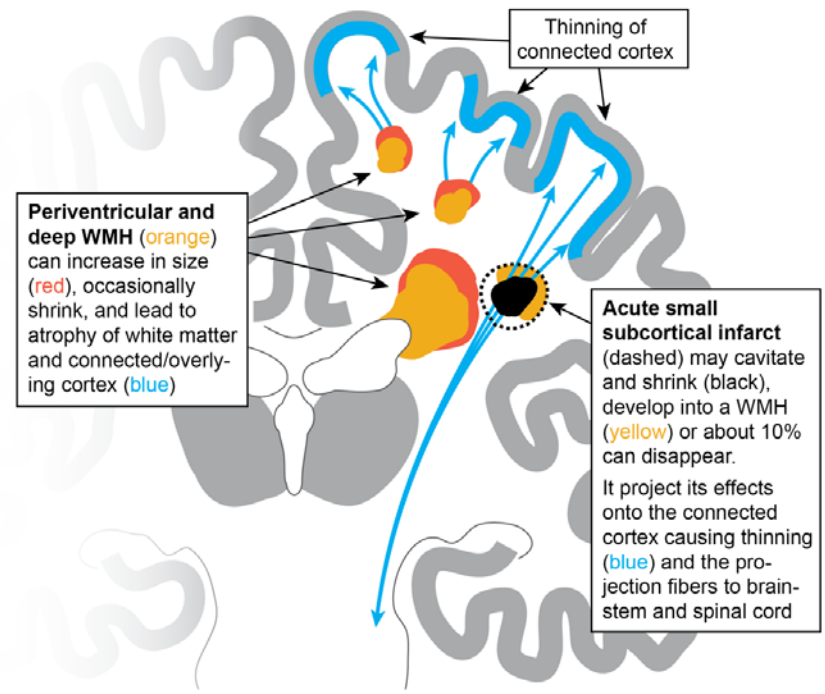

Figure illustrating the dynamic, local and global impacts of cerebral microvascular disease. Figure produced by M Duering, adapted from JM Wardlaw.

Cognitive assessments should be performed in, and relevant to, vascular disease:

- Cognitive testing should be applicable to vascular patients and adapted to reflect their specific cognitive deficits and the limitations of the environment in which vascular patients typically present. Here, testing must be rapid and feasible in patients with neurological deficits.
- A particular focus on executive function and processing speed in addition to memory is important.
- Data on cognitive function long term, ie beyond one to two years after stroke,1;8 is lacking, as is information on long term, ie beyond five years, in vascular cognitive impairment – long term follow-up and methods to improve its practicality, should be encouraged.
- Prior cognitive ability and proxy measures such as educational attainment should be assessed routinely in any studies of cognition and vascular disease, or cognition and other forms of dementia to avoid mistaking lifelong stable traits for late life change.9
- Cognition should be assessed routinely in all clinical trials testing new treatments to prevent or treat stroke of all types; tests need to be sensitive to executive function, processing speed, and not just memory; they should be applicable in individuals with specific deficits such as dysphagia, visual loss, and hand paresis; they should be 'light touch' to avoid confounding by the fatigue which is common after stroke; they should include a measure of pre-morbid cognitive ability such as the National Adult Reading Test and/or educational attainment to avoid confounding of analyses by life-long stable traits; the IQCODE is useful to assess cognition in the immediate period prior to presentation but requires an informant who knows the patient; and trials should also assess depression or mood changes, as both are common in patients with vascular disease and may confound measures of cognitive ability.

- Assessment of cognitive symptoms, and cognitive-related impairments in activities of living, are required from cohorts of patients with symptomatic cerebrovascular disease (e.g. stroke and TIA) to better discriminate between asymptomatic impairment, subjective cognitive decline, mild cognitive impairment and dementia.
- Socio-economic factors have an as yet undetermined major influence on vascular disease over and above that which can be attributed to vascular risk factors alone10 and should be assessed routinely, as well as new targeted research being required.

Assess physical function across several domains routinely:

- Gait and balance should be assessed routinely, as well as continence, in patients with suspected vascular neurodegeneration and in other forms of cognitive impairment and dementia. Walking speed is a sensitive and practical early marker of diffuse cerebrovascular disease.11 These forms of dysfunction have been somewhat neglected to date but are important to patients, limit independence and increase the risk of falls and institutionalization.

Use standard approaches that account for vascular disease:

- Core sets of standard assessments (clinical, cognitive, imaging, biomarkers etc.) shared among studies are important to facilitate future meta-analyses – standardised approaches to core data collection should be encouraged.
- Wherever possible, studies should make use of recently published standards such as the NINDS-CSN Vascular Cognitive Impairment Harmonization Standards or the STRIVE standards for neuroimaging.
- Imaging should routinely include scan types suitable for identifying vascular disease.12 On Magnetic Resonance imaging (MRI), these should include core structural sequences (T2, T1, FLAIR, T2* or other susceptibility weighted sequences), and diffusion tensor imaging for acute ischaemic lesions and to assess tissue integrity; additionally, where relevant, other relevant sequences include perfusion, angiography, permeability, vasoreactivity, spectroscopy and functional imaging sequences. A good quality CT brain scan is an alternative where MR is not available. Molecular tracers for imaging amyloid proteins, inflammation and other relevant processes, with positron emission tomography, are becoming available although are expensive, still inaccessible to most patients, and more studies in more diffuse populations are needed to advance knowledge of their sensitivity and specificity.

Brain tissue collection:

- Collection of post mortem brain tissue, including from regions of the brain that are commonly affected by vascular disease (ie not just the hippocampus) from research subjects that underwent detailed phenotyping in life, is very limited.
- Notwithstanding the limitations of post mortem material in generally representing end stage disease, the material is valuable and resources to store and analyse this material and experts to perform these analyses, should be supported by research funders.
- In particular, more data are needed from individual lesions to determine the pathological changes that underpin the different individual cerebrovascular lesions commonly identifiable on imaging. At present, imaging-pathological correlation is limited to about 30 brain microbleeds, an unknown number of lacunes and white matter hyperintensities – there is little information on the pathological substrates of different amounts and signal changes in common vascular lesions so as to better understand the imaging representations of tissue damage.

Make better use of existing cohort data:

- A considerable amount of relevant data are available in existing completed or ongoing population, cohort, or hospital-based studies, not represented in other neurodegenerative initiatives, that would enable better understanding of vascular disease and neurodegeneration.
- With minimum additional funding, these data could be meta-analysed to provide clinically informative and more precise estimates of effect of vascular risk factors on neurodegeneration clinical or imaging features.
- This would complement the substantial efforts already ongoing in genetics of stroke and vascular disease.
- Studies should be registered and study protocols should be made publicly available to facilitate identification of novel and ongoing studies for meta-analyses.

Specific recommendations for future research:

- Initiating and future studies should aim to collect information on clinical characteristics and vascular risk factors, etc, in standard domains, variables, definitions and parameters, to facilitate future individual patient data analyses.
- Cerebrovascular disease and Alzheimer's disease share multiple risk factors (e.g. smoking, hyperglycemia, diabetes, and obesity). More research is needed to disentangle the relationship between risk factors, vascular disease, neurodegenerative disease, and dementia.
- Vascular risk factors may exert their major effects in mid-life, not just in later life, and therefore research into detection and prevention should start much earlier in life and have mechanisms to continue follow-up for several decades.
- The impact of important vascular risk factors on brain damage may differ at different epochs in life – eg hypertension may be more important in mid than late life, cholesterol may be more important in late than mid-life. Research should be sensitive to these lifecourse effects.
- More research is required to determine outcome event rates and orders: rates and timings of decline in cognitive and physical function, and the typical sequences of events, in order to power clinical trials and inform patients more effectively.
- More research is needed on the interaction of AD pathology and cerebrovascular pathology, how they evolve and how they combine to cause clinical consequences. Cohorts should be generated and sustained that include both careful assessment of cerebrovascular disease as well as molecular imaging, or other assessments of aspects of AD pathology (e.g. by positron emission tomography amyloid imaging).
- More research is needed to define the neurobiological consequences of cerebrovascular disease on brain function, including studies of how small vessel disease causes neurodegeneration and atrophy, and the consequences of this neurodegeneration for function of brain networks and, ultimately, clinical symptoms. Such research should include use of multimodal neuroimaging analysis (e.g. by linking structural and functional MRI methods) and innovative analytic methods (e.g. by graph theory-based analyses of whole-brain networks).
- More data are needed on long term cognitive, physical, psychiatric outcomes, as well as on recurrent vascular events across vascular and neurodegenerative disease presentations to calculate effect sizes and provide patients, health services and governments with more reliable information.

- Studies should be registered and study protocols should be made publicly available to facilitate identification of novel and ongoing studies for meta-analyses – this point is repeated in view of its importance for advancing knowledge.

The Group are now piloting several projects using data collected in the survey. This includes an assessment and further testing of the SVD burden score,13;14 an individual patient data analysis of vascular risk factor profiles and white matter hyperintensities in different cohorts, an analysis of small subcortical infarct aetiologies and association with size, shape and location,15;16 an analysis of patterns of amyloid angiopathy in a wider range of subjects than has occurred to date to improve diagnosis,17 and a survey of neurologists' opinions about secondary prevention and management in case scenarios based around silent brain infarcts and microbleeds, amongst other activities.

The JPND survey and Workgroup has encouraged others in different world regions to consider similar data sharing initiatives within their region, in collaboration with the European and North American-lead initiative. The Group are using the survey information to encourage more awareness of vascular disease in new National Initiatives, including the Dementia Platform UK, UK Biobank, The Rhineland Study, and new Canadian, Australian, Chinese, Korean and Japanese population studies, amongst others.

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Acknowledgments

We would like to thank the JPND funders: Medical Research Council (MRC) in the UK, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) in Germany, and the Canadian Institutes for Health Research. We would also like to thank the Siemens Foundation who provided the venue for the meeting in Munich and the Scottish Funding Council (SFC) who contributed to Professor Wardlaw's attendance through the PEER fund.

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