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Importance of psychiatric examination in predictive genetic testing for Huntington disease

Znaczenie badania psychiatrycznego w predykcyjnych badaniach genetycznych w kierunku choroby Huntingtona

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Abstract

Background and purpose: Huntington disease (HD) is an autosomal dominant hereditary neurodegenerative disease with multiplication of CAG triplet in the short arm of chromosome 4, manifested by motor symptoms, cognitive dysfunction progressing to dementia, and various types of neuropsychiatric disorders. The diagnosis of HD is confirmed by a genetic test, which may also be carried out presymptomatically.
Material and methods: We studied differences in psychiatric examination and psychometric measures among the 52 people at risk of HD, who were recommended to postpone or to continue in the predictive protocol. In addition to the psychiatric examination, we administered the Eysenck Personality Questionnaire (EPQ-A), the Symptom Checklist 90 (SCL-90), and quality of life questionnaire (MANSA).
Results: People at risk of HD with the recommended test postponement showed lower rate of neuroticism and EPQ-A lie score, higher values on the phobia and the so-called 'positive symptom distress index' in SCL-90 and lower quality of life than people at risk of HD with the recommendation to continue.
Conclusions: Our results indicate that the formalized testing does not bring significant information whereas the clinical

Streszczenie

Wstęp i cel pracy: Choroba Huntingtona (ChH) jest dziedziczoną autosomalnie dominująco chorobą zwyrodnieniową układu nerwowego ze zwiększoną liczbą powtórzeń trypletów CAG na krótkim ramieniu chromosomu 4. Manifestuje się zaburzeniami ruchowymi, zaburzeniami poznawczymi postępującymi do otępienia oraz rozmaitymi zaburzeniami neuropsychiatrycznymi. Rozpoznanie ChH jest potwierdzane badaniem genetycznym, które może być wykonywane również u osób przed wystąpieniem objawów klinicznych.
Materiał i metody: Autorzy oceniali różnice w zakresie wyników badania psychiatrycznego i miar psychometrycznych wśród 52 osób zagrożonych rozwojem ChH, u których zalecano kontynuowanie lub odroczenie postępowania zmierzającego do wykonania badania genetycznego. Oprócz badania stanu psychicznego stosowano *Eysenck Personality Questionnaire* (EPQ-A), *Symptom Checklist 90* (SCL-90) oraz kwestionariusz oceniający jakość życia (MANSA).
Wyniki: Osoby zagrożone wystąpieniem ChH, u których zalecano odroczenie badania genetycznego, uzyskiwały mniejszą punktację w skali Neurotyzmu i Kłamstw EPQ-A, większą punktację w skali oceny fobii i tzw. dodatniego wskaźnika obciążenia objawami w SCL-90, a także miały gorszą

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psychiatric examination remains the main decisive factor in the recommendation to perform a predictive genetic test. The motivation of applicants is considered as the most important factor in the decision-making proces.

Key words: Huntington disease, predictive genetic test, people at risk.

jakość życia niż osoby zagrożone ChH, u których zalecano kontynuowanie procedury zmierzającej do wykonania badania genetycznego.

Wnioski: Uzyskane wyniki wskazują, że sformalizowana ocena nie dostarcza istotnych informacji, podczas gdy kliniczne badanie psychiatryczne pozostaje głównym czynnikiem decydującym o zalecaniu wykonania badania genetycznego. Najważniejszym czynnikiem w podejmowaniu decyzji jest motywacja osób zgłaszających się na badanie.

Słowa kluczowe: choroba Huntingtona, predykcyjne badania genetyczne, osoby obciążone ryzykiem.

Introduction

Huntington disease (HD) is an autosomal dominant hereditary neurodegenerative disease with multiplication of CAG triplet in the short arm of chromosome 4 [1], manifested by motor symptoms (chorea, dystonia, postural instability and voluntary movements impairment are typical in particular), cognitive dysfunction progressing to dementia, and various types of neuropsychiatric disorders (behavioral, affective, etc.). Since 1993, this mutation can be determined in both patients and 'people at risk' of HD (PAR). People at risk are immediate offsprings or siblings of patients or persons tested positive for HD.

The information on carrier status is burdened with a high stress level and serious consequences for further quality of life: the disease is incurable and causes progressing devastation of the motor and mental status, entails 50% hereditary risk for the next generation, and last but not least, it also has multiple negative impacts on 'healthy' family members. Presymptomatic testing related to this fatal diagnosis is thus associated with many ethical problems [2,3].

An international protocol-based presymptomatic testing procedure has been designed with the aim to minimise the disastrous consequences [4], which includes several genetic consultations and neurological, psychological and psychiatric examinations. Individual sessions are aimed at providing a detailed introduction of the disease and the testing procedure to the applicant, and subsequently at verifying his/her insight in the issue, clarifying his/her motivation and benefit of the test, and last but not least, at determining the applicant's adaptation mechanisms to burdensome situations. The entire process of the predictive protocol reduces the risk of suicidality considerably [5]; however, without eliminating it. Short-term and long-term consequences of predictive testing have been dealt with in many studies [5-14].

Physicians may not forbid the applicant to do the predictive test as per the protocol; however, they may recommend its postponement. Besides clear contraindications such as suicidality and depression, a whole number of other situations may arise whose importance is determined on quite a subjective basis though, depending on the personality of the given psychiatrist (for example, willingness to accept risk versus preference of a totally formal attitude with no personal engagement of the examining person). As a rule, the psychiatrist recommendation to continue or postpone the test stems only from clinical experience. The most important role in this respect is probably played by the motivation of the PAR or its absence or vagueness, respectively; furthermore by their personality structure, maturity, adaptation mechanisms, duration of HD awareness and knowledge of the issue, quality of their background and other factors.

Many years of experience with the predictive protocol at many centres worldwide show that the implementation rate of the genetic test in PAR is relatively low, ranging between 5% and 25% in various countries [15-21].

The aim of our work is to characterize the differences in psychiatric examination and psychometric measures between PAR who were recommended to postpone the test, and persons at risk who were recommended to continue the predictive protocol. Our results could have an additional value for those psychiatrists who are less experienced or educated in complex assessment of PAR in the process in predictive protocol.

Material and methods

In total, 162 persons at risk of HD asked for the predictive test between 2003 and 2009. The persons were

acquainted with the protocol procedure based on the international recommendation [4] and started undergoing individual examinations performed by our multidisciplinary team.

Out of this number, 52 persons (32 women, 20 men, mean age 33 years, standard deviation [SD] 8.8 years, range: 20-57 years) followed the protocol as far as to undergo the psychiatric examination, which is its final part.

The fundamental psychiatric examination includes a structured questionnaire defined by the international protocol and related particularly to the HD knowledge, motivational questions and adaptation mechanisms, as well as common clinical exploration of medical history and psychopathology with subsequent elaboration of an objective finding. In our study, the applicants were moreover examined also using Eysenck Personality Questionnaire (EPQ-A) [22] in order to capture basic personality characteristics, and the self-assessment The Symptom Checklist 90 (SCL-90) [23]. Finally, the applicants completed the Quality of Life Questionnaire (MANSA) [24]. Further testing was not bearable due to the overall duration of the examination (duration of approx. 3-4 hours). Recommendations concerning further procedure in the preparatory protocol were provided based on the clinical examination; the tests were analysed ex post.

Out of 52 PAR who asked for the presymptomatic test, postponement was recommended to 11 applicants (5 men and 6 women) (group C); out of the remaining 41 individuals, 19 were tested subsequently with positive results (group A), i.e. the mutation was confirmed, and the gene carrier status was excluded in 22 persons (group B). Essential characteristics of individual groups are shown in Table 1. Twenty-five from 41 (61%) tested PAR, and 4 from 11 (36.4%) PAR with recommended postponement had children.

The results were statistically processed using the non-parametric Mann-Whitney test or the Kolmogorov-Smirnov test.

Results

Persons at risk with recommended postponement of the test showed statistically significantly higher neuroticism level; however, also a significantly lower EPQ-A lie score than persons who were recommended to continue the test – see Table 2.

As for the General Psychopathology Scale (SCL-90), PAR with recommended postponement of the test showed significantly higher values only for the phobia scale and for the so called 'positive symptom distress

Table 1. Demographic data of studied patients at risk (PAR)

	PAR tested positive later	PAR tested negative later	PAR with recommended postponement
Number	19	22	11
Sex (women/men)	11/8	15/7	6/5
Age [years]; mean ± SD	32.9 ± 7.6	34.6 ± 9.3	30 ± 9.9
Age [years]; range	21-57	22-57	20-49
Education [years]; > 12/ < 12	15/4	19/3	10/1
Partnership [yes/no]	15/4	20/2	9/2
Children [yes/no]	12/7	13/9	4/7

PAR – 'people at risk' of HD, SD – standard deviation

Table 2. Results of Eysenck Personality Questionnaire (EPQ) in patients at risk group with recommended continuation of the test compared to the group with recommended postponement

	Mean of tested patients at risk (group A + B)	Mean of patients at risk with postponement (group C)	*p* value
EPQ-N	7.53	11.09	0.019
EPQ-E	10.70	11.36	0.34
EPQ-L	5.19	3.81	0.014

EPQ-N – neuroticism subscore, EPQ-E – extraversion subscore, EPQ-L – lie score
Group A – individuals tested positive later, group B – individuals tested negative later

index' that characterizes mean seriousness of a symptom – see Table 3. Persons with recommended postponement of the test showed statistically significantly lower quality of life based on MANSA scale than PAR who continued the test.

The listing of specific reasons that led to the recommendation of postponing the genetic test in 11 PAR is shown in Table 4.

Discussion

The predictive protocol represents not only stress and difficult decisions for PAR; it is also a heavy burden of responsibility and making decisions for the medical team found in a dilemma of respecting the autonomy and preferring the benefit for PAR [8,25]. A lot of studies have been done dealing with the issue of predictive testing and PAR problems. However, most of them take into account particularly incipient subclinical prediagnostic markers of the disease and their progression [26,27]. Another large group of studies focuses on the PAR dilemma in its entire complexity [2,8,25,28-32]. However, according to our knowledge, no studies have been elaborated, which would discuss the dilemmas of professionals and offer possibilities of an optimal procedure in non-standard or atypical PAR.

The psychiatrist decision of recommending the genetic test or its postponement is often very difficult, burdened with a certain level of doubts inside of the physician whether he/she has made the right decision. Formalized procedures and scopes of examination show significant differences at individual centres. Some facts that provide evidence of the need to postpone the genetic test are apparent – depression, suicidal ideation, paralyzing anxiety, or asking for the test due to external pressure without feeling any need inside [4]. Some centres where the predictive protocol has been implemented stem only from these few minimal non-surpassable criteria and all the other parameters are omitted. Lower risks and consequences fall entirely in the PAR competences and making an intervention in them is viewed as an intervention in the PAR's autonomy.

On the contrary, other centres including ours undertake a much more global evaluation of the PAR's status in the deciding process, while an assessment and feedback for the PAR are deemed to be a mandatory part of the whole protocol, which obviously includes an overall evaluation of the psychopathological and further clinical finding, of the social context, adaptation mechanisms and in particular, motivation for undergoing the test.

However, even an experienced psychiatrist may doubt his/her own decision. The psychiatrist's surety could be

Table 3. Results of General Psychopathology Scale (SCL-90) in patients at risk with recommended continuation of the test compared to the group with recommended postponement

	Mean ± SD (A + B)	Median ± IQR (A + B)	Mean ± SD (C)	Median ± IQR (C)	*p* value
GSI	37.21 ± 23.83	34.00 ± 25.25	59.82 ± 47.33	49.00 ± 37.75	0.114
PST	27.68 ± 14.28	28.00 ± 17.50	37.54 ± 22.15	38.00 ± 29.75	0.197
PSDI	1.32 ± 0.27	1.22 ± 0.29	1.47 ± 0.30	1.36 ± 0.28	0.028
SCL-90 subscores					
Somatisation	4.66 ± 3.88	5.00 ± 6.00	6.82 ± 7.05	4.00 ± 8.50	0.620
Obsession-compulsion	8.05 ± 4.42	7.00 ± 5.25	10.18 ± 6.00	10.00 ± 9.50	0.305
Interpersonal sensitivity	4.93 ± 4.08	4.00 ± 6.00	7.73 ± 6.74	5.00 ± 6.75	0.219
Depression	5.68 ± 5.06	4.00 ± 6.00	9.73 ± 8.40	8.00 ± 8.75	0.112
Anxiety	4.07 ± 3.33	3.00 ± 3.25	6.18 ± 6.66	3.00 ± 2.00	0.504
Anger-hostility	1.76 ± 1.97	1.00 ± 1.25	3.82 ± 4.85	2.00 ± 2.75	0.149
Phobia	1.20 ± 1.33	1.00 ± 2.00	3.18 ± 3.03	2.00 ± 3.75	0.013
Paranoidity	2.54 ± 2.42	2.00 ± 2.00	4.18 ± 4.51	2.00 ± 6.00	0.499
Psychoticism	1.68 ± 2.35	1.00 ± 2.00	3.36 ± 4.25	1.00 ± 5.75	0.465

GSI – overall score of SCL-90 scale, PST – number of items with non-zero scores, PSDI – total score/PST, A – individuals tested positive later, B – individuals tested negative later, SD – standard deviation, median A + B – median value in the group recommended to continue the test, IQR – interquartile range, C – individuals with recommended postponement

Table 4. Specific reasons for recommending presymptomatic test postponement in 11 applicants

Sex, age	Reasons for recommending postponement
♀33	Has an identical twin who does not want to know the result
	Protracted partnership problems with high probability of separation if the result is positive
	Insufficient further background (cold relationships with the parents)
	Reduced adaptation mechanisms; repeated need of psychological care in burdensome situations in the medical history
	Expectation of a 'favourable' test result that will solve all other problems
	Tenacious effort to avoid standard psychological examination in the protocol (attempt at its replacement with a vague report of a psychologist of the applicant's workplace)
♂31	Obtaining a clearly favourable result is the main motivation; 'certainty of being healthy'
	Considers a possibility of not testing himself but the foetus – 'if the foetus tests negative, a hope would remain'
	The test and considerations in respect of a future descendant have not been consulted with the partner
	Nonverbal manifestations indicate that he actually does not want any test
♀38	Insufficient background: Anomalous personality of the husband incapable of being confronted with HD, unable to provide support
♂49	An effort to meet the son's wish is the only motivation
	Massive pressure on part of the family
	Insufficient knowledge of HD
	Presence of psychopathology requiring medication (dysthymia)
♀22	'Unconvincing' motivation
	Elevated risk level that the initial stage may be present – benefit of the result for the future should be clarified
♂29	Current diagnosis of generalized anxiety disorder in a predisposed personality – priority need of treatment
	The utterance indicates that the applicant actually is not interested in the test; his major need consists in clarifying his current problems
♂21	Insufficient information about HD; non-clarified motivation
	HD tabuised by the mother (burden on part of the father) causing that the mother is not informed about the son's test either
	The mother would most likely not be able to deal with a positive result and would not be able to provide support; on the contrary, she would increase the stress level unbearably
♂22	Non-clarified motivation
	Clear expectation of a favourable result combined with immature and neurotic personality disposition
	Reduced adaptation mechanisms
	Absolute absence of any benefit of information on positivity
	Plans for the future quite independent of the result
	Questionable background
♀43	Debatable adaptation mechanisms
	Controversial ability of support on part of the husband
	Side diagnosis of premenstrual syndrome
	Recommendation of postponement was suggested only as one of the possibilities – and was welcome by the applicant herself

Table 4. Cont.

Sex, age	Reasons for recommending postponement
♀20	Absence of personal experience with HD and at the same time, vehement refusal of personal confrontation with HD and of obtaining information
	Short time of awareness of HD existence in the family
	Progressing psychosomatic problems with impaired social functioning, together with puzzling minimal effort to solve the problems
	Need of proper diagnostics of psychosomatic problems and subsequent therapy
	Very vague motivation to undergo the test
	Markedly immature personality with impaired adaptation mechanisms
	Problematic relationship with the partner
♀22	Suspected initial stage of the disease – the test is motivated by an effort to determine the cause of the current problems
	At the same time, fear of the results, would like to keep some hope – asking for the test due to the pressure of external circumstances (problems at work due to initial symptoms)
	Visible relief when a possibility to solve the situation is proposed which does not necessitate the test

♀ female; ♂ male; HD – Huntington disease

enhanced by obtaining additional arguments having the role of warning or positive signals that the consequences of the genetic test are managed, and which in our opinion could reduce the subjective nature of his/her decision. This is why we tried to seek such indicators using our preset battery of scales and tests mapping psychopathological symptoms of the whole spectrum and the personality.

The aim of the psychiatric examination in the predictive protocol is to assess the HD knowledge, preparedness for an adverse outcome, adaptative mechanisms, as well as present and potentially high-risk psychopathology. The tests we selected were targeted at related characteristics, i.e. personality (EPQ-A), general psychopathology (SCL-90) and the quality of life (MANSA).

Our results indicate that the PAR group with postponement differs from the group undergoing the test only in a higher level of neuroticism and on the contrary, in a lower lie score, higher distress and higher score of the phobia scale.

Specific reasons were highly diverse and individual in our 11 PAR with recommended postponement, and thus cannot be capture using a unified scale battery. No one of them strictly fulfilled the given contraindications authorizing to refuse the test; only postponement was recommended in all of them, while its reasons were discussed in detail with the PAR. In a certain way, it was surprising that all 11 PAR accepted the recommendation and no one of them insisted on performing the test. For our part, it was not a strict recommendation or order to postpone the test; it was only a warning concerning risk factors found that were discussed in detail in the final interview with PAR. The decision was always up to PAR.

Problematic motivation was the most significant reason (7 cases) for postponing the test; furthermore, insufficient background and absence of support occurred in 5 cases, and impaired adaptation mechanisms in 4 cases. Assessing the motivation is very difficult: Quite an identical answer (usually 'I just want to know in order to plan my things accordingly') has quite a different meaning in various PAR based on their personality structures and the overall context of the life situations.

These reasons were captured by the psychiatric examination and showed no convincing correlate in the tests performed. Higher neuroticism found in EPQ-N, higher overall distress and higher phobia score in SCL are considered as secondary consequences of the individual reasons for postponement detected by us. However, these pathological scores cannot be used to make opposite deductions, i.e. the finding itself of increased neuroticism or distress need not indicate presence of a serious reason to postpone the test.

The reasons explaining superiority of the psychiatric examination conclusions over the data obtained using the scale battery may be as follows: (1) the test battery chosen by us is not sufficiently sensitive or is not capable of encompassing the decisive factors; (2) factors important in the deciding process regarding the test are not scalable – and neither our chosen ones nor other

scaling and testing methods capture the complexity of life, inner motives and their connectedness with the social context and possibly psychopathology; this broad context can be understood only by clinical examination and cannot be replaced with scaling even if extensive; (3) highly speculative alternative explanation might stem from the determination of a lower lie score in PAR with recommended postponement (persons with a higher lie score, i.e. with better self-presentation and higher censorship of psychological difficulties would 'pass' through the preparation); (4) if the testing fails to provide objective warning signs and the psychiatrist evaluation is burdened with a significant subjectivity level, it is possible that the psychiatrist recommendation to postpone or continue the protocol has no significant value and the postponement may be indicated needlessly; this explanation was contradicted by 100% acceptance of the recommendation in our set – none of the probands was 'forbidden' to pass the test, and all of them were only informed of the reasons why we deemed the postponement to be a more advantageous choice.

It was a shortcoming of our study that we also had not obtained data in the post-test period. This was due to low PAR compliance, their unwillingness to take part in examinations during this period, as well as the need to travel long distances (during the study, predictive testing was only conducted in one centre in the Czech Republic). Another shortcoming of the study was the selection of psychometric tests in 2002, which would now be constructed differently, based on new knowledge.

Regarding the quality of life measured using MANSA scale, we found that PAR with recommended test postponement showed a significantly worse quality of life than PAR who continued the test. In our opinion, this finding is in accordance with some specific reasons for recommending postponement (insufficient social background, partnership issues, etc.). The Quality of Life Questionnaire is the only one of all the scales applied that is related to multiple areas forming the applicant's life, and thus it is the only scale used in our research that may grasp in a certain extent the complexity of evaluation within the framework of the psychiatric examination.

In our opinion, the quality of life accurately reflects the degree of distress during decision making. It is an important supporting argument for appropriate timing of the test. Within the subsequent communication of an adverse test result, the accumulation of more life stressors represents higher risks for a breakdown in the adaptative mechanisms.

Conclusions

1. The results of our study indicate that formalized psychological testing (taking the form of our battery at the minimum) in prediction of the recommendation to perform the genetic test or to postpone the test provides no significant information.
2. Clinical psychiatrist examination remains the decisive factor in the process of indicating or postponing the predictive genetic HD test.
3. Motivation of the applicant is considered by us to be one of the most important factors in the deciding process, which cannot be assessed by a scaling' procedure.

Disclosure

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Authors report no conflict of interest.

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