


Hyperventilation-Induced High-Amplitude Rhythmic Slowing and Its Impact on Migraine Frequency in Children: A Retrospective Observational Cohort Study

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ABSTRACT

Objectives: The most common primary headache disorder in children is migraine. Some children with hyperventilation (HV) may exhibit hyperventilation-induced high-amplitude rhythmic slowing (HIHARS) in their electroencephalogram (EEG). The study aims to evaluate the correlation between HIHARS and a child's future migraine onset risk.

Materials & Methods: The present study evaluated HIHARS during the HV maneuver in children aged 7 to 12 admitted to the Electroencephalography Monitoring Unit for diverse referral reasons. After six years, the researchers assessed Long-term video-EEG monitoring data for migraine disease according to the International Classification of Headache Disorders, Third Edition (ICHD-3). The clinical and neurophysiological data were analyzed using appropriate statistical methods.

Results: The study revealed that among children with HIHARS, migraine was higher ($P=0.049$) after six years. Additionally, 15 children (68.18%) with HIHARS had a family history of migraine, compared to 12 children (40%) without HIHARS, which was significant ($P=0.044$). Interestingly, no significant difference was observed between patients with seizures and those without ($P=0.1$), suggesting that seizures do not act as a confounding factor in this study.

Conclusion: This is the first study on the correlation of HIHARS with migraine in children. Patients aged 7 to 12 years old with HIHARS had more susceptibility to migraine headaches. It is suggested that children with HIHARS and a history of migraine in first-degree family members will be more susceptible to developing migraine in life

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Introduction

Traditionally, pediatric rheumatology has focused on immune dysregulation as the leading cause of inflammation. Emerging evidence shows that

metabolism — the way cells process nutrients, produce energy, and maintain balance — is also vital in the immune system function (1). The idea of immune metabolism has changed the understanding of

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inflammation (2). Through metabolic pathways, immune cells can be activated to perform their functions (3). For instance, immune cells like effector cells and M1 macrophages rely on glycolysis for energy. In contrast, regulatory T cells and M2 macrophages use oxidative metabolism and fatty acid oxidation to support the long-term balance of immune function.

In children, migraine is the most prevalent type of primary headache, with prevalence rates ranging from 7.7% to 17.8% worldwide (1, 2, 3). The frequency of migraine increases with age and is correlated with the duration of puberty, occurring in girls between the ages of 8 and 14 and boys between the ages of 9 and 15 (4). Therefore, migraine is a common neurological disorder in the developmental age (5). While clinical diagnosis is the primary method for identifying migraines, neurophysiologic assessments can provide valuable insights. Long-term video-EEG monitoring (LTM) is a specialized EEG technique that records clinical behaviors on video while continuously monitoring brain activity (6,7). “H response” or enhanced photic drive to flicker stimulation (Intermittent Photic Drive above 20 Hz) is the most common electroencephalographic finding and a posterior dominant rhythm abnormality in migraine (6). Nevertheless, it is not easily seen on routine EEG recordings. Moreover, a common explanation for migraine, specifically aura, is the electrocortical phenomenon known as cortical spreading depression (CSD) (8). However, several previous studies focused on vasogenic changes (9-12). Additionally, the hyperventilation (HV) maneuver can cause high-amplitude, slow, and rhythmic non-epileptic brain activity in some epileptic and non-epileptic people. This phenomenon, referred to as hyperventilation-induced high-amplitude rhythmic slowing (HIHARS), may be a prognostic indicator of migraine (7). Researchers have not yet identified specific prognostic factors that can accurately predict migraine. Identifying these factors is vital for developing more effective treatment methods and personalized management strategies for those who experience migraines. Therefore, this study used LTM data to assess the correlation between neurophysiologic findings, such as HIHARS, with migraine.

Materials & Methods

The study included fifty-nine children aged 7 to 12 years who were admitted to the Electroencephalography Monitoring Unit with various reasons, including medication-resistant epilepsy, suspected seizures, and previous standard EEGs at the Children’s Medical Center in Tehran, Iran, over one year from 2016. Six years after LTM, in 2022, the researchers evaluated

LTM data for signs of migraine. Seven participants withdrew from the study due to uncooperative behavior during the history-taking phase. The remaining fifty-two patients were evaluated for the presence of migraine headaches by a pediatric neurologist. The Neurofax EEG-1200 diagnostic and monitoring platform, 64 channels (Nihon Kohden Singapore Pte Ltd., 1 Maritime Square, # 10-34 HarbourFront Centre, Singapore 099253), with dedicated night-vision cameras, was used for all LTMs—a clinical neurophysiologist evaluated all recorded documents. HIHARS was evaluated during the HV maneuver. The time lag between the start of HV and the manifestation of HIHARS was studied, as were the frequency and amplitude of the first three HIHARS waves. Migraine was diagnosed by a pediatric neurologist based on the International Classification OF Headache Disorders, 3rd edition (ICHD-3). A history of migraine headaches in the first-degree family was also mentioned. Gathered Data, both clinical and neurophysiological, were evaluated by the appropriate statistical analyses (IBM SPSS Statistics V26).

Results

Fifty-two patients were enrolled in the study. The mean age at LTM performance was 9.86 ± 1.69 years. The male-to-female ratio was 1.26 (55.8% male and 44.2% female). HIHARS was detected in only 42.3% of patients ($n = 22$) during the HV maneuver. HIHARS was observed in 14 (48.27%) of the boys and eight (34.78%) of the girls, which was not significant between the two genders ($p = 0.4$). Over six years, migraine headaches were detected more frequently in males (34.48% males and 26% females); however, the difference was not statistically significant ($P = 0.56$). The mean time of starting HIHARS from HV was 79.09 ± 49.79 seconds (20-180 seconds). The mean amplitude and frequency of the first three HIHARS waves were $165.31 \pm 47.87 \mu\text{v}$ (110-275 μv) and 4.19 ± 0.54 Hz (3.15-5 Hz), respectively. The occurrence of HIHARS was significantly increased with age ($P = 0.019$). Among children with HIHARS, 15 (68.18%) patients had a family history of migraine but only 12 (40%) children without HIHARS, had a history of migraine in the family, which was significant ($P = 0.044$). Moreover, it is noteworthy that there was no significant difference in the induction of HIHARS between patients with seizures and those without ($P = 0.1$); thus, seizure does not act as a confounding factor in this study. Additionally, among children with HIHARS, ten (45.5%) had migraine, and among children without HIHARS, six (20%) had migraine, which was statistically significant ($P = 0.049$) (Figure 1).

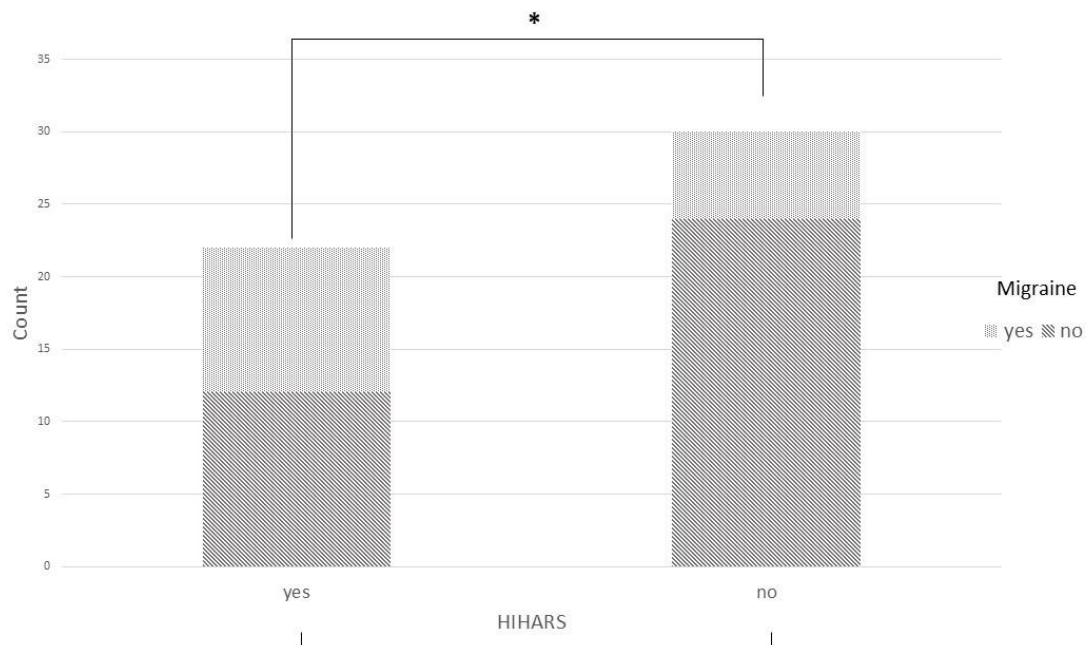


Figure 1. The prevalence of HIHARS. Overall assessment of children, suggests a potential difference in the prevalence of HIHARS between children with Migraine and those without when considering all children together. The star (*) indicates $P=0.049$.

Discussion

This is the first study to assess the correlation between HIHARS and migraine. A lack of studies exists on HIHARS prevalence in pediatric migraine. This study found that children with HIHARS who are 7-12 years old are more prone to migraine disease. The current research also showed the importance of a family history of migraine in children with HIHARS. Migraine disease is among the most prevalent and debilitating neurological disorders in children and adolescents (13). However, with the widespread impairment caused by migraine, the disorder is still underdiagnosed and undertreated (1). The innovative electroencephalographic research that highlighted abnormal electrocortical activity in patients with migraine was conducted several decades ago (14). The H response to flicker stimulation, also referred to as enhanced photic driving, and abnormal resting-state EEG rhythmic activity have been the most commonly reported electrocortical phenomena in migraine patients over the last 60 years of publication (15, 16). However, it was not readily apparent in routine EEG recordings. Moreover, HV, at least 2-3 minutes, is another provocative maneuver used during EEG recording (17). HV-induced high-amplitude rhythmic slowing (HIHARS) refers to generalized rhythmic slowing occurring between 2.5 and 5 Hz, with an amplitude $\geq 100 \mu\text{V}$ and lasting ≥ 3 s. This

phenomenon affects roughly 34% of children aged 5 to 15 and is considered relatively common (18). Previous studies on HIHARS have focused on how it differs from absence seizures (19, 20). The present research revealed that children with HIHARS are more likely to experience migraine, even though it is a rather common childhood occurrence. Furthermore, this study does not include seizures as a confounding factor. As a result, standard EEG recording with the HV maneuver may be recommended for migraine diagnosis and may help prevent overtreatment of non-epileptic HIHARS. In the future, a larger sample size is required to assess this phenomenon in children with migraines.

In Conclusion

The obtained findings indicate that children aged 7–12 with HIHARS seem to be at a higher risk of developing migraine disorders. Furthermore, children with HIHARS may be at risk for migraine in the future if they have a history of migraine-afflicted first-degree relatives. Thus, considering HIHARS in standard EEG assessment could help identify children at risk and estimate the probability of future migraines.

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Author Contribution

Mahmoud Mohammadi, Project administration, Supervision. Reza Shervin Badv, Methodology, Project administration, Supervision. Zahra Rezaei, Investigation, Validation. Mahmoud Reza Ashrafi, Investigation, Methodology, Project administration. Gholam Reza Zamani, Investigation, Validation,

Visualization. Morteza Heidari, Validation. Mahsa Vatanparast, Formal analysis, Writing – review & editing. Hosein Eslamiyeh, Validation. Najmeh Ahangari, Writing – review & editing. Bitra Barazandeh, Writing – review & editing. Mehran Beiraghi Toosi, Data curation, Formal analysis, Investigation, Validation, Writing – original draft.

Conflict of Interests

The authors declare that they have no competing interests.

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