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Hemiplegic Migraine in Children: Clinical Presentation, Diagnosis, and Management Challenges in Pediatric Practice

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ABSTRACT

Hemiplegic migraine represents one of the most distinctive and diagnostically challenging forms of migraine with aura encountered in pediatric neurology practice yet remains critically understudied in Black children and other underserved populations. Characterized by transient unilateral motor weakness accompanying the typical migraine aura complex, this rare condition affects children as young as five to seven years of age and presents unique diagnostic and therapeutic considerations. The condition manifests in both familial and sporadic forms, with familial hemiplegic migraine linked to mutations in CACNA1A, ATP1A2, and SCN1A genes, while sporadic cases occur without identifiable family history. The clinical presentation often mimics stroke, epilepsy, or encephalopathy, leading to frequent misdiagnosis, with Black and Hispanic children experiencing significantly lower rates of accurate migraine diagnosis compared to White children in emergency settings. This comprehensive review examines the current understanding of pediatric hemiplegic migraine, including its pathophysiology, clinical manifestations, diagnostic approaches, and management strategies, with particular emphasis on the documented healthcare disparities affecting minority populations. Attention is given to the differential diagnosis challenges in children, the role of genetic testing, and the critical need for culturally competent care to address the substantial inequities in recognition, testing, and treatment that disproportionately impact Black children with this condition.

Keywords
Aura, Headache, Hemiplegic migraine, Pediatric migraine, Racial disparities.

Introduction
Hemiplegic migraine represents a rare but clinically significant subtype of migraine with aura that predominantly affects the pediatric population, with initial presentations commonly occurring during childhood and adolescence [1,2]. This neurological condition is characterized by the presence of transient unilateral motor weakness or paralysis as part of the migraine aura complex, distinguishing it from other forms of migraine through its dramatic and often alarming clinical presentation [2]. Hemiplegic migraine is a rare migraine subtype with an overall prevalence of about 0.01% in the general population [3]. A study based on population data from Denmark reported a prevalance rate of .002% [1]. Pediatric specific epidemiological data are scarce; most available data combines adults and children. Pediatric cohorts remain

limited, reflecting both the rarity of the condition and diagnostic challenges in children [1].

The significance of hemiplegic migraine in pediatric neurology extends beyond its rarity, particularly given the documented healthcare disparities that disproportionately affect Black children and other minority populations in neurological care. Recent studies have demonstrated that Black and Hispanic children presenting to pediatric emergency departments with headache complaints are significantly less likely to receive a migraine diagnosis compared to their White counterparts, with migraine diagnosis rates of 28.2% for Black children and 28.3% for Hispanic children versus 45.5% for White children [4,5]. This disparity represents a critical gap in healthcare equity that has profound implications for children with hemiplegic migraine, whose dramatic neurological presentation often requires immediate recognition and appropriate management.

The underdiagnosis and inadequate treatment of migraine conditions in Black children has been largely overlooked in neurological literature, despite evidence suggesting that minority populations experience greater migraine burden, frequency, and severity compared to non-Hispanic White populations [4-7]. This systematic neglect in research and clinical attention has created knowledge gaps that may contribute to delayed diagnosis, inappropriate treatment, and worse outcomes for Black children with hemiplegic migraine. The dramatic nature of the neurological symptoms, particularly the unilateral weakness that can range from mild motor impairment to complete hemiplegia, often prompts urgent medical evaluation and consideration of serious conditions such as acute stroke, epileptic seizures, or intracranial pathology [1,3,8].

The pathophysiology of hemiplegic migraine involves complex neurochemical mechanisms centered around cortical spreading depression, a wave of neuronal depolarization that propagates across the cerebral cortex at a rate of approximately 3-5 millimeters per minute [3,9,10]. In hemiplegic migraine, this process appears to involve motor cortical areas more extensively than in typical migraine with aura, resulting in the characteristic motor symptoms that define the condition [3]. The genetic forms of hemiplegic migraine have provided valuable insights into the molecular mechanisms underlying this process, with identified mutations in CACNA1A, ATP1A2, and SCN1A genes affecting ion channel function and neuronal excitability [11,12].

Historical Perspective and Classification

The recognition of hemiplegic migraine as a distinct clinical entity has evolved significantly over the past century, with early descriptions dating back to the late 1800s when physicians first documented cases of migraine accompanied by transient paralysis [13,14]. The formal classification of hemiplegic migraine within the International Headache Society diagnostic framework has undergone several revisions, reflecting advancing understanding of the condition's pathophysiology and genetic basis.

The current International Classification of Headache Disorders, Third Edition, recognizes two primary forms of hemiplegic migraine: familial hemiplegic migraine, defined by the presence of at least one first- or second-degree relative with similar attacks, and sporadic hemiplegic migraine, occurring in individuals without family history of the condition [15]. This classification system has proven particularly valuable in pediatric practice, where family history assessment may reveal previously unrecognized cases in relatives or help predict genetic risk in affected families.

The historical evolution of hemiplegic migraine classification has been closely linked to advances in genetic research, particularly the identification of specific gene mutations associated with familial forms of the condition [11-13]. The discovery of mutations in CACNA1A, ATP1A2, and SCN1A genes has not only enhanced diagnostic capabilities but has also provided crucial insights into the underlying pathophysiological mechanisms that distinguish hemiplegic migraine from other neurological conditions [9,11,13].

Epidemiology and Demographics in Pediatric Populations

Hemiplegic migraine demonstrates distinctive epidemiological patterns in pediatric populations that differ significantly from adult presentations and other forms of childhood migraine. The condition typically manifests during childhood or early adolescence, with reported ages of onset ranging from as early as five years to the late teenage years [1]. The peak incidence appears to occur during the school-age years, corresponding to a period of significant neurological development and maturation.

Gender distribution in pediatric hemiplegic migraine shows interesting patterns that evolve with age [8]. Unlike typical migraine, which demonstrates a clear female predominance after puberty, hemiplegic migraine in younger children shows a more balanced gender distribution or even slight male predominance in some studies [1]. This pattern suggests that hormonal factors may play a less prominent role in hemiplegic migraine compared to other migraine subtypes, though definitive conclusions require larger epidemiological studies.

The familial forms of hemiplegic migraine demonstrate autosomal dominant inheritance patterns with high penetrance but variable expressivity [16]. This genetic pattern means that children of affected parents have a 50% likelihood of inheriting the condition, though the severity and frequency of attacks may vary significantly even within the same family [17]. Genetic counseling becomes particularly important in these families, especially when planning for additional children or assessing risk in extended family members.

Sporadic hemiplegic migraine, representing cases without identifiable family history, accounts for approximately 50-75% of pediatric presentations [1,2]. However, careful family history assessment may reveal previously undiagnosed cases in relatives, particularly in families where medical care access has been limited or where symptoms were attributed to other conditions. The true proportion of sporadic versus familial cases may therefore be lower than initially estimated in some populations.

Pathophysiology and Genetic Mechanisms

The pathophysiological mechanisms underlying hemiplegic migraine represent a complex interplay of genetic, molecular, and neurophysiological factors that distinguish this condition from typical migraine presentations. Central to the pathophysiology is the phenomenon of cortical spreading depression, a slowly propagating wave of neuronal and glial depolarization that moves across the cerebral cortex at characteristic rates and involves both gray and white matter structures [3,9,18].

In hemiplegic migraine, cortical spreading depression appears to involve motor cortical areas more extensively and persistently than in typical migraine with aura [3,9]. This enhanced involvement of motor regions is thought to underly the clinical presentation of unilateral weakness and may explain the prolonged duration of motor symptoms compared to other aura phenomena [3,9,19]. Studies have demonstrated that the cortical spreading depression in hemiplegic migraine can extend beyond the primary motor cortex to involve supplementary motor areas and subcortical motor circuits [3,19,20].

The genetic basis of familial hemiplegic migraine has been extensively characterized through the identification of mutations in three primary genes: CACNA1A, ATP1A2, and SCN1A [1,3,9,11]. Each of these genes encodes proteins crucial for neuronal excitability and ion channel function, providing direct mechanistic links between genetic abnormalities and clinical phenotypes. CACNA1A mutations, responsible for familial hemiplegic migraine type 1, affect P/Q-type calcium channels and account for approximately 50% of familial cases [3,11,12,21]. These mutations result in altered calcium channel function that affects neurotransmitter release and neuronal excitability patterns [11,12,21].

ATP1A2 mutations, causing familial hemiplegic migraine type 2, affect the alpha-2 subunit of the sodium-potassium ATPase pump and represent approximately 20% of familial cases [9,21]. These mutations impair the normal function of this crucial enzyme, leading to altered ionic gradients across neuronal membranes and increased susceptibility to cortical spreading depression [9,21]. The clinical phenotype associated with ATP1A2 mutations often includes additional neurological features such as seizures, intellectual disability, or cerebellar signs [22].

SCN1A mutations, responsible for familial hemiplegic migraine type 3, affect voltage-gated sodium channels and represent a smaller proportion of familial cases [9]. Interestingly, SCN1A mutations are also associated with various epilepsy syndromes, highlighting the complex relationship between ion channel dysfunction and different neurological phenotypes [9,21]. The overlap between hemiplegic migraine and epilepsy genetics provides important insights into shared pathophysiological mechanisms.

Beyond these three well-characterized genes, additional genetic loci have been identified in families with hemiplegic migraine, suggesting that the genetic architecture of the condition is more complex than initially recognized [9,21]. Whole-genome sequencing and other advanced genetic techniques continue to identify novel genes and pathways involved in hemiplegic migraine pathogenesis, potentially leading to new therapeutic targets and diagnostic approaches [21,23,24].

Multifactorial Contributors to Pathophysiology

The pathophysiology of pediatric hemiplegic migraine extends far beyond the primary genetic mechanisms to encompass a complex interplay of genetic, environmental, social, psychological, and developmental factors that collectively influence disease expression, severity, and clinical course. Understanding these multifactorial contributors is essential for developing comprehensive treatment approaches and addressing the unique needs of children and families affected by this condition.

Genetic Complexity and Modifier Factors

While mutations in CACNA1A, ATP1A2, and SCN1A represent the primary genetic causes of familial hemiplegic migraine, the clinical expression of these mutations is significantly influenced by genetic modifier factors that remain incompletely understood. Penetrance and expressivity vary considerably even within families carrying identical mutations, suggesting that additional genetic variants contribute to phenotypic diversity. Recent genome-wide association studies have identified common genetic variants that may influence migraine susceptibility and severity, and these same variants likely contribute to the clinical heterogeneity observed in hemiplegic migraine [3,21,23-25].

Epigenetic mechanisms represent another layer of complexity in hemiplegic migraine pathophysiology, with DNA methylation patterns, histone modifications, and microRNA expression potentially influencing gene expression and neuronal excitability [26,27]. Environmental factors during critical developmental periods may induce epigenetic changes that affect long-term disease expression, providing a mechanistic link between early life experiences and later clinical phenotypes.

The concept of genetic burden suggests that multiple rare variants of small effect may collectively contribute to hemiplegic migraine susceptibility, particularly in sporadic cases where no single causative mutation can be identified. This polygenic model is supported by observations that many children with apparently sporadic hemiplegic migraine have family histories of other neurological conditions or migraine subtypes, suggesting shared genetic susceptibility factors [9,21].

Developmental and Neurobiological Factors

The developing pediatric brain demonstrates unique vulnerabilities to the pathophysiological processes underlying hemiplegic migraine, with critical periods of neuronal development, myelination, and synaptic pruning potentially influencing disease expression and severity [27]. The immature blood-brain barrier in children may allow greater penetration of inflammatory mediators and other substances that could trigger or exacerbate attacks, while developmental changes in neurotransmitter systems may influence both susceptibility and recovery patterns.

Hormonal factors play increasingly important roles as children progress through puberty, with sex hormones influencing neuronal excitability, vascular reactivity, and pain processing pathways. The observed changes in gender distribution of hemiplegic migraine from childhood through adolescence likely reflect these hormonal influences, though the specific mechanisms remain incompletely characterized [1].

Sleep architecture and circadian rhythm development represent additional developmental factors that may influence hemiplegic migraine pathophysiology in children [28]. The maturation of sleep-wake cycles, melatonin production, and circadian gene expression patterns occur throughout childhood and adolescence, potentially creating windows of vulnerability or protection against migraine attacks.

Psychological and Stress-Related Contributors

The psychological dimension of hemiplegic migraine pathophysiology encompasses both the direct effects of stress on neurobiological processes and the complex psychological responses to living with a chronic, unpredictable neurological condition. Acute and chronic stress activate the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol levels and other hormonal changes that can influence neuronal excitability and vascular reactivity [29].

Children with hemiplegic migraines often develop anticipatory anxiety related to the unpredictable nature of attacks and their dramatic clinical presentation [1,8]. This anxiety can create a cycle where psychological stress potentially triggers attacks, which in turn increases anxiety levels and stress sensitivity. The development of maladaptive coping strategies, avoidance behaviors, or learned helplessness can further compound these psychological contributions to disease pathophysiology.

Family dynamics and parental anxiety may influence the psychological environment of children with hemiplegic migraine [30]. Parental overprotection, catastrophic thinking about symptoms, or family dysfunction may exacerbate the child's psychological distress and potentially influence attack frequency or severity through stress-mediated mechanisms.

School-related stress represents a particularly important psychological contributor in pediatric populations, with academic pressures, social challenges, and the fear of experiencing attacks in public settings creating chronic stress that may influence disease expression [8]. The cognitive demands of learning and academic performance may also be compromised during the post-attack recovery period, creating additional psychological burden.

Social and Environmental Contributors

The social environment plays a crucial role in shaping the experience and potentially the pathophysiology of hemiplegic migraine in children. Social support systems, family functioning, peer relationships, and community resources all contribute to the overall stress burden and coping capacity of affected children [31]. Strong social support may provide protective effects against stress-induced attacks, while social isolation or dysfunction may exacerbate vulnerability.

Environmental triggers represent well-recognized contributors to migraine pathophysiology, though their specific roles in pediatric hemiplegic migraine remain incompletely characterized. Dietary factors, including food additives, artificial sweeteners, and specific food sensitivities, may trigger attacks in susceptible children [8]. Sleep disruption, whether from lifestyle factors, screen time, or other causes, may represent another important environmental contributor.

Exposure to environmental toxins, air pollution, or other chemical agents during critical developmental periods may influence neuronal development and migraine susceptibility, though definitive causal relationships have not been established. The "hygiene hypothesis" suggests that reduced early-life exposure to infectious agents may increase susceptibility to allergic and inflammatory conditions, potentially including migraine, though this remains speculative for hemiplegic migraine specifically [32].

Metabolic and Physiological Factors

Metabolic factors unique to childhood and adolescence may contribute to hemiplegic migraine pathophysiology through effects on neuronal energy metabolism, vascular function, and inflammatory processes. Growth-related metabolic demands, nutritional deficiencies common in pediatric populations, and the metabolic changes associated with puberty all represent potential contributors to disease expression.

Mitochondrial dysfunction has been implicated in migraine pathophysiology generally, and may be particularly relevant in hemiplegic migraine given the high energy demands of maintaining ionic gradients disrupted by the underlying ion channel mutations. Children may be particularly vulnerable to mitochondrial dysfunction due to their high metabolic demands for growth and development [8].

Inflammatory processes, including both systemic and neuroinflammation, may contribute to hemiplegic migraine pathophysiology through effects on neuronal excitability, vascular permeability, and pain processing [33]. The developing immune system in children may respond differently to inflammatory triggers compared to adults, potentially influencing attack patterns and recovery.

Comorbidity Interactions

The presence of comorbid conditions significantly influences the pathophysiology and clinical expression of hemiplegic migraine in children. Attention deficit hyperactivity disorder, anxiety disorders, mood disorders, and other psychiatric comorbidities are overrepresented in children with migraine and may share common pathophysiological mechanisms [8]. These comorbidities may also influence treatment response and require integrated management approaches.

Sleep disorders, including sleep apnea, restless leg syndrome, and circadian rhythm disorders, are commonly comorbid with migraine and may both trigger attacks and be exacerbated by them [34-36]. The bidirectional relationship between sleep and migraine creates complex interactions that must be addressed in comprehensive treatment planning [8].

Epilepsy and hemiplegic migraine share genetic and pathophysiological mechanisms, with some children experiencing both conditions [8]. The overlap between these disorders highlights the common underlying mechanisms involving neuronal excitability and ion channel function, while also creating unique management challenges when both conditions are present.

Health Disparities and Cultural Considerations in Pediatric Hemiplegic Migraine

Understanding the impact of racial, ethnic, cultural, and socioeconomic factors on pediatric hemiplegic migraine is essential for providing equitable care and addressing the unique challenges faced by diverse populations. Health disparities in neurological conditions, including migraine, have been well-documented across various demographic groups, and these disparities likely extend to hemiplegic migraine, though specific research in this rare condition remains limited.

Racial and Ethnic Considerations

The epidemiological understanding of hemiplegic migraine across different racial and ethnic groups remains incomplete, primarily due to the rarity of the condition and the historical underrepresentation of diverse populations in neurological research. Most published case series and genetic studies have predominantly included individuals of European ancestry, creating significant knowledge gaps regarding the prevalence, clinical presentation, and genetic architecture of hemiplegic migraine in other racial and ethnic groups [21,37].

Genetic research in hemiplegic migraine has revealed important racial and ethnic differences in the frequency and types of causative mutations. The three major genes associated with familial hemiplegic migraine (CACNA1A, ATP1A2, and SCN1A) show variable mutation frequencies across different populations, with some mutations appearing to be population-specific or enriched in particular ethnic groups [21,38]. For example, certain CACNA1A mutations have been reported more frequently in families of Mediterranean ancestry, while specific ATP1A2 variants may be more common in Northern European populations.

These genetic differences have important implications for diagnostic approaches and genetic counseling in diverse populations. Standard genetic testing panels developed based on predominantly European cohorts may miss important mutations that are more common in other racial or ethnic groups. Expanded genetic testing approaches or population-specific panels may be necessary to ensure accurate diagnosis across all demographic groups.

The clinical presentation of hemiplegic migraine may also vary across racial and ethnic groups, though systematic studies are lacking. Differences in pain perception, expression of symptoms, and help-seeking behaviors across cultural groups may influence the clinical recognition and diagnosis of hemiplegic migraine. Cultural factors may affect how children and families describe neurological symptoms, potentially leading to diagnostic delays or misinterpretation of clinical presentations.

Socioeconomic Disparities and Access to Care

Socioeconomic factors significantly influence access to specialized neurological care, genetic testing, and advanced treatments for children with hemiplegic migraine [4]. The rarity of the condition necessitates evaluation by pediatric neurologists or specialized headache centers, which may be geographically inaccessible or financially prohibitive for families from lower socioeconomic backgrounds.

The cost of genetic testing represents a significant barrier for many families, particularly those without adequate insurance coverage or those facing high deductibles and copayments. The complexity of genetic counseling and the need for specialized interpretation of results may create additional access barriers for families with limited healthcare navigation experience or language barriers.

Preventive medications for hemiplegic migraine, including calcium channel blockers and antiepileptic drugs, may be expensive and require ongoing monitoring by specialized providers. Insurance coverage for these medications varies significantly, and prior authorization requirements may create delays in treatment initiation. The newer CGRP-targeted therapies, while potentially beneficial, are particularly expensive and may be inaccessible to families with limited insurance coverage.

Emergency department utilization patterns for hemiplegic migraine attacks may vary significantly across socioeconomic groups, with families from lower socioeconomic backgrounds potentially facing longer delays in recognition and appropriate treatment [4,5,7]. The dramatic presentation of hemiplegic migraine often necessitates expensive emergency evaluations, including neuroimaging and laboratory testing, creating significant financial burdens for uninsured or underinsured families.

Cultural Factors Influencing Disease Expression and Management

Cultural beliefs about illness, pain, and neurological symptoms significantly influence how children with hemiplegic migraine and their families understand and respond to the condition. Some cultures may attribute neurological symptoms to spiritual or supernatural causes, potentially delaying medical evaluation or creating conflicts with biomedical treatment approaches.

Language barriers represent significant challenges in the diagnosis and management of hemiplegic migraine, particularly given the complex neurological symptoms and the need for detailed symptom characterization. The availability of culturally and linguistically appropriate healthcare services varies significantly across healthcare systems. Stockwell et al. conducted a study across 16 hospitals and found that hospitalized Latino children are more likely to experience an adverse event than non-Latino white children [39].

Cultural and attitudes toward genetic testing and genetic conditions vary significantly across different ethnic and religious groups. Some cultures may view genetic conditions as stigmatizing or may have religious objections to genetic testing, creating challenges in the diagnostic evaluation of suspected familial hemiplegic migraine. Strong religious beliefs may also present additional barriers for family analysis and genetic testing, specifically in regions with strong religious or conservative beliefs [40]. Healthcare providers must be sensitive to these cultural considerations while advocating for appropriate medical care.

Family structure and decision-making patterns vary across cultural groups and may influence treatment of adherence and care coordination. In some cultures, extended family members or community leaders may play important roles in medical decision-making, requiring culturally sensitive approaches to patient and family education. Cultural competency emphasizes the need for health care systems and providers to be aware of and responsive to patients' cultural backgrounds [41]. To deliver patient centered care, the provider must consider the patient's diverse lifestyle, experiences, and perspectives to ensure proper care, individualized treatment, interpersonal skills, and effective communication [42].

Geographic and Rural Disparities

Geographic location significantly influences access to specialized care for pediatric hemiplegic migraine, with rural and remote areas often lacking pediatric neurologists or specialized headache centers. The need for genetic testing and specialized treatments may require travel to distant medical centers, creating significant burdens for rural families. Additionally, there is a shortage of genetic providers, and the majority work in large urban and academic settings resulting in substantial disparities in access to genetic specialists [43,44].

Telemedicine represents a potential solution for addressing geographic disparities in hemiplegic migraine care, though access to reliable internet connectivity and appropriate technology remains limited in some rural areas. The complex nature of neurological evaluation and the need for physical examination during acute attacks may limit the effectiveness of telemedicine approaches for some aspects of care.

Emergency medical services and local hospital capabilities vary significantly across geographic regions, potentially affecting the acute management of hemiplegic migraine attacks. A recent study found that rural populations may experience significantly higher emergency medical services utilization for migraines and are more likely to receive subpar treatment [45]. Rural hospitals may lack neurological expertise or advanced neuroimaging capabilities, potentially leading to unnecessary transfers or delays in appropriate care.

Immigration Status and Documentation Barriers

Undocumented immigration status creates significant barriers to accessing specialized neurological care for children with hemiplegic migraine. Research has shown that undocumented immigrants significantly underutilize the health care system due to fear of deportation [46]. Fear of deportation may prevent families from seeking medical care, particularly conditions that require ongoing specialist follow-up and expensive treatments. Emergency-only care patterns may result in fragmented management and increased healthcare costs. Hacker et al. conducted a literature review and found that fear of deportation, whether real or imagined, was identified as a barrier to seeking medical services in 65% of articles. Undocumented immigrants reported avoiding seeking help and reported waiting until health issues are critical to seek services [47].

Children with hemiplegic migraine who are undocumented immigrants may face particular challenges accessing genetic testing, specialized medications, and preventive care [4-6,48]. The lack of insurance coverage or eligibility for government-funded healthcare programs creates significant financial barriers to comprehensive care.

Educational and Advocacy Implications

Addressing health disparities in pediatric hemiplegic migraine requires targeted educational and advocacy efforts focused on increasing awareness among healthcare providers who serve diverse populations. Community health centers, safety-net hospitals, and providers serving predominantly minority populations need specific education about recognizing hemiplegic migraine and appropriate referral patterns.

Professional organizations and advocacy groups must prioritize diversity and inclusion in research initiatives, ensuring that future studies include representative populations and address the specific needs of underserved groups. Funding agencies should prioritize research proposals that specifically address health disparities in rare neurological conditions.

The development of culturally appropriate educational materials about hemiplegic migraine in multiple languages represents an important step toward reducing disparities in care. These materials must be developed with input from community stakeholders and cultural experts to ensure appropriate messaging and cultural sensitivity.

Healthcare policy initiatives should address the specific barriers faced by families affected by rare neurological conditions like hemiplegic migraine, including insurance coverage for genetic testing, access to specialized care, and support for families facing significant travel or financial burdens for medical care.

Clinical Presentation and Symptomatology

The clinical presentation of hemiplegic migraine in children encompasses a distinctive constellation of neurological symptoms that evolve in characteristic temporal patterns and can cause significant alarm among patients, families, and healthcare providers. The hallmark feature of hemiplegic migraine is the presence of unilateral motor weakness that develops as part of the migraine aura complex, distinguishing it from all other forms of migraine and creating unique diagnostic challenges in pediatric practice [1,8,9].

The motor aura in hemiplegic migraine typically develops gradually over minutes to hours, beginning with subtle weakness that may progress to complete paralysis of the affected side [1,3,9]. In pediatric patients, the weakness commonly affects the face, arm, and leg on one side of the body, though the distribution and severity can vary significantly between attacks and between individual patients [1]. The weakness may be accompanied by sensory symptoms including numbness, tingling, or altered sensation in the affected regions, creating a complex neurological presentation that can mimic stroke or other serious conditions [1,3,8,9].

Speech and language disturbances represent another prominent feature of pediatric hemiplegic migraine, occurring in approximately 90% of attacks according to large case series [1,8]. These disturbances can range from mild dysarthria or word-finding difficulties to complete aphasia, depending on which hemisphere is affected and the extent of cortical involvement. In younger children, speech difficulties may be the most noticeable symptom to parents and teachers, prompting urgent medical evaluation.

Visual aura phenomena are common in hemiplegic migraine, occurring in patterns similar to typical migraine with aura but often more prolonged and severe [1,3,9]. Children may experience scintillating scotomas, fortification spectra, hemianopsia, or complete visual loss during attacks [1]. The visual symptoms typically precede or accompany the motor symptoms and may serve as warning signs for children and families who have learned to recognize the attack pattern.

Cognitive and behavioral changes during hemiplegic migraine attacks in children can be particularly distressing for families and may include confusion, disorientation, memory impairment, or altered consciousness [1,8]. Some children experience fever during attacks, which can further complicate the clinical picture and raise concerns about infectious or inflammatory conditions [1,2,9]. The combination of neurological symptoms and fever has led to misdiagnoses of encephalitis or meningitis in some pediatric cases [1,49,50].

The headache component of hemiplegic migraine may differ from typical migraine patterns, with some children experiencing severe, prolonged headaches that persist for hours to days after the resolution of neurological symptoms [1,8]. However, not all children with hemiplegic migraine experience significant headaches, particularly during the acute phase when neurological symptoms predominate [1,8]. The relationship between headache severity and neurological symptom intensity varies considerably among pediatric patients.

Recovery from hemiplegic migraine attacks typically occurs gradually, with neurological symptoms resolving in reverse order of their appearance [1,9]. Complete recovery usually occurs within 24 hours, though some children may experience residual weakness, fatigue, or cognitive difficulties for several days after an attack [8]. Rarely, permanent neurological deficits may occur, particularly in cases with severe or prolonged attacks, emphasizing the importance of appropriate acute management [3,51].

Diagnostic Challenges and Differential Diagnosis

The diagnosis of hemiplegic migraine in children presents significant challenges that stem from the rarity of the condition, the dramatic nature of the clinical presentation, and the extensive differential diagnosis that must be considered when a child presents with acute-onset unilateral weakness. The initial presentation of hemiplegic migraine often occurs in emergency department settings, where the acute neurological symptoms prompt immediate evaluation for stroke, seizures, or other serious neurological conditions.

The differential diagnosis of pediatric hemiplegic migraine is extensive and includes both common and rare conditions that can present with similar neurological symptoms. Acute stroke, while rare in children, represents the most serious condition to exclude and typically requires immediate neuroimaging and vascular assessment [1,8,9,52]. Pediatric stroke can result from various causes including arterial dissection, cardioembolic disease, or hematological disorders, and the clinical presentation may be indistinguishable from hemiplegic migraine during the acute phase [53].

Seizures, particularly complex partial seizures with post-ictal weakness (Todd's paralysis), represent another important differential diagnosis. The distinction between hemiplegic migraine and seizure-related weakness can be particularly challenging, as both conditions may present with altered consciousness, motor symptoms, and post-event confusion. Severe hemiplegic migraines can be accompanied by seizures, comas, fever, cerebral edema or cerebral infarction and are often misdiagnosed as Todd's paresis, postictal confusion or epilepsy [22,50]. To detect brain abnormalities, EEG is needed to measure electrical disturbances in the human brain to identify and exclude seizure activity [54]. However, normal EEG findings do not definitively rule out seizure-related causes.

Infectious and inflammatory conditions of the central nervous system, including encephalitis, meningitis, or acute disseminated encephalomyelitis, must be considered, particularly when fever accompanies the neurological symptoms. The combination of fever, altered consciousness, and focal neurological deficits often necessitates lumbar puncture and extensive infectious workup before the diagnosis of hemiplegic migraine can be confidently established. Moreover, the combination of fever and neurological symptoms and the rarity of a hemiplegic migraine diagnosis require extensive neurological testing and examination to rule out diagnoses that mirror HM [55].

Metabolic disorders, particularly those affecting mitochondrial function or causing intermittent neurological symptoms, represent another category of conditions that may mimic hemiplegic migraine. MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and other mitochondrial disorders can present with recurrent neurological episodes that may be difficult to distinguish from hemiplegic migraine without specific metabolic testing [3]. Patients may also be subject to muscle weakness, seizures, and cognitive decline which may further contribute to difficulty in proper diagnosis [3].

The diagnostic process for hemiplegic migraine relies heavily on clinical criteria established by the International Headache Society, which requires the presence of motor weakness during the aura phase along with typical migraine features [17]. However, applying these criteria in pediatric populations can be challenging, particularly in younger children who may have difficulty describing their symptoms or in cases where the headache component is minimal or absent.

Neuroimaging plays a crucial role in the diagnostic evaluation of suspected hemiplegic migraine, primarily to exclude other serious conditions rather than to confirm the diagnosis. Computed tomography and magnetic resonance imaging are typically normal between attacks, though some studies have reported subtle changes in white matter or cerebellar regions in patients with familial hemiplegic migraine [56]. During acute attacks, neuroimaging may show cytotoxic edema or other changes that can be confused with stroke, emphasizing the importance of clinical correlation [56,57].

Genetic Testing and Molecular Diagnosis

Genetic testing has revolutionized the diagnostic approach to hemiplegic migraine in pediatric patients, providing definitive molecular confirmation of familial cases and enabling accurate genetic counseling for affected families. The availability of comprehensive genetic panels and whole-exome sequencing has made genetic diagnosis increasingly accessible, though the interpretation of results requires specialized expertise in neurogenetics.

The decision to pursue genetic testing in pediatric hemiplegic migraine depends on several factors, including family history, clinical presentation patterns, and the presence of additional neurological features. Additionally, HM is one of the monogenic conditions that have been identified and mutations in CACNA1A, ATP1A2, and SCN1A determine a significant number of familial and sporadic cases [1,37]. Children with clear family histories of hemiplegic migraine are obvious candidates for genetic testing, as confirmation of a familial mutation can establish the diagnosis and provide valuable prognostic information. However, genetic testing may also be valuable in apparently sporadic cases, as de novo mutations or previously unrecognized family history may be identified [1].

The current genetic testing approach typically involves targeted sequencing of the three known hemiplegic migraine genes: CACNA1A, ATP1A2, and SCN1A [1,37]. This targeted approach is cost-effective and provides results that are relatively straightforward to interpret. However, as additional hemiplegic migraine genes are identified, expanded gene panels or whole-exome sequencing may become the preferred approach, particularly in families where targeted testing has been negative.

The interpretation of genetic testing results requires careful consideration of variant classification criteria and the clinical context. Pathogenic mutations in hemiplegic migraine genes are relatively rare, and many identified variants are of uncertain clinical significance [1]. The classification of variants requires assessment of multiple factors including population frequency, predicted functional impact, segregation within families, and comparison with established pathogenic mutations.

Genetic counseling represents an essential component of the genetic testing process, particularly given the autosomal dominant inheritance pattern of familial hemiplegic migraine. Families require detailed information about inheritance risks, the implications of positive or negative test results, and the potential for genetic testing of other family members [17]. The psychological impact of genetic diagnosis must also be addressed, particularly in families where multiple children may be at risk.

The clinical utility of genetic testing extends beyond diagnosis to include prognosis and treatment planning. Certain genetic subtypes of hemiplegic migraine are associated with specific clinical features or comorbidities that may influence management decisions. For example, CACNA1A mutations may be associated with cerebellar dysfunction or epilepsy, while ATP1A2 mutations may be linked to intellectual disability or psychiatric symptoms [11,17,22].

Neuroimaging Findings and Their Clinical Significance

Neuroimaging in pediatric hemiplegic migraine serves multiple purposes including the exclusion of structural abnormalities, the assessment of acute changes during attacks, and the identification of long-term consequences of recurrent episodes [58]. The neuroimaging approach must be tailored to clinical presentation and may require multiple modalities to fully characterize the condition and exclude alternative diagnoses.

During acute hemiplegic migraine attacks, conventional magnetic resonance imaging may demonstrate various abnormalities that can be confused with stroke or other serious conditions [58]. Diffusion-weighted imaging may show hyperintense lesions in affected cortical regions, representing cytotoxic edema associated with cortical spreading depression [59]. These changes are typically reversible and resolve completely after the attack, distinguishing them from true ischemic lesions.

Perfusion imaging during hemiplegic migraine attacks has revealed complex patterns of cerebral blood flow changes that correlate with the clinical symptoms and the progression of cortical spreading depression [60]. Initial hyperperfusion may be followed by prolonged hypoperfusion in affected brain regions, creating imaging appearances that can mimic stroke or other vascular conditions. Understanding these perfusion patterns is crucial for appropriate interpretation of neuroimaging findings [60].

Between attacks, routine structural neuroimaging is typically normal in children with hemiplegic migraine, though some studies have reported subtle abnormalities in patients with frequent or severe attacks. White matter hyperintensities, cerebellar atrophy, or cortical thinning have been described in some series, though the clinical significance of these findings remains unclear [50]. Longitudinal imaging studies are needed to determine whether these changes represent consequences of recurrent attacks or underlying predisposing factors.

Advanced neuroimaging techniques including magnetic resonance spectroscopy, diffusion tensor imaging, and functional magnetic resonance imaging have provided insights into the pathophysiology of hemiplegic migraine and may eventually contribute to diagnostic approaches. These techniques have demonstrated metabolic abnormalities, altered white matter integrity, and functional connectivity changes that distinguish hemiplegic migraine from other conditions [61].

The timing of neuroimaging in relation to symptom onset is crucial for appropriate interpretation of findings. Imaging performed during the acute phase may show changes that resolve completely, while imaging performed days to weeks after an attack may be completely normal. Emergency department physicians and neurologists must understand these temporal relationships to avoid misinterpretation of imaging findings.

Treatment Approaches and Management Strategies

The management of hemiplegic migraine in children requires a comprehensive approach that addresses both acute symptom relief and long-term prevention, while considering the unique physiological and developmental characteristics of pediatric patients. Treatment strategies must be individualized based on attack frequency, severity, functional impact, and the presence of comorbid conditions, while carefully weighing the benefits and risks of various therapeutic interventions.

Acute management of hemiplegic migraine attacks in children focuses primarily on supportive care and symptom relief, as the dramatic neurological presentation often resolves spontaneously within hours to days. However, the severity of symptoms and family distress often necessitate hospitalization for monitoring and supportive care, particularly during initial presentations when the diagnosis has not yet been established [1].

The use of traditional migraine abortive medications in hemiplegic migraine requires special consideration due to theoretical concerns about vasoconstriction in the setting of already compromised cerebral circulation [1]. Triptans and ergot alkaloids are generally contraindicated in hemiplegic migraine due to their vasoconstrictive properties and the theoretical risk of exacerbating cerebral hypoperfusion. This contraindication is particularly important in pediatric practice, where these medications might otherwise be considered for severe migraine attacks [1,8].

Alternative acute treatment approaches for pediatric hemiplegic migraine include non-steroidal anti-inflammatory drugs, which may provide both analgesic and anti-inflammatory effects during attacks [8]. Acetaminophen and ibuprofen are commonly used and generally well-tolerated in children, though their effectiveness for the neurological symptoms of hemiplegic migraine is limited. Antiemetic medications may be helpful for associated nausea and vomiting [8].

Emerging acute treatment options for severe hemiplegic migraine include intranasal ketamine, which has shown promise in case reports and small series [9,10,62,63]. Ketamine's unique mechanism of action as an NMDA receptor antagonist may provide specific benefits in the context of cortical spreading depression and the pathophysiology of hemiplegic migraine [9,10,62,63]. However, the use of ketamine in pediatric patients requires careful consideration of dosing, monitoring, and potential adverse effects.

Preventive treatment represents the cornerstone of management for children with frequent or severe hemiplegic migraine attacks. The goals of preventive therapy include reducing attack frequency and severity, minimizing functional impairment, and improving quality of life for both patients and families. The choice of preventive medication must consider the child's age, weight, comorbid conditions, and family preferences.

Calcium channel blockers, particularly verapamil and flunarizine, are considered first-line preventive treatments for hemiplegic migraine in children [64,65]. These medications have demonstrated efficacy in reducing attack frequency and are generally well-tolerated in pediatric populations. Flunarizine, while not available in all countries, has shown particular promise in pediatric hemiplegic migraine prevention and may have fewer cardiac effects than verapamil [64,65].

Antiepileptic drugs represent another important category of preventive medications for pediatric hemiplegic migraine. Lamotrigine has demonstrated efficacy in several case series and may be particularly appropriate for children with concurrent seizure disorders [1,3,8,9]. Valproate and topiramate have also been used successfully, though their use requires careful monitoring for potential adverse effects including cognitive impairment and metabolic complications [1,3,8,9].

The newer category of calcitonin gene-related peptide (CGRP) receptor antagonists and monoclonal antibodies represents a promising development in migraine prevention, though experience in pediatric hemiplegic migraine remains limited [66]. These medications have demonstrated efficacy in adult migraine prevention and may offer advantages in terms of tolerability and mechanism of action, though pediatric safety and efficacy data are still being collected.

Prognosis and Long-term Outcomes

The long-term prognosis of hemiplegic migraine in children is generally favorable, with most patients experiencing stable or improving clinical courses over time. However, the condition can significantly impact quality of life, educational achievement, and social development during childhood and adolescence, emphasizing the importance of comprehensive management approaches that address both medical and psychosocial aspects of the condition [8].

Attack frequency and severity tend to vary significantly among pediatric patients with hemiplegic migraine, with some children experiencing rare, isolated episodes while others have frequent attacks that significantly impact daily functioning [8]. Longitudinal studies suggest that many children with hemiplegic migraine experience a reduction in attack frequency and severity with age, though some may continue to have attacks into adulthood [8].

The relationship between genetic subtype and long-term prognosis is an area of active research, with some studies suggesting that certain mutations may be associated with more severe phenotypes or additional neurological complications. Children with CACNA1A mutations may be at increased risk for cerebellar dysfunction or epilepsy, while those with ATP1A2 mutations may have higher rates of intellectual disability or psychiatric comorbidities [11,17,22,67,68].

Educational outcomes in children with hemiplegic migraine can be significantly impacted by frequent attacks, particularly when they occur during school hours or result in prolonged recovery periods [8]. School accommodations may be necessary to address absences, cognitive effects of medications, or residual symptoms following attacks. Collaboration between healthcare providers, families, and school personnel is essential for optimizing educational outcomes.

The psychological impact of hemiplegic migraine on children and families should not be underestimated, as the dramatic nature of attacks often creates significant anxiety and fear. Children may develop anticipatory anxiety about attacks, while parents may become overly protective or vigilant [8,30]. Psychological support and counseling may be beneficial for both patients and families.

Rare complications of hemiplegic migraine include permanent neurological deficits, typically resulting from severe or prolonged attacks [3,51]. These complications are more common in certain genetic subtypes and may include persistent weakness, cognitive impairment, or cerebellar dysfunction [3,22,50]. The risk of complications emphasizes the importance of aggressive preventive treatment in children with frequent or severe attacks.

Future Directions and Research Opportunities

The field of pediatric hemiplegic migraine continues to evolve rapidly, with advancing understanding of genetic mechanisms, pathophysiology, and therapeutic approaches creating new opportunities for improved diagnosis and treatment. Several areas of active research hold particular promise for enhancing outcomes in affected children and their families.

Genetic research continues to identify new genes and pathways involved in hemiplegic migraine pathogenesis, potentially leading to expanded diagnostic testing panels and novel therapeutic targets. Whole-genome sequencing and other advanced genetic techniques are revealing the complex genetic architecture underlying hemiplegic migraine and may identify modifier genes that influence phenotype severity or treatment response [3,9,11,12,21,23,24].

Biomarker research represents another promising area of investigation, with the goal of identifying blood or cerebrospinal fluid markers that could aid in diagnosis, prognosis, or treatment monitoring [3,9]. Inflammatory markers, metabolites, and other molecular signatures may provide insights into disease mechanisms and therapeutic response [3,9].

Advanced neuroimaging techniques are providing new insights into the pathophysiology of hemiplegic migraine and may eventually contribute to diagnostic approaches or treatment monitoring. Functional magnetic resonance imaging, magnetic resonance spectroscopy, and other techniques are revealing abnormalities in brain networks and metabolism that may persist between attacks [1-3,8,9].

Therapeutic research is focusing on novel treatment approaches that target specific pathophysiological mechanisms involved in hemiplegic migraine. CGRP-targeted therapies, glutamate receptor modulators, and other mechanism-based approaches may offer improved efficacy and tolerability compared to current treatments [66].

The development of pediatric-specific treatment guidelines and protocols represents an important research priority, as most current recommendations are extrapolated from adult data or based on limited pediatric experience. Randomized controlled trials specifically designed for pediatric populations are needed to establish evidence-based treatment approaches.

Conclusion

Hemiplegic migraine in children represents a complex and challenging neurological condition that requires specialized knowledge and expertise for accurate diagnosis and effective management, with particular urgency needed to address the documented healthcare disparities that disproportionately affect Black children and other minority populations. The dramatic clinical presentation often leads to initial misdiagnosis and extensive medical workup, a problem compounded by the significantly lower rates of migraine diagnosis observed in Black and Hispanic children compared to White children in emergency department settings [4-7].

The identification of genetic causes has revolutionized understanding of the condition and enabled precise molecular diagnosis in many cases, while also revealing the complex pathophysiological mechanisms underlying the dramatic clinical phenotype. Mutations in CACNA1A, ATP1A2, and SCN1A genes account for the majority of familial cases, though genetic testing remains underutilized in minority populations due to access barriers and disparities in specialized care [4-7]. The management of pediatric hemiplegic migraine requires a comprehensive approach that addresses both acute symptoms and long-term prevention, while considering the unique developmental and physiological characteristics of children and the cultural factors that may influence symptom expression and help-seeking behaviors.

Current treatment approaches emphasize the use of calcium channel blockers such as verapamil and flunarizine, along with antiepileptic drugs including lamotrigine and valproate for prevention, while avoiding traditional migraine abortive medications like triptans that may be contraindicated due to their vasoconstrictive properties [1,3,8,9,65]. However, access to these specialized treatments and the neurological expertise required for optimal management remains inequitable, with substantial barriers facing minority families including geographic limitations, insurance coverage restrictions, and systemic biases in healthcare delivery.

The epidemiological understanding of hemiplegic migraine in Black children remains critically incomplete due to historical exclusion of diverse populations from neurological research and the persistent underdiagnosis of migraine conditions in minority communities. Available evidence suggests that Black children may experience more severe migraine presentations and greater functional disability, yet they are less likely to receive appropriate neuroimaging, specialty referrals, and intensive treatment compared to White children [4-7]. This disparity represents not only a failure of healthcare equity but also a missed opportunity to understand how genetic, environmental, and social determinants of health interact to influence the expression and progression of hemiplegic migraine across diverse populations.

The prognosis for children with hemiplegic migraine is generally favorable, though the condition can significantly impact quality of life and development during the pediatric years, with potentially greater impact on Black children who face additional stressors related to structural racism, socioeconomic disadvantage, and limited access to comprehensive neurological care [4-7]. The psychological burden of living with an unpredictable neurological condition may be exacerbated in minority families who may distrust healthcare systems, have limited access to mental health resources, or face language barriers in navigating complex medical information [4-6,39].

Ongoing research continues to advance understanding of the genetic basis, pathophysiology, and optimal treatment approaches for this rare but important neurological condition. However, the striking absence of diverse populations in hemiplegic migraine research represents a critical knowledge gap that must be urgently addressed. Future studies must prioritize the inclusion of Black, Hispanic, and other underrepresented populations to understand potential differences in genetic susceptibility, clinical presentation, treatment response, and long-term outcomes. Enhanced awareness of healthcare disparities, improved diagnostic approaches that account for cultural factors in symptom presentation, and evidence-based treatment protocols that address access barriers will be essential for optimizing outcomes in affected children and their families.

The complexity of hemiplegic migraine in children underscores the importance of multidisciplinary care involving pediatric neurologists, geneticists, and other specialists working collaboratively to provide comprehensive evaluation and management. However, this idealized model of care remains inaccessible to many Black children and families due to systemic barriers in healthcare access, geographic maldistribution of pediatric subspecialists, and implicit biases that affect clinical decision-making. Addressing these disparities will require intentional efforts to increase diversity in neurological training programs, implement bias reduction strategies in clinical practice, expand telemedicine capabilities to underserved communities, and advocate for policy changes that improve insurance coverage for genetic testing and specialized treatments.

The documented underrepresentation of Black children in neurological research has created substantial knowledge gaps regarding the natural history, genetic architecture, and treatment response patterns of hemiplegic migraine in this population. Recent investigations have revealed concerning disparities in emergency department management, with Black and Hispanic children receiving less intensive treatment including decreased likelihood of intravenous therapies and reduced rates of neuroimaging compared to White children, despite similar initial pain scores [4-6]. These findings suggest that systemic biases in clinical decision-making may contribute to suboptimal outcomes for minority children with hemiplegic migraine, potentially leading to delayed recognition of the condition, inadequate acute management, and reduced access to preventive treatments.

Furthermore, the intersection of hemiplegic migraine with social determinants of health in Black communities creates additional layers of complexity that have been largely ignored in the neurological literature. Environmental factors such as neighborhood stressors, exposure to structural racism, economic instability, and limited access to healthy foods may influence migraine triggers and severity in ways that are not well understood [5,6,8]. The psychological impact of experiencing dramatic neurological symptoms in the context of historical medical trauma and ongoing healthcare discrimination may exacerbate the burden of illness for Black children and their families, potentially affecting treatment adherence, help-seeking behaviors, and long-term outcomes [69,70].

As our understanding of hemiplegic migraine continues to evolve, the commitment to health equity must be central to research priorities, clinical practice guidelines, and healthcare policy development. The prospects for improved diagnosis, treatment, and outcomes for affected children remain promising, but achieving these improvements for all children, regardless of race or socioeconomic status, will require sustained attention to the persistent disparities that have long characterized neurological care in the United States. Only through such comprehensive efforts can we ensure that advances in the understanding and treatment of hemiplegic migraine benefit all children equitably, addressing the historical neglect of minority populations in neurological research and clinical care.

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