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Full Length Article

Risk factors for the onset and progression of Huntington disease

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ABSTRACT

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by chorea, behavioural and psychiatric manifestations, and dementia, caused by a CAG triplet repeat expansion in the huntingtin gene. Systematic review of the literature was conducted to determine the risk factors for the onset and progression of HD. Multiple databases were searched, using terms specific to Huntington disease and to studies of aetiology, risk, prevention and genetics, limited to studies on human subjects published in English or French between 1950 and 2010. Two reviewers independently screened the abstracts and identified potentially relevant articles for full-text review using predetermined inclusion criteria. Three major categories of risk factors for onset of HD were identified: CAG repeat length in the huntingtin gene, CAG instability, and genetic modifiers. Of these, CAG repeat length in the huntingtin gene is the most important risk factor. For the progression of HD: genetic, demographic, past medical/clinical and environmental risk factors have been studied. Of these factors, genetic factors appear to play the most important role in the progression of HD. Among the potential risk factors, CAG repeat length in the mutant allele was found to be a relatively consistent and significant risk factor for the progression of HD, especially in motor, cognitive, and other neurological symptom deterioration. In addition, there were many consistent results in the literature indicating that a higher number of CAG repeats was associated with shorter survival, faster institutionalization, and earlier percutaneous endoscopic gastrostomy.

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by chorea, behavioural and psychiatric manifestations, and dementia. Huntington's disease is caused by a CAG triplet repeat expansion in the huntingtin gene, which encodes an expanded polyglutamine stretch in the huntingtin protein. The average CAG tract length in the general population is 16 to 20 repeats. In HD, the CAG tract is expanded to 36 repeats or greater. Intermediate alleles from 27 to 35 repeats do not cause HD but are potentially unstable during reproduction.

HD prevalence is estimated at 5.7 per 100,000 people in Europe, North America and Australia, and 0.4 per 100,000 in Asia (Pringsheim et al., 2012). Symptom onset usually begins between 35 and 45 years of age, but can also occur in childhood or in the elderly.

The progression of HD manifests as a triad of motor, cognitive, and psychiatric symptoms that begin insidiously and progress over many years, until the death of the individual. Although the average length of survival after clinical diagnosis is typically 10–20 years, there is significant variation in the progression rate among different patients. Investigation of the factors associated with disease progression in individuals with HD is worthwhile in order to understand the natural history of this incurable disease.

In the published literature, there are many studies investigating the association of disease progression with the genetics of the condition, such as CAG repeat length and the effect of paternal inheritance. In addition, other studies have investigated the association between the progression of HD and demographic factors, environmental factors, and clinical features. Results from these studies have demonstrated inconsistent results regarding these potential associated factors. A systematic review of the literature was performed in order to provide a clear view of the associated risk factors with the onset and progression of HD.

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2. Methods

2.1. Risk factors for onset of HD

The methods as outlined in the Methodology article (Hersi et al., 2017) with respect to the literature search and data extraction were followed.

2.1.1. Electronic searches and selection of studies

The search strategy was developed for the Risk Factors for Onset of Neurological Conditions Project as a whole by a research librarian, in consultation with the authors (Supplementary material I). The Medline, Embase, PsycINFO, ProQuest Dissertations & Theses, TOXNET and HuGENet databases were searched, using terms specific to Huntington disease and to studies of aetiology, risk, prevention and genetics, limited to studies on human subjects published in English or French between 1950 and 2010. Two reviewers independently screened the abstracts and identified potentially relevant articles for full-text review using predetermined inclusion criteria. Disagreements were resolved by consensus between two reviewers. Reviews, commentary articles, papers using non-original data, animal studies, and medical hypotheses were excluded. Full-text review was done in a duplicate manner in distiller, an online application designed specifically for the screening and data extraction phases of a systematic review. The inclusion criteria are 1) about onset of Huntington disease; 2) Huntington disease should be confirmed by genetic diagnosis; 3) about specific risk factors for onset of Huntington disease; and 4) should be an original study with fully published article available. Articles meeting all the criteria were included for data extraction.

2.1.2. Data extraction

Data extraction was done in DistillerSR (DistillerSR, Evidence Partners, Ottawa, Canada). Data extraction of all included articles was conducted by the primary reviewer. The secondary reviewer extracted data from a randomly selected 5% sample of studies to ensure accuracy of information extracted. The following information was recorded: 1) geographic location of the study, race, study period and sample size; 2) characteristics of cases including age at the time of study, age of onset, male/female distribution, CAG repeats length range, disease duration and severity; 3) if given, characteristics of controls, including age at the time of study, male/female distribution, CAG repeats length range, controls' relation to cases; 4) diagnostic criteria of Huntington disease, definition of age of onset, measurement method of CAG repeats length, detection method of other risk factors; and 5) study results, including risk estimate and indicators of statistical significance.

2.2. Risk factors for progression of HD

2.2.1. Electronic searches and selection of studies

A search strategy was developed in consultation with a research librarian (Supplementary material II). The Medline, Embase and PsycINFO databases were searched, limited to studies on human subjects published in English or French through November 2012. Two reviewers independently screened the abstracts and identified potentially relevant articles for full-text review using predetermined inclusion criteria. Disagreements were resolved by consensus. Reviews, commentary articles, case reports, papers without original data and animal studies were excluded. The inclusion criteria for studies were: 1) articles pertaining to the progression of HD; 2) articles pertaining to specific risk factors for progression of HD; and 3) original study with fully published article available. Outcome measures for HD progression include: 1) the time to a clinical endpoint such as death; 2) the time to a clinically relevant stage such as time to institutionalization, nursing home admission, forced lifestyle change or insertion of a percutaneous endoscopic gastrostomy (PEG); and 3) decline in total functional capacity or deterioration in the three domains of HD symptoms (motor, neuropsychiatric and cognitive) measured by validated scales or scales accepted by consensus. Articles meeting all of these criteria were included for data extraction.

2.2.2. Data Extraction

The primary reviewer conducted data extraction of all included articles. A random 20% sample of included articles were extracted by a second reviewer to confirm accuracy. The following information was recorded: 1) Study period and sample size; 2) characteristics of cases including age, male/female distribution at first evaluation, CAG repeats length range, age of onset, disease duration; 3) risk factors and outcome measures of progression; 4) methods used for statistical analyses; and 5) study results, including risk estimate and indicators of statistical significance.

3. Results

3.1. Risk factors for the onset of HD

The electronic searches yielded 7557 abstracts, with 140 abstracts selected for full-text review. Of these 140, 14 studies were excluded because they were case reports, non-original data or conference abstracts for which fully published articles could not be found. Data extraction was done on 126 articles (Fig. 1).

Based on the analysis, three major categories of risk factors for onset of HD were identified: (1) CAG repeat length in the huntingtin gene, (2) CAG instability, and (3) genetic modifiers. As a recent systematic review was published on genetic modifiers, systematic reviews on the first two topics were performed and an overview of the existing review on genetic modifiers was provided in this article.

3.1.1. CAG repeat length

The clinical diagnosis of HD is based on the development of chorea, other movement disorders, or behavioural/psychiatric features. Genetic studies of HD have shown an inverse correlation between the age of onset of symptoms and the number of CAG repeats in the huntingtin gene. We sought to synthesize data through a systematic review of all published studies examining the correlation between age of onset and CAG repeat length, in order to provide an overall summary estimate of the strength of the correlation between these two factors. The relationship between this correlation and several factors, including the mean reported CAG repeat length, the mean reported age of onset, publication year, and the geographic region under study was also examined.

In the studies investigating the correlation between CAG repeat length and age of onset, there were three different methodological approaches. First, some studies calculated the correlation coefficient between CAG repeat length and age of onset under the assumption of a linear relationship between these two variables. The second approach was to estimate the correlation between CAG repeat length and the natural logarithm of age of onset because an exponential relationship between the variables was noted, and this resulted in a better fit for the data. The third type of approach was to investigate the correlation between the natural logarithms of both the CAG repeat length and the age of onset. If there was no clear description about the natural logarithm transformation of the data, it was assumed that a linear relationship was used. In studies which provided both results of linear relationship and natural logarithm transformation of the age of onset, the natural logarithm transformation data were used. In studies with original data, the natural logarithm transformation of age of onset was used to