Vital Surveillances

Geographic Diversity in the Incidence of Human Prion Diseases — China, 2006–2019

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ABSTRACT

Introduction: Human prion diseases (PrDs) are rare, fatal encephalopathies requiring comprehensive diagnostic analysis. This study examines hospital referral patterns to the Chinese National Surveillance for Creutzfeldt-Jakob Disease (CNS-CJD) from 2006 to 2019.

Methods: We assessed 1,970 PrD cases referred by various hospitals to CNS-CJD. Referral distributions were analyzed based on provincial-level administrative divisions (PLADs). Differences in referral numbers and confirmed cases between monitored and non-monitored PLADs were statistically evaluated.

Results: The study included cases from 344 hospitals across 29 Chinese PLADs. Hospital referrals increased over the surveillance years: from 28.2 hospitals annually during 2006–2010, to 64 in 2011–2015, and 107 in 2016–2019. Of these, 12.2% (42/344) of hospitals reported ≥10 PrD cases, accounting for 70.0% (1,379/1,970) of total cases. Referral numbers varied across PLADs, with the top 5 of Beijing (41), Henan (26), Shanghai (21), Guangdong (21), and Jiangsu (21) leading. Additionally, 12 CJD-surveillance PLADs had more referring hospitals and PrD cases than the other 17 non-surveillance PLADs.

Conclusions: Geographical variations in PrD recognition exist across Chinese PLADs, with certain regions and major cities reporting notably higher case numbers.

Human prion diseases (PrDs) encompass a suite of transmissible spongiform encephalopathies (TSEs) induced by the unwelcome prion pathogen. This set of diseases includes Kuru disease, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI) (*1–2*). Human PrDs can manifest in sporadic, genetic, or iatrogenic forms. Among these, sporadic CJD (sCJD) is the most prevalent form of human PrDs, constituting approximately 85%–90% of all PrD cases (*3–4*). The global morbidity for human PrDs is estimated at 1–2 individuals per million annually, with mortality invariably standing at 100% (*2–3*). Clinical manifestations of human PrDs can be diverse; however, rapid progressive dementia typically serves as the primary symptom. The definitive diagnosis of human PrDs currently relies on the neuropathological examination of biopsied brain tissue or postmortem analyses (*1–2,5*).

Recognition and diagnosis of human PrDs in China remained largely absent until the end of the 1980s due to its rarity. Prior to the implementation of the China National Surveillance for Creutzfeldt-Jakob Disease (CNS-CJD) in 2006, only a handful of Chinese CJD cases were reported in scholarly literature (*6–7*). The initiation of the CNS-CJD, however, led to an increase in diagnoses as hundreds of hospitals across China began to recognize and identify PrD cases (*8–10*).

Nonetheless, there was notable variance in both the number of participating hospitals and diagnosed PrD cases between different provincial-level administrative divisions (PLADs) in China (*9*). Utilizing CNS-CJD surveillance data, we conducted an analysis of the relevant factors pertaining to participating hospitals. This analysis was undertaken to evaluate the disparities in PrD recognition capacities across different PLADs.

METHODS

CNS-CJD

The development and execution of the CNS-CJD project has previously been discussed in depth (*10*). To summarize, the CNS-CJD initiative was officially launched in 2006. This project encompasses 12 provincial CDCs and 15 sentinel hospitals, spanning across 12 PLADs, including Beijing, Shanghai, Tianjin, Chongqing, Jilin, Shaanxi, Hubei, Guangdong, Guizhou, Anhui, Henan, and Xinjiang

(*9*–*10*). Surveillance data indicated that clinical records and samples from suspect patients were procured by local hospital clinicians, while pertinent epidemiological data were gathered by provincial CDC personnel. Compiled data and samples [including cerebrospinal fluid (CSF), blood, and brain tissue] were then forwarded to the Chinese CDC's national reference laboratory for CNS-CJD for lab testing and ultimate diagnosis.

Case Definition

The suspected cases of CJD referred to as CNS-CJD were identified and subtyped based on the diagnostic criteria released by the Chinese National Health Commission. This criteria framework was adapted from the diagnostic criteria for CJD developed by World Health Organization (WHO). Patient clinical and epidemiological data were gathered using specially designed questionnaires. A spectrum of clinical examination results were amassed, including magnetic resonance imaging (MRI), electroencephalography (EEG), and routine CSF biochemistry, along with laboratory tests such as CSF 14-3-3, CSF tau, CSF and skin real time-quaking induced conversion assay (RT-QuIC), and *PRNP* PCR and sequencing. A panel of experts consisting of neurologists, neuropathologists, epidemiologists, and laboratory staff were responsible for determining the interim or final diagnosis (*9*).

Data Collection

This study incorporated a total of 1,970 distinct PrD cases, comprising patients with sCJD and a variety of genetic PrDs (gPrD). Hospitals that reported diagnosed cases to CNS-CJD were identified as the referring hospitals in this investigation. Separate counts were maintained for the annual and cumulative totals of PrD cases reported from each hospital. The distribution of referring hospital numbers and their diagnosed PrD cases were established based on the varied PLADs.

Statistical Analysis

The differences in the numbers of the referring hospitals and the diagnosed PrD cases between surveillance and non-surveillance PLADs were assessed by two-tailed Student's t test using the SPSS 22.0 (International Business Machines Corporation, Armonk, New York, USA) statistical package. The data were presented as mean±standard deviation (SD).

RESULTS

The Number of Referring Hospitals for Human PrDs Increased Over the Duration of the Surveillance Years

This study enrolled a total of 1,970 human PrD cases of CNS-CJD from 2006 to 2019, encompassing sCJD, FFI, and various genotypes of gCJD and GSS. These PrD cases derived from 344 distinct hospitals across 29 of the 31 PLADs in Chinese mainland. Remarkably, 89% (308/344) of these referring hospitals represent Grade III class A medical institutions, the highest level according to Chinese standards for hospital classification. The annual tally of both the referring hospitals and the diagnosed PrD cases was compiled for the years 2006 through 2019. Concurrent with the uptick in diagnosed PrD cases was an increase in the number of referring hospitals throughout these surveillance years (Figure 1). The average number of referring hospitals during the first five years (2006–2010) and the second five years (2011–2015) were 28.2 and 64 respectively, this number increased to 107 in the most recent four years (2016–2019). This suggests that an increasing number of hospitals have been identifying and diagnosing human PrD cases over the surveillance period.

A Significant Number of PrD Cases Reported from a Small Subset of Hospitals

The referring hospitals were categorized based on the number of PrD cases they diagnosed (Table 1). Among these, 12.2% (42/344) reported and diagnosed ten PrD cases within the study period, collectively representing 70.0% (1,379/1,970) of all PrD cases. Leading the group was Beijing Xuanwu Hospital, which diagnosed the highest number of PrD cases (163). Moreover, ten additional hospitals referred between 40 and 99 PrD cases, distributed among Beijing (4 hospitals), Henan (2), Guangdong (1), Jilin (1), Shanghai (1), and Sichuan (1). An additional 31 hospitals reported between 10 and 39 cases. Despite this, the majority of the hospitals (263, accounting for 76.5%) reported merely one or a handful of PrD cases (less than 5).

The Referral Hospitals in China Unevenly Distributed Among the PLADs

We evaluated the diversity of the referring hospital

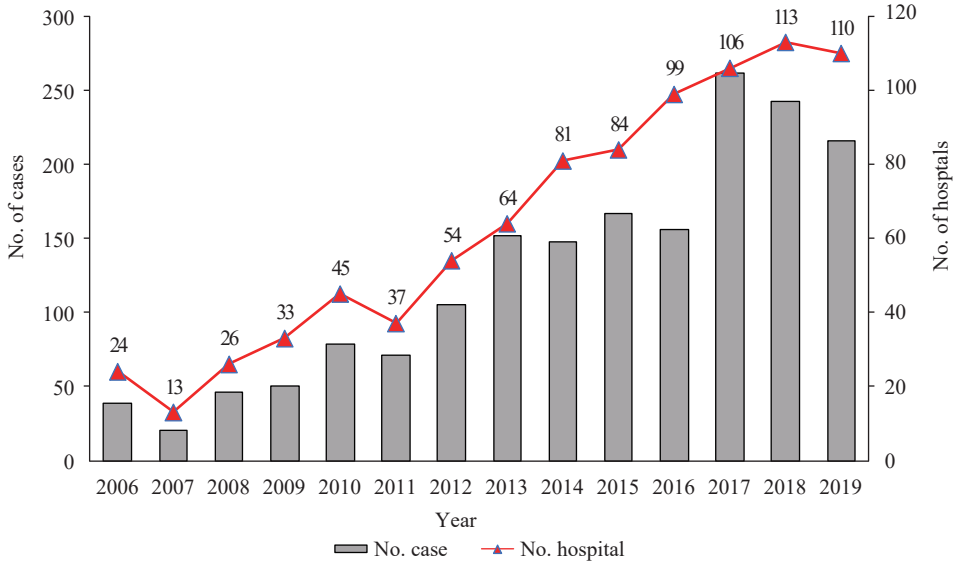

FIGURE 1. Annual number of referred hospitals and PrD cases from 2006 to 2019.
Note: Right Y-axis represents the number of referring hospitals (indicated by red triangles), while the Left Y-axis represents the number of PrD cases (depicted by gray columns).
Abbreviation: PrD=prion disease.

TABLE 1. Distribution of referring hospitals based on the number of diagnosed prion disease cases.

Case	>100	80–99	60–79	40–59	20–39	10–19	5–9	1–4	Total
No. of hospitals (%)	1 (0.3)	1 (0.3)	3 (0.9)	6 (1.7)	10 (2.9)	21 (6.1)	39 (11.3)	263 (76.5)	344
No. of cases (%)	163 (8.3)	95 (4.8)	215 (10.9)	287 (14.6)	262 (13.3)	285 (14.5)	255 (12.9)	408 (20.7)	1,970

distributions within the PLADs, based on the number of referring hospitals and the PrD cases reported in each PLAD. Table 2 indicates that Beijing had the highest number of referring hospitals and diagnosed PrD cases. During the study period, 41 hospitals from Beijing reported 546 PrD cases, constituting 11.9% of the referring hospitals and 27.7% of the total reported PrD cases. Five other PLADs reported equal to or more than 20 referring hospitals: Henan (26), Shanghai (21), Guangdong (21), Jiangsu (21), and Hebei (20). An additional seven PLADs had referring hospital numbers ranging from 10 to 19. The reported cases from these 13 PLADs represented 82.6% of all PrD cases (1,628 out of 1,970). While there was a strong correlation between the numbers of referring hospitals and diagnosed PrD cases, diversities were observed in several PLADs. For instance, Jiangsu and Hubei had a larger number of referring hospitals but a relatively small number of PrD cases, whereas Jilin, with fewer referring hospitals, reported a higher number of PrD cases.

Table 2 further delineates the distribution of hospitals in various PLADs in China that referred 10 or more PrD cases. Of the 29 PLADs reporting PrD cases, 19 had a range of hospitals referring at least 10 PrD cases. The most significant numbers of such hospitals were located in Beijing (11) and Shanghai (5), which reported 472 and 107 PrD cases, respectively. Two provinces, Shandong and Shaanxi, each had three hospitals referring 10 or more PrD cases, and five PLADs — Chongqing, Henan, Guangdong, Hebei, and Zhejiang — each had two hospitals doing the same. Among these, two hospitals in Henan reported notably higher case numbers, with 152 cases. In contrast, 10 PLADs had only one hospital referring 10 or more PrD cases, with the most cases reported in Jilin (49), Sichuan (47), and Fujian (28). These data highlight substantial variation in both the number of referring hospitals and those referring 10 or more PrD cases. Given its unparalleled medical resources, Beijing demonstrates its superior capacity for recognizing and diagnosing PrDs among the varied PLADs.

The Majority of Referring Hospitals Located in Provincial Capital Cities

The disparities in the number of referral hospitals

TABLE 2. Distribution of the numbers of total referring hospitals and the hospitals with 10 diagnosed PrD cases in PLADs.

PLADs	Total		≥10 cases	
	No. of hospitals (%)	No. of cases (%)	No. of hospitals (%)	No. of cases (%)
Beijing Municipality	41 (11.9)	546 (27.7)	11 (26.2)	472 (34.2)
Shanghai Municipality	21 (6.1)	146 (7.4)	5 (11.9)	107 (7.6)
Chongqing Municipality	10 (2.9)	72 (3.7)	2 (4.8)	44 (3.2)
Tianjin Municipality	9 (2.6)	48 (2.4)	1 (2.4)	30 (2.2)
Henan Province	26 (7.6)	205 (10.4)	2 (4.8)	152 (11.0)
Guangdong Province	21 (6.1)	146 (7.4)	2 (4.8)	89 (6.6)
Jiangsu Province	21 (6.1)	44 (2.2)	0 (0.0)	0 (0.0)
Hebei Province	20 (5.8)	62 (3.1)	2 (4.8)	33 (2.4)
Fujian Province	19 (5.5)	59 (3.0)	1 (2.4)	28 (2.0)
Zhejiang Province	18 (5.2)	72 (3.7)	2 (4.8)	45 (3.3)
Shandong Province	17 (4.9)	98 (5.0)	3 (7.1)	73 (5.3)
Hubei Province	13 (3.8)	31 (1.6)	0 (0.0)	0 (0.0)
Shaanxi Province	12 (3.5)	78 (4.0)	3 (7.1)	65 (4.7)
Sichuan Province	12 (3.5)	69 (3.5)	1 (2.4)	47 (3.4)
Xinjiang Uygur Autonomous Region	9 (2.6)	19 (1.0)	0 (0.0)	0 (0.0)
Guizhou Province	8 (2.3)	32 (1.6)	1 (2.4)	18 (1.3)
Anhui Province	8 (2.3)	28 (1.4)	1 (2.4)	12 (0.9)
Liaoning Province	8 (2.3)	21 (1.1)	0 (0.0)	0 (0.0)
Gansu Province	8 (2.3)	20 (1.0)	0 (0.0)	0 (0.0)
Jilin Province	6 (1.7)	58 (2.9)	1 (2.4)	49 (3.5)
Shanxi Province	6 (1.7)	16 (0.8)	0 (0.0)	0 (0.0)
Guangxi Zhuang Autonomous Region	6 (1.7)	6 (0.3)	0 (0.0)	0 (0.0)
Hunan Province	5 (1.5)	23 (1.2)	1 (2.4)	12 (0.9)
Jiangxi Province	5 (1.5)	23 (1.2)	1 (2.4)	10 (0.7)
Yunnan Province	5 (1.5)	21 (1.1)	1 (2.4)	12 (0.9)
Heilongjiang Province	3 (0.9)	15 (0.8)	1 (2.4)	10 (0.7)
Ningxia Hui Autonomous Region	3 (0.9)	6 (0.3)	0 (0.0)	0 (0.0)
Hainan Province	2 (0.6)	4 (0.2)	0 (0.0)	0 (0.0)
Inner Mongolia Autonomous Region	2 (0.6)	2 (0.1)	0 (0.0)	0 (0.0)
Total	344 (100)	1,970 (100)	42 (100)	1,379 (100)

Abbreviation: PLADs=provincial-level administrative divisions; PrD=prion disease.

and reported PrD cases between provincial capital cities and other cities received further analysis. Excluding four municipalities (Beijing, Shanghai, Tianjin, and Chongqing), 146 hospitals from the 25 provincial capital cities reported 947 PrD cases, while 117 hospitals from other cities reported 209 cases (Table 3). Although the overall ratio of referral hospitals in provincial capital cities to those in other cities was not significantly different (55.5% *vs.* 44.5%, P=0.359), the ratio of diagnosed PrD cases showed a significant disparity (81.9% *vs.* 18.1%, P=0.001). On average, the number of referral hospitals and PrD cases in the 25 provincial capital cities were 5.84 (range: 1–17 hospitals, median: 5) and 37.88 (range: 1–169 cases, median: 21), respectively. Considering the actual number of other prefecture-level cities (281 cities excluding the capital cities) in those 25 PLADs, the average number of referral hospitals was 0.41 (range: 0–17), and the average number of PrD cases was 0.74 (range: 0–36 cases). This discrepancy underlines the predominant role of provincial capital cities in identifying PrD patients.

TABLE 3. Comparison between provincial capital cities and other cities in terms of the number of referring hospitals and PrD cases.

PLADs	No of hospital (%)		No. of case (%)	
	Provincial capital city	Other cities	Provincial capital city	Other cities
Henan Province	9 (34.6)	17 (65.4)	169 (82.4)	36 (17.6)
Guangdong Province	17 (81.0)	4 (19.0)	140 (95.9)	6 (4.1)
Jiangsu Province	7 (33.3)	14 (66.7)	16 (36.4)	28 (63.6)
Hebei Province	4 (20.0)	16 (80)	36 (58.1)	26 (41.9)
Fujian Province	10 (52.6)	9 (47.4)	41(69.5)	18 (30.5)
Zhejiang Province	8 (44.4)	10 (55.6)	59 (81.9)	13 (18.1)
Shandong Province	6 (35.3)	11 (64.7)	64 (66.7)	32 (33.3)
Hubei Province	12 (92.3)	1 (7.7)	30 (96.8)	1 (3.2)
Shaanxi Province	8 (66.7)	4 (33.3)	74 (94.9)	4 (5.1)
Sichuan Province	5 (41.7)	7 (58.3)	59 (85.5)	10 (14.5)
Xinjiang Uygur Autonomous Region	7 (77.8)	2 (23.2)	14 (73.7)	5 (26.3)
Guizhou Province	6 (75.0)	2 (25.0)	30 (93.8)	2 (6.2)
Anhui Province	5 (62.5)	3 (37.5)	25 (89.3)	3 (10.7)
Liaoning Province	3 (37.5)	5 (62.5)	13 (61.9)	8 (38.1)
Gansu Province	6 (75.0)	2 (25.0)	18 (90.0)	2 (10.0)
Jilin Province	4 (66.7)	2 (33.3)	56 (96.6)	2 (3.4)
Shanxi Province	6 (100)	0 (0.0)	16 (100)	0 (0.0)
Guangxi Zhuang Autonomous Region	4 (66.7)	2 (33.3)	4 (66.7)	2 (33.3)
Hunan Province	3 (60.0)	2 (40.0)	21 (91.3)	2 (8.7)
Jiangxi Province	3 (60.0)	2 (40.0)	16 (69.6)	7 (30.4)
Yunnan Province	5 (100)	0 (0.0)	21 (100)	0 (0.0)
Heilongjiang Province	2 (66.7)	1 (33.3)	14 (93.3)	1 (6.7)
Ningxia Hui Autonomous Region	3 (100)	0 (0.0)	6 (100)	0 (0.0)
Hainan Province	2 (100)	0 (0.0)	4 (100)	0 (0.0)
Inner Mongolia Autonomous Region	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Total	146 (55.5)	117 (44.5)	947 (81.9)	209 (18.1)

Abbreviation: PLADs=provincial-level administrative divisions; PrD=prion disease.

A Greater Number of Referring Hospitals Found in the Surveillance PLADs Compared to the Non-surveillance PLADs

Evaluation of the numerical differences between referring hospitals and diagnosed PrD cases in both surveillance and non-surveillance PLADs was undertaken. A mean of 15.3 referring hospitals were counted in the 12 surveillance PLADs (range 6.0–41.0), above the average of the 17 non-surveillance PLADs (9.9 hospitals, range 2.0–21.0); however, the observed discrepancy did not reach statistical significance (P=0.073). Conversely, diagnosed PrD cases in surveillance PLADs presented a noticeable average increase, with 117.4 cases (range 31.0–516.0) compared to the 34.9 cases (range 2.0–98.0) of non-surveillance PLADs (P=0.028) (Figure 2A).

Assessing the historic data spanning 2006–2019, calculations of hospitals referring 10 cases and their corresponding PrD diagnoses were performed. Surveillance PLADs averaged 2.4 hospitals referring a minimum of 10 cases (range 0.0–11.0) and their corresponding average PrD diagnoses were 86.4 (range 0.0–472.0), significantly greater compared to non-surveillance PLADs. Non-surveillance PLADs averaged at 0.8 for hospitals referring 10 cases (range 0.0–3.0, P=0.042), with an average of 15.9 PrD diagnoses (range 0.0–78.0, P=0.036) (Figure 2B).

Moreover, within the timeframe of investigation, it was recorded that in 47.1% of non-surveillance PLADs

(8/17) and 16.7% (2/12) of surveillance PLADs, no hospital had diagnosed 10 cases. The results highlight a comparatively robust capacity in the recognition and diagnosis of PrDs within the surveillance PLADs.

DISCUSSION

In the present study, we have analyzed the annual- and geographic-distributions and case reporting frequencies of the hospitals diagnosed and referred human PrDs in China in the past 15 years. Accompanying with the increase of the annual diagnosed PrD cases, more and more hospitals referred PrD cases to CNS-CJD actively, particularly in the last four year that the numbers of referring hospitals are over 100 continually. Notably, some local and small hospitals (below Grade III) started to report PrD cases actively in recent years. It implies that the awareness and recognition of human PrDs in the medical institutions in China have been gradually improved in the past 15 years.

There is a notable disparity in the frequency of case reporting across referring hospitals, characterized by a majority of diagnosed PrD cases originating from a limited number of these institutions. The majority of PrD cases are referred by a select few — primarily university hospitals boasting robust neurology departments — amongst the top 20 referring hospitals. Conversely, the majority (over 75%) of referring hospitals reported a relatively low number of PrD cases (less than 5), with 168 (48.8%) of these hospitals having only reported a single case in the last 15 years. These findings suggest a significant variation in the recognition capacity for human PrDs among hospitals in China.

Our findings suggest a significant geographic disparity in the distribution of both referring hospitals and PrD cases. Expectedly, the eastern region of China records a higher number of referring hospitals and PrD cases than its western counterparts. The four municipalities directly governed by the central government — Beijing, Shanghai, Chongqing, and Tianjin — report high rates of referring hospitals and PrD cases. Notably, Beijing, the capital city, reports a significantly higher number with 4 out of the top 10 hospitals reporting the most cases situated there. Conversely, PLADs such as Inner Mongolia, Hainan, Ningxia, and Heilongjiang, located in the border regions and characterized by lower population density and underdeveloped economies, report fewer referring hospitals and/or PrD cases. Notably, the PLADs of Qinghai and Xizang have no medical institutions actively reporting any PrD cases. This geographic disparity, to some extent, reflects the variable

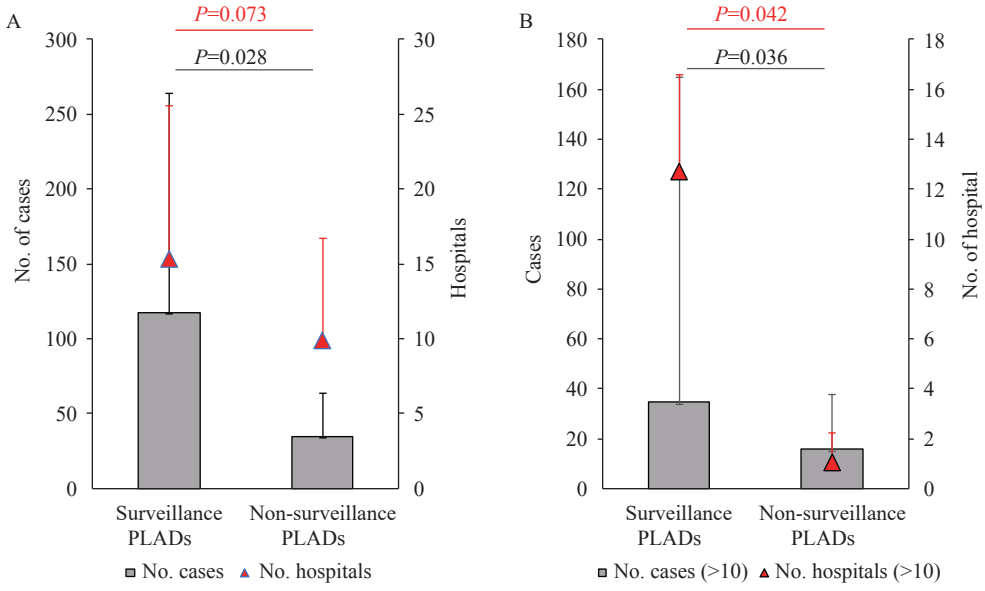

FIGURE 2. Comparison of the number of referring hospitals and PrD cases between CJD-surveillance and non-surveillance PLADs. (A) Total numbers. (B) Number of hospitals diagnosing 10 cases.
Note: Right Y-axis: number of referring hospitals (red triangle). Left Y-axis: number of PrD cases (grey column). *P* values indicating differences in hospital numbers (red) and case numbers (grey) between surveillance and non-surveillance PLADs are displayed above the graphs.
Abbreviation: PrD=prion disease; CJD=Creutzfeldt-Jakob disease; PLAD=provincial-level administrative division.

provincial-level capacity for recognizing human PrDs in China.

A prominent trend observed is the elevated detection of human PrD cases heavily concentrated in larger, central cities. Aside from the four municipalities, the incidence of reported PrD cases in provincial capital cities significantly surpasses the cumulative incidents from other cities. Aside from these four municipalities, the overwhelming majority of hospitals with at least ten reported PrD cases in PLADs are situated in provincial capitals. This disparity in PrD detection between major, central cities and smaller, outlying regions is strongly linked to variances in access to medical resources and economic proficiency. Predominantly, large, reputable hospitals — particularly university-affiliated hospitals — are located within provincial capital cities.

We have found a significant difference in the PrD recognition capacity between CJD surveillance and non-surveillance PLADs, especially notable during the first and second five-year periods of surveillance. In addition to the available medical resources, we attribute this disparity to the more established CJD surveillance activities, annual human PrD training courses and workshops, as well as relatively active academic exchanges concerning human PrDs and other neurodegenerative diseases, organized by various local entities. This significantly bolsters PrD recognition and diagnostic capacity within the surveillance PLADs. This is exceedingly pronounced in Beijing and Shanghai where all Grade III hospitals have been incorporated into their local CJD surveillance systems (*11*). Moreover, an increasing number of provincial CDCs and medical institutions from non-surveillance PLADs are being included in the annual workshops and other activities hosted by CNS-CJD in recent years. We believe this is a positive step towards enhancing PrD recognition capacity in these non-surveillance PLADs.

Despite significant improvements in PrD recognition capacity in China, largely due to the implementation of CNS-CJD since 2006, the yearly case count remains underestimated compared to data from numerous countries in Europe and North America (*12*–*14*). This is the case even in large, developed central cities. Even though the China CDC implemented a diagnostic protocol for CJD surveillance in 2006, and the National Health Commission issued diagnostic criteria for CJD in 2017, most PrD patients only receive their final diagnoses after being transferred multiple times between hospitals, typically from smaller local facilities to larger central institutions. As PrDs represent a rare set of neurological diseases lacking specific clinical manifestations, misdiagnoses are frequent (*15*). Increased awareness and recognition of human PrDs are warranted, particularly in smaller cities. Key strategies for improvement include the widespread promotion and implementation of CJD diagnostic criteria among clinicians, the sequential development of training programs on prions and PrDs for clinicians, public health personnel, and laboratory staff, and an emphasis on related scientific literacy and health education for the general public.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the Grant (2021SKLID101, 2019SKLID603) from the State Key Laboratory for Infectious Disease Prevention and Control, China CDC.

doi: 10.46234/ccdcw2023.181

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Submitted: September 11, 2023; Accepted: October 24, 2023

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