

Development of a Validated Clinical Case Definition of Generalized Tonic–Clonic Seizures for Use by Community-based Health Care Providers

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Summary: *Purpose:* To develop and test a clinical case definition for identification of generalized tonic–clonic seizures (GTCSs) by community-based health care providers.

Methods: To identify symptoms that can help identify GTCSs, patients with history of a jerky movements or rigidity in any part of the body ever in life were recruited from three sites: the community, secondary care hospital, and tertiary care hospital. These patients were administered a 14-item structured interview schedule focusing on the circumstances surrounding the seizure. Subsequently, a neurologist examined each patient and, based on available investigations, classified them as GTCS or non-GTCS cases. A logistic regression analysis was performed to select symptoms that were to be used for case definition of GTCSs. Validity parameters for the case definition at different cutoff points were calculated in another set of subjects.

Results: In total, 339 patients were enrolled in the first phase of the study. The tertiary care hospital contributed the maximal number of GTCS cases, whereas cases of non-GTCS were mainly from the community. At the end of phase I, the questionnaire was shortened from 14 to eight questions based on statistical association and clinical judgment. After phase II, which was conducted among 170 subjects, three variables were found to be significantly related to the presence of GTCSs by logistic regression: absence of stress (13.1; 4.1–41.3), presence of frothing (13.7; 4.0–47.3), and occurrence in sleep (8.3; 2.0–

34.9). As a case definition using only three variables did not provide sufficient specificity, three more variables were added based on univariate analysis of the data (incontinence during the episode and unconsciousness) and review of literature (injury during episode). A case definition consisting of giving one point to an affirmative answer for each of the six questions was tested. At a cutoff point of four, sensitivity was 56.9 (47.4–66.0) and specificity, 96.3 (86.2–99.4). Among the 197 GTCS and 26 new non-GTCS patients recruited from hospitals from select SEAR Member Countries, in phase III, the sensitivity of this clinical case definition was 72% and specificity, 100%. A stratified analysis by gender in all the three phases did not show any differences between the sexes.

Conclusions: Based on these criteria, we recommend that all patients with a history of two or more episodes of jerking or rigidity of limbs, having a score of ≥ 4 in the case definition, be identified as having GTCSs and started on antiepileptic medications. This clinical case definition can be very useful for community-based health care providers to identify and manage cases of GTCSs in the community. This should play a major role in the reduction of treatment gap for epilepsy in developing countries. **Key Words:** Epilepsy—Generalized tonic–clonic seizures—Case definition—Validity—Community-based health care providers—Treatment gap.

Epilepsy is a chronic neurologic disorder, characterized by recurrent unprovoked seizures. According to the International League Against Epilepsy, ~50 million individuals have epilepsy globally. It is estimated that >35 million of these individuals live in developing countries (1). Review of available evidence has shown that a large treatment gap (defined as the proportion of people with

active epilepsy not getting appropriate treatment from all those with epilepsy) exists of ~80–90% in these countries (2), with a scarcity of skilled manpower, such as psychiatrists and neurologists. In rural areas, even a qualified physician is not available, and people often seek treatment with faith healers. Thus to reduce the treatment gap, a need exists to make epilepsy treatment more accessible by training community-based health care providers in identifying and managing epilepsy.

Among the different types of epilepsy, generalized tonic–clonic seizures (GTCSs) can potentially lend themselves to easy identification by community-based health

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care providers because the manifestations of such seizures are very obvious. GTCS also are amenable to effective treatment with relatively inexpensive drugs. They account for ~70–80% of all epilepsy (3). Thus this study focused only on GTCSs. To the best of our knowledge, no validated identification instrument and clinical case definition for GTCSs exists for use by community-based health care providers based on which treatment could be started. The available diagnostic criteria are for epidemiologic purposes and for screening by laypersons followed by referral to a neurologist for confirmation (4). As they are used as a screening tool, they have generally been designed to have a high sensitivity to ensure that few cases are missed. However, in a condition like epilepsy, which has a substantial social stigma, false labeling of subjects as individuals has a high social cost.

Therefore we decided to develop a simple questionnaire that could assist community-based health care providers in deciding whether a person who has had an episode of jerking of the body and limbs needs treatment with anti-convulsants (AEDs). It was a priori decided that the clinical case definition of GTCSs should have $\geq 90\%$ specificity, that is, no more than 10% of cases are incorrectly identified as having GTCSs and started on AEDs. The investigators were willing to accept a sensitivity of ~60–70%, as it is a great improvement over the current level of treatment of patients in the South East Asia Region of WHO. The long-term goal of this project is to reduce the treatment gap of GTCSs by training community-based health care providers in identification and management of GTCSs.

METHODS

The study was done in three phases. The first phase was development of the preliminary identification instrument. The second phase was devoted to finalization of the instrument and validation of the case definition in the same study setting (i.e., New Delhi, India). The third phase was validation of the identification instrument and the case definition in other member countries of WHO-SEA Region.

Study sites and recruitment of patients

The subjects were recruited from three sites representing different levels of health care. The first two sites were situated at the Comprehensive Rural Health Services Project (CRHSP), Ballabgarh, in the adjoining state of Haryana, one being the community served by the Project (Intensive Field Practice Area), and the second being the epilepsy clinic of the CRHSP at the secondary care hospital at Ballabgarh. The third site was the neurology OPD at All India Institute of Medical Sciences (AIIMS), a tertiary care hospital in New Delhi.

Phase 1

Identification instrument development

The first draft of the interview schedule was prepared by a group of experienced clinicians based on their knowledge of epilepsy and review of existing screening tools for epilepsy. Based on review, the two most important differential diagnoses identified were nonepileptic seizure and syncope. The clinical features that assist in distinguishing were taken from available literature (4–8).

The final instrument had two parts: the first part was for identification of suspected patients who may have had an attack of GTCSs (screening questions), and the second part was to collect more information about the seizure (confirmatory questions) (Box 1).

Screening of suspected cases (screening questions)

To identify all cases of seizures, the screening questions initially included questions on disorientation during episode, loss of consciousness and rigidity of the body, and jerky movements of the body during the episode. The questionnaire inquired about the lifetime experience of such an episode (i.e., having had any such episode ever in life until the present moment). All those answering “yes” to any one of the screening questions were administered the confirmatory section of the questionnaire.

Detailed information about the seizure (confirmatory section)

The section had 14 questions on the signs, symptoms, and circumstances surrounding the seizure. These questions were classified as those related to events occurring before, during, and after the seizure. If the information in any question had occurred even once during any seizure, it was taken as positive.

Data collection

Especially trained paramedical workers administered the questions. They were trained to ask the question, explain the meaning, and interpret the different possible answers to the question. The questionnaire was pretested at all the three study sites before the actual data collection was begun. In the community, the screening questions were put to any adult member of the family who was asked about the status of all the family members.

In both the hospitals in Ballabgarh and New Delhi, new and old patients attending the clinics were enrolled. At all three sites, the questions were put to a relative who had witnessed an attack. Based on a pilot study among the patients and their relatives at AIIMS Hospital (85 pairs), where in we had found a significant degree of agreement between patient’s and relative’s versions (kappa value of >0.6 for all the questions), we supplemented the eyewitness account with the patient response wherever necessary. A written consent was taken from all the respondents for taking part in the study.

Confirmation of diagnosis

A neurologist examined each screened positive individual defined as having answered “yes” to any one or more of the screening questions. After a detailed history (from an eyewitness, not necessarily the same as in the screening), examination, and review of available investigations, he or she classified them as having GTCSs or another diagnosis. Diagnostic criteria for each condition were based on ICD-10. GTCSs were defined as an episode of generalized rigidity and/or jerking of limbs with or without altered sensorium. Both primarily and secondarily GTCSs were included (generalization was the essential feature). Non-GTCSs included all those who had rigidity and/or jerking with retained consciousness and were diagnosed to have nonepileptic seizures, cases suspected to have partial complex seizures, simple partial seizures, and other nonclassifiable events

Blinding of investigators

In the community, the neurologist’s examination was conducted separately and after the screening phase. Thus the interviewers were automatically blinded to the patients’ status. In the hospitals, the diagnosis of the patient was made beforehand by the clinician. In these cases, the interviewers were blinded to the status and filled their forms independent of the clinician’s opinion.

Phase 2

Based on the analysis of data from phase 1, the identification instrument was modified and shortened in the second phase. The data for second phase were collected from the same three sites. The data from this phase were used to finalize the identification instrument and the case definition.

Phase 3

The third and final phase of development of the case definition was done by recruiting patients with history of rigidity or jerkiness in the outpatient clinics from other SEAR member countries (Bhutan, Myanmar, Nepal, Sri Lanka, Thailand). The instrument finalized in phase 2 was used by neurologists/psychiatrists from these countries to

test its applicability. The completed forms were sent to WHO-SEARO for pooled analysis of the data.

Statistical methods

The data were entered into Microsoft Excel and analyzed by using the SPSS software. Univariate and multivariate analyses were performed to calculate crude and adjusted odds ratios. Variables found significant in the univariate analysis ($p < 0.1$) were included in step-wise multiple logistic regression analysis. For the final case definition, we calculated the sensitivity and specificity of groups of questions. ROC curves were drawn for different scores of the case definition.

RESULTS

Phase 1

In the first phase, 380 patients were recruited (i.e., screened positive to the screening part of the identification instrument). A preliminary review of the data revealed that some of those who screened positive had been identified only because of the “disorientation and unconsciousness” screening questions. As the primary purpose of the case definition was for use by community-based health care providers to identify cases of GTCSs, it was decided to restrict the screening question to rigidity/jerkiness of body. As a result, 41 (11%) of the total recruited subjects were excluded. These were mainly from the tertiary care hospital and were distributed equally among the subjects with GTCSs and without GTCSs. However, as in clinical experience, unconsciousness is an important component of the definition of GTCSs, this question was shifted to confirmatory section for the phase 2.

The final diagnosis of the 339 patients included in phase 1 was as follows: GTCSs, 252, and non-GTCSs, 87. The number of patients recruited from each site and the investigations done on each patient are shown in Table 1. Although the maximum number of GTCSs patients were from the neurology OPD at AIIMS, those with other diagnoses were mainly from the community in Ballabgarh. The degree of investigations was, as expected, in keeping with the location of recruitment. Whereas at the

TABLE 1. Profile of GTCS and non-GTCS cases in phase I of the study

	GTCS Cases			Non-GTCS cases		
	Tertiary level hospital	Secondary level hospital	Community survey	Tertiary level hospital	Secondary level hospital	Community survey
Number of patients	112	63	77	13	21	53
% with EEG	97.4	79.4	31.2	30.8	0	0
% with video-EEG	14.3	0	0	15.4	0	0
% with CT scan	72.3	14.3	35.1	53.8	0	0
% with MRI scan	59.8	0	3.9	30.8	0	0
% females	41.1	27	26	38.5	71.4	77.4
% <10 yr	15.2	0	20.8	23.1	0	15.1
% ≥40 yr	11.7	3.2	14.3	46.2	19.0	47.2

GTCS, generalized tonic-clonic seizure; CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 2. Adjusted odds ratios (95% CI) of questions used for identifying GTCSs in the three study sites (data from phase 1)

Screening question	AIIMS hospital	Secondary hospital	Community	All sites
Disorientation	0.38 ^a (0.16–0.94)	9.3 ^b (1.7–50.8)	3.2 (0.7–15.4)	0.96 (0.43–2.12)
Unconsciousness	0.9 (0.3–2.6)	0.6 (0.2–2.6)	2.0 (0.4–9.6)	1.4 (0.6–3.4)
Stress	0.5 (0.2–1.3)	0.05 ^d (0.01–0.24)	0.21 ^b (0.08–0.54)	0.22 ^d (0.11–0.44)
Premonition	2.5 ^a (1.1–5.8)	2.0 (0.7–5.9)	1.9 (0.8–4.7)	1.9 (1.0–3.9)
Incontinence	1.6 (0.6–4.2)	2.3 (0.7–8.0)	1.0 (0.4–2.8)	1.5 (0.7–3.3)
Injury	3.6 ^b (1.4–9.2)	7.5 ^c (2.3–24.2)	1.8 (0.7–4.9)	3.0 ^b (1.4–6.3)
Eyes closed	0.32 ^a (0.13–0.77)	0.22 ^b (0.07–0.67)	0.66 (0.28–1.53)	0.43 ^a (0.22–0.84)
Frothing	3.1 ^b (1.3–7.2)	0.73 (0.2–2.3)	2.8 ^a (1.1–6.8)	2.3 ^a (1.2–4.5)
Occurs in sleep	4.8 ^c (2.1–11.2)	1.7 (0.6–5.0)	2.5 ^a (1.0–6.0)	3.5 ^c (1.7–7.1)
Occurs outside	2.1 ^a (1.0–4.5)	1.8 (0.7–4.8)	1.4 (0.6–3.1)	1.7 (0.9–3.2)
Weakness	3.4 ^a (1.2–9.8)	1.6 (0.5–5.5)	1.9 (0.7–5.1)	2.2 ^a (1.0–4.9)

^ap < 0.05.^bp < 0.01.^cp < 0.001.^dp < 0.0001.

tertiary care hospital, 14% of cases had video-EEG and 60% had magnetic resonance imaging (MRI), at the community level, this figure was none and 4%, respectively. Among the non-GTCS cases, 70% were female patients compared with 26% to 41% among the GTCS cases in different sites. Non-GTCS cases also were more likely to be older than 40 years, as compared with GTCS cases.

It was initially planned to analyze the data separately for the three sites of recruitment for phase 1. However, as the number of non-GTCS cases at each site was too few, data were pooled. The results of the first phase of the study at all the three sites are shown in Table 2.

No variable was found to be significantly associated with GTCSs at all the three sites. Only eight of the 14 questions in the confirmatory section significantly differentiated between GTCS and non-GTCS cases at any one site. A stratified analysis by gender showed that the direction of the odds ratios was same in both the sexes as well as the combined analysis. The other six questions were dropped from further study. The questions on premonitory symptoms and closure of eyes also were dropped after discussion with the interviewers showed that the respondents had difficulty in understanding the question, even though these were statistically significantly associated with presence of GTCSs. Based on clinical experience and available review of literature, it was decided to retain the question on incontinence during the episode for phase 2. Thus eight questions were included for the second phase of testing of the questionnaire, including the question on unconsciousness.

Phase 2

For the second phase, new patients were recruited at the AIIMS neurology OPD and epilepsy clinic at Ballargarh, but at the community level, the previously identified patients were asked the revised question on unconsciousness. The gap between the two interviews was ~1 month. For this phase, we had 116 GTCS patients and 54 non-GTCS patients. The analysis was done by pooling all data on all patients.

The univariate and multivariate analysis of the questions is shown in Table 3. Only three variables were found to be significantly related to the presence of GTCSs after multivariate analysis, as evident from odds ratios. These were absence of stress (13.1; 4.1–41.3), presence of frothing (13.7; 4.0–47.3), and occurrence in sleep (8.3; 2.0–34.9).

TABLE 3. Crude and adjusted odds ratios (95% CI) of revised questionnaire to identify GTCS (phase 2 data)

Screening question	Crude odds ratio	Adjusted odds ratio
No stress	20.8 (8.9–48.4) ^c	13.1 (4.1–41.3) ^c
Incontinence	5.4 (1.8–16.1) ^b	0.7 (0.1–4.3)
Injury	1.7 (0.9–3.6)	1.5 (0.4–5.5)
Frothing	29.1 (11.2–75.8) ^c	13.7 (4.0–47.3) ^c
Occurs in sleep	17.0 (5.0–57.6) ^c	8.3 (2.0–34.9) ^b
Occurs outside	1.7 (0.9–3.3)	1.4 (0.5–4.1)
Unconscious	4.2 (1.7–10.4) ^b	1.3 (0.4–4.4)
Weakness	2.5 (1.0–6.0) ^a	1.6 (0.4–6.0)

^ap < 0.05.^bp < 0.01.^cp < 0.0001.

BOX 1. *The original instrument used in the study*

No	Questions	Yes/No/ Don't Know
SCREENING SECTION		
	Has any one of your current family members, ever in their life, suffered from episodes described as follows:	
S1	<i>In which they were disoriented to their surroundings</i>	
S2	<i>In which they were completely unconscious?</i>	
S3	<i>In which their body became stiff/had thrashing movements of one or more limbs/had jerky movements of the whole body?</i>	
CONFIRMATORY SECTION		
1	<i>Events before the episode</i>	
1.1	Was the person subjected to stressful events, such as examinations, quarrels, conflict with mother-in-law, or other stressful events before the episode?	
1.2	Were there any warning symptoms before the attack, such as strange feelings, by which the person would become aware that the attack is going to occur?	
2	<i>Events during the episode</i>	
2.1.	Did he/she have vomiting during or after any episode?	
2.2	Did he/she pass urine or stool in his/her clothes during that episode?	
2.3.	Did he/she ever injure him/herself (including tongue bite) during such an episode?	
2.4.	Were the eyes shut tightly during any episode? (imitate tightly shut eyes)	
2.5.	Were the eyes rolled up or turned to one side during any episode?	
2.6.	Did the pattern of body/limb movement or the pattern of body stiffness remain exactly the same in all episodes?	
2.7.	Could the person respond to your commands during the episodes?	
2.8.	Was there any frothing from the mouth during any episode?	
3.	<i>Other details of the attack</i>	
3.1	Did he/she ever have such an attack during sleep?	
3.2.	Did any episode ever occur outside the home?	
4.	<i>Information from patients</i>	
4.1	Do you remember anything about the events later?	
4.2	Do you have weakness, drowsiness, headache after such an attack?	

These three variables were identified in both sexes in the stratified analysis by sex.

Development of clinical case definition for GTCS

A simple scoring system was devised with the three variables mentioned earlier to see whether it could be used as a clinical case definition of GTCSs. Presence of any two of these three signs in a person with history of jerks/rigidity of the body gave a sensitivity of 83% and specificity of 89%. However, the lower 95% confidence interval (CI) of specificity was 77%, which was not acceptable, because of the high number of false-positive cases. It was thought by the investigators that using only three questions can give rise to many errors of judgment by community-based health care providers. Increasing the number of items in any scale is a method for increasing its reliability (9). Therefore it was decided to add three more questions to the list of questions. Two of these were identified based

on univariate analysis of the second-phase data (incontinence during the episode and unconsciousness) and one on the clinical judgment and review of literature (injury during the episode) (4–8). Weakness after the seizure was considered as well, as it was significant by univariate analysis. However, based on input from the interviewers and experience of clinicians, it was thought that the differentiation between postictal weakness and feigned weakness of pseudoseizure by community-based health care providers could be difficult. Therefore it was not included in the final case definition.

Thus a total of six questions were included for the clinical case definition of GTCSs (Box 2). We used a scoring system of giving one point to an affirmative answer for each question. Thus a patient suspected to have GTCSs could get a maximum score of six and a minimum of 0. We examined the sensitivity and specificity for each score from 0 to 6 in the same data set (Table 4). With the

BOX 2. *The case definition developed at the end of the study*

No	Questions	Yes/No/ Don't know
1.	Did he/she pass urine or stool in his/her clothes during an episode?	
2.	Did he/she ever injure himself/herself or have tongue/cheek bite during an episode?	
3.	Was there any frothing from the mouth during an episode?	
4.	Did he/she ever have such an episode while asleep?	
5.	Was the patient completely unconscious during an episode?	
6.	Has an episode ever occurred WITHOUT preceding mental/emotionally stressful events?	

Answering "yes" to four or more questions of these six questions in patients with a history of two or more episodes of jerking or rigidity of limbs indicates the occurrence of GTCSs.

TABLE 4. Performance of the final clinical case definition of GTCSs (phase 2 data)

Cut-off score*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR	Negative LR
1	100% (96–100)	11.1% (4.6–23.3)	70.7% (63.0–77.4)	100% (51.7–100)	1.1	0
2	97.4% (92.1–99.3)	55.6% (41.5–68.8)	82.5% (74.9–88.2)	90.9% (74.5–97.6)	2.2	0.05
3	84.5% (76.3–90.3)	87.0% (74.5–94.2)	93.3% (86.3–97.0)	72.3% (59.6–82.3)	6.5	0.18
4	56.9% (47.4–66)	96.3% (86.2–99.4)	97.1% (88.8–99.5)	51.0% (40.9–60.9)	15.4	0.45
5	31.9% (23.7–41.3)	96.3% (86.2–99.4)	94.9% (81.4–99.1)	39.7% (31.4–48.6)	8.6	0.71
6	8.6% (4.4–15.7)	98.1% (88.8–99.9)	90.9% (57.1–99.5)	33.3% (26.2–41.3)	4.5	0.93

Six questions were finally included: absence of stress, presence of injury, incontinence, unconsciousness, frothing, and occurrence in sleep. Affirmative response to each would be given a score of 1.

GTCS, generalized tonic-clonic seizure; CI, confidence interval; PPV, positive predictive value; LR, likelihood ratio.

essential requirement of a minimum specificity of 90%, the best sensitivity was achieved at a cutoff point of four. The sensitivity and specificity at this score were 56.9% (47.4–66.0) and 96.3% (86.2–99.4), respectively. The lower 95% CI of specificity of 86% was acceptable. Among male subjects, the sensitivity was 56.6% (45.3–67.3), and specificity was 100% (71.7–100.0). Among female subjects, sensitivity was 57.6% (39.4–74.0), and specificity, 95.1% (82.2–99.2). The ROC curve for different cutoff points is shown in Fig. 1. The positive likelihood ratio was also highest for the cutoff point of 4. We also tried combinations of these six questions using “AND” or “OR” to get a case definition that gives a better sensitivity and specificity. The sensitivity and specificity were in a similar range with different combinations. Therefore we decided to keep the scoring system of 1 point for each “yes” answer, as it had the advantage of simplicity.

The validity parameters (sensitivity, specificity, and positive and negative predictive values) also were estimated by site for the cut-off point of four. They ranged between 66.7% (49.7–80.4), 96.3% (86.2–99.4), 92.9%

(75.0–98.8), and 80.0% (67.9–88.5), respectively, for AI-IMS, and 51.9% (40.3–63.4), 96.3% (86.2–99.4), 95.2% (82.6–99.2), and 58.4% (47.5–68.6), respectively, at community the level.

Phase 3

The clinical case definition as defined earlier was then tested in the third and final phase of development among subjects recruited from psychiatry outpatients from other SEAR member countries (Bhutan, Myanmar, Nepal, Sri Lanka, and Thailand). The pooled analysis of 197 GTCS patients and 26 non-GTCS cases revealed a sensitivity of 72.1% (65.2–78.1) and specificity of 100% (84.0–100.0). The performance was similar in both sexes, as revealed by stratified analysis.

Based on these criteria, we recommend that all patients with a history of two episodes of jerking or rigidity of limbs, having a score of four or more in the case definition, be identified as having GTCSs and be started on AEDs. Those scoring below four may need to be followed up, especially those with borderline scores of 2 or 3.

DISCUSSION

The South East Asia Regional Office of the World Health Organization has been working on a strategy that will ensure at least basic minimum neuropsychiatric services to be delivered to the community. The Intercountry meeting on Development of strategies for community-based neuropsychiatric services in Bangkok in November 2001 had identified epilepsy and psychosis as two disorders to be addressed in the first phase of the strategy to provide basic minimum services for select neuropsychiatric disorders to all (10).

As this study focused only on GTCSs, the entry point into the algorithm was restricted to individuals having jerkiness or rigidity of the whole body or all limbs. Our approach was to provide a case definition to be used on these subjects for whom a positive diagnosis of GTCSs can be

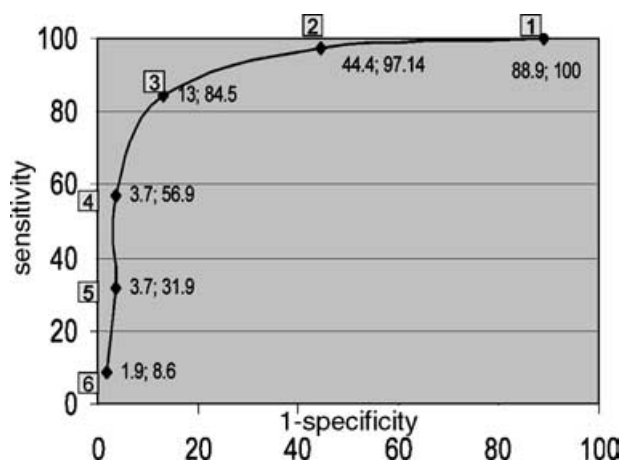


FIG. 1. ROC curve of case definition for GTCS.

made and treatment initiated. In their work on identifying historical criteria that distinguish syncope from seizures, the investigators had similarly restricted the entry point to loss of consciousness, as their purpose was to identify syncope (6).

We used neurologists' examinations with available investigations as the reference method for diagnosis of GTCSs. In an ideal setting, one would hope for a full spectrum of investigations [EEG, video-EEG, computed tomography (CT) scan, or MRI] to be done on all screened positives for a more assured diagnosis. However, availability and use of these investigations is extremely limited in most clinical situations across the region. Not enough neurologists are available in many countries of the region. However, lack of adequate diagnostic support means that misclassification could not be ruled out. At AIIMS, the investigators interviewed the subjects after the neurologist's examination, unlike in the other two settings. This could have resulted in an ascertainment bias at the level of AIIMS. Epilepsy has much social stigma in the community, and the possibility of subjects not disclosing the truth cannot be ruled out.

To estimate specificity of 95% with precision of 5% (so that a lower estimate does not go beyond 90%), we needed 76 cases of non-GTCSs, and for estimating sensitivity of 75% with 5% precision (so that lower estimate does not go beyond 70%), we needed 300 cases of GTCSs. Our total sample size was in this range. However, we did not have enough sample size to comment on the performance of the criteria by the site.

Our final case definition is based on a combination of statistical analysis (absence of stress, frothing, and occurrence in sleep) and clinical judgment and supported by the literature (presence of injury, incontinence, unconsciousness). Frothing, injury, incontinence, and loss of consciousness are included in all clinical descriptions of a GTCS (7,8). Tongue biting also has been found to be highly specific to GTCSs (5). Absence of stress and occurrence in sleep, both found to be statistically significant in this study, help us to rule out the possibility of pseudoseizures or nonepileptic seizures in these subjects. In the only other clinical criterion that we found to be in use in a demonstration project in China, in addition to rigidity or generalized tonic-clonic movements (entry points in our study), loss of consciousness, incontinence, injury, and postictal weakness were included (4). Although we would have preferred to base the definition only on evidence from this study, statistically significant association of clinical symptoms with disease does not always get translated into a good case definition of the disease, as seen in malaria (11).

The final case definition for GTCSs has high specificity and moderate sensitivity. High specificity was decided a priori as we clearly wanted to avoid overtreatment with AEDs of persons who did not have GTCSs. It is possi-

ble that those with only a few seizures may not be picked up by this case definition. We believe that these patients will become positive on follow-up if more seizures develop, which is likely, given the fact that they would not be receiving treatment. Thus this will at worst only delay the diagnosis of borderline cases. This underscores the essential need for follow-up. This is equally true for cases given treatment, as well as for borderline cases, to ensure successful management of the conditions.

If this project is successfully implemented in all 11 member countries of the South East Asia Regional office of WHO, it will translate into identification and management of 60–70% of the total number of cases of GTCSs (i.e., 7–8 million patients). This is a major improvement over the <2–5% of the estimated 11–12 million patients with GTCSs in the region, particularly in rural areas, who are currently getting appropriate treatment. This will be a big step in reducing the treatment gap for GTCS type of epilepsy in the region.

This clinical case definition of GTCSs was developed in only one country (India), although it was later tested in other SEAR countries in a hospital-based setting. As is well known, the validity of a case definition is dependent on the setting of use; because of bayesian prior probability, the case definition must be tested in different settings. It is important that this be done at the level where it is intended to be used (i.e., by community-based health care providers). WHO-SEAR is testing this instrument by training community-based health care providers in some member countries. The results of this testing would further lend support to its applicability in the field. It should be borne in mind that this definition is valid only for those with a reported episode of rigidity or jerkiness of limb(s) or body, and it does not apply to other individuals.

Coupled with the recommendation for use of phenobarbitone at the community level (12), availability of a standard clinical case definition has a potential to revolutionize the treatment of GTCSs. Also, by making the services more accessible through the community-based health care providers, we hope to give more patients treatment, reduce the patronization of quacks or faith healers, and thereby also reduce the stigma attached to the disease. These steps are essential to provide at least minimal basic services for epilepsy to the community.

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