

DESIGN-BASED STEREOLOGICAL ASSESSMENT OF THE HEART ATROPHY CAUSED BY HUNTINGTON'S DISEASE IN TRANSGENIC MICE: PRELIMINARY RESULTS

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Abstract.

Huntington's disease (HD) is an autosomal dominant hereditary and fatal neurodegenerative disorder caused by mutation in the HD gene, characterized by the progressive degeneration of the striatum and the corticostriatal pathway. However, recently, in addition to changes in the central nervous system have also been described changes in peripheral organs, especially and potentially dangerous, disorders in cardiovascular system, with autonomic imbalance and structural alterations. Epidemiological studies have shown that cardiac insufficiency is an important cause of death among HD-patients (30%) and alterations in the autonomic nervous system (ANS) have been described, which are characterized by a decrease in cardiac modulation, increasing the risk of cardiac syncope. Since 1996 when the transgenic mouse strains were developed, several transgenic strains are widely used to study the effects of mutant huntingtin (mhtt) in several tissues, and this models are suitable for studying some aspects of the Huntington's disease. In this study, was used left ventricles from 12-week old male transgenic R6/2 mice (G2) ($n=5$) and the respective wildtype littermates (G1) ($n=5$). The myocardium and lumen of the left heart ventricle volume was estimated by Cavalieri's principle and the total volume of the left ventricle is a sum of both. This method is the most accurate and trustworthy stereological procedure for cavity organs. Preliminary results are shown as mean (Coefficient of variation): The myocardium volume of left heart ventricle was: G1 = 64.1 mm³ (0.20) and G2 = 48.04 mm³ (0.20); The lumen volume was: G1 = 4.96 mm³ (0.57) and G2 = 2.45 mm³ (0.44); The total left ventricle volume was: G1: 69 mm³ (0.20) and G2 = 50.49 mm³ (0.18). The volumetric differences between mean groups, were significant for myocardium ($p=0.046$) and total volume of left ventricle ($p=0.032$) and were not significant for lumen ($p=0.058$), here we can observe a border line effect. So, the volume of myocardium and volume of left ventricle in transgenic mice decrease 25% and 26% respectively. Therefore, this preliminary results provides morphoquantitative data of the cardiac structure in this mouse model of Huntington's disease, showing a marked atrophy in mice heart, what could to imply in function disorders, which will studied in the next step of this study.

DESTINATION MEMORY IN PATIENTS WITH HUNTINGTON'S DISEASE: "WHERE DID I PUT THE KEYS?"

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Abstract.

Introduction: Destination memory, a component of episodic memory, refers to the ability to remember the destination of produced events (e.g., "Where did I put the keys?"). This memory component is found to be deteriorated in several neuropsychological populations.

Objectives: Episodic memory has been found to be impaired in patients with Huntington's disease (HD), but destination memory has never been tested in these patients. In this study, we investigated destination recall in a group of HD patients recruited from the Huntington's patient population receiving annual medical and neuropsychological monitoring in the Department of Neurology of the University Hospital of Angers.

Methods: Fourteen French speaking HD patients (7 women and 7 men; mean age=47.71, SD=9.57; mean years of schooling=12.41, SD=1.41) with clinically diagnosed and genetically confirmed Huntington's disease [mean CAG-length=44.6, SD=2.8] and 16 age, gender, and education matched healthy control subjects (8 women and 8 men, mean age=49.32, SD=12.44; mean years of schooling=13.72, SD=2.87) voluntarily took part in the study. HD patients were early in the course of the disease (mean duration of symptoms=5.4, SD=3.2 years; mean score on the Unified Huntington Disease Rating Scale motor scale=23.62, SD=17.87; mean Mattis Dementia Rating Scale score=136.5, SD=5.2). In order to assess their destination recall, participants were asked to put 6 familiar objects (e.g. eyeglasses) in a 20 × 20 cm black square box and 6 other familiar objects in a 20 × 20 white square box. On a 15-min delayed recognition task, participants were exposed to the 12 objects and were required to remember the destination to which each object was originally designated (i.e., the black or the white square box). Results Huntington's Disease patients showed poorer ($p=0.01$) destination recall (mean score=8.71, SD=0.71) than control participants (mean score=10.63, SD=0.49). The destination memory deterioration as seen in Huntington's Disease patients was found to be significantly correlated ($Rho=0.57$, $p<0.05$) with their episodic performance, as assessed with the Hopkins Verbal Learning Test.

Conclusion: Our results confirm that destination memory could be early impaired in HD patients. These findings highlight new tool for assessing episodic memory impairments in patients with HD.

DIETARY INTAKE OF PATIENTS WITH HUNTINGTON'S DISEASE. SPANISH MULTICENTER STUDY OF THE EUROPEAN GROUP FOR HUNTINGTON'S DISEASE

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Abstract.

Background: The energy and nutrient needs of a healthy person are determined by the basal metabolism, the physical

activity level, and the diet-induced thermogenesis. The dietary intake in HD is not well known at the moment.

Objectives: To describe the dietary intake in patients with HD.

Methods: Spanish multicenter, cross-sectional study of the European Register of HD. Dietary intake was assessed by a 24-hours recall questionnaire. Macro and micronutrients and energy intake information were obtained using the software Alimentación and Salud, version 2.0.

Results: 128 patients were included, of which 53.9% were women, with a mean age of 49 ± 14 years. The mean energy intake (kcal/day) was higher in men (2497) than women (2051), $p < 0.001$. The mean daily caloric distribution was fat (36.8%), proteins (18.3%) and carbohydrates (44.9%). Mean consumption of cholesterol is 313.2 mg/day. According to Spanish Dietary Recommended Intakes (SDRI), in terms of quality fatty acids, this sample has a normal median ratio (MUFA+PUFA)/SFA (2.1) and by contrast has a low median ratio PUFA/SFA (0.4). As compared to SDRI, the intakes of patients assessed had deficit of (in% of patients): energy (55%), fiber (76%), folic acid (57%), vitamin E (74%), iodine (83%), biotin (88%), copper (58%) and chlorine (80%). In contrast, there is an excessive intake of: protein (93%), vitamin C (82%), vitamin A (54%), vitamin B1 (67%), vitamin B12 (90%), iron (68%), zinc (61%), selenium (61%), vitamin B2 (71%), niacin (87%), pantothenate (52%), pyridoxine (83%), phosphorus (92%) and sodium (54%). Our sample shows 5%, 6%, 9%, 12% and 58% of patients only covered a quarter of the SDRI for energy, fiber, iodine, chlorine and biotin respectively. Conclusions: Energy and nutrient intakes of patients with HD deviate far from the recommendations. Inadequate diet consuming is a risk factor that may place patients with HD for developing malnutrition later. Identifying population groups of HD at risk of a nutritionally unbalanced diet will facilitate targeted intervention, necessary as part of integrated nutrition surveillance. Acknowledgements: We gratefully acknowledge to European Huntington's Disease Network for financial support to this work.

DIFFUSIVITY OF THE CORTICAL SPINAL TRACT IN HUNTINGTON'S DISEASE

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Abstract.

Introduction: Motor impairments are a critical feature of Huntington's disease (HD) and have been demonstrated in Presymptomatic HD (PreHD) subjects. Furthermore, white matter abnormalities have been shown in presymptomatic and symptomatic HD subjects using Magnetic Resonance Imaging (MRI), and Diffusion Tensor Imaging (DTI).

Objectives: To examine the crucial white matter motor tract that connects the primary motor cortex to the spinal cord, the cortical spinal tract (CST), using DTI tractography in HD.

Methods Subjects: (25 HD, 25 PreHD, 50 healthy controls). DTI data was acquired (3T Allegra for 3 repeats), using SE echo-planar imaging (TE/TR: 89/8500 ms, bandwidth: 2126 Hz/voxel, matrix: 128×128 , 80 axial slices, voxel size:

$1.8 \times 1.8 \times 1.8$ mm) with 30 isotropically distributed orientations for the diffusion sensitizing gradients at a b value of 1000 s/mm² and 6 b=0 images. DTI images were processed with FMRIB's Software Library. Tractography was done in TrackVis. Tractography was performed by manually drawing two regions of interest on each individuals fractional anisotropy color map. A general linear model was used to test for differences between groups with sex and age included as covariates. Correlations analysis was done between CAG repeat length, Disease Burden and UHDRS1 (motor assessment). **Results:** Tractography results showed decreased fractional anisotropy and increased axial and radial diffusivity in the CST of HD patients. PreHD and HD, CST FA, AD, and RD were correlated with CAG repeat length and Disease burden, as well as motor (UHDRS1) assessment.

Conclusion: We have shown using DTI tractography, that the CST is impaired in HD patients. Furthermore, the tract is correlated with motor scores, underscoring the important functional role it plays in motor impairment in HD. CAG repeat length negatively affects the connectivity of the CST, suggesting a strong genetic component for structural connectivity.

DNAJB6: A PEPTIDE CHAPERONE THAT DELAYS DISEASE IN THE HUNTINGTON R6/2 MOUSE MODEL

Harm H Kampinga

Abstract. DNAJB6 is a member of the DNAJ family of chaperones that was found to have superior anti aggregation activity in cell, Drosophila and Xenopus models of Huntington's disease (1). We found that DNAJB6 prevents aggregation initiated by toxic fragments as generated during proteolysis of the huntingtin protein or as may arise due to alternative splicing of the huntingtin mRNA (2,3). Transgenic mice expressing DNAJB6 in the brain were viable and showed no abnormalities up to 1 year of age. Crossing the DNAJB6 mice with R6/2 Huntington mice (200 CAG repeats) revealed that DNAJB6 strongly delayed aggregate formation in the brain. In addition, DNAJB6 $\times$ R6/2 mice showed slower decline in functional parameters (clasping, rotarod) and lived 23% longer than their R6/2 litter mates. Thus, DNAJB6 is the chaperone showing the largest protection against Huntington's disease reported to date. (1) Hageman et al., Mol. Cell. 37 (2010) 355-369. (2) Gillis et al., J. Biol. Chem (2013), in press (3) Mansson et al., submitted.

DOES PRESYMPTOMATIC TESTING CHANGES AGE AT ONSET: A PROSPECTIVE STUDY IN HUNTINGTON DISEASE (PAON STUDY)

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Abstract. In PAON, we studied prospectively the impact of presymptomatic testing (PT) on the onset of symptoms in