

Breath Holding Spells – A Tale of 50 Years

PREETI SINGH AND *ANJU SETH

Department of Pediatrics, Lady Hardinge Medical College, New Delhi, India. *anjuseth.peds@gmail.com

August 1965 issue of Indian Pediatrics comprised of 36 pages with three research papers, four case records, a synopsis of current literature and notes/news. Amongst these, we zeroed down on an original research article on breath holding spells (BHS). BHS is a common behavioral disorder of early childhood associated with a lot of parental anxiety, besides carrying a potential for misdiagnosis.

THE PAST

Historical background and past knowledge:

The earliest reference to BHS, then referred to as infantile form of temper tantrums or infantile syncope, were made by Rillet and Barthezin in 1843, and by Meigsin in 1848. Subsequently in the 20th century, various authors published their clinical viewpoints on its pathophysiology and prognostic significance. Based on the color change demonstrated by the child during the spell, BHS were classified as cyanotic, pallid and mixed. Till the 1960's, despite several hypotheses, the pathophysiology and etiology remained largely nebulous and uncertainties existed regarding the outcome.

Multiple factors like disturbed parent-child relationship, hereditary autonomic instability, self asphyxiation, decreased cerebral blood flow secondary to increased intrathoracic pressure due to spontaneous valsalva manoeuvre and altered cerebral mechanism secondary to various stimuli were implicated for cyanotic BHS [1]. For the pallid form, circulatory failure secondary to asystole leading to cerebral anoxia was considered the most probable hypothesis [2].

The striking association of anemia with BHS was first reported in 1963 by Halowach and Thurston [3]. It was hypothesized that the low hemoglobin causes rapid cerebral anoxia due to decreased oxygen carrying capacity of blood that in turn leads to the BHS. It was also

thought that the anemic children being irritable may be more predisposed to BHS.

The reported article: The publication by Chandra, *et al.* [4], reported in August 1965 issue of *Indian Pediatrics*, was one of the earliest to demonstrate association between BHS and anemia [4]. This study was carried out in Chandigarh with the objective of assessing the hemoglobin levels in children with BHS (referred to as 'breath holding attacks'), and determining the therapeutic role of iron in its management. Authors studied 133 children with history of BHS to estimate the

presence, degree and the type of anemia. A control group comprising of 46 healthy children, 23 children with epilepsy and 16 infants with febrile convulsions were also enrolled. The level of hemoglobin was compared between the study and control groups. Of the cases with BHS, 46 were treated with oral hematinics while 40 received placebo. These two groups were matched for baseline characteristics including age, duration of symptoms, initial hemoglobin level and nutritional status. The frequency and severity of BHS was monitored for 12 weeks.

The authors reported that the children with BHS had significantly lower hemoglobin as compared to the control groups. Among the study group, 86 children had hemoglobin between 4-9.9 g/dL with evidence of microcytic hypochromic anemia on peripheral smear, while 6 children had dimorphic anemia. Thirty-nine of 46 children who received oral iron (and folic acid for the 6 children with dimorphic anemia), demonstrated partial to complete response in BHS as judged by reduction in frequency and severity of episodes after 12 weeks of treatment as compared to placebo group where only 15 of 40 children reported similar relief. The results were reported to be statistically significant.

In addition to reporting on a newly emerging



association of BHS with anemia, this study was amongst the early studies to demonstrate and support the therapeutic role of iron in management of children with BHS. Subsequently the association of iron status with BHS was consistently demonstrated by other authors. It was also shown that iron therapy showed a more remarkable therapeutic benefit in controlling the spells in children with evidence of iron deficiency [5].

THE PRESENT

BHS is a fairly common entity reported in 4-5% of the pediatric population. A positive family history in 20-30% cases points towards a possible genetic predisposition. Dysregulation of the autonomic nervous system is hypothesized as the most plausible mechanism responsible for its occurrence [6]. The more common cyanotic form is considered to be due to inhibition of respiratory effort due to autonomic instability, or intrapulmonary shunting as a result of abnormal pulmonary reflexes. Pallid spells are considered to be caused by an exaggerated vagal response to noxious stimuli leading to bradycardia or a brief asystole which in turn produces cerebral hypoperfusion. Children with pallid spells are more prone to vasovagal syncope as adolescents or adults. A recent case control study from Turkey reported maturation delay in myelination of the brainstem as assessed from the inter-peak latencies on brainstem auditory evoked potential as the cause of breath-holding spells [7].

Iron has role as a cofactor in catecholamine metabolism in central nervous system [6]. It is thought that interaction of cerebral erythropoietin, nitric oxide and interleukin-1 may be responsible for clinical profile and hematological associations of BHS [8]. It is now well established that a trial of iron therapy is beneficial in reducing the frequency of BHS, especially in children with laboratory evidence of anemia. However, not all children with BHS have iron deficiency at baseline, and some children without anemia also respond to iron therapy as there may be a relative deficiency of iron stores and distribution rather than a depletion of the total amount of body iron [9].

Diagnosis of BHS remains primarily clinical, based on suggestive history with a normal physical and nervous system examination. There is no change in basic management of BHS which comprises chiefly of parental counseling and reassurance. Treatment with iron is recommended in children with iron deficiency anemia and a trial can be considered even without its presence [10]. Some cases of prolonged asystole associated with frequent and severe pallid spells have been treated with atropine or scopolamine to antagonize vagal

hyperactivity. Refractory cases have benefited from implantation of cardiac pacemaker [11]. Recently, evidence for safe and effective use of piracetam, especially in hyperactive children, to control BHS has emerged but it still lacks FDA approval [12]. Individual case studies have used drugs like glycopyrrolate, theophylline (positive chronotropic effects and capacity to stimulate the medullary respiratory center), fluoxetine, and levetiracetam but larger robust studies documenting their safety and efficacy are not available. There have been no trials to compare the efficacy of different drugs or their combined effect in controlling BHS.

To summarize, pathophysiology of breath holding spells is clearer since the publication of this article. The role of iron in its treatment has got well established and newer drugs have found a role in management of severe and refractory cases.

REFERENCES

1. Lombroso CT, Lerman P. Breath holding spells (cyanotic and infantile syncope). *Pediatrics*. 1967;39:563-81.
2. Gastaut H, Fischer Williams M. Electroencephalographic study of syncope, its differentiation from epilepsy. *Lancet*. 1957;2:1018.
3. Holowach J, Thurston DL. Breath holding spells and anemia. *New Engl J Med*. 1963;268:21.
4. Chandra RK. Association of breath-holding attacks with anemia and their treatment. *Indian Pediatr*. 1965;2:295-7.
5. Daoud AS, Batieha A, Al-Sheyyab M, Ebuekteish F, Hijazi S. Effectiveness of iron therapy on breath-holding spells. *J Pediatr*. 1997;130:547-50.
6. DiMario FJ, Burleson JA. Autonomic nervous system function in severe breath-holding spells. *Pediatr Neurol*. 1993;9:268-74.
7. Vurucu S, Karaoglu A, Paksu SM, Oz O, Yaman H, Gulgun M, *et al*. Breathholding spells may be associated with maturational delay in myelination of brain stem. *J Clin Neurophysiol*. 2014;31:99-101.
8. Masuda S, Okano M, Yamagishi K, Nagao M, Ueda M, Sasaki R. A novel site of erythropoietin production: Oxygen-dependent production in cultured rat astrocytes. *J Biol Chem*. 1994;269:19488-93.
9. Mocan MC, Mocan H, Aslan Y, Erduran E. Iron therapy in breathholding spells and cerebral erythropoietin. *J Pediatr*. 1998;133:583-4.
10. Zehetner AA, Orr N, Buckmaster A, Williams K, Wheeler DM. Iron supplementation for breath-holding attacks in children. *Cochrane Database Syst Rev*. 2010;5:CD008132.
11. Kelly AM, Porter CJ, McGoan MD, Espinosa RE, Osborn MJ, Hayes DL. Breath-holding spells associated with significant bradycardia: Successful treatment with permanent pacemaker implantation. *Pediatrics*. 2001;108:698-702.
12. Sawires H, Botrous O. Double blind, placebo-controlled trial on the effect of piracetam on breath-holding spells. *Eur J Pediatr*. 2012;171:1063-7.