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Responses to reviewers (2)

Editor

1. **Bruyn's 1968 review of 150 cases**

We have added specific reference to this review of cases in the Introduction

Reviewer 1

2. **Usage of the terms 'symptoms' and 'signs'**

We agree that the discrimination of these terms requires more clarity. It is particularly relevant when discussing JHD as children may lack the ability to report on their symptoms making clinical examination findings (ie signs) even more important. We have amended the manuscript where appropriate to include terms such as 'symptoms and signs'; 'symptoms or signs' or 'clinical features' instead of just 'symptoms'.

Clinical presentation and features of Juvenile-onset Huntington's disease: a systematic review

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Abstract

BACKGROUND: Juvenile-onset Huntington's disease (JHD) is defined by onset at the age of 20 or younger and represents approximately 5% of all HD cases. Patients with JHD present with a broad range of symptoms and signs that only overlap partially with adult-onset HD. A greater awareness and understanding of the presentation of JHD would improve the diagnosis and treatment of this condition.

OBJECTIVE: To undertake a systematic review of the literature relating to the clinical features at first presentation of JHD.

METHODS: We searched MEDLINE and EMBASE for all studies describing presenting features of JHD patients, performed quality control, and collated and analysed the data.

RESULTS: We screened 2917 records for eligibility, and included 79 studies (n=285 individuals) in the analysis. All were case reports and case series, synthesising data from 25 different countries. Thirty-four different clinical features at presentation were identified. Four groups of symptoms or signs were present in more than 15% of cases: behavioural disturbance, falls/gait disturbance, cognitive impairment and parkinsonian features. Where data were available, the median age of onset was 9 years, 52% were female, the mutant *HTT* allele was transmitted paternally in 80% of cases, and the median CAG repeat length was 64.

CONCLUSIONS: JHD can present with a wide variety of symptoms and signs, with non-motor characteristics being observed most frequently. Greater recognition of these presentations will facilitate early diagnosis and management. Tailored rating scales to score motor, non-motor, and functional impairments specifically in JHD are required to standardise research studies, and are under development.

Keywords: Huntington Disease, Juvenile onset Huntington Disease, review, diagnosis, signs and symptoms

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that affects approximately 1 in 8,000 people in Western populations [1]. Symptoms typically start between the ages of 40 and 60, although there is considerable variation. Patients with HD develop a mixture of involuntary movements, psychiatric and behavioural problems, and cognitive impairment and these typically progress over 10-30 years with resultant morbidity and mortality [2]. A small proportion of HD patients (approximately 5%, but variable depending on population [3]) develop clinical features before the age of 20: they have been conventionally defined as having Juvenile-onset HD (JHD) based on a review of 150 cases by Bruyn in 1968 [4]. Since a number of studies in recent years have also included onset at 20 years as JHD, we have used a definition of JHD as onset at 20 years or younger here. JHD cases have been further arbitrarily subdivided into childhood-onset (at or before 10 years of age) and adolescent-onset (between 11 and 20 years of age) in some reports to facilitate analyses of age-relevant factors [5]. Approximately 20% of JHD cases have onset in childhood [3]. It is worth noting that the use of 'Juvenile-onset' as a classifier is under review and is likely to be replaced in the future by 'Paediatric HD' for gene-positive individuals manifesting disease under the age of 18, rather than defining a group of individuals according to an arbitrary age at onset.

Although adult-onset HD and JHD patients share the same causative mutation (an expanded tract of at least 36 tandem CAG repeats in exon 1 of the *HTT* gene), and despite the age-based distinction being arbitrary, there are significant phenotypic differences between the two patient cohorts [6]. Most descriptions of JHD feature a parkinsonian syndrome of rigidity, dystonia and bradykinesia, compared to the chorea typically associated with adult-onset HD. In addition, JHD cases may also feature cerebellar signs and epilepsy, as well as behavioural problems and developmental delay [6]. This broad phenotypic range has considerable overlap with many other neurodevelopmental/neurodegenerative disorders that can present in childhood, such as

mitochondrial diseases, epilepsies, Wilson's disease, some spinocerebellar ataxias (e.g. SCA2, SCA3, SCA17), dentatorubral-pallidoluysian atrophy (DRPLA), and juvenile-onset Parkinson's disease, leading to delays in accurate diagnosis as well as inadequate genetic counselling and treatment [7].

JHD is a rare disorder, affecting approximately 1 in 200,000, and consequently the published literature on clinical manifestations of JHD is limited to case reports and a few small case-series. In order to improve awareness and understanding of the diverse initial presentations of JHD we have systematically identified and collated all the existing published data on presenting features and patient characteristics. We have also assessed whether there are significant correlations between CAG repeat length, age at clinical onset and clinical presentation in our combined dataset.

Materials and Methods

No specific published protocol was used for this review.

Search strategy

A search strategy was developed to identify all articles in MEDLINE and EMBASE. Scoping searches were carried out beforehand to refine the search terms and ensure that relevant studies were obtained. The search terms used in the 'abstract' and 'title' fields were Huntington* AND juvenile OR child* OR early* OR young* OR paediatric OR Westphal OR infant* (*indicates searches including unlimited truncations of the target word). The database was searched from January 1969 (when JHD was defined by Bruyn [4]) to May 2017. References were exported to the reference management software Mendeley Desktop v1.17.10. Duplicates were removed and non-English language studies were excluded.

Further hand searches were performed through screening the bibliographies of full-text records that were accessed, and using the Google Scholar 'cited by' feature to find articles that had cited these publications.

Study selection

Titles and abstracts were screened and only primary research studies reporting on the initial presenting clinical features of JHD were considered for selection. Any study design was accepted. Studies that selected cases based on the presence of specific clinical manifestations but not necessarily at presentation (e.g. seizures) were not included to avoid giving disproportionate weight to those features in the data synthesis. Studies were also excluded if data were reported on both adults and children and it was not possible to extract the juvenile case data. In addition, studies that reported on published data from other papers already included in the analysis were also excluded.

Quality assessment

Once a short-list of eligible studies for potential inclusion had been assembled, one reviewer assessed the quality of these studies. These were all case series and case reports. There is no universally accepted tool for evaluating the quality of such studies. Therefore, matrices for assessing the quality of case series and case reports were developed from recommendations using several sources [8-11], including the National Institutes of Health (NIH) and The Joanna Briggs Institute (JBI). Quality was assessed across eight domains for case series: methodology, description of demographics, whether multi-centred, clear inclusion/exclusion criteria, consecutive recruitment, clear clinical information, clear outcomes reported, appropriate statistics. Case series that received unsatisfactory ratings in fewer than four domains were included in this review (supplementary material Table S1). Quality was assessed across five domains for case reports: description of demographics, clear patient history, clear clinical information, appropriate diagnostic

tests/assessment methods, clear outcomes reported. Case reports that received unsatisfactory ratings in fewer than three domains were included in this review (supplementary material Table S2).

Data extraction

Data were extracted from the selected studies by one review. Studies were divided into 'aggregated data studies' (case series reporting data aggregated for all patients) and 'individual data studies' (case series and case reports reporting data for separate patients). The following were extracted from all studies: lead author, year of publication, country of study, study design and sample size. Sex, mode of transmission, age at onset, and CAG repeat length were also extracted where possible. In 'aggregated data studies' the raw data were extracted whenever possible.

For 'individual data studies', data on presenting features or features were extracted using a coding system developed from prior interrogation of the literature. For instance, features that were considered similar were combined (e.g. 'seizures' and 'epilepsy' were combined into a single category: 'seizures'). Within case series, data from individuals could usually be extracted. If not, aggregated data referring to presenting features were utilised where clear.

Data analysis

Characteristics of reported cases and their described clinical manifestations were summarised as percentages. Age at onset of symptoms or signs was extracted where possible, and median values calculated. CAG repeat lengths were noted when available. In two studies with aggregated data individual ages at onset and CAG repeats were not reported: these were omitted from the analysis. Statistical analyses consisted of Pearson's correlation coefficient to investigate the association between CAG repeat length and age at onset of symptoms or signs, Fisher's exact test to compare age of onset, and binomial distribution to compare differences between males and females, as well as paternal and maternal transmission.

Results

Literature search and case selection

The search strategy and decision tree are shown in Fig. 1. A total of 2917 articles were screened by title and abstract. 2815 studies were excluded for a variety of reasons including being reviews and not containing data relevant to the research question. The remaining 102 articles were screened by full-text. A further 23 articles were excluded for various reasons: being unrelated to the research question, having unextractable JHD data, not being primary research, focussing on one clinical manifestation of JHD, presenting data previously published elsewhere, or not meeting the quality criteria. This left a total of 79 studies eligible for analysis (supplementary material references).

The 79 studies included in our analysis here comprised 69 case reports and 10 case series (the largest having 30 cases) and yielded a total sample size of 285 cases of JHD. Studies were conducted in 25 countries and included some from Europe, Asia, North and South America, and South Africa. We were able to extract at least partial data on sex, mode of transmission, age at onset, and CAG repeat length for 229 individual JHD cases out of the total number of 285. The remaining 56 cases were described in larger case series with data presented as pooled results: this prevented extraction of individual case data for our analyses.

Demographics, inheritance and CAG repeat lengths of JHD cases

The sex of individuals with JHD could be ascertained in 189 cases. There was no significant difference between the numbers of affected males and females (Figure 2A; 92 males, 97 females; $p = 0.32$), and this was also true in the childhood and adolescent onset subgroups (Figure 2B). However, almost 80% of JHD patients inherited the disease-causing *HTT* allele from their father, in keeping with known increased genetic anticipation through the paternal line (Figure 2A; 166 paternally inherited, 42 maternally inherited; $p = 0.0001$). A slightly greater proportion of

childhood-onset cases were inherited paternally compared with adolescent-onset cases (Figure 2B; 87.0% and 72.7% respectively; p = 0.02). The age at onset of first symptoms or signs was individually reported for 228 cases and ranged from age 1 to 20 with a median age at onset of 9 years (Figure 2C). A total of 127 cases (56%) had childhood onset (between ages 0-10 inclusive) and 101 (44%) had adolescent onset (age 11-20).

The age at onset of clinical features and the CAG repeat length were both reported for 154 JHD cases. The median CAG repeat length was 64 repeats, but there was a wide range of 39 to 265 repeats (Figure 2D). As expected, there was a significant inverse relationship between CAG repeat length and age at onset of clinical symptoms or signs (Pearson's correlation coefficient -0.56, $p < 0.00001$), although this correlation was weaker at longer repeat lengths. Interestingly, cases of JHD presenting between age 11 and 20 had CAG repeat lengths almost exclusively between 39 and 75 (excepting one case of an 11 year old with 92 repeats), whereas there was a much broader range of repeat length in those cases of JHD presenting between age 1 and 10 (41-265 CAG repeats). Many of the younger presentations up to the age of 10 had much longer CAG tracts, often over 100 repeats (Figure 2D).

Features of JHD at first presentation

A wide range of different presenting features were reported in the 285 JHD cases analysed here (Table 1). In total, 34 different presenting features were identified, and these were grouped into categories of related features to facilitate analysis. For example, 'seizures' and 'epilepsy' were grouped together, as were 'rigidity', 'bradykinesia' and 'parkinsonism' (Table 1). Seven clinical presentations occurred in at least 10% of cases: behavioural disturbance/personality change (26%), falls/gait disturbance (14%), cognitive decline/memory impairment (18%), features of parkinsonism (16%), chorea (12%), declining school performance (12%), and speech disturbance/dysarthria (12%). We were able to extract data pertaining to 229 individual cases, with

the remaining information coming from grouped case series. A single clinical feature was reported at presentation for over half of the JHD cases collated here (131/229 cases, 57%). The remaining 98 patients each displayed more than one clinical feature at presentation: 55/229 (24%) reported two features, 32/229 (14%) reported three features, and 11/229 (5%) reported four features.

Presenting features were also investigated by age at onset, comparing the childhood (0-10 years) and adolescent (11-20 years) ranges. This analysis was possible only for the 228 individuals where data could be extracted. There were significant differences in the frequencies of particular presenting features in the two age groups (Table 1): falls/gait disturbance, speech disturbance, seizures, and developmental delay/regression were all more common in the childhood-onset cases, whereas fine motor disturbance, depression/suicidal ideation and behavioural/personality change were all more common in the older, adolescent-onset cases.

Discussion

This systematic review of the presenting features of JHD is the largest to date, collating data from 285 individual cases reported in 79 studies from 25 countries over more than 40 years. Although not all studies reported complete datasets, overall there were sufficient numbers to allow analysis. Over half of the JHD cases included here reported childhood onset of disease before the age of 11, contrasting with previously published population estimates of just 20% [3]. The range and balance of presenting symptoms and signs described here likely reflects this distribution of cases. A cross-sectional analysis of 1766 HD patients in the European HD REGISTRY showed that over 67% had motor problems (mostly chorea) at presentation, while 22% and 9% had psychiatric and cognitive presentations, respectively. Since just 2.1% of these cases were classified as JHD, this range of presenting features mainly represents adult-onset disease [12]. These findings contrast with the JHD presentations collated here. Whilst presentation with motor symptoms or signs was still common in JHD (approximately 50% of cases), only 12% had chorea and there was a similar prevalence of a rigid, bradykinetic, parkinsonian phenotype (Table 1). These figures are broadly similar to those

reported elsewhere for motor phenotypes in all JHD (not just presentation) where all patients had a motor phenotype of some sort: approximately 60% were mainly rigid and 40% mainly choreic [13,14]. The parkinsonian motor phenotype is rare in adulthood, although such features may develop later in the disease course [6]. Although there is increasing recognition of early cognitive and psychiatric problems in adult-onset HD, they remain more prevalent in JHD: presentation with behavioural disturbances, cognitive impairment, learning difficulties at school and developmental regression were all frequently reported (Table 1).

Very early, childhood JHD (age 0-10) is characterised by neurodevelopmental as well as neurodegenerative pathology. For example, seizures, developmental delay or regression, falls/gait problems, and speech disturbance are all particularly prevalent in this age group. Seizures are reported at presentation in approximately 15% of childhood JHD cases here, in contrast to a previous study that found them to be rare [15]. Overall they have been reported in up to a third of JHD cases, sometimes developing later in the disease course [14,15]. Given that seizures occur in up to 0.5% children in the general population, it can be difficult for clinicians to diagnose JHD on the basis of seizures alone. Similar problems arise when considering other neurodevelopmental phenotypes, all of which are not specific for HD and have a broad differential diagnosis, particularly in the absence of a family history of HD. The older age group of adolescent-onset JHD (age 11-20) display more features of adult-onset HD, such as motor impairment and psychiatric pathologies, although non-motor features remain common, in agreement with prior studies [13].

There are unavoidable biases and limitations in this study: data collection was retrospective; methodologies were heterogeneous; only cases, and not controls, were reported; inconsistent and ambiguous language was often used in reporting, and different terms relating to specific symptoms and signs were used in different studies, making collation of data difficult (e.g. ‘ataxia’, ‘imbalance’, ‘unsteadiness’ and ‘gait imbalance’ may all refer to the same feature, but combining them in the analysis makes the assumption that they do). Furthermore, given that we have included studies from

before 1993 when genetic diagnosis became widely available, we do not have definitive genetic evidence of JHD in all cases. Historically, a lack of awareness of JHD might have led to the earliest presenting symptoms or signs being missed and some patients with adolescent-onset but adult diagnosis not being recorded as JHD. A further bias against reporting of adolescent-onset JHD comes from publication of younger-onset cases that are sometimes perceived as more unusual and interesting. Lastly, some phenotypic features such as depression and behavioural/personality problems are particularly difficult to diagnose in younger age-groups and so there might be an inherent bias towards their reporting in the adolescent-onset group.

CAG repeat lengths showed the expected inverse relationship with age at onset of disease, although there was considerable variation (Fig. 2B). Onset of JHD in childhood (0-10 years of age) was particularly variable, associated with CAG repeat lengths ranging from 41 to 265, the majority (59%) having over 80 repeats. Onset of JHD in adolescence (11-20 years of age) was associated with a tighter range of 39-75 CAGs, although there was still considerable variation in CAG repeat length between people with the same age at onset. This variability likely reflects the influence of modifier genes and environmental factors that can affect the pathogenesis of an expanded CAG repeat in cells [16]. In addition, technical developments in CAG repeat assays over the last 25 years mean that contemporary reporting of long repeat lengths is likely to be much more accurate than that from early genetic studies in the 1990s. We did not have adequate numbers to test the association of CAG repeat length with clinical features of JHD at presentation. Significantly more cases of JHD were inherited paternally than maternally, especially those with earlier onset, in agreement with several previous studies (summarised in [4]). However, it is important to note that JHD can also arise through the maternal line.

A recent retrospective analysis of 36 JHD patients from Italy and Argentina divided them by CAG repeat length into highly expanded (>80 CAG) or low expansion (<80 CAG) groups and showed that the former group presented at a younger age and tended to progress more rapidly. The highly

expanded group often presented with gait disturbance and/or neurodevelopmental phenotypes in contrast to the low expansion group where loss of hand dexterity was most common [17]. These findings corroborate the trends described in this systematic review.

Implications for practice

The data in this review reinforce the knowledge that JHD can present with a mixture of both motor and non-motor symptoms and signs, many of which are found in a range of neurodevelopmental paediatric diseases and not solely JHD. These porblems can affect a wide range of functions and require input from a multidisciplinary team for effective management. It has been shown previously that the exact presenting phenotype of HD is a poor predictor of a positive gene test for HD and that a family history of HD is the most useful indicator [18]. Current clinical guidance is not to test unaffected at-risk children under the age of 18 for the HD mutation unless the child, usually an older adolescent, specifically requests the test and engages with a period of genetic counselling beforehand [19]. Children with symptoms or signs consistent with JHD under the age of 18 may have a diagnostic HD gene test. Often this will be in the context of a family history of HD, but there are two groups of affected children without a known family history who might be diagnosed with JHD during clinical work-up. First, genetic anticipation means that a child may present with features of JHD before anyone else in their family, even if a family history were later to emerge. There are a number of case reports of this situation in the literature [20,21] and it is common in other diseases caused by expanded repeats such as myotonic dystrophy. Clearly a diagnosis of JHD would then have implications for older generations and so careful discussion with parents should be undertaken before testing. Second, true *de novo* mutations can arise at a low rate (approximately 10% of all HD cases), usually from expansion of an intermediate range CAG repeat allele (27-35 repeats) in a parent into the disease-causing range in the child. Therefore, JHD should be considered in children with an undiagnosed neurodevelopmental and/or motor syndrome and no family history of HD.

Finally, there is still a lack of clinical tools for assessing and monitoring JHD. Adult HD is followed in longitudinal studies such as Registry-HD and Enroll-HD using scoring systems for motor (Unified HD Rating Scale (UHDRS) motor), behavioural (Problem Behaviours Assessment, PBA) and functional (UHDRS Total Functional Capacity, Functional Assessment, and Independence Scale) abilities. These assessments all require reasonable (adult) cognitive abilities, such as the ability to follow instructions, and ask questions about occupation, finances, driving, and everyday living that are specifically framed for the adult patient. These tools have been modified for use in paediatric populations, but the low prevalence of JHD means that validation of these adapted scales is still lacking [22,23]. Tailored clinical JHD assessments, based on the broader and phenotypically different presentations illustrated here, will improve our understanding of this rare condition and be central to longitudinal observations both in disease natural history studies and clinical trials. These tools are being developed by the European HD network working group on JHD. This working group is also discussing a change in nomenclature from JHD to 'paediatric HD', defined as clinical onset of HD before the age of 18. In addition, if disease-modifying therapies for HD emerge over the next few years, then early treatment to prevent neuronal loss will be central to disease management, and the advice against testing for JHD in unaffected at-risk children may need to be revisited.

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Conflict of Interest

The authors have no conflict of interest to report

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Tables

Table 1. Clinical characteristics of JHD patients at first presentation, grouped by similarity and ranked by frequency in the collated JHD population of 285 individuals.

Clinical characteristics	All cases (0-20 y; n=285) No./Total No. (%)	Childhood onset (0-10 y; n=127) No./Total No. (%)	Adolescent onset (11-20 y; n=101) No./Total No. (%)	p value
Behavioural disturbance/ personality change	75/285 (26.3)	25/127 (19.7)	30/101 (29.7)	> 0.05
Falls/ gait disturbance/ ataxia/ cerebellar signs/ imbalance/ unsteadiness	60/285 (21.1)	46/127 (36.2)	9/101 (8.9)	0.0001
Cognitive/ memory impairment	51/285 (17.8)	17/127 (13.4)	17/101 (16.8)	> 0.05
Rigidity/ bradykinesia/ parkinsonism	41/285 (14.3)	22/127 (17.3)	17/101 (16.8)	> 0.05
Chorea	35/285 (12.3)	9/127 (7.1)	10/101 (9.9)	> 0.05
Declining school performance	35/285 (12.3)	18/127 (14.1)	17/101 (16.8)	> 0.05
Speech disturbance/ dysarthria	35/285 (12.3)	23/127 (18.1)	6/101 (5.9)	0.008
Seizures	26/285 (9.1)	19/127 (15.0)	2/101 (1.9)	0.0008
Other movement disorder (including dystonia/ tics/ shoulder twitching/jerking / action myoclonus/ excessive blinking)	20/285 (7.0)	12/127 (9.4)	7/101 (6.9)	> 0.05
Developmental regression/delay	17/285 (6.0)	17/127 (13.4)	0/101 (0)	0.0001
Depression/ suicidal ideation	16/285 (5.6)	3/127 (2.4)	13/101 (12.9)	0.003
Fine motor disturbance/ tremor/ writing alteration	16/285 (5.6)	3/127 (2.4)	9/101 (8.9)	0.03
Incoordination/ clumsiness	13/285 (4.6)	6/127 (4.7)	7/101 (6.9)	> 0.05

All relevant information was not available or extractable for every case hence the variable numbers. Similar clinical features described in different ways in different articles have been combined into single sections for clarity: for example, ‘seizures’ and ‘epilepsy’. Some individuals with JHD presented with multiple clinical features, up to a maximum of four, all of which are included in the table. Presenting characteristics found in fewer than 10 cases of JHD were not included in the table. These were swallowing disturbance/sialorrhoea (9), substance misuse (8), psychosis (3), binge eating (1) and oculomotor abnormalities (1). The p values in the right column are derived from Fisher’s exact test of the null hypothesis that there is no significant difference between the prevalence of individual features in childhood and adolescent onset JHD.

Figure Legends

Figure 1. Flow diagram displaying the search strategy employed and the article inclusion and exclusion process. In total, 79 studies were included in the final collation for analysis.

Figure 2. Baseline characteristics of cases included in this review. A. Sex and parental source of expanded CAG repeat. B. Comparison of the sex and parental source of the expanded CAG repeat between childhood-onset (age 0-10 years) and adolescent-onset (age 11-20 years) cases. C. Histogram showing the numbers of cases of JHD in this study presenting at each age, where data available (n=228). D. Scatter plot of CAG repeat length against age at onset of first symptoms or signs of JHD for cases where data available (n=154).

Figures

Figure 1

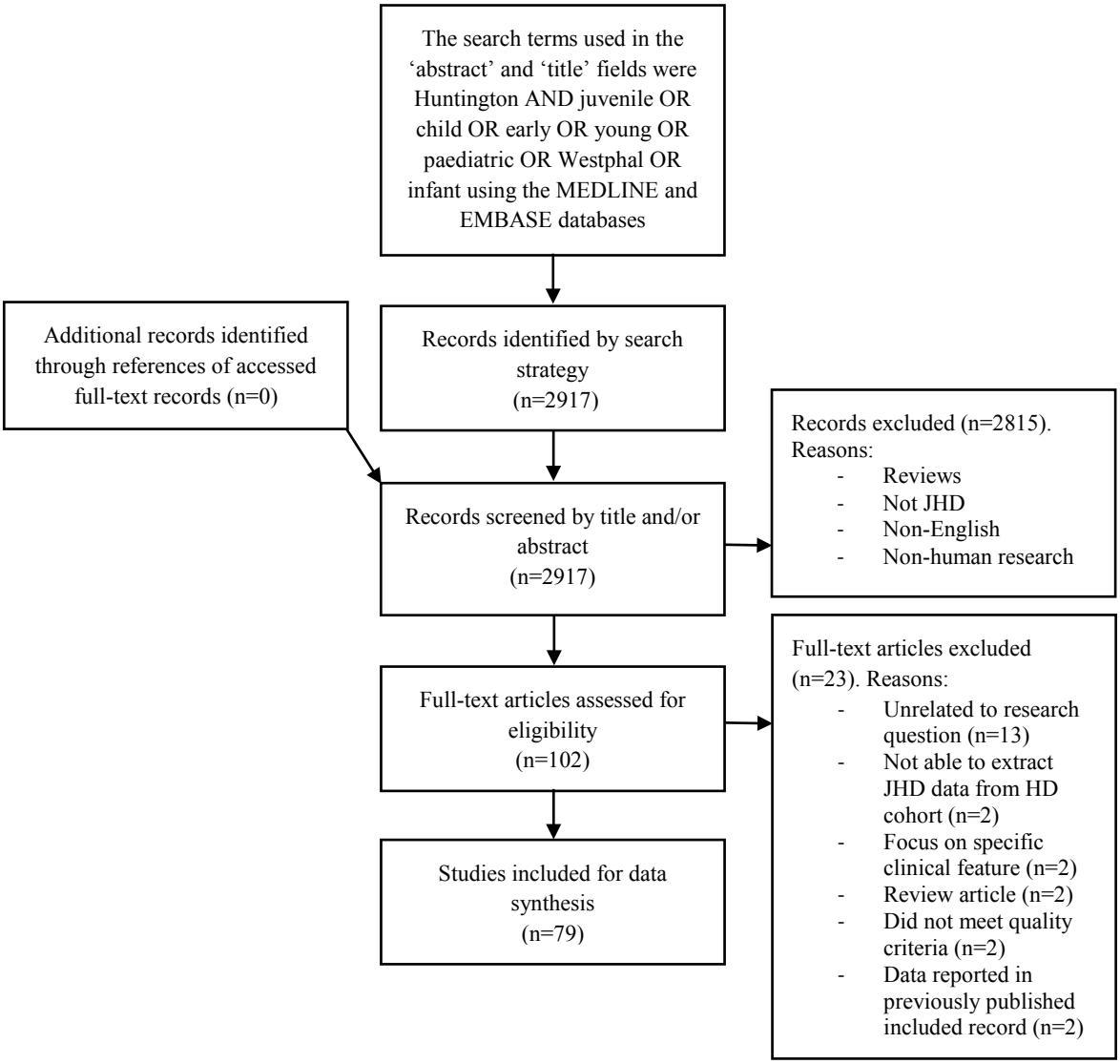


Figure 2

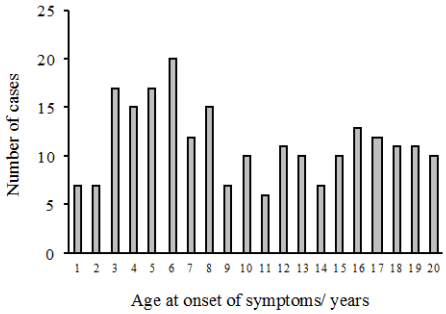
A

	Number of cases (%)	p value
Sex		
Male	92 (48.7)	
Female	97 (51.3)	0.32
Transmission		
Paternal	166 (79.8)	
Maternal	42 (20.2)	0.0001

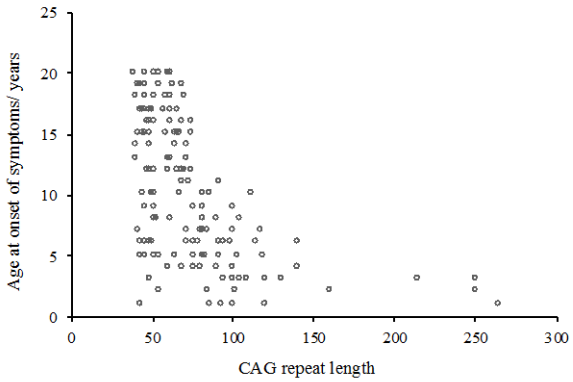
B

	Childhood onset (0-10 y)	Adolescent onset (11-20 y)	p value
Male sex			
No./ total No. (%)	49/98 (50.0)	36/78 (46.2)	0.65
Paternal transmission			
No./ total No. (%)	94/108 (87.0)	64/88 (72.7)	0.02

C



D



Supplementary Material

Table S1. Quality assessment matrix for the 10 case series included in this study. Unsatisfactory (N) ratings in fewer than four domains permitted inclusion.

Case series [ref]	1. Are valid methods used for identification of the condition for all participants included in the case series?	2. Are demographics of the participants clearly and fully described?	3. Are the cases collected in more than one centre?	4. Are the inclusion and exclusion criteria for entry into the study clearly stated?	5. Were participants recruited consecutively?	6. Are there clear reporting of clinical information of the participants?	7. Are the outcomes or follow up results of cases clearly reported?	8. If statistical analysis was performed, was it appropriate?	Include
Gatto [1]	Y	Y	Unclear	N	Y	Y	Y	Y	Y
Gonzalez-Alegre [2]	Y	Y	N	Y	Y	Y	Y	N/A	Y
Ho [3]	Y	N	N	Y	Unclear	Y	Y	N/A	Y
Koutsis [4]	Y	Y	N	Y	Y	Y	N	Y	Y
Nance [5]	Y	N	Y	N	N/A	Y	N	N/A	Y
Rasmussen [6]	Y	N	N	N	Y	Y	Y	N/A	Y
Reynolds [7]	Y	Y	N	Y	Unclear	Y	Y	N/A	Y

Ribaï [8]	Y	Y	N	N	Y	Y	Y	Y	Y
Siesling [9]	Y	N	Y	Y	Y	Y	Y	Y	Y
Squitieri [10]	Y	N	Y	N	Unclear	Y	N	N/A	Y

Table S2. Quality assessment matrix for the 69 case reports included in this study. Unsatisfactory (N) ratings in fewer than three domains permitted inclusion.

Case report [ref]	1. Are demographics of the patient clearly and fully described?	2. Is the patient's history clearly described and presented?	3. Is the clinical condition of the patient on presentation clearly described?	4. Are diagnostics tests or assessment methods, and results clearly described?	5. Is the outcome or follow up of the case clearly reported?	Include
Angelini [11]	Y	Y	Y	Y	N	Y
Bird [12]	Y	Y	Y	N	Y	Y
Bodensteiner [13]	Y	Y	Y	Y	Y	Y
Brooks [14]	Y	Y	Y	Y	Y	Y
Byers [15]	Y	Y	Y	N	Y	Y
Cislaghi [16]	Y	Y	Y	Y	Y	Y
Chuo [17]	Y	Y	Y	Y	Y	Y
Cubo [18]	Y	Y	Y	Y	Y	Y
Comunale [19]	Y	Y	Y	Y	N	Y
Dayananthan [20]	Y	Y	Y	Y	Y	Y
Dewhurst [21]	Y	Y	Y	Y	Y	Y
Duesterhus [22]	Y	Y	Y	Y	Y	Y

Findling [23]	Y	Y	Y	Y	Y	Y
Gambardella [24]	Y	Y	Y	Y	N	Y
Geevasinga [25]	Y	Y	Y	Y	Y	Y
Gencik [26]	Y	Y	Y	Y	Y	Y
Goebel [27]	Y	Y	Y	Y	Y	Y
Gosk [28]	Y	Y	Y	N	N	Y
Gadomska [29]	Y	Y	Y	N	N	Y
Haslam [30]	Y	Y	Y	Y	Y	Y
Hattori [31]	Y	Y	Y	Y	N	Y
Hofgartner [32]	Y	Y	Y	Y	N	Y
Holinski-Feder [33]	Y	Y	Y	Y	Y	Y
Isobe [34]	Y	Y	Y	Y	Y	Y
Jongen* [35]	Y	Y	Y	Y	N	Y
Karagöl [36]	Y	Y	Y	Y	N	Y
Katafuchi [37]	Y	Y	Y	Y	Y	Y
King [38]	Y	Y	Y	N	Y	Y
Koul* [39]	Y	Y	Y	N	Y	Y
Krishnappa [40]	Y	Y	Y	Y	Y	Y

Landau [41]	Y	Y	Y	Y	N	Y
Lenti [42]	Y	Y	Y	Y	Y	Y
Levy* [43]	Y	Y	Y	Y	N	Y
Liu* [44]	Y	Y	Y	Y	N	Y
Lopez-Castellanos [45]	Y	Y	Y	N	Y	Y
Marconi [46]	Y	Y	Y	Y	Y	Y
Matthews [47]	Y	Y	Y	Y	Y	Y
Milunsky [48]	Y	Y	Y	Y	N	Y
Monrad [49]	Y	Y	Y	Y	N	Y
Nahhas [50]	Y	Y	Y	Y	Y	Y
Navarrete* [51]	Y	Y	Y	Y	Y	Y
Naphade [52]	Y	Y	Y	Y	N	Y
Nicolas [53]	Y	Y	Y	Y	N	Y
Oliver* [54]	Y	Y	Y	N	N	Y
Osborne* [55]	Y	Y	Y	N	Y	Y
Papapetropoulos [56]	Y	Y	Y	Y	Y	Y
Patra [57]	Y	Y	Y	Y	Y	Y

Revuelta [58]	Y	Y	Y	Y	Y	Y
Reyes Molón [59]	Y	Y	Y	Y	Y	Y
Rodda [60]	Y	Y	Y	Y	Y	Y
Rossi Sebastiano [61]	N	Y	Y	Y	N	Y
Ruocco* [62]	Y	Y	Y	Y	Y	Y
Saffer* [63]	Y	Y	Y	Y	Y	Y
Sakazume [64]	Y	Y	Y	Y	N	Y
Santos [65]	Y	Y	Y	Y	Y	Y
Schapiro [66]	Y	Y	Y	Y	N	Y
Scrimgeour [67]	Y	Y	Y	Y	N	Y
Seneca [68]	Y	Y	Y	Y	N	Y
Squitieri [69]	Y	Y	Y	Y	Y	Y
Srivastava [70]	Y	Y	Y	Y	N	Y
Sunwoo [71]	Y	Y	Y	Y	Y	Y
Topper [72]	Y	Y	Y	Y	N	Y
Toufexis* [73]	Y	Y	Y	Y	N	Y
Ullrich [74]	Y	Y	Y	Y	Y	Y
Vargas [75]	Y	Y	Y	Y	Y	Y

Waugh [76]	Y	Y	Y	Y	Y	Y
Wojaczyńska-Stanek [77]	Y	Y	Y	Y	Y	Y
Xing [78]	Y	Y	Y	Y	Y	Y
Yoon* [79]	Y	Y	Y	Y	N	Y

*Denotes case reports with more than one subject

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