Breath-holding spells and its management: a prospective study on patient and disease characteristics, evaluation of novel guidelines, parental handling, and long-term follow-up in breath-holding spells

Content

Main investigators

Sanna Hellström Schmidt
Skånes University Hospital, Skåne, Sweden / Lund University
sanna.hellstrom:schmidt@med.lu.se

Cornelis Jan Pronk
Skånes University Hospital, Skåne, Sweden / Lund University
Kees-jan.pronk@med.lu.se

Involved centers

The number is so far unknown. Patients will be included from pediatric outpatient care, emergency care and from family centers (in Swedish: *barnavårdcentral*). All within Region Skåne, in southern Sweden. The study will be coordinated from a single center (Skåne University Hospital / Lund University). For project coordination reasons the family centers with 900 and more listed patients will be invited to participate. If this does not yield enough of family centers, the limit for listed patients will be lowered to 500.

Title

Breath-holding spells and its management: a prospective study on patient and disease characteristics, evaluation of novel guidelines, parental handling, and long-term follow-up in breath-holding spells

Protocol ID

In clinicaltrials.gov: 2023-03363-01

Key words

disease definition, electrocardiography, iron deficiency anemia, long QT syndrome, parental support

Project summary

In 2015-2016, Sanna Hellström Schmidt (SHS) and Cornelis Jan Pronk (CJP) conducted an initial collaborative study, which was published in 2016 and received the Acta Paediatrica award for both SHS and CJP.[1] That study involved the collection of a substantial cohort of patients with breath-holding spells (BHS), surpassing any previously reported cohort. From 2018 to 2019, we expanded the cohort to include data up to 2018, resulting in a cohort of 519 patients. During this period, we also performed extended analyses. By reviewing medical files, we obtained data on patient and spell characteristics, as well as results from diagnostic interventions. Of importance, our findings revealed an excessive use of EEG and ECG, with a low yield of pathological results, and a limited utilization of blood testing for anemia and iron deficiency. As a result, we refined the disease description for typical BHS and developed guidelines for the management of typical BHS upon presentation to healthcare. Of note, such management guidelines are lacking in local, national, and international literature. Our results and the management guidelines are further described in our article published in Acta Paediatrica in 2024.[2] In 2021, the project formalized and extended into a PhD project in which additional aims and sub-studies were defined. The study presented herein, the BAM-study, is the prospective study focusing on BHS, and expected to start recruitment of patients during 2024. The aim of the BAM-study is mainly to evaluate the impact of the BHS management guidelines that we established based on our retrospective cohort, described in greater detail in the outcome measures-section below.

Study population

Inclusion

Children and their parents that actively seek medical attention for, or mention symptoms consistent with, breath-holding spells at any center that participates in the study, can be included if they are below the age of five years and are residents of Skåne Region. The only exclusion criteria is if the participant previously been investigated for suspected BHS.

End participation in the study

The participant or their caregivers can discontinue their participation in the study at any point of time. They can also choose to not participate in certain parts of the study (as the interview sub-study) and not be excluded if enough data can be collected for other Outcome Measures to be analyzed. However, they need to attend the initial doctor's appointment to be able to be included.

Study design

A prospective population-based nonrandomized interventional study. Although the study is primarily performed in the manner of an observational study, the nature of the study is interventional since the refined diagnose description and management guidelines are so new that they are not yet implemented in any of the health care centers included in the study. Since the management guidelines are the first of its kind (in breath-holding spells) the analysis is expected to be partly explorative in its nature.

Arms	Assigned Interventions
Typical spells Patients with typical spells should be investigated according to our guidelines	Diagnostic Test: Guidelines Participants with typical spells will be investigated according to our guidelines. These include that participants with heredity for or signs and symptoms of cardiac disease will be subjected to an ECG and participants with two or more spells should be subjected to blood tests for anemia and iron deficiency
No Intervention: Non-typical spells Patients with non-typical spells will be investigated individually, as it is done today	

Outcome measures

Primary Outcome Measures

Safety of the guidelines

The number of wrongful and missed diagnoses (definition: managed and diagnosed as breath-holding spells at physician assessment within study but later found to be another cause for the symptoms, like long QT syndrome or epilepsy).

[Time Frame: From date of inclusion to end of follow up at 36 months]

Usability of the guidelines

Assessed according to the following:

- Number of patients with a diagnostic interventions for each intervention in the guidelines: ECGs and bloodtests.

- Number of found pathologies for each intervention (blood tests and ECGs)- for patients with typical spells handled according to the guidelines and those with non-typical spells managed individually. This includes a retrospective assessment of ECG (a complete assessment including rythm, long QT syndrome, AV-block, ST-segment changes) and blood test results (for anemia and iron deficiency; i.e. values outside of the age adapted normal range).
- Retrospective analysis of the clinical doctors compliance with managment guidelines, evaluated through the number of interventions for each patient that were not recommended in the guidlines (for instance number of EEGs).

[Time Frame: From date of inclusion until last diagnostic intervention, expected to be within 2 weeks from inclusion.]

Usability of the disease definition

Assessed according to the following:

- Adherence to the the prespecified definition of typical spells through comparison of clinical physicians assessment and a retrospective assessment by study physician, i.e. the number of cases with a discrepant judgment of the clinical presentation.
- The number of typical spells compared to the number of non-typical spells and other diagnsoses.
- Compilation of patient and spell characteristics (defined in the variable list in the attached documents) and comparison with the current definition of typical spells.

[Time Frame: From the inclusion date until end of physicians assessment]

Secondary Outcome Measures

Need of information and support to parents

Through interview study (qualitative study) gather information on given information and support and their need for more information and support. Will be conducted on parents of children with more than 5 spells in total at the 6 month follow up (assessed as frequent spells).

[Time Frame: From 6 months after inclusion until interview is performed, expected to be within three months of six month digital survey]

Effect of iron supplement treatment on spell frequency and severity

In cases of iron treatment (initiated by the clinical physician). Assessed according to the following:

- Comparison of spell frequency (number of spells/time unit) before start of treatment, during treatment and after completion of treament.
- Comparison of spell severity (simple or severe spells defined as spells without and with loss of consciousness) before start of treatment, during treatment and after completion of treament.
- Anemia and iron deficiency blood test values (Hb, MCV, reticulocytes, ferritin, CRP if signs of infection, iron, iron saturation and transferrin) comparison between patients with effect of iron treatment on spell frequency and severity, versus the group without a clinical effect of iron treatment.
- Patient compliance for iron supplementation as per survey question with answer altneratives yes/no/don't know

[Time Frame: From the date of inclusion until evaluation of iron treatment, most probably within 12 months from inclusion.]

Other Pre-specified Outcome Measures

Natural course of the spells through long term follow-up

Assessed according to the following parameters, through digital surveys:

- Spells during the last 3 months (yes or no)
- Number of spells the previous month (0, 1, 2-5, 6-10, >10)
- Total number of spells (free text)
- Uncontactable or unconscious (=severity of spells) (Yes, No, Don't know)
- Alterations in spell semiology? (Yes, No, Don't know)

[Time Frame: 36 months]

Contact with health care during long term follow-up

Evaluation of the following questions:

1- Do parents follow the advice to reach out to health care if the spell semiology change?
2- Planned follow up?

Above questions are assessed in a digital survey:

- Further contact with healthcare. Answer alternatives: (Yes, No, Don't know). If yes: (acute or planned)

[Time Frame: 36 months]

Burden of care

Will be assessed through a combined evaluation of the following variables:

- Number of acute health care visits
- Number of planned health care visits including follow-up appointments over phone
- Number of over-night hospital stays (number of nights)
- Number of ambulance rides to the hospital

[Time Frame: 36 months]

Dietary impact on iron status

At first visit, parents will answer questions on the child and family's diet in a questionnaire, to evaluate a possible association between diet and iron status (and further, to breath-holding spell frequency and severity).

The questions are as follows:

- Mark all alternatives that is correct about your childs diet: (breatmilk/formula/cow's milk/taste portions/family meals)
- Does your child drink more than 3 dl of cow's milk per day? (yes/no)
    - If yes, estimate the amount of cow's milk your child drink during a day in dl: (a number in free text)
- Do you eat vegetarian or vegan food only? (yes/no)

[Time Frame: From inclusion to blood test results, within 2 weeks from initial visit]

Visits and examinations

At diagnosis and follow up

All eligible patients will undergo evaluation by a medical doctor upon suspicion of BHS. Following a comprehensive patient history and clinical assessment, the medical doctor will determine whether the symptoms align with typical BHS, non-typical BHS, or another diagnosis. Based on this evaluation, the patients with typical BHS will be managed in accordance with our guidelines. Data will be collected from surveys from the doctor and from a parent or legal guardian at first visit and from the medical files. Follow-up will involve a digital survey at 3, 6, 12, and 36 months post-inclusion.

Qualitative interview sub-study

Parents of patients with 5 or more spells in total at the 6 month follow-up survey will be asked to participate in the interview study. The interview will be conducted by SHS using an interview guide that focuses on the information provided, strategies employed by parents to prevent and manage spells, and the consequences associated with these spells and the data will be analyzed according to qualitative content analysis.

Study assessments

The table below visualizes the frequency and timing of the assessments.

Variable(s) / data collection tool	First visit	3 months	6 months	12 months	36 months
Neurological status	x				
Blood samples	(x)*				
ECG	(x)				
Parental questionnaire	x				
Doctors' questionnaire	x				
Digital follow up survey		x	x	x	x
Data collection from medical files	x			x	x
Parental interview			(x)		

(x) = depending on type of spell and frequency of spells
*initial test results will decide whether more blood tests will be necessary

Projected sample size

We extrapolate the following based on numbers from our retrospective study:

Year	Eligible for inclusion	If 70% recruitment rate
1	45	32
2	45	32

3	45	32

These numbers are from hospital care only. We hope that inclusion of family centers will increase the number of included patients to around 120 patients.

Considering the primary outcomes (safety and usability of the guidelines), we (together with a statistician) could not perform a power and sample size calculation. There are several diagnoses that is possible to mistake for breath-holding spells and some of them are rare (for example LQTS). However, for the most important aspect, the safety of the guidelines, a single misdiagnosis (mistaking a serious diagnosis like LQTS for BHS) will warrant review of the case and if there is a need for guideline revision.

Inclusion in the qualitative interview study is expected to be 2-3 pilot interviews and 10-15 interviews based on the number of interviews needed in similar previous qualitative studies.

Study period

Inclusion is planned to begin in 2024. Inclusion will continue for three years or until the target sample size of 120 patients is reached. Follow-up will be conducted over a period of 36 months. Partial data analysis will be possible for some outcome measures (see above), after which the first publication can be anticipated. We expect to collect the final 36-month follow-up survey data in 2030.

Database

Data will be stored in a RedCap database. The interviews will be digitally recorded and subsequently transcribed. All data will be pseudonymized, and the key will be stored in safe storage within Region Skåne.

Ethical approval

The study is approved by the Swedish Ethical Review Authority/Board (in Swedish: *Etikprövningsnämnden*), approval number: 2023-03363-01. The study also has approval for data collection from the relevant medical data systems, KVB number: 332-23.

References

1. Hellstrom Schmidt S, Tedgard U, Pronk CJ. Breath-holding spells occur disproportionately more often in children with transient erythroblastopenia. *Acta Paediatr*. Sep 2016;105(9):1088-93. doi:10.1111/apa.13428

2. Hellström Schmidt S, Smedenmark J, Jeremiasen I, Sigurdsson B, Eklund EA, Pronk CJ. Overuse of EEG and ECG in children with breath-holding spells and its implication for the management of the spells. *Acta Paediatr*. Feb 2024;113(2):317-326. doi:10.1111/apa.17020