Theory of mind impairment in Huntington’s disease patients and their relatives

Déficits en teoría de la mente en pacientes con enfermedad de Huntington y sus familiares

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ABSTRACT

Huntington disease (HD) is an autosomal dominant genetic disorder characterized by movement disorders, cognitive impairment, and psychiatric symptoms. Relatives of HD patients experience a great burden as the latter suffer from altered social conduct and deterioration of interpersonal relationships. Theory of mind (ToM) is the ability to attribute mental states (to oneself and others). Deficits in ToM are thought to have a role in the changes in empathy and interpersonal difficulties that HD patients face. Methods: We conducted a cross-sectional study to compare ToM task scores of patients with mild to moderate HD, their relatives (spouse or at-risk first-degree relative with a negative gene test) and controls. Individuals with dementia or depression were excluded. The ToM test battery included Spanish versions of the Reading Mind in the Eyes Test (RMET), Happé’s Strange Stories (Social and Physical Stories subtests) and the Hinting Task. Results: The series comprised 12 HD patients, 12 relatives and 12 controls. The HD patients showed lower affective ToM scores than controls (RMET 19 [3.5] vs 23.9 [2.7], p = 0.016). Cognitive ToM tasks scores were lower in HD patients than controls as well (Happé’s Social Stories 9 [2.6] vs 13 [1.9], p = 0.001; the Hinting Task 13.6 [3.4] vs 17.5 [4.0], p = 0.009). In the Hinting Task, HD relatives had lower scores than controls (13 [3.2] vs 17.5 [4.0], p = 0.009) and similar scores to controls in the rest of the battery. Conclusion: HD patients with mild to moderate disease severity and their relatives show ToM deficits. Keywords: Huntington disease; neuropsychological test; dementia.

RESUMEN

La enfermedad de Huntington (EH) es una enfermedad genética autosómica dominante caracterizada por trastornos del movimiento, deterioro cognitivo y síntomas psiquiátricos. Los familiares de las personas con EH experimentan gran carga dado que los pacientes sufren de conducta social alterada y deterioro de relaciones interpersonales. La Teoría de la mente (ToM) consiste en la habilidad para atribuir estados mentales (a uno mismo o a otros). Se piensa que déficits en ToM tienen un rol en los cambios en empatía y en las dificultades interpersonales que los pacientes con EH enfrentan. Métodos: Condujimos un estudio transversal para comparar el desempeño en puntajes de tareas de ToM en pacientes con EH leve a moderada, sus familiares (pareja o familiar en riesgo con prueba genética negativa) y controles sanos. Se excluyó a sujetos con demencia o depresión. La batería de pruebas de ToM incluyó versiones en español de la prueba de lectura de la mente en los ojos (RMET), Historias Extrañas de Happé (subpruebas Social y Física) y Hinting Task. Resultados: La serie consistió de 12 pacientes con EH, 12 familiares y 12 controles. Los pacientes con EH mostraron puntajes menores de tareas de ToM afectiva que los controles (RMET 19 [3.5] vs 23.9 [2.7], p = 0.016). Los puntajes de tareas de ToM cognitiva fueron inferiores a los controles en los pacientes con EH (Historias Sociales de Happé 9 [2.6] vs 13 [1.9], p = 0.001; Hinting task 13.6 [3.4] vs 17.5 [4.0], p = 0.009). En la Hinting task los familiares de pacientes con EH mostraron puntajes inferiores a los de los controles (13 [3.2] vs 17.5 [4.0], p = 0.009) y puntajes similares a aquellos de los controles en el resto de la batería. Conclusión: Los pacientes con EH con enfermedad leve a moderada y sus familiares muestran déficits en tareas de ToM. Palabras-clave: Enfermedad de Huntington; pruebas neuropsychológicas, demencia.

Huntington disease (HD) is an autosomal dominant genetic disorder characterized by movement disorders, cognitive dysfunction and psychiatric symptoms1. Theory of mind (ToM) is the ability to attribute mental states (beliefs and feelings) to oneself and others, and to understand that others have beliefs and feelings different

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from one’s own point. In clinical practice, ToM is evaluated using neuropsychological tasks, and these tasks are further classified as “affective ToM” (evaluates beliefs about feelings) and “cognitive ToM” (evaluates beliefs about beliefs). Affective ToM is thought to be mediated mainly by the ventromedial prefrontal cortex, whereas cognitive ToM appears to be mediated by the prefrontal cortex as a whole. The ToM deficits have been shown to be present in HD in both cognitive and affective modalities.

Relatives of HD patients experience a great burden as the patients suffer from social conduct and interpersonal relationship deterioration. Deficits in ToM are thought to play a role in the changes in empathy and interpersonal difficulties that HD patients face.

METHODS

We conducted a cross-sectional study to compare ToM task scores of patients with mild-to-moderate HD, their relatives (spouse or at-risk first-degree relative with a negative gene test) and unrelated healthy controls.

Participants

Twelve consecutive HD patients from our outpatient clinic with a confirmed diagnosis by direct mutation analysis of the number of CAG repeats (four males, eight females) were included. The relatives accompanying the HD patients were invited to participate; 12 were included (nine gene-negative at-risk individuals and three spouses). Twelve unrelated individuals were paired by age and education with the HD patients. Clinical and epidemiological data were collected. We excluded individuals with dementia, depression (Center for Epidemiological Studies – depression scale score > 16), or those unable to read or unwilling to give their informed consent. The local research and ethics committees reviewed and approved the protocol. The research project complied with the requirements of the Declaration of Helsinki as revised in Fortaleza, Brazil, 2013. The participants’ confidentiality was preserved.

Instruments

Disease severity and motor dysfunction

The severity of HD was assessed using the Total Functional Capacity (TFC) scale, which evaluates the ability to work, handle finances, perform domestic chores, live independently and self-care tasks. The TFC categorizes a functionality deficit as mild (TFC = 10–13) or moderate (TFC = 7–9). Motor dysfunction was evaluated with the Unified Huntington’s Disease Rating Scale (UHDRS). It is used. Cognitive ToM

Cognitive ToM was assessed with the Reading the Mind in the Eyes Test (RMET). This test comprises a portfolio of 36 pictures of a person’s gaze associated with a feeling or thought. For each picture the participant chooses one feeling/thought option (out of four) that best fits. A score of 1 is given for correct choices and 0 for incorrect ones. The Castilian Spanish version of the RMET for adults was from the Autism Research Centre website and adapted into Mexican Spanish.

Affective ToM

Affective ToM was assessed with the Reading the Mind in the Eyes Test (RMET). This test comprises a portfolio of 36 pictures of a person’s gaze associated with a feeling or thought. For each picture the participant chooses one feeling/thought option (out of four) that best fits. A score of 1 is given for correct choices and 0 for incorrect ones. The Castilian Spanish version of the RMET for adults was from the Autism Research Centre website and adapted into Mexican Spanish.

Statistical analysis

Descriptive statistics are presented in medians and interquartile ranges, percentages and absolute numbers. Inferential statistics were performed in categorical variables with the chi square test and in quantitative variables with the Friedman test. To test for correlation, Spearman’s method was used. Significant differences were considered at p < 0.05. Computing was performed in R package version 3.4. Charts were generated in R using the ggplot2 library.

RESULTS

This series comprised 36 participants allocated to three groups: 12 HD patients, 12 HD relatives and 12 healthy, unrelated controls. The series comprised young and middle age adults, predominantly women with a median 15.5 (IQR 5) years of education. There was no significant difference among the groups’ participant age, proportion of sexes or years of education (Table).
The HD group functionality, according to the TFC scores, was preserved in seven patients, mildly affected in three and moderately in two. Nine patients had involuntary movements with a median evolution of 6.8 (IQR 6.1) years. Four patients were taking antidepressants and one was also taking olanzapine. The TFC scores correlated positively with the MoCA scores (Spearman’s rho = 0.636, p < 0.05) and negatively with the UHDRS (Spearman’s rho = -0.789, p < 0.01), (Table).

Neuropsychological assessment

Montreal cognitive assessment

The MoCA scores were not significantly different among groups (Table), although 7/12 HD patients presented with mild cognitive impairment (MoCa score < 26 points). The MoCa scores did not correlate with education across groups (Spearman’s rho = 0.08, p = 0.65).

Pictures of facial affection

The POFA scores among groups showed no differences (Table). No selective emotion recognition deficit was found in HD patients. Whole-series POFA scores showed a positive correlation with scores of the RMET (Spearman’s rho = 0.472, p = 0.003).

Theory of mind tasks

Affective ToM

The RMET scores were lower in HD patients than those of HD relatives and controls (19 [3.5] vs 24.5 [3.7] vs 23.9 [7.2], p = 0.016) (Table and Figure).

Cognitive ToM

The HD patients had lower scores than controls in the Happé’s Social Stories subtest (9 [2.6] vs 12.5 [1.9], p = 0.001), while Happé’s Physical Stories scores showed no significant difference among the groups. Happé’s Social Stories subtest scores negatively correlated with the UHDRS scores (Spearman’s rho = 0.753, p = 0.005). The Hinting Task scores were significantly lower in HD patients and HD relatives than in controls (13.6 [3.4] vs 13 [3.2] vs 17.5 [4.0], p = 0.009).

Across groups, cognitive ToM tasks and MoCa scores were positively correlated with Happé’s Social Stories (Spearman’s rho = 0.336, p = 0.04), Happé’s Physical Stories (Spearman’s rho = 0.328, p = 0.04), as well as the Hinting Task (Spearman’s rho = 0.516, p = 0.001).

DISCUSSION

HD patients with mild to moderate disease severity showed impaired performance in affective ToM tasks (RMET) and cognitive ToM tasks (Happé’s Social Stories and Hinting Task). This finding has previously been reported in HD patients performing related tasks. Because our HD patients had a mild-to-moderate disease and no statistically significant lower MoCA or POFA scores, ToM tasks score may represent an early marker of dysfunction in HD. A previously-reported correlation between RMET and MoCA scores in HD patients was not replicated in this study. This may be explained by an even lower severity of disease in terms of functionality and motor impairment in our series. These findings need to be confirmed in a larger series, as ToM tasks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD patients</th>
<th>HD relatives</th>
<th>Controls</th>
<th>p-value</th>
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<tr>
<td>N</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Sex: Female (%)</td>
<td>8 (67%)</td>
<td>7 (58%)</td>
<td>9 (75%)</td>
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<tr>
<td>Age in years, median (IQR)</td>
<td>42.7 (11.3)</td>
<td>44.7 (22.3)</td>
<td>37.1 (15.8)</td>
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<td>Years of education</td>
<td>16.0 (5.0)</td>
<td>16 (6.2)</td>
<td>14.5 (7.5)</td>
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</tr>
<tr>
<td>TFC Score</td>
<td>13.5 (1.2)</td>
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<td></td>
<td></td>
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<tr>
<td>UHDRS motor score</td>
<td>12.5 (11.0)</td>
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<td>Neuropsychological assessment</td>
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<tr>
<td>MoCA</td>
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<td>27.0 (1.0)</td>
<td>28.5 (1.5)</td>
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<td>24.5 (3.7)</td>
<td>24 (2.7)</td>
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<tr>
<td>Happé’s Strange Stories total</td>
<td>15.2 (6.3)</td>
<td>20.2 (5.5)</td>
<td>23.9 (7.2)</td>
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<tr>
<td>Happé's Social Stories</td>
<td>9 (2.6) *</td>
<td>10.7 (2.7)</td>
<td>12.5 (1.9)</td>
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<tr>
<td>Happé’s Physical Stories</td>
<td>7.2 (4.9)</td>
<td>9.2 (4.6)</td>
<td>9.9 (4.3)</td>
<td>0.132</td>
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<td>Hinting Task</td>
<td>13.6 (3.4)</td>
<td>13 (3.2)</td>
<td>17.5 (4.0)*</td>
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</table>

Absolute values and percentage (for sex distribution) or medians ± interquartile range (IQR; for all other variables) are shown. Chi square and Friedman test significance (p) values. ToM: Theory of Mind; TFC: Total functionality score; UHDRS: Unified Huntington’s disease rating scale; MoCA: Montreal cognitive assessment; POFA: Pictures of facial affection; RMET: Reading the mind in the eyes test. *statistically significant difference.
may have a relevant role in tracking HD progression and correlate with frontal lobe dysfunction.

The HD relatives showed dysfunction in cognitive but not in affective ToM and had a similar performance to controls in the rest of the tests. Similarly, ToM deficits in first degree relatives of schizophrenia patients have been reported. The ToM dysfunction may be related either to a genetic trait or an effect of family interaction with HD patients, and requires validation. Limitations of this study are the small sample size and type 1 error, and that the test versions used were not validated translations. Further study in this area may help clarify the particular social difficulties HD families face and may be relevant in genetic counseling.

To our knowledge, this is the first study assessing ToM performance in Latin American HD patients and their relatives. These findings suggest a role of ToM testing in the early cognitive profile and social and family interaction of HD patients and these may parallel those found in schizophrenia and their relatives.

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**References**


