Paroxysmal hemicrania in children and adolescents: A systematic review

Maryam Bemanalizadeh MD\textsuperscript{1,2} | Homayoun Baghaei Oskouei MD\textsuperscript{3} | Alireza Hadizadeh MD\textsuperscript{3} | Mohammad Sedigh Dakkali MD\textsuperscript{4} | Reihane Qahremani MD\textsuperscript{3} | Vahid Mansouri MD\textsuperscript{1,2}

\textsuperscript{1}Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
\textsuperscript{2}Department of Pediatrics Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
\textsuperscript{3}School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{4}School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

Correspondence
Vahid Mansouri, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan 1411719135, Iran.
Email: mansoury.vahid@gmail.com; v.mansoury@edc.mui.ac.ir

Abstract

Objective: We aimed to report the accessible demographic, clinical, and radiological characteristics of reported pediatric paroxysmal hemicrania (PH).

Introduction: It has been a while since PH in a child was first described. However, it is still unknown whether children's PH follows the same patterns as adults.

Methods: This study followed the latest version of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Web of Science, and Scopus were searched systematically without time limitation. We included all English-language, peer-reviewed articles, including observational or interventional studies reporting PH cases in children or adolescents based on the International Classification of Headache Disorders (ICHD) criteria. Data extracted included PH class; sex; age; age of onset; frequency, duration, site, severity, and quality of pains; triggers; and autonomic and migrainous symptoms, as well as a sense of restlessness/agitation, response to treatment, laboratory investigations, imaging, comorbidity, and family history. For quality assessment, two independent reviewers (MB and VM) assessed the methodological quality of the included studies through the Joanna Briggs Institute's critical appraisal checklist.

Results: A total of 182 records were identified and reduced to 116 after removing duplicates. After screening, 22 articles met the inclusion criteria. Overall, the studies represented 35 children or adolescents with PH. We found a boy-to-girl ratio of 1.125:1. Onset occurred at a broad range of 1 to 14 years old. The mean age of onset among reported cases in children and adolescents was 6.5 years, while the mean age of diagnosis was 8.2 years. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, 6.3 and 7.9 years were changed to 6.5 and 8.2 years, respectively.] The attacks’ frequency and duration were greatly varied. Left-sided pain occurred twice as often as right-sided pain. The characteristics of the pain were usually severe in intensity. In nearly all of the cases, it was accompanied by ipsilateral cranial autonomic features. While most attacks were spontaneous, there were some common triggers. The physical examination, electroencephalogram, and brain magnetic resonance imaging had normal findings. Almost all patients benefited from...
INTRODUCTION

Trigeminal autonomic cephalalgias, including cluster headaches, paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing/cranial autonomic features, are approximately 100 times less prevalent than migraine. They are defined by severe unilateral short episodes of pain. They share rhinorrhea, nasal congestion, lacrimation, and conjunctival injection as ipsilateral cranial autonomic symptoms. They do, however, differ in duration, frequency, and type of treatments.

PH is classified as chronic paroxysmal hemicrania (CPH) and episodic paroxysmal hemicrania (EPH) in the International Classification of Headache Disorders, 3rd edition (ICHD-3). In EPH, attacks occur in periods lasting 7 days to 1 year, separated by pain-free periods lasting 1 month or longer. In CPH, attacks occur for more than 1 year without remission or with remissions lasting less than 1 month. Reports from clinical reviews and expert opinions often note that PH typically begins in adulthood. However, reports have indicated a several-year delay in diagnosis, which could be attributed to atypical headache features in children and adolescents (migraine, for example, can have a shorter duration in pediatric patients). While PH in adults is a well-known diagnosis among neurologists, current awareness and knowledge of PH in children are not satisfying.

Even though it has been a long time since the first presentation of PH in a child was reported, it is unknown whether PH in children follows the same patterns as in adults. There is a lack of awareness of PH in pediatricians, as well as difficulty in taking children’s history of attacks and pain characteristics.

This study aims to describe the broad age ranges of PH in children and adolescents and to report the accessible demographic, clinical, and radiological characteristics of reported pediatric PH, as well as their response to treatment.

METHODS

Study selection

The protocol of this study was registered with PROSPERO (ID: CRD42022306190). We followed the latest version of the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines. We searched for studies up to January 2022 without time limitation in the following databases: PubMed, Web of Science, and Scopus. A literature search was conducted for studies investigating PH among children or adolescents under 18 years of age using combinations of the following keywords: “paroxysmal hemicrania” AND (“infants” OR “children” OR “adolescents”) and their equivalent keywords and phrases based on Medical Subject Headings of the US National Library of Medicine (Table S1 in supporting information). The relevance of these terms was determined based on some previous reviews. Our search strategy in different databases is available in Table S2 in supporting information. Moreover, references from relevant articles were evaluated for potentially missed studies. After excluding duplicate publications, two researchers (MB and VM) independently screened titles and abstracts of the retrieved studies. Likewise, studies that remained of interest were then screened based on their full text by MB and VM. In the screening and eligibility steps, disagreements were settled by discussion between the two researchers. In all cases, a consensus was reached.

Inclusion and exclusion criteria

Studies included in the present systematic review met the following criteria: (1) all types of observational or interventional studies, (2) published in English-language, peer-reviewed journals, (3) known PH cases based on the latest version of ICHD in the date of publication, and (4) age of onset of 18 years or less. Meeting abstracts and similar articles that may have less strict peer review, as well as articles published prior to 1988, were excluded. Although we did not limit the date in our primary search, we chose 1988 as the starting date for screening because the first edition of the ICHD was published that year. In addition, because of a wide range of publication dates from 1989 to 2021 based on our primary search, the ICHD version varied between 1 to 3. However, we discussed all symptoms based on ICHD-3 criteria. Furthermore, studies were screened for duplicate data based on authors, publication year, participant numbers, and characteristics. When possible duplicate data were found, the authors were contacted to clarify whether the data sets were independent.
Data extraction

Two authors (MB and VM) independently extracted data elements from each article. Included studies were entered into a prepiloted form for assessment of study quality and evidence synthesis. The items extracted from the included studies were first author; publication year; country; PH class; sex; age; age of onset; frequency; duration, site, severity, and quality of pains; triggers; symptoms accompanied by headaches, including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead/facial sweating, miosis and ptosis, nausea, photophobia, and phonophobia, as well as a sense of restlessness/agitation; response to treatment; laboratory investigations; imaging; comorbidity; and family history.

Statistical measures

The mean of the continuous variables, including the age of onset and age of diagnosis, was calculated from the included data. Also, the sex ratio was calculated by dividing the number of boys by the number of girls. SPSS version 24 (SPSS Inc.) was used for calculations. Studies that missed the corresponding measures were excluded from the parameter calculation.

Quality assessment

For quality assessment, two independent reviewers (MB and VM) assessed the methodological quality of the included studies through the Joanna Briggs Institute’s (JBI’s) critical appraisal checklist, which is a reliable and valid quality index for the appraisal of case reports and case series. Discrepancies were resolved through discussion and the involvement of a third reviewer (MSD) where necessary. JBI’s critical appraisal checklists were structured into fixed sets of questions for case reports and case series of 8 and 10 questions, respectively, focusing on different aspects of bias in the study’s design, conduct, and analysis. Bias was assessed as a judgment with yes, no, unclear, or not applicable answers for each question. Prior to critical appraisal evaluation, decisions about the scoring system and the cutoff for inclusion of a study in the review were determined in advance and agreed on by all participating reviewers. All reviewers agreed that studies with three or more negative responses were assumed to be of low methodological quality and should be excluded from the final results.

RESULTS

A total of 182 records were identified and reduced to 116 after removing duplicates. After screening and the application of the eligibility criteria, 22 articles met the inclusion criteria. Figure 1 presents the flow diagram of the included and excluded articles in our review according to PRISMA.

Owing to the lack of detailed case presentation in some cases, we could not ascertain the diagnosis of PH by the latest version of ICHD according to the provided information (Table 1). Instead, we decided to rely on the authors’ claims about the diagnosis mentioned in each article. However, we made sure that the authors made the diagnosis based on the latest version of ICHD according to the publication date. Table 1 provides an overview of the patients’ characteristics and outcome measures. The included studies consisted of 5 case series and 17 case reports. There were no cohort or case-control studies, or clinical trials. Overall, the studies represented 38 children suspected of PH. However, we excluded six cases from the final analysis because the patients did not have concomitant autonomic symptoms.

To the best of our knowledge, the first pediatric case of PH was reported by Kudrow in 1989. Among previous studies in the pediatric population, CPH, EPH, and unspecified PH were reported in 23, 7, and 5 patients, respectively. PH has been described among children and adolescents in various parts of the world, but the races were not specified in most of the studies. With the exception of one study, the sex was reported in all cases. In our review of all pediatric PH cases, we found a boy-to-girl ratio of 1.125:1 (18 boys vs. 16 girls). The youngest age of onset was reported by de Almeida et al. They reported a 10-year-old girl who had complained of left unilateral headache attacks since she was 1 year old. After excluding the cases with unknown ages of onset or diagnosis, the mean age of onset among reported cases in children and adolescents was 6.5 years, while the mean age of diagnosis was 8.2 years.

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The pain was typically unilateral, but could alternate 9,20,38 and was only rarely bilateral.32 Left-sided pain was approximately twice as common as right-sided headaches (11 left sided vs. 6 right sided). The characteristics of the pain in PH were usually severe in intensity (led to crying/screaming, awakening the child at night, and wishing to die) in almost all cases and have been described by patients as sudden, sharp, stabbing, shooting, throbbing, and excruciating.

Attacks of PH invariably occur in association with ipsilateral cranial autonomic features in all cases except six children, which we noted above.29,30,38 The most frequent attacks were attributed to a 14-year-old girl with 32–48 attacks per day and the least frequent attacks were described in a 10-year-old girl with one attack per week. The duration of attacks varied between 2 minutes and 40 minutes. The pain was typically unilateral, but could alternate sides between attacks38 and was only rarely bilateral.32 Left-sided pain was approximately twice as common as right-sided headaches (11 left sided vs. 6 right sided). The characteristics of the pain in PH were usually severe in intensity (led to crying/screaming, awakening the child at night, and wishing to die) in almost all cases and have been described by patients as sudden, sharp, stabbing, shooting, throbbing, and excruciating.

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA-2020) flow diagram. TACs, trigeminal autonomic cephalalgias.
| Author, year of publication, country | Case | Classification | Sex | Age, y | Age of onset | Frequency, No. | Duration | Severity | Site | Quality | Headache accompanied by: | A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|------------------------------------|------|----------------|-----|--------|-------------|----------------|----------|----------|------|---------|----------------------------|------------------------|----------------------|----------|---------|
| Abu-Arabe, 2016, UK               | 1    | EPH            | Girl | 14     | NA          | 32–48/day      | 2–10 min  | Severe, lead to crying | Right side of face + eye | Sharp and sudden | Ipsilateral swelling of the eyelid, redness over the cheek | Extreme distress and agitation (thrashing movements of the arms and legs) | Partial response: indomethacin | EEG during and between attacks, biochemical and hematological investigation: NL urine tests for toxicology: negative | Brain MRI: NL |
| de Almeida, 2004, Brazil          | 2    | CPH            | Girl | 10     | 1           | 1/week at 1 year of age; then many times/day at 4 years of age | 5–40 min  | Severe, lead to crying | Left fronto-temporal-orbital ± periauricular region | Sudden, cold sensation | Ipsilateral lacrimation, conjunctival hyperemia, eyelid edema | Remaining seated but with occasional standing. | No response: NSAIDs, amitriptyline, propranolol, and carbamazepine | Complete response: indomethacin + verapamil | Neurological, clinical, and ophthalmological examination: NL audiometry and blood tests: NL | Brain CT scan, Brain MRI (three times), and skull X-ray: NL thermography: a cold patch image in left frontal area characteristic of hemifacial spasmotic headaches |
| Blankenburg, 2009, Germany        | 3    | CPH            | Boy  | 3.9    | 2.5         | 7/day          | Mean: 5 min | 5/10     | Unilateral supraorbital and midline of forehead pain | NA | Facial paleness | No | Complete response: indomethacin | NA | Brain MRI: no abnormalities |
| Blankenburg, 2009, Germany        | 4    | CPH            | Girl | 3.8    | 2.9         | 8/day          | Mean: 20 min | 10/10    | Unilateral supraorbital and midline of forehead pain | NA | Ipsilateral forehead and facial sweating | No | No response: oxygen inhalation | Partial response: indomethacin | NA | Brain MRI: no abnormalities |
| Blankenburg, 2009, Germany        | 5    | EPH            | Girl | 12.2   | 3.7         | 6/day          | Mean: 5 min | 7/10     | Unilateral supraorbital pain | NA | Ipsilateral conjunctival lacrimation, eyelid edema, mild nausea, exhaustion | No | Partial response: indomethacin | NA | Brain MRI: no abnormalities |
| Blankenburg, 2009, Germany        | 6    | CPH            | Boy  | 4.9    | 4.8         | 9/day          | Mean: 20 min | 10/10    | Unilateral supraorbital pain | NA | Facial paleness, ipsilateral forehead and facial sweating | No | No response: oxygen inhalation | Partial response: indomethacin | NA | Brain MRI: no abnormalities |
| Blankenburg, 2009, Germany        | 7    | CPH            | Boy  | 6      | 5.8         | 6/day          | Mean: 5 min | 8/10     | Unilateral supraorbital pain | NA | Ipsilateral conjunctival lacrimation, forehead and facial sweating, miosis/ ptosis, mild nausea, phono phobia | No | Partial response: indomethacin | NA | Brain MRI: no abnormalities |
| Blankenburg, 2009, Germany        | 8    | PH             | Boy  | 7.2    | 7.0         | 8/day          | Mean: 20 min | 9/10     | Unilateral supraorbital pain | NA | Ipsilateral conjunctival lacrimation, forehead and facial sweating, phono phobia | No | No response: oxygen inhalation | Partial response: indomethacin | NA | Brain MRI: no abnormalities |
| Author, year of publication, country | Case Classification | Sex | Age, y | Age of onset, No. | Frequency, Duration, Severity | Site | Quality | Headache accompanied by: | A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|------------------------------------|---------------------|-----|--------|------------------|-------------------------------|------|---------|---------------------------|------------------------|---------------------|----------|--------|
| Blankenburg, 2009, Germany         | 9                   | EPH | Boy    | 7.9              | 7.3                           | 10/day Mean: 20 min           | Unilateral supraorbital pain | NA                     | Ipsilateral forehead and facial sweating, miosis/ptosis | No response: indomethacin | Complete response: toplamate | NA       | Brain MR: no abnormalities |
| Blankenburg, 2009, Germany         | 10                  | CPH | Girl   | 10.3             | 12.9                          | 12/day Mean: 5 min            | Unilateral supraorbital pain | NA                     | Ipsilateral forehead and facial sweating, phonophobia | Partial response: indomethacin | NA       | Brain MR: no abnormalities |
| Borius 2021, France                | 11                  | CPH | Girl   | 13               | 11                            | 10–15/day Mean: 30 min        | Severe, left-sided, supraorbital pain radiating to left side of face to the neck | No                      | No response: amitriptyline, verapamil, flunarizine, propranolol, carbamazepine, toplamate, suboccipital betamethasone injection | Partial response: oxygen therapy | Complete response: indomethacin, occipital nerve stimulation | NA       | |
| Broeske, 1993, USA                 | 12                  | CPH | Girl   | 5                | 3                             | 2–5/day Mean: 15–20 min       | Severe, awakening her at night left-sided, orbitofrontal region | No                      | Ipsilateral ptosis, conjunctival lacrimation, rhinorhea, ptosis, deformity of face, nausea, phonophobia | Complete response: indomethacin | Cervical venous hum, neurological examination, biochemical and hematological investigation: NL | MR (first): unchanging focal volume loss and abnormal signal in the left occipital lobe consistent with hemosiderin deposition, consistent with a previous infarction | MR angiogram (second): NL |
| Evers, 2020, Germany               | 13                  | CPH | Girl   | 2                | 1.5                           | 5–10/day Mean: 5–10 min       | Severe, lead to crying left-sided, constricting and excruciating pain | No                      | Ipsilateral laceration, conjunctival injection | No response: ibuprofen, acetaminophen, metamizole, diazepam, and amitriptyline | Neurological exam and EEG between the attacks: NL | Brain MR scan (T1 and T2 sequences, MR angiography, and venography and orbital slices): NL |
| Frusciante, 2015, Italy            | 14                  | EPH | Boy    | 11               | 6                             | Daily 20–40 min               | Frontal pain constricting and excruciating pain | NA                      | Eyelid edema, nasal congestion, vomiting | No response: pizotifen, amitriptyline, verapamil, toplamate and prednisone | Complete response: indomethacin | General and neurological exams, including fundus oculi: NL | MR: NL |

**TABLE 1 (Continued)**
| Author, year of publication, country | Case | Classification | Sex | Age, y | Age of onset | Frequency, No. | Duration | Severity | Site | Quality | Headache accompanied by: | A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|----------------------------------|------|---------------|-----|--------|-------------|---------------|----------|----------|------|---------|-------------------------|----------------------|----------------------|---------|---------|
| Gladstein, 1994, USA             | 15   | CPH           | Boy | 8.5    | 8           | 3/day         | 15-30min  | Severe, wishing to die | Right-sided headaches | Excruating pain | Lacrimation, rhinorrhea | Screaming and running around | No response: oxygen, acetaminophen, and propranolol | Partial response: prednisone | Complete response: indomethacin | Dental, neurological, ophthalmological, and psychological evaluations, and EEG: NL |
| Ishii, 2019, Japan               | 16   | PH            | Boy | 11     | 11          | 20-30/day     | 2-20min   | Severe, 8/10 | Left-sided, orbitofrontal and temporal regions | Sharp, pulsating | Conjunctival injection, lacrimation, nasal congestion, eyelid edema, ptosis | No | No response: acetaminophen, oxygen | Complete response: indomethacin | Neurological examination, and biochemical and hematological exams: NL | Brain MRI/MRA/ MRV: NL |
| Klassen, 2000, Canada            | 17   | CPH           | Boy | 6      | 5           | 1-3/week     | <10 min   | Severe | Left periorbital and temporal regions | NA | Ipsilateral conjunctival injection, lacrimation, eyelid swelling, photophobia, intermittent vomiting | NA | Spontaneous improvement within two weeks of beginning the diary | General and neurological exam: NL | NA |
| Kudrow, 1989, USA               | 18   | CPH           | Boy | 9      | 6           | 16/day       | 30-20min  | Severe, awakening him at night | Left retroorbital and supraorbital regions | Excruating and nonthrobbing pain | Ipsilateral lacrimation, nasal stuffiness, ptosis, conjunctival injection | NA | No response: acetaminophen, phenobarbital | Complete response: baby aspirin | Mental status testing, cranial nerve evaluation, motor and sensory examination, tendon reflexes and coordination testing and EEG: NL | Brain MR: MRA/ MRV: NL |
| Mauritz, 2021, Germany          | 20   | EPH           | Boy | 4.1    | 1.2         | >5/day       | Mean: 25min | Severe, 3/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Nasal congestion and/or or rhinorrhea forehead and facial sweating, miosis/ ptosis | No | Complete response: indomethacin | NA | Brain MR: NL |
| Mauritz, 2021, Germany          | 21   | CPH           | Boy | 6      | 5.8         | >5/day       | Mean: 20min | Severe, 6/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Forehead and facial sweating | Yes | Complete response: indomethacin | NA | Brain MR: NL |
| Mauritz, 2021, Germany          | 22   | CPH           | Girl | 7.3    | 6.8         | >5/day       | Mean: 30min | Severe, 3/10 | Unilateral orbital, supraorbital, and/or temporal | NA | No symptoms | Yes | Complete response: indomethacin | NA | Brain MR: NL |
| Mauritz, 2021, Germany          | 23   | CPH           | Boy | 7.3    | 7           | >5/day       | Mean: 30min | Severe, 7/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Conjunctival injection/ lacrimation, forehead and facial sweating | No | Complete response: indomethacin | NA | Brain MR: NL |
| Mauritz, 2021, Germany          | 24   | EPH           | Boy | 7.9    | 7.3         | >5/day       | Mean: 30min | Severe, 6/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Forehead and facial sweating, miosis/ ptosis | No | Complete response: indomethacin | NA | Brain MR: NL |
| Author, year of publication, country | Case Classification | Sex | Age, y | Age of onset | Frequency, No. | Duration | Severity | Site | Quality | Headache accompanied by | A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|-----------------------------------|--------------------|-----|--------|-------------|----------------|----------|----------|------|---------|-----------------------|-------------------------|-----------------------|----------|---------|
| Mauritz, 2021, Germany            | 25                 | Boy | 9.3    | 7.9         | >5/day         | Mean: 15 min| Severe, 5/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Nasal congestion, rhinorrhea, miosis, ptosis | Yes | Complete response: indomethacin | NA | Brain MRI: NL |
| Mauritz, 2021, Germany            | 26                 | Girl| 10.7   | 10.4        | >5/day         | Mean: 5 min | Severe, 4/10 | Unilateral orbital, supraorbital, and/or temporal | NA | Conjunctival injection, lacrimation, nasal congestion, rhinorrhea | Yes | Complete response: indomethacin | NA | Brain MRI: NL |
| Mauritz, 2021, Germany            | 27                 | Boy | 11.9   | 11.8        | >5/day         | Mean: 3 min | Severe, 10/10 | Unilateral orbital, supraorbital, and/or temporal | NA | No symptoms | Yes | Complete response: indomethacin | NA | Brain MRI: NL |
| Moorjani, 2001, Germany           | 19                 | Girl| 4.5    | 4           | 2/day          | NA        | Severe, lead to crying and awakening her at night | Left side of face without aura | NA | No symptoms | Fatigue and irritability | No response: aspirin, Partial response: acetaminophen, Complete response: indomethacin | Neurological and ophthalmological exam, laboratory test: NL | MRI: an incidental pineal cyst without any mass effect or hydrocephalus and opacification of the sphenoid sinuses |
| Myers, 2013, Canada               | 28                 | Girl| 2.5    | NA          | 1-2/day        | 1 min     | Severe, causing the patient to immediately stop what she was doing | Unilateral head pains which alternated sides and were maximal at the temples | Sudden | No eyelid edema, miosis, facial sweating, conjunctival injection, nasal congestion, rhinorrhea, nausea or vomiting, photophobia, phonophobia, and no pallor | NA | Partial response: indomethacin | Physiologic exam: mild joint laxity, Psychiatric exam: NL | MRI and MRA: no intracranial abnormality other than the apparently incidental finding of a small arachnoid cyst |
| Myers, 2013, Canada               | 29                 | Boy | 5      | 3           | 3-4/day        | 15-20 min | Severe, lead to crying | In the middle of the forehead | Sharp | No autonomic symptoms, nausea, vomiting, or focal neurologic deficits | NA | Partial response: ibuprofen, Complete response: indomethacin | Physical examination: NL, Complete blood count, electrolytes, thyroid stimulating hormone, glucose, creatinine, and liver enzymes: NL, antinuclear antibody: elevated | MRI and MRA: NL |
| Author, year of publication, country | Case | Classification | Sex | Age, y | Age of onset | Frequency, No. | Duration | Severity | Site | Quality | Headache accompanied by: | A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Raieli, 2015, Italy | 30 | PH | Girl | 8 | 75 | 4-8/day | 15-30 min | Severe, preferring to lie down | Right orbital region radiating to frontal region, jaw, and neck | NA | Ipsilateral lacrimation, eyelid edema and conjunctival injection, photophobia and allodynia | NA | No response: ibuprofen, ketoprofen, ketorolac, acetaminophen | Partial response: topiramate | Psychomotor development: NL | Brain MRI (angiographic sequences): NL |
| Rho, 2009, Korea | 31 | PH | Girl | 10 | 7 | Daily to 4/day | 20-30 min | Severe, as a feeling of squeezing | Bilateral in the forehead region | Throbbing quality | Vomiting, osmophobia, lightheadedness, bilateral lacrimation, paresthesia around eyes (sensation of heat) | NA | Partial response: hydration and metoclopramide, flunarizine, ibuprofen | Complete response: indomethacin | Hematological and biochemistry tests, neurologic exam, EEG: NL | Brain MRI, MRA: NL |
| Seidel, 2009, Austria | 32 | PH | Boy | 17 | NA | 10/day | 30-15 min | Severe | Right frontotemporal region | Stabbing headache | Ipsilateral ptosis and conjunctival injection, photophobia | NA | No response: acetaminophen, ibuprofen | Complete response: indomethacin | Physical and neurologic exam: NL | Brain MRI, MRA: NL |
| Shabbir, 1994, USA | 33 | CPH | Girl | 13.5 | 12.5 | 8-9/day | Several minutes | Severe, awakening her at night | Left frontotemporal region | Nonpulsatile, lancinating headache | NA | NA | No response: Midrin, amitriptyline, aspirin, acetaminophen, valproic acid | Complete response: indomethacin + verapamil, verapamil monotherapy | Neurological exam: NL EEG (first): NL EEG (second): occasional biposterior sharp and slow waves and a single burst of generalized sharp and slow waves, which were not temporarily related to the headache | Brain MRI: NL |
| Shabbir, 1994, USA | 34 | CPH | Girl | 14 | 14 | 8/day | <15 min | Severe | Right hemicranial | NA | NA | NA | No response: acetaminophen, caffeine | Complete response: verapamil monotherapy | Neurological exam: NL, except for a coarse tremor of the hands on barre maneuver | Brain CT scan: NL |
| Author, year of publication, country | Case | Classification | Sex | Age, y | Age of onset, No. | Frequency, Duration | Severity | Site | Quality | Headache accompanied by: A sense of restlessness | Response to treatment | Exam/lab | Imaging |
|-------------------------------------|------|----------------|-----|--------|-------------------|---------------------|----------|------|---------|-----------------------------------------------|---------------------|----------|---------|
| Talvik, 2006, 2009, Estonia         | 35   | CPH            | Girl | 5.3    | 2.25              | 2-3/week: after 4 months, 5-20/day | Severe | Left-sided orbital and suprorbital regions | NA | Ipsilateral lacrimation, Agitation | No response: carbamazepine, carbamazepine +lamotrigine, oxcarbazepine + valproate Complete response: indomethacin | Neurological examination: NL, otologic examination: NL, language, cognitive, emotional and social development: NL ophthalmologic investigation: NL, Sleep EEG (first): a minor right temporal slowing with sharp waves, which were initially interpreted as focal seizure activity, routine hematologic and blood chemistry: unremarkable |
| Tarantino, 2011, Italy              | 36   | CPH            | Boy  | 7      | 1-3/day           | 5-30min             | Severe, excruciating, and lead to crying | Unilateral pain, located in the right orbitofrontal region without side shift | Throbbing headache | Conjunctival injection, eyelid edema, rhinorrhea, vomiting, photophobia | During the attacks, the patient cried and found difficult to lie still, showing marked agitation and restlessness | No response: NSAIDs, acetaminophen, ketoprofen, and aspirin; amitriptyline, flunarizine Partial response: indomethacin Complete response: indomethacin + topiramate, indomethacin + sodium valproate | Psychomotor development exam, psychological screening tests, neurological exam, hematological tests, EEG: NL |
| Tarantino, 2011, Italy              | 37   | CPH            | Boy  | 11     | 3-4/day           | 5-40min             | Severe | Left fronto-orbital and temporal region | Throbbing pain | Ipsilateral lacrimation, conjunctival injection, ptosis and nasal congestion, osmophobia | No response: acetaminophen, NSAIDs (ibuprofen), topiramate Complete response: indomethacin | Neurological exam, blood tests: NL | Skull CT scan, brain MR (the angiographic sequences): NL |
| Vieira, 2006, Portugal              | 38   | PH without autonomic symptoms | Boy  | 9      | NA                | 5-30min             | Severe | Unilateral, frontal, and retroorbital pain | NA | No ipsilateral parasympathetic autonomic symptoms, and nausea | No response: acetaminophen, NSAIDs, nonsteroidal anti-inflammatory drugs | Ophthalmological Examination including intraocular pressure: NL | MRI: sphenoidal sinusitis |

Abbreviations: CPH, chronic paroxysmal hemicrania; CT, computed tomography; EEG, electroencephalogram; EPH, episodic paroxysmal hemicrania; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; NA, not available; NL, normal; NSAIDs, nonsteroidal anti-inflammatory drugs; PH, paroxysmal hemicrania.

[Corrections added on 22 August 2022, after first online publication: The misspelling of the author names “Muritz” and “Borious” was corrected to “Mauritz” and “Borius” and the text in the columns “Site” and “Quality” was shifted to the appropriate columns. Further details were added throughout Table 1 regarding the patients.]
features including nausea, vomiting, phonophobia, photophobia, and osmophobia were also reported in some patients. Patients were often restless or agitated during an attack. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, Ref. 21 was added]. While most attacks were spontaneous, common triggers included heat waves, tobacco smell, stress such as school-attributed problems, lack of sleep, bouncing on a trampoline, and quick movements of the head. Brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and physical examination were performed for most of the patients, although there were some studies lacking information about the EEG and physical examination findings of the patients. Overall, the physical examinations and EEG results were normal. An incidental pineal cyst, an arachnoid cyst, sphenoid sinusitis, and a previous ipsilateral occipital infarction were separately reported in four cases. The findings of the brain MRIs in all other patients were completely normal. Medical history for Kawasaki’s disease, sphenoid sinusitis, and unspecified headaches were reported in children and adolescents whereas we found several cases with family history positive for migraine and unspecified headaches, breath-holding, and bipolar disorder. Almost all patients benefited from indomethacin and showed complete response to treatment, while some needed combination treatment of indomethacin with other medications, such as a combination of topiramate and sumatriptan, verapamil, sodium valproate, and topiramate. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, Refs. 21 and 29 were added.] There is also one successful report on aspirin prophylaxis in pediatric PH. In addition, Shabbir and McAbee reported two cases with effective treatment of PH by verapamil monotherapy. One study suggested using a headache diary as both an idea for diagnosis and an initial nonpharmacological therapeutic intervention in children with PH. In addition, a recent study described a child treated by occipital nerve stimulation for CPH. To the best of our knowledge, this is the first child reported to undergo this new treatment option, which is used for patients who are not responding to other treatments.

Risk of bias and heterogeneity

Table S3 in supporting information shows the results of the quality assessment of the included studies. Following the results of the JBI tools for case reports and case series studies, almost all studies had an overall high quality, except for the Vieira et al. study.

DISCUSSION

To the best of our knowledge, PH was first described in two adult patients by Sjaastad and Dale in 1974. In 1988, CPH was introduced to the International Headache Society’s classification system. A year later, the first pediatric case of CPH with excruciating unilateral orbital-frontal pain was reported by Kudrow in 1989. The patient was a 9-year-old boy who had experienced headaches for about 3 years. Over subsequent years, it became apparent that not all patients experienced a chronic, unremitting pattern of symptoms; in some patients, prolonged pain-free remissions were reported between attacks. This remitting pattern was named EPH, which led to the subdivision of PH into episodic and chronic forms in the 2004 International Headache Society’s criteria. Thereafter, to the best of our knowledge, the first pediatric patients with EPH were reported by Blankenburg et al. in 2009.

PH is a rare condition. The incidence and prevalence of PH in children and adolescents, as well as adults, are unknown. Although there are no data available, the observed frequency in pediatric clinics seems comparable to what can be seen in adult settings. The prevalence of PH was estimated to be 1% to 3% of the prevalence of cluster headaches. Given that the prevalence of cluster headaches is approximately 1 in 500, the prevalence of PH would be approximately 1 in 25,000. We identified that PH has been described among the pediatric population in three continents (excluding Africa, Australia, and Antarctica). However, epidemiologic data are scarce, and many cases of PH are probably still overlooked.

The current literature on pediatric PH suggests that PH can start early in life, with the youngest documented case at 1 year old. We calculated the average years of delay in diagnosis (by subtracting the age of diagnosis from the age of onset and calculating the mean years of delay in diagnosis). Presumably owing to the rare incidence of PH in children, delays in diagnosis have been noted, often exceeding 1.5 years from symptom onset. The shortest course of pediatric PH was reported by Ishii et al. in an 11-year-old boy from Japan. He underwent treatment with indomethacin (at 0.9 mg/kg/day for 14 days) within 2 days of his first referral by his primary care physician. He had not experienced any recurrence of headaches after more than 1 year of follow-up. This case suggests the importance of improving awareness of pediatric PH among general practitioners.

In our review, we found a boy-to-girl ratio of 1.125:1. This result is in contrast to some recent retrospective studies in adults that showed a female predominance. Two other studies in the adult population reported an approximately equal prevalence in women and men. Comprehensive and well-designed epidemiologic studies are needed to find the true extent of the sex ratio in PH.

In these 38 cases that we systematically reviewed, there was no evidence of a family history positive for PH whereas we found family history positive for breath-holding, bipolar disorder, migraine, and unspecified headaches (rather than migraine). [Correction added on 22 August 2022, after first online publication: The number of cases was changed from 35 to 38.] To the best of our knowledge, PH has been reported just in 1 family (a 52-year-old mother presented with PH for 10 years and her 24-year-old daughter with PH for 2 years). This study was not included in our review because it did not fulfill the inclusion criteria. There is also a report on hemicrania continua, which belongs to the classification of trigeminal autonomic cephalalgias, in a family (a 44-year-old mother presented with hemicrania...
TABLE 2  Diagnostic criteria of paroxysmal hemicrania based on different versions of ICHD (16–18)

| ICHD 1st edition, 1988 | ICHD 2nd edition, 2004 | ICHD 3rd edition, 2018 |
|-----------------------|------------------------|------------------------|
| **Diagnostic criteria:** | **Diagnostic criteria:** | **Diagnostic criteria:** |
| At least 50 attacks fulfilling | At least 20 attacks fulfilling criteria B–D | At least 20 attacks fulfilling criteria B–E |
| Attacks of severe unilateral orbital, supraorbital, and/or temporal pain always on the same side lasting 2 to 45 min | Attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 2–30 min | Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 min |
| Pain is associated with at least 1 of the following signs and symptoms on the pain side: | | |
| a. Conjunctival injection | | |
| b. Laceration | | |
| c. Nasal congestion | | |
| d. Rhinorrhea | | |
| e. Phtisis | | |
| f. Eyelid edema | | |
| Attack frequency > 5/days for more than half the time (periods with lower frequency may occur) | | |
| Absolute effectiveness of indomethacin (150 mg/day or less) | | |
| At least 1 of the following: | | |
| 1. History, physical, and neurological exams do not suggest one of the disorders listed in groups 5–11 | | |
| 2. History, physical, and/or neurological exams do suggest such disorder, but it is ruled out by appropriate investigations | | |
| 3. Such disorder is present, but chronic paroxysmal hemicrania does not occur for the first time in close temporal relation to the disorder | | |
| | | |
| **Notes:** | | |
| 1. To rule out incomplete response, indomethacin should be used in doses of ≥150 mg daily orally or rectally or ≥100 mg by injection, but for maintenance doses are often sufficient | | |
| 2. Indomethacin in doses of 225 mg daily. The dose by injection is 100–200 mg. Smaller maintenance doses are often used | | |
| 3. Prevented absolutely by therapeutic doses of indomethacin | | |
| Not better accounted for by another disorder | | |
| 1. During part, but less than half, of the active time course of paroxysmal hemicrania, attacks may be less frequent | | |
| 2. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100–200 mg. Smaller maintenance doses are often used | | |

Abbreviation: ICHD, International Classification of Headache Disorders.

continua for 32 years and her 23-year-old daughter with hemicrania continua for 10 years). Genetic studies on PH are hampered by small sample sizes.

The clinical features of PH based on different versions of ICHD criteria are given in Table 2.

In the ICHD criteria, it was noted that attacks have a frequency of more than five per day for more than half the time, although periods with lower frequencies may occur. In several cases, the frequency of PH attacks was reported to be lower than five attacks per day. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, Ref. 23 was removed.] Overall, in 8 of 22 studies (36.4%), the frequency of attacks was fewer than five attacks per day. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, 9 is changed to 8, and 40.9% was changed to 36.4%.] Although periods with low-frequency attacks of fewer than five per day might occur, it remains unclear whether these individuals ever did meet the five-attack-per-day criterion, which is the required frequency for most of the clinical course. As noted in the results section, because of lack of information in some cases, we assumed that these individuals met the five-attack-per-day criterion because the authors made the diagnosis based on one of the versions of ICHD criteria.

The mean frequency of headaches in these atypical cases was approximately 2.1 per day [Correction added on 22 August 2022, after first online publication: the mean frequency was changed from 1.7 to 2.1]. However, given the small number of cases, future studies would be needed to determine a cutoff for headache frequency in children or adolescents with PH. Ipsilateral cranial autonomic features were reported in almost all cases. However, in one case, bilateral autonomic features were also reported.

Although earlier research used the ICHD criteria to identify individuals, we consider that it has several limitations in the pediatric population. Almost all the items are signs or symptoms that are difficult for a child to explain or to be distinguished by parents or pediatricians. Moreover, some key symptoms of PH might be overshadowed by others. For example, the intensity of pain might lead to crying, which could mask ipsilateral lacrimation, rhinorrhea, and some other autonomic features of the face. Distinguishing a sense of restlessness and its cause in younger children is not simple. Several features might be interpreted as restlessness, while they are not specifically related to PH. This description was discussed in a systematic review and meta-analysis of trigeminal autonomic cephalalgias in pediatrics, in which cranial autonomic features and restlessness occur at a lower rate in pediatric patients. We also suggest that these characteristics might be under- or over-diagnosed, particularly in younger children.

Furthermore, the safety and efficacy of indomethacin in pediatric patients 14 years of age and younger have not been established, which
limits the applicability of an “indomethacin trial” as a criterion of PH. Concerns about liver or pancreas problems, stomach bleeding, and kidney damage should be addressed as a result of long-term usage of indomethacin as a prophylactic medication. In addition, indomethacin might worsen asthma in children and is contraindicated in patients with a history of asthma. As asthma was a common comorbidity in children with PH, this issue should be considered in the treatment of PH in children. Migrainous features were reported in at least 22.8% of the reviewed cases. As we discussed before, there were six children with PH-like diagnoses in the literature who were suspected of having more atypical presentations of PH [Correction added on 22 August 2022, after first online publication: The number of cases was changed from three to six.]. However, after reviewing these six cases, we realized that all of them lacked autonomic features and fit more closely with a migraine phenotype [Correction added on 22 August 2022, after first online publication: The number of cases was changed from three to six.].

Presumed incidental findings were reported in four patients, including sphenoidal sinusitis, ipsilateral occipital infarction, pineal cyst, and arachnoid cyst. It is unclear whether the nature of headaches in these patients is primary headaches or secondary headaches owing to these structural findings. Authors have assumed that these findings are incidental. However, it should be acknowledged that the secondary causes of headaches could rule out the PH diagnosis. Given the considerable number of these incidental findings, future studies should seek any probable correlation between these findings and PH.

We presented all treatment options for children and adolescents in Table 1. Despite the ICHD-3 diagnostic criteria for the indomethacin trial, it seems that some cases might benefit from other treatment options as well as indomethacin, while most of the patients showed complete response to the indomethacin trial. [Correction added on 22 August 2022, after first online publication: In the preceding sentence, Refs. 21 and 29 were added.] Combination treatments are another option for controlling this type of headache in children and adolescents. Future studies should be more focused on comparing treatment modalities and their effectiveness in the pediatric population.

Several limitations should be considered for this study. First, we considered articles that made the diagnosis of PH using the ICHD criteria, even if all the diagnostic criteria items were not mentioned in the article. We could not ascertain the diagnosis of PH by the latest version of ICHD because not all cases included all the necessary criteria of ICHD-3 in their presentations. Second, given the design of the included studies, which were merely case reports or case series, the findings must be interpreted with caution. This limitation is mostly related to the concern that a disproportionate number of atypical cases of PH are more likely to be reported in case reports and case series, which can lead to bias. Moreover, case reports and case series are uncontrolled study designs that are susceptible to bias, so this information may not be generalizable to the larger population. Third, an incomplete evaluation of atypical and undifferentiated PH-like headaches in pediatrics might occur as our search criteria may not have been mentioned in the title or abstract. Additionally, it is reasonable to think that the full range of atypical or undifferentiated PH-like headaches are not reported in the literature and require a methodology other than a systematic review (such as an observational study of atypical PH). Finally, during the screening step, we decided to consider the age of diagnosis, not the age of onset, to decrease the heterogeneity of the included studies. During our primary search, we realized that most case reports or case series focused on the clinical characteristics of patients during adulthood. We assumed that even if the age of onset was in childhood in these cases, the symptoms might change eventually, as some evidence declared that the nature of paroxysmal headaches changes over time, or even changes to another type of headache. Thus, we tried to focus on the studies on child and adolescent populations.

CONCLUSION

In summary, the current literature strongly suggests that PH can start very early in life. Although pediatric-onset PH has similar features to adult-onset PH and similar criteria are used to diagnose PH in either the pediatric or adult population, there are challenges with some ICHD diagnostic criteria when used in younger children, so definite diagnosis may be limited in younger children. As for expanding the ICHD-4 criteria for pediatric PH, we have only preliminary data from three atypical cases, which suggests that the cranial autonomic features and restlessness sometimes extend beyond the official criteria or may be underdiagnosed or overdiagnosed in younger children. The frequency, duration, severity, quality, and unilateral of pain were the most matched items to adults. MRI findings should be more noticed in future patients with PH to discover any possible associations. Moreover, because of concomitant migrainous features, PH may be confused with migraine in children and adolescents.

AUTHOR CONTRIBUTIONS

Study concept and design: Maryam Bemanalizadeh, Vahid Mansouri. Acquisition of data: Maryam Bemanalizadeh, Homayoun Baghaei Oskouei, Alireza Hadizadeh, Mohammad Sedigh Dakkali, Reihane Qahremani, Vahid Mansouri. Analysis and interpretation of data: Maryam Bemanalizadeh, Vahid Mansouri. Drafting of the manuscript: Maryam Bemanalizadeh, Homayoun Baghaei Oskouei, Alireza Hadizadeh, Mohammad Sedigh Dakkali, Reihane Qahremani, Vahid Mansouri. Revising it for intellectual content: Maryam Bemanalizadeh, Vahid Mansouri. Final approval of the completed manuscript: Maryam Bemanalizadeh, Homayoun Baghaei Oskouei, Alireza Hadizadeh, Mohammad Sedigh Dakkali, Reihane Qahremani, Vahid Mansouri.

ACKNOWLEDGMENT

We are very grateful to Dr. Negin Badhian for her kind assistance with the systematic review search.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

PROTOCOL REGISTRATION

This study was registered as a systematic review in PROSPERO (CRD42022306190).
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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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**How to cite this article:** Bemanalizadeh M, Baghaei Oskouei H, Hadizadeh A, Dakkali MS, Qahremani R, Mansouri V. Paroxysmal hemicrania in children and adolescents: A systematic review. *Headache*. 2022;62:952-966. doi: [10.1111/head.14354](https://doi.org/10.1111/head.14354)