ORIGINAL RESEARCH

A New Score for Sharp Discharges in the EEG Predicts Epilepsy

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Purpose: A challenge in EEG interpretation is to correctly classify suspicious focal sharp activity as epileptiform or not. A predictive score was developed from morphologic features of the first focal sharp discharge, which can help in this decision.

Methods: From a clinical standard EEG database, the authors identified 2,063 patients without a previous epilepsy diagnosis who had a focal sharp discharge in their EEG. Morphologic features (amplitude, area of slow wave, etc.) were extracted using an open source one-click algorithm in EEGLAB, masked to clinical classification. A score was developed from these features and validated with the clinical diagnosis of epilepsy over 2 to 6 years of follow-up. Independent external validation was performed in Kural long-term video-EEG monitoring dataset.

Results: The score for the first focal sharp discharge had a moderate predictive performance for the clinical designation as the EEG being epileptiform (area under the receiver operating characteristics curve = 0.86). Best specificity was 91% and sensitivity 55%. The score also predicted a future epilepsy diagnosis (area under the receiver operating characteristics curve = 0.70). Best specificity was 86% and sensitivity 38%. Validation on the external dataset had an area under the receiver operating characteristics curve = 0.80. Clinical EEG identification of focal interictal epileptiform discharges had an area under the receiver operating characteristics curve = 0.73 for prediction of epilepsy. The score was based on amplitude, slope, difference from background, slow after-wave area, and age. Interrater reproducibility was high (ICC = 0.91).

Conclusions: The designation of the first focal sharp discharge as epileptiform depends on reproducible morphologic features. Characteristic features were amplitude, slope, slow after-wave area, and difference from background. The score was predictive of future epilepsy. Halford semiquantitative scale had similar diagnostic performance but lower reproducibility.

Key Words: Epileptiform, Morphology, Quantitative, SCORE, Validation, Feature.

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Detection of interictal epileptiform discharges (IEDs) is a major task in the clinical review of EEG.[1–3] A common challenge in EEG interpretation is to classify focal sharp-appearing activity as epileptiform or not. Visual analysis is the current gold standard for this classification, but interrater agreement is only moderate.[4–7]

No quantitative guidelines exist to help in classifying sharp-appearing activity as epileptiform or not. The score in the study by Halford et al.[8] classified discharges for likelihood of being epileptiform on a 1 to 5 Likert scale, but this score has limited use and variable reproducibility. The 2017 EEG glossary[9] introduced a criterion-based scoring of epileptiform activity, but with limited data to support the criteria. These new criteria apply qualitative terms for morphologic properties of IEDs and do not give any quantitative definitions. The EEG reader has to rely on experience and training when evaluating whether a transient fulfills qualitative IED criteria. Kural et al.[10] examined the new criteria and concluded that five of six criteria should be fulfilled for optimal visual acceptance of epileptiform discharges.

Misdiagnosis of epilepsy is common.[11] Missed epileptiform activity in the EEG occurs on occasion.[12] Specialized epilepsy centers report a high prevalence of false-positive EEGs[12–14] and urge a conservative approach in IED assessment. While a higher specificity may be sensible for such centres, meta-analyses of EEG interpretation after a first seizure show the need to balance sensitivity and specificity.[1,15]

Most studies involving IED quantification have included development and application of automated spike detectors.[16–19] A few studies have examined specific quantitative IED features and their relation to a future epilepsy diagnosis,[20] their correlation with human IED detection,[21] their reproducibility,[20] age dependency,[22,23] and how they can contribute to epilepsy syndrome classification.[24,25]

The aim of this article was to develop a publicly available predictive score, the Bergen Epileptiform Morphology Score (BEMS), from morphologic features of the first suspicious sharp discharge, which can help in the classification of sharp-appearing as epileptiform or not. We improved an existing freely available algorithm[22] to measure morphology of sharp-appearing activity with one click on the pointed peak. The best morphologic features were combined into a predictive score.

METHODS

Patients and EEGs

We included all consecutive inpatients and outpatients who had standard EEGs or sleep-deprived EEGs recorded in our EEG

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laboratory facilities at Haukeland University Hospital, during the period March 4, 2013 to October 29, 2017, that were reported in SCORE EEG,[26] and that had nonepileptiform sharp transients or focal epileptiform activity (Fig. 1).

We excluded all patients who had an EEG before the inclusion period, a prior clinical diagnosis of epilepsy (since January 1, 1999), or a nonfocal epilepsy finding on EEG. For each of the remaining patients, we selected their first EEG with either (1) interictal epileptiform discharges (IEDs) and an EEG conclusion of focal epilepsy, hereafter simplified as "focal IEDs," or (2) sharp transients, wicket spikes, small sharp spikes (benign epileptiform transients of sleep), 6-Hz spike and slow wave, rudimentary spike–wave complex, hereafter simplified as "sharp transients," without an EEG conclusion of epilepsy. The EEG conclusion was drawn by the EEG interpreter during the initial clinical evaluation of the EEG and based on the EEG findings together with available clinical and paraclinical information, similar to the recommended "clinical correlation" section of the American Clinical Neurophysiology Society Guideline report template.[27] Patients were categorized into clinical outcomes of (1) epilepsy or (2) not epilepsy according to whether they had received a clinical diagnosis of epilepsy in the hospital records during follow-up until November 27, 2019. We selected for each patient the first EEG that contained sharp activity, and in that EEG,

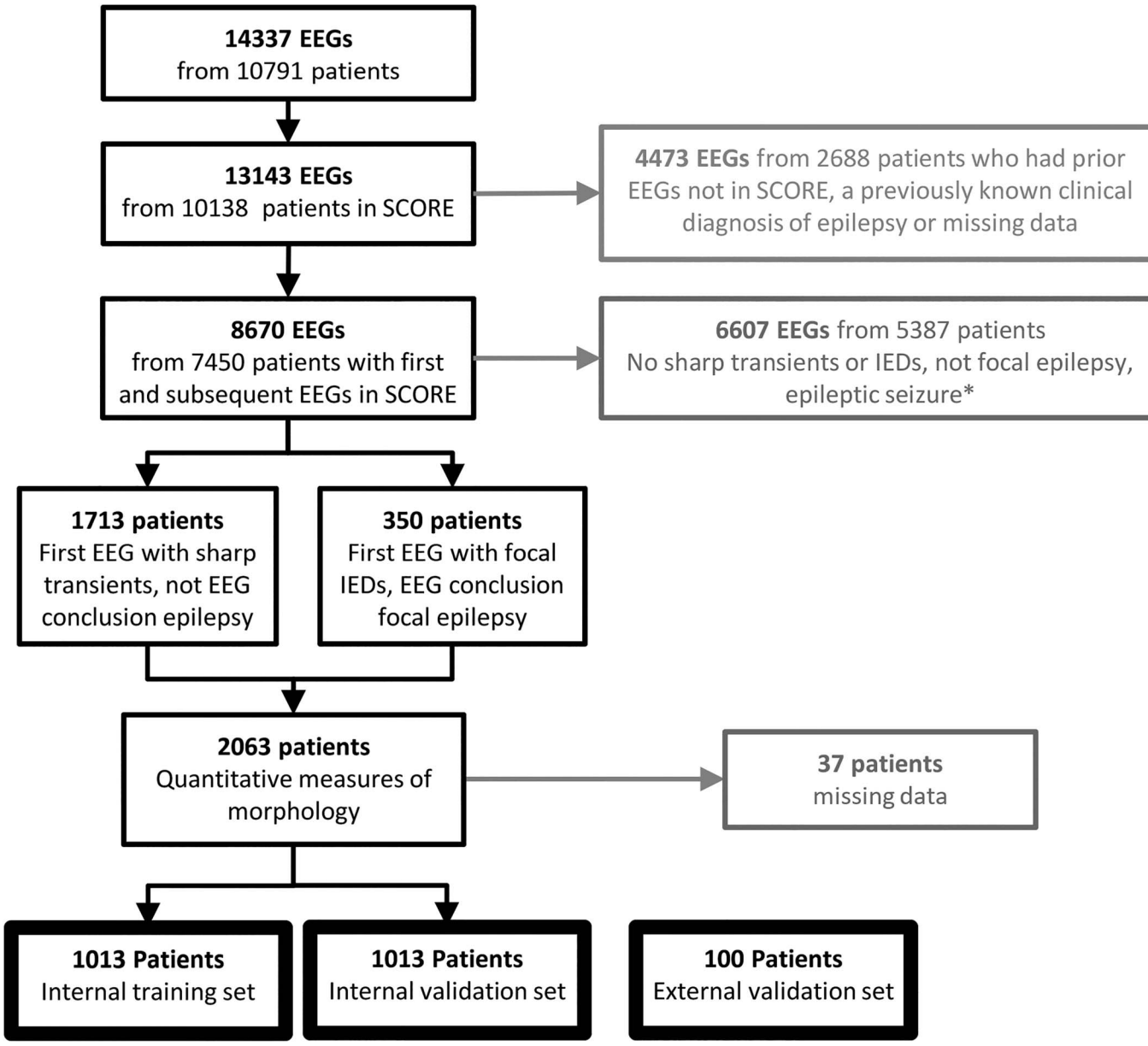

FIG. 1. Flow chart of patients. *EEG recordings with epileptic seizures were excluded.

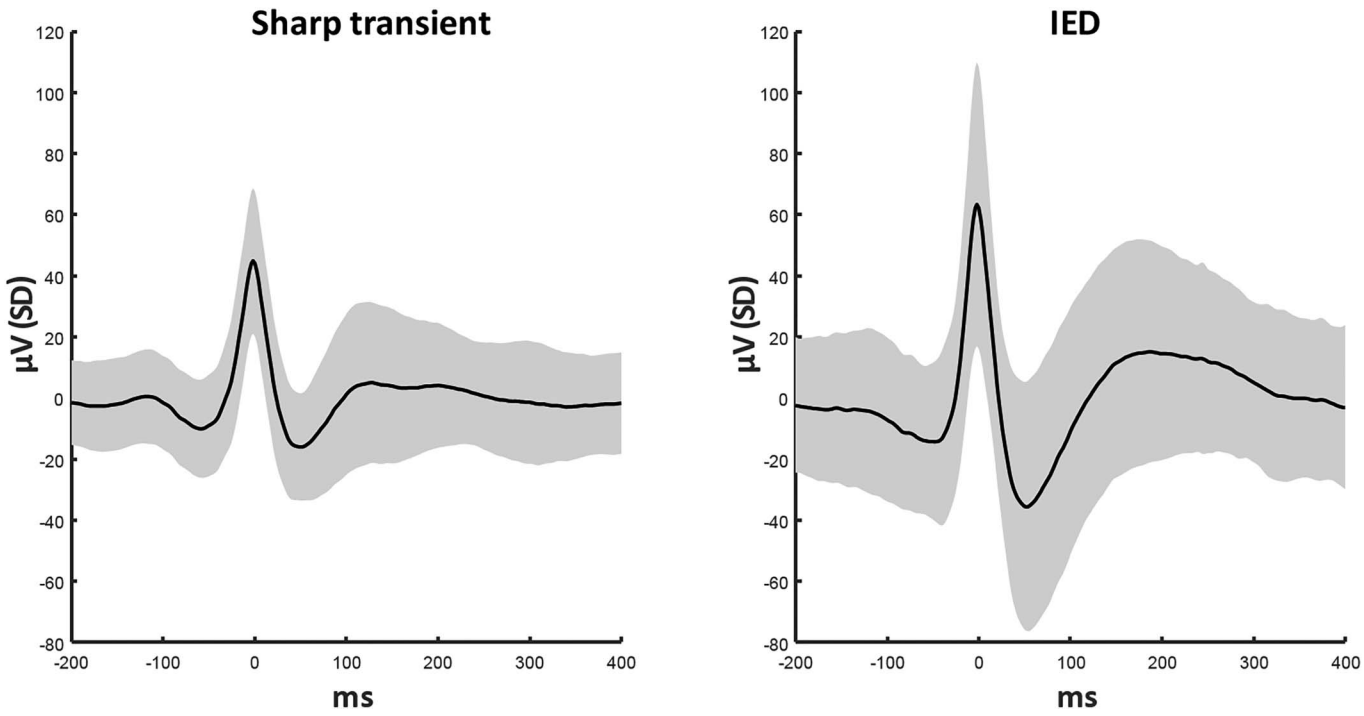

FIG. 2. Morphologic averages of sharp transients and focal IEDs in standard EEG. Average time series of sharp transients ($N = 1{,}677$) and IEDs ($N = 349$). One SD is shown by shaded grey areas. The average was calculated with the spiky component peak defined as time = 0 ms, from 200 ms before until 400 ms after the peak, and from the electrode where the sharp transient or IED was most convincingly epileptiform. IED, interictal epileptiform discharge.

we measured morphologic features of the first sharp discharge. The EEGs were randomized into two equally sized groups for multivariate analysis; one training set for dose–response modeling and elimination of similar features and another validation set.

EEG Recordings

Electrodes were applied according to the 10 to 20 system with a minimum of 21 and a maximum of 26 electrodes. Recording length was 20 minutes for standard EEGs and 60 minutes for sleep-deprived EEGs. NicoletOne EEG system was used to record and display EEGs.

IED Features

We selected the first sharp discharge marked as a sharp transient or an IED during the clinical EEG review. If several sharp appearing waves were present on the same EEG page, the most convincing epileptiform wave was chosen. Blinding was done for the clinical description as either a sharp transient or a focal IED. The first author of this article evaluated all sharp discharges, and the last author evaluated a random subset of 244 sharp discharges. All discharges were also scored according to the 5-point Likert scale by Halford et al.[8] We assessed the interrater reproducibility of Halford scale on the 244 sharp discharges evaluated by both authors.

Morphologic features of the sharp discharges were obtained using a custom-built tool in MATLAB[28]/EEGLAB[29] described previously.[22] The code is freely available (https://github.com/janbrogger/EpiOneClick). The software automatically determines 11 features of the sharp discharge. These were ascending and descending spike amplitudes, ascending and descending spike slopes, spike sharpness according to Frost,[30] spike duration, spike asymmetry according to Henze et al.,[31] spike to background power, slow after-wave area, background amplitude, and spatial extent of the negative spike pole. A detailed description of the algorithm is given in **Supplemental Digital Content 1** (see **S1**, http://links.lww.com/JCNP/A155), interrater reproducibility data for two authors using it in **Supplemental Digital Content 1** (see **S2**, http://links.lww.com/JCNP/A155), and inter-method data for sharp discharges that were annotated in a previous study[22] using four mouse clicks in **Supplemental Digital Content 1** (see **S3**, http://links.lww.com/JCNP/A155).

Multivariate Predictive Modeling

The model included spike descending amplitude, spike onset slope, slow after-wave area, spike to background power, and patient age as predictor variables. This model was applied on the validation set and an independent external dataset.[10] The BEMS was calculated by multiplying the model coefficients by 10, rounding and centering the score. Model probabilities by this score were calculated by averaging probabilities from the logistic regression model.

Validation on an External Dataset

The developed BEMS was applied on an external and independent dataset[10] to assess generalizability. This dataset consists of one short EEG segment per patient. Each EEG

segment contains a sharp transient (epileptiform or nonepileptiform). Characteristics that differed from our primary dataset were patient selection (long-term video-EEG monitoring), greater pretest probability of epilepsy (54%), and an outcome defined by recorded seizures as either epileptic or nonepileptic on long-term video-EEG monitoring.

Statistics

The diagnostic performance of the multivariate predictive model and of each sharp discharge feature for both EEG and clinical outcome was quantified as sensitivity, specificity, and area under the receiver operating characteristics curve (AUC) for included EEGs. Accuracy, the percentage of correctly classified observations, was calculated for the BEMS performance in the external dataset. The multivariate logistic model building was performed with univariate dose–response estimation using locally weighted regression[32] and quartiles to guide the selection of multiple cut points for each feature. We used logistic regression with EEG outcome as the dependent variable to exclude nonsignificant features by using Wald test. The cumulative incidence of a diagnosis of epilepsy was estimated with Stata stcrreg,[33] accounting for death as a competing risk.[34] The diagnostic performance of the clinical EEG conclusion and the BEMS score in predicting clinical outcome (future epilepsy) was estimated from the cumulative incidence of epilepsy at up to 6 years of follow-up. Interrater agreement for the BEMS score was calculated using intraclass correlation. Interrater agreement for Halford semiquantitative score was calculated with Cohen[35] kappa.

A formal sample size calculation was not performed for the main study as we used all the available data. However, we decided that events per variable should be >10.[36] We selected 50% of the EEGs for the prediction model development and 50% for validation to have sufficient statistical power for all categorical variables in the final validation model.

Software

Nicolet EEG system was used to record and display EEGs for clinical visual analysis. Clinical EEG reports were made with SCORE EEG (versions 1.0.9.4012 to 2.9.16.24). All EEG reports were stored in the SCORE EEG database, a structured SQL database. Quantitative annotation was implemented in custom software built on EEGLAB. All statistics were handled in Stata.[33]

Ethical Approval

The study was approved by the Regional Committees for Medical and Health Research Ethics (reference code 2017/1512/REK vest).

RESULTS

Demography

Two thousand twenty-six patients were included after excluding 653 patients that were not reported in SCORE EEG,[26] 2,688 patients who had an EEG before the inclusion period, a previously known clinical diagnosis of epilepsy or missing data, 5,387 patients who did not have sharp transients or focal IEDs in their EEGs or who had an epileptic seizure during their EEG recordings, and 37 patients because of missing data with regard to morphologic measurements. Included patients had a wide age range (see **Table S4**, **Supplemental Digital Content**

TABLE 1. BEMS for Classifying a Sharp Discharge as Focal IED or as a Sharp Transient

Predictor	Corresponding Epileptiform Criterion	Category	Points
Spike descending amplitude (μV)	Criterion 1	0–69	1
		70–89	0
		90–119	7
		>119	17
Spike onset slope (μV/ms)	Criterion 1	0–0.9	0
		1.0–1.4	4
		1.5–1.9	5
		>1.9	11
Spike to background power (%)	Criterion 3	>8.5	0
		4.7–8.5	9
		2.6–4.6	6
		0–2.5	14
Slow after-wave area (weber)	Criterion 4	0–4	0
		5–9	6
		10–19	11
		>19	19
Age (years)	None	0–9	16
		10–19	0
		20–59	12
		>59	25

BEMS is calculated by summing the individual scores for spike amplitude, spike onset slope, spike to background power, slow after-wave area, and age. See Fig. 3 for BEMS-to-probability translation.

BEMS, Bergen Epileptiform Morphology Score; IED, interictal epileptiform discharge.

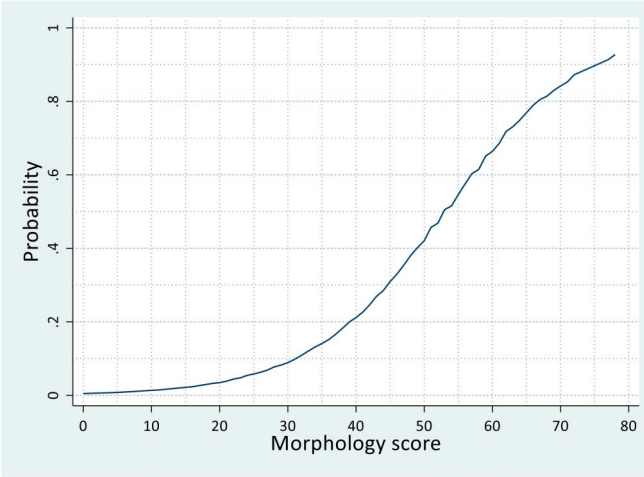

FIG. 3. Mean model-predicted probability of IED by morphology score in the validation set. IED, interictal epileptiform discharge.

1, http://links.lww.com/JCNP/A155), with a mean age of 39 years (SD = 27) and a female overrepresentation (56%). Patients with focal IEDs (n = 350) were 5 years older on average than patients with sharp transients (n = 1,713). Ninety percent of included EEGs were the patient's first EEG, and 93% were standard EEGs, reflecting the aim to examine the earliest EEG containing sharp activity. Seventy-six percent of patients were referred with a clinical suspicion of epilepsy. The time interval between the date of the included EEG and follow-up ranged from 769 to 2,447 days. Sixty-five percent of the patients who was diagnosed with epilepsy during follow-up had one or several acute emergency hospital admissions for epilepsy.

Morphologic Features

The distribution of morphologic features, except for spike duration, differed significantly between the two EEG outcome categories (see **Table S1**, **Supplemental Digital Content 1**, http://links.lww.com/JCNP/A155). However, there was also considerable overlap between them (see **Table S2**, **Supplemental Digital Content 1**, http://links.lww.com/JCNP/A155; Fig. 2). Descending amplitude, slow after-wave area and preceding background power had an AUC >0.7. Spike to background power, spike sharpness, duration, onset slope, descending slope, ascending amplitude, Henze asymmetry, and number of channels had an AUC ≤ 0.7. The BEMS score had the same performance as the visually assessed Halford score; AUC = 0.84 for both. The AUC was 0.70 for both BEMS and Halford score for the clinical outcome of epilepsy and was ≤0.64 for all univariate quantitative features.

Prediction of EEG Outcome in Validation Set

Table 1 shows how the IED features contributed to the BEMS score in the validation set (N = 1,013). The AUC for the BEMS score and in the multivariate logistic regression model was the same, with AUC = 0.86. A cut point of 46 on BEMS had a specificity of 91% for a clinical EEG conclusion of epileptiform activity, with a sensitivity of 55%. A cut point of 29 had a specificity of 57% with a sensitivity of 90%. The translation from the BEMS score to probability based on this model is given in Fig. 3. Odds ratios for the BEMS categories in the validation dataset are shown in **Supplemental Digital Content 1** (see **Figure S3**, http://links.lww.com/JCNP/A155).

Prediction of Epilepsy

A higher BEMS was associated with a higher risk of epilepsy (Fig. 4A; N = 2026). The cumulative incidence of a clinical diagnosis of epilepsy in up to 6 years of follow-up was 10% in patients with a BEMS of 0 to 16 points, 14% with a BEMS of 17 to 23 points, 23% with a BEMS of 24 to 32 points, 34% with a BEMS of 33 to 43 points, and 50% with a BEMS of 44 to 79 points. The receiver operating AUC was 0.70 for both Halford score and for BEMS in five quantiles with clinical

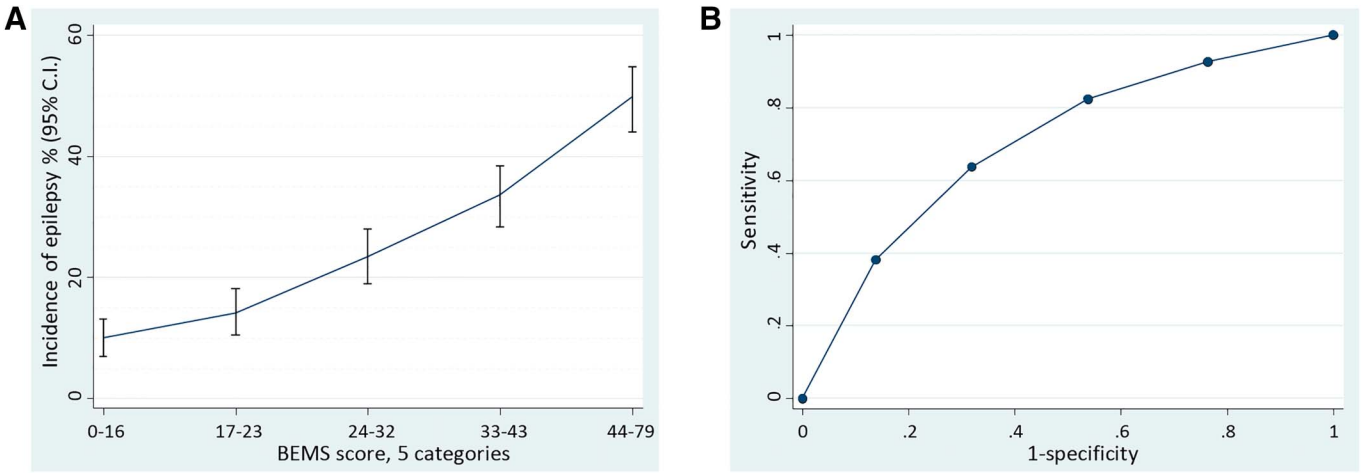

FIG. 4. **A**, Cumulative incidence of epilepsy after 6 years of follow-up according to BEMS in five quantiles. **B**, Receiver operating characteristic curve for cut points of the BEMS score in five quantiles. The area under the receiver operating characteristics curve is 0.7. BEMS, Bergen Epileptiform Morphology Score.

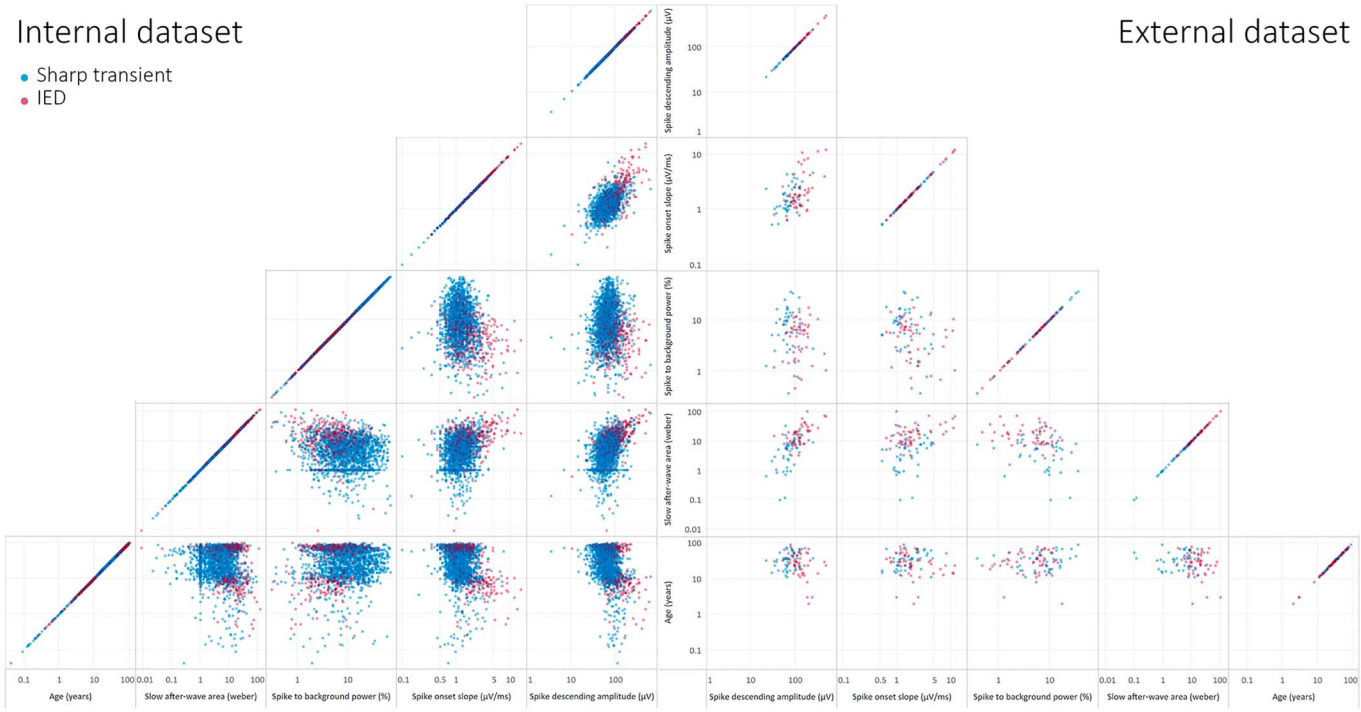

FIG. 5. Scatter plot matrix of the predictors for the internal dataset (left half) and the external dataset (right half).

epilepsy diagnosis as the outcome (Fig. 4B). The cumulative incidence of epilepsy was 60% with a BEMS score of 54 or greater.

Compared with BEMS, the clinical EEG identification of focal IEDs had better diagnostic prediction of epilepsy (see **Figure S4**, **Supplemental Digital Content 1**, http://links.lww.com/JCNP/A155). Eighty-nine percent of patients with epilepsy were diagnosed within 1 year after their EEG. The cumulative incidence of epilepsy at 6 years of follow-up was 16% in those with EEGs containing sharp transients only and 78% in those with focal IEDs. This corresponds to a sensitivity of 52%, a specificity of 95%, and an AUC of 0.73.

Validation on an External Dataset

The external and independent dataset[10] contained 100 short EEG segments from 100 patients, out of which 54 had epilepsy. The receiver operating AUC for BEMS was 0.80. A cut point of 53 on BEMS gave a specificity of 91%, sensitivity of 41%, and accuracy of 64% for a clinical and EEG-based diagnosis of epilepsy. A cut point of 29 on BEMS had a specificity of 50%, sensitivity of 98%, and accuracy of 76%. A cut point at 46, equal to the best performing cut point in our internal validation set, had a specificity of 83%, sensitivity of 57%, and accuracy of 69%. The distributions of morphologic features are shown in Fig. 5 alongside the internal dataset for comparison.

DISCUSSION

We have shown that distinct morphologic features of the first suspicious sharp discharge in an EEG can be combined into a simple score. This score predicts classification as epileptiform activity with a value similar to that of a visually assessed semiquantitative Halford score but with higher reproducibility. Application of the BEMS annotation tool on sharp EEG activity is fast (less than 1 second) and straightforward (one click on the peak). The score should be of interest to treating physicians as a higher score carries a higher risk of epilepsy. It can provide instant feedback to EEG readers in training by the score and its contributing features. Three of the criteria for epileptiform activity[9] (spike sharpness, different wave duration, and slow after-wave) are included in our new score. They were all shown to be important predictors of IEDs and for a clinical diagnosis of epilepsy. The same criteria had the highest interrater reproducibility among seven raters in a recent article by Kural et al.[10,37] and also among three raters in their successive article. A combination of spike sharpness, slow after-wave, and a dipole suggesting a source within the brain gave the highest accuracy regarding a clinical diagnosis of epilepsy (93%) in their latter paper.[37]

The score had a similar and good performance when applied to an external and independent dataset, demonstrating generalizability of BEMS. This result confirms that the included morphologic features are relevant not only locally but also where the sharp discharge selection, patient population, pretest probability, and outcome assessment differ.

Four of the features included in the score correspond to criteria in the definition of epileptiform EEG activity.[9] Whether these criteria capture the essence of IED morphology has not been proven. However, we have now shown that the first, second, and fourth criteria represent important and reproducible predictors for epileptiform activity. Spike descending amplitude and

spike onset slope are both features that correspond to the visual perception of spikiness (criterion 1). Spike to background power associates with the amount of background activity having a similar wave duration as the spike (criterion 2). Slow after-wave area is a relevant measure for slow wave prominence (criterion 4). While no single measure is able to cover all subjective interpretations of qualitative criteria, we consider these BEMS features to fit criterion 1, 2, and 4 well. Applying the score elucidates the visual features that contribute to the evaluation of sharp discharges. Such transparency should benefit EEG readers and also in their education.

Only those features that contributed to the classification of EEG outcome in the multivariate model were included in BEMS. The omitted features might be considered in future attempts to further improve the epileptiform criteria. Spike asymmetry according to Henze[31] was not statistically significant in the multivariate model. This was surprising as spike asymmetry is included in the definition of epileptiform activity. Findings from our previous study also suggested that spike asymmetry was a prominent feature in all age groups.[22] Jing et al.[38] noted that IED candidates were more likely to be scored as IEDs on visual inspection if they were asymmetric. Asymmetry seems therefore to be a characteristic feature of all IED candidates but not important to distinguish between focal IED associated with epilepsy and sharp transients.

An advantage of BEMS was its high reproducibility. The new annotation tool reported in this article is an improvement of our previous tool,[22] requiring only one mouse click instead of four. This reduces the workload for research studies and clinical use. Some of the features in the score can be assessed using any clinical EEG software. Our univariate reference ranges provide guidance for these simple features. This algorithm should be easy to implement for any EEG vendor. A click on the same IED peak will always produce identical markings and measures. Any rater differences stem only from each rater's subjective assessment in a narrow time window as to which sharp discharge is selected for analysis.

We found a poor interrater agreement of Halford score for single sharp discharges, in line with previous reports.[8] Morphology-based EEG assessment is one way of improving reproducibility. The agreement regarding whether an EEG contains any IEDs is higher than agreement regarding the evaluation of individual IEDs.[38–43] In visual EEG evaluation, a single sharp discharge is rarely sufficient to confidently conclude whether an IED is present. Our findings of imperfect AUCs for both the Halford score and the BEMS illustrate this. Definitions of IED do not include intra-EEG IED frequency or variation. However, in routine visual evaluation, consecutive sharp discharges might accumulate evidence to tip the scale in favor of IED. A measure for spike incidence may add predictive power concerning the clinical diagnosis of epilepsy, even though it is not an intrinsic morphologic feature.

This study represents a large cohort of unselected patients with epileptiform activity. A strength of this study is that we have examined one training dataset, one validation dataset, and a third independent and external dataset. This study has some limitations. Detailed information regarding how the clinical diagnosis of epilepsy was made is lacking. The EEG interpretation may have impacted the clinical conclusion. The predictive model's performance measures for the clinical epilepsy diagnosis are therefore likely to be optimistic. The study would have benefited from a broader panel of expert raters to substantiate measures of interrater reproducibility.

The designation of the first focal suspicious sharp discharge as epileptiform depends to a large degree on reproducible morphologic features that can be made into a clinical score. Best separating features were amplitude, slope, slow after-wave area, and difference from background. Duration and asymmetry did not contribute. The score was predictive of future epilepsy.

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