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REVIEW

Development of Research on Huntington Disease in China

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Abstract Huntington disease (HD) is a progressive autosomal dominantly inherited neurodegenerative disorder, characterized with the typical manifestations of involuntary movements, cognitive dysfunction, and psychiatric or behavioral disturbance. It results from an expansion in the number of CAG repeats in the first exon of the *huntingtin (HTT)* gene. In China, since the first case report in 1959, the knowledge of this disorder has been involving a lot, especially in the latest decade. In this review, we meta-analysis and summarize the research reports that were published by Chinese researchers since 1959, so that researchers whose native language were not Chinese can get a general idea of the research development of HD in China. Briefly, the research of HD in China can be broadly divided into three stages. Firstly, before 1993, there were scattered case reports of HD that were solely based on Clinical features and family history. Then, with the discovery of the HD gene in 1993, it became possible for the genetic confirmation of the reported cases that made the diagnosis more accurate and informative. In the last few years, Chinese researchers who were active in the HD research started to build their own database to study the clinical and genetic feature of this disorder and also collaborated a lot in this field. The progress outlined in this review indicates the beginning of an exciting new era in HD research in China.

Keywords Huntington disease · China · Research

Introduction

Huntington disease (HD) is a progressive, autosomal-dominant, inherited neurodegenerative disorder characterized by a typical triad of symptoms:movement disorder, cognitive dysfunction, and psychiatric or behavioral disturbance. These symptoms are caused by an expansion in the number of CAG repeats in the first exon of the *huntingtin (HTT)* gene, located on chromosome 4p16.3.3 [1]. Neuropathologically, it manifests as profound atrophy of the striatum as well as severe loss of neurons in the cerebral cortex [2]. While HD has been known by various names, such as Huntington's chorea, inherited chorea, and chronic progressive chorea, it was George Huntington's insightful clinical description in 1872 that led to its current well-recognized name [3]. The overall prevalence of HD in Asia in 2012 is 0.40/100,000, much lower than the 5.70/100,000 in the Caucasian population [4]. In China, since the first case report in 1959 [5], the understanding of HD has been evolving, especially in the last decade. In this review, we provide a meta-analysis and a summary of research reports concerning Chinese HD patients since 1959, to illustrate the general scenario of HD research in China.

Case Reports in Mainland China

In China, the first documented case report of HD was in 1959 [5], describing two HD patients from two Han Chinese families in Henan Province. One was a 29-year-old

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housewife who presented with progressive choreiform movements and memory impairment at the age of 18 years. It was reported that her father had developed similar symptoms around the age of 18 but was killed by the Japanese army in his 30th year. Her mother was 50 years old when the patient was diagnosed and was free of neurological symptoms. The other patient was a 32-year-old male farmer who presented with choreiform movements and dysarthria for 8 years. The symptoms progressed gradually and his memory was also severely impaired. Because this patient had left his family of origin in early adulthood, a detailed family history was not available. At that time, a diagnosis was made based on the typical clinical presentation of choreiform involuntary moment and progressive cognitive decline. In addition, a positive family history of movement disorder in combination with cognitive decline raised the possibility of HD. Before this report, HD was thought to exist exclusively in Caucasians. This case report showed physicians in China that HD also exists in the Chinese population.

Since then, hundreds of cases and family reports have emerged in Mainland China. However, it has been very difficult to find all the original reports due to the lack of E-format publications before the 1990s. Fortunately, in 1994, Zuo *et al.* [6] made a thorough meta-analysis of these reports, in which 335 HD patients from 105 families were included. Information was gathered concerning the sex of the patient, age at onset (AAO), age at death, sex of the affected parent, and disease duration. The number of patients with gender information was 208. There were more male (132, 63.5%) than female patients (63, 36.5%). The mean AAO was 38.25 years, ranging from 4 to 75. The most frequent AAO ranged from 30 to 39 (37.93%) and the second most frequent AAO ranged from 40 to 49 (35.47%). In other words, 73.4% of these patients had an AAO between 30 and 49 years. Nine patients (4.44%) had an AAO younger than 20, and three (1.48%) were older than 60. The mean age at death was 52, with the most frequent ranging from 40 to 49 (34.62%) and the second from 50 to 59 (25.64%). The mean disease duration was 12.9 years, the longest being 30 years. Forty-six patients (63.9%) had paternal transmission and 26 (36.1%) had maternal transmission. Among the 105 families, most (88, 83.81%) reported a positive family history, 14 (13.33%) denied a positive history, and the rest 3 (2.86%) had no clear history. In patients with a history that affected 3 to 4 generations, the phenomenon of anticipation was prominent. This was the first meta-analysis of case reports, providing the baseline information on the clinical characteristics of HD in China.

Since the discovery of *HTT* as the causative gene of HD in 1993 [7], genetic testing has become possible for suspected cases, providing an accurate and informative diagnosis. However, most hospitals in China cannot provide genetic testing for HD patients and their family members at risk. As a result, most case reports after 1993 still lack genetic information. In this review, we used the keywords "Huntington Disease", "HD", "inherited chorea", and "Huntington's chorea" to search the National Knowledge Infrastructure (CNKI) and WANFANG databases in China for HD-related case reports and clinical studies conducted between January 1, 1993 and December 1, 2015. As a result, 68 suitable reports were identified. After exclusion of studies and case reports without genetic information, only 19 remained for the current meta-analysis. The total number of patients in these studies was 90, of whom 56 (62.22%) were HD patients and 34 (37.78%) were classified as premanifest HD. The geographical distribution of the affected patients was very broad, from almost every province in China. Most of the reported cases were Han Chinese, with only 2 patients from a family of Hui nationality. The percentage of affected males (52, 57.78%) subjects was slightly higher than females (38, 42.22%). Among those who had clinical symptoms, the mean AAO was 39.67, ranging from 17 to 65 years. Two (3.57%) were classified as juvenile onset (younger than 21 years) and 2 (3.57%) as late onset (older than 60 years). Movement disorder was the predominant symptom at onset, accounting for 95.83% of the reported cases. Only one patient first manifested with cognitive impairment and another was characterized by personality change. Both developed movement disorders during disease progression and eventually manifested the typical triad. The mean CAG triplet repeat number in the shorter allele was 18.58 (16–24), and that in the longer allele was 47.07 (36–70). The detailed data of these cases are shown in Table S1. Although this study cohort was comparatively small, the information drawn from these cases was consistent with that reported in Caucasian populations [8].

Clinical and Genetic Investigations

In the last few years, after decades of accumulating knowledge from domestic case reports and research progress in the west, researchers in China were not satisfied with merely discovering new cases and providing a genetic diagnosis. Instead, research has centered on the use of gene testing to build their own HD databases. With these databases, it was possible to further study the clinical and genetic features of HD in the Chinese population. Currently, several centers are very active in HD research. The following are some of their contributions to the clinical and genetic features of HD in Chinese.

Juvenile HD

The prevalence of juvenile HD (JHD) is ~5%–10% in Caucasian populations [9]. Although cases of JHD have been reported in Mainland China, the exact incidence is unknown due to the lack of epidemiological data. In the meta-analysis of Zuo *et al.* [6]., the number of patients who had an AAO younger than 20 was 9 (4.44%), and in the above meta-analysis, 2 (3.57%) were classified as JHD, both less prevalent than in Caucasians [9]. The clinical features of JHD can be very different from adult-onset HD, including rigidity, bradykinesia, dystonia, parkinsonism, and even difficult-to-treat seizures [10]. It is widely believed that the AAO is inversely correlated with the number of CAG repeats, so JHD is generally caused by many CAG repeats (> 60). For example, in 2014, Liu *et al.* [11] studied 4 unrelated patients carrying >60 CAG repeats from among 119 patients in their study cohort and found that they all had JHD with a mean AAO of 9.8 ± 1.71 years. In 2007, Tang *et al* [12] reported a large HD family from Wuhan, among whom two individuals were considered to have JHD; their AAOs were 17 (with 67 repeats) and 21 (with 63 repeats). The pathogenic alleles were transmitted from the fathers. One of the fathers had a CAG number of 48 and presented with the disease at the age of 33, while the AAO and genetic features of the other father were unavailable due to early death. In 2012, Hao *et al.* [13] from Beijing studied the genetic features of 109 HD patients and one with an AAO of 14 years was discovered as JHD. The CAG triplet number of the affected boy was 15/68, and the CAG numbers of his father was 17/37 and of his mother 15/17. These are examples of dynamic expansion of CAG repeats in the intergenerational transmission that leads to anticipation.

Patients Presenting with Behavioral Symptoms

The prevalence of HD with predominantly behavioral symptoms is reported to be ~23–36% in Caucasians [14]. However, few cases with predominantly behavioral symptoms have been reported in China. As in the above meta-analysis, only one patient first manifested with personality change. This low prevalence may indicate a lack of identification of the problem. For example, patients with predominantly behavioral symptoms such as delusions, hallucinations, or attempted suicide are easily misdiagnosed as having psychological disorders and are treated with antipsychotic medicines. When the patients develop movement disorders with disease aggravation, psychiatrists with limited knowledge of HD may attribute the symptoms to the antipsychotic drugs. As a result, there might be a hidden population of patients with behavioral symptoms who have not been correctly recognized.

HD with Atypical Onset

Although the symptoms in the early stages of HD can vary, diagnosis is typically made after the onset of involuntary choreiform movements [15]. It has been reported that chorea is present in >90% of the individuals affected with this disorder [16]. However, other predominant manifestations, such as cognitive impairment, psychiatric disturbance, and dystonia or tics, have been infrequently reported at the onset of HD [17, 18]. As a result, when patients present with atypical symptoms, the clinical diagnosis can be very challenging. For example, in 2013, Dong *et al.* [19] reported that seven of their HD patients who presented with ataxia had initially been diagnosed as having spinocerebellar ataxia. Three of the patients developed chorea as the disease progressed, but the others did not. Dong *et al.* were unable to find a relationship between the number of CAG repeats and the presence of atypical motor symptoms, consistent with previous reports [20]. Thus, other factors, apart from the number of CAG repeats, may influence the phenotype and should be further investigated. These cases underscore the heterogeneity of symptom presentation in the early stages of HD before the onset of chorea.

CCG Polymorphisms

Another triplet sequence, the CCG repeat, is located on the 3′ adjacent to the CAG repeats in the *HTT* gene. The triplet sequences are also polymorphic and alleles of 7 and 10 repeats are predominant in most populations [21]. Strong linkage disequilibrium between the allele of 7 repeats and HD has been shown in the Caucasian population [22]. It has been hypothesized that, in a CCG 7 background on a normal allele, the CAG repeat number is unstable and tends to expand into the pathogenic range [22]. In contrast, in 2012, Zhang *et al.* from Zhejiang found that the distributions of the 7 and 10 CCG alleles were almost equal in patients with HD in Mainland Chinese families. As a result, they hypothesized that the CCG polymorphisms in the *HTT* gene may have no effect on the pathogenesis in Chinese HD patients [23]. This result needs to be further investigated in a larger cohort.

Research Collaboration

Because of the comparatively low prevalence of HD in China, the patient cohort of each center is very small. In our center (Department of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine), we currently have 285 HD patients from 190 families and this is the largest study cohort in China. As a result, researchers

realized that, to better study this disorder, their patient resources should be combined. Thus, researchers active in HD research have been collaborating and an academic organization named the Chinese Huntington Disease Network (CHDN) was established in 2013. Thereafter, patient evaluation and documentation has changed from being separately performed in each research center to a unified and collaborative effort among centers, with a standard research protocol for HD research. In 2014, the CHDN had its first publication by Jiang *et al.* [24], who studied the CAG repeat numbers in 368 Chinese HD patients and 483 controls from six centers. The CAG triplet repeat number in normal controls ranged between 9 and 35 (mean 18.9 $\pm$ 2.57), of which 2.5% ranged between 26 and 35. In the patient cohort, triplet repeats in the shorter allele were from 8 to 37 and in the longer allele from 36 to 120. The mean AAO was 38 years, with a range of 2–70 years. Twenty-three patients (6%) with a juvenile onset were found. In addition, an inverse correlation between AAO and the number of triplet repeats in the larger allele was noted. This study included the largest Chinese HD cohort so far and provides the baseline clinical and genetic characteristics of HD in China.

Future Directions

Over the last 10 years, we have gained great insight into the clinical and genetic features of HD in China. Although the research is still comparatively limited due to the rarity of HD in the Chinese population, from another perspective, much remains to be explored. First, since HD is a rare disorder in China and requires well-trained neurologists to recognize it, patients in remote regions of the country may remain undiagnosed. As a result, further studies are needed for an epidemiological overview of HD in China. Second, it is well known that the prevalence of HD varies widely among different populations, so the genetic backgrounds of different populations should be further explored. Besides, studies analyzing the onset of symptoms in HD indicate a 70% contribution from CAG repeat number. The remaining variation is thought to be due to modifier genes or environmental factors, which may account for the disparities seen in different populations. We should further investigate the genetic and environmental factors that may modify the clinical phenotypes of affected patients in the Chinese population. Last but not least, identification of the early signs of HD has been the focus of many recent investigations [25–27]. With the availability of diagnostic and predictive genetic testing in many hospitals and institutions in China, increasing numbers of premanifest patients have been identified. These are valuable resources for studying the early signs of HD as well as the underlying pathophysiology.

Conclusion

In conclusion, HD is the most widely studied genetic neurodegenerative disease in the Caucasian population and research on this disorder has just begun in China in the last decade. The progress outlined in this review indicates the beginning of an exciting new era of HD research in China.

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