EMIF Deliverable 2.6: Definition of extreme phenotypes based on resilience to dementia

Executive summary

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Rationale: It is estimated that 35.6 million people over age 60 years lived with dementia worldwide in 2010. In the US, the oldest old individuals (85+ years old) represent the fastest growing segment of the population; the number of oldest old living with dementia in the US could grow from 1-2 million in 2010 to more than 8 million by 2050 or 2060. Thus, improved diagnostic criteria and neuropsychological norms are urgently needed to ensure accurate diagnosis in this specific population. A full understanding of the prevalence of dementia among the oldest old of different socioeconomic, ethnic, and racial backgrounds is also required. Of specific interest to us is the need to gain a better understanding of the characteristics/traits/biomarkers associated with resilience to dementia to a fraction of the oldest old who are able to maintain age appropriate cognitive function. Patients/volunteers will be asked to participate in a study evaluating their cognitive function, amyloid load (analysis of biomarkers in the CSF obtained via lumbar puncture and amyloid PET imaging), genotyping, and phenotyping across a number of visits.

Objective: The main objectives are to understand how clinical markers and biomarkers previously identified in younger and older dementia cohorts apply to the extreme elderly (90+ years old) and to identify novel biomarkers linked with resilience to developing Alzheimer's disease (AD) in extreme elderly subjects.

Study population: We will enrol 60 cognitively normal subjects and 60 subjects suffering from cognitive impairment, 90+ years old, from EHR, the Manchester and Newcastle Aging Study (MNAS), and the VUmc.

Main study parameters/endpoints: The main outcome is the identification of clinical, biochemical, and genetic factors associated with resilience to cognitive decline in extreme elderly subjects. At baseline we will test the association between cognitive resilience and amyloid aggregation, neuropsychological, clinical, and physical markers, brain connectivity as assessed by electroencephalography (EEG), magnetoencephalography (MEG) or Magnetic Resonance Imaging (MRI), brain atrophy as assessed by MRI, vascular changes as assessed by MRI, retinal imaging or duplex of the carotid arteries, genetic markers, and CSF and blood (plasma, serum, RNA, DNA) markers.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Neuropsychological testing might be tiring. CSF collection is associated with post-lumbar puncture headache in 5% of patients. Other rare (<1%) complications can include bleeding, infection, or leakage. The PET scan is associated with a radiation load of 4.1 mSv with 185 MBq and very rarely with an idiosyncratic reaction to the tracer. For retinal imaging, pupil dilatation is needed and one hour after dilatation patient's eyesight is normal again. The study will not have any direct health benefits for participants, but it will add enormous value for understanding and preventing AD.

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