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New-onset unprovoked seizures in a cohort of children in South India: Application of the new ILAE 2014 definition of epilepsy

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Abstract

Objective: To study the application of International League Against Epilepsy (ILAE) 2014 definition of epilepsy in children with new-onset unprovoked seizure. *Methods:* The study cohort included 7,408 children accessing Government Primary Schools in a province in south India. They were followed up for new-onset unprovoked seizures through first to sixth grade (January 2006 to December 2012). At the time of first visit the following data was collected: demographic data, age of onset, history of febrile seizures, family history of seizures, seizure semiology and neurologic examination. All children had EEG, and plain and contrast brain. *Results:* Of the 58 children with new-onset epileptic seizures during the study period, 37 had new-onset unprovoked seizures: focal onset seizures in 13 (30%); generalized onset seizures in 7 (19%); and unknown onset in 17 (46%). Of these children, 30 met the new ILAE 2014 definition of epilepsy, 20 (66.6%) children received the diagnosis of epilepsy after first seizure: electro-clinical genetic epilepsy syndromes in 11 (36.7%) and epilepsy due to structural cause in 9 (30%). In the remaining 10 (33.3%) children diagnosis of epilepsy was established after second unprovoked seizure during follow-up study period. Focal or generalized interictal epileptiform discharges in the EEG and normal CT were associated with the diagnosis of genetic epilepsy syndromes and abnormal neuroimaging and normal EEG were associated with the diagnosis of epilepsy with structural lesion with enduring predisposition for recurrent seizure. The type of epilepsies seen in this cohort was the epilepsies seen in this age group.
Conclusion: This study shows that with the new ILAE 2014 definition of epilepsy in a cohort of children in South India, four fifth of new-onset unprovoked seizures received the diagnosis of epilepsy; a third each from structural cause, epilepsy syndrome, and second seizure.

Keywords: International League Against Epilepsy, epileptic seizures, epilepsy, epilepsy syndrome, definition, classification, applicability

INTRODUCTION

The current commonly employed definition of epilepsy requires to have at least two unprovoked seizures occurring >24 h apart. This definition does not allow a patient to outgrow epilepsy. The International League Against Epilepsy (ILAE) has expanded the definition of epilepsy to incorporate a single unprovoked (or reflex) seizure with a probability of future seizures. It also incorporates "diagnosis of epilepsy syndrome" into the diagnostic structure. According to the new ILAE definition of epilepsy, epilepsy is a disease of brain defined by the following conditions: (1) two unprovoked (or reflex) seizures occurring more than 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome. It also stipulates that epilepsy can be considered "resolved" and can be considered under the following circumstances: (1) in a patient with an age-dependent epilepsy syndrome who is older than the age in which this syndrome is active or a patient has been seizure free for 10 years, with no seizure medicines for the last 5 years.[1] The recent Italian Long-Term Prognosis of Epilepsy (PROLONG) study has assessed the applicability of

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the new ILAE 2014 epilepsy definition in clinical practice in all age groups.[2] Implementation of new definition of epilepsy in the Norwegian Mother and Child Cohort Study (MoBa) increased the overall proportion with confirmed epilepsy in the cohort from 0.52% to 0.54%.[3] This study reports the application of new ILAE 2014 definition in new-onset unprovoked seizures in a cohort of school children in South India.

METHODS

This is a prospective longitudinal study in school children studying in the 18 Government Primary Schools adopted by NICE Foundation, Hyderabad, a nongovernmental organization under its School Health Program. The study cohort included 7,408 school children aged between 5-15 years, registered on rolls as on January 1, 2006. This cohort was followed for the new-onset seizures through first to fifth grades. The study period between January 1, 2006 and December 31, 2012. This study has the approval of the Institution Ethics Committee.

Under the School Health Program, NICE Foundation runs School Outpatient Clinics for the health needs of children in the schools adopted by the Foundation. Children with new-onset seizures identified in the Clinic were referred for further workup to Neurology Outpatient Clinic, CARE Hospitals, Hyderabad. Children with new-onset unprovoked seizures were included in the present study. Criteria proposed by ILAE was used to categorize new-onset seizures into unprovoked seizures.[4] At the first visit, the data collected included: demographic details, history of antecedent events, history of febrile seizures, family history of epilepsy, date of onset of first seizure, seizure semiology with emphasis on features for focal onset, and neurologic findings. All children had 40 minute EEG, and contrast computed tomography (CT) brain. Children were prescribed appropriate anti-epileptic drugs (AEDs) when required. NICE Foundation provided mostly the standard AEDs free of cost. Children were followed for recurrence of seizures.

The data collected during the first visit of the child and the follow-up data was used to classify the seizure type,[5] and epilepsy classification.[6] Seizures were classified into focal onset, generalized onset, and unknown onset using the new ILAE 2017 classification of seizures types.[5] The new ILAE definition of epilepsy was used to define the epilepsy: (1) two unprovoked (or reflex) seizures occurring more than 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome.[1] The etiological classification was as proposed by ILAE.[6] Diagnostic clinic-radiological criteria for neurocysticercosis (NCC) proposed by Del Brutto *et al*.[7] were used for radiologic diagnosis of NCC, small calcific lesion measuring less than 20 mm on plain CT was diagnosed as calcific stage of NCC (cNCC). Seizures due to cNCC were categorized under unprovoked seizures.[8] Children with a single unprovoked seizure due cNCC lesion(s) were considered to have epilepsy as this lesion has been shown to have an enduring predisposition for seizure recurrence.[9]

Classification of epilepsies was done using the new ILAE 2017.[6] The first step in the classification of epilepsies was to define seizure type by onset.[5] This was followed by classifying the epilepsy by onset. The next step was classifying the epilepsy type and the aetiology.[6]

Classification of seizure type and applicability of ILAE 2014 definition was done by the first two authors, neurologists with special interest in epilepsy. In case of any dispute, it was resolved by mutual discussion and also evidence from investigations

RESULTS

Of the 7,408 children aged between 5 and 15 years, there were 3297 (44.5%) boys and 4111 (55.5%) girls. All the children were from low socio-economic strata, mostly from slums surrounding the schools. During the study period January 2006 to December 2012, 37 children were referred for new-onset unprovoked seizure to the Out-patient Clinic, Department of Neurology, CARE hospitals, Hyderabad. Of the 37 children with unprovoked seizures, seven (29.4%) children had no seizure recurrence during the study period of seven years. The remaining 30 children (81%, mean age 9.47 years, range 5-15 years, M:F: 1:1) fulfilled the criteria of new ILAE definition of epilepsy.[1]

Of the 30 children with new-onset unprovoked seizure, 20 (66.7%) children received the diagnosis of epilepsy after a single seizure. The remaining 10 (33.3%) received diagnosis of epilepsy after a second seizure during the follow-up study period of seven years (Table 1). Of the 20 children who received the diagnosis of epilepsy after first seizure, 11 (36.6%) received

Table 1: Diagnosis of epilepsy in children with new-onset unprovoked seizure

1. At least two unprovoked seizures occurring >24 h apart	10 (33.3%)
2. One unprovoked seizure and a probability of further seizures similar to the general risk (>60%) after two unprovoked seizures occurring over the next 10 years	9 (30%)
3. Diagnosis of an epilepsy syndrome	11 (36.6%)

a diagnosis of electro-clinical epilepsy syndrome and 9 (30%) received the diagnosis of epilepsy due to a structural lesion. In the 10 children who had second seizure during the follow-up, the seizure type was unknown onset motor seizure. Neurological examination and EEG (except in one, non-specific rhythm) were normal. The second seizure occurred within 6 to 40 months of first seizure.

The predictors of epilepsy diagnosis after the first seizure were interictal epileptiform discharges in the EEG and abnormal findings on neuroimaging. Focal or generalized interictal epileptiform discharges in the EEG and normal CT were associated with the diagnosis of genetic epilepsy syndromes and abnormal neuroimaging and normal EEG were associated with the diagnosis of epilepsy with structural lesion with enduring predisposition for recurrent seizure (Table 2). Classification seizure type by onset, epilepsy by onset, and epilepsy and epilepsy syndromes by ILAE 2017 classification systems is given in Table 3.

DISCUSSION

The Italian Long-Term Prognosis of Epilepsy (PRO-LONG) study has assessed the applicability of the new epilepsy definition in clinical practice in all the age groups.[2] The results of the study support the applicability of the new epilepsy definition in clinical practice. In a clinic-based study, among 1,006 patients with newly diagnosed epilepsy, 152 (15.1%) were diagnosed after a single seizure. Long-term recurrence in patients diagnosed with the new definition was 83.6% at 10 years and 89.1% at 15 years. In the present study, among the 30 children with new-onset unprovoked seizure, 20 (66.7%) children received the diagnosis of epilepsy after a single seizure: 11 (36.3%) received the diagnosis of electro-clinical genetic epilepsy syndromes and 9 (30%) received diagnosis of epilepsy due to a structural lesion with probable enduring predisposition for seizure recurrence. The remaining 10 (33.3%) children received the diagnosis of unknown onset epilepsy due to unknown cause. All these children had normal neurologic examination, EEG and CT brain. In a study of first unprovoked seizures in children aged less than 14 years, children with cryptogenic (unknown) etiology, the estimated recurrence risk was 36% and 43% at 1 and 2 years respectively.[10] In the PRO-LONG study, in patients diagnosed by new ILAE definition of epilepsy after a single seizure, focal seizures or abnormal findings in at least one among the following: neurologic examination, EEG, or neuroimaging predicted seizure recurrence.[2]

The predictors of epilepsy diagnosis after the first seizure were interinctal epileptiform discharges in the EEG and abnormal findings on neuroimaging. Focal or generalized EEG patterns with normal CT brain were associated with the diagnosis of genetic epilepsy syndrome. Structural abnormalities on CT brain with no EEG abnormalities were associated with the diagnosis of epilepsy due to structural lesion with enduring predisposition for seizure recurrence. In PRO-LONG study, compared to patients diagnosed using the traditional definition, patients diagnosed according to the new definition showed higher proportion of subjects with an abnormal neurologic examination and focal seizures.[2] The Mexican

Table 2: ILAE 2014 epilepsy definition: Epilepsies and epilepsy syndromes

After second seizure		10 (33.3%)
• *Unknown epilepsy due to unknown cause*	*10*	
After first seizure		20 (66.6%)
• *Genetic focal epilepsy syndrome*	*4*	
• *Genetic generalized epilepsy syndrome*	*7*	
• *Epilepsies due to structural cause*	*9*	

Table 3: Classification seizure type by onset, epilepsy by onset, and epilepsy and epilepsy syndromes by ILAE 2017 classification systems

Seizure type (n=37)	Focal onset: 13 (35%)	Generalized onset: 7 (19%)	Unknown onset: 17 (46%)
Epilepsy by mode of onset (n=30)	Focal epilepsies: 13 (43.3%)	Generalized epilepsies:7 (23.3%)	Epilepsies of unknown onset: 10 (33.3%)
Epilepsy syndromes (n=13)	Genetic focal epilepsy syndrome: 4 (13.3%) • *Genetic focal epilepsy with centro-temporal spikes: 4*	Generic generalized epilepsy syndromes: 7 (23.3%) • *Childhood absence epilepsy: 1* • *Juvenile absence epilepsy: 1* • *Juvenile myoclonic epilepsy: 5*	
Epilepsies (19)	Focal epilepsies due to structural cause: 9 (30%) • *Single cNCC: 5* • *Gliotic scar: 2* • *Hemispherical atrophy: 1* • *Neonatal hypoglycemia: 1*		Epilepsies due to unknown cause: 10 (33.3%)

cNCC: calcified neurocysticercosis

study[11] in adult epilepsy population studied the applicability of ILAE 2010 classification system.[12] In this study EEG was performed in 179 patients, focal EEG patterns in 45.3% and generalized EEG patterns in 19%. Generalized EEG patterns were more commonly seen when the cause of epilepsy was genetic electro-clinical epilepsy syndrome ($p = 0.03$).[11]

The results of this study shows the application of the new ILAE 2014 definition of epilepsy in a cohort of Indian children in resource-poor setting. Focal or generalized interictal epileptiform discharges in the EEG and normal CT were associated with the diagnosis of genetic epilepsy syndromes and abnormal neuroimaging and normal EEG were associated with the diagnosis of epilepsy with structural lesion with enduring predisposition for recurrent seizure. The major limitation of the study is that the study was in a highly selective cohort of school children from low socioeconomic strata. The epilepsies and epilepsy syndromes observed in this cohort were the common types of epilepsies seen in this age group. Severe epilepsies of childhood were not represented.

DISCLOSURE

Conflict of interest: None

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