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LATE ONSET HUNTINGTON'S DISEASE PHENOTYPE PROGRESSION. 2 YEARS FOLLOW-UP IN 220 PATIENTS FROM ENROLL-HD PDS4

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Background

Age of onset in **Huntington's disease (HD)** is primarily determined by the **number of CAG triplets** and is **inversely correlated** with the **trinucleotidic expansion**. CAG repetitions when ≥ 40 are fully penetrant and negatively correlate with age of onset, even if at most common **range <50CAG** there is a **wider variability** as triplets number accounts for **up to 70%** of the variation. **Late onset Huntington's disease (LoHD)** occurring in tardive adulthood **(≥ 60 years)** is recently gaining attention **[1, 2]**. We examined LoHD patients' clinical, cognitive and behavioral data **over 2 years** to investigate **disease progression** in this particular phenotype.

Materials & methods

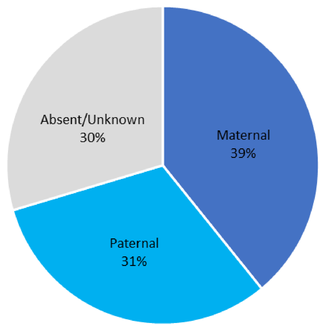
From **Periodic Dataset of Enroll-HD (PDS4)** released in December 2018 comprising longitudinal clinical data from more than 15.000 participants followed by Study Sites worldwide since the beginning in 2012, we extracted data collected in Europe of **220 caucasian LoHD motor manifest patients** with at least **2 annual follow-ups** :**T0 [baseline]; T1 [375±61.01 days]**; **T2 [746.39±74.8 days].** Repeated measures ANOVAs were performed to monitor changes over time. Statistical significance was set at p<.05.
Age, sex, education, higher pathological and normal allele length, family history, cognitive and psychobehavioral measures were investigated.

Results

❖ **Characterization of the sample at baseline (T0)**

LoHD Subjects with Motor Onset age ≥ 60 years n=220	T0 Baseline		
Gender M/F (%)	114/106 (51.8 / 48.2)		
Education Isced, median (range)	3	(0-6)	
Age at motor onset (mean ± SD)	64.66	±	4.13
CAG Normal Allele (mean ± SD)	18.19	±	2.86
CAG Expanded Larger Allele (mean ± SD)	40.75	±	1.29
Current Age (mean ± SD) years	71.00	±	5.00
Disease Duration (mean ± SD) years	6.34	±	3.89

HD Inheritance in LoHD patients



❖ **Longitudinal changes**

✓ **Clinical features**

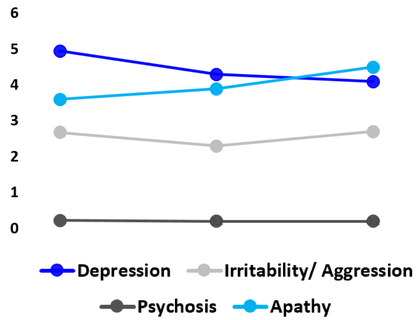
Body Mass index (BMI) remained stable at T1 and T2. **UHDRS Total Motor Score** significantly **worsened** at T2 (p=.008) and **UHDRS Total Functional Capacity reduced** by .80 point at T1 (p=.051) and 1.41 at T2 (p<.001).

✓ **Psychobehavioural status**

No significant changes over 2 years in Problem Behaviors Assessment–Short composite scores evaluating **depression, irritability/aggressivity, psychosis, apathy.**

LoHD n=220 (mean ± SD)	T0 Baseline			T1 1 year Follow-up			T2 2 years Follow-up			p-value T0-T1	p- value T0-T2
Body Mass Index (BMI)	25.44	±	4.25	25.50	±	4.17	25.36	±	4.33	.999	.999
Total Motor Score UHDRS (TMS)	39.48	±	17.84	42.20	±	18.28	44.70	±	18.29	.349	**.008**
Total Functional Capacity UHDRS (TFC)	7.90	±	3.40	7.10	±	3.60	6.49	±	3.57	**.051**	**<.001**
Behavioural Evaluation											
Depression Suicidality and Anxiety	4.94	±	6.74	4.29	±	5.13	4.05	±	5.47	.716	.319
Irritability and Aggressivity	2.68	±	3.87	2.32	±	3.41	2.73	±	4.59	.999	.999
Psychosis	.22	±	1.06	.22	±	1.03	.21	±	1.16	.999	.999
Apathy	3.69	±	4.49	3.90	±	4.72	4.51	±	5.01	.999	.206
Neuropsychological Evaluation											
Mini Mental State Examination (MMSE)	24.03	±	4.56	23.51	±	5.63	23.84	±	5.26	.999	.999
Symbol Digit Modality Test	18.36	±	10.72	18.03	±	10.60	16.62	±	11.19	.999	.356
Categorial fluency (Animals)	11.41	±	5.32	11.62	±	5.35	10.07	±	5.52	.999	**.033**
Phonological fluency	19.95	±	11.89	19.41	±	12.67	18.72	±	12.36	.401	.999
Stroop Color Naming Test	37.35	±	16.25	36.05	±	15.07	33.38	±	16.12	.999	**.034**
Stroop Word Reading Test	51.84	±	21.83	49.19	±	21.20	45.80	±	22.84	.659	**.017**
Stroop Interference Test	18.79	±	10.18	18.14	±	10.41	17.80	±	10.43	.999	.999
Trail Making Test (TMT) – part A (Time)	93.23	±	57.11	92.66	±	55.9	93.76	±	57.21	.999	.999
Trail Making Test (TMT) – part B (Time)	182.54	±	67.71	187.44	±	63.41	183.04	±	66.18	.999	.999

Problematic Behaviors Asssessment- Short Version



✓ **Neuropsychological profile**

No significant cognitive changes over two years were observed on MMSE and in most of the scales examining subcortical executive domain Phonological Fluency, Symbol Digit Modalities Test, Trail Making Test A&B and Stroop Interference Test.

Lower scores were detected at T2 on

- **Stroop Color Naming** (p=.034),
- **Stroop Word Reading** (p=.017),
- **Categorical Fluency** (p=.033).

Conclusion

LoHD evolution over **2 years** is characterized by **significant reduction** in **daily functionality and motor worsening**, whereas **psychiatric status** remained **stable**. In **cognitive performance** significant changes were reported in tasks involving **psychomotor speed** in spoken context, that can be attentioned as **potential markers** of disease progression in LoHD.
Data on **HD inheritance** confirmed an **higher percentage** of tardive onset subjects **with missing/unknown family history** of disease **[3]**. A further effort must be done to define **optimal counseling strategies** for newly discovered at risk family members and support programs **to facilitate** risk **communication within family**, and **test decision making**.

Bibliography

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