Quality evaluation for the surveillance system of human prion diseases in China based on the data from 2010 to 2016

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\textbf{ABSTRACT.} The surveillance of CJD or human prion diseases (PrDs) has been conducted for 10 y in China. To evaluate the quality of China CJD surveillance system, the collections of the clinical and epidemiological information, the sampling, the clinical examinations and laboratory tests and follow-up survey were separately analyzed based on the data from 2010 to 2015. The obtaining rates of clinical-information table, epidemiological-information table, sample inspection sheet and medical record of the referring patients from reporting units to the center of CJD surveillance maintained or reached at very high levels, being close to 100\% in the past 3 y. 93.82\%, 85.23\%, 96.21\% and 94.70\% of the reported cases had the data of MRI, EEG, CSF 14-3-3 and \textit{PRNP} sequencing, respectively. Follow-up surveys were conducted in about 50\% cases in 2010 and 2011, 93.39\% cases in 2012 and 100\% cases in the last 3 y. High obtaining rates of the clinical and epidemiological data, high conducting rates of the relevant clinical examinations and laboratory tests, high performing rates of follow-up survey for every referring case reflect a good implemental capacity in China CJD surveillance system, which supplies solid basis for recognition and diagnosis of human prion diseases and guarantees good quality of China CJD surveillance system.

\textbf{KEYWORDS.} Creutzfeldt-Jakob disease, evaluation, human prion diseases, surveillance, quality
Human prion diseases (PrD) are a group of rare fatal and transmissible neurodegenerative diseases, covering Creutzfeldt-Jakob disease (CJD), Kuru, Gerstmann–Sträussler–Scheinker syndrome (GSS) and fatal familial insomnia (FFI). Human PrD has an incidence of 1 or 2 cases per million ones per year with rapidly progressive dementia, cerebellar ataxia, myoclonus and behavioral changes. About 85% of all CJD cases are sporadic (sCJD), 10-15% are inherited or genetic form (gCJD) and less than 1% is acquired, namely iatrogenic CJD (iCJD). The clinical, pathological and pathogenic features of various subtypes of human prion diseases may vary largely.

In the last decade of the 20th century, countries in Europe, North America, as well as Australia and Japan started and restarted national surveillance for human PrDs, because of the outbreak of bovine spongiform encephalopathy (BSE) in the middle of 1980s and emergence of variant CJD (vCJD) 10 years later. Later, some other countries and regions in South America and Asia began their national or regional CJD surveillance, gradually forming global network for human PrDs. As lacking of special clinical manifestations and convenient diagnostic tool, it is sometimes difficult to recognize and diagnose human PrD promptly and correctly, which needs combinations of the data of clinical manifestations, epidemiology, clinical examinations and laboratory tests. Therefore, obtaining the clinical and epidemiological information and performing relative clinical examinations and laboratory tests for the suspected PrD patients are essential in PrD surveillance. Moreover, follow-up survey in CJD surveillance is also important for correction and revision of the diagnosis of the reporting patients.

**CJD Surveillance in China from 2010 to 2015**

China CJD surveillance consists of 12 provincial CDCs and 15 reference hospitals, covering Beijing, Shanghai, Tianjin, Chongqing, Jilin, Shaanxi, Hubei, Guangdong, Guizhou, Anhui, Henan and Xinjiang. The surveillance program and the relevant documents were issued by China CDC. The diagnostic criteria of CJD and other human prion diseases using in the surveillance system were based on the relevant documents issued by WHO with slightly modification. Based the surveillance documents, the “suspected case of human prion disease” is the patient who has the symptoms in accordance with the diagnosis criteria for any subtype of human prion diseases, or the case that is believed by the physicians to be necessary to exclude the possibility of CJD.

From 2010 to 2015, totally 1585 suspected CJD cases were referred to the China surveillance system of human prion disease. Among them, 700 cases were diagnosed as sCJD (2 definite, 560 probable and 138 possible), 81 cases were diagnosed as genetic human prion disease (5 GSS, 25 FFI and 51 different gCJD) (Fig. 1A). Majority (86.75%, 1375 cases) of the reported cases came from the surveillance provinces, while 13.25% (210 cases) were reported from non-surveillance provinces. Either the numbers and rates of reporting cases from non-surveillance provinces or the number of non-surveillance provinces that reported suspected cases increased along with the surveillance years (Fig. 1B).

**Collection of the Information of the Suspected Patients from the Reporting Units**

In practice, the clinical data and specimens of the suspected patients were collected by the clinician from hospitals, while the epidemiological data were collected by the staff of provincial CDCs. The collected data and sample were referred to the national reference laboratory for human prion disease in China CDC for laboratory tests and final diagnosis. Several tables or sheets were designed for the information collection. Clinical Information Table (Clin-inf table), which was filled by the clinician, contained the data of the reporting unit, the general information of the patients, the onset time and symptoms, the major clinical manifestations, the death time (if it had) and the results of clinical examinations (EEG and
MRI). Epidemiological Information table (Epi-inf table) contained the data of reporting unit, the permanent residence of the patients, the family disease history, the past medical history (such as neurosurgical operation, organ transplantation, usages of extracted hormones and blood transfusion), special profession (such as medical or veterinary staff, butcher). Specimen inspection sheet covered the information of the specimens, such as the sampling time, kinds and amounts of the samples (including CSF, blood, brain or other tissues if it is possible). In addition, the medical record, sometimes the graphs of EEG and MRI, of the suspected CJD patient was also asked to be provided.

As shown in Fig. 2, the integrity of the documents for each reporting case maintained at high level in the past surveillance years. Both Clin-inf tables that were filled and uploaded by local physicians and Epi-inf tables that were filled and uploaded by local CDC staffs were obtained close to 100%, especially in the past 3 y. Medical records of the suspected cases were also copied and submitted at high level (from 91.62% in 2010 to more than 99% in the past 4 y). The inspection sheets of the collected CSF and/or blood samples of the suspected CJD cases were obtained from 95.84% cases, increasing from about 90% in the first 3 y to more than 99% in the last 3 y.

**Performance of Clinical Examinations and Laboratory Tests**

According to the diagnostic criteria, the diagnoses of probable and definite PrD cases need further clinical examinations and laboratory tests. For the clinical examinations, 93.82% (1497 out of 1585) of the reporting cases relieved MRI scanning at least one time during the hospitalizations. The examining rates of MRI increased from roughly 90% in 2010 and 2011 to more than 94% in the past 4 y (Fig. 3A). Average 85.23% (1351 out of 1585) cases had EEG examinations. However, the examining rates of EEG decreased year by year, from 89.14% in 2010 to 81.15% in 2015 (Fig. 3A).

The enrolled laboratory tests in CJD surveillance currently included Western blot for CSF protein 14-3-3, PRNP PCR and sequencing based on blood sample, neuropathology, PrPSc specific Western blot and immunohistochemistry (IHC) based on brain tissues. The standard operation protocol (SOP) for those tests were described previously and issued by China CDC. 96.21% (1525/1585) cases underwent CSF 14-3-3 tests, varying from 94.70% to 96.99% in the 6 surveillance years, while 94.01% (1490/
cases had PRNP sequencing data ranging from 91.73% to 95.65% (Fig. 3B). Only two cases in the past 6 surveillance years underwent brain postmortem, which let us conduct neuro-pathological and PrPSc assays.

Follow-Up Survey, Preparation of the Master Table of the Patient and Feedback of the Recommendation for Diagnosis and Handling

All data of a suspected case, including the clinical and epidemiological information, the results of clinical examinations and laboratory tests, were summarized and prepared as master table for this patient. During this process, some information was usually updated and amended, according to the review of the medical record and/or follow-up survey. The suggestion for diagnosis and further handling each reporting case was made by the center of CJD surveillance and feedback to the reporting local CDC and hospital.

Follow-up survey was conducted either the staffs from China CDC or from local provincial CDCs. The interviewee was either the family member or the physician for confirmation of main items or disease development. The follow-up results were noted in the follow-up sheet. The patients who had at least one time telephone-interview or face to face interview were considered to be positive in follow-up survey. As shown in Fig. 4, the follow-up rates were about 50% in 2010 and 2011, increased to 93% in 2012 and reached to 100% in the last 3 y. The master table of the reporting patient was prepared by the staff in China CDC and revised after the follow-up survey. Review of the master tables of all referring cases in the past 6 surveillance years illustrated that almost all items were completed, except 3 cases in 2010 lacking of the onset times and one lacking of initial symptoms.

After comprehensive analysis of the clinical, epidemiological and laboratory data of each reporting case, the center of CJD surveillance gave a written suggestion of diagnosis to the reporting units (local CDC and/or hospital). The types of the suggested diagnosis included definite, probable, possible PrD (sCJD, gCJD, FFI, GSS), not suggested as CJD (non-CJD)
DISCUSSION

In this study, we have verified very high obtaining rates of 3 information sheets (Clin-Inf table, Epi-Inf table and Specimen inspection sheet) of the referring cases in the past 6 years, which are required to be uploaded from the reporting units to the center of CJD surveillance in China CDC based on the document of CJD surveillance. The supplying rates of the medical records of the reporting cases are also very high. It reflects a good implemental capacity in our CJD surveillance system, which supplies solid basis for PrDs recognition and diagnosis.

The performance rates of the clinical examinations maintain at high levels in the past 6 surveillance years, especially MRI scanning that has been brought into the diagnostic criteria for probable sCJD since 2012. We have
also noticed that the rates of EEG decline along with years, which is possibly associated with the more accessible MRI scanning in clinical. High sampling rates for CSF and blood let more than 94% and 92% referring patients be conducted with CSF 14-3-3 assay and PRNP sequencing. No doubt, performances of those assays increase the reliability and accuracy of the diagnosis of PrDs, especially probable sCJD. Obtaining of the data of PRNP sequences of the overwhelming majority of the referring cases let us efficiently avoid of misdiagnosis of genetic PrDs, especially for those without clear disease associated family histories. In the past few years, RT-QuIC assay of CSF has been used in some European countries, USA and Japan, showing desired sensitivity and specificity for sCJD. Such method has been recently established in our laboratory and the clinical trial is being conducted (Xiao et al, in preparation). It is undoubted that RT-QuIC will benefit greatly to the CJD surveillance system in China where the rates of brain biopsy and autopsy are extremely low.

We believe that continue follow-up survey is absolutely benefit to our CJD surveillance. Actually, numbers of the required items for the information of the reporting cases have been replenished, amended and revised during the follow-up processes. Revision of the diagnoses, particularly for the group of “pending case,” largely depends on follow-up survey. In practice, due to the limited time for feed-back, some numbers of the patients are considered as pending cases for uncertain of clinical signs and/or clinical examinations.

Many other issues also contribute to the quality of our CJD surveillance. Among them, knowledge education and technique training are particularly important. We have conducted CJD surveillance annual meeting each year and CJD laboratory technique training course every 2 y for the staffs from local units in the surveillance provinces since 2006, and expended to the staffs from the provinces officially not belonging to our CJD surveillance network yet in the past 2 y. As a positive response, both the numbers referring cases and reporting provinces show constantly increase in the past years.\textsuperscript{17-18} As a rare disease, CJD or other subtypes of human PrDs is still not well recognized in China yet. Brain postmortem rate in China
maintains extremely low, probably related with the tradition. Hence, comprehensive obtaining of the clinical and epidemiological data, conducting of the relevant clinical examinations and laboratory tests, performing of follow-up survey for every referring case are particularly important for the Chinese CJD surveillance system.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

**ACKNOWLEDGMENTS**

We appreciate all staffs in Chinese CJD surveillance system for their great work. We also thank all referring patients and their family members for supplying the required information and donating specimens.

**FUNDING**

This work was supported by Chinese National Natural Science Foundation Grants (81301429, 81572048) and SKLID Development Grant (2012SKLID102, 2015SKLID503).

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