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

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Content

Introduction

Brief summary

The goal of this prospective population-based study is to evaluate the new disease description and management guidelines for breath-holding spells (BHS) in children (Hellström Schmidt et al, Acta Paediatrica 2024) below the age of 5 years in southern Sweden.[1] The main questions it aims to answer are:

- Is the clinical managements guidelines easy and safe to use?
- Does the disease description and management guidelines lead to the expected reduction in diagnostic interventions?
- If iron supplementation is given, does it reduce the frequency and severity of the spells?
- What information and support do parents to children with breath-holding spells need?

Participants will undergo evaluation by a medical doctor and if typical breath-holding spells are diagnosed, be managed according to the new guidelines. If iron deficiency is found, iron supplementation is recommended. Digital surveys will be distributed during a three-year follow-up period, and parents of patients with frequent spells will be eligible for participation in an interview sub-study.

Disclaimer

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.

Study objectives and endpoints

Please see Study protocol under *Outcome measures*.

Summary of the most important endpoints

1. Safety of guidelines (for example the number of missed diagnoses)
2. Usability of guidelines
3. Outcome of guidelines (number or ECGs, EEGs, blood tests and number of pathological test results)
4. Interview study: information and support needed by parents
5. Effect of iron treatment on spell frequency and severity

Study method

Please see Study protocol under *Study Design*.

Sample size

Please see Study protocol under *Projected sample size*.

General analysis considerations

Timing of analyses

- The final analysis will be performed 36 months after the inclusion of the last patient, including evaluation of the long-term follow-up and any wrongful or missed diagnoses.
- Analysis of data on iron treatment is expected to be possible 12 months after the inclusion of the last patient.
- Analysis of dietary impact on iron status and breath-holding spells will be performed after inclusion of the last patient.
- Analysis of data with the purpose of refining the disease description will be possible after inclusion of the last patient (the disease description of data available at diagnosis) but will need the full follow-up time for data on for example the normal age for the spells to abate.

- Analysis of data with the purpose of evaluating the management guidelines will most likely require the full follow-up time to allow for time to discover all cases of delayed diagnosis or wrongful diagnoses, however part of the data is expected to be able to be analyzed within the first year of inclusion of the patient (such as comparison of management of sub-groups at diagnosis).
- Analysis of data from the interview sub study will be possible after the last interview is performed, possible earlier than the BAM-study will finish in its entirety.

Analysis populations

Each analysis population might be further divided according to the other population-characteristics defined here; for example, patients with heredity for cardiac disease might be divided into sub-groups according to severity of spell, type of spell or into other groups for comparison within the population with patients with heredity for cardiac disease. Depending on the data, more sub-group analyses might be performed than described here and in the project plan.

Full Analysis Population

- All patient included in the study that completed all patient follow-up surveys including the 36-month survey
- It will be possible to use data for sub-analysis including:
    - All patients included in the study that completed the initial doctors visit
    - All patients included in the study that completed the 12-month survey

Typical breath-holding spells population

- All patients included in the study with ***typical*** breath-holding spells that was managed according to the new guidelines

Frequent spells population

- All patients included in the study that have frequent spells (with 5 or more spells in total) at the 6 months follow-up survey
- Will be eligible for inclusion in the interview sub-study

Other groups that will be used in analyses:

- Non-typical breath-holding spells patients
    - Participants with breath-holding spells that does not adhere to the criteria for typical spells
- Breath-holding spells patients
    - Participants with both typical and non-typical breath-holding spell
- Other diagnoses patients
    - Participants initially suspected to have a breath-holding spell diagnosis but during the study received another explanatory diagnosis
- Patients managed within primary care
    - Patients managed entirely within primary care (not referred for tests or evaluations), should only be typical spells patients according to the study design, but that need to be evaluated
- Anemia- and iron deficiency patients
    - Patients with anemia or iron deficiency according to the national PM for iron deficiency anemia in Sweden[2]
- Iron treatment patients
    - All patients treated with iron supplements during the study period

- Breath-holding spells heredity patients
    - All patients with heredity for BHS in a first-degree or second-degree relative
- Cardiac disease heredity patients
    - All patients with heredity for relevant cardiac diseases or suspicion of the same disease, se footnotes to the management algorithm in Acta Paediatrica[1] for detailed information
- Simple and severe spells patients
    - Patients with simple and severe spells, defined by whether or not loss of consciousness occur
- Cyanotic, pallid and mixed spells patients
    - Patients with cyanotic or pallid spells, defined by the change of color in the face during spells. Mixed spells are defined as both types of color change in one patient in different spells or both cyanotic and pallid color change in the same patient during one spell
- Patients with severe spells and age above 24 months at onset
    - Patients with at least one severe spell AND age above 24 months at first symptom of ***typical*** BHS
- Patients with more than one spell in total
    - Patients with more than one spell in total, spells before and during the study period counted AND ***typical*** BHS
- Patients with a wrongful diagnosis or missed diagnosis of potentially dangerous disease
    - Patients diagnosed with or suspected to have BHS that were later (delayed diagnosis by at least 6 months) found to have another diagnosis for example epilepsy or long QT syndrome.
- Prematurely born patients
    - Patients born before 37+0 weeks gestation with special interest in patients with birth weight <2,5 kilos
- Patients with previous iron treatment or iron deficiency
    - Patients with anamnestic iron treatment or iron deficiency with treatment concluded before inclusion in the study and normal blood values if blood tests were taken
- Patients with early onset spells
    - Patients ≤3 months of age at first symptom of BHS
- Patients with an intake of cow's milk of more than 3 dl per day
    - Among all BHS-patients

Participant sex and co-morbidities will be documented but will not lead to exclusion or subgroup-analysis (only descriptive statistics).

Further analyses between more sub-groups might be performed depending on the data.

Missing data

Missing data will be quantified for each variable.

Patients lost during follow up can be included in analysis if all required data is collected. This will be thoroughly described in such cases (see Study protocol for timing of study assessments).

Interim analyses and data monitoring

No analyses of data are planned before complete data collection for that objective is complete. Please see in the Study protocol for timing of study assessments (indicating the first available time to analyze

data for the different objectives). We have specified in the ethical application as well as in the Participant information (to be handled out to the parent or legal guardian before signed consent) that we will not be able to interfere in the clinical management. If we find inconsistencies in the management or missed or wrongful diagnoses, we will not stop or interfere in the study. These patient's data will also be included in the analysis.

Clinical Laboratory Evaluations

Relevant blood tests in this study are:

- Hemoglobin count*
- MCV**
- Reticulocytes**
- Iron*
- TIBC*
- Transferrin saturation*
- Ferritin*
- CRP if signs of infection**

* normal range depending on age will be decided according to the range in the national PM for iron deficiency anemia in Sweden[2]
** normal range according to Analysportalen[3], the regional laboratory database

These blood tests should be taken in cases of typical breath-holding spells, according to our guidelines. Blood tests sampled before inclusion can not be taken into account. Blood tests may be delayed because of local routines (for example because of referral to another laboratory) or because of infection in the child. The blood samples should be collected within 2 weeks of the doctor's appointment (the decision that blood tests are necessary) and before the start of iron supplementation. Further tests for clinical control/follow up after start of iron supplementation are up to the treating physician and will be assessed according to the above.

Summary of study data

A list of variables can be found in the appendix.

Descriptive statistics

All continuous variables will be summarized using descriptive statistics: N (sample size), mean ± standard deviation, median (range). For categorical measures, the frequency and percentages will be reported. All summary tables will include any missing observations.

Exploratory data analysis

Boxplot, scatterplot and histogram with normal curve will be used to visualize normal distribution of variables within groups and look for outliers.

Hypothesis testing

Comparisons between groups

The groups are described above.

For comparison of means, independent samples t-test will be used. Non-parametric test: Mann-Whitney test will be used.

Proportions will be compared using Fisher exact test.

Repeated measurements

In some cases, it will be possible to compare outcomes in groups before and after intervention, in those cases paired samples t-test (parametric) or Wilcoxon signed rank test (non-parametric) will be used.

Correlation

Pearson correlation test will possibly be used, and in relevant cases regression analysis.

Level of statistical significance

In hypothesis testing, a p-value <0.05 will be considered significant.

Reporting conventions

The mean and standard deviation will be reported with one decimal greater than the original data. Median and range will be reported with the same number of decimals as the original data. P-values will be reported to three decimal places.

Statistical program

Descriptive statistics and hypothesis testing will be performed in STATA (Stata/BE 18.0) or newer versions.

References

1. 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
2. hematologi Vfp. Järnbrist och järnbristanemi - Riktlinjer för diagnostik, utredning och behandling. 2020.
3. LabmedicinSkåne. Analysportalen. Internet. Region Skåne. 2021. Accessed 1st of September, 2021. http://www.analysportalen-labmedicin.skane.se

Appendix

List of variables

For all participants	
General	Center included from If referral/referred: where and why
Initial Doctor´s visit, anamnesis	Current and previous diseases and conditions Current and previous medications Pregnancy and birth Heredity If previously sought medical care for same symptoms Onset of spells Total number of spells Spells during sleep or during activities in water Trigger Symptoms that precede the spells The course of the spell (change of color in the face, apnea, unconscious, seizure semiology, duration and if postictal) Interventions during spells Other symptoms Previous ECGs
Initial Doctor´s visit, physical examination (the minimum for the study)	Neurological examination (age appropriate) Heart auscultation Lung auskultation Look for signs of anemia or heart disease
Survey for doctors, at initial visit	Date of inclusion Location at inclusion Physicians name Assessment of physical status Assessment of type of spell (typical, non-typical, not breath-holding spells, can not differentiate) Decision on further investigations (according to guidelines or individual investigation, and more details on which investigations are completed or planned, as well as the interpretation of results) Decision on iron treatment (yes or no and why) Decision on follow up (planned or not)
Survey for caregivers, at initial visit	Sex Date of inclusion Location at inclusion Caregivers name and relationship to the participant Arrived by ambulance (yes or no) Heredity Born i gestational week (number) Current medical problems Current medications Previous iron deficiency, anemia or seizure disorders Current or previous iron treatment

	Diet Total number of spells Number of visits for the same symptoms Trigger Change of color in the face Apnea Uncontactable Unconscious Seizure semiology Focal or general seizure activity Duration Postictal symptoms
Survey caregiver, follow up at 3, 6, 12 and 36 months	Relationship to the participant Received other diagnosis that explains the symptoms? Spells during the last 3 months (yes or no) Treatment with iron (yes or no, compliance, if the treatment has affected the spell frequency or severity) Number of spells the previous month Total number of spells Uncontactable or unconscious (=severity of spells) Alterations in spell semiology? Diagnosed with other disease (that we could have missed) Further contact with healthcare (acute or planned) Space for comments Feed back on the survey

Variables relevant if heredity for heart disease or sudden death exist, or if the child had a severe spells and was older than 24 months of age at onset	
ECG module (medical files)	Machine interpretation, rhythm, QTc time (own calculation according to Bazetts formula)
Information in free text in the medical files	The physicians interpretations of performed investigations and diagnostic interventions

Variables relevant if the participant has more than one spell (at diagnosis or later)	
Blood samples – from the Lab module in the medical files	Hb, MCV, reticulocytes, iron, TIBC, iron saturation, ferritin. CRP if signs of infection.
Information in free text in the medical files and the prescription module	The physician's interpretation of blood sample results and iron treatment, if given.

Variables if the participants has non-typical spells	
Information in free text in the medical files, results in the lab module, radiology module and ECG module	The physician´s interpretations in free text in the medical files and any results of diagnostic

	interventions like EEG, ECG, radiology or blood samples.

Interview sub-study	
Background	Caregiver: Name Age Relationship to participant Profession Family situation
Level of knowledge about breath-holding spells	Their experience of the spells (where and when) Information from who and where What information has been given or found
Strategies for managing spells	Strategies to prevents spells (good and bad) Strategies to break spells (good and bad) Support and information they wish they had received from their health care provider Advise they would give to caregivers in the same situation
Consequences of spells	Spells at preschool Spells in dangerous situations Needed assistance or help during spells Conscequences of the spells for the caregiver