Successful Treatment of Pallid Breath-Holding Spells With Fluoxetine

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ABBRévIATION
PBH—pallid breath-holding

Dr Walsh was involved in data collection and primary manuscript writing; Dr Knilans, Director of Electrophysiology, was responsible for concept of using fluoxetine in this patient population and was integral in manuscript revision and data analysis; Dr Anderson was responsible for revision of manuscript; and Dr Czosek, senior author, was responsible for the concept of the manuscript, data collection, and manuscript creation.

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abstract

Pallid breath-holding (PBH) is a childhood condition that presents with recurrent syncope. Although typically benign, severe cases can lead to asystole and anoxic seizures. Previous studies have advocated pacemaker placement to abbreviate symptoms. This was a retrospective study of patients treated with fluoxetine for PBH spells. Clinical response, side effects and avoidance of pacemaker implantation were reviewed in six patients (12–60 months) treated with fluoxetine for PBH. Patients were referred because of concern of arrhythmia and failed medical treatment strategies. Two patients had previously implanted loop recorders, 5 patients had documented episodes of asystole, and 2 patients had generalized seizures. Fluoxetine resulted in alleviation of syncope in 5 of 6 patients. Time to symptomatic improvement symptoms ranged from 2 days to 1 month (median, 2 weeks). Median duration of treatment with fluoxetine was 12 months (12–24 months). One patient demonstrated no improvement and had a pacemaker implanted. There were no reported side effects to fluoxetine. Fluoxetine can be used to treat childhood PBH spells and may obviate the need for permanent pacing in a significant subset of this population. Considering its safe side-effect profile it is a worthwhile first-line agent to treat this disorder. Pediatrics 2012;130:e685–e689
Pallid breath-holding (PBH) is a childhood condition that presents with recurrent syncope associated with a distinct set of emotional triggers. Syncopal episodes during PBH may be associated with anoxic seizures and are thought to be secondary to autonomic dysregulation leading to profound bradycardia or asystole. Treatment of PBH can be challenging predominantly because most medical therapies are ineffective. In the majority of patients with PBH, symptoms can be managed by parental counseling, although, in more severe or refractory cases, medical interventions maybe appropriate. Previous studies have advocated for placement of permanent pacing systems to alleviate clinical symptoms in severe cases of PBH defined as “complex cases with severe and frequent spells that are unresponsive to medication and are associated with seizures, life-threatening bradycardia or asystole.” Although these studies have demonstrated improvement in clinical symptomatology, permanent pacing in this cohort is not without significant morbidity and complications.

In an effort to avoid permanent pacing, we have attempted treatment of patients referred for severe PBH with fluoxetine before pacemaker implantation. Similar to patients with autonomic dysregulation resulting in neurocardiogenic syncope, we anticipated that fluoxetine might be a safe and effective treatment of PBH and may obviate the need for permanent pacing to obtain adequate symptomatic relief.

METHODS

This case series was conducted with approval of the Institutional Review Board at Cincinnati Children’s Hospital Medical Center (1010-1267). All patients were referred for cardiovascular evaluation of severe PBH between 2001 and 2010. In addition to a retrospective review of medical records, an attempt was made to contact each of the patients for purposes of long-term follow-up.

RESULTS

Seven patients were identified with PBH spells that had been treated with fluoxetine. One patient was not able to be contacted, and there was insufficient documentation to determine outcome; this patient was not included in the evaluation. (Table 1)

All patients were referred to cardiology after failed medical management. Because differentiation of PBH from other potentially life-threatening mechanisms of cardiac syncope is of the utmost importance, all patients were thoroughly questioned with regard to family history of syncope, arrhythmias, and sudden cardiac death. No patient had any family history of significant arrhythmias, cardiomyopathy, ion-channelopathy, or familial sudden cardiac death in individuals under the age of 30 years. All 6 patients had documented episodes of either asystole or profound bradycardia during PBH episodes (Fig 1). Two patients had previously implanted loop recorders; however, no patients had undergone implantation of a permanent pacing system. One patient had documented bradycardia induced torsade de pointes (Fig 2). This patient had a normal QTc interval on baseline electrocardiogram, and no family history concerning for long-QT syndrome. Four patients were unsuccessfully treated with alternate medications for PBH episodes: 2 were treated with propranolol, 1 with carbamazepine, and 2 with glycopyrrolate. One patient had a PBH spell followed by asystole and seizure activity on EEG and was prescribed phenobarbital. Patients were commenced on a dose of between 1 and 4 mg once daily, depending on their weight and age, and titrated for effect. In 2 cases, the dose was increased from 2 to 4 mg in 1 patient, and from 4 to 6 mg in another patient. In one of these cases the increased dose resulted in resolution of PBH symptoms that had been incomplete before the increase in dosage. The duration of treatment in the study ranged from 1 to 2 years.

Median age at the time of follow-up was 7 years. Fluoxetine was successful in decreasing the frequency of the breath-holding episodes in 5 of 6 cases according to parental and medical reports. In 3 cases, there was complete resolution of PBH episodes. Two parents reported occasional breath-holding episodes, albeit much less severe and less frequent than previously. Most reported that their child would appear to have the prodromal symptoms of a PBH spell, but they would recover without having a syncopal event. Improvement in clinical symptomatology was typically seen from 48 hours to 2 weeks, although, in 1 case, improvement was not seen until 1 month after treatment was commenced.

Fluoxetine was tolerated well in all patients. One parent reported a mildly decreased appetite, and another parent reported mild tremors in their child. These symptoms improved a couple of weeks after the initiation of fluoxetine treatment. The duration of treatment with fluoxetine was from 1 to 2 years, at which time improvement in symptoms prompted discontinuation of fluoxetine without subsequent adverse effects. None of the parents of the 5 successfully treated patients reported any ongoing symptoms at the time of study follow-up.

DISCUSSION

Pallid breath-holding is associated with recurrent syncope and often anoxic seizures. This study demonstrates that, within a small cohort of pediatric patients, fluoxetine can be used successfully to treat PBH spells. In total, 5 of the 6 patients in this study were successfully treated with fluoxetine and avoided...
The implantation of a permanent pacing device is the first description of the use of fluoxetine in the treatment of PBH. The term PBH is in itself a misnomer, because syncope episodes are not necessarily associated with breath-holding. This is an important delineation because failure to recognize these spells as PBH in etiology can lead to erroneous diagnosis of more concerning and potentially lethal primary arrhythmic disorders. As seen in this small cohort of patients, concern for possible primary arrhythmic etiologies led to the erroneous diagnosis of congenital long-QT syndrome in 1 patient and to implanted loop recorders in 2 patients.

In response to the severity of clinical symptoms and failed medical treatment strategies, permanent pacing has been advocated for symptomatic relief. A previous retrospective analysis by Kelly et al. published a series of 10 patients who underwent permanent pacemaker implantation for severe PBH episodes. Age of implant in these patients was 10 months to 5 years; 1 epicardial and 9 endocardial pacemakers were implanted. These patients were of similar ages and had clinical symptomology similar to our cohort. Also similar to our findings, treatment with a variety of medical therapeutic strategies had failed in the patients in this study, although no patients were treated with serotonin reuptake inhibitors. Clinical response to permanent pacing was favorable, although complication rates were high. Two patients required lead reimplantation for lead capture failure, 1 patient underwent pacemaker lead capture failure, and 1 patient underwent pacemaker lead retraction and end of battery life. Despite a relatively high complication rate, the authors conclude that permanent pacemaker therapy for children with PBH spells

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at PBH Onset, mo</th>
<th>Age at Fluoxetine Initiation, mo</th>
<th>Patient Symptoms</th>
<th>Treatment Before Fluoxetine</th>
<th>Seizures</th>
<th>Initial Fluoxetine Dose, mg</th>
<th>Maximum Dosage, mg</th>
<th>Side Effects of Fluoxetine</th>
<th>Age at Follow-up</th>
<th>Clinical Course After Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>24</td>
<td>30</td>
<td>Cyanosis, syncope, loop recorder implantation with 5.7-s asystolic pause</td>
<td>Propranolol, loop recorder; home automatic defibrillator</td>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>5</td>
<td>Symptomatic improvement &lt;48h, 1 episode while on fluoxetine</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>6</td>
<td>10</td>
<td>Cyanosis, loss of consciousness, 10-s asystolic episode</td>
<td>Atenolol, atropine, pacemaker discussion</td>
<td>No</td>
<td>1</td>
<td>4</td>
<td>Decreased appetite</td>
<td>7</td>
<td>Clinical improvement in 2 wk with no episode after initiation of fluoxetine</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>18</td>
<td>55</td>
<td>Cyanosis, seizure activity, 16-s documented asystolic pause</td>
<td>Glycopyrrolate, complete activity restriction</td>
<td>No</td>
<td>4</td>
<td>6</td>
<td>Mild tremors</td>
<td>9</td>
<td>Clinical improvement in 2 wk with no episode after initiation of fluoxetine</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>12</td>
<td>43</td>
<td>Anoxic seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>12</td>
<td>22</td>
<td>Syncope, 10-s asystolic episode</td>
<td>Tegretol, glycopyrrolate</td>
<td>No</td>
<td></td>
<td>3</td>
<td>None</td>
<td>7</td>
<td>Clinical improvement in 4 wk with rare episodes while on fluoxetine</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>4</td>
<td>24</td>
<td>Daily episodes of syncope, asystolic episode with associated self-resolving torsade de pointes</td>
<td></td>
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**TABLE 1 Demographics of Patients Treated With Fluoxetine for Breath-Holding Episodes**

- **Patient Symptoms**: Seizures, initial fluoxetine dose, maximum dosage, side effects of fluoxetine, age at follow-up, clinical course after fluoxetine.

- **Seizures**: Yes/No, if yes, details of seizures.

- **Initial Fluoxetine Dose, mg**: Initial dose of fluoxetine.

- **Maximum Dosage, mg**: Maximum dose of fluoxetine.

- **Side Effects of Fluoxetine**: Details of side effects.

- **Age at Follow-up**: Age at follow-up.

- **Clinical Course After Fluoxetine**: Clinical course after fluoxetine treatment.
associated with severe bradycardia is safe, efficacious, and warranted. It has been well documented that morbidity associated with permanent pacing systems in pediatrics is associated with an increased risk of complication and device failure compared with adult cohorts. Similarly, in our study, the single patient who underwent pacemaker implantation also had a significant complication that resulted in conversion from a transvenous to an epicardial system secondary to development of a pericardial effusion. Although permanent pacing is an efficacious and relatively safe treatment modality, because of its relatively high rate of associated complications, an effective medical treatment option may have a significantly improved risk/benefit profile.

Previous studies by DiMario and Burleson and Shore and Painter described the mechanistic underpinning in patients with PBH to be associated with abnormal blood pressure and heart rate responses with postural change, implying autonomic dysregulation similar to neurocardiogenic syncope. Although the link between these 2 disorders is not well delineated, it is likely that they share similar underlying pathophysiological mechanisms and, in turn, may respond to similar treatment modalities. Several previous studies have evaluated the utility and potential treatment mechanisms of fluoxetine for neurocardiogenic syncope. These previous studies have shown that central serotonin-mediated mechanisms participate in cardiovascular hemodynamic regulation by inhibiting the sympathetic nervous system. In neurocardiogenic syncope, lower levels of serotonin production have been postulated to increase the postsynaptic receptor density causing a hypersensitivity response. Increasing serotonin levels by use of a selective serotonin reuptake inhibitor such as fluoxetine may prevent this aforementioned compensatory response. Fluoxetine has been shown to be effective in treating adult patients with neurocardiogenic syncope and more effective than β-blockers in treating presyncope. We postulate that the mechanism of action in breath-holding episodes in similar to that seen in neurocardiogenic syncope.

**FIGURE 1**
Telemetry rhythm strip recordings from implanted loop recorders in 2 patients with PBH. A, Patient 1 rhythm strip demonstrates profound bradycardia followed by a 5.7-second asystolic pause. Telemetry correlates with clinical PBH spell. B, Patient 5 rhythm strip demonstrates abrupt bradycardia followed by a pause in excess of 10 seconds.

**FIGURE 2**
Electrocardiogram rhythm strip of bradycardia induced torsade de pointes in Patient 6. At the beginning of the tracing, there is sinus bradycardia followed by a period of asystole and a brief episode of bradycardia-induced torsade de pointes that is self-terminating followed by asystole.
In this small cohort, clinical improvement was similar to previous reports with pacemaker implantation. In total, 5 of the 6 patients were able to avoid implantation of a permanent pacing device; 2 patients had complete resolution of symptoms and 2 additional patients had significant improvement in symptomatology. In the 1 patient who went on to have permanent pacing, only a short attempt of fluoxetine was tried before device implant secondary to previously documented bradycardia-induced torsade de pointes.

In all cases, fluoxetine was well tolerated, which is consistent with published pediatric data. Initial symptoms of decreased appetite and tremors that occurred in 2 patients were transient. Interrogation of previously implanted loop recorders did not demonstrate any episodes of prolonged asystole after initiation of fluoxetine. Upon patient follow-up, all of the successfully treated patient families, parents who were interviewed would have recommended the treatment to other patients with a similar condition, and no patients were found to have ongoing symptoms. Whether this patient population is at risk for more typical symptoms of neurocardiogenic syncope as they enter adolescence is yet to be determined.

There are several significant limitations in this analysis. First, because of the retrospective nature of the study, direct therapeutic causality or identification behind the potential mechanism of treatment seen with medical therapy could not be inferred, and no control group was available. Second, all of the patients in this cohort had severe clinical symptomatology and were all referred after failed medical treatment by previous subspecialty services. The external validity of this small cohort and whether these results can be extrapolated to patients with less severe symptoms cannot be determined. With these limitations in mind, permanent pacing may continue to play an important role in patients with severe PBH, although considering the higher potential for complications and relatively short duration of symptomatology seen in children with PBH, it is our belief that pacemaker insertion should only be considered after a trial of fluoxetine. Furthermore, given the relative safety and efficacy seen in this small proof-of-concept cohort, fluoxetine can be an important treatment option in the therapeutic arsenal in this complex patient population.

**CONCLUSIONS**

Fluoxetine can be used to treat childhood PBH spells and may obviate the need for permanent pacing in a significant subset of patients with severe PBH. Considering its safe side-effect profile and efficacy seen in this small patient cohort, it may be used as a first-line agent to treat this disorder. Further studies will be required to evaluate its external validity to a larger population and potentially less severe cases of pediatric patients with PBH.

**REFERENCES**

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