

Evaluating the brainstem in children with breath-holding spells

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ABSTRACT

OBJECTIVE: Breath-holding spells (BHSs) are a non-epileptic paroxysmal phenomenon characterized by frequent apnea episodes, loss of consciousness, and changes in skin tone and postural tone triggered by negative stimuli of childhood. The pathophysiology of the disease remains unclear; autonomic dysregulation caused by delayed myelination is believed to play a role. In this study, we aimed to evaluate the brainstems of children with BHS using diffusion tensor imaging (DTI) and investigate the etiology of this phenomenon.

METHODS: The study group consisted of 16 children with a history of severe breath-holding episodes (accompanied by loss of consciousness and tonic contraction due to prolonged anoxic response) and 18 age-, gender-, and handedness-matched controls. All children underwent systemic, neurologic, and cardiologic evaluation, including complete blood count, blood biochemistry, serum iron and ferritin level, serum vitamin B12 level, electrocardiogram, and electroencephalograms. Magnetic resonance imaging was performed using a 1.5-Tesla Siemens Aera scanner (Siemens, Germany).

RESULTS: Evaluation of brainstem (midbrain, pons, and medulla oblongata) volumes revealed no statistically significant differences between the BHS patient and control groups. In a voxel-wise analysis of DTI data, the BHS patient group had significantly lower fractional anisotropy (FA) values than the control group in the bilateral midbrain and medulla, right corticospinal tract, bilateral corpus callosum body and splenium, and left corpus callosum genu. In contrast, there were no significant differences in FA values in the pons, cerebellum, left corticospinal tract, and right corpus callosum genu.

CONCLUSION: Based on our findings, we think that patients with BHS should be treated with an approach similar to other neurodevelopmental diseases and that this study may help elucidate the pathophysiology and establish the groundwork for future studies on its treatment.

Keywords: Brainstem; breath-holding; child.

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Breath-holding spells (BHSs) are a non-epileptic paroxysmal phenomenon characterized by frequent apnea episodes, loss of consciousness, and changes in skin

tone and postural tone triggered by negative stimuli in childhood. BHS is classified as cyanotic and pallid. The cyanotic type is triggered by anger, sudden fear, or crying



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due to pain and is characterized by sudden cessation of crying, development of tonic posture followed by apnea, decreased muscle tone, and occasionally loss of consciousness. The pallid type is characterized by pallor following mechanical or emotional trauma, opisthotonus, urinary incontinence, bradycardia, and short-term asystole. Loss of consciousness/tone and rarely convulsions can be seen due to prolonged cerebral hypoxia [1–5]. Although less common in developed countries, the prevalence is 4% to 27% among children between 6 months and 6 years of age (most common at 6–18 months) in different studies [6, 7]. Boys are more frequently affected than girls [1–5, 8].

BHS is primarily attributed to cerebral anoxia secondary to autonomic dysregulation that leads to altered cardiac function and subsequent reduction in cerebral blood flow. Differences in the sequence of events and color changes between cyanotic and pallid BHS might be related to the dominant autonomic dysregulation component, sympathetic overactivity in cyanotic, and parasympathetic in pallid BHS [1–5, 9].

The pathophysiology of the disease remains unclear; however, due to factors such as spontaneous regression with age and positive family history in 25–30% of cases, autonomic dysregulation caused by delayed myelination is believed to play a central role. There are conducted many etiological studies that indirectly demonstrate brainstem myelination [1–5].

Advances in magnetic resonance imaging (MRI) technology have enabled the evaluation of brain myelination, brain metabolites, and non-structural white matter changes. Diffusion tensor imaging [DTI] is a non-invasive conventional MRI technique that recently gained popularity among clinicians and researchers to examine the organization of white matter in the developing brain by providing information on the subvoxel microstructure through measuring water diffusion within white matter regions and tracts [10].

DTI by providing reproducible quantitative measures such as fractional anisotropy (FA) by detecting water diffusion direction. FA represented as the index value of white matter organization in the brain, which varies between 0 and 1, with 0 being perfectly isotropic and 1 being perfectly anisotropic diffusion [11–13]. Therefore, it can represent an index of the structural integrity of white matter [10, 14]. Anomalous development of white matter bundles components, particularly axons, can reduce FA values, reflecting less directed diffusion. In this study, we aimed to evaluate the

Highlight key points

- Breath-holding spells (BHSs) should be evaluated with an approach similar to other neurodevelopmental diseases.
- There may be a difference in brain structures in patients with BHS, as in other neurodevelopmental diseases, and that BHS should be addressed in this respect.
- The evaluation of region-specific myelination revealed that myelination was retarded in the midbrain and medulla. We also examined not only the brainstem but also other parts of the brain.

brainstems of children with BHS using DTI MRI and investigate the etiology of these episodes.

MATERIALS AND METHODS

The study group consisted of 16 children with a history of severe BHS episodes (accompanied by loss of consciousness and tonic contraction due to prolonged anoxic response) and 18 age, gender, and handedness matched controls. Informed consent was obtained from the guardians. The study was approved by the Erciyes University, Faculty of Medicine Clinical Research Ethics Committee (date: 25.11.2015; no: 2015/490). The research was carried out in accordance with the conditions of the declaration of Helsinki Ethics Principles.

BHS was diagnosed based on the presence of color change in the face and abdomen, loss of consciousness, and tone change following a brief episode of stiffening and apnea with an open mouth occurring after provocation. Inclusion criteria for the BHS patients were normal neurological and systemic examination and normal growth and development, with no concomitant systemic or neurodevelopmental disease (mental retardation, tic disorder, attention deficit hyperactivity, etc.), chronic drug use, or history of head trauma.

Control subjects were selected from healthy children. Inclusion criteria were normal MRI and no diagnosed pathology or history of cyanotic and pallid BHS. None of the children in the study was receiving medical treatment.

All children underwent systemic, neurologic, and cardiologic evaluation, including complete blood count, serum iron and ferritin level, serum vitamin B12 level, electrocardiogram (ECG), and electroencephalograms. Laboratory results were described as normal, low, or high according to their age-specific reference ranges. They were evaluated with Denver Developmental Screening Test II.

TABLE 1. Comparison of hemoglobin, iron, ferritin, and vitamin b12 levels between the patient and control groups. Data are expressed as mean±standard deviation

	Patients (n=16)	Controls (n=18)	t-value	p
Hemoglobin	11.75±0.97	12.23±0.65	1.672	0.107
Iron	38.92±4.59	41.68±4.89	1.708	0.100
Ferritin	28.25±7.35	32.41±6.98	1.694	0.102
Vitamin B 12	352.62±70.8	359.8±136.6	0.202	0.847

Neuroimaging was performed using a 1.5-Tesla Siemens Aera scanner (Siemens, Germany). Structural images were acquired using a T1-weighted 3D magnetization prepared rapid gradient echo sequence in the sagittal plane, using these parameters: echo time (TE) / repetition time =1900 ms/2.84 s, flip angle =5, acquisition matrix =256×256, field-of-view [FOV] =280 mm², number of slices =160, and slice thickness =1.0 mm.

A twice-refocused spin-echo sequence based on single-shot echo-planar acquisition was used as the DTI sequence. Balanced diffusion gradients were applied along 20 orthogonal directions using b values of 0 and 1000 s/mm², and other parameters were: TR=3500 ms, TE=83 ms, FOV=230 mm², matrix=128×128, and slice thickness=3.5 mm. The acquisition time per dataset was approximately 4 min. The original raw data were transferred from the scanner in DICOM format and anonymized.

In DTI and volume processing, we used MriCloud (www.mricloud.org) to calculate diffusion parameters. To calculate the volumes of intracranial structures, processing was performed using volBrain (v.1.0, <http://volbrain.upv.es>), a free online MRI brain volumetry system. volBrain uses a fully-automated segmentation technique, in which the algorithm is based on multi-atlas patch-based label fusion segmentation technology.

The DTI datasets were first transferred to a Windows platform computer and were further processed offline using MriStudio (www.mristudio.org) [15].

MriStudio has become widely used in neuroimaging studies of MRI and DTI data [15–17] which consists of three programs: DtiStudio, DiffeoMap, and ROIEditor [18–20]. DtiStudio is a package for the visualization and processing of diffusion MRI data. ROIEditor uses the results of DiffeoMap to perform image analysis concerning a single atlas both at the voxel and regional level [19, 20].

Statistical Analysis

Histogram and q-q plots were assessed and Shapiro–Wilk’s test was performed to test the normality of data distributions. Differences between patient and control brain part volumes were analyzed using an independent-samples t-test. Statistical analysis was performed using the IBM SPSS software v23 (IBM SPSS Statistics for Windows, Version 23, Armonk, NY, USA) with p-value less than 0.05 considered statistically significant.

RESULTS

The study included a total of 34 subjects (16 children with BHS and 18 healthy controls). The mean ages of the study and control groups were 1.93±1.22 and 2±1.94 years, respectively. The study group consisted of 9 (56.3%) boys and 7 (43.8%) girls, and the control group consisted of 10 (55.5%) boys and 8 (44.5%) girls. There was no significant difference between the groups in terms of gender or age (p=0.837, p=0.847). In addition, there was no statistically significant difference in hemoglobin or serum vitamin B12 level in the patient group when compared with the control group. Serum ferritin and iron levels were lower in the BHS patients than in the control group, but the difference was not statistically significant (p=0.102, p=0.100) (Table 1). All patients and controls had normal electroencephalography and ECG findings.

Evaluation of brainstem volumes revealed no statistically significant differences between the BHS patient and control groups in the volume of the midbrain, pons, or medulla oblongata (p>0.05). Mean cerebellum volume was 97489.63 mm³ in the study group and 178558.06 mm³ in the control group (p=0.03) (Table 2).

In a voxel-wise analysis of DTI data, the BHS patient group had significantly lower FA values than the control group in the bilateral midbrain (p=0.010 right, p=0.008 left) and medulla (p=0.001 right, p=0.002 left), right corticospinal tract (p=0.009), bilateral corpus callosum corpus (p=0.042 right, p=0.005 left), and splenium (p=0.003 right, p=0.008 left), and left corpus callosum genu (p=0.020). In contrast, there were no significant differences in FA values in the pons (p=0.550 right, p=0.525 left), cerebellum (p=0.570 right, p=0.295 left), left corticospinal tract (p=0.219), and right corpus callosum genu (p=0.067 right) (Table 2).

TABLE 2. Comparison of brain part volumes between the patient and control groups. Data are expressed as mean±standard deviation

	Patients (n=16)	Controls (n=18)	p
Midbrain	9787.12±4006.69	10910.22±5663.45	0.506
Pons	13567.38±19319.11	8440.8333±5630.83	0.144
Medulla	2703.69±1985.49	3393.9444±2244.3	0.348
Brainstem	25150.25±17886.6	23109.00±11662.86	0.701
Cerebellum	97489.63±47113.11	178558.06±93500.23	0.003

TABLE 3. Mean fractional anisotropy values by region and group

	Patients (n=16)		Controls (n=18)		p
	Right	Left	Right	Left	
Mesencephalon	0.2789	0.3011	0.3204	0.3426	0.010 (right) 0.008 (left)
Pons	0.2355	0.2813	0.2195	0.2693	0.550 (right) 0.525 (left)
Medulla	0.3066	0.2948	0.3548	0.3413	0.001 (right) 0.002 (left)
Cerebellum	0.2082	0.2061	0.2114	0.2107	0.570 (right) 0.295 (left)
CC splenium	0.5045	0.4977	0.5524	0.5436	0.003 (right) 0.008 (left)
CC corpus	0.4131	0.4121	0.4539	0.4732	0.042 (right) 0.005 (left)
CC genu	0.4958	0.5070	0.5275	0.5419	0.067(right) 0.020 (left)
CST	0.3874	0.4206	0.4409	0.4597	0.009 (right) 0.219 (left)

FA: Fractional anisotropy index; CC: Corpus callosum; CST: Corticospinal tract.

DISCUSSION

BHS often occurs in the first 2 years of life and disappears spontaneously before school age. It has a good prognosis, and major complications such as cerebral hypoxemia due to severe attacks and loss of consciousness accompanied by opisthotonic posture is rarely observed. Concomitant seizures are reported in 0% to 4.8% of cases, and the frequency of neurodevelopmental abnormalities is 3.6% [1–5]. Our patients had normal neurological findings and exhibited no neurodevelopmental delays. Consistent with the literature, boys predominated in our study group (56.3%).

Antioxidant-oxidant imbalance and deficiencies of trace elements such as zinc, iron, and selenium are thought to predispose to autonomic dysfunction which can cause BHS [9, 21]. There were established relations between the deficiency combination of trace elements (especially zinc) and iron with the pathogenesis of BHS [21]. It has been observed that the frequency of fetal iron deficiency anemia is higher in patients with BHS [1–9]. As no other types of anemia have been linked to BHS in the literature, the problem seems to be related to iron and not anemia [1]. The mean serum iron concentration was lower in the BHS patients in

this study than in the healthy controls, but the statistical analysis did not reveal a significant difference.

Different cellular mechanisms, including myelin volume, axonal cell membrane integrity, and building of axon bundles affect FA value (coherent organization-higher and the crossing of bundles-lower FA). With the increase in the myelin volume (e.g., during brain development), FA value also increases and vice versa (e.g., during demyelination as in multiple sclerosis). At the same time, myelination and high FA value seen across the developing brain, focal increases can also be seen during childhood and adolescence [22]. In neurodevelopmental and psychiatric conditions, FA decreases have also been reported [11, 14, 23–28].

Our study indicates that children with BHS show significantly smaller cerebellum volumes than the healthy subjects. Although the volumes of the midbrain, pons, and medulla were found to be similar between children with BHS and healthy subjects, FA in the midbrain and medulla was significantly decreased in the children with BSH compared to healthy subjects ($p < 0.05$) (Table 2, 3).

We believe that there may be a difference in brain structures in patients with BHS, as in other neurodevelopmental diseases, and that BHS should be addressed in this respect. The midbrain regulates vision, hearing, eye movement, and body movement, whereas the medulla regulates vital body functions such as breathing and heart rate and pain adaptation, and the pons is involved in motor control and sensory analysis. Our data showed decreased connectivity in the midbrain and medulla in the BHS group ($p < 0.01$). This decreased connectivity in the midbrain of patient group explains the pathophysiology of BHS. The myelination contrary to other studies, we evaluated region-specific myelination and found that myelination was retarded in the midbrain and medulla. We also examined not only the brainstem but also other parts of the brain.

In a study conducted by Chang et al. [11], children who stutter exhibited significantly reduced FA relative to controls in white matter tracts that interconnect auditory and motor structures and the corpus callosum and tracts interconnecting cortical, subcortical areas. It was noted that the aberrant white matter development in the corpus callosum might also suggest poor interhemispheric connectivity. Peterson et al. [14] also found that patients with attention deficit hyperactivity disorder had significantly higher FA in the right superior frontal gyrus and posterior thalamic radiation and left dorsal posterior cingulate gyrus, lingual gyrus, and parahippocampal

gyrus, while no regions showed significantly decreased FA. Please et al. [23] reported reduced interhemispheric white matter connectivity in children with Tourette syndrome. Lower FA in corpus callosum regions may reflect fewer interhemispheric fibers or reduced axonal myelination [23, 29].

Song et al. [30] detected volumetric brainstem changes in major depressive patients, elevated FA in the brainstem and substantia nigra, and elevated FA in the amygdala, hippocampus, brainstem, and substantia nigra. In the present study, FA was significantly decreased in BHS patients' bilateral midbrain, medulla, and corpus callosum body and splenium, left corpus callosum genu, and right corticospinal tract. In contrast, no significant difference was detected in the pons, cerebellum, right corpus callosum genu, or left corticospinal tract. FA was particularly low in the corpus callosum, which may be associated with an abnormal neuroplastic response.

While BHS is considered to have a good prognosis and is self-limiting, Olsen et al. [31] showed that 30.6% of patients had fainting problems, and 29.4% had concentration issues. Di Mario et al. [32] also reported syncope attacks and hypoxic convulsions. Based on our findings, we think that patients with BHS should be evaluated with an approach similar to other neurodevelopmental diseases and that this study may help elucidate the pathophysiology and establish the groundwork for future studies on BHS treatment.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 25.11.2015, number: 2015/490).

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