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ORIGINAL WORK

Automated Pupillometry for Assessment of Treatment Success in Nonconvulsive Status Epilepticus

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Abstract

Background: Altered pupillary function may reflect nonconvulsive status epilepticus (NCSE). Neurological pupil index (NPi) assessed by automated pupillometry is a surrogate marker of global pupillary function. We aimed to assess NPi changes in relation to NCSE treatment response.

Methods: In this prospective observational study, serial automated pupillometry was performed in 68 NCSE episodes. In accordance with local standards, patients were treated with clonazepam (1–2 mg), levetiracetam (40 mg/kg), and lacosamide (5 mg/kg) in a stepwise approach under continuous electroencephalography monitoring until NCSE was terminated. Patients with refractory NCSE received individualized regimens. NPi was assessed bilaterally before and after each treatment step. For statistical analysis, the lower NPi of both sides (minNPi) was used. Nonparametric testing for matched samples and Cohen's *d* to estimate effect size were performed. Principal component analysis was applied to assess the contribution of baseline minNPi, age, sex, and NCSE duration to treatment outcome.

Results: In 97.1% of 68 episodes, NCSE could be terminated; in 16.2%, NCSE was refractory. In 85.3% of episodes, an abnormal baseline minNPi ≤ 4.0 was obtained. After NCSE termination, minNPi increased significantly ($p < 0.001$). Cohen's *d* showed a strong effect size of 1.24 (95% confidence interval 0.88–1.61). Baseline minNPi was higher in clonazepam nonresponders vs. responders ($p = 0.008$), minNPi increased in responders ($p < 0.001$) but not in nonresponders. NCSE refractivity was associated with normal baseline minNPi (principal component analysis, component 1, 32.6% of variance, $r = 0.78$), male sex, and longer NCSE duration (component 2, 27.1% of variance, $r = 0.62$ and $r = 0.78$, respectively).

Conclusions: Automated pupillometry may be a helpful noninvasive neuromonitoring tool for the assessment of patients with NCSE and response to treatment.

Keywords: Nonconvulsive status epilepticus, Pupillometry, Neurological pupil index

Introduction

Diagnosing nonconvulsive status epilepticus (NCSE) may be challenging because of the absence of specific clinical features in many cases [1–3]. Early initiation of adequate treatment is a predictor of favorable outcome [4]. Altered pupillary function can be a subtle neurological feature of NCSE [5–7]. Pupils may be either of normal width, miotic, or mydriatic and may show a delayed response to light [8]. Pupillary parameters may change quickly during

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a seizure, such as in the rare finding of pupillary hippus [9, 10]. Changes of pupillary response to light in NCSE can be attributed to functional alterations of the central autonomous network [11]. Both the sympathetic and parasympathetic system can be either activated or inhibited depending on localization and duration of electric seizure activity [12]. Because of the variability of potential pupil abnormalities in NCSE, it may become difficult to interpret routine pupil assessment findings in NCSE.

The neurological pupil index (NPi), as measured by automated pupillometry, forms a surrogate marker of global pupillary function, which is supposed to be independent of absolute pupillary parameters, such as pupil width, and less dependent on external features, such as ambient lighting conditions and experience of the examiner [13–15]. NPi is formed through a proprietary mathematical algorithm and can take values from 0–5, with lower values indicating reduced global pupillary function. In neurocritical care, values below 3.0 may indicate critical increases of intracranial pressure [16–18]; decreasing NPi may be an early indicator of neurological deterioration in large hemispheric infarction or subarachnoid hemorrhage [19, 20]. NPi values below 2.0 to 2.4 are related to nonbeneficial outcome after cardiac arrest [21–23]. All these disorders go along with major brain injury resulting in a structural lesion of the pupillary functional network, including the oculomotor nerve. However, recent data indicate that even in the absence of major brain injury changes of pupillary function can be detected by automated pupillometry, for example, related to increased intracranial pressure during head-down tilt test [24] or to transient, mostly cholinergic, dysfunction in delirium [25].

In a recent study, we showed that NPi was significantly lower in patients with NCSE compared with patients post ictal, with larger differences between the left and right sides [26]. Best discrimination was achieved for the lower NPi of both sides (minNPi) ≤ 4.0. However, it remained unclear whether NCSE was causative for NPi alterations, and the sample size was rather low. Moreover, it was not examined whether NPi normalized after NCSE termination. In this study, we aimed to assess NPi and its alterations depending on treatment success in a larger cohort of patients with NCSE. We hypothesized that most patients with NCSE will exhibit minNPi ≤ 4.0 at the time of NCSE diagnosis and that minNPi will significantly increase when NCSE is terminated.

Methods

In this prospective observational study, we investigated treatment response and NPi during 68 NCSE episodes in 61 adult patients within a period of 24 months from October 2018 to October 2020. The study was approved by the Hesse Medical Association Ethical Board and included a consent waiver for bedside pupillometry (institutional review board: FF 20/2018).

Inclusion criteria were (1) age ≥ 18 years, (2) altered mental status, (3) electroencephalography (EEG) diagnosis of NCSE according to Salzburg Consensus criteria [27], and (4) continuous EEG monitoring. Altered mental status was defined as one or more of the following features: altered level of consciousness (somnolence, sopor, or coma), impaired cognitive performance compared with individual baseline level (including alterations of attention, memory, praxis, and other cognitive domains), and abnormal behavior. Exclusion criteria were (1) ocular comorbidity (which did not allow NPi assessment on both sides, i.e., glass eye), (2) prior anticonvulsant treatment for the actual NCSE episode, and (3) patients who were post cardiac arrest. According to local policy, patients with clear clinical signs suggestive for status epilepticus (SE), such as motor convulsions, aphasia, myoclonus, or nystagmus, receive initial therapy immediately, prior to EEG confirmation. Hence, these patients could not be included in the study. Figure 1 displays the study inclusion flowchart.

Treatment Protocol

After confirmation of NCSE by EEG criteria, patients were immediately treated according to the local NCSE treatment standard under continued EEG monitoring (Fig. 2). NCSE stages were classified according to

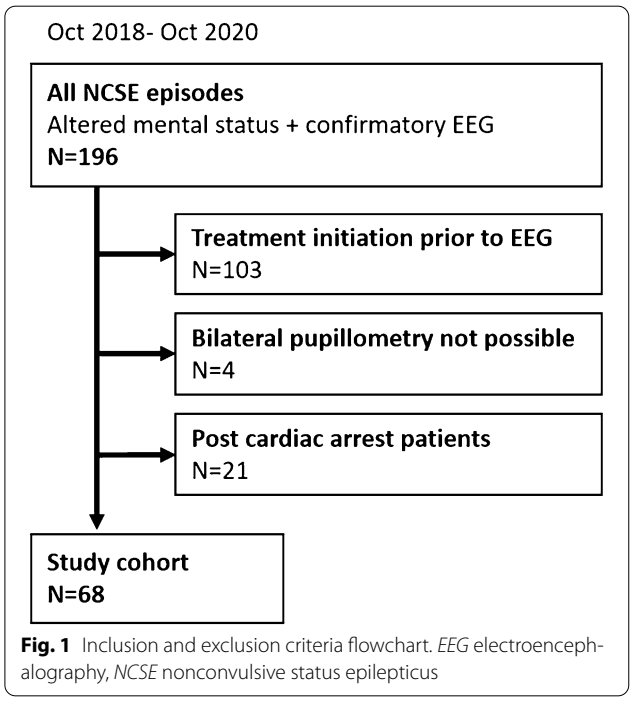

Fig. 1 Inclusion and exclusion criteria flowchart. *EEG* electroencephalography, *NCSE* nonconvulsive status epilepticus

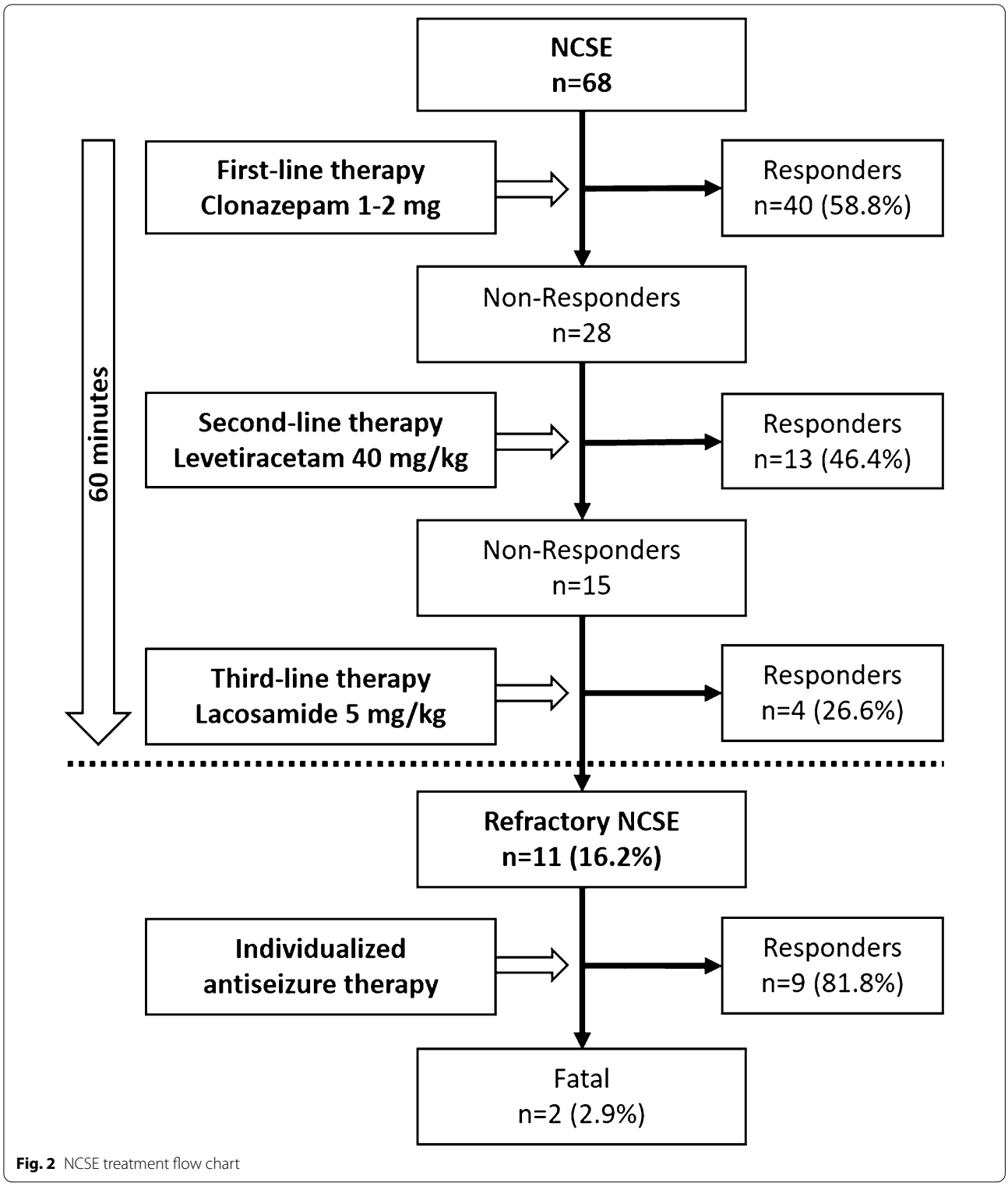

Fig. 2 NCSE treatment flow chart

International League Against Epilepsy (ILAE) consensus criteria [28, 29]. Positive treatment response for each treatment step was stated only when NCSE was terminated. As first line treatment, clonazepam (CZP) 1 mg i.v. was administered (step 1). The dosage was repeated once if no NCSE termination was observed after 10 min. Second line treatment for established NCSE was levetiracetam (LEV) 40 mg/kg i.v. (maximum

4.5 g), administered within 10 min (step 2). If NCSE was not terminated after 20 min, lacosamide (LCM) 5 mg/kg i.v. (maximum 400 mg) was administered and treatment response was observed for a further 20 min (step 3). If NCSE was not terminated within that time (overall 60 min), further individualized treatment was initiated for refractory NCSE (Step 4).

Automated Pupillometry

NPi was assessed by automated pupillometry (NPi200 pupillometer; NeurOptics, Laguna Hills, CA) before drug administration and at the end of each treatment step. Ambient light conditions remained unchanged. NPi of the left and right sides were assessed separately. Because of the relevant NPi asymmetry in NCSE, we used minNPi for further analysis [26]. Accordingly, we defined a minNPi ≤ 4.0 on either side as abnormal for this cohort [26].

Statistical Analysis

For statistical analysis we used IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY). Descriptive data are given either as median and range or as percentages. Duration of NCSE until treatment initiation was estimated from the time interval between last seen normal and administration of first CZP dose. Baseline and final minNPi were compared using nonparametric statistics (Wilcoxon signed-rank test). Effect size was estimated applying Cohen's d for repeated measures, including correction for correlation of baseline and final minNPi. Further, for each treatment step minNPi before and after treatment were compared for nonresponders and responders (Wilcoxon test). Additionally, the percentage of normalized minNPi values was compared between responders and nonresponders (χ^2 test). Bonferroni's p value correction was performed for multiple comparisons. Results were assumed to be significant at $p < 0.05$.

To better understand the contribution of baseline minNPi to the prediction of treatment response, we performed principal component analysis, including nonrefractory NCSE as target parameter and age, sex, NCSE duration, and baseline minNPi as factors. To address the correlation between NPi change and treatment response, we performed partial correlations, including NCSE duration, age, and sex as confounders.

Results

Median age was 65 (18–93) years; 57.4% were women. Median duration of NCSE prior to treatment initiation was 8.5 (1–128) hours. Median duration from first neurologist contact to treatment initiation was 71 (0–1,820) minutes. Median duration from EEG confirmation of NCSE to treatment initiation was 4 (1–28) minutes. Eleven episodes (16.2%) were classified as refractory NCSE, with five of these episodes (7.4%) being superrefractory NCSE. Overall mortality was 14.7%. Table 1 shows patient and seizure characteristics grouped by refractory vs. nonrefractory NCSE. There was a numerical tendency toward higher age, longer NCSE duration, higher percentage of progressive seizure etiology, and higher mortality in the refractory NCSE group, however, without statistical significance.

Treatment Response

NCSE could be terminated in all but two cases (97.1%, Fig. 2). First line therapy with a median CZP dose of 18 µg/kg (8–34 µg/kg) was effective in 58.8% of patients. Nonresponders were more often men (χ^2, $p = 0.012$) and had longer NCSE duration (Mann–Whitney, $p = 0.036$); age did not differ between groups. Second line therapy with a median LEV dose of 46 mg/kg (40–65 mg/kg) for established NCSE was effective in 46.4%. There were no differences between responders and nonresponders regarding age, sex, and NCSE duration. Third line therapy with a median LCM dose of 5.3 mg/kg (3.5–7.1 mg/kg) was effective in 26.7%. Median CZP dosages were higher in nonresponders vs. responders (Mann–Whitney, $p = 0.02$); LEV and LCM dosages did not differ between groups.

Eleven patients (16.2%) with refractory NCSE were subjected to individualized treatment schemes. In nine of these patients (81.8%), NCSE could be terminated after a median treatment duration of 92 (7–384) hours and a medium of 4 (3–6) combined antiseizure drugs (ASD). Treatment regimen consisted of various ASD combinations, including LEV ($n = 11$), LCM ($n = 11$), valproic acid ($n = 9$), perampanel ($n = 7$), topiramate ($n = 4$), CZP ($n = 4$), phenytoin ($n = 2$), gabapentin ($n = 2$), and phenobarbital ($n = 2$). Six patients underwent induced burst suppression coma for a median duration of 46 (26–180 h). Anesthesia was maintained by midazolam plus ketamine in four patients; two patients received isoflurane. Table 2 summarizes initial bolus dosages for all antiseizure drugs used in this study. Targeted normothermia was established in all patients. Additionally, two patients underwent mild hypothermia (33–35 °C) for 72 h. Four patients received a steroid pulse with methylprednisolone 1,000 mg/day for 3 to 5 days. Two patients were put on a ketogenic diet.

Neurological Pupil Index

Median baseline NPi was 3.5 (1.5–4.6) for the left side and 3.6 (1.4–4.7) for the right side. Median baseline minNPi was 3.4 (1.4–4.7). An abnormal baseline minNPi ≤ 4.0 was found in 85.3%. Median posttreatment minNPi was 4.3 (2.3–4.9), which was significantly higher than baseline minNPi (Wilcoxon, $p < 0.001$). Cohen's d

Table 1 Cohort characteristics

	Overall	Nonrefractory NCSE	Refractory NCSE	*p* value
Episodes (*n*)	68	57 (83.8%)	11 (16.2%)	
Demographic data				
Age, median (range)	65 (18–93)	64 (18–93)	75 (26–92)	0.51
Female sex (%)	57.4%	59.6%	45.5%	0.38
Known epilepsy	35.3%	35.1%	36.3%	0.72
In-hospital NCSE	70.6%	68.4%	81.8%	0.34
Duration to treatment (h)	8.5 (1–128)	8 (1–120)	18 (2–128)	0.11
Mortality	14.7%	12.3%	27.3%	0.20
Seizure type (ILAE)				
Focal onset	38.2%	38.6%	36.4%	0.70
Generalized onset	5.9%	5.3%	9.1%	0.56
Unknown onset	55.9%	56.1%	54.6%	0.82
Seizure etiology (ILAE)				
Acute symptomatic	49.9%	54.4%	27.3%	0.34
Remote	22.1%	21.1%	27.3%	0.68
Progressive	20.6%	17.6%	36.4%	0.24
Defined electroclinical syndrome	–	–	–	–
Unclear	7.4%	7.0%	9.0%	0.40
Baseline pupillometry				
minNPi	3.4 (1.4–4.7)	3.4 (1.4–4.7)	3.7 (2.4–4.3)	0.05
minNPi ≤ 4.0 (%)	85.3%	87.7%	72.7%	0.20

ILAE International League Against Epilepsy, *minNPi* lower neurological pupil index of both sides, *NCSE* nonconvulsive status epilepticus

Table 2 Medication and dosages applied in the study cohort

	Bolus dose	Max. bolus dose	Application
Early NCSE			
Clonazepam	1 mg	2 mg	i.v
Established NCSE			
Levetiracetam	40 mg/kg	4.5 g	i.v
Refractory NCSE			
Lacosamide	5 mg/kg	400 mg	i.v
Valproic acid	40 mg/kg	3,600 mg	i.v
Perampanel	6–12 mg	n/a	p.o
Phenytoin	20 mg/kg	1,500 mg	i.v
Midazolam	0.2–0.3 mg/kg	0.6 mg/kg	i.v
Ketamine	1–2 mg/kg	5 mg/kg	i.v
Superrefractory NCSE			
Phenobarbital	2 mg/kg	n/a	p.o
Isoflurane	MAC 0.5–1.3 Vol%	MAC 3.0 Vol%	inh
Topiramate	50–100 mg	n/a	p.o
Gabapentin	600 mg	n/a	p.o

All medication and dosages according to local standard of practice (institutional protocol 09/2018)

inh inhalativ, *i.v.* intravenous, *Max* maximum, *NCSE* nonconvulsive status epilepticus, *p.o.* per os

for repeated measures showed a strong effect size of 1.24 (95% confidence interval 0.88–1.61), given a Pearson correlation of pretreatment and posttreatment measures of $r = 0.46$.

Figure 3 shows development of minNPi before and after each treatment step for responders and nonresponders. Baseline minNPi was higher in CZP nonresponders compared with responders (Mann–Whitney, $p = 0.008$). After CZP administration, minNPi increased significantly in responders (Wilcoxon, $p < 0.001$) but not in nonresponders. Normalization of abnormal baseline minNPi was observed in 75.7% vs. 9.5%, respectively (χ^2, $p < 0.001$). The association between lower baseline minNPi and positive CZP response remained significant after correction for age, sex, and NCSE duration (partial correlations, $r = -0.26$, $p = 0.01$).

After LEV administration, minNPi increased significantly in responders (Wilcoxon, $p = 0.003$) but not in nonresponders. Normalization of abnormal predose minNPi was observed in 77.8% vs. 10.0%, respectively (χ^2, $p = 0.003$). After LCM administration, minNPi increase in responders missed significance after correction for multiple comparisons (Wilcoxon, $p = 0.06$) and was not significant in nonresponders. Normalization of abnormal

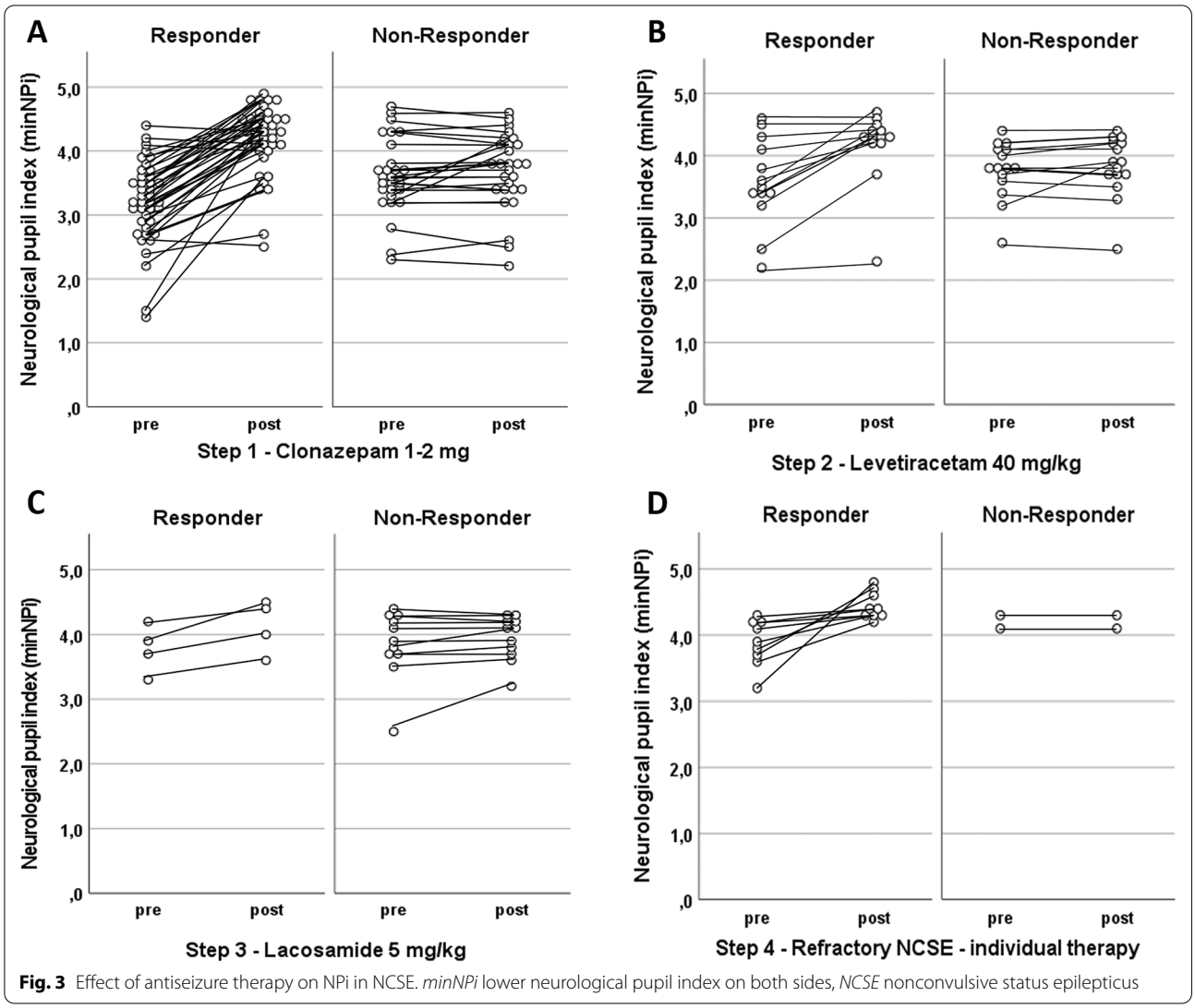

Fig. 3 Effect of antiseizure therapy on NPi in NCSE. *minNPi* lower neurological pupil index on both sides, *NCSE* nonconvulsive status epilepticus

predose minNPi was observed in 33.3% vs. 16.7% (not significant).

In the cohort of 11 patients with refractory NCSE, the small group size did not allow proper statistical testing. Six patients (54.5%) had normal NPi prior to initiation of step four individualized therapy; three of them (27.8%) had normal baseline minNPi and three (27.8%) had minNPi normalized during NCSE treatment. All five patients with abnormal minNPi responded to the therapy and all showed minNPi normalization. Four patients with normal minNPi also responded to the therapy with unchanged minNPi. The two cases of nonsuccessful NCSE termination had normal baseline minNPi, which did not change during treatment.

Overall, in 66 episodes NCSE could be terminated. In 58 of these (87.9%) abnormal baseline minNPi was observed. In 45 of these (77.6%) minNPi normalized after successful NCSE treatment. The remaining 13 cases showed a significant increase of baseline to final minNPi (Wilcoxon, $p=0.004$), although absolute minNPi remained within abnormal range.

Principal component analysis with nonrefractory NSCE as target parameter and baseline minNPi, age, sex, and NCSE duration as factors revealed two components explaining 59.7% of overall variance (component 1 32.6%, component 2 27.1%). Main contributor to component 1 was baseline minNPi ($r=0.78$). Main contributors to component 2 were NSCE duration ($r=0.78$) and female sex ($r=0.62$). Age did not relevantly contribute to the model.

Discussion

To the best of our knowledge, this is the first report of prospective serial automated pupillometry for monitoring of treatment response in NCSE. Data showed abnormal global pupillary function in most patients with NCSE that normalized after successful NCSE termination.

Cohort characteristics were comparable with previous reports on adult cohorts with SE regarding age and sex distribution, seizure types, and etiology as well as response rates to antiseizure treatment [3, 4, 30, 31]. Remarkably, NCSE duration was rather long, with a median of 8.5 h prior to treatment initiation. Potential explanations are (1) the exclusion of patients who received treatment prior to EEG confirmation, (2) the high proportion of in-house patients (70.6%) hospitalized for other medical conditions potentially resulting in a delay of NCSE recognition compared with emergency cohorts, and (3) the calculation of NCSE duration based on the time the patient was last seen well, which can be considerably longer than the actual NCSE duration.

In line with a previous report, the majority of patients with NCSE (85.3%) showed minNPi $\leq$ 4.0 [26]. Increase of minNPi and NPi normalization were significantly associated with positive treatment response. Cohen's *d* showed a strong effect size for NPi increase related to treatment response, indicating a finding of clinical relevance. However, an increase of minNPi during a certain treatment step did not predict treatment response on a single patient basis. In some patients, minNPi normalized although EEG patterns showed ongoing epileptic activity. One explanation may be the relatively short time intervals between each treatment step. This may have caused a potential mismatch between detection of delayed EEG normalization and earlier minNPi normalization in some responders. Moreover, the pathophysiological connection between alterations of the autonomous pupil function and (prolonged) seizure activity is not yet fully understood. A causative relationship between NCSE termination and normalization of pupillary function can therefore not be established. However, our data support a pathophysiological association between abnormal pupil function and NCSE.

Abnormal baseline minNPi was observed in most patients and increased (normalized) after successful NCSE termination. In contrast, normal baseline minNPi was related to nonresponse to CZP and NCSE refractivity, as were longer NCSE duration and male sex. According to current pathophysiological concepts, sustained SE goes along with maladaptive changes of brain synaptic receptor and neuropeptide status, resulting in a downregulation of is gamma-amino-butyric acid (GABAergic) inhibitory and an upregulation of glutamatergic excitatory pathways [32]. It is hypothesized that the resulting disequilibrium of excitatory and inhibitory function may contribute to SE refractivity, drug resistance to benzodiazepines, and sustained response to NMDA receptor antagonists [33–35]. The potential impact of these changes on pupillary function has not been studied so far. Currently, to the best of our knowledge, there is no evidence of GABAergic modulation of pupillary response to light. However, there is some evidence for glutamatergic modulation of pupillary light response: the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine may partially inhibit pupillary response to light, suggesting that increased glutamatergic drive may facilitate pupillary function [36–38]. Regarding pupillometry, the latter may potentially result in an increasing NPi. Reduced minNPi in most patients with NCSE, increasing minNPi during prolonged ictal activity and the association of normal baseline minNPi with resistance to benzodiazepines as well as refractory NCSE may then reflect facilitated pupillary function resulting from maladaptive changes during sustained NCSE.

In a previous study, we could show that single measurement pupillometry may contribute to the diagnosis of NCSE in patients with seizures with a prolonged postictal interval [26]. In conjunction with these previous findings, our data suggest that altered NPi in NCSE may be a dynamic feature, possibly most prominent in early stages. It may then help to identify patients with NCSE and monitor response to treatment. This may be especially interesting when EEG expertise is not available 24/7, such as in emergency or even in preclinical settings. Diagnosing NCSE may be difficult in patients who are unconscious after a seizure or in coma of unknown etiology without an obvious structural brain lesion when EEG is not at hand. In these cases, reduced minNPi may possibly promote early antiseizure treatment even in the absence of EEG confirmation, which may contribute to a favorable outcome. Further, pupillometry may complement noninvasive neuromonitoring in patients with NCSE in neurocritical care settings. For example, it may potentially help with the interpretation of common wake-up EEG abnormalities, such as generalized periodic epileptic discharges and the early detection of recurrent NCSE after therapeutic coma. Future studies will have to address the value of both pupillometry in the evaluation of patients with coma of unknown etiology and its potential role for monitoring of patients with NCSE during the wake-up phase after therapeutic coma.

Limitations

Our study has some limitations. We examined a selected cohort of therapy-naïve patients with NCSE; our findings cannot be generalized to all patients with SE in all clinical conditions. For example, it remains unclear whether

NPi may also help in the identification of patients with recurrent NCSE in neurocritical care settings and during the wake-up phase after therapeutic coma. There are many potential confounders that need to be considered in individual treatment settings, including the impact of narcotics, analgesia, vasopressors, underlying brain injury (especially in dynamic disease stages), ocular comorbidity, diabetes, delirium, and many others. We did not control for any of these factors. Nevertheless, in most patients NCSE termination was related to an individual significant increase of NPi, suggesting that minor NPi alterations may indicate alterations of brain function related to epileptic activity, which can be helpful for noninvasive neuromonitoring. The drug-related effect of antiseizure drugs on NPi has not been examined so far. Therefore, we cannot exclude the applied drugs as potential confounders. However, our data suggest that, at least for CZP and LEV, the impact may be small because significant NPi changes have only been observed in responders but not in nonresponders.

Further, the absolute NPi reduction was less prominent compared with many other conditions in neurocritical care; most observed values would have been considered normal in these cohorts [16, 17, 19, 20, 39]. This may be attributed to the nature of pupillary changes. Altered pupil function in the previously examined conditions is mostly due to structural defects of the oculomotor nerve mediated either through compression with increasing intracranial pressure [17, 18, 24, 40] or ischemia [21, 41]. In contrast, in NCSE the pupillary network is rather functionally than structurally altered. Therefore, it appears plausible that NPi changes are less prominent in this cohort [26]. Our data demonstrate that even those smaller changes can be reliably detected and may be of pathophysiological and clinical relevance.

Conclusions

In summary, automated serial pupillometry showed NPi alterations in most patients with NCSE that normalized after successful NCSE termination. Hence, automated pupillometry may be a helpful tool for noninvasive neuromonitoring of patients with NCSE. However, the informative value of automated pupillometry seems to decline with longer NCSE duration and during treatment course. Further studies are needed to confirm and extend our understanding of the value of automated pupillometry in NCSE.

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Author contributions
JG is corresponding author and responsible for manuscript submission. JG and JB contributed to conceptualization, review, editing, figure and table creation. JR, KB, GN and SK contributed to review and editing of text, tables and figures. All authors approved the final version of the manuscript.

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Conflicts of interest
JR reports personal fees from Eisai GmbH, outside the submitted work. JB reports personal fees from Medtronic, personal fees from Zoll, personal fees from Böhringer Ingelheim, grants from German Neurocritical Care Society (DGNI), grants from Patient-Centered Outcomes Research Institute (PCORI), outside the submitted work. All remaining authors have no conflicts to disclose.

Ethical approval/informed consent
The study was performed in adherence to ethical guidelines. Ethical approval including a formal consent waiver for observational pupillometry was granted by the Hesse Medical Association Ethical Board (FF 20/2018).

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