Received: 9 August 2019 | Accepted: 23 August 2019

DOI: 10.1111/epi.16361

GRAY MATTERS

Epilepsia®

Letter

Salzburg criteria for nonconvulsive status epilepticus: Details matter

To the Editors:

We have read with great interest the paper entitled, "The difficulty of diagnosing NCSE in clinical practice; external validation of the Salzburg criteria" by Goselink et al.[1] We agree on the importance of "careful weighing of both clinical and EEG information on an individual basis,"[1] which we have also emphasized in papers describing the Salzburg criteria for nonconvulsive status epilepticus (NCSE).[2–4]

However, we have several comments on the methods and reporting of the study, which question the conclusions of the authors.

1 | SENSITIVITY

In the study flowchart showing the primary results, the authors stated that, in the validation group, the number of true positives (TPs) was nine and the number of false negatives (FNs) was three. This gives a sensitivity of 75% (95% confidence interval = 42.81-94.51%). It is not clear why in Table 1 the authors state different numbers (changing one TP to FN).

The low sensitivity in this study is not surprising, because the authors analyzed electroencephalographic (EEG) recordings of only 30-60 minutes for each patient.[1] It is well documented that continuous EEG recordings[5,6] and repeated short-duration recordings increase the sensitivity of EEG in NCSE and in comatose patients.[7] Using repeated short-duration recordings (median = 2 per patient, range = 1-15) and continuous EEG recordings (median = 74.8 h, range = 5–142 h), we achieved a sensitivity of 97.7%.[4]

It seems that the authors missed an important element of the Salzburg criteria: assessment of the modulatory effect of intravenous (IV) antiepileptic drugs (AEDs) on the EEG. Goselink et al stated that the "decision to give antiepileptic drugs is a step in the Salzburg criteria that cannot be taken retrospectively." This depends entirely on the clinical practice at the centers where the study was performed. In our multicenter study, IV AEDs were given in most patients when indicated, and five of the 42 TPs (12%) were eventually identified by this criterion.[4] This deviation from the published criteria could have contributed to the lower sensitivity in the study by Goselink et al.[1]

2 | SPECIFICITY

The authors stated the following: "We feel that the main reason for not being able to apply the Salzburg criteria successfully in all patients is that there are inherent pitfalls in applying the criteria to patients with an epileptic encephalopathy (…). These patients will have an overall abnormal background recording and usually will show epileptiform discharges for >10 seconds that are often in the 2-5 cycles/seconds range with some fluctuation. That automatically puts these patients in the possible NCSE group, without the need for any additional abnormality that would positively indicate an additional NCSE in this group."[1] This statement is not correct. For patients with epileptic encephalopathy, the Salzburg criteria specified the need for additional criteria (Figure 1) to avoid "automatically putting" patients with epileptic encephalopathy in the NCSE category.[2–4]

3 | STATISTICS

The authors found highly significant, yet moderate Spearman correlations ($r_s = 0.41$, $P < .001$) between raters. Gwet AC1 coefficient might be a more appropriate method for assessment of interrater agreement,[8] as Spearman correlations could yield paradoxical results, similar to Cohen kappa. There were only four cases of disagreement in 191 EEGs, so the interrater agreement should be good.

Confidence intervals were not provided. This contradicts the very basic principles of reporting (item 24, STARD criteria[9]). Given the moderate subgroup sizes and the resulting considerable variance, the strong conclusions are questionable from a methodological point of view.

4 | EXTERNAL VALIDATION OF THE SALZBURG CRITERIA

We agree on the importance of validating the Salzburg criteria by groups of experts who did not participate in their development. Such a study has been previously published.[10] In a cohort of 284 consecutive patients referred to EEG on suspicion

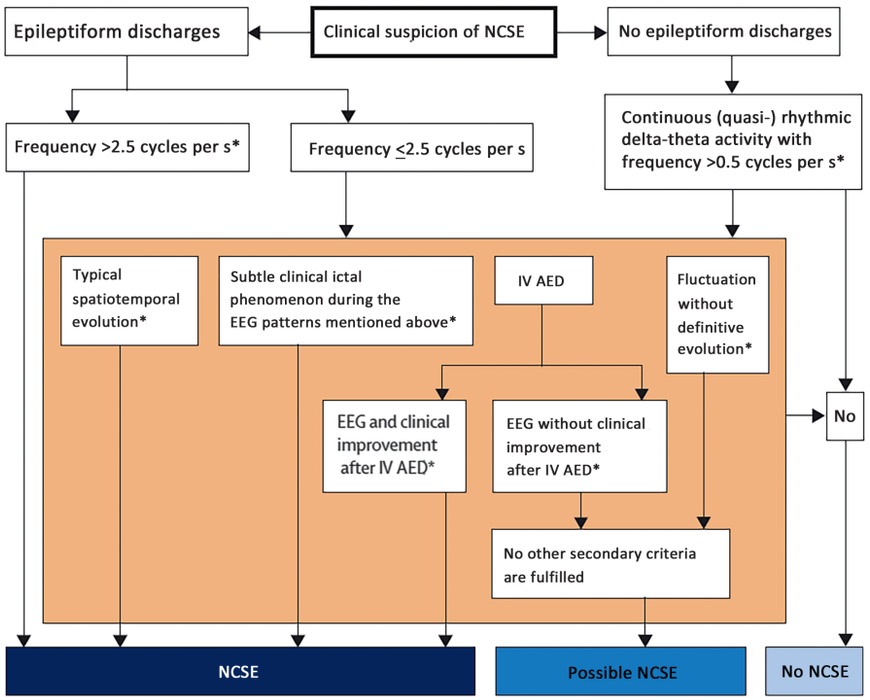

FIGURE 1 Salzburg electroencephalographic (EEG) criteria for the diagnosis of nonconvulsive status epilepticus (NCSE). To qualify for a diagnosis of NCSE, the whole EEG recording should be abnormal, and EEG criteria have to be continuously present for at least 10 seconds. If criteria are not fulfilled at any stage, EEG recording will not qualify for a diagnosis of NCSE or possible NCSE. AED, antiepileptic drug; IV, intravenous. *Patients with known epileptic encephalopathy should fulfil one of the additional secondary criteria: increase in prominence or frequency of the features above when compared to baseline, and observable change in clinical state; or improvement of clinical and EEG features with IVAEDs. (With permission from The Lance Neurology)

of NCSE, the authors found a high agreement ($k = 0.88$) between the Salzburg criteria and the reference standard.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Markus Leitinger[1,2]
Eugen Trinka[1,2]
Georg Zimmermann[1,2]
Sándor Beniczky[3,4,5]

[1]*Department of Neurology, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria*
[2]*Center for Cognitive Neuroscience, Salzburg, Austria*
[3]*Department of Clinical Neurophysiology, Danish Epilepsy Center, Dianalund, Denmark*
[4]*Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark*
[5]*Department of Clinical Medicine, Aarhus University, Aarhus, Denmark*
Email: sbz@filadelfia.dk

REFERENCES

1. Goselink RJM, van Dillen JJ, Aerts M, et al. The difficulty of diagnosing NCSE in clinical practice; external validation of the Salzburg criteria. Epilepsia. 2010;60:e88–e92.
2. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013;54(Suppl 6):28–9.
3. Leitinger M, Beniczky S, Rohracher A, et al. Salzburg consensus criteria for non-convulsive status epilepticus—approach to clinical application. Epilepsy Behav. 2015;49:158–63.
4. Leitinger M, Trinka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol. 2016;15:1054–62.
5. Sutter R, Fuhr P, Grize L, Marsch S, Rüegg G. Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU. Epilepsia. 2011;52:453–7.
6. Crepeau AZ, Fugate JE, Mandrekar J, et al. Value analysis of continuous EEG in patients during therapeutic hypothermia after cardiac arrest. Resuscitation. 2014;85:785–9.
7. Alvarez V, Sierra-Marcos A, Oddo M, Rossetti AO. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. Crit Care. 2013;17:R190.
8. Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. Br J Math Stat Psychol. 2008;61:29–48.

9. Bossuyt PM, Reitsma JB, Bruns DE, et al. An updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.

10. Krogstad MH, Høgenhaven H, Beier CP, Krøigård T. Nonconvulsive status epilepticus: validating the Salzburg criteria against an expert EEG examiner. J Clin Neurophysiol. 2019;36:141–5.

Received: 11 September 2019 | Accepted: 13 September 2019

DOI: 10.1111/epi.16365

GRAY MATTERS

Epilepsia®

Letter

Response: The difficulty of diagnosing nonconvulsive status epilepticus in clinical practice

To the Editors,

We wish to thank Drs Leitinger, Trinka, Zimmerman, and Beniczky for their interest in and comments on our article.[1]

We certainly agree with the authors that a longer electroencephalogram (EEG) duration is known to increase the sensitivity to nonconvulsive status epilepticus (NCSE) in patients. Longer monitoring will very likely lead to better detection of NCSE. However, we think that a short EEG duration, as often performed in our study patients, does represent a significant part of current clinical practice in many hospitals, and it therefore must be weighted as a contributing factor for external validation of the Salzburg criteria. We therefore discussed this as a factor for the lower sensitivity we found in our study. As an afterthought, one could argue that perhaps the next version of the criteria should include the need for longer monitoring, although we feel it would be hard to provide a minimum duration for such monitoring (3 hours? 6 hours? 24 hours?) at this point.

We do not fully understand what the authors are trying to convey with their comment on the decision to give antiepileptic drugs. As we executed a retrospective study, it was impossible to decide to give antiepileptic drugs while scoring the registrations using the Salzburg criteria. That decision was taken earlier by the treating neurophysiologist and neurologist, often not precisely following the Salzburg criteria, however, as the treating physicians were not aware of those in our study. It is therefore a limitation of both our[1] and the authors' original[2] retrospective studies.

The authors refer to the additional criterion for patients with an epileptic encephalopathy. We agree with the authors that this could have been highlighted more clearly in our discussion section. However, we still find our conclusion justified that epileptic encephalopathy patients are at risk for misdiagnosis of NCSE with the Salzburg criteria.

The comment on the different number of true positives in the validation group is completely correct, and we regret the error in our flowchart that apparently eluded our attention during the preparation of this paper. The correct numbers are as stated in Table: eight true positives and four false negatives, giving a sensitivity of 66.7% (95% confidence interval [CI] = 34.89-90.08%). There are various ways to evaluate interrater agreement and interrater reliability, all with their own advantages and disadvantages[3,4]; based on the ordinal outcomes, we chose Spearman to calculate the interrater agreement.

We regrettably did not provide CIs; we hereby list the CIs of the stated results. Overall sensitivity in the validation group was 67% (95% CI = 34.89-90.08%), and the specificity was 89% (95% CI = 80.85-95.04%). The negative predictive value was 95% (95% CI = 89.48-97.70%), and the positive predictive value was 47% (95% CI = 29.86-64.98%). In the control group, the specificity was 89.2% (95% CI = 81.11-94.72%).

Again, we thank the authors for their comments and wish to conclude with the statement that "careful weighing of both clinical and EEG information on an individual basis" and the goal of improving diagnostics and care for NCSE patients are shared by all.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Rianne J. M. Goselink[1,2]
Jeroen J. van Dillen[1]
Machiel Zwarts[2]
Nens van Alfen[1]

[1]*Department of Neurology and Clinical Neurophysiology, Donders Institute for Brain Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands*
[2]*Department of Neurology, Academic Center for Epileptology Kempenhaeghe and Maastricht University Medical Center, Heeze, the Netherlands*
Email: rianne.goselink@radboudumc.nl

ORCID

Rianne J. M. Goselink https://orcid.org/0000-0001-9640-6053

Machiel Zwarts https://orcid.org/0000-0003-3254-5438

REFERENCES

1. Goselink RJM, van Dillen JJ, Aerts M, et al. The difficulty of diagnosing NCSE in clinical practice; external validation of the Salzburg criteria. Epilepsia. 2019;60:e88–92.
2. Leitinger M, Trinka E, Rohracher A, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol. 2016;15:1054–62.
3. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm. 2013;9:330–8.
4. Xu S, Lorber MF. Interrater agreement statistics with skewed data: evaluation of alternatives to Cohen's kappa. J Consult Clin Psychol. 2014;82:1219–27.

DOI: 10.1111/epi.16376

Epilepsia®

Announcements

Epilepsy Society of Australia 33rd Annual Scientific Meeting

6–8 November 2019
Sydney, Australia
https://www.ivvy.com.au/event/ESA19/

SOBR 2019 Student Symposium

12 November 2019
Parkville, Victoria, Australia
Students of Brain Research website: https://www.ilae.org/congresses/sobr-2019-student-symposium

EEG Course

14–16 November 2019
Kuwait
Information: https://www.ilae.org/congresses/eeg-course

Congreso Argentino de Neurología

19–22 November 2019
Mar del Plata, Argentina
http://www.sna.org.ar/web/congreso.php

2nd MAGNIMS-ESNR Course

27–28 November 2019
Neurology & Neuroradiology of Multiple Sclerosis: A Comprehensive Clinical Update
Cairo, Cairo, Egypt
http://www.misr2000online.net/ConfDetails.aspx?id=263

First Course on Epilepsy & EEG

28–29 November 2019
Marrakech, Morocco
Information: https://www.ilae.org/congresses/first-course-on-epilepsy-and-eeg

Le 3ème Congrès Marocain de Neurophysiologie & La 4ème Session des Ecoles EEG & EMG

29 November–1 December 2019
Marrakech, Morocco
Information: https://www.ilae.org/congresses/le-3-me-congr-s-marocain-de-neurophysiologie

American Epilepsy Society

6–10 December 2019
Baltimore, MD, USA
https://meeting.aesnet.org/abstracts

10th EPODES Advanced II

20–24 January 2020
Paediatric Epilepsy Surgery, Palliative surgery & Neuromodulation
Brno, Czech Republic
http://www.ta-service.cz/epodes2020/

1st Regional Autism Conference (RAC2020)

24–26 January 2020
Muscat, Oman
https://autism2020.org/

2020 British Paediatric Neurology Association (BPNA) Annual Conference

29–31 January 2020
Belfast, Northern Ireland
https://bpna.org.uk/conference/2020/

14th Escuela Latino Americana de Verano de Epilepsia (LASSE)

February–6 March 2020
São Paulo, Brazil
https://lasse.med.br/

2020 Epilepsy Review Course and Best Practices

4–6 March 2020
Cairo, Egypt
Information: https://www.ilae.org/congresses/2020-epilepsy-review-course-and-best-practices

EEG in the First Year of Life -- from newborn to toddler

6–8 March 2020
Kerala, India
Information: https://www.ilae.org/congresses/eeg-in-the-first-year-of-life1

7th International Conference on Non-Invasive Brain Stimulation (NIBS)

24–26 March 2020
Baden-Baden, Germany.
https://www.nibs-conference.de/

64th annual meeting of the German Society of Clinical Neurophysiology

26–28. March 2020
64. Jahrestagung
der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung
Baden-Baden, Germany
https://www.dgkn-kongress.de/

14th World Congress on Controversies in Neurology (CONy)

26–29 March 2020
London, UK
http://cony.comtecmed.com/

3rd International Training Course on Neuropsychology in Epilepsy

29 March–3 April 2020
Bordeaux, France
Information: https://www.ilae.org/congresses/3rd-international-training-course-on-neuropsychology-in-epilepsy

International Training Course on Neuroimaging of Epilepsy

14–17 May 2020
Montreal, Canada
Course website: https://www.mcgill.ca/neuro/events/international-training-course-neuroimaging-epilepsy

XI Congreso Latinomericano de Epilepsia

23–26 May 2020
Medellín, Colombia
Website: https://www.epilepsycongress.org/lace/

55th Annual Meeting of the German Society of Epileptology

10–13 June 2020
55. Jahrestagung der Deutschen Gesellschaft für Epileptologie (DGfE)
Breisgau, Germany
https://www.epilepsie-tagung.de/

38º Congresso da Liga Brasileira de Epilepsia – Curitiba 2020

10–13 June 2020
Curitiba, Brazil
http://epilepsia.org.br/evento/38o-congresso-liga-brasileira-de-epilepsia-curitiba-2020/

21st Annual Meeting of Infantile Seizure Society International Symposium on Pathophysiology of Developmental and Epileptic Encephalopathy (ISSET)

19–21 June 2020
Okayama, Japan
Website: https://www.emedevents.com/c/medical-conferences-2020/the-21st-annual-meeting-of-infantile-seizure-society-international-symposium-in-pathophysiology-of-developmental-and-epileptic-encephalopathy

14th European Congress on Epileptology (ECE)

5–9 July 2020
Geneva Switzerland
Website: http://www.epilepsycongress.org/ece/

ESTM 2020: Epilepsy Surgery Techniques Meeting

9–10 July 2020
Geneva, Switzerland
https://www.estm2020.com/

Dianalund Summer School on EEG & Epilepsy 5th edition

12–18 July 2020
Dianalund, Denmark
https://www.ilae.org/congresses/5th-dianalund-summer-school-on-eeg-and-epilepsy

2020 Advanced San Servolo Epilepsy Course

20–31 July 2020
Bridging Basic with Clinical Epileptology - 7: Accelerating Translation in Epilepsy Research
San Servolo (Venice), Italy
https://www.ilae.org/congresses/2020-advanced-san-servolo-epilepsy-course

34th International Epilepsy Congress

28 August–1 September 2020
Paris, France
Website: https://www.epilepsycongress.org/iec/

11th Summer School for Neuropathology and Epilepsy Surgery (INES 2020)

10–13 September 2020
Erlangen, Germany
https://www.ilae.org/congresses/11th-international-summer-school-for-neuropathology-and-epilepsy-surgery-ines-2020

First North American Epilepsy Congress (NAEC)

25–27 September 2020
Toronto, Canada
Website: https://www.epilepsycongress.org/naec/

13th Asian and Oceanian Epilepsy Congress (AOEC)

8–11 October 2020
Fukuoka, Japan
Website: https://www.epilepsycongress.org/aoec/