Comparing Two Classification Schemes for Seizures and Epilepsy in Rural China

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Running Title: New ILAE Classification in Rural China
Key Words: Classification, Epilepsy syndromes, Terminology, Aetiology, Rural
Total word count of the manuscript including title page, references, legends and structured abstract: 3340

AUTHOR CONTRIBUTIONS

The study was conceptualised and designed by DD, WW, JWS and PK. Data was collected by WW, BY, YW, TW and WL. Data was analysed and interpreted by FW, ZC, ID, CH, DD, JWS and PW. The manuscript was drafted by FW and ZC and critical intellectual input was provided by DD, JWS and PK. All authors revised and approved the submitted version.

ABSTRACT

Background

The International League Against Epilepsy (ILAE) updated the classifications of seizures and epilepsies in 2017. We compared the 2017 classifications with the 1980's classifications in rural China.

Methods

People with epilepsy were recruited from rural areas in China receiving treatment under the National Epilepsy Control Programme. Their seizures and epileptic syndrome were classified using the 1980's ILAE classification system and then re-classified according the 2017 system. Differences in seizure, epilepsy and aetiology classifications were identified.

Results

A total of 597 individuals (58% males, aged 6-78 years) were included. Among them 535 (90%) had a single seizure type, 57 (9.55%) had two types, and five (0.84%) had three. There was complete agreement between the 1981 and 2017 classifications for the 525 individuals with focal seizures. Seizures originally classified as generalised in 10 of 65 individuals were re-classified as unknown in the 2017 classifications. Compared to the 1980's classifications, the proportion of individuals with unknown seizures and unknown epilepsy increased from 1.2% (7/597) to 2.8% (17/597, p=0.002), and unknown aetiology increased from 32% (189/597: 182 cryptogenic and seven unclassified) to 39% (230/597; p<0.001) in the 2017 classifications.

Conclusions

The 1980's and 2017 classifications had 100% agreement in classifying focal seizures and epilepsy in rural China. A small but significant proportion of generalised seizures and epilepsy

and aetiologies classified in the old classifications were re-classified to unknown in the new classifications. These results highlight the need for improvement in clinical evaluation of people with epilepsy in resource-poor settings.

INTRODUCTION

Accurate classification of seizure and epilepsy is critical for optimal clinical management, effective communication among healthcare providers and research. In 2017, the International League Against Epilepsy (ILAE) presented a new classification scheme for seizures and epilepsies.[1, 2]

The new scheme has a number of important conceptual differences from the previous scheme in use since the 1980s.[3, 4] One of these is the requirement of a confidence level of at least 80% as a prerequisite to classify seizure type, otherwise it should be classified as unknown. Achieving the confidence level would likely involve evidence from investigations, such as EEG and neuroimaging. The old system dichotomised epileptic syndromes into either generalised or focal but the new scheme introduced the category of "combined" epilepsy type which aims to provide a more accurate description of some syndromes. There is also a greater emphasis on putative aetiologies at each classification step in the new scheme compared to the previous version. Epilepsy aetiology is now stratified at several levels allowing multiple aetiologies in a given individual.

While the new scheme is generally welcomed it is important to evaluate its applicability in different clinical settings. Previous schemes have been evaluated mainly at specialised healthcare settings.[5-7] The great majority of people with epilepsy, however, live in rural areas or in resource-poor setting.[8] We applied the new classifications scheme at primary care level in rural China and compared them with the previous versions.

METHODS

Participants

People with epilepsy aged 2–80 years were recruited from rural areas in four Chinese provinces (Henan, Hebei, Ningxia and Shanxi) between 1 July 2010 and 31 December 2012. They were receiving treatment in the National Epilepsy Control Program which aims at delivering epilepsy care at primary and secondary care.[8] People with non-epileptic seizures, seizures related to alcohol or illicit drug abuse, or as the result of progressive, degenerative neurological or systemic disorders were excluded. Those in whom MRI was contraindicated (such as metallic implants or devices or with claustrophobia), were also excluded.

The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Research Ethics Committee (CRE-2010.185) in Hong Kong and the institutional review board of the Beijing Neurosurgical Institute in China. Written informed consent was obtained from all participants or their legal guardians.

Clinical assessments

Using predesigned epilepsy history and seizure classification questionnaires, primary care physicians interviewed participants or their carers to collect medical history and seizure information. The clinical questionnaire consisted of 19 points covering birth, developmental, family, epilepsy, other medical and drug history. The 33 questions seizure classification form covered a broad range of seizure semiology for classification in accordance with the updated ILAE terminology.[9] The questionnaires were developed based on those previously employed for seizure classification.[10-12] The questionnaires were piloted before deployment. Training and standardization workshops for physicians involved were conducted by senior epileptologists (JWS and PK).

After the interview at primary care, participants underwent specialist neurological evaluation at the higher level of care (corresponding provincial hospitals) including history taking and physical examination. All underwent routine EEG and brain MRI using standardised protocols. Interictal EEG recordings were obtained according to the international 10-20 system. The recording and reporting protocols were in accordance with guidelines from American Clinical Neurophysiology Society. MRI brain (1.5T) was performed at the specialist centre following a common acquisition protocol. This consisted of a T1-weighted volumetric acquisition sequence with 1 mm partitions, oblique coronal dual-echo proton-density and T2-weighted as well as fluid attenuated inversion recovery (FLAIR) sequences. The MRI were systematically evaluated on Osirix PACS (Pixmeo, Geneva) by qualified neuroradiologists (ID and CH).

Case classification

Based on all information collected at the rural clinic and provincial hospital each participant's seizure and epilepsy types were classified. All were first classified using the 1981 ILAE seizure classification and 1989 ILAE epilepsy classification system and then re-classified according to the 2017 ILAE seizure and epilepsy classifications. Two inter-rater agreement analyses were performed. In the first analysis, 60 (10%) individuals were randomly selected and classified by two epileptologists (JWS and PK) using the 1980s system. They had substantial agreement in seizure and epilepsy classifications with Cohen's kappa statistics of 0.78 (95% confidence interval [CI]: 0.73-0.84) for seizures and 0.75 (95% CI: 0.51-0.89) for epilepsy. In another randomly selected 61 (10%) participants using the 2017 classification, two raters (PK and FW) demonstrated similar substantial agreement in seizure (Kappa=0.72, 95% CI: 0.62-0.80) and epilepsy classifications (Kappa=0.75, 95% CI: 0.69-0.85).

Statistical analysis

Descriptive analysis was performed to summarise demographics. McNemar's test was used to compare the differences in classifying seizures, epilepsies and aetiologies between the 1980's and 2017 classification schemes. All statistical tests were performed by using *Stata14* (StataCorp, College Station, TX).

Study funding

This study was supported by NINDS/Fogarty grant (R21NS069223-01) and Key Research Project of the Chinese Ministry of Science and Technology (2016YFC0904400).

RESULTS

Demographics

A total of 637 individuals were recruited and interviewed by rural physicians, one was excluded due to data entry issues and 39 were excluded as MRI incompatible. Among the 597 participants with evaluable datasets (seizure and epilepsy questionnaire, clinical data, EEG and MRI copies and reports from specialist hospitals), 344 (58%) were males. The median age at recruitment was 38 years (interquartile range [IQR] 27-48, range 6-78) and the median age of epilepsy onset was 14 years (IQR 6-25, range 0-66).

Seizure Classification

Among the 597 participants, 535 (90%) had single seizure type, 57 (9.55%) had two seizure types, and five (0.84%) had three seizure types.

Among those with single seizure type, 473 (88%) had focal seizures, 55 (10%) had generalised seizures, and seven (1.31%) had unclassified seizures according to the 1981 seizure

classification (Table 1a). For focal seizures this was almost identical when using the matching terminology of the 2017 ILAE seizure classification (Table 1b). Ten participants, however, (sTable 1) originally classified as having generalised seizures were re-classified as unknown according to the 2017 classification (Table 2a). Overall, the proportion of participants with unknown onset seizures increased slightly from 1.2% (7/597) in the 1989 scheme to 2.8% (17/597) using the 2017 classification (p=0.002).

For participants with multiple seizure types, similar classifications were made when using the 1981 and 2017 schemes. Among the 57 with two seizure types, 51 were classified as having focal onset seizures (eight were simple partial or focal aware seizures and 43 were complex partial or focal impaired awareness seizures) and partial to secondarily generalised or focal to bilateral tonic-clonic seizures, and six only had generalised seizures (three generalised tonic-clonic seizure [GTCS] and absence, one GTCS and atonic, one GTCS and myoclonic, and one absence and atonic). Among the five participants with three seizure types, three only had generalised seizures, one only had focal seizures, and one had focal and generalised seizure using the 2017 system but was classified as having generalised onset seizures using the 1981 system.

Epilepsy Classification

Similar to seizure classifications, the 1989 and 2017 epilepsy classifications had complete agreement when applied to 525 (88%) individuals with focal epilepsy (Table 2b). The 10 who had generalised seizures re-classified as unknown seizures under the 2017 seizure classifications also had generalised epilepsy re-classified as unknown epilepsy. This led to the overall slight increase in the proportion of unknown type of epilepsy from 1.2% (7/597) in the 1989 scheme to 2.8% (17/597) in the 2017 scheme (p=0.002). One participant (sTable 2, case

1) who was classified as generalised epilepsy under the 1989 classification was re-classified as having combined focal and generalised epilepsy using the new scheme.

Aetiology Classification

According to the 1989 classification, the aetiologies of epilepsy were identified as idiopathic in 47 (7.9%) individuals, symptomatic in 361 (60%), cryptogenic in 182 (30%) and unclassified in 7 (1.2%). By using the 2017 classification, aetiology was re-classified to unknown in 9 (19%) of the individuals originally diagnosed with idiopathic aetiology owing to lack of family history and clinical associated syndromes; 44 (12%) of those with symptomatic aetiology owing to lack of clear epileptogenic lesion in MRI; and 170 (93%) of those with cryptogenic epilepsy (Table 3). Twelve cryptogenic cases were re-classified as having genetic aetiology owing to the strong family history. The number of epilepsy with unknown aetiology increased from 189 (32%, 182 cryptogenic and seven unclassified) in 1989 classification to 230 (39%) cases in 2017 classification ($p<0.001$). In addition, 47 individuals with structural aetiology were also classified as having genetic (n=14) and infectious aetiologies (n=33).

DISCUSSION

Since its release the new ILAE seizure and epilepsy classifications have been critically appraised.[13,14,15] This is one of the first studies to compare their applicability with the previous scheme in the rural area. We found an overall excellent agreement in classifying focal seizures and focal epilepsies and the main inconsistency was found in generalised seizures. The increase in unclassified cases was statistically significant but it only affected a small number of cases.

A possible explanation for the discrepancy is the introduction of the '80% confidence level' concept, requiring more detailed clinical evidence for classification. For instance, an individual (sTable 2, case 2) was classified as having generalised seizure and generalised epilepsy with idiopathic aetiology by using the old classifications. In the 2017 scheme, he was classified as having unknown seizure and epilepsy type due to the lack of supportive evidence to attain the confidence level to make a diagnosis of generalised epilepsy. Therefore, the use of 80% confidence level and more requirements for objective evidence in the 2017 classifications can help highlight the knowledge gap in the clinical evaluation of people with epilepsy.

Another advantage of the 2017 classification method is that it includes some of the rarer seizure types, such as eyelid myoclonia and epileptic spasm, which were undetermined in the 1980s system. These seizure types were not seen in our cohort but their diagnosis often requires supportive findings from prolonged video-EEG recording which is generally only available in specialised settings.

According to the 2017 classifications, one individual with generalised epilepsy (sTable 2, case 1) was re-classified into the combined group. This change of epilepsy type provides a better representation of the individual's clinical manifestations and disease mechanism. Similar to the seizure classification, the proportion of individuals with unknown epilepsy has also risen since more objective evidence is required in the new scheme. For example, neuroimaging findings are required for allocation into the structural aetiology group (sTable 2, case 3).

As more evidential findings are required in the new classifications, while seizure and epilepsy classifications were unchanged, the aetiology was re-classified as unknown in some cases due to lack of positive neuroimaging. This applied to people with a history of head trauma or birth

hypoxia without abnormality on neuroimaging, despite the temporal association between the brain insult and onset of epilepsy. In these cases, technical limitations of the scanners or imaging acquisition protocols might have missed subtle cerebral damages.

In the new scheme people with epileptic encephalopathy and associated learning disability were classified as unknown aetiology due to the lack of genetic evidence or a positive family history (sTable 2, case 4). Progress in understanding of the genomics of epilepsy has driven genetics to become a separate aetiological category. Autosomal dominant trait can be used as an evidence for a genetic aetiology but for the majority of individuals, finding the underlying genetic cause is challenging, particularly for people living in resource-poor settings.

Infection was listed as an independent aetiology in the 2017 classification. As a result, 38 participants were classified into this group. This can potentially help clinicians determine treatment strategy. In the study cohort, no individual was classified as having metabolic or immune aetiology. The identification of these two aetiologies requires support from molecular biology and genetic examination techniques, which were generally not available in the rural setting.

Our study has its limitations. All the participants underwent EEG and MRI which are not routinely available in the rural area, hence potentially less individuals in such setting might have sufficient evidence to reach a confident classification. Assessment of interrater agreement involved epilepsy experts and may yield different findings among primary care physicians or local neurologists. The schemes agreed perfectly for focal-onset seizure subtypes, probably due to the fact the new classifications just applied new terminologies for focal onset seizures so there was wide overlap between the new and old classifications. There was also bias towards

convulsive seizures (either generalised or focal onset) and 88% of the cohort had focal onset seizures. A possible explanation is that people with non-convulsive seizures were less likely to seek medical care in this rural setting. The cohort, however, reflects the real-world situation of epilepsy care in resource-poor areas. Future study in other healthcare settings is needed to evaluate the agreement between the two classifications for non-convulsive seizures.

In conclusion, our study provided insight into the applicability of the new classification scheme in areas with scarce healthcare resources. Compared with the previous system, the new classification has advantages in allowing clearer description of the clinical manifestations, aetiology and mechanisms of seizure and epilepsy. The introduction of combined epilepsy types and multiple aetiologies removes the mutually exclusive approach in the previous scheme. These advantages can help physicians establish more appropriate treatment plans and may improve prognosis. The new system, however, requires a higher level of confidence and standard of clinical evidence. Further research is needed to evaluate the impact of the new classification scheme on clinical practice in terms of the investigation and treatment of epilepsy in areas with scarce medical resources.

ACKNOWLEDGEMENT

JWS and ID are based at University College London Hospitals Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's NIHR Biomedical Research Centres funding scheme. JWS receives research support from the Dr Marvin Weil Epilepsy Research Fund and his current position is endowed by the UK Epilepsy Society. KWe are grateful to Dr Yifan Ren for translating the Chinese clinical records into English.

FUNDING

This study was supported by NINDS/Fogarty grant (R21NS069223-01) and Key Research Project of the Chinese Ministry of Science and Technology (2016YFC0904400).

DISCLOSURE

FW, ZC, ID, CH, DD, WW, BY, YW, TW and WL report no disclosures. JWS has received research grants and honoraria from UCB, Eisai, Bial and Janssen which are involved in the manufacturing of antiepileptic drugs.. PK has received speaker or consultancy fees and/or research grants from Eisai, GlaxoSmithKline, Johnson & Johnson, Pfizer, and UCB Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCE

1. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522-30.
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512-21.
3. Commission of Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:489-501.
4. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.
5. ILAE classification of epilepsies: its applicability and practical value of different diagnostic categories. Osservatorio Regionale per L'Epilessia (OREp), Lombardy. Epilepsia. 1996;37:1051-9.
6. Uttam AK, Joshi R, Dwivedi R, Prasad K, Padma MV, Bhatia R, et al. Applicability of the new ILAE classification for epilepsies (2010) in persons with epilepsy at a tertiary care center in India. Epilepsia. 2013;54:751-6.
7. Leyva IR, Gomez JFH, Enriquez FC, Sierra JFH. Usefulness of Ilae 2010 classification in Mexican epilepsy patients. J Neurol Sci. 2017;376:13-5.
8. Wang W, Wu J, Dai X, Ma G, Yang B, Wang T, et al. Global campaign against epilepsy: assessment of a demonstration project in rural China. Bull World Health Organ. 2008;86:964-9.
9. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676-85.
10. Reutens DC, Howell RA, Gebert KE, Berkovic SF. Validation of a questionnaire for clinical seizure diagnosis. Epilepsia. 1992;33:1065-71.
11. Placencia M, Suarez J, Crespo F, Sander JW, Shorvon SD, Ellison RH, et al. A large-scale study of epilepsy in Ecuador: methodological aspects. Neuroepidemiology. 1992;11:74-84.
12. Ottman R, Barker-Cummings C, Leibson CL, Vasoli VM, Hauser WA, Buchhalter JR. Validation of a brief screening instrument for the ascertainment of epilepsy. Epilepsia. 2010;51:191-7.
13. Beghi E, Sander JW. The ILAE classification of seizures and epilepsies: implications for the clinic. Expert Rev Neurother. 2018:1-5.
14. Beghi E. Epilepsy: New classification of seizures and epilepsies - an advance? Nature Reviews Neurology. 2017;13:324-5.
15. Nickels K. How Have We Come This Far? Epilepsy Classification Through the Ages. Epilepsy Curr. 2017;17:229-31.