RESEARCH PAPER

INCLEN Diagnostic Tool for Epilepsy (INDT-EPI) for Primary Care Physicians: Development and Validation

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Objective: To evaluate the diagnostic accuracy of a new diagnostic instrument for epilepsy – INCLEN Diagnostic Tool for Epilepsy (INDT-EPI) – with evaluation by expert pediatric neurologists.

Study design: Evaluation of diagnostic test.

Setting: Tertiary care pediatric referral centers in India.

Methods: Children aged 2-9 years, enrolled by systematic random sampling at pediatric neurology out-patient clinics of three tertiary care centers were independently evaluated in a blinded manner by primary care physicians trained to administer the test, and by teams of two pediatric neurologists.

Outcomes: A 13-item questionnaire administered by trained primary care physicians (candidate test) and comprehensive subject evaluation by pediatric neurologists (gold standard).

Results: There were 240 children with epilepsy and 274 without epilepsy. The candidate test for epilepsy had sensitivity and specificity of 85.8% and 95.3%; positive and negative predictive values of 94.0% and 88.5%; and positive and negative likelihood ratios of 18.25 and 0.15, respectively.

Conclusion: The INDT-EPI has high validity to identify children with epilepsy when used by primary care physicians.

Keywords: *Childhood neuro-developmental disorders, Resource-limited settings, Psychometric evaluations.*

Epilepsy contributes to significant morbidity with reported prevalence of 2.4-5.6 per 1000 in India [1-3]. However, nearly 75% of these do not receive appropriate treatment [4], many due to a lack of proper diagnosis. The situation is no different in other developing countries [5-9]. The reported rate of misdiagnosis of epilepsy among pediatricians ranges from 30-39% [10-13]. The diagnosis of epilepsy is mostly based on clinical history supported by neuro-imaging and electroencephalography. In the absence of an objective "gold standard" diagnostic test, the decision of a team of experienced pediatric neurologists with access to all investigations may be considered as nearest to the "gold standard" for diagnosis of childhood epilepsy [14].

As per 2003 estimates, the Indian populations of over 1 billion were being served by only about 500 neurologists [4,15] most of whom serve in large cities. Similarly, most pediatricians are also concentrated in urban areas while the majority of Indians still live in the villages and small towns where such expertise is not available. The most effective way to reduce the treatment gap of people with epilepsy in developing countries is delivery of epilepsy services through primary health care [16]. Hence, there is a need to for a diagnostic instrument for use by primary care physicians to help them in identifying cases with epilepsy as well as ruling out non-epileptic events. There are no comprehensive, validated tools that can be administered by such physicians for diagnosis of epilepsy. The INCLEN Diagnostic Tool for Epilepsy (INDT-EPI) has been developed with the major aim of increasing the access to care for seizure disorders of large segments of populations residing in rural areas

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and small towns where specialists care may not be available. The present study was conducted to evaluate the psychometric properties of this new instrument for childhood epilepsy as part of a nation-wide, multi-centre prevalence study for common neuro-developmental disorders among children aged 2-9 years.

METHODS

This diagnostic test evaluation study was conducted on children attending the pediatric neurology outpatient clinics of three public sector tertiary care pediatric referral centers [All India institute of Medical Sciences (AIIMS), Lady Hardinge Medical College (LHMC) and Maulana Azad Medical College (MAMC)] in New Delhi, India. These centers receive referred cases for complex medical problems as well as simple ailments seen at primary care level, mostly from National Capital Region and nearby states. Children (2-9 years) of either gender attending the pediatric neurology outpatient clinics were eligible for inclusion in the study. Children who had poor general condition requiring admission (e.g. respiratory distress requiring supplemental oxygen, altered sensorium, peripheral circulatory collapse, suspected sepsis and bleeding), and those who were not accompanied by a primary caregiver were excluded from the study. At each study site, a team of two pediatric neurologists with at least three years experience in the diagnosis and management of epileptic children, one study coordinator and one graduate (MBBS) physician participated in the study. Ethical approval was obtained from IndiaCLEN Review Board and the Institutional Review Board of all the study sites. The instrument development and data collection were done from January 2008 to April 2010.

Diagnostic instruments

Gold standard: The diagnosis of epilepsy was established at each site by consensus of the two pediatric neurologists following detailed history and physical examination with access to electroencephalogram, computed tomography and/or magnetic resonance imaging of Brain, as indicated. The instrument included a summary assessment (diagnosis): 'epilepsy', 'epilepsy with other neuro-developmental disorder (NDD)', "NDDs other than epilepsy" and "No NDD/Epilepsy".

Candidate test: INDT-EPI which has been developed on the standard definitions of seizures and epilepsy proposed by the International League Against Epilepsy (ILAE) [17] through consensus among multidisciplinary national and international team of experts (49 national and 6 international).

Instrument Development

The INDT-EPI was developed as consensus clinical criteria (CCC) for diagnosing epilepsy by the Technical Advisory Group (TAG) consisting of pediatricians, developmental pediatricians, child psychiatrists, pediatric neurologists, pediatric otorhinolaryngology, community physicians, clinical psychologists, special educators, specialist nurses, speech therapists, occupational therapists, and social scientists through a series of discussions and meetings using Delphi method and over three rounds of 2-day workshops.

INDT-EPI included questions in simple language to elicit the history of common seizure types (generalized and partial motor seizures, absence seizures and myoclonic seizures) (questions 1,2,10,11), the number of seizures and duration between first and last seizures is captured through question 3 and 4, provoked seizures such as febrile seizures, seizures occurring during neuro-infections, with head trauma or during systemic illnesses (question 5 for febrile seizures, 6 for acute symptomatic seizures, 7 for neonatal seizures) and seizure mimics such as breath holding spells (question 8) and syncopal attacks (question 9). Question 12 and 13 are final diagnosis. The instrument was translated from English to Hindi and back translated to English before the study was undertaken. The Hindi instrument was pretested in 20 children to look for difficulties in administering/understanding the questions and time needed to complete assessment. The instrument is available as ***Web Appendix* I**.

Enrolment and assessments

Enrolment was done through systematic random sampling. Two computer-generated random numbers were provided to the study coordinator daily in a sealed envelope. The first number (between 1 and 9) determined the starting point, and the second random number (between 5 and 15) determined the nth number (sample interval) to be sampled starting from the first random number. Every nth child in the age group of 2-9 years was assessed for eligibility and enrolled after obtaining written, informed consent from the primary caregiver until the final sample was achieved. If consent or inclusion criterion was not achieved, (n+1)th child was enrolled. The day's enrollment stopped once 15 children were enrolled in above manner or OPD registration was over, whichever happened first. Consecutive study subjects were enrolled in the above manner until desired number of children were identified based on gold standard diagnosis. Since the subjects were recruited from pediatric neurology outpatients, stoppage of recruitment was linked to achieving desired sample of children with 'no epilepsy' and 'no NDD'.

At all three sites, subjects were first administered the INDT-EPI (candidate test) by the primary care physician and later evaluated by the expert team of pediatric neurologists (gold standard). Administration of INDT-EPI took approximately 30-40 minutes. These findings were filled in a predesigned instrument, enclosed in separate sealed, opaque envelop bearing the subject's unique identification number and handed over to the coordinator. The sealed envelopes of expert team (gold standard) were opened at the end of day by the coordinator, who was not part of the assessment team to enlist the number of cases of epilepsy, epilepsy with other neuro-developmental disorders (NDDs), NDDs other than epilepsy, and group with no epilepsy or NDDs, based on the gold standard assessments.

Sample size: Assuming sensitivity and specificity of INDT-EPI to be 85% with relative precision of 10% at 95% confidence level, sample size was calculated to be 68 in each category. To account for drop-outs, it was decided to enrol at least 80 children in each category (epilepsy, epilepsy with other NDD, NDDs other than epilepsy, and group with no epilepsy or NDD).

Training and quality assurance: INDT-EPI training manual for administration and caregiver's response interpretation was prepared. General physicians were trained (eight hours of didactic manual-based teaching and instrument administration on five cases each) by pediatric neurologists during a two-day comprehensive, hands-on, structured workshop.

The team of pediatric neurologists (gold standard) was blinded to the assessment of the physician (candidate test). The study coordinator at the site assessed children attending the out-patient clinic for eligibility and enrolled them after taking written, informed consent from the primary caregiver, but did not take part in any of the assessments.

Statistical analysis: The data were analyzed using STATA version.10. The utility and psychometric properties of INDT-EPI were calculated in comparison with the assessments by the team of pediatric neurologists.

RESULTS

Out of 531 children assessed for eligibility, 514 (341 boys) were included; 11 children refused consent and 6 were not accompanied by primary caregiver. Mean (SD) age of included children was 60.1 (1.0) months. Of the 240 children with epilepsy, 97 (40%) had only epilepsy, and 143 (60%) had epilepsy with NDDs according to gold standard. Of 274 children without epilepsy, 194 (71%) had NDDs other than epilepsy, and 80 (29%) had no NDDs. ***Fig.* 1** details the study flow. Out of 240 children with epilepsy, 203 (84%) had generalized or focal motor seizures, 12 (5%) had absence seizures, and 16 (6.6%) had myoclonic. The team of neurologists could not assign a clear classification to 9 children. ***Table* I** details the performance of INDT-EPI instrument in comparison to the gold standard. The possible reasons for the false diagnoses (4.7% false positives and 14.2% false negatives) by the candidate test are summarized in ***Web Table* I** and ***Web Table* II**.

DISCUSSION

INDT-EPI for diagnosis of childhood epilepsy by the primary care physician demonstrated good psychometric properties. To the best of our knowledge, there are no validated instruments for diagnosing epilepsy. The tools currently available include screening questionnaires, with confirmation done by specialists [1,18-24].

Differentiating children with epilepsy from those with other NDDs like cerebral palsy and intellectual disability (overlapping symptomatology) is often challenging. The specificity of INDT-EPI increased to 97.4% when it was administered to children with other NDDs. The specificity of the instrument in subgroup of children without any NDD was lower (90%) compared to subgroup with other NDDs (97.4%). It is possible that parents of normal children are less likely to be forthcoming in terms of thoughtful responses than parents of children with other NDDs. This can also be attributed to different health seeking behavior of the parents.

In an earlier study assessing the nature of multiple events (epileptic or non-epileptic), it was seen that 4.6% children with non-epileptic events were initially misdiagnosed as having epilepsy (false positive) and 5.6% children with epilepsy were initially diagnosed as having 'no epilepsy' (false negative) [14]. The assessments in that study were comprehensive including detailed evaluation by a panel of pediatric neurologists supported by electroencephalography and neuro-imaging, when required. In the present study, the assessments were done by graduate physicians trained to administer the structured clinical instrument. The rate of false positives in the current study is comparable to the above-mentioned study and is much lower compared with the reported rates of misdiagnosis of epilepsy [10,11,13]. To minimize the misclassification of epilepsy as acute symptomatic seizures (neuro-infections, head trauma, and systemic illness), clear-cut definitions with durations can be introduced for defining the seizures occurring in 'close' temporal association with brain infections as highlighted by the recent ILAE guidelines [17,25]. With the addition of duration cut-off to define acute

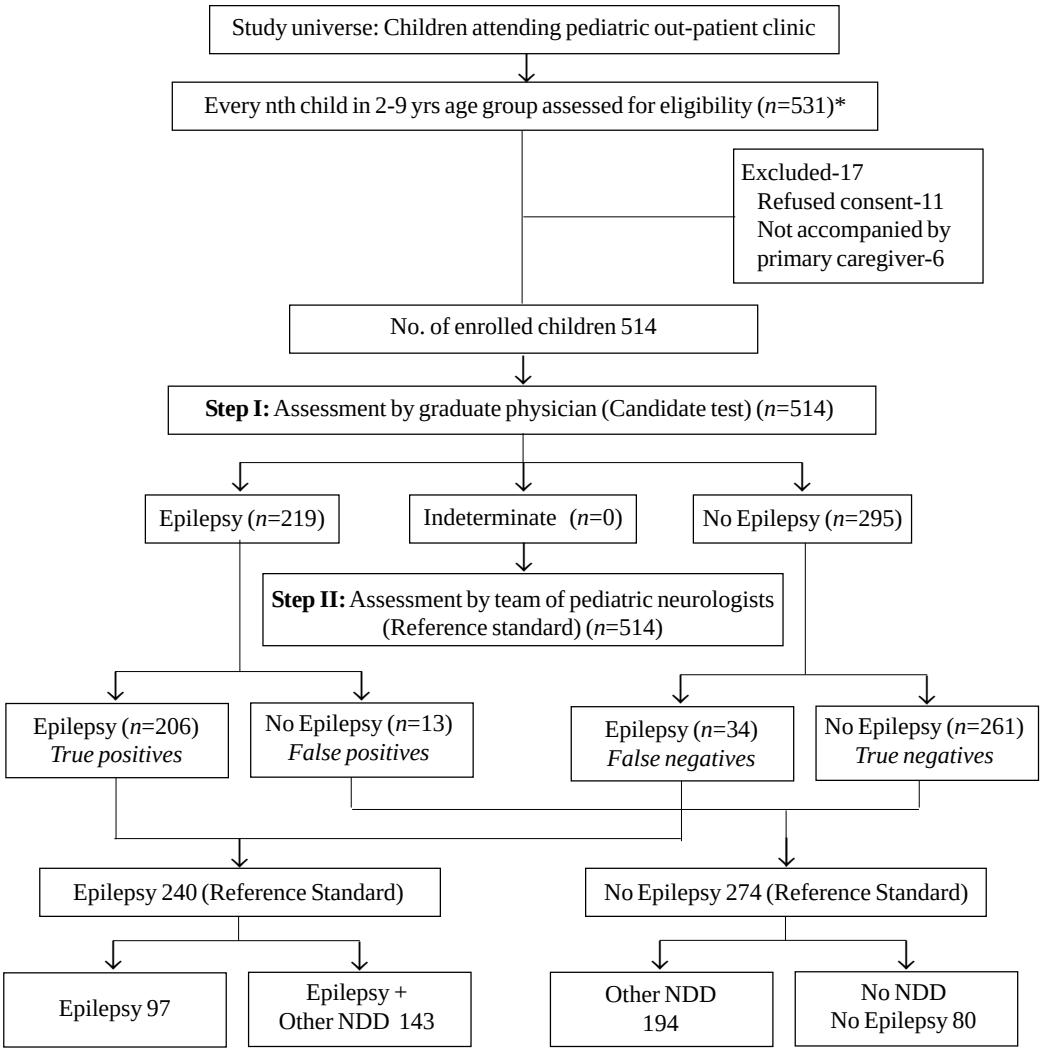

FIG. 1 *The study plan.*

TABLE I PSYCHOMETRIC PROPERTIES OF INCLEN DIAGNOSTIC TOOL FOR EPILEPSY (INDT-EPI)

Sensitivity	85.8 (80.8-90.0)	Specificity	95.3 (92.0-97.4)
LR of positive test	18.2 (10.6-30.8)	LR of negative test	0.15 (0.11-0.20)
Positive predictive value	94.0 (90.6-96.8)	Negative predictive value	88.5 (84.3-91.9)

LR: Likelihood ratio; All values in %(95% CI).

symptomatic seizures, the sensitivity of the INDT-EPI is likely to increase.

Limitation of the present study was that the included subjects from the tertiary care referral centers might not be representative of the community. The 240 patients of epilepsy out of 514 children reflect the referral bias in pediatric neurology outpatients. The instrument, in its present form, does not have the provision for differentiating between active and prevalent cases. The primary care physician has to suspect epilepsy in his/her setting before the tool is administered; tool should pick up both prevalent as well as active cases in such situation.

To conclude, INDT-EPI is a useful tool for diagnosis of childhood epilepsy by non-expert medical professionals (with adequate training) in different clinical settings, and for future epidemiological studies. This instrument can also be used in day-to-day clinical practice for diagnosing epilepsy by the primary health

WHAT IS ALREADY KNOWN?

- The diagnosis of epilepsy in children requires evaluation by experienced pediatricians or pediatric neurologists along with supporting investigations like EEG and neuro-imaging.

WHAT THIS STUDY ADDS?

- The INDT-EPI tool for diagnosing epilepsy has good sensitivity and specificity when used by primary care physicians with short training.

care physicians thereby expanding the care for epilepsy patients and reducing diagnosis management gap in resource-limited settings. Further studies on the instrument are recommended to assess its performance in different community and healthcare settings.

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REFERENCES

1. Mani KS, Rangan G, Srinivas HV, Kalyanasundaram S, Narendran S, Reddy AK. The yelandur study: A community-based approach to epilepsy in rural south India–epidemiological aspects. Seizure. 1998;7:281-8.
2. Koul R, Razdan S, Motta A. Prevalence and pattern of epilepsy (Lath/Mirgi/Laran) in rural Kashmir, India. Epilepsia. 1988; 29:116-22.
3. Radhakrishnan K, Pandian JD, Santhoshkumar T, Thomas SV, Deetha TD, Sarma PS, *et al.* Prevalence, knowledge, attitude, and practice of epilepsy in Kerala, south India. Epilepsia. 2000; 41:1027-35.
4. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia. 1999; 40:631-6.
5. Gu L, Liang B, Chen Q, Long J, Xie J, Wu G, *et al*. Prevalence of epilepsy in the People's Republic of China: a systematic review. Epilepsy Res. 2013;105:195-205.
6. Malik MA, Akram RM, Tarar MA, Sultan A. Childhood epilepsy. J Coll Physicians Surg Pak. 2011; 21:74-8.
7. Benamer HT, Grosset DG. A systematic review of the epidemiology of epilepsy in Arab countries. Epilepsia. 2009; 50:2301-4.
8. Somoza MJ, Forlenza RH, Brussino M, Centurión E. Epidemiological survey of epilepsy in the special school population in the city of Buenos Aires. A comparison with mainstream schools. Neuroepidemiology. 2009; 32:129-35.
9. Calisir N, Bora I, Irgil E, Boz M. Prevalence of epilepsy in Bursa city center, an urban area of Turkey. Epilepsia. 2006; 47:1691-9.
10. Chadwick D, Smith D. The misdiagnosis of epilepsy. BMJ. 2002; 324:495-6.
11. Chinthapalli RN. Who should take care of children with epilepsy? BMJ. 2003; 327:1413.
12. Cockerell OC, Hart YM, Sander JW, Shorvon SD. The cost of epilepsy in the United Kingdom: an estimation based on the results of two population-based studies. Epilepsy Res. 1994; 18:249-60.
13. Uldall P, Alving J, Hansen LK, Kibaek M, Buchholt J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. Arch Dis Child 2006;91:219-21.
14. Stroink H, van Donselaar CA, Geerts AT, Peters ACB, Brouwer OF, Arts WFM. The accuracy of the diagnosis of paroxysmal events in children. Neurology. 2003; 60:979-82.
15. Krishnamoorthy ES, Satishchandra P, Sander JW. Research in epilepsy: development priorities for developing nations. Epilepsia. 2003; 44 Suppl 1:5-8.
16. Carpio A, Hauser WA. Epilepsy in the developing world. Curr Neurol Neurosci Rep. 2009; 9:319-26.
17. ILAE Commission Report. The epidemiology of the epilepsies: future directions. Epilepsia. 1997; 38:614-8.
18. Placencia M, Sander JW, Shorvon SD, Ellison RH, Cascante SM. Validation of a screening questionnaire for the detection of epileptic seizures in epidemiological studies. Br J Neurol. 1992; 115:783-94.
19. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of epilepsy in the Parsi community of Bombay. Epilepsia. 1988; 29:111-5.
20. Gourie-Devi M, Gururaj G, Satishchandra P, Subbakrishna DK. Neuro-epidemiological pilot survey of an urban population in a developing country. A study in Bangalore, south India. Neuroepidemiology. 1996; 15:313-20.
21. Osuntokun BO, Adeuja AO, Nottidge VA, Bademosi O, Olumide A, Ige O, *et al.* Prevalence of the epilepsies in Nigerian Africans: a community-based study. Epilepsia. 1987; 28:272-9.
22. Anand K, Jain S, Paul E, Srivastava A, Sahariah SA, Kapoor SK. Development of a validated clinical case definition of generalized tonic-clonic seizures for use by community-based health care providers. Epilepsia. 2005; 46:743-50.
23. Das SK, Biswas A, Roy T, Banerjee TK, Mukherjee CS, Raut DK, *et al.* A random sample survey for prevalence of major neurological disorders in Kolkata. Indian J Med Res. 2006; 124:163-72.
24. Banerjee TK, Ray BK, Das SK, Hazra A, Ghosal MK, Chaudhuri A, *et al*. A longitudinal study of epilepsy in Kolkata, India. Epilepsia. 2010; 51:2384-91.
25. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, *et al.* Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010; 51:671-5.