Does Late-Onset Huntington Disease Represent a Distinct Symptomatic Picture? Evidence for a Selective Deficit in Executive Function and Emotion Recognition, in the Absence of Behavioral and Psychiatric Disorders

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Abstract: Huntington Disease (HD) is an autosomal-dominant, neurodegenerative disorder, including motor, cognitive, emotional and behavioral symptoms. Motor symptoms used to set the clinical onset, typically emerge in the middle age. Here, we describe the case of a patient, who received a genetic diagnosis at 75 years and developed motor symptoms at 80. The Patient shows severe motor symptoms in the absence of personality changes or psychiatric disorders typically observed in HD. For what attain neuropsychological profile, it results unaltered apart from a specific deficit in emotion recognition and general slowness on executive functioning tasks, reflecting a specific trade-off between accuracy and rate of performances, that is a selective impairment in fine-tuning of resources. Both of these deficits in the Patient could be ascribable to the frontotriatral atrophy, evidenced by Computed Tomography. While deficit in emotion recognition is a well-known symptom in HD, a deficit in fine-tuning of resources regards a specific aspect of executive function. The ability of fine-tuning resources is the latest step in the development of executive functions, and it could be also the first level to be impaired in HD. We proposed that deficit in fine-tuning of resources could be the core of the neuropsychological deficit in late-onset HD.

Keywords: Huntington's chorea, Affective Processing, Cognition, Late-onset Huntington's disease.

BACKGROUND

Huntington disease (HD) is an autosomal-dominant progressive neurodegenerative disorder, including chorea and dystonia, incoordination, cognitive decline, and emotional and behavioral disorders [1]. Genetic markers, known since 1983, consist in a mutation located on the short arm of chromosome four (4p), associated with an expanded trinucleotide repeat which number seems to correlate with the age of onset: larger is the number of CAG repetitions, earlier is the onset [2,3]. Normal 4p alleles contain several CAG repetitions smaller than 27. CAG repetitions between 27 and 35 are generally considered “intermediate”, while CAG repetitions between 36 and 40 indicate an “incomplete penetrance” and repetitions exceeding 40 indicate a fully penetrant disease. The variation in the number of CAG repetitions accounts for about 70% of the variation in HD age of onset [2,3].

Usually, the age of onset falls between 20 and 60 years, even though more frequent is within 30 and 50 years. Onset before 25 is considered juvenile, while late-onset has been recently restricted to patients with onset after 60 [4]. Kremer and coworkers [5], from a cohort of 133 late-onset patients, demonstrated that late-onset is related to a smaller number of CAG repeats in HD patients with onset before 60 years, but they could not confirm the relationship between age of onset and number of CAG repetitions in over 60 years old individuals [5]. Moreover, late-onset HD has been considered rare, encompassing only 4.7% of clinical HD cases [6].

Principal motor symptoms of HD are characterized by chorea (rapid involuntary movements of the face, trunk, and limbs), motor impersistence and deficit of the fine motor skills [1]. These symptoms are used to state the onset of disease even when the genetic diagnosis occurred many years before their occurrence. HD is also characterized by a worsening multiple-domain cognitive impairment, often sparing long term memory, but affecting executive functions, planning abilities, problem-solving and acquisition of new motor skills [1].
Late-onset HD could be due to intermediate CAG repeats [7] or a smaller number of repeats [8,9]. Moreover, an increase in the number of CAG repeats is considered as strongly related to the more severe expression of the disease, atrophy in the striatum [10,11] and the rate of clinical progression [12,13]. The age of onset is also related to the symptomatic picture and its progression. Indeed, Myers and coworkers [14] reported that 25 subjects with the late-onset of HD presented the same clinical futures presented by mid-onset HD, but in late-onset HD the disease progression was slower, and the degree of neural atrophy was significantly less severe. The most common symptoms of late-HD patients were chorea, presence of cognitive impairments, dysarthria and gait disturbance.

Lipe and Bird [15] reported a sample of 34 HD individuals with onset ranging from 60 and 79 years of age and trinucleotide expansions from 38 to 44 CGA repetitions. All of the patients showed motor symptoms, 29 showed chorea, but cognitive deficits and psychiatric symptoms were present only in about 30% of them.

In recent work, Koutsis and colleagues [16] found a significant negative correlation of upper CAG repeat size and age at the onset in late-onset HD, showing that 23.4% of the variance in age at onset could be attributed to CAG repeat size.

Sipilä and coworkers [4] ascertained 52 patients with late-onset HD, namely age at onset ranged between 64.6-72.7 years, finding that they had more motor signs and their functional disability was slightly more advanced at the time of diagnosis than patients with mid-age-onset HD. However, they found no difference in disease progression or survival between the two groups.

Similar results underline the great variability that occurs in HD-phenotype along the life-span, suggesting also the need for further investigations to understand the factors determining the age-related variability. In the present paper, we report a single case study on a Patient with late-onset HD. The Patient's onset occurred at 80 years, making him, at least to our knowledge, the HD with the latest onset in literature. Since his very late-onset corresponded to an atypical symptomatic picture and clinical history, we analyzed him to better understand the HD disease and its expression along the life span, especially for what attains the expression of cognitive, behavioral and emotional symptoms.

CASE PRESENTATION

The Patient is an 84 years old man, with no history of neuropsychological and/or psychiatric disease preceding the HD onset. When he was 75, having his daughter being diagnosed with HD, he was submitted to genetic testing and reported to be affected by HD mutation. Since the genetic diagnosis, his clinical status was monitored for the occurrence of HD symptoms.

Before the 80s he never suffered for any postural, movements, psychiatric or cognitive disorder. He developed his first symptoms at the age of 80s. Symptoms comprised motor deficit, chorea, and dysphagia. In the following paragraphs, we describe exhaustively his neuropsychological and psychiatric profile.

Clinical Observation and Neuropsychological Assessment

The Patient underwent an exhaustive neuropsychological and psychiatric assessment (Table 1). We also recollected information from his relatives about possible changes in his mood and personality and any possible psychiatric disorder related to HD-onset.

He is well oriented in both space and time, and able to reports correct spatial coordinates. The Patient accurately reports his history, showing to be fully aware of his clinical condition and the progression of the disease.

Reasoning-Intelligence

Logical-deductive reasoning on non-verbal [17] and verbal materials [18] appears to be spared in the Patient.

Executive and Attentional Functioning

Executive functions, in particular, planning abilities, flexibility and ability to suppress automatic responses and interferences are assessed through Verbal Fluencies [19] and Stroop Test [20].

Performances on both categorical [21] and phonemic verbal fluencies [22] result well within the normal range. On the Stroop test, performances are accurate and error-free, but the Patient needs a too long time to complete the tasks, showing difficulty in inhibiting the interference [20].

Dissociation between accuracy and time of performance is observed also in other tests, which
Table 1: Neuropsychological and Neuropsychiatric Inventory

| Test                              | Cognitive domain                                      | Accuracy | Time       |
|----------------------------------|------------------------------------------------------|----------|------------|
| Temporal Orientation Test        | Temporal Orientation                                  | 99/100*  | -          |
| Colored Progressive Matrices     | Logical-deductive reasoning                           | 20/36*   | -          |
| Cognitive Estimation             | Verbal critical judgment                               | 4/5*     | -          |
| Phonemic Fluencies               | Executive functions                                    | 19*      | -          |
| Categorical Fluencies            | Executive functions                                    | 12*      | -          |
| Stroop Test                      | Cognitive flexibility and ability to inhibit interference | 1*       | 116s (***) |
| Visual Search                    | Selective attention                                   | 16* 55*  | -          |
| TMT-A                            | Selective attention                                   | 25/25*   | 196s (***) |
| TMT-B                            | Selective attention and cognitive flexibility          | 26/26*   | 377s (***) |
| TMT B-A                          | Cognitive Flexibility                                  | -        | 181s (***) |
| Stars Detection                  | Visuospatial attentional orientation                  | 54/54*   | -          |
| Constructive Apraxia             | Visuo-Constructive abilities                          | 14/14*   | -          |
| Street Completion Task           | Visuospatial abilities                                 | 9/14*    | -          |
| Digit Span Forward               | Verbal short-term memory                              | 4        | -          |
| Digit Span Backward              | Verbal short-term memory                              | 4        | -          |
| Corsi span                       | Visuospatial short-term memory                         | 4        | -          |
| 15 Rey’s Words (immediate recall) | Learning                                              | 25/75*   | -          |
| 15 Rey’s Words (delay recall)    | Long-term Memory                                      | 2/15*    | -          |
| 15 Rey’s Words (recognition)     | Recognition                                           | 14/15*   | -          |
| Short history 1                  | Episodic Memory                                       | 15/28*   | -          |
| Short history 2 (immediate recall)| Episodic Memory                                      | 5.4*     | -          |
| Short history 2 (delay recall)   | Episodic Memory                                       | 3.4*     | -          |
| Naming on description            | Language (production)                                 | 36.5*    | -          |
| Token Test                       | Language (understanding)                              | 27*      | -          |
| NPI (Daughter)                   | Delirium                                              | 0*       | -          |
|                                  | Hallucinations                                        | 0*       | -          |
|                                  | Aggression                                            | 0*       | -          |
|                                  | Depression                                            | 3*       | -          |
|                                  | Anxiety                                               | 9*       | -          |
|                                  | Euphoria                                              | 0*       | -          |
|                                  | Apathy                                                | 0*       | -          |
|                                  | Disinhibition                                         | 0*       | -          |
|                                  | Irritability                                          | 0*       | -          |
|                                  | Motor aberrant behavior                                | 0*       | -          |
|                                  | Sleep                                                 | 9*       | -          |
|                                  | Feeding                                               | 3*       | -          |
|                                  | Obsessive-Compulsive behavior                         | 0*       | -          |
|                                  | Phobia                                                | 0*       | -          |

*Number of correct responses.
*Number of errors.
Correct responses in 45".
Frequencies * severity.
Lower Limit of the normal range.
Pathological score.
require an increased attentional load. The Visual Search Test [19] which assesses selective attention, requires individuals to cross out target numbers within distracters; three trials are presented with an increasing number of targets (one, on the first trial, two on the second and three on the thirds). The Patient is very accurate but is not able to perform the tasks within the time limits and the time needed to perform the test increased accordingly to the attentional load (it is shorter in the first trial and longer in the third one).

Visual selective attention and cognitive flexibility in manipulating more than one information at the same time are evaluated through the Trial Making Test A and B, [23,24]. Performance is error-free, but it is affected by a general slowness resulting at the lower limit of the normal range for execution time.

Instead, Star cancellation [25] and other tests of attentional spatial orientation are performed well within the normal ranges.

Altogether these results suggest a dissociation between pathologically slow execution time and within normal range level of performances, confirmed also by the observation that performances in tests without time pressure were all within the normal range (see Table 1).

**Visuo-Constructive and Visuo-Spatial Abilities**

Despite his general motor impairment, the Patient is spared in constructive praxis, assessed by drawing tasks (Constructive Apraxia, [19]). Pictures recognition from fragmented stimuli (assessed by Street Completion Task, [19]) results well within the normal range.

**Short-Term and Long-Term Memory**

Verbal short-term memory, assessed by digit span forward and backward, and visuospatial short-term memory assessed by the Corsi span [19] are both spared.

Long-term memory is assessed through the Italian version of the Auditory Verbal Learning (AVL) and of two short stories [26]. No deficit of long-term memory is evidenced, even if the delayed recall of AVL results at the lower limits of the normal range.

**Language: Production and Understanding**

Spontaneous speech is understandable, informative, correctly structured and appropriate from a pragmatic point of view, despite the presence of dysarthria. Naming on the description is also spared in the Patient [26]. Comprehension of language is tested through a modified version of the Token test [27], in which tokens are substituted by objects [28]. We choose this version because objects being greater than tokens make easier the handling by the Patient, leaving unchanged the contextless understanding for simple and complex orders, which results to be spared in the Patient.

**Emotions Recognition**

Being the impairment in attributing emotional state a well-known symptom of HD [29], we assess the abilities of the Patient to recognize emotions in facial expressions, by using the seminal Ekman’s faces (FACS; [30]). He correctly identifies emotions in only 47.06% of cases for which subjects [30,31] shown 100% concordance in emotion recognition. The patient’s errors are not limited to some types of emotion (for example, positive emotions); furthermore, in about 50% of errors, the Patient named the expression with an emotion that had never been attributed to that expression in the normative Ekman’s sample [31]. For example picture JB1-16 recognized by 100% of controls as disgust is identified by the Patient as an expression of anger (Table 2).

### Table 2: Emotions Recognition (Ekman’s Faces)

| Emotion | Number of errors* | False Recognition** |
|---------|-------------------|---------------------|
| Happiness | 7 | 2 |
| Sadness | 7 | 1 |
| Fear | 9 | 4 |
| Anger | 7 | 3 |
| Surprise | 6 | 9 |
| Disgust | 7 | 3 |

*Considering more than 50% of concordance (Ekman's normative data).
**Considering the wrong attribution of emotional state in 0% of concordance (Ekman's normative data).
Does Late-Onset Huntington Disease Represent a Distinct

Psychiatric Inventory

The patient's daughter underwent the Neuropsychiatric Inventory (NPI, [32]) to assess behavioral and psychiatric disorders. NPI shows the merging of the recent trend of pathological dimensions, such as depression, anxiety, sleep disorders and change in feeding (overeating and compulsive eating), dated from the last two weeks.

Neuroimaging Data

The neuroimaging study was performed using Computed tomography (CT) on a multislice scanner (LightSpeed 64 channel VCT XT, General Electric Healthcare). Brain CT showed a diffuse brain sulcal enlargement, prominent in the frontal and interhemispheric subarachnoid spaces, and, in the temporal lobes, associated with a moderate lateral ventricular system enlargement, symmetrical at the midline. None significant focal lesion, in the cortical and subcortical structures, was observed (Figure 1).

DISCUSSION

First of all, we want to observe that at the moment the Patient is the HD case with the latest onset ever described. His neuropsychological and psychiatric profile, reported in the present study, could be fundamental to integrate previous literature about late-onset HD.

The Patient severe general motor impairment does not seem to affect most of the investigated neuropsychological domains. We observe two selective pathological domains: attribution of emotional state and executive functions when a high level of attentional load is required.

Selective impairment is founded at the level of attribution of emotional state. This is coherent with previous literature about emotion recognition in Huntington Disease [29]: a deficit in the attribution of emotional state characterize HD since the earlier stages of the disease and could be considered as the pathognomonic deficit of different phenotypes of HD, detectable also in pre-manifest HD [33]. In other words, the deficit in the attribution of emotional state may be considered as a symptom detectable since the earlier stages of the disease, shared by both late and juvenile-onset. These results are consistent with the recent work of Snowden and colleagues [6] in which it showed substantial evidence that patients with HD have difficulties in processing facial expressions of emotions, in particular, disgust, even in the preclinical phase.
The Patient shows a small deficit in executive functions when they are assessed by task requiring a high level of attentional load (for example Visual Search and TMT) and high cognitive control. We evidenced a particular trend of performance in the Visual Search test: the Patient made a larger number of errors when a number of the target to cross out increases. Performance in TMT confirms this data. We exclude that worst performance is due to motor impairment, since the pathological performance in another test, such as the Stroop test, does not require any motor control. On the contrary, we propose that the Patient shows a small deficit in a task requiring high attentional load and fine monitoring of performance. We hypothesized that this deficit is the expression of a selective impairment in fine-tuning of resources, necessary to solve the task. According to a developmental model by Anderson [34], the ability of fine-tuning resources is the latest step in the development of executive functions. We hypothesized that the Patient expresses a selective deficit at this level, considering this last step of acquisition the first level to be impaired in HD.

Snowden and colleagues [6] show that one of the earliest changes and the best predictor of disease progression is psychomotor slowing, demonstrated on timed tasks such as Stroop Test, Digit Symbol Substitution and Trail Making Test. Cognitive slowing is found in the "pre-manifest" stages of HD and is reported to be a predictor of functional ability in daily life. Executive deficits in HD include problems in planning, cognitive flexibility, verbal fluency and set-shifting. Memory difficulties occur with poorer performances in free recall than recognition and cued recall, problems in source and prospective memory. Those deficits suggest a strong executive contribution to memory failures. According to these findings, the Patient shows slow execution time in every time pressure task (executive and attentional tasks), within a normal range of level performances.

The deficit in both the attribution of the emotional state and the fine-tuning of the resource are ascribable to the frontostriatal atrophy, evidenced by Computed Tomography (CT).

The Patient is well conscious of the disease and its progression (no anosognosia). Memory functions, both for short-term memory (visuospatial and verbal) and long-term memory, result well within the normal range, as well as language (both for production and understanding) and visuospatial and visuoconstructive abilities.

Psychiatric and behavioral symptoms also occur, even if their progression may not follow a characteristic profile, since subjects could become irritable, aggressive, and their relatives often note restlessness and fidgeting also before the onset [35,36]. Depression is frequent in HD together with psychosis and maniac symptoms [35,37]. Before the onset and full clinical diagnosis, HD subjects often show subtle personality changes, as well as a deficit in cognition and motor control [35,38,39]. This phase is called the presymptomatic phase and could last many years before the onset [38].

Instead, the patient shows no personality changes or any psychiatric disorders. The psychiatric assessment, performed with the Neuropsychiatric Inventory, suggests the merging of a reactive syndrome: Patient's daughter reports depression, in addition to modification of sleep and feeding, together with a higher level of anxiety, date from the last two weeks, probably due to the worsening of motor symptoms and hospitalization.

The Patient description makes possible to shed more light on the cognitive functioning of patients with late-onset of HD. An attempt to define the late-onset HD cognitive profile has been made by Gómez-Tortosa and coworkers [40] who directly compared cognitive profile in Juvenile-onset and late-onset, by means of an extensive neuropsychological battery, evidencing impairments in three different areas defined by the authors as "Prefrontal Functions" (i.e. Executive functions, assessed by Verbal fluencies, Stroop Test, Trial Making Test, Digit span and Symbol Digit Test), "Verbal Memory" (assessed by California Verbal Learning Test) and "Visual Factor" (Rey Complex Figure and Hooper Visual Organization Test). They also assessed Global Cognitive Status by using the Mini-Mental State Examination [41]. Scores from Prefrontal Functions seem to correlate with CAG repeats. At the same time, it was the only factor with greater impairment in juvenile than in the late-onset. Indeed, patients with juvenile-onset seem to be worst than late-onset on Prefrontal Functions, but they were better than the others on visual and verbal memory. Juvenile-onset seems also to have a greater motor deficit. In other words, while the cognitive status of late-onset HD seems to be more generally impaired (global cognitive decline), juvenile-onset HD seems to be impaired due to motor and prefrontal dysfunction. In
late-onset, functional disability depends more on global cognitive status, while in juvenile-onset it depends more on motor and prefrontal deficit [40].

The Patient seems to be spared on most of the cognitive functions examined by neuropsychological assessment, and he was able to find an efficient strategy to cope with deficit. Selective impairment is found at the level of ability to recognize facial emotions, in the presence of completely spared visuoconstructive and spatial abilities.

CONCLUSION

Our description of a late-onset HD Patient may help in understanding the factors determining the age-related variability of symptoms known in HD. Concerning the neuropsychological assessment, the Patient shows only general slowness in executive function tests and deficit in emotion recognition. Interestingly this cognitive profile is not associated with psychiatric disorders, frequently found in patients with HD. These findings may be explained by the late-onset itself of the disease: the neuropsychological profile may be affected primarily in the executive functions and emotion recognition, sparing the other cognitive domains and behavioral functioning, at the difference with juvenile-onset.

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