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# Prevalence of Bilateral Vocal Fold Palsy in Cases with Perinatal Hypoxia

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## ABSTRACT

### Introduction

There is a notable gap concerning the potential impact of perinatal hypoxia on laryngeal innervation and its role as a causative factor for bilateral vocal fold palsy (BVFP) in children. This study aims to assess the prevalence of BVFP in cases with perinatal hypoxia.

### Methods

This cross-sectional study took place at the Department of Ear, Nose, and Throat (ENT) and the Department of Pediatrics of Institute of Medicine, Kathmandu, Nepal. Institutional Review Board approval was obtained. From November 2019 to March 2023, all children under 2 years of age with documented perinatal hypoxia were included. Exclusion criteria comprised cases without parental consent, identification of another identifiable cause of BVFP, or the child being on oxygen support during examination, preventing laryngoscopy. Additionally, a retrospective cohort analysis included all BVFP patients at the department between January 2013 and November 2019 to validate our findings.

### Results

The study included 21 cases, and none of those with perinatal hypoxia exhibited BVFP. Furthermore, the retrospective cohort of BVFP cases presenting at our department did not reveal a significant history of perinatal hypoxia.

### Conclusion

Our study did not yield compelling evidence linking perinatal hypoxia with BVFP however, considering the constraints of our study, insights from existing literature and absence of prior research in this area, the hypothesis of perinatal hypoxia's impact on laryngeal innervation merits further, more comprehensive research in this area.

**Keywords**
*Hypoxic injury; perinatal hypoxia; vocal fold palsy*

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## INTRODUCTION

Bilateral vocal fold palsy (BVFP) in the pediatric population is a relatively rare occurrence, but it carries significant clinical importance due to its potential for complications and the complexity of treatment approaches. The estimated incidence of BVFP is 0.75 cases per million births per year.[1] Various underlying causes have been proposed. In a retrospective study conducted by Daya et al., it was found that 46% of BVFP had no identifiable cause. Neurological factors, such as Arnold Chiari malformation, severe hypoxia, congenital hydrocephalus, and neurofibromatosis, as well as iatrogenic and birth trauma, were among the other contributing factors observed.[2] The results of a recently conducted systematic review showed a similar pattern, with the majority of cases (58.5%) having an unidentifiable cause, followed by cases attributed to neurological, iatrogenic, and traumatic factors. [3]

The root pathology in these cases involves a disruption in motor innervation to the larynx which is via the recurrent laryngeal nerve. The specific pathogenic processes leading to nerve dysfunction can vary. However, in most cases the cause of BVFP is idiopathic and the precise mechanism of injury remains elusive.

The impact of hypoxia on neurons has been extensively investigated. Hypoxic brain injury triggers an inflammatory cascade that activates and recruits immune cells, ultimately leading to neuronal damage[4]; however, the potential link between hypoxic brain injury and BVFP is largely unknown. While Daya et al. mention two cases of hypoxic injury resulting in BVFP, these cases were not comprehensively elucidated in terms of causality, severity, and other pertinent findings.[2] Given this knowledge gap, our exploratory study aims to investigate the prevalence of BVFP in children with a documented history of perinatal hypoxia. To our knowledge, this is the first research endeavor to investigate this relationship.

## METHODS

This cross-sectional study was a collaborative effort between the Department of Ear, Nose, and Throat (ENT) and the Department of Pediatrics. The study was approved by the Institutional Review Board [Ref: 229 (6-11)E[2] 076/077]. Between 11/2019 and 03/2023, all children under two years of age and with a documented history of perinatal hypoxia were included in the study. Perinatal hypoxia was defined as having an 10 minutes APGAR score equal to or less than 5 or an umbilical cord pH level equal to or less than 7, or need for resuscitation for more than 10 mins.[5] Grading of hypoxic ischemic encephalopathy was done based on Sarnat's classification.[6] Exclusion criteria included cases where parental consent for participation was not obtained, when another identifiable cause of BVFP was identified, or if the child was on oxygen support during examination that precluded laryngoscopy. To assess cases meeting the inclusion criteria, we conducted examinations in the outpatient department (OPD) using a PENTAX 2.7 mm flexible endoscope to document vocal fold mobility. Taking into account the potential impact of hypoxia on the vagal nuclei or the vagus nerve, we formulated a plan to assess aspiration with either a functional endoscopic evaluation of swallowing (FEES) or a static endoscopic evaluation of swallowing (SEES) in cases who had BVFP. The objective was to assess laryngeal sensation, offering insights into the integrity of the superior laryngeal nerve. For cases with perinatal hypoxia, with or without hypoxic-ischemic encephalopathy (HIE), magnetic resonance imaging (MRI) scans were not routinely conducted in patients with normal vocal fold function due to resource limitation, unless deemed necessary by the pediatrician. However, for patients with perinatal hypoxia and BVFP, a protocol was established to conduct MRI scans aimed at ruling out other potential causes and pinpointing sites of brain injury.

In order to validate our findings, an additional analysis was conducted of a retrospective cohort of all patients with BVFP presenting at our department between 01/2013 and 11/2019. These cases underwent a detailed history-taking and thorough ENT and neurological examinations, followed by flexible endoscopy. All patients in the retrospective cohort had previously undergone contrast-enhanced MRI (CE MRI) followed by endoscopic evaluation under general anesthesia to assess distal airway and cricoarytenoid joint mobility. Data collection was accomplished using Google Forms and Google Sheets, with subsequent data analysis conducted using SPSS version 26. We used Z-test to assess the significance of the difference in proportion of BVFP in two different population: our study involving cases with perinatal hypoxia, and the general population, assuming an incidence of 0.75 cases per million live births for BVFP.[1] P-value of $<0.05$ was considered significant.

## RESULTS

A total of 29 cases with documented perinatal hypoxia were assessed in the prospective arm of the study, but eight cases were excluded from the analysis; three of these individuals declined to provide consent, while five had incomplete documentation. The age of our patients ranged from nine days to two years. Among these cases, four were evaluated within the first month of life, while the remainder were assessed during follow-up visits. In this cohort, there were 16 males and five females (Table 1).

Among the 21 cases included in the analysis, two had mild/stage I HIE, 12 had moderate/stage II HIE, and one had severe/stage III HIE. Additionally, four cases had concurrent seizure disorders, and two exhibited symptoms of spastic quadriparesis (Table 1).

Flexible endoscopy revealed that all cases had functioning bilateral vocal cords. FEES/SEES assessments were not conducted in the prospective group because no patient had BVFP. Two cases underwent MRI brain scans, which indicated global hypoxic injury. In one case, multicystic encephalomalacia was also noted to replace the majority of the supratentorial brain parenchyma, sparing the periventricular white matter, bilateral basal ganglia, and thalami. The imaging also revealed grossly dilated lateral and third ventricles with a patent aqueduct, a normal fourth ventricle, an enlarged cisterna magna, and a poorly developed corpus callosum (Fig 1).

Z- score test to assess the significance of the difference in proportion of BVFP in our study involving cases with perinatal hypoxia, compared to the general population (assuming an incidence of 0.75 cases per million live births for BVFP) showed a statistically significant difference (p-value <0.05) (Table 2).

BVFP

Furthermore, we conducted an analysis of a retrospective cohort of eight cases with BVFP presenting at our department between January 2013 and November 2019. The parental history did not indicate a likelihood of hypoxic insult during delivery in any patients in this group. However, APGAR scores and umbilical cord pH data were

*Table 1. Clinical profile of cases with perinatal hypoxia (n=21)*

| Characteristics | number |
|---|---|
| Age (range) | |
| 9 days - 2 years | - |
| Gender | |
| Male | 16 |
| Female | 5 |
| Sarnat's HIE grading | |
| Stage I | 2 |
| Stage II | 12 |
| Stage III | 1 |
| Associated neurological disorders | |
| Spastic quadriparesis | 2 |
| Seizure disorder | 4 |
| Vocal cord mobility in endoscopy | |
| Mobile | 21 |
| Paralyzed | 0 |

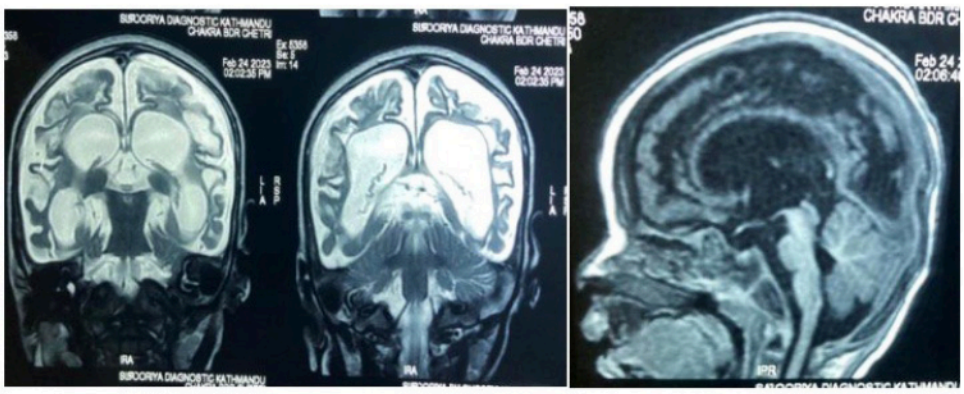

*Figure 1. MRI brain showing encephalomalacia, dilated ventricles and poorly developed corpus*

*Table 2. Z-score test comparing two population proportions*

| Population (n) | Proportion of cases with BVFP | Z-Score test | p-value |
|---|---|---|---|
| Cases with perinatal hypoxia from our study (21) | 0/21 | -7.937 | p<0.001 |
| General population (1,000,000) | 0.75/ 1,000,000 | - | - |

*Table 3. Cases with BVFP with their etiology and MRI findings*

| Cases | Age | Gender | Cause of BVFP | MRI findings | H/O hypoxic event |
|---|---|---|---|---|---|
| Case 1 | 9 M | F | Idiopathic | Normal | None |
| Case 2 | 3 years | F | Idiopathic | Normal | None |
| Case 3 and 4 | 3 years | F | Idiopathic | Normal | None |
| Case 5 | 3 years | M | Button battery esophagus | Normal | None |
| Case 6 | 4 years | M | Brainstem inflammatory lesion under evaluation | Non-specific inflammatory lesion in the braistem | None |
| Case7 | 6 years | M | Idiopathic | Normal | None |
| Case 8 | 14 years | M | Idiopathic | Normal | None |

not available to confirm this. The age of these patients ranged from nine months to 14 years. In all cases, there was an acute onset of stridor beyond the perinatal period. A nonspecific history of upper respiratory tract infection (URTI) was evident in three cases, and one case developed stridor following the ingestion of a button battery, which was subsequently retrieved from the cricopharyngeal junction (Table 3).

To investigate these cases further, MRI scans were performed for all patients. Remarkably, only one case showed an inflammatory lesion in the brainstem, while the remaining scans yielded normal findings.

## DISCUSSION

Although various etiological factors for BVFP have been proposed, possibility of the hypoxic neuronal injury resulting in laryngeal denervation has not been extensively studied. Our study analyzed a cohort of 21 cases with documented perinatal hypoxia for the prevalence of BVFP.

Neuronal injury following a hypoxic event, such as perinatal hypoxia, has been extensively researched. Following hypoxic insult, the cells undergo anaerobic metabolism, which depletes ATP and ultimately leads to the failure of ATP-dependent ion pumps. This results in the intracellular influx of calcium and sodium, leading to membrane depolarization, an increased extracellular glutamate concentration, cellular swelling, and necrosis. Subsequently, a secondary energy failure occurs, accompanied by an augmented inflammatory response that produces pro-inflammatory cytokines, reactive oxygen species, nitric oxide, hydrogen peroxide, and other molecules. These factors contribute to delayed neuronal death. [4]

Broadly, three different patterns of hypoxic brain injury have been described namely: watershed injury, basal ganglia-thalamus injury and total brain injury. [7] The manifestations can range from periventricular leukomalacia, germinal matrix intraventricular hemorrhage, to cystic encephalomalacia.[8] During periods of hypoxic injury, the regions most affected are primarily determined by their level of myelination and metabolic activity, with areas characterized by early myelination and high metabolic rates suffering the greatest impact. Neuronal myelination commences during the second trimester and continues until 18 months of age. Commonly affected brain regions in cases of hypoxic-ischemic injury include the periventricular white matter, basal ganglia, thalamus, posterior limb of internal capsule, and medial temporal lobe.[7,8]

The area of our interest was the brainstem, with a specific emphasis on the medulla oblongata, which harbors vagal nerve nuclei. Quattrochi et al. conducted a thorough review that highlighted the remarkable resistance of the brainstem to hypoxic injury. However, in instances of severe hypoxia, the brainstem can be affected specially in its dorsal portion. This susceptibility can be attributed to the elevated metabolic activity in the dorsal brainstem and the fact that the tegmentum serves as a watershed area within the vertebrobasilar vascular system. This selective infratentorial involvement of dorsal brain stem has also been named as dorsal brainstem syndrome (DBSS).[9,10]

A retrospective case series involving patients with perinatal hypoxia evaluated for MRI findings and oral motor dysfunction specifically in terms of swallowing and aspiration issues revealed a significant statistical association between infratentorial brainstem lesions and oral motor dysfunction. Among the cases examined, MR images indicated the presence of infratentorial lesions in 46%, affecting various levels of the brainstem, ranging from the midbrain to the medulla; among these cases, 77.8% (14 out of 18) exhibited signs of oral motor dysfunction. This finding is particularly significant because the process of swallowing is

a highly intricate physiological function that relies on the coordination of several cranial nerves (V, VII, IX, and X), which have their nuclei located within the pons and medulla regions of the brainstem. Therefore, the results of this study strongly indicate that hypoxic injury can indeed impact the brainstem and the associated cranial nerve nuclei located in these critical areas. However, it is worth mentioning that this study did not provide any commentary on the vocal fold mobility of the cases under investigation. [9] Furthermore, Colleti et al. reported a case of DBSS in a patient who had developed sepsis due to meningoencephalitis. The resulting hypoxic-ischemic injury (HII) led to the manifestation of DBSS, characterized by cardiorespiratory failure and evidence of altered signal intensity in the dorsal brainstem as observed in imaging.[10] In addition to these clinical observations, post-mortem studies of infants who succumbed to HII have provided compelling evidence of brainstem involvement. These studies have consistently revealed findings of destructive and cavitary lesions within the brainstem, alongside similar pathological changes in other areas of the brain. [11,12]

The likelihood of hypoxic or ischemic injury resulting in VFP can further be strengthened by several reported cases where VFP developed following stroke. The recurrent laryngeal nerve receives motor input from nucleus ambiguous. The nucleus ambiguous, in turn, receives corticobulbar innervations from the larynx motor area of the primary motor cortex and premotor cortex located in the frontal lobes.[13] Sawalha et al. documented a case characterized by right hemiparesis and left VFP following ischemic stroke stemming from the occlusion of the left internal carotid artery (ICA). Perfusion imaging localized the affected regions, encompassing the basal ganglia, cortex, subcortex, insula, and operculum within the territory of the left ICA. The VFP was later improved following therapeutic hypertension, undertaken to enhance perfusion in the ischemic areas amenable to salvage. [13] Similarly Shaw reported two adult cases who developed BVFP along with contralateral hemiparesis and VII upper motor neuron palsy following left cortical infarct due to cardioembolic stroke.[14] A classic example of BVFP due to hypoxic injury in the brain stem was reported by Allam et al. where an adult patient presented with BVFP and quadriparesis following two sequential brainstem infarcts: first a right medial medullary followed by left paramedian pontine infarct. Given the presence of the nucleus ambiguous in the medulla and supranuclear corticobulbar fibers for vagus in the pons, BVFP was attributed to ischemic injury in these areas.[15] Another case series by Venketasubramanian et al. evaluated 54 cases with acute ischemic stroke for VFP. Eleven patients were found to have VFP. Among these, all five cases with lateral medullary syndrome had VFP, with four having VFP on the ipsilateral side and one on the contralateral side. The remaining six cases had infarct in supranuclear locations such as the internal capsule, corona radiata, putamen, temporal, parietal and straitocapsular regions. Those with supranuclear involvement had VFP on the contralateral side. These findings suggest motor innervation to the larynx can also be affected at supranuclear cortical levels.[16] Despite these studies' being reported in the adult age group, they provide valuable anatomical and pathological insights into the various levels where the motor innervation to the larynx can be affected by hypoxic-ischemic injury.

Our study, on the contrary, did not yield evidence that hypoxic injury to the brain due to perinatal hypoxia can affect motor innervation to the larynx in pediatric patients. While our study did yield statistically significant results suggesting a reduced likelihood of BVFP in children with perinatal hypoxia compared to the general population, it is important to acknowledge that the generalizability of our findings is limited due to the small sample size; it seems unlikely that perinatal hypoxia would have a protective effect in this regard. Additionally, our literature review revealed that significant brainstem injury typically necessitates a considerable degree of hypoxia. Among the cases in our study, only one exhibited severe hypoxia(Stage III HIE), accompanied by cystic encephalomalacia in the supratentorial region of the brain. It is worth noting that our study also lacked imaging data for most patients, primarily due to cost-related issues in this resource-limited setting.

Based on our review of the existing adult literature, it is plausible to hypothesize that perinatal hypoxia could potentially impact the brainstem in children, including the vagal nuclei. However, an isolated presentation with BVFP in these cases would likely be rare considering the broader range of potential areas that could be impacted by hypoxic-ischemic injury beyond the vagal nuclei alone.

## CONCLUSION

In conclusion, our study did not yield compelling evidence linking perinatal hypoxia with BVFP however, considering the constraints of our study, insights from existing literature and absence of prior research in this area, the hypothesis of perinatal hypoxia's impact on laryngeal innervation merits further, more comprehensive research in this area.

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## CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

## AUTHOR CONTRIBUTIONS

Study concept and design: BRG, RG, HPD, KB, DS, Data collection: BRG , SP, SB, Analysis and interpretation of data: BRG, KB, Drafting of the manuscript: BRG,KB,LS . All the authors read and approved the final manuscript

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