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Dementia 1
Tau oligomers as a therapeutic target for Alzheimer's disease

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Background: The majority of neurodegenerative tauopathies are associated with the pathological accumulation of additional amyloid proteins, notably amyloid-β in Alzheimer's disease (AD). Studies have shown that intermediate aggregates known as oligomers are the most toxic species in disease. The common toxic factor in these diseases, the tau oligomer, is a promising therapeutic target in mixed pathology diseases. We have recently shown that passive immunotherapy with a novel tau oligomer-specific antibody is effective in two different pure tauopathy models, P301L and Htau mice. Here we directly test the interaction between tau and amyloid oligomers and the efficacy of anti-tau oligomer immunotherapy in a model of AD.
Methods: We have evaluated brain tissue and oligomers derived from AD patients for the interaction between amyloid proteins and tau using biochemical and immunohistochemical analysis with our novel oligomer-specific antibodies. To investigate the efficacy of immunotherapy with anti-tau oligomer monoclonal antibody (TOMA) in an AD model, we examined the behavior and pathology of treated Tg2576 mice.
Results: We found that Aβ oligomers can seed the aggregation of tau *in vitro* and are colocalized in disease, forming hybrid oligomers. Treatment with TOMA reverses cognitive detriment and decreases tau oligomer levels in Tg2576 mice, while increasing stable Aβ plaque levels.
Conclusions: Our results suggest that oligomeric Aβ has a synergistic relationship with tau oligomers. This combined with passive immunotherapy results suggest that tau oligomers are a good therapeutic target in AD and potentially in other mixed pathology tauopathies.

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Variations in public and professional stakeholders' awareness and attitudes on diagnosis and care provisions for dementia — A national survey

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Introduction: Sir William Beveridge Foundation (SWBF), a charity based in London & Bangladesh pioneered a service provision for Dementia care in Bangladesh (population 166 million). There is no specific clinical or governmental strategy despite increasing size of the patient cohort and expanding economy.
Objectives: To assess the baseline situation and advise the government to develop a clinical, educational and socio-political strategy for Dementia care.
Patients and methods: A mixed methodological approach of quantitative survey and Qualitative appraisal of seven categories of stakeholders ranging from policy makers to carers and clinicians. Purposive sampling on stakeholders from seven cities was performed.

Given the prevalence rate, population size, confidence level and design effect, the sample size of different categories of respondents was estimated using the general formulae (Cochran):

$$n = N_0^{/1+N0} / N = n^0 / C.$$

Total sample size >1000 people e.g. 65 clinicians who have treated about 90,484 patients that year. Data collection methods included telephone, face to face and internet based interactions. Response rate was 70%.
Outcome tools: Semi-structured questionnaire, in-depth interview, Talking Points for key Informant Interviews.
Results: There is wide-spread variation in the level, accuracy and source of knowledge and perceptions amongst and within specific categories of stakeholders. Comparison analysis with prevalence data from Alzheimer's International, it appears that number of AD patients in Bangladesh will be 1.781 million in 2050.
Conclusion: An evidence-based formal national Dementia Awareness Campaign is now possible. A multi-pronged educational approach is needed for clinicians, charities and society at large.

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0022-510X/$ – see front matter.

Neuropsychological profile of milder forms of HIV-associated neurocognitive decline after the antiretroviral era

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Introduction: Neuropsychological profile of HIV-Associated Neurocognitive Disorder (HAND) was described before and at the beginning of the highly active antiretroviral therapy (HAART) era by psychomotor slowing, decreased attention, impairment in executive functions and memory (learning and recall) with relatively preserved language, and visuoconstructive abilities, all consistent with a "subcortical" pattern of cognitive impairment. Since the prevalence of severe forms of HAND has decreased because of HAART, the incidence of mild forms of HAND (asymptomatic neurocognitive impairment, ANI and mild neurocognitive disorder, MND) continues to increase. New studies that describe the neuropsychological profile of milder forms of HAND are needed to characterize patients in early stages of cognitive impairment.
Methods: 46 HIV patients without history of head injury trauma or opportunistic infections of the CNS were recruited from the HIV clinic, underwent a thorough clinical interview and neuropsychological testing using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The subtests included attention and speeded information processing, episodic memory, working memory, executive function and visuoperception. Verbal fluency was examined using FAS.
Results: Prevalence of HAND diagnoses were 26.2% for ANI, 33.3% for MND, and 40.5% were diagnosed as cognitive healthy. HAND patients showed impairment in executive functions, episodic memory and verbal fluency, but no significant changes in psychomotor slowing.
Discussion: The neuropsychological profile of HAND changed after the HAART era: Mild forms of HAND are characterized principally by executive dysfunction and episodic memory impairment, but not overall psychomotor slowing. This is relevant for early diagnosis and the development of new HAND screening tools.

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Clinical, neuropsychiatric, and ioflupane SPECT imaging findings in REM sleep behavior disorder

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Background: There is little data regarding which features among those with REM sleep behavior disorder (RBD) predict the eventual phenoconversion to dementia with Lewy bodies (DLB) or Parkinson's disease (PD).
Methods: We analyzed findings among subjects with RBD (n = 14) who did not have mild cognitive impairment (MCI), DLB or PD. The Neuropsychiatric Inventory was used to measure neuropsychiatric (NP) burden (sleep domain was excluded). The UPDRS was used to measure parkinsonism. Values ≤2.2 for the mean putamen to occipital ratio on ioflupane SPECT imaging were categorized as abnormal (DaT+).
Results: The sample included 13 (93%) men with a mean age of 62.3 ± -8.2 years, mean Mini-Mental State Examination score of 29 ± 1 and mean UPDRS score of 0.625 ± 1. Nine subjects had ≥3 NP features with irritability (n = 8) and apathy (n = 6) being most frequent across all subjects. Six had subjective cognitive complaints (SCC), 6 had UPDRS >0, and 7 were DaT+. Among the 9 subjects with ≥3 NP features, 6 had SCC, 4 had UPDRS >0, and 5 were DaT+. Of the 6 with SCC, all 6 had ≥3 NP features, 2 had UPDRS >0, and 3 were DaT+. Among the 6 subjects with UPDRS >0, 4 had ≥3 NP features, 2 had SCC, and 4 were DaT+. Among the 7 subjects who were DaT+, 5 had ≥3 NP features, 3 had SCC, and 4 were DaT+. Only 2 subjects had no NP features plus no SCC plus UPDRS = 0, 1 of whom was DaT+.
Conclusions: Varying degrees of cognitive complaints, NP burden, parkinsonism and ioflupane SPECT findings were present among RBD subjects. Longitudinal assessment of RBD subjects using clinical and imaging measures may predict subsequent phenoconversion of RBD to MCI/DLB versus PD.

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Mitochondria-targeted therapeutics for Alzheimer's disease

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We have previously demonstrated that alterations in mitochondrial dynamics precede the onset of memory phenotype and the development of amyloid plaques in three transgenic animal models of familial Alzheimer's disease (FAD). The objective of the study was to develop a treatment to restore mitochondrial dynamics and function. Here we provide evidence that treatment with CP2, a member of a family of tricyclic pyrone compounds, restores axonal trafficking *in vivo*, and averts cognitive and motor deficit in multiple animal models of AD (APP, PS1 and APP/PS1) *in vivo*. Animals were administered CP2 *via* drinking water. Cognitive and behavior tests were applied at the end of a lifetime treatment (13 months) or short-term treatments (2 and 4 months). Changes in mitochondrial dynamics and function *in vivo* and *in vitro* were evaluated using real-time imaging of mitochondrial motility; an XF24 Seahorse Extracellular Flux Analyzer; the activity of OXFOS Complexes I–V was done using enzymatic reactions; and metabolic changes were measured using LC– and GC–MS-based metabolomics. Behavior and memory functions were detected with a battery of tests. Alleviation of the motor and memory phenotype was accompanied with partial reduction in amyloid burden. Investigation of the molecular mechanism revealed that CP2 modulates mitochondria energetics and activates a cascade of events protecting mitochondrial dynamics. Our findings, for the first time, demonstrate that restoration of mitochondrial trafficking protects against cognitive dysfunction in AD. Our data validate mitochondrial motility as an early therapeutic target for AD and poise CP2 as a promising therapeutic compound.

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Prevalence of dementia among older people from rural Hmong and non-Hmong communities living in Vangvieng, Lao People's Democratic Republic

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