Chapter 3

Adverse childhood experiences of persons at risk for Huntington's disease or BRCA1/2 hereditary breast/ovarian cancer

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Abstract

Introduction

Huntington's disease (HD) is known to have a negative impact on family life. Offspring of HD patients may be exposed to adversity in childhood because of the parent's disease and its psychological consequences. BRCA1/2 Hereditary Breast and Ovarian Cancer (BRCA1/2) increases the risk for offspring of being exposed to parental disease or loss. Childhood adversity is associated with psychopathology and various other problems in later life.

Methods

Adverse childhood experiences (ACEs) before age 16 were assessed in adults at 50% risk for HD (*n* = 74) or BRCA1/2 (*n* = 82) and in controls (*n* = 101), using the Negative Life Events Scale. Mean number and occurrence of ACEs were compared between groups.

Results

The odds of having experienced adversity in childhood were higher in HD offspring and BRCA1/2 offspring than in controls. HD offspring reported a higher mean number of ACEs than controls or BRCA1/2 offspring. In HD offspring, the prevalence of parental disease and parental dysfunction experienced before age 16 was higher than in controls. In BRCA1/2 offspring, parental loss before age 16 was higher than in controls.

Discussion

This study indicates that 53% of HD offspring and 45% of BRCA1/2 offspring are exposed to adversity in childhood or adolescence. The relevance of these findings for counseling in predictive testing programs, reproductive decision-making, and child rearing matters is discussed.

Introduction

Huntington's disease (HD) and *BRCA1/2* Hereditary Breast and Ovarian Cancer (BRCA1/2) are late onset, autosomal dominant hereditary disorders. The disease process of both HD and BRCA1/2 generally starts in mid-adulthood, a period of the life cycle where many people raise children. Offspring of HD or BRCA1/2 patients may therefore be exposed to serious parental disease at a young age. Family dynamics are likely to be negatively influenced by the parent's disease process, and offspring of persons with HD or BRCA1/2 may be exposed to adverse childhood experiences (ACEs). Exposure to ACEs, such as physical or psychiatric disease of a parent, loss of a parent, domestic violence, or abuse, is strongly associated with psychopathology, particularly mood and anxiety disorders, in children and adults.[1,2] ACEs may cause alterations in a child's perceptions of self and others and may have neurobiological and psychiatric consequences, increasing the risk for personal, social, and emotional difficulties throughout life.[1-3]

HD is a fully penetrant progressive neurodegenerative genetic disorder, associated with motor, cognitive, and psychiatric disturbances.[4] The mean age of onset of HD is between 30 and 50 years, and the mean duration of the disease is 17–20 years.[5] There is no cure for HD; the disease leads to increasing dependency and finally death.[5] Psychiatric symptoms, such as depressed mood, irritability, and apathy, occur frequently in HD.[6] HD patients and their relatives perceive psychiatric symptoms in particular as distressing.[7,8] Given the clinical characteristics of HD, it can be argued that offspring of a parent with HD are more likely to experience chronic disease or death of a parent in childhood or adolescence, compared to the general population. HD affects family life considerably.[9-12] Offspring of a parent with HD report high levels of conflict and low levels of cohesiveness and expressiveness (i.e., the extent to which family members are encouraged to express their feelings directly) in their families.[12] There is a higher chance of dysfunctional parenting, such as overcontrol and abuse, of both the affected and the unaffected parent.[12] Depression or other psychiatric symptoms associated with HD may interfere with the parents' sensitivity to the needs of their children and with their ability to create a secure emotional environment.[13] Psychiatric disorders of parents are associated with an increased risk of psychological and developmental difficulties in their children.[14] Offspring may be at risk of developing an insecure attachment style, which is associated with various negative outcomes throughout life.[3]

BRCA1 or *BRCA2* Hereditary Breast and Ovarian Cancer is a partially penetrant genetic cancer predisposition syndrome associated with breast cancer and ovarian cancer, as well as other cancers. The risk of developing cancer is variable. For female carriers, before age 60, the risk of breast cancer is 58% (*BRCA1*) or 48% (*BRCA2*) and the risk of ovarian cancer is 40% (*BRCA1*) or 6% (*BRCA2*).[15] For male carriers, the lifetime risk of breast cancer is ~1% (*BRCA1*) or 7% (*BRCA2*); compared to the general population, the risk of prostate cancer is double (*BRCA1*, men under

65) or up to sevenfold (*BRCA2*). In addition, the risks of pancreatic, gastric and hematologic cancers have also been reported to be higher in *BRCA* carriers than in non-carriers.[16] Given these risks, it can be argued that offspring of *BRCA1/2* mutation carriers are more likely to be exposed to parental cancer or death of a parent in childhood or adolescence, compared to the general population.

A subgroup of individuals at risk for HD or BRCA1/2 presents for predictive mutation testing. During the process of testing and receiving test results, ACEs related to the parent's disease process may be reactivated in test applicants, because experiences with affected relatives will be part of psychological assessment and counseling.[17] As childhood adversity predisposes for increased vulnerability to stressful life events in adulthood,[18] individuals who experienced ACEs may be especially vulnerable to the negative effects of this stressful period and may be at risk for maladaptive reactions to testing. ACEs may also play a role in family planning for couples where one partner is at risk for HD or BRCA1/2, or is a mutation carrier. Couples may reflect on reproductive decisions and future family life using disease-related childhood experiences of the at risk spouse.

The aim of this paper is to explore ACEs experienced before age 16, as reported by adult persons at 50% risk for HD or BRCA1/2. We expect adult HD offspring and BRCA1/2 offspring to report more ACEs, compared to a group of persons with a negative family history for HD or BRCA1/2. Given the complex symptomatology of HD, in particular the presence of behavioral and psychiatric symptoms, we expect to find more ACEs in HD offspring than in BRCA1/2 offspring.

Materials and Methods

Participants

Persons who applied for predictive testing for HD or BRCA1/2 in the Department of Clinical Genetics of the Leiden University Medical Center in Leiden, The Netherlands (January 2008 – December 2010), or in the Department of Clinical Genetics of the Erasmus Medical Center in Rotterdam, The Netherlands (January 2009 – December 2009), were asked to participate in the study. Inclusion criteria were being at 50% risk for HD or BRCA1/2 and being ≥ 18 and ≤ 65 years of age. Partners of persons who applied for predictive testing were asked to participate as controls, i.e., persons with a negative family history for HD or BRCA1/2. Participants were recruited after intake for predictive testing.

The study was reviewed and approved by the Medical Ethics Committees of both participating hospitals.

Instruments

After informed consent, participants received a coded booklet with questionnaires on demographic data and ACEs, which they were asked to complete and return within 2 weeks.

A custom made questionnaire was used to gather demographic data (sex, age, marital status, educational level, paternal or maternal transmission of risk, parent affected or not, age of participant at parental disease onset, parent's year of birth, parent's year of death).

ACEs were assessed using the Negative Life Events Scale (NLES).[19] This 19-item self-report checklist measures negative life events concerning self or significant others, such as death of someone close, parental divorce, and abuse experiences, in three periods of life (before age 16; between age 16 and 1 year before assessment; the year before assessment). This study focuses on events associated with parents and family life, before age 16. Three thematic clusters of events were composed and analyzed in this study: parental dysfunction (psychiatric problems of parent, domestic violence, alcohol or drug abuse, suicide attempt of parent), parental loss (death of parent, divorce of parents), and abuse (sexual abuse, physical abuse). With these clusters, more light may be shed on the differential impact of HD and BRCA1/2 on offspring's childhood and adolescence.

Statistical analysis

Data were analyzed with SSPS 17.0 software, using *t*-tests to compare the mean number of ACEs between groups, and logistic regression to compare the occurrence of specific ACEs reported by HD offspring, BRCA1/2 offspring, and controls. Bivariate correlations were conducted to look at relationships between the mean number of ACEs and demographic variables.

Results

The group of HD offspring consisted of 74 persons (103 approached, response rate 71.8%). The group of BRCA1/2 offspring consisted of 82 persons (113 approached, response rate 72.6%). As controls, 53 partners of HD offspring participated (81 approached, response rate 65.4%) and 48 partners of BRCA1/2 offspring participated (94 approached, response rate 51.1%). Non-responders were not asked why they were not willing to participate; however, of those who did mention a reason (n = 43; 32.1% of non-responders), e.g., during a counseling visit, 38 (88.4%) found the questions too confrontational or emotion-laden and 5 (11.6%) were preoccupied

by a major life event. Participants did not differ significantly from non-participants in age or gender. Demographic data of participants are presented in *Table 1*.
As no significant differences between partners of HD offspring and partners of BRCA1/2 offspring were found in any of the outcome variables, all partners were used as a single control group (n = 101).

The mean number of ACEs was negatively correlated with age (r = -0.15, p = 0.02). Of 142 female participants, 45.8% (n = 65) reported having experienced at least one ACE before age 16, against 31.3% (n = 36) of 115 male participants (OR = 1.85, p = 0.02). Of females, 8.5% (n = 12) reported sexual abuse before age 16, against 0.9% (n = 1) of males (OR = 10.52, p = 0.02). The prevalence of the other ACEs did not differ between females and males. Both age and sex were used as covariates in the logistic regressions below.

HD offspring reported a significantly higher mean number of ACEs (M = 1.18, SE = 0.17) than controls (M = 0.49, SE = 0.10), $t(173) = 3.73$, p = 0.001. The mean number of ACEs was not significantly higher in BRCA1/2 offspring (M = 0.67, SE = 0.13) than in controls, $t(181) = 1.18$, p = 0.24. HD offspring reported a significantly higher mean number of ACEs (M = 1.18, SE = 0.17) than BRCA1/2 offspring (M = 0.67, SE = 0.13), $t(137) = 2.38$, p = 0.02.

The mean number of ACEs was negatively correlated with the mean age of participants at the time of their parent's disease onset, in HD offspring (r = -0.37, p = 0.009) as well as in BRCA1/2 offspring (r = -0.39, p = 0.03). No relationship was found between the mean number of ACEs and the mean age of the risk-transmitting parents at birth of the participant or the mean age of participants at the time of their parent's death.

Approximately 53% of HD offspring and 45% of BRCA1/2 offspring reported having experienced at least one ACE before age 16, against almost 25% of controls *(Table 2)*.

Compared to controls, a significantly higher percentage of HD offspring experienced at least one ACE before age 16 (OR = 2.96, p = 0.001). A significantly higher percentage of HD offspring experienced serious disease of a parent (OR = 2.27, p = 0.04). The percentage of HD offspring who experienced parental dysfunction (psychiatric problems of parent, domestic violence, alcohol or drug abuse, or suicide attempt of parent) was significantly higher than in controls (OR = 2.71, p = 0.01). In particular, psychiatric problems of a parent were reported relatively frequently in HD offspring (OR = 7.76, p = 0.002). There was a trend towards a higher percentage of HD offspring, compared to controls, having experienced parental loss (OR = 2.22, p = 0.06), in particular, death of a parent (OR = 3.44, p = 0.06). Odds ratios indicate that abuse (sexual abuse, physical abuse) is a more common experience in HD offspring than in controls, although not significantly so (OR = 4.17, p = 0.09).

Table 1. Demographic variables of participants (*n* = 257)

	HD offspring (*n* = 74)	BRCA1/2 offspring (*n* = 82)	Controls (*n* = 101)	*p*-value among groups
Male, *n* (%) [a]	34 (45.9)	13 (15.9)	68 (67.3)	< 0.001
Age (years), mean; range (SD) [b]	35.4; 18-65 (11.5)	40.0; 18-65 (13.6)	38.8; 18-64 (12.2)	0.06
Married/Common law, *n* (%) [a]	59 (79.7)	65 (79,3)	95 (94.1)	0.01
Education ≥ 11 years, *n* (%) [a]	35 (47.3)	37 (45.1)	46 (45.5)	0.96
Paternal transmission of risk, *n* (%) [a]	36 (48.6)[c]	36 (43.9)[d]		0.55
Parent affected at time of study, *n* (%) [a]	68 (91.9)	68 (82.9)		0.09
Parent's[e] age (years) at offspring's birth, mean; range (SD)[b]	29.6; 20-40 (4.9)	29.9; 19-47 (6.3)		0.75
Participant's age (years) at parental disease onset, mean; range (SD)[b]	20.4; 0-49 (11.7)	21.7; 1-41 (10.0)		0.60
Participant's age (years) at parent's[e] death, mean; range (SD)[b]	28.2; 3-48 (12.0)[f]	33.9; 7-56 (11.2)[g]		0.09

HD = Huntington's disease; BRCA1/2 = BRCA1/2 Hereditary Breast and Ovarian Cancer.
[a] Pearson's Chi-square.
[b] Oneway analysis of variance (ANOVA).
[c] Line of risk transmission unknown in three cases.
[d] Line of risk transmission unknown in three cases; both paternal and maternal risk transmission in one case.
[e] Risk-transmitting parent.
[f] *n* = 23.
[g] *n* = 27.

Table 2. Comparison of occurrence of adverse childhood experiences before age 16, HD offspring, BRCA1/2 offspring, and controls using logistic regression

	HD offspring (*n* = 74)		**BRCA1/2 offspring (*n* = 82)**		**Controls (*n* = 101)**		**HD offspring vs Controls [a]**		**BRCA1/2 offspring vs Controls [a]**		**HD offspring vs BRCA1/2 offspring [a]**	
Adverse Childhood Event (ACE)	*Count [b]*	*(%) [b]*	*Count*	*(%) [b]*	*Count*	*(%) [b]*	*OR*	*p-value*	*OR*	*p-value*	*OR*	*p-value*
Serious disease of parent	21	(28.4)	18	(22.0)	14	(13.9)	2.27	0.04	1.76	0.20	1.30	0.51
Psychiatric problems of parent	16	(21.6)	2	(2.4)	3	(3.0)	7.76	0.002	0.68	0.69	11.35	0.002
Divorce of parents	11	(14.9)	11	(13.4)	8	(7.9)	1.61	0.36	1.64	0.38	0.98	0.97
Domestic violence	9	(12.2)	2	(2.4)	7	(6.9)	1.60	0.39	0.25	0.11	6.30	0.02
Alcohol or drug abuse	8	(10.8)	4	(4.9)	7	(6.9)	1.55	0.43	0.71	0.63	2.18	0.24
Death of parent	8	(10.8)	9	(11.0)	4	(4.0)	3.44	0.06	3.26	0.08	1.07	0.91
Suicide attempt of parent	6	(8.1)	1	(1.2)	3	(3.0)	2.55	0.21	0.33	0.36	7.40	0.07
Sexual abuse	5	(6.8)	6	(7.3)	2	(2.0)	2.43	0.31	1.85	0.48	1.32	0.67
Physical abuse	3	(4.1)	2	(2.4)	1	(1.0)	4.89	0.18	3.16	0.39	1.55	0.66
Parental dysfunction [c]	23	(33.1)	5	(6.1)	13	(12.9)	2.71	0.01	0.39	0.11	6.96	<0.001
Parental loss [d]	18	(24.3)	20	(24.4)	12	(11.9)	2.22	0.06	2.47	0.04	0.91	0.80
Abuse [e]	7	(9.5)	7	(8.5)	2	(2.0)	4.17	0.09	2.89	0.22	1.45	0.53
Any ACE [f]	39	(52.7)	37	(45.1)	25	(24.8)	2.96	0.001	2.29	0.02	1.30	0.46

[a] Odds ratios, adjusted for age and sex
[b] Number (%) of persons in each group who report having experienced ACE
[c] Psychiatric problems of parent, domestic violence, alcohol or drug abuse, suicide attempt of parent
[d] Death of parent, divorce of parents
[e] Sexual abuse, physical abuse
[f] At least one ACE reported

A significantly higher percentage of BRCA1/2 offspring experienced at least one ACE before age 16, compared to controls (*OR* = 2.29, *p* = 0.02). The percentage of BRCA1/2 offspring who experienced parental loss was significantly higher than in controls (*OR* = 2.47, *p* = 0.04). As odds ratios indicate, losing a parent through death before age 16 was more common in BRCA1/2 than in controls, although not significantly so (*OR* = 3.26, *p* = 0.08).

Compared to BRCA1/2 offspring, the percentage of HD offspring who experienced parental dysfunction was significantly higher (*OR* = 6.96, *p* < 0.001). HD offspring more frequently reported psychiatric problems of a parent (*OR* = 11.35, *p* = 0.002) and domestic violence (*OR* = 6.30, p = 0.02) than BRCA1/2 offspring. Odds ratios indicate that a suicide attempt of a parent is more common in HD offspring than in BRCA1/2 offspring, although not significantly so (*OR* = 7.40, *p* = 0.07) *(Table 2).*

Discussion

To our knowledge, this is the first quantitative study of ACEs of adult persons at 50% risk for HD or BRCA1/2. Approximately 53% of HD offspring and 45% of BRCA1/2 offspring experienced adversity in childhood and adolescence. The odds of having experienced ACEs were higher in HD offspring and BRCA1/2 offspring than in controls. The mean number of ACEs in HD offspring was higher than in controls and also higher than in BRCA1/2 offspring. HD offspring and BRCA1/2 offspring who were younger at the time of their parent's disease onset experienced more ACEs.

As expected, HD offspring more frequently experienced serious parental disease and parental dysfunction, compared to controls. Parental loss was reported more often in BRCA1/2 offspring than in controls. HD offspring experienced more parental dysfunction, especially psychiatric problems of a parent or domestic violence, than BRCA1/2 offspring.

As both HD and BRCA1/2 are autosomal dominant hereditary disorders, with disease onset generally in mid-adulthood, there is a considerable risk for offspring of being exposed to the parent's disease process in childhood or adolescence. This is reflected in the relatively high percentage of offspring who reported having experienced parental disease. HD offspring differed significantly from controls for this ACE, whereas BRCA1/2 offspring did not. This may be associated with the fact that HD is fully penetrant, whilst BRCA1/2 is associated with an elevated risk of developing cancer. In 17.1% of BRCA1/2 offspring in this study, the parent was not affected at the time of the study (11.9% of carrier mothers and 25% of carrier fathers). The subgroup of HD offspring with a parent who was unaffected at the time of the study was 8.1%. This may account for the lower percentage of BRCA1/2 offspring who grew up with parental disease. Moreover, almost 44% of BRCA1/2 offspring in this study had a father who was a

BRCA1/2 mutation carrier. For male mutation carriers, the risk of malignancy is lower than for female carriers.[16] None of the ACEs were significantly more reported by offspring of BRCA1/2 mothers or offspring of BRCA1/2 fathers.

The rate of BRCA1/2 offspring who had a parent with cancer *(Table 1)* was higher than would be expected based on average risks of developing cancer for *BRCA1* or *BRCA2* mutation carriers (see the introductory text). Clinical observation suggests that persons who present for predictive testing often do so because they have a parent with cancer who recently received positive results of *BRCA1/2* mutation testing, which motivates test applicants to try and prevent the disease and its consequences in their own lives. The high rate of persons who had a parent with cancer in our sample may be explained by the fact that participants were included in the context of predictive testing.

Both HD and BRCA1/2 are associated with a reduced life expectancy,[5,20] which makes it more likely for offspring to experience death of a parent in childhood or adolescence. This corresponds with the findings in this study, where both HD offspring and BRCA1/2 offspring experienced death of a parent in childhood or adolescence relatively frequently. In a previous study on a sample of adults at 50% risk for HD, we found death of a parent or loss of a parent through psychiatric hospitalization, in childhood or adolescence, to be associated with having an insecure adult attachment style (reflecting a lack of confidence in the availability and reliability of others), which is related to various negative outcomes throughout life.[3]

Psychiatric and behavioral symptoms are common in HD.[6] In the present study, more than a fifth of HD offspring experienced psychiatric problems of a parent, before age 16. Psychiatric disorders may play an important role in dysfunctional parenting and are associated with an increased risk of psychological and developmental problems in offspring.[3,13,14] The finding that almost a third of HD offspring experienced parental dysfunction corresponds with what is known on the associations between psychiatric disorders and parenting, and on the extent to which HD affects family life.[9-12]

In the total group of participants, women were more likely than men to have experienced at least one ACE before age 16 or to have experienced sexual abuse before age 16. This is in line with other studies in which women reported more ACEs, especially sexual abuse.[2] Younger persons reported more ACEs in the total sample. Although retrospective assessment of ACEs is considered to be reliable,[21] this may be caused by recall bias, where older respondents have more trouble remembering what they experienced before age 16, or response bias, where older respondents are less inclined to report negative things about their childhood.
The present study indicates the percentages of HD or BRCA/2 offspring having adverse experiences associated with different aspects of the parent's disease, before age 16. These

findings are relevant for professionals working with persons at risk for HD or BRCA1/2. In predictive testing programs, the at-risk person's experiences with an affected father or mother are part of the context in which the testing process takes place and are often explicitly addressed during pre-test counseling and/or follow-up sessions. These experiences may include parental loss, parental dysfunction, or traumatic experiences, in childhood or adolescence. The reactivation of such ACEs could lead to enhanced stress levels and lower psychological well-being during and after testing. Persons with a background of childhood adversity may be especially vulnerable to maladaptive reactions to testing, such as depression or anxiety disorders.[1,2,18] Tailored psychological counseling is required to mitigate these reactions.

Prenatal or pre-implantation diagnostics may be considered by couples at risk for HD or, to a lesser extent, BRCA1/2, as ways to avoid transmitting the gene mutation onto offspring. The risk for future children of being exposed to parental disease and related ACEs should receive attention during the process of reproductive decision making.

The findings of this study may be meaningful in childrearing matters, especially in HD families. Every effort should be taken to prevent ACEs for children growing up with an HD-affected father or mother. Some of the ACEs, such as serious disease of a parent, or death of a parent, are inextricably bound up with the parent's disease, and may therefore be largely unpreventable. Other ACEs, especially parental dysfunction and abuse, may be prevented to some extent in future generations with timely psychological interventions, e.g., assertive outreach intervention.[22]

Psychiatric problems in a parent, which is a common ACE for HD offspring, could possibly be prevented to some extent as well, with timely diagnosis and adequate pharmacological and/or psychotherapeutic treatment. This could also help prevent some of the other ACEs associated with parental dysfunction.

A limitation of this study is the relatively small sample size, and the differences in male/female ratios between groups. This may account for the lack of significance where odds ratios suggested differences between groups, especially for ACEs that are relatively rare. As ACEs were assessed in a yes/no format, we have no information on severity, frequency, and duration of the reported ACEs. Such information would have been useful, because more severe, repeated and/or long lasting ACEs are known to have greater psychological impact.[1] The findings of this study are based on persons who present for predictive testing, and who are known to be a resourceful, self-selected group.[11] On the basis of the findings of other studies that describe differences between those who present for testing and those who do not,[23,24] we speculate that, if anything, non-testers would report more childhood adversity. Moreover, it is possible that persons who chose not to participate in this study because they found the questions too

confrontational experienced more childhood adversity than participants. Partners of persons at risk for HD or BRCA1/2 may differ from the general population, in that they share with their spouses a background of ACEs. According to the 'similarity attraction' hypothesis, mate selection is based, to some extent, on homogamy for numerous characteristics.[25] There may be an even larger difference in rates of ACEs between clinical groups in this study and the general population. Unfortunately, data from other studies on ACEs were not suitable for valid comparisons, because either the study sample was different (e.g., socioeconomic status (SES), cultural background, clinical setting), or the ACEs were defined in a different way, or childhood was defined as a different period than in this study or was not defined at all. It is recommended that future studies compare the prevalence of ACEs in offspring of persons with a genetic disorder such as HD or BRCA1/2 with a sample from the general population.

Conclusions

According to this study, persons at 50% risk for HD as well as persons at 50% risk for BRCA1/2 are more likely to have experienced childhood adversity than controls. Persons at 50% risk who were younger at the time of their parent's disease onset reported more ACEs. Persons at risk for HD had often been exposed to parental disease or parental dysfunction in childhood or adolescence. A considerable proportion of persons at risk for BRCA1/2 had lost their parent before age 16. Professionals should be aware of these findings when counseling individuals or couples at risk for HD or BRCA1/2 in predictive testing programs, or when discussing reproductive decision making or child rearing matters. Additional psychological assessment and/or support may be required for persons at risk for HD or BRCA1/2 who experienced adversity in childhood.

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