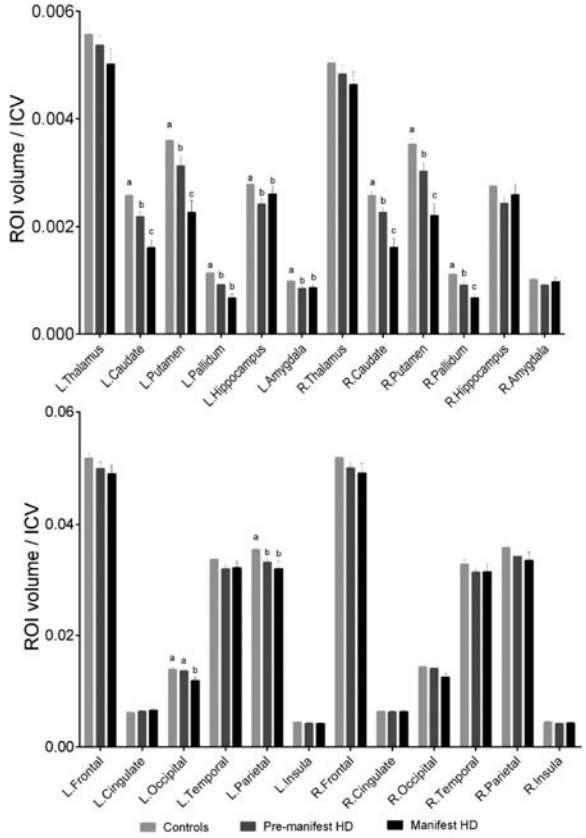

Figure 2: Brain regional volumes of patients with Huntington's disease (HD) and controls. Significant differences between groups are indicated by different letters (Kruskal-Wallis test followed by Dunn's multiple comparisons test).

FIG. 2 (45)

associated with worse atrophy in DGM, hippocampus, and putamen. Lower pallidum volume was associated with a worse score in PBA–irritability/aggression subscale. Atrophy in ROIs such as caudate and hippocampus was associated with worse cognitive performance, as evaluated by the SDMT and VFT. Regarding manifest patients with HD, atrophy in striatal regions was associated with worse motor symptoms. Lower volumes in other subcortical ROIs such as pallidum, hippocampus, and amygdala were associated with worse cognitive performance, as observed by the scores at the SDMT, VFT, and Stroop interference test.

Conclusions: Brain atrophy is an early event in HD and antedates motor symptoms. Brain atrophy in premanifest and manifest HD is not restricted to the striatum, being observed in other subcortical regions as hippocampus and amygdala. Decreased volumes in subcortical structures are associated with behavioral/cognitive symptoms in premanifest HD carries and with motor/cognitive symptoms in manifest patients with HD.

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NBIA-like MRI findings in a patient with Huntington's disease

T. Shimizu, T. Matsukawa, Y. Abe, H. Suga, N. Tominaga, M. Nagai, T. Iizuka, H. Ishiura, J. Mitsui, S. Tsuji, R. Hanajima, K. Nishiyama (Yonago, Japan)

Objective: To report a rare case of Huntington's disease (HD) with MRI findings resembling neurodegeneration with brain iron accumulation (NBIA).

Background: HD and NBIA are both neurodegenerative disorders that present with cognitive decline and chorea. The neurological symptoms are similar but brain MRI usually differentiates these two disorders; routine brain MRI findings showing iron accumulation in the basal ganglia raises suspicion of NBIA. Previous studies showed iron accumulation in the brain in animal HD model, and elevated absolute iron levels in the basal ganglia of post-mortem brain at the end-stage of HD patients as well. Furthermore, MRI technique using R2 or R2* mapping has recently shown iron deposition in the basal ganglia in HD patients. However, NBIA-like MRI findings in HD patients on routine MRI is very rare.

Methods: Case report.

Results: A 39-year-old man was admitted to our hospital with cognitive decline and chorea which developed since his early 30s. Brain MRI showed atrophy of bilateral caudate and hypointensities in bilateral caudate, putamen, globus pallidus, substantia nigra, red nucleus and dentate nucleus on T2WI and T2*WI. Genetic testing revealed both heterozygous CAG repeat expansion (54/23) in the HTT gene and heterozygous p. Lys1010Thr mutation in the exon 13 of the ATP7B gene, while serum ceruloplasmin and urine copper levels were normal, suggesting a carrier of Wilson's disease. Neither known mutation nor rare variant was found in the causative gene of NBIA1-8, aceruloplasminemia, Mucolipidosis IV and FAHN by exome sequencing. Acanthocytosis was not identified on peripheral blood smear. Familial history of HD in his uncle was subsequently confirmed.

Conclusions: We report a rare patient with HD showing NBIA-like MRI findings. Long CAG expansion in the HTT gene or heterozygous mutation in the ATP7B gene may be associated with these MRI findings. Our case suggests that the presence of NBIA-like MRI finding may not exclude the diagnosis of HD.

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A safety, tolerability and biomarker update from an ongoing open-label extension study of RG6042 in adults with early manifest Huntington's disease

S. Tabrizi, B. Leavitt, P. Sanwald Ducray, E. Wild, V. Schlegel, G. Hooper, A. Nicotra, J. Chevure, A. Smith, R. Lane, F. Bennett, L. Boak, R. Doody, S. Schobel (London, United Kingdom)

Objective: To present the safety, tolerability and biomarker effects of RG6042 (previously, IONIS-HTTRX) during an open-label extension (OLE) study in adults with early manifest Huntington's disease (HD).

Background: HD is a genetic, neurodegenerative and ultimately fatal disease that has a devastating impact on families across generations. HD is characterised by behavioural symptoms, as well as progressive cognitive and motor decline, resulting in increasing disability and loss of independence. RG6042, an intrathecally administered antisense oligonucleotide (ASO) targeting huntingtin (HTT) mRNA, is the first investigational treatment to show a dose-dependent, reversible lowering of HTT protein. Preclinical models have demonstrated improved motor function and delayed disease progression with RG6042. RG6042 was well tolerated in the IONIS-HTTRx Phase I/IIa study in patients with early HD (NCT02519036) and is currently being evaluated in this ongoing OLE study (NCT03342053).

Methods: This OLE study (NCT03342053) is evaluating the long-term safety, tolerability, pharmacokinetics and pharmacodynamics of 120mg RG6042, administered intrathecally, monthly or bi-monthly, for 15 months in adults (N=46) with early manifest HD (Stage I/II) who previously participated in the Phase I/IIa study (NCT02519036). Exploratory endpoints include assessment of standard and digital clinical outcomes, as well as biomarkers.

Results: At the time of abstract submission, over 350 doses of RG6042 have been administered. OLE participants in the monthly regimen have had between 8 and 15 doses of RG6042 and participants in the bi-monthly regimen have had between 4 and 7 doses. Interim safety, tolerability and biomarker data will be presented.

Conclusions: RG6042 is the first HTT-lowering treatment to be evaluated in patients with HD. The data presented here inform on the longer-term safety, tolerability and biomarker profile of RG6042. These data complement other studies in the RG6042 Global Development Program such as the RG6042 pivotal Phase III study GENERATION HD1.

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Usefulness of Heart Rate Variability to Identify the Risk of Falling in Huntington's Disease

C. Terroba-Chambi, D. Vigo, M. Merello (Buenos Aires, Argentina)

Objective: To evaluate the relationship between the HRV and the risk of falling in HD patients.

Background: Huntington's disease (HD) patients have a high prevalence of falls, on the other hand, autonomic nervous system dysfunction

has been reported from early stages of the disease. However, there is lack of evidence regarding the relationship between heart rate variability (HRV) and falls in this population.

Methods: Eighteen HD patients were assessed by short-term HRV analysis EKG were recorded during 5 minutes in resting and standing states. Time domain (MeanRR, SDNN, RMSSD), frequency domain (VLF, LF, HF, LF/HF) and non-linear (DFA α1, DFA α2 and SampEn) parameters were calculated. Data in each state and its difference between were analyzed. Additionally, data regarding falls, measurements of the risk of falling [Berg balance Scale (BBS), Timed-up go test (TUG), Tinetti mobility test (TMT)] and specific-diseases scales were collected.

Results: The prevalence of falls was 38.9% reporting at least one or no one fall (single faller) and 61.1% reporting two or more falls (recurrent fallers) in the past 12 months. There was no difference in age, gender, illness duration, number of CAG repetitions, total motor score (UHDRS-TMS), functional capacity (UHDRS-TFC) or any scale of risk of falling between groups. Recurrent fallers had significantly lower RMSSD in resting state ($p=0.020$), higher LF/HF ratio in both states (resting, $p = 0.011$; standing, $p = 0.044$) and higher DFA α1 in both states (resting, $p = 0.027$; standing, $p = 0.011$). Patients classified with high risk of falling by BBS in resting state showed higher power of low frequency ($p=0.044$) and higher DFA α2 ($p=0.011$). Correlations were found in resting state between the RMSSD and [number of falls ($r=-0.486$, $p = 0.041$), UHDRS-TMS ($r=-0.408$, $p = 0.030$), BBS ($r=0.049$, $p = 0.470$)] and LF/HF ratio and number of falls ($r=0.539$, $p = 0.021$)). No significant differences were found between recurrent and single fallers for any blood pressure measures.

Conclusions: The observed HRV pattern is consistent with a higher sympathetic prevalence associated with a higher risk of falls. The short-term HRV assessment is a useful and rapid tool to assess the risk of falling in HD. The decrease of parasympathetic HRV values adequately identifies the high risk of falling, independently of orthostatic phenomena, in this specific population.

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Digital monitoring of Huntington's disease with smartphone and smartwatch wearable technology: The Digital-HD study

R. Tortelli, T. Kilchenmann, F. Rodrigues, L. Byrne, A. Bamdadian, F. Lipsmeier, S. Schobel, M. Lindemann, E. Wild (London, United Kingdom)

Objective: To investigate the tolerability and feasibility of using wearable smartphone and smartwatch technologies to monitor the motor, behavioural, cognitive and quality of life (QoL) impact of Huntington's disease (HD), and generate reliable and meaningful biomarkers of disease progression.

Background: Advances in wearable sensors and communication technologies permit unobtrusive, continuous, accurate, real-world monitoring of chronic diseases. This has the potential to overcome many limitations of clinic-based, intermittently administered clinical measures.

Methods: The Digital-HD study is a single-centre, prospective observational study that aims to enrol patients with manifest HD (n=40), pre-manifest HD (n=20) and healthy controls (n=20). Data are captured from passive monitoring and daily active tests. Passive monitoring involves wearing a smartwatch and carrying a GPS-enabled smartphone, both containing tri-axial accelerometers and gyroscopes. Active tests measure motor and non-motor manifestations of HD, and include questions about QoL and mood, cognitive tests, and motor tasks. Participants are trained on active tests during an on-site equipment issue visit (EIV) and perform these tests at home upon prompting. During the EIV, participants undergo clinical assessments using the Unified HD Rating Scale motor, cognitive and functional subscales, as well as the Timed-up-and-go test and selected items from the Berg Balance Scale alongside a Kinect sensor. These in-clinic tests are used to "anchor" the digital biomarker assessments. Encrypted phone data are securely transferred via the internet and analysed to extract clinically meaningful measurements for group discrimination and correlation with clinical parameters.

Results: The study is ongoing; recruitment began in January 2019 and will be completed by June 2019. Representative examples of digital and in-clinic data will be presented, along with interim data on acceptability and adherence.

Conclusions: This is the first study to compare the use of wearable technologies for continuous monitoring in patients at various stages of HD and healthy controls. Thanks to the high temporal and spatial resolution of this approach, it has the potential to generate sensitive, accurate and meaningful outcomes to enhance the conduct of clinical trials in HD.

*ML and EJW share senior authorship.

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Changes in GABAergic transmission of striatal neurons in presymptomatic Huntington's Disease

M. Treven, F. Zirpel, I. Mody (Vienna, Austria)

Objective: To determine whether parameters of synaptic and extrasynaptic GABAergic inhibition of striatal projection neurons are altered in presymptomatic BACHD mice.

Background: One attractive early hypothesis of HD pathogenesis was that of a GABA deficiency disorder, with hopes for a substitution therapy similar to levodopa for PD. While this turned out to be a drastic oversimplification, direct and indirect pathway striatal projection neurons (SPNs) nevertheless require GABAergic inhibition as protection from excitotoxicity via extensive cortical glutamatergic inputs. Mutant huntingtin impairs receptor trafficking and surface expression, leading to reduced surface GABAA receptors. Reduced tonic GABA currents have been described in rapidly symptomatic R6/2 and Q175 mouse models, likely contributing to striatal neurodegeneration. The BACHD model employed here resembles the disease course in humans more closely, with late onset and slow progression of motor symptoms. This allows a longitudinal observation of SPN GABAergic transmission in HD.

Methods: Brain slice preparations of transgenic BACHD, asymptomatic Q31, and wild type FvB mice between 4 and 12 months of age were used for voltage clamp recordings of IPSCs, EPSCs and tonic GABA currents of striatal GFP-tagged D1-SPNs and D2-SPNs.

Results: Tonic GABA currents were significantly reduced in D1- and D2-SPNs of 4 month old presymptomatic BACHD versus control mice of the same age (Ctrl 4M: 30.93 ± 2.73 pA; BACHD 4M: 21.64 ± 1.90 pA; $p = 0.0074$). In contrast, parameters of phasic, synaptic GABAergic transmission of SPNs (IPSC amplitudes and frequency) did not differ between presymptomatic BACHD and control mice. Reduced SPN tonic GABA currents in BACHD persisted into symptomatic disease stages up to 12 months of age.

Conclusions: Reduced SPN tonic GABA currents possibly contribute to the selective vulnerability of these neurons. Our findings suggest that these changes precede loss of neurons and disease onset. Ways of enhancing tonic GABAergic transmission in HD, via direct positive receptor modulation or GABA reuptake blockers, might be explored to counter excitotoxicity and delay striatal neurodegeneration.

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Novel exploratory outcome assessments in GENERATION HD1

D. Trundell, S. Schobel, R. Roos, K. Anderson, A. Thobhani, G. Hooper, M. Nguyen, S. Tabrizi (Welwyn Garden City, United Kingdom)

Objective: To improve collection of outcomes meaningful to patients with Huntington's disease (HD) and their families, through the development of novel assessments of daily functional ability, irritability, and speech difficulty.

Background: With an increasing focus on clinical research, there are a number of recently developed outcome measures in HD, particularly patient-reported outcome measures, notably the HD-PRO-TRIAD, HD-Health Index and the FuRST 2.0. Despite these valuable additions, there is still need for a clinician-reported outcome (ClinRO) measure of daily function that can assess change in a more granular fashion than existing ClinROs.

With multidimensional diseases, such as HD, there is a need to measure a broad range of symptoms and impacts. Gaps were identified while evaluating the holistic measurement strategy for GENERATION HD1 against qualitative research (indicating the core symptoms and impacts from the perspectives of patients and their families). To balance patient burden with the desire for comprehensive measurement, it was determined that in addition to a novel ClinRO assessing daily functional ability, brief measures of patient-reported speech difficulty, and companion-reported irritability were also required.