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Title page

Title: A method for identifying associations between seizures and possible trigger events in adults with intellectual disability

Running title: Identifying seizure triggers

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Summary

Objectives:

Precipitants of seizures are often reported by patients and carers, but the accuracy of these claims remains unknown. Focussing on epilepsy in people with intellectual disability (ID), the aims of this work were to (a) identify a set of methods for assessing the validity of reported seizure triggers in individual patients and (b) undertake an initial assessment of the ease of implementation and acceptability of the method by applying it to a series of cases.

Methods:

Data collection materials (developed with carer involvement) consisted primarily of carer diaries of seizure and trigger occurrences. Statistical analysis of diary data was using the self-controlled case series method. Unlike previously used methods, the analysis method included a means of choosing the time window, following trigger exposure, during which changes in seizure likelihood are to be assessed.

Results:

The method developed was trialled in five adults with ID and epilepsy, who had a range of ID severities and living circumstances. Examples of the application of the method in two of the five cases are presented for illustrative purposes. The method was acceptable to participants and most aspects successfully implemented.

Significance:

This method may be useful to clinicians and researchers wishing to investigate possible triggers in individual patients with epilepsy and ID. It also supports the identification of a statistically defined time window following exposure to a precipitant, during which the risk of developing a seizure is increased. The identification of such a window has value not just in

contributing to clinical management, but also in guiding future work into the mechanisms of seizure precipitation.

Manuscript

1. Introduction

Precipitants for individual seizures are often reported by patients and carers¹⁻⁴. However, doubts remain regarding the accuracy of these reports and a reliable method of identifying events or processes that for an individual patient are associated with an increased risk of seizure occurrence would have important implications. Clinically it would create the potential for reducing seizure occurrence by avoiding these events (where possible).

Theoretically, investigation of mechanisms by which these events increase seizure risk could provide novel insights into why seizures occur when they do.

Focusing on seizure precipitants in epilepsy, existing studies⁵⁻⁸ have used various methods for data collection and analysis. We sought to develop, describe and trial a complete set of methods to investigate seizure precipitants in epilepsy. We sought to address an important shortcoming of existing methods; namely the use of poorly justified assumptions regarding the time course (or ‘risk window’) over which proposed triggers may act. Furthermore, we sought a clinically focused method that enabled direct investigation of whether one or more carer- or patient-reported triggers are indeed associated with increased seizure likelihood in individual patients.

In this study we have investigated possible seizure triggers in people with an intellectual disability (ID). As a group, people with ID are at increased risk of epilepsy⁹ and less likely to be seizure free¹⁰ compared to the rest of the population but whilst some previous investigations of potential seizure triggers have included people with ID^{11,12}, most have focused on people with an IQ in the normal range. In this initial investigation of the proposed methods, the participants studied all received 24-hour support enabling third party recording of observations. However, the approach taken would be applicable to people without ID, with

alterations in how observations are made for those without 24-hour support. The aims of this study were to (a) identify a method for assessing the validity of reported seizure triggers in individual patients with ID and epilepsy and (b) undertake an initial assessment of the ease of implementation and acceptability of the method.

2. Method

2.1. Identification of method

We have aimed to develop a prospective diary-based method to enable: (a) investigation of carer- or patient-reported triggers in individual patients, and (b) a statistical approach that includes a method for selecting ‘risk windows’.

The authors could not identify any published prospective studies of seizure triggers in people with ID. Following an extensive literature search ten published studies were identified (list available from the authors) in which participants without ID used daily diaries to record occurrences of seizures and possible triggers or prodromal symptoms during everyday life. These studies showed considerable methodological heterogeneity, both in how trigger and seizure occurrences were recorded and how the possible relationship between them was analysed. We therefore chose to develop the methods described in this paper with the aim that they would satisfy specific requirements; a reproducible method of identifying seizure triggers and a robust, within patient method of statistical analysis to identify significant temporal associations. The diary recording methods needed to be able to be completed by participants’ carers during their routine caring duties and draft diary formats were discussed with 14 carers to develop an appropriate format, including agreeing seizure descriptions and definitions of potential triggers that took the form of subjective states, such as ‘stress’ and, ‘excitement’.

The statistical analysis method employed was selected as it allowed for the repeated occurrence of both seizure and trigger events, it allowed for single-subject analyses and it enabled multiple different trigger variables to be investigated in the same analysis

2.2. Description of method

The main features of the method are described below. Two worked examples are presented in Section 3.

i. Seizure and trigger diary

Prior to the start of data collection information on carer-reported triggers was collected and a Basic Seizure and Trigger Diary (see Supplementary Data 2) tailored to each individual. This pen-and-paper diary comprised a series of questions, asking carers to record occurrences of carer-reported and pre-specified possible triggers, and times and descriptions of all seizures. Diaries were completed by carers 2-4 times per day for four months, with completion schedules decided in collaboration with carers.

To address the question of whether the events recorded in the diary were epileptic seizures, carers were provided with a video camera and asked to record two examples of each of the person's 'seizure types', for independent review by two experienced clinicians (MM, HR).

ii. Analysis of diary data: The self-controlled case series method

The analysis method used was the self-controlled case series method (SCCS)¹³. This method is used to investigate whether the rate of occurrence of an outcome event (e.g. seizure) is increased during the presence of a possible risk (e.g. trigger), if the outcome event occurs at least once during the study period. It can be conducted within a single subject.

The SCCS method is described in detail elsewhere in its general form¹³, and example analysis scripts are available (<http://statistics.open.ac.uk/sccs/index.htm>). As applied to the current question, the method is briefly as follows. The study period is divided into ‘risk periods’ (during which time the person was exposed to the trigger) and ‘control periods’ (during which time s/he was not). For momentary risk events, a period following the risk event is specified as the risk period (Figure 1).

[Insert Figure 1 about here]

Poisson regression is used to analyse the relationship between risk status and seizure occurrence. An incidence rate ratio (IRR) is computed, representing the ratio of the seizure rate in risk periods compared to control periods (and is equal to the exponential of the poisson regression coefficient). Treatment changes during the study period can also be incorporated, by dividing the study period into treatment phases and including treatment status as a variable in the analysis. Multiple trigger variables may be included simultaneously in the analysis (with an IRR output for each), enabling evaluation of the relative importance of different potential triggers.

IRRs above 1 indicate greater seizure frequency in risk than control periods, and IRRs below 1 indicate lower seizure frequency. Because IRRs above (or below) 1 may be observed due to chance variation alone, the statistical significance of each IRR is assessed by calculating a z-score (the ratio of the poisson coefficient (from which the IRR is derived) to its standard error) and an associated p-value; these are provided by all analysis packages and interpreted using a criterion for statistical significance of $p < 0.05$.

iii. Identification of ‘risk windows’ to use in data analysis

Like methods used in previous studies, the SCCS method requires risk periods used in the analysis to be specified. For some potential triggers the appropriate risk period will be the time during which the trigger was actually present. However, for others it might be a window of time following the trigger event. In these cases, we argue careful consideration should be given to the length of risk window to use as this will influence the IRR output and thus the conclusions reached.

When no well-justified *a priori* risk window is suggested in the literature, a method has been described for use with the SCCS approach, for identifying the optimal risk window length to use from the data¹⁴. The optimal risk window length is an estimation of the ‘true’ risk window length and is, theoretically, the length yielding the greatest IRR¹⁴. Optimal risk window lengths are therefore also outcomes in themselves, as they suggest possible time courses for mechanisms linking triggers and seizures.

The published method for identifying optimal risk windows¹⁴ refers to situations in which the trigger event happens just once during the study period (which is unlikely to be the case for some seizure precipitants). Applying the published method¹⁴ with some modifications to the current question, the process is briefly as follows. For the trigger in question, the SCCS poisson regression (as described above) is run multiple times, using a range of risk window lengths all starting at the end of trigger exposure. In these analyses a treatment change variable is also included as described above, if applicable, but no other additional variables (e.g. representing other triggers of interest) are included. This produces a number of IRRs for the trigger, one for each risk window length (L) tested. Next, for each value of L, the mean actual risk window length (T(L)) is calculated, by taking the total time the person spent ‘at risk’ (i.e. during risk windows) during the study period and dividing it by the number of discrete (non-overlapping) risk periods that occurred (Xu, personal communication). IRRs are then plotted against 1/T(L) and the optimal window read from the graph. The optimal

risk window is usually found by identifying the value of $1/T(L)$ at which IRR was maximal (for details and exceptions, see Xu and colleagues¹⁴). This is the risk window then used in the main SCCS analysis, which will also include other trigger variables and treatment changes, if applicable.

iv. Additional considerations

When applying these methods to seizure precipitation, additional issues to consider include how to address possible seizure clustering, issues relating to the investigation of multiple triggers simultaneously, and how to apply the cross-validation techniques proposed by Xu and colleagues¹⁴ (to address possible bias introduced by selecting optimal risk windows from the dataset) to data of this nature. These topics are further discussed in Supplementary Data 1 and 2.

2.3. Application of method to a series of patients

The method was trialled in five adults with ID and epilepsy.

i. Participants

A convenience sample of five adults with epilepsy and ID (with at least one seizure per month) was recruited from epilepsy clinics in neurology and community ID services, and an ID charity. Patients were only recruited if they received 24 hour support and sufficient carers were willing to participate to enable continuous data collection.

As the emphasis of this work was on the description and evaluation of the method developed, descriptions of its application to two of these cases are provided as worked examples. These are simplified account to illustrate the main features of the method; complete results for these cases are in Supplementary Data 2.

ii. Evaluation of implementation and acceptability

Implementation was measured by (a) % of diary pages completed and (b) % of seizure types video recorded. Acceptability to participants was measured by (a) % retention in the study, (b) carer feedback using a structured questionnaire, and (c) patient feedback (if possible) using a structured interview.

iii. Standard protocol approvals, registrations and patient consents

The study was approved by National Research Ethics Service (NRES) Committee London – Camden and Islington. All carers involved in data collection gave written consent. Patients gave written informed consent if they had capacity to do so; for those deemed not to have capacity to consent, their participation was in accordance with the Mental Capacity Act (England and Wales) 2005¹⁵.

iv. Carer training

Training was provided to carers in how to complete the diaries, with written guides provided for carers. Training in how carers should identify and describe potential triggers that were subjective states (e.g. stress and excitement) was provided to increase the reliability with which these were reported in the diaries. Using a structured interview with participants' main carers (available from the authors), the researcher elicited detailed descriptions of how these states were expressed by the person with ID. Similarly, detailed descriptions of each seizure type experienced by participants was also obtained. A written summary of the interview was produced by the researcher, checked by the main carers and attached to the diary for reference by all participating carers.

3. Results

3.1. Patient characteristics

Participants varied in age (22-52 years), ID severity (mild to profound), living circumstances (supported living, group homes or with family) and seizure frequency (13-606 seizures within the 4 months). Carers involved in data collection per patient ranged from two to eighteen.

Three participants were female and two were male.

3.2. Example of application of the method (Case 1)

i. Introduction

Case 1 was female with mild ID and idiopathic generalised epilepsy, in supported accommodation. Sixteen paid carers co-operated to complete 3 diary entries per day for 4 months. This example focuses on just one of the triggers investigated in this patient – times of heightened stress. The relevant diary question was, ‘Were there any times when she was particularly stressed?’; if so, approximate times were given. Carers were also requested to provide times and descriptions of all seizures. The main carer provided a description of the signs shown by the patient when stressed, to facilitate consistent reporting of stress by multiple caregivers. During the study the patient had 124 seizures and one treatment change (an alteration to her vagus nerve stimulator (VNS) settings).

ii. Choice of risk windows

Risk windows comprising times of stress were used. Also, risk windows after termination of these periods of stress were included using a risk window length identified using the method of Xu and colleagues¹⁴. Figure 2 shows the graph derived using this method and the resulting optimal risk window length (585 minutes, i.e. almost 10 hours). The graph was produced using L-values from 15 minutes to 48 hours (at 15 minute intervals). When running these analyses, a binary variable dividing the study period into before and after the VNS change was included.

[Insert Figure 2 about here]

iii. SCCS analysis

The SCCS analysis was conducted using STATA/IC for Windows, version 13.1¹⁶. Analysis scripts were adapted from those available on the SCCS website (<http://statistics.open.ac.uk/sccs/index.htm>).

Table 1 illustrates the relevant section of the SCCS output (the complete output, including other triggers investigated, is found in Supplementary Data 2). IRRs were above 1 both for during, and after, episodes of stress; however, these effects were not statistically significant.

[Insert Table 1 about here]

3.2. Example of application of the method (Case 2)

i. Introduction

Case 2 was female with mild ID and focal seizures. She lived with her family, two of whom provided care for her. Both these family carers co-operated to complete 2 diary entries per day for 4 months. This example focuses on one of the triggers investigated in this patient – the time after a period of constipation. A common definition of constipation is less than 3 bowel movements per week, equating to less than one every 2.33 days¹⁷. The participant was said to be constipated if more than 2.33 days had passed since the previous bowel movement, with the period of constipation ending at the following bowel movement. During the study the patient had 13 seizures over the four-month observation period.

ii. Choice of risk window

The length of the risk window to consider following the end of the period of constipation was identified using the method of Xu and colleagues¹⁴. Figure 3 shows the graph derived using this method and the resulting optimal risk window length (1410 minutes, i.e. 23.5 hours).

The graph was produced using L-values from 15 minutes to 48 hours (at 15 minute intervals).

[Insert Figure 3 about here]

iii. SCCS analysis

The IRR for this potential trigger was 4.529 and the effect was significant ($p=0.031$). The proportion of time spent at risk was 0.154, z-score was 2.16. These figures were obtained from a multivariate analysis which took into account other simultaneously investigated potential triggers, described in Supplementary Data 2. Validation of the risk window was undertaken (see Supplementary Data 1 for a general description of this method). The graphical method for determining the optimal risk window was repeated separately on the first and then second halves of the data set. The optimal risk window was 1365 minutes using the first half and 1410 minutes using the second half of the dataset (compared with 1410 minutes when using the entire dataset). This result suggested good reliability of the risk window estimation. Further SCCS analyses for Case 2 are reported in Supplementary Data 2).

3.3. Evaluation of implementation and acceptability

i. Implementation

Percentage of diary pages completed ranged from 87-100%. However, video recordings were only obtained for one participant, with reasons for a lack of video recordings included pragmatic difficulties, safety concerns, and carer uneasiness.

ii. Acceptability

No patients withdrew from the study. Carer ratings for ease of diary completion ranged from 91-99 on a 1-100 scale (where 100 is easiest). Challenges reported included ensuring the whole care team stayed involved, and completing diaries covering overnight periods. When teams of paid carers were involved, continued engagement of the whole care team was facilitated by managers, who were supportive of the study. Patient feedback (available for 3 participants) was also positive; participants liked taking part, particularly mentioning helping others, enjoying the visits from the researcher, and helping carers with some of the diary questions.

4. Discussion

Seizure triggers are commonly reported in patient and carer surveys^{2,3,18} and many authors have called for prospective studies, using patient diaries, to confirm these reports¹⁹⁻²¹. While several such studies have been undertaken^{5,6,8}, the question of how hypotheses about possible triggers in individual patients can be tested has hitherto not been directly addressed. We identified and described a method for doing so, which was trialled with five patients with ID and epilepsy and found to be acceptable to patients and carers. Worked examples are presented focusing on stress and constipation as possible triggers and whilst seizure rate was not significantly increased during or following episodes of stress in Case 1, in Case 2 seizure rate was increased during the 24 hours after the first bowel movement following a period of constipation.

Avoiding triggers with the aim of improving seizure control is only indicated if the trigger is indeed associated with increased seizure likelihood. The method described therefore has potential utility for guiding treatment, by ascertaining whether suspected triggers are indeed associated with increased seizures. While it requires time and resources that may not be

available to clinicians (in particular, using statistical analysis packages such as STATA), user-friendly applications could readily be developed to allow the analysis to be conducted more easily in clinical settings.

An important aspect of the method was a means of choosing ‘risk windows’ to use. The risk window is crucial to the results of the analysis and must be chosen carefully, especially if the results are to inform patient management. The fact that to date risk windows chosen have not been well justified reflects a wider problem; the lack of consensus and clarity about how we define seizure triggers, including the time course over which they may be expected to act²². The statistical method suggested here¹⁴ for identifying an optimal risk window has value not just in ensuring risk windows used are well justified, but also in guiding future work into mechanisms of seizure precipitation.

Sample size calculations for use with the SCCS method are available²³. These could guide the number of seizures required to conduct the analysis in a single patient. These were not used in the current application because they require information on the proportion of time spent during risk periods²³, which was unknown at the study outset. Negative results may therefore be due to a lack of statistical power. In future use of the method, pilot work could estimate the proportion of time an individual is likely to spend at risk, enabling sample size calculations to estimate the length of the data collection period.

The method presented has several limitations. First, the reliability of recordings in the diaries was not measured during our study, and it is possible that different carers interpreted the diary questions differently. Future work could test inter-rater reliability of the diaries.

Second, some researchers have raised doubts regarding the trustworthiness of data collected using pen-and-paper diaries, instead advocating electronic diaries²⁴. These allow time-stamping of diary entries and greater control over when diaries are completed, reducing the

potential for retrospective reporting and recall bias²⁵. We considered using electronic diaries, but consultation with carers revealed significant feasibility concerns.

We attempted to validate our diagnoses with video recording but this proved unsuccessful, raising uncertainties around the diagnosis of attacks as epileptic. Future use of the method might include periods of video-EEG monitoring.

The method depends upon the accurate recording of seizure and trigger events. In terms of the wider applicability of this approach, while there are other challenges of investigating triggers in people with ID, many have 24 hour support, enabling continuous observation by carers. For those without this support developments in monitoring technologies could be employed to help identify occurrences of seizures and potential triggers. Hence the method could be adapted for people without ID.

Finally, the method described cannot ascertain whether the trigger event has a causal influence on seizures. However, we argue that determining whether a suspected trigger is indeed associated with increased seizure likelihood is an important first step in establishing causation.

To conclude, we present a method for investigating possible seizure triggers, for use both in research and clinical contexts. We plan to develop an application to maximise the accessibility of the method in clinical practice.

KEY POINTS

- A method for testing the statistical association between repeated occurrences of possible seizure triggers and seizures is described

- The analysis method used was the self-controlled case series method, which can be conducted in single individuals
- We describe an approach to identify the optimal risk window during which a trigger is most likely to be associated with seizure occurrence
- Risk window identification has clinical value and could also inform research into mechanisms of seizure precipitation

Supplementary Data:

- 1- Further details of analysis method
- 2- Further details of application of method in Cases 1 and Basic Seizure and Trigger Diary.

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Disclosure

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.

Legends for figures

Figure 1.

Data for SCCS analysis

Data format for analysis using the SCCS method (using hypothetical data). This illustrates repeated occurrences of a single trigger, though multiple trigger variables may be included in the analysis. The horizontal arrow from left to right represents continuous time from start to end of data collection. Times of seizure occurrence are marked by 'S' and times of occurrence of the trigger are marked by 'T'. Risk periods are represented by grey boxes. All other time periods (white boxes) are treated as control periods. The final trigger occurrence (marked with an asterisk) is within the risk period of the penultimate trigger occurrence, to illustrate how this results in a single extended risk period.

Figure 2.

Determination of risk window

Graph used to determine optimal risk window for 'stress' for Case 1 using the method of Xu and colleagues (2011).

Figure 3.

Determination of risk window

Graph used to determine optimal risk window for 'after constipation' for Case 2 using the method of Xu and colleagues (2011).

Table 1

Trigger investigated	Risk window used	Proportion of time spent 'at risk'	Incidence rate ratio (IRR)	Poisson regression coefficient	Standard error of coefficient	z-score	p-value
During stress (specific episodes)	During specific times of stress	0.002	2.978	1.091	1.098	0.99	0.320
After stress (specific episodes)	During the 585 minutes following specific times of stress	0.087	1.718	0.541	0.316	1.71	0.087
Change in VNS treatment*	From change in VNS treatment to the end of the study period	0.645	1.576	0.455	0.213	2.14	0.033

Table 1. Part of the SCCS output for Case 1, illustrating results regarding the association between episodes of stress and seizure occurrence. The statistics in the table were calculated while taking all other measured trigger variables into account. *The change in VNS treatment was a simultaneous reduction in signal frequency (from 30Hz to 20Hz) and increase in cycling option (from 30 seconds on 3 minutes off to 30 seconds on 1.8 minutes off). Output generator current was kept constant at 1.50mA.

VNS = Vagus Nerve Stimulation

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