Brain & Development 37 (2015) 2–12

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Pacemaker in complicated and refractory breath-holding spells: When to think about it?

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Received 15 July 2013; received in revised form 2 February 2014; accepted 5 February 2014

Abstract

Background: Breath-holding spells (BHS) are benign non-epileptic paroxysmal events of infancy, rarely occurring with high frequency and complicated by prolonged syncope, convulsions and even status epilepticus. In these cases response to medical treatment is often unsatisfactory. Pacemaker implantation is a possible therapeutic option, but its indications, efficacy and complications have not been clarified yet. *Objective:* To report a new case of BHS treated with pacemaker and to review its indications and efficacy in patients with severe BHS. *Methods:* We extensively searched the literature in PubMed on cardiac pacing in patients with BHS and we described a new case. *Results:* A previously healthy boy presented at the age of 4 months with frequent BHS inconstantly associated to prolonged syncope and post-anoxic non-epileptic and epileptic seizures. Parental reassurance, iron supplementation and piracetam were ineffective. After cardiac pacing at the age of 16 months, BHS and their complications disappeared. We identified 47 patients with BHS treated with pacemaker in the literature. Based on the available data, in all patients asystole or marked bradycardia were documented during BHS or stimulating maneuvers; syncope complicated BHS in 100% of cases and post-anoxic convulsions in 78.3%. Medical treatment before pacing, when administered, was ineffective or poorly tolerated. After pacing, BHS complications disappeared in 86.4% of cases, and decreased in 13.6%. Technical problems with the device were reported in 25.7% of patients and mild medical complications in 11.4%. *Conclusions:* Pacemaker could be reasonably considered in subjects with frequent and severe BHS, poor response to medications, and demonstration of cardioinhibition during spells.

Keywords: Breath-holding spells; Pacemaker; Cardiac pacing; Asystole; Syncope; Reflex anoxic seizures; Post-anoxic convulsions; Post-anoxic convulsive epileptic seizures

1. Introduction

Breath-holding spells (BHS) are well-known benign non-epileptic paroxysmal events occurring in about 0.1–4.6% of healthy children with onset generally between 6 and 18 months of age [1]. BHS are usually elicited by provocation, pain or frustration and are clinically characterized by inconstant cry, apnea, change in skin color (cyanosis or pallor), brief loss of consciousness and of postural tone, with spontaneous resolution [1,2]. Iron-deficiency anemia [3–6] and a possible underlying genetically determined autonomic dysfunction [7–12] have been hypothesized in their pathogenesis.

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http://dx.doi.org/10.1016/j.braindev.2014.02.004
0387-7604/

The prognosis is excellent, with disappearance around school age and normal neurologic development [7].

Despite their benign nature, BHS may be complicated by prolonged loss of consciousness and in 15% of cases by the occurrence of non-epileptic post-anoxic convulsions as a consequence of relative cerebral ischemia or hypoxia due to marked bradycardia or asystole [7,13]. In rare cases, a prolonged and severe cerebral hypoxia may also precipitate true epileptic post-anoxic convulsive events and even status epilepticus [14,15].

Given their benign nature and favorable outcome, parental reassurance and counseling are the mainstay of therapy in non-complicated forms [7]. By contrast, in frequent or severe BHS several medications such as iron, piracetam, atropine, antiepileptic drugs and fluoxetine, have been used with variable results [3–6,16–20]. In rare complicated cases, refractory to parental counseling and medical treatment, pacemaker (PM) implantation has been considered a therapeutic option in the last two decades. Unfortunately, clinical indications, efficacy and complications of cardiac pacing have not been systematically studied in the population of children affected by complicated BHS yet.

The aim of the present study was to evaluate, through literature review and analysis of a personal case, the clinical indications to PM implantation in BHS, its efficacy and complications. The reported case is documented with video, EEG and ECG recordings.

2. Methods

The literature search was conducted through MEDLINE, using the following search term combinations without additional filters: "pacemaker" [All Fields] AND "breath-holding spells" [All Fields]; "cardiac pacing" [All Fields] AND "breath-holding spells" [All Fields]; "pacemaker" [All Fields] AND "reflex anoxic seizures" [All Fields]; "cardiac pacing" [All Fields] AND "reflex anoxic seizures" [All Fields].

We searched in all the identified cases a comprehensive set of clinical and instrumental data including gender, type of BHS (cyanotic, pallid or mixed), age at onset, frequency and severity of the episodes (occurrence of bradycardia, asystole, loss of consciousness, non-epileptic and epileptic convulsions), medical treatment, age at PM implantation, type of PM, follow-up, efficacy of the pacemaker on BHS and on their complications, and PM-related complications. When not available in the articles, we marked as "NR" the data not reported by the authors. In some reports information was available for a group of cases with no specification for each patient.

The classification of BHS type was based on the interpretation of the authors or on the description of the episodes in the original articles. The age at BHS onset and at PM implantation was reported as specified in the original papers, but in cases where the age could only be inferred by the text, it was reported at the best of our interpretation and marked with the symbol "≈". We regarded as clinical BHS complications episodes of loss of consciousness (LOC) and post-BHS convulsions; the latter were subspecified as anoxic non-epileptic seizures (ANES), anoxic epileptic seizures (AES) or status epilepticus (SE).

In order to classify the epileptic or non-epileptic nature of post-BHS convulsive phenomena, we considered as epileptic only the convulsive phenomena interpreted as such by the authors in the original papers, or the cases confirmed by ictal EEG. Criteria for classifying post-BHS motor phenomena as epileptic seizures were not specified in the original papers except for Horrocks and coworkers [15]. According to the currently accepted operative definition of status epilepticus [21], we regarded and listed as status epilepticus the epileptic seizures longer than 5 min.

Maximum length of asystole or bradycardia were reported by the authors in different clinical settings: during BHS, oculocardiac response, tilt testing, or cardiac monitoring. We searched for medications used prior to cardiac pacing, their efficacy and side effects, when available. The type of PM implanted (epicardial vs. endocardial; VVI vs. DDD) and the length of follow-up were also reported, if available in the original papers. Based on the efficacy of PM implantation, we identified the following outcome groups: BHS persistence, with cessation of BHS complications (A1); BHS persistence, with decreased BHS complications (A2); disappearance of BHS and of their complications (B1); decrease of BHS and disappearance of their complications (B2); not reported (NR).

3. Results

3.1. Case report

A previously healthy boy with family history of BHS (mother and maternal grandfather) presented at the age of 4 months with BHS occurring after mild provocation, such as undesired postural changes: the child cried vigorously, with subsequent apnea, marked pallor with perioral cyanosis and inconstant brief loss of consciousness. The frequency at onset ranged between 2 and 8 episodes monthly (most often 2 per month, with higher frequency observed during febrile infective illnesses).

Since the age of 12 months BHS frequency increased up to 2–3 per day, with lowering triggering threshold; beside the usual spells, parents reported also some episodes of BHS followed by a prolonged phase (up to 15 min) described as characterized by decreased consciousness and sometimes purposeless limbs movements and inconstant trismus followed by subsequent deep and protracted sleep.