ORIGINAL ARTICLE

Multimodal nocturnal seizure detection: Do we need to adapt algorithms for children?

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Abstract

Objective: To assess the performance of a multimodal seizure detection device, first tested in adults (sensitivity 86%, PPV 49%), in a pediatric cohort living at home or residential care.

Methods: In this multicenter, prospective, video-controlled cohort-study, nocturnal seizures were detected by heartrate and movement changes in children with epilepsy and intellectual disability. Participants with a history of >1 monthly major motor seizure wore Nightwatch bracelet at night for 3 months. Major seizures were defined as tonic–clonic, generalized tonic >30 s, hyperkinetic, or clusters (>30 min) of short myoclonic or tonic seizures. The video of all events (alarms and nurse diaries) and about 10% of whole nights were reviewed to classify major seizures, and minor or no seizures.

Results: Twenty-three participants with focal or generalized epilepsy and nightly motor seizures were evaluated during 1511 nights, with 1710 major seizures. First 1014 nights, 4189 alarms occurred with average of 1.44/h, showing average sensitivity of 79.9% (median 75.4%) with mean PPV of 26.7% (median 11.1%) and false alarm rate of 0.2/hour. Over 90% of false alarms in children was due to heart rate (HR) part of the detection algorithm. To improve this rate, an adaptation was made such that the alarm was only triggered when the wearer was in horizontal position. For the remaining 497 nights, this was tested prospectively, 384 major seizures occurred. This resulted in mean PPV of 55.5% (median 58.1%) and a false alarm rate 0.08/h while maintaining a comparable mean sensitivity of 79.4% (median 93.2%).

Significance: Seizure detection devices that are used in bed which depend on heartrate and movement show similar sensitivity in children and adults. However, children do show general higher false alarm rate, mostly triggered

while awake. By correcting for body position, the false alarms can be limited to a level that comes close to that in adults.

KEYWORDS

nocturnal, seizure detection epilepsy, nightly, Nightwatch, seizure, seizure detection

1 | INTRODUCTION

About 30% of people with epilepsy continue to have seizures despite medication. Getting help fast during a seizure is one of the concerns of living with epilepsy. Especially, nocturnal seizures are easily missed and have a higher risk of sudden unexpected death in epilepsy (SUDEP),[1–3] particularly in the case of nocturnal tonic clonic seizures.[3–5] Automated seizure detection can improve the quality of care,[6,7] reassure patients and caregivers, improve their sleep and possibly prevent SUDEP.[5,8,9] Various devices have entered the market over the last decade, usually based on non-EEG sensors that are worn on the body. They use continuous measurements of muscle activity (EMG), movement (accelerometry), sounds and autonomous features (heart rate and electrodermal activity)[10–18] and are sometimes multimodal. In close collaboration with a start-up company, we developed the Nightwatch®, a bracelet worn on the upper arm during the night, with sensors for heart rate (HR, by photoplethysmography [PPG]) and movement (3-dimensional accelerometry [ACC]). Its feasibility and efficacy were demonstrated in a number of previous studies in adults.[19–22] We showed that automated seizure detection has a high sensitivity in detecting major nocturnal motor seizures in adults living in residential care facility.[19] Initial trials did not involve children, who represent an important target population for these devices.

Concerns of missing a seizure may impact parents as they may take precautions to optimize their response to seizure sounds (either with or without baby monitor) or taking the child into their own bedroom. This can be a stressful situation for a family. Some parents may developed a protective behavior, driven by this fear. Although major motor seizures may look similar in children and adults, we had a number of concerns if our bracelet would perform equally well. For instance, we know that the basal heart rate is higher in children, and arousal-related and seizure-related heart rate changes may behave differently. Movements, especially, the frequency of clonic movements, an important feature in accelerometry, may be similar, but the amplitude may be different because a child's limb is shorter. We therefore found it crucial to assess the performance of our multimodal algorithm in a pediatric cohort.

Key points

- A wearable seizure detection device, based on PPG and ACC data for detection of nocturnal major motor seizures, previously tested on adults, was validated for children living at home and in residential care.
- The device showed similar sensitivity in children and adults.
- Children do show general higher false alarm rate, mostly triggered while awake.
- By correcting the algorithms sensitivity for body position, the false alarms could be limited to a level that comes close to that in adults.

2 | METHODS

2.1 | Study design

We conducted a multicenter, prospective, cohort study in children with refractory epilepsy.

2.2 | Standard protocol approvals, registrations, and participant consents

The trial was registered at the Dutch Trial Registry (www.trialregister.nl; NTR4115/NR395) and was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained from the participants or assent from parents or legal guardians.

2.3 | Nocturnal major seizures

The following seizure types were considered clinically urgent and denoted as major: (a) Generalized tonic clonic and focal to bilateral tonic clonic (TC) seizures; (b) long (> 30 s) tonic (T) seizures; (c) hyperkinetic (HK) seizures and (d) other major (OM) seizures, consisting of TC-like seizures with atypical semiology and clusters of minor

seizures lasting >30 min. We focused on these motor seizures because parents would want to go to the child for intervention or support, and because of the increased risk of status epilepticus, SUDEP and other complications.[19,21,23] All other seizures were classified as minor and their detection was considered as false positives. Video assessment by experts was the gold standard to ascertain the seizure and establish the seizure type. Before inclusion, the seizure types and frequencies in all children were evaluated in the diagnostic process, usually including video EEG recording.

2.4 | Participants

We recruited children (aged 3–18 years old) with refractory epilepsy and an intellectual disability (ID) living at home or in a specialized institutional residential care setting. All children had a history of at least one major nocturnal seizure per month. Exclusion criteria were a movement disorder that may cause false alarms, and having a pacemaker. Also, strong skin pigmentation/tattoo at the measurement location was regarded as exclusion criterion as it might interfere with the green light-based PPG of the HR sensor.

2.5 | Outcome

The primary outcome was performance in terms of sensitivity, positive predictive value (PPV), false-negative "alarm" rate (FNAR), and false-positive alarm rate (FPAR) of the multimodal nocturnal seizure detection device with the algorithm that was previously validated in an adult cohort.

2.6 | Device measurement, event collection

The device (the Nightwatch) consists of a bracelet (Figure 1) that measures HR derived from PPG and movements by ACC and has been developed by the Dutch Tele-Epilepsy Consortium together with a commercial partner LivAssured (Leiden, The Netherlands).

The bracelet is fixed around the upper arm with an elastic band, preferably on the side where seizures clinically initiate. The multimodal sensor uses HR and ACC data to determine and transmit real-time alarms wirelessly to a base station connecting to a laptop. For the purpose of the trial, we also collected synchronous data from to an infrared-sensitive video camera that was installed in the bedroom of the child. The video recording was started

FIGURE 1 The Nightwatch bracelet

when the participant went to bed, and stopped when getting out of bed the next morning. Parents or nursing staff kept a logging of events during the night, based on the device alarm and own observations. Video images were reviewed in "Nightview," an interface developed specifically for this trial to annotate seizures. All alarms generated by the device and all events in the log files were evaluated and classified by an expert. Also, a random sample of about 10% of the nights in all patients were fully screened for seizures that were missed by both caregivers and the device.

The detection algorithm used was developed in adults and has been described in more detail in a previous publication.[19] Briefly, HR values were determined every second and compared with a 5-min moving average of past individual peak-to-peak heart beat intervals. During most major seizures, HR shows an increasing slope, and may exceed an absolute threshold (tachycardia) or a relative threshold compared to baseline HR. Simultaneously, a signal quality index is calculated for each HR value that is based on the PPG waveform. The signal quality lower margin was set to 60%, under which HR is considered unreliable, in which case the algorithm would only use ACC for detection.

The ACC sensor module provides a motion and a position indicator in three perpendicular axes every second. The motion is a representation of the movement rhythmicity during a seizure and is based on the number of zero crossings for each axis per second. The position parameter indicates whether the child is in a horizontal position or otherwise, such as sitting or standing. Any alarm from the device depends on HR change, movement detection or both. During the study, the multimodal sensor had fixed settings that were not externally modified.

2.7 | Algorithm adaptation

During the course of the study, we noticed after 1014 nights in 18 patients that there were much more false alarms than during the previous trial in adults. We evaluated the false alarms and found that many were related to the child stepping out of the bed, or starting playing in the bed. We therefore decided to adapt the algorithm and to prospectively validate it. We altered the alarm triggering algorithm such that an alarm was generated only when the child was in a horizontal position. This was made prospectively, before registration. This avoided many false alarms, while not significantly compromising general sensitivity. So, the adapted algorithm generated only an alarm if the position sensors indicate a horizontal position and the threshold for HR (slope or tachycardia) was exceeded or the motion value stays above threshold for at least 7 s.

2.8 | Data exclusion

Twenty-five children were included in the trial. Two children were excluded from analysis as they did not comply to the trial procedure (in one of them the device alarm was turned off, another child slept most nights in a medical tent, which made it impossible to review the video images).

Of the remaining participants, 18 were recorded with the unadapted adult algorithm for 1014 nights and 14 children with the position-adapted algorithm for 497 nights.

Our aim was to measure about 90 nights per participant. In four children, we recorded a shorter period because of study withdrawal (n = 1), moving to another institution ($n = 2$) and an epilepsy surgery diagnostic procedure (n = 1). The latter three children were included for further analysis, as the recordings were judged to be long enough (> 30 days) for analysis.

Some children continued use of the device after 90 days, because the device was seen as beneficial.

2.9 | Performance measuring

An event was considered a true positive when an alarm was given within 3 min before or 5 min after the clinical start of a major seizure (annotated on video). The latter limit is chosen to allow detection of slowly developing focal to bilateral spreading seizures or atypical seizure types. Repeated detections within 3 min were scored as one. Performance (sensitivity, PPV, FNAR, and FPAR) was calculated per child. For normalization and comparison purposes, FNAR and FPAR were calculated per hour.

2.10 | Study size and bias

The sample size of 25 children was chosen to obtain acceptable confidence limits of the sensitivity and was based on preliminary results of the preceding in-hospital EEG/video study. Because the participants should have >1 seizure per month and the trial lasted 3 months, we expected >35 seizures. Because of the variability of the number of seizures per participant, a more appropriate estimation of the required number of participants was not possible. Inclusion bias was minimized by using a low inclusion threshold and only few exclusion criteria.

2.11 | Statistics

Sensitivity and PPV are used as performance measures at the population level. The strongly varying number of seizures per participant led us to calculate detection rates as averages per person and then use these figures for the descriptive group statistics. Rank order, nonparametric statistics were used to estimate the median parameter values across the average of within participant parameters.

3 | RESULTS

3.1 | Participants, seizure types and annotated nights

Demographic and clinical characteristics of the children are presented in Table 1. All children had major motor seizures.

3.2 | Initial (unadapted) algorithm results (Table S1)

The children had with the initial algorithm a median of 16 seizures (mean 74, range 0–420).

The number of fully screened nights ranged from 0 to 118 nights. Within the registered nights, 4189 alarms occurred. The median false alarm rate per hour was 0.2 per hour (mean 1.27, range 0.01-18.91).

The distribution of the annotated major seizure types was (total/mean) TC 275 (15), T 183 (10), HK 141 (8) and OM 727 (40).

The multimodal sensor detected 1059 of 1326 annotated major seizures, representing an average seizure sensitivity of 79.9%. The median sensitivity per patient was 75.4% (mean 70.94%, range 28%–100% [95% CI 30.2–100%]). The median FNAR was 0.01 per hour (range 0.001–0.2). The median PPV was 11.1% (mean 26.7%, range 1.70%–74.1%).

TABLE 1 Demographic and clinical characteristics of the participants (n-23) (individual details)

Code	Sex	Age	Diagnosis	ASM nr	VNS	Maj. Seizure types
1	M	5.1	Focal epilepsy, polymicrogyria	2	No	TC, HK
2	M	16.6	Focal epilepsy, gabra-1 mutation	2	No	TC
3	F	6.1	Generalized epilepsy, scn1a mutation	2	No	TC, T
4	M	7.9	Lennox gastaut syndrome	3	No	TC, T
5	F	9.9	Aicardi, lennox gastaut, heterotopia	4	Yes	TC, T, At
6	M	15.5	Focal epilepsy	2	No	TC, HK, At
7	M	15.5	Generalized epilepsy, scn2a mutation	2	No	TC
8	M	17.1	Generalized epilepsy, cri-du-chat syndrome	3	No	TC, T, At
9	F	16.3	Focal epilepsy	2	Yes	T
10	F	4.9	Focal epilepsy, cdkl mutation	2	No	TC, T
11	F	14.4	Focal epilepsy, gabra-1 mutation	2	No	T
12	M	4.4	Focal epilepsy, tsc-1	2	No	T
13	M	3.2	Focal epilepsy	3	No	T
14	M	6.2	Generalized epilepsy, gse-1 mutation	1	No	TC, T
15	M	9.5	Focal epilepsy, cortical dysplasia	4	No	TC, T, HK
16	M	11.2	Progressive myoclonic encephalopathy	2	Yes	TC, T, M
17	M	5.6	Progressive myoclonic encephalopathy	4	Yes	TC, T, At, M
18	F	5.4	Dcdkl-5 syndrome	2	No	T, M
19	M	13.8	Focal epilepsy, multicysts	3	Yes	TC, T, At, M
20	F	10.1	Focal epilepsy and genetic	4	No	TC, T, At
21	F	4.4	Focal epilepsy, cortical dysplasia	2	No	TC, HK
22	F	14.7	Dravet syndrome	3	Yes	TC, T, HK, At, M
23	M	5.2	Myoclonic absence epilepsy	3	No	TC, T, At, M

Note: Age ranges from 3.2–17.1 y, mean 9.7. Sex 9 female, 14 male. ASM (antiepileptic drugs) 1–4 per patient. VNS: 4 patients had vagal nerve stimulation.

3.3 | Adapted algorithm results (Table S2)

With the position-adapted algorithm, a median of 27 seizures were detected (mean 17, range 0–87).

The number of fully screened nights ranged from 0 to 9 nights. Within the registered nights, 882 alarms occurred. On average, the children had 0.24 alarms per hour.

The distribution of the annotated major seizure types was (total/mean) TC 103 (7), T 24 (2), HM 146 (10) and OM 111(8).

The multimodal sensor detected 305 of 384 annotated major seizures, representing an average seizures sensitivity of 79.4%. The median sensitivity per patient was 93.2% (mean 85.9%, range 47.4%–100% [95% CI 59.9–100%]). The median FNAR was 0.02 per hour (range 0.003–0.12). The median PPV was 58.1% (mean 55.5%, range 1.2–86.6%).

The total sensitivity for TC seizures during the initial algorithm was 86.18% (237/275) and during the adapted algorithm, it was 89.32% (92/103).

3.4 | Analysis of true and false alarms

Although the inclusion criteria required a history of at least one nocturnal seizure a month, 5 children did not show any major seizures in the study period.

We explored the determinants of the false and true alarms triggered by the three main detection criteria: Rapid Heart Rate Increase, Tachycardia, and ACC. It should be emphasized that one single alarm could have been triggered by multiple criteria. Therefore, the sum of the individual numbers and percentages for each criterion can be larger than the total number of false and true alarms.

We found that of the total of 1364 true alarms in both the initial and the adapted algorithm results, 1038 were triggered by the HR increase criterion (76%), 338 (25%) were triggered by the Tachycardia criteria and 324 (24%) were triggered by the ACC criterion. Consequently, 25% true alarms have been triggered by multiple criteria.

An analysis of the false alarms in the Initial algorithm results shows that 3011 (96%) false alarms were caused by the HR increase criterion, 704 (22%) false alarms could be

attributed to the Tachycardia criterion and 38(1%) false alarms were triggered by the ACC criterion. Consequently, 623 (46%) false alarms were triggered by multiple criteria. A total of 862 (28%) false alarms were caused by minor seizures.

In the adapted algorithm, we found that only 350 (61%) false alarms were triggered by the HR increase criterion, 76 (13%) were triggered by Tachycardia, and 228 (40%) were triggered by the ACC criterion. Consequently, 77 (6%) false alarms were triggered by multiple criteria. A total of 168 (29%) false alarms were caused by minor seizures.

4 | DISCUSSION

In this study, we show that it is feasible to reliably detect major seizures in children using a combination of heart rate (HR) and accelerometry (ACC) parameters. To our knowledge, there are no studies in children to compare these results with. The device was well tolerated in a group of children (age range 3–17 years old) living at home or in residential care. Median sensitivity was comparable to the results achieved in adults. However, the false alarm rate was initially higher as in the previously published adult results. To reduce the false alarm rate of the NightWatch in children while maintaining its high sensitivity, the algorithm was extended such that alarms were only triggered when the child was in a horizontal position. This resulted in a 60% reduction in false alarm rate from 0.2 per hour to 0.08 per hour, while maintaining similar sensitivity. Retrospective analysis of this algorithm on our previous adult data[19] did not show a significant change in sensitivity or PPV, allowing us to maintain a generic algorithm for both adults and children.

When compared to no seizure detection at all, some caregivers may take a relatively high false alarm rate for granted, depending on the circumstances and wishes. Further research can address this issue.

A minority of our seizure detections relies on ACC. This is probably due to the requirement of at least 7s of sustained rhythmic movements, causing seizures with a short clonic phase to be missed. Still, adding ACC ensures better performance, in terms of higher PPV. The less favorable PPV results in children compared to adults can be best explained by the higher and more variable resting HR in children.[24] This sets a challenge for devices relying on autonomic parameters such as HR.[25] In children with a high false positive alarm rate, the instant availability of video verification by parents or caregivers at a distance might help. This, however, raises concern on privacy aspects especially in older children.

As in our previous study in adults, a limitation of this study is the absence of EEG verification. Long-term EEG is not feasible in an out-clinic setting. Nevertheless, all our participants had video-EEG verification in the clinical work-up to determine their type of epilepsy and seizure type(s). In the previous study, it was shown that there was substantial interobserver agreement to justify the use of video only as a gold standard.[19]

The device has been developed for patients and caregivers to provide more safety and improve quality of life of both children with epilepsy and caregivers.[26] We therefore focused on a broader range of clinically urgent, major seizures without limiting detections to tonic clonic seizures. For motor seizures other than tonic clonic ones, relying on video judgment only, can be difficult, which might be improved, for example, by measuring surface EMG[14] or infrared video.[15] It is therefore possible that the Nightwatch sensitivity, particularly for tonic seizures, is lower than we reported. The overall sensitivity for the detection of major seizures in our study is in line with previous studies mainly focusing on tonic clonic seizures.[27]

The Nightwatch has been developed together with patients and caregivers to provide more safety and improve quality of life of both children with epilepsy and caregivers.[26] User surveys indicated that most parents prefer to be alerted for a broad range of seizure types. We therefore deliberately focused on clinically urgent, major seizures without limiting detections to tonic clonic seizures.

Nevertheless, we do not cover the full spectrum of seizures thus limiting the use of such a device in full seizure counting and treatment evaluation. Detection of daytime major seizures is another challenge that we currently do not address and is subject of further research.

5 | CONCLUSION

The seizure detection device that was used which depend on HR parameters and movement shows similar sensitivity in children and adults. However, in children, the device did show at first a general higher false alarm rate. By measuring the body position of the wearer, an alarm is enabled only if that position is horizontal, reducing the false alarm rate to a level that comes close to that in adults.

Nightwatch device, has obtained an exclusive license to implement or use the data in the future for commercial purposes or in commercial enterprises in exchange for a percentage of the revenue for the institutes.

CONFLICT OF INTEREST

Neither of the authors has any conflict of interest to disclose. The authors are part of the Dutch TeleEpilepsy Consortium, which has an agreement with LivAssured that future profits from its commercial device NightWatch will result in research donations from LivAssured to the consortium. No one from the TeleEpilepsy consortium, including the authors, has any direct financial links with LivAssured, or holds shares. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTION

Statistical analysis conducted by P.C. and R.L. Other contributions: J.A., R.D.T., T.G., J.V.D., F.T., and F.L. contributed to the study design. J.v.A., R.L. and J.A. did the literature search. Data were obtained by T.G., J.A., R.D.T., W.H., R.L and P.C. P.C. and R.L. created the figures. All authors contributed to the interpretation of results, reviewed and critically revised the article, and approved the final version for submission.

DATA AVAILABILITY

Individual de-identified participant data are available. Requests for reanalysis of the complete database, which contains privacy-sensitive (video) information, will have to be approved by the Medical Research Ethics Committee of the University Medical Center Utrecht and the members of the Dutch Tele-Epilepsy Consortium. Data availability is limited by exclusive rights for LivAssured with regard to commercial applications.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX 1

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