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The clinical, imaging and biological features of psychosis in Han Chinese patients with Huntington's disease

Xiao-Yan Li [a,1], Bin Gao [a,1], Juan-Juan Xie [a], Yu-Feng Bao [a], Yi Dong [a,b], Zhi-Ying Wu [a,c,*]

[a] Department of Neurology and Research Center of Neurology in Second Affiliated Hospital, and Key Laboratory of Medical Neurobiology of Zhejiang Province, Zhejiang University School of Medicine, Hangzhou, China
[b] Department of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China
[c] CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai, China

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ABSTRACT

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease involving motor, cognitive and psychiatric disturbances. HD patients with psychosis symptoms usually have bad prognosis. It is of great significance to explore the clinical, imaging and biological characteristics of HD patients with psychosis. A total of 118 Han Chinese patients with HD confirmed by *Huntingtin* genetic testing were recruited during 2013–2020. They were assessed by Unified Huntington's Disease Rating Scale (UHDRS) and followed up in an average of 34 months by telephone or clinical visits. Psychosis was determined by the presence of delusions or hallucinations using UHDRS-Problem Behavior Assessment. Data of magnetic resonance imaging (n = 28) and serum neurofilament light chain (NfL, n = 28) were collected in some patients. Among 118 patients (mean age 46.0 years, SD 12.0; female 53.5%), the frequency of psychosis was 14.4% (n = 17) in the cross-sectional analysis and 17.8% (n = 21) in the longitudinal observation. Probands with psychosis were predominantly female (82.3%). They exhibited worse motor, cognitive, behavioral and functional performances compared with patients without psychosis. Furthermore, the lateral ventricle volume was larger in patients with psychosis compared with patients without psychosis ($p = 0.0013$) while there was no difference in NfL levels between two groups. NfL levels of patients with psychosis were negatively correlated with caudate volumes ($r = -0.54$, $p = 0.044$) and white matter volumes ($r = -0.57$, $p = 0.035$). In summary, HD patients with psychosis had distinct clinical, imaging and biological features. These features might help clinicians to identify psychosis in HD patients early and provide protective interventions before adverse outcomes occur.

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of cytosine-adenine-guanine (CAG) repeats in the first exon in *Huntingtin* (*HTT*) gene. The principal symptoms of HD are choreiform movements, cognitive impairment, psychiatric and behavioral disturbances (The Huntington's Disease Collaborative Research Group, 1993). The disease generally starts at the age of 30–50 years, and gradually progresses for approximately 15–20 years until patients' death (Roos et al., 1993). HD occurs worldwide but the prevalence varies across populations. Among populations of European descent, the prevalence is between 10.6 and 13.7 cases per 100,000 people (Bates et al., 2015). However, in the Chinese and other East Asian populations, the prevalence is much lower, reported to be 0.1–0.65 cases per 100, 000 people (Chen and Lai, 2010; Nakashima et al., 1996).

In a European HD cohort, neuropsychiatric symptoms are very common in HD patients with a prevalence of 73% reported (van Duijn et al., 2014). Neuropsychiatric symptoms include depression, irritability, aggression, apathy, obsessive/compulsive behaviors and psychosis. Prevalence of psychosis ranges from 3% to 11% in HD patients (Rocha et al., 2018; van Duijn et al., 2007), which is much higher than the 1% in the general population. The formal definition of "psychosis" is not given in the Diagnostic Statistical Manual-5 (American Psychiatric Association, 2013), and it lacks a unified definition (Gaebel and Zielasek, 2015).

* Corresponding author. Department of Neurology and Research Center of Neurology in Second Affiliated Hospital, and Key Laboratory of Medical Neurobiology of Zhejiang Province, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou, 310009, China..
E-mail address: zhiyingwu@zju.edu.cn (Z.-Y. Wu).
[1] Authors contributed equally to this work.

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Table 1
Comparisons of demographic and clinical features between HD probands with and without psychosis.

Characteristics	Univariate analysis			Bivariate logistic regression	
	HD with psychosis (n = 17)	HD without psychosis (n = 101)	*p value*	OR (95% CI)	*p value*
Demographics					
Female, n (%)	14 (82.3%)	49 (48.5%)	0.009	0.111 (0.008–1.472)	0.950
Age, years	48.7 (14.3)	46.0 (11.4)	0.394	1.070 (0.957–1.198)	0.235
Education	7.1 (3.5)	8.6 (4.0)	0.156	1.306 (0.836–2.040)	0.242
Clinical characteristics					
CAG repeats, number	46.2 (8.4)	44.4 (4.6)	0.220	/	/
Age at onset of chorea or motor symptoms, years	42.7 (14.8)	40.4 (10.5)	0.324	/	/
Age at onset of psychiatric symptoms, years	44.9 (15.2)	/	/	/	/
Duration of disease, year	6.0 (4.0)	6.5 (6.3)	0.764	/	/
Total motor scores	56.9 (26.9)	35.1 (21.8)	<0.001	1.089 (0.908–1.305)	0.357
Chorea score (0–28)	10.3 (7.8)	9.2 (5.3)	0.471	0.682 (0.509–0.913)	0.010
Dystonia (0–20)	8.7 (5.5)	4.2 (4.2)	<0.001	1.528 (1.056–2.210)	0.025
Balance (0–12)	5.9 (2.7)	3.7 (2.8)	0.003	0.586 (0.345–0.995)	0.048
Cognition					
MMSE (0–30)	12.8 (9.8)	22.0 (6.2)	<0.001	0.824 (0.613–1.106)	0.197
Stroop word test-right	20.3 (26.7)	49.6 (19.1)	<0.001	0.889 (0.823–0.962)	0.003
Stroop color test-right	16.8 (21.4)	33.7 (16.8)	<0.001	1.014 (0.872–1.179)	0.856
Stroop interference test-right	8.9 (12.8)	17.2 (12.9)	0.010	1.110 (0.829–0.994)	0.037
SDMT	4.5 (9.0)	16.6 (14.3)	0.001	0.885 (0.995–1.003)	0.080
Trail Making Test A (s)	192.9 (70.9)	130.2 (72.8)	0.028	0.979 (0.955–1.003)	0.169
Trail Making Test B (s)	225.2 (36.6)	194.9 (62.4)	0.055	/	/
Psychiatric history					
Suicidal attempts, n (%)	8 (47.0%)	9 (9.0%)	<0.001	137.05 (4.349–4318.770)	0.005
Depression, n (%)	12 (70.6%)	35 (34.7%)	0.005	1.747 (0.079–38.879)	0.724
Obsessive/compulsive behaviors, n (%)	6 (35.3%)	22 (21.8%)	0.231	/	/
Irritability, n (%)	14 (82.3%)	70 (69.3%)	0.388	/	/
Aggression, n (%)	9 (52.9%)	27 (26.7%)	0.030	1.479 (0.083–26.200)	0.790
Apathy, n (%)	10 (58.8%)	34 (33.7%)	0.5882	/	/
TFC (0–13)	4.3 (3.4)	8.6 (3.5)	<0.001	0.704 (0.436–0.932)	0.020
Presence of family history of psychosis, n (%)	7 (41.2%)	9 (8.9%)	0.002	/	/
Number of relatives with HD and psychosis, n (%)	12 (22.6%)	9 (3.6%)	<0.001	/	/

Numbers in brackets indicate SD for continuous variables and percentages for categorical variables. Abbreviations: MMSE, Mini-mental State Examination; SDMT, Symbol Digit Modalities test; PBA, Problem Behavior Assessment; TFC, total functional capacity.
Logistic regression analysis (backward model) for "HD patients with psychosis" versus "HD patients without psychosis".

Psychosis includes a range of symptoms but involves one of the two core clinical features: hallucinations and delusions. In this study, patients with psychosis were determined by the presence of delusions or hallucinations using Problem Behavior Assessment (PBA) from the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996), which was based on previous studies (Connors et al., 2020; van Duijn et al., 2014). Psychosis usually occurs after motor manifestations, and predates the motor symptoms in a few HD cases (Amann et al., 2000; Nagel et al., 2014).

It has been shown that HD patients with psychosis have poor cognitive and lower functional performances compared with those without psychosis in a European cohort (Connors et al., 2020). Psychosis has a profound impact on both patients' and caregivers' quality of life. We hypothesized that HD patients with psychosis may have distinct clinical, imaging and biological characteristics compared to patients without psychosis. Also, serum neurofilament light protein (NfL), a marker of axonal damage, was proved to be a sensitive biomarker to reflect the cerebral degeneration (Byrne et al., 2017; Li et al., 2019). And brain magnetic resonance imaging (MRI) is a good tool to detect the cerebral atrophy in HD (Tabrizi et al., 2013). Thus, a cohort of Chinese HD patients were included to describe the clinical features and familial aggregation of psychosis, exploring its underlying imaging and biological characteristics.

2. Methods

2.1. Participants enrollment

During August 2013 to September 2020, 118 Han Chinese HD patients from unrelated families, confirmed by genetic testing of *HTT* gene were recruited at the departments of neurology in two medical centers, the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou) and Huashan Hospital of Fudan University (Shanghai). Each patient was examined by at least two senior neurologists, including detailed physical and neurological examination according to DeJong's the neurologic examination (Campbell, 2013). Medical data and blood samples were collected. UHDRS was performed by trained raters. Patients underwent MRI scanning with their consents. Patients were followed up by clinical visits or by telephone for 34 months on average. The study was approved by the ethics committees of the two hospitals mentioned above. Informed consents were signed by patients or their guardians.

2.2. Genetic testing of HTT gene

Genomic DNA from peripheral blood was extracted by using a DNA extraction kit (Qiagen Inc, Valecia, CA). Genetic testing of *HTT* gene was performed using the method reported previously (Dong et al., 2013). The forward primer was 5′-CAGAGCCCCATTCATTGCC-3′ and reverse was 5′-TGAGGAAGCTGAGGAGGC-3′. The length of CAG repeats was determined by Sanger sequencing which was described previously (Dong et al., 2016).

2.3. Clinical assessment

Patients were assessed by UHDRS and Mini-Mental State Examination (MMSE). UHDRS is a common tool to assess HD, which comprises motor performance, behaviors, cognition and functional capacity assessments. Motor disturbance was assessed by using the UHDRS-motor assessment, which is comprised of 15 items with a total score of 124, with higher scores indicating greater impairment. In the scale, the item 12 for chorea (range: 0–28), item 11 for dystonia (range: 0–20), and item

Table 2
Comparisons of demographic and imaging features between patients with and without psychosis.

	HD with psychosis (n = 14)	HD without psychosis (n = 14)	t/χ 2	*df*	*p*
Demographics					
Female, n (%)	2 (14.3%)	2 (14.3%)	0.00	1	1.00
Scanning age, years[a]	50.0 (14.0)	48.0 (10.1)	0.416	26	0.68
Education, years	6.9 (3.8)	7.4 (4.8)	−0.262	26	0.79
Clinical characteristics					
CAG repeats, number	45.3 (7.4)	43.6 (3.7)	0.783	26	0.44
Age at onset of motor symptoms, years	42.9 (13.9)	41.9 (10.0)	0.218	26	0.83
Duration of disease, years	7.0 (4.5)	6.1 (3.7)	0.597	26	0.55
Total motor scores	56.2 (19.1)	45.1 (24.7)	1.326	26	0.20
MMSE	13.6 (8.9)	20.4 (8.4)	−2.067	26	0.04
TFC (0–13)	4.5 (3.0)	8.1 (4.5)	−2.445	26	0.02
Imaging characteristics					
Caudate volume/ICV (10^-3)	1.33 (0.52)	1.38 (0.50)	−0.289	26	0.77
Putamen volume/ICV (10^-3)	1.86 (0.50)	1.91 (0.54)	−0.250	26	0.81
Grey matter volume/ICV (10^-1)	3.94 (1.16)	3.60 (1.27)	0.75	26	0.46
White matter volume/ICV (10^-1)	2.77 (0.35)	2.99 (0.53)	−1.317	26	0.20
Lateral ventricle volume/ICV (10^-2)	4.01 (1.2)	2.63 (0.78)	3.587	26	0.001
Neurofilament light chain (pg/mL)	41.7 (16.2)	47.6 (19.2)	−0.870	25	0.393

[a] Data are present as mean (SD). MMSE, Mini-mental State Examination; TFC, total functional capacity; ICV, intracranial volume.

13–15 for balance (range: 0–12) were analyzed for each performance. Behavioral disturbance was assessed using PBA (range: 0–176) to evaluate 11 neuropsychiatric symptoms by frequency and by severity. Each subscore ranges from 0 to 4, with 0 indicating no neuropsychiatric symptoms and 4 indicating frequent or severe symptoms. Higher scores mean more severe behavioral symptoms. The psychosis subscale in the PBA (range 0–32 points) consists of two symptoms: delusions and hallucinations. Cognitive assessment of UHDRS is comprised of Symbol Digit Modalities Test (SDMT), Stroop color word interference test (including Stroop word test, Stroop color test and Stroop interference test) and Trail Making Test A and B. They were used to evaluate the executive functioning. SDMT and Stroop color word interference test are scored on the correct number in the given times. Trail Making Test A and B are scored on the time after finishing the task. MMSE was used to assess the global cognition (Pangman et al., 2000). Total functional capacity (TFC) was used to assess daily functioning, with score ranging from 13 (normal function) to 0 (loss of function). Huntington's disease Clinical Characteristics scale is a structure questionnaire that asks about the age at onset (AAO) of different neuropsychiatric symptoms. Psychosis was diagnosed by the presence of delusions or hallucinations with PBA. The AAO of psychosis was when patients first experience delusion or hallucination. The severity of psychosis was assessed with psychosis score in PBA.

2.4. MRI acquisition and processing

The 1.5 Tesla (T) MRI scanning (signa HDx Echospeedg, GE Healthcare, United States) was performed in the Second Affiliated Hospital of Zhejiang University School of Medicine and 7 T MRI scanning (Magnetom, Siemens Healthcare, Erlangen, Germany) was performed in Zhejiang University. The imaging parameters of 1.5 T T1-weighted images were the followings: repetition time (TR) = 3720.0 ms, echo time (TE) = 9.4 ms, Field of view (FOV) = 24 cm × 24 cm, sagittal slices to cover the entire brain with a slice thickness of 6.0 mm with no gap between slices. Additionally, the imaging parameters of 7 T MRI T1-weighted images were the followings: TR = 5000 ms, inversion time (TI)1 = 900 ms, TI2 = 2750 ms, TE = 2.27 ms, voxel size: 0.7 × 0.7 × 0.7 mm^3. Structural T1-weighted images preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Volumetric measures of intracranial volume (ICV), putamen, caudate, grey matter, white matter, and the lateral ventricle were derived from T1-weighted images by ITK-SNAP (Yushkevich et al., 2006).

2.5. Serum NfL measurement

Venous blood was collected from patients in BD Vacutainer tubes (Plymouth PL6 7BP, UK) containing separation gel. Serum was obtained from blood samples centrifuged at 2000×*g* for 10 min. Serum NfL was measured by the single-molecule (Simoa) array method on an HD-1 platform (GBIO, Hangzhou, China). The detailed method was previously reported (Li et al., 2019).

2.6. Statistical analysis

Data analysis was performed by SPSS 20.0 (IBM, Armonk, NY). Unpaired two-sample *t*-test was used for continuous variables and χ^2 test was used for comparison of categorical variables. Shapiro-Wilk test was used to test the normality of variables. Correlation analysis used Pearson's correlation if variables were normally distributed or Spearman rank correlation if variables were not normally distributed. Logistic regression with presence of psychosis as a binary outcome was used to test the association between disease features and psychosis. A *p*-value less than 0.05 is considered statistically significant. Bonferroni correction was used for multiple-comparison.

3. Results

3.1. Familial aggregation of psychosis in HD

Of 118 patients, the mean age (SD) was 46.0 (12.0) years, and 53.5% were female. Using PBA, we identified 17 patients (14.4%) with psychosis in our cohort at baseline, who were predominantly woman (82.3%). Patients were followed up on an average of 34 months (range 1–85 months) by clinical visits or by telephone. We found 4 patients who didn't show any psychosis at baseline developed psychosis afterwards. Thus, the frequency of psychosis increased to 17.8% in the longitudinal observation. In this cohort, 4 patients developed psychosis before motor symptoms onset, 12 patients after motor disturbance onset, and 5 patients had concurrent movement disorders and psychosis.

To exam the familial aggregation of psychosis, comparisons between 17 probands with psychosis and 101 probands without psychosis were made (Table 1). The estimated risk of developing psychosis for relatives was much higher (22.6%) in psychosis group compared with 3.6% in non-psychosis group. Moreover, no relative was found only with psychosis but without HD, indicating psychosis was highly associated with HD.

3.2. Distinct clinical features in patients with psychosis

To explore the clinical features of psychosis in HD patients (Table 1), univariate analysis was used. Significant differences were found in total motor score, dystonia score, balance score, MMSE, SDMT, Stroop color word interference test, Trail Making Test A and TFC ($p < 0.05$). Patients with psychosis had higher rates of suicidal attempts, depression and

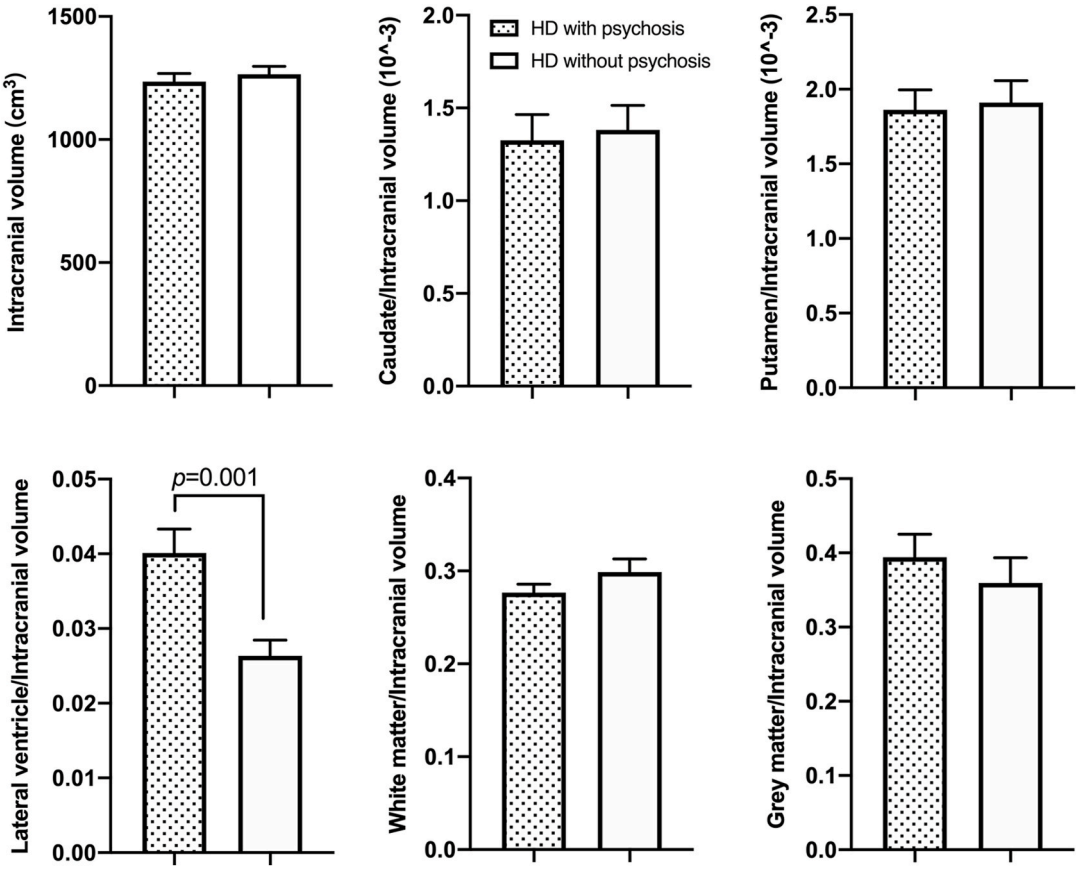

Fig. 1. The imaging features of HD patients with psychosis. (A–F) Volumes of caudate, putamen, lateral ventricle, white matter, grey matter corrected for intracranial volume were compared between patients with psychosis (n = 14) and patients without it (n = 14). Only lateral ventricle volumes showed a significant difference between two groups ($p = 0.0013$).

aggression history ($p < 0.001$, $p = 0.005$, $p = 0.030$, respectively). Then, bivariate logistic regression was performed to adjust for sex, age and education years. Patients with psychosis showed worse motor function (chorea, dystonia and balance), worse cognition (lower Stroop word test score), more severe behavioral problems (higher suicidal attempts) and lower TFC score compared with those without psychosis.

AAO of psychosis was inversely associated with length of CAG repeats ($R^2 = 0.648$). The longer the CAG repeat length is, the earlier psychosis occurs. In addition, correlation between length of CAG repeats and AAO of motor symptoms was also examined with R^2 of 0.730 (**Supplemental Figure**).

3.3. Imaging differences between patients with and without psychosis

Among 118 HD patients, brain MRI data of 14 patients with psychosis (9 patients with 1.5 T MRI and 5 patients with 7 T MRI) and 14 age- and sex-matched patients without psychosis (9 patients with 1.5 T MRI and 5 patients with 7 T MRI) were analyzed. Comparisons of demographic and imaging features between patients with and without psychosis are shown in Table 2. Patients in two groups had similar sex ratio, scanning age, education years, motor AAO and CAG repeat numbers. But patients with psychosis had significant larger lateral ventricle volumes than those without psychosis after Bonferroni correction ($p = 0.0013$). However, there was no difference in volumes of caudate, putamen, white and grey matter adjusting for ICV (Fig. 1). In addition, MRI images of several typical HD patients with psychosis are shown in Fig. 2.

3.4. Serum NfL was associated with clinical and imaging features in HD patients with psychosis

Serum NfL concentration was available in 15 patients with psychosis and 13 patients without psychosis. There was no difference in serum NfL level between two groups (Table 2). In psychosis group, serum NfL was negatively associated with MMSE score ($r = -0.45$, $p = 0.049$) (Fig. 3), but not significantly associated with Stroop word test and TFC scores ($r = -0.50$, $p = 0.105$; $r = -0.44$, $p = 0.112$, respectively). Additionally, there was no association between NfL concentration and PBA score, psychosis score in PBA or total motor score. We also analyzed the correlations between serum NfL and imaging features. Serum NfL showed negative correlations with caudate volumes ($r = -0.54$, $p = 0.044$) and white matter volumes ($r = -0.57$, $p = 0.035$).

4. Discussion

This study first gives a description of the imaging and biological profile in HD patients with psychosis, and reveals the prevalence of psychosis in the Chinese HD cohort cross-sectionally and longitudinally. HD patients with psychosis exhibited worse motor, cognitive and functional performances than patients without psychosis. Accordingly, these patients also had larger lateral ventricle volumes. However, there was no difference in serum NfL levels between the two groups.

The prevalence of psychosis was 14.4% at baseline in our cohort and increased to 17.8% in a 34-month follow-up. This suggests that the proportion of psychiatric patients will increase with longer observation time. Additionally, the prevalence of psychosis in our cohort was similar to that in the European cohorts. In two recent large-sample cross-sectional studies from Europe, the prevalence of psychosis is about

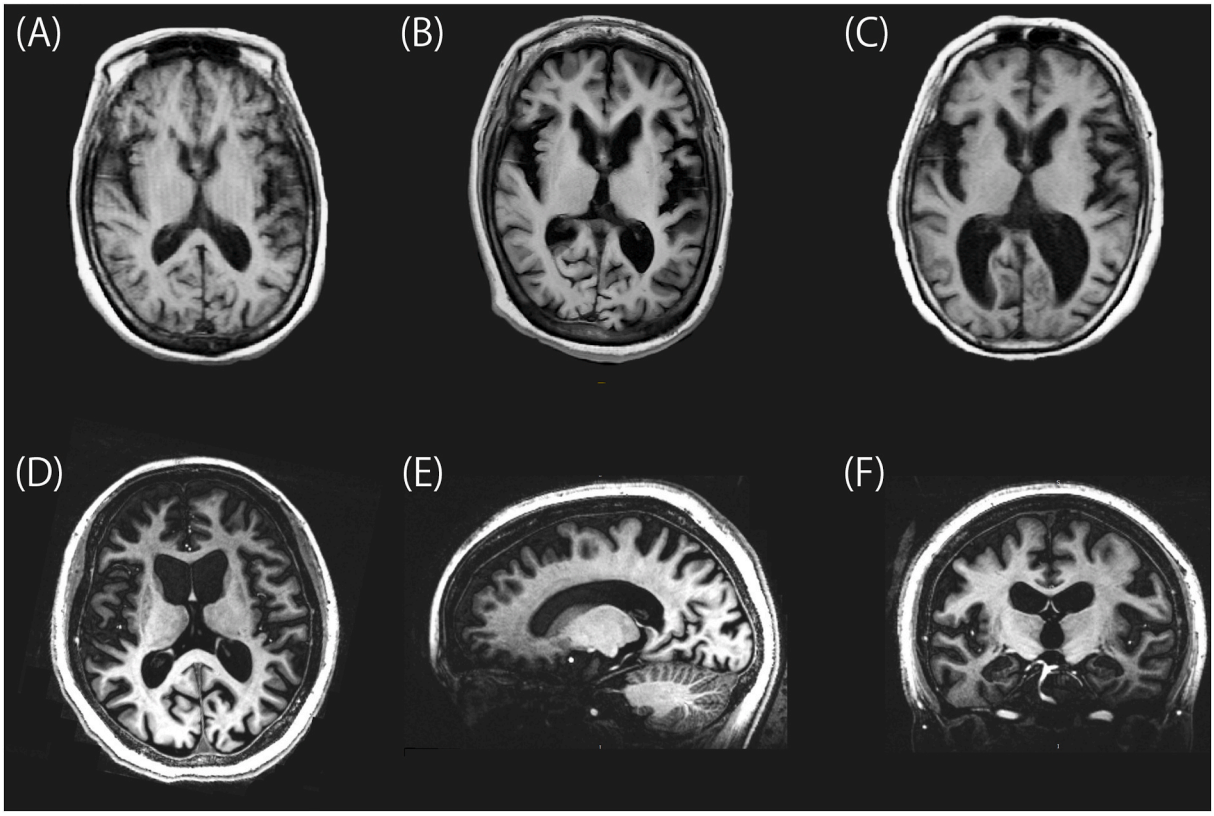

Fig. 2. T1-weighted brain magnetic resonance imaging (MRI) images of three typical HD patients with psychosis. (A–B) A 56-year-old woman with HD, was longitudinally followed up and underwent 1.5 T MRI scanning in 2017 and 2020, respectively. In 2017 she didn't show any psychosis symptoms while in 2020 she had serious delusion and hallucination. The MRI images showed the enlargement of lateral ventricle and atrophy of temporal lobe. (C) A 56-year-old woman, diagnosed both as HD and schizophrenia, had 4-year disease duration. Her lateral ventricle was remarkably enlarged. (D–F) The 7 T MRI images of a 40 years old woman with 9 years of disease duration. She developed serious and refractory psychosis after having a high fever. The lateral ventricle was enlarged accompanied by severe cerebral atrophy including caudate, putamen, parieto-temporal lobe and hippocampus.

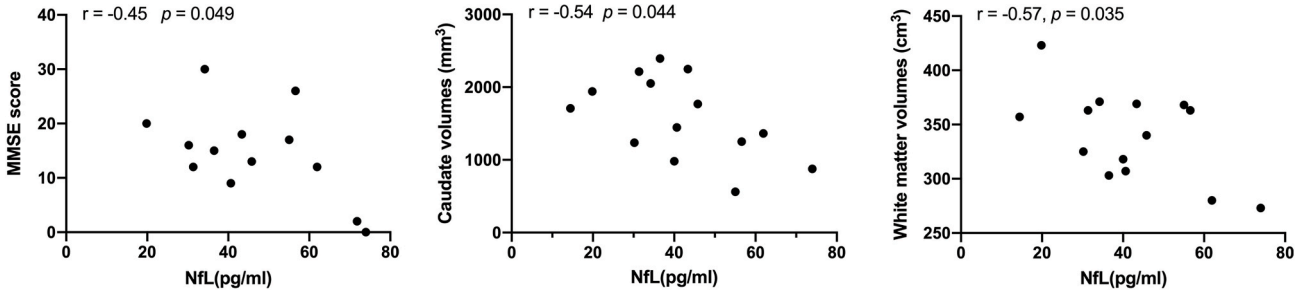

Fig. 3. Correlations between serum NfL and MMSE score, caudate and white matter volumes. MMSE, the Mini-Mental State Examination. NfL: neurofilament light.

10.8%–13.0% (Jaini et al., 2020; Rocha et al., 2018), and in another longitudinal study, the prevalence was higher (18.0%) (Connors et al., 2020).

In our cohort, women were easier to be affected with psychosis in our study than men, indicating sex might be an important factor for developing psychosis in HD. However, previous studies of European and American cohorts found there was no sex difference between HD patients with and without psychosis (Connors et al., 2020; Tsuang et al., 2000). There are several possible explanations for the controversial findings, including sample sizes, different cultural and environmental factors, and varied genetic backgrounds between the Chinese population and the Caucasian population.

Patients with psychosis had distinct clinical features in this cohort. They not only had familial predisposition to develop psychosis, but also exhibited worse cognition, higher suicidal attempts than patients without psychosis, which was consistent with a previous study of European cohort with HD (Connors et al., 2020). In addition, patients with schizophrenia also had similar phenotypes. On the one hand, twin and several studies have shown that genetic factors play a role in developing schizophrenia, with estimated heritability of 80% (Sullivan et al., 2003). On the other hand, patients with schizophrenia had cognitive impairments and high attempted suicide (10%–50%), which contributed significantly to functioning disability (Guo et al., 2019; Ventriglio et al., 2016).

Larger lateral ventricle volume was found in HD patients with psychosis compared to patients without psychosis. However, there was no difference in caudate or putamen volumes. This finding indirectly showed the enlargement of lateral ventricle might be caused by psychosis symptoms rather than neurodegeneration brought by HD itself. Lateral ventricle enlargement was also reported in patients with

schizophrenia (Shenton et al., 2001). Therefore, we hypothesized that psychosis in HD and schizophrenia might share some common imaging features underlying the phenotypes. Recently, a genome-wide association study also supported the hypothesis in a genetic way (Ellis et al., 2020). The study demonstrated that some genetic risk factors for schizophrenia were associated with increased risk of the corresponding psychiatric symptoms in HD.

There were several limitations in this study. First, the use of antipsychotic medication may have led to an underestimation of the number of HD patients with psychosis. Second, as psychosis in HD is not common, the sample size is relatively small, which may have caused some bias in the imaging analysis. Third, the follow-up time was not long, and part of the data collection was obtained by telephone, which may have caused some bias to the results.

Despite these limitations, the current study provides evidence that patients with psychosis have a distinct clinical course and imaging characteristics compared with those without psychosis. HD patients with psychosis tend to have large lateral ventricle volumes. These features may help physicians to detect psychosis early and give a more successful management. Moreover, identifying specific genetic modifiers or neural circuitry for psychosis in HD may be an important direction for the future.

CRediT authorship contribution statement

Xiao-Yan Li: Writing – original draft, Data curation, Investigation, Formal analysis. **Bin Gao:** Writing – original draft, Data curation, Investigation. **Juan-Juan Xie:** Data curation, Investigation. **Yu-Feng Bao:** Data curation. **Yi Dong:** Formal analysis. **Zhi-Ying Wu:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.07.024.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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