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CHILDHOOD AND ADOLESCENT HEADACHE (SE EVERS, SECTION EDITOR)

The Enigma of New Daily Persistent Headache: What Solutions for Pediatric Age?

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Abstract

Purpose of review To analyze systematically the evidence currently available from the literature regarding the diagnosis, clinical characteristics, treatment and outcome of new daily persistent headache (NDPH).

Recent findings NDPH is a primary headache characterized by an abrupt onset with continuous daily pain that can persist for many months. Although self-limiting forms have been described, NDPH is frequently associated with high disability even in children and adolescents. For this reason, it is very important to recognize it from a diagnostic point of view and to treat it.

Summary We found little specific data on NDPH in developmental age. Most of the therapy studies have been conducted on adults with conflicting data. Currently, pediatric NDPH therapy is based on experiences in adult patients and in individuals with other forms of primary chronic headache, hence the need for more pediatric studies to fill this information gap.

Keywords New daily persistent headache · Daily headache · NDPH · Therapy · Children

Introduction

NDPH is defined as a persistent and continuous headache from its onset, which is generally well remembered by patients. The qualitative characteristics of the pain can be varied and recall either migraine or tension headache or thunder headache [1•].

The prevalence of NDPH varies from 0.3% to 0.1% of the general population although in developmental age it is higher and can reach 10% of all chronic headaches of pediatric age [1•, 2••, 3, 4•].

The pathogenesis of NDPH is not known although from the literature we know that often the onset of the disease is preceded by trigger events such as infections, surgery or psychologically stressful events [1•, 2••].

NDPH often poses a challenge to the physician for both diagnosis and treatment. In the first case, in fact, many secondary forms of headache can mimic NDPH and some of which can even be dangerous for the patient's life. For this reason, a careful diagnostic workout is necessary, which includes instrumental and biochemical investigations [2••].

Regarding therapy, there are no definitive data on which pharmacological or non-pharmacological treatment is most indicated in cases of NDPH. The risk of overuse of seizure drugs in these patients must also be considered. Very often the choice of drug treatment is made taking into account the characteristics of pain, and therefore drugs used to treat migraine or tension-type headache are chosen [2••].

NDPH remains one of the most difficult forms of primary headache to manage and associated with a high risk of disability [3]. Although self-limiting forms of NDPH have been described [5, 6] in many cases the duration of the headache can be more than 1 year from onset [2••, 4•].

The purpose of this review is to summarize the evidence available in the literature to date regarding NDPH in particular in the context of therapy and outcome.

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Methods

We performed a PubMed and EMBASE search including new daily persistent headache and children as keywords. Since 1996, 17 manuscripts have been identified consisting of 1 systematic review, 4 standard reviews and 12 case reports Comments or letters to the editor were not considered. Individual pediatric case report was excluded. The research selected 8 articles that we used to analyze the following aspects: modality of onset, clinical features, comorbidities, therapy and outcome (Table 1).

Clinical Features

The peculiar characteristic of NDPH is that it is a headache that begins immediately with a continuous and non-remitting course [14]. It means that mostly it affects subjects who do not have a previous history of headache and this represents a key point of distinction with other chronic forms of headache, such as chronic migraine where for a long time the attacks can be episodic and then also abruptly worsening with daily and continuous pain [15].

Nevertheless, according to ICHD 3, patients with prior headache (1. Migraine or 2. Tension-type headache) are not excluded from this diagnosis, but they should not describe increasing headache frequency prior to its onset. Similarly, patients with prior headache should not describe exacerbation associated with or followed by medication overuse [14]. Recently, some authors criticized the need to distinguish NDPH from other collected forms of primary headache. The authors found that most of the patients with onset of NDPH had pain characteristics superimposed on chronic migraine, with similar aspects also in comorbidities and in the response to treatment. In addition, patients had frequently a previous history of headache. They suggested that the new-persistent aspect of the disorder is a mode of onset rather than a unique phenotype and thus NDPH with migraine or tension-type headache phenotype should be classified in the respective sections of the ICHD 3 [16].

In the ICHD 3 version, for the definition of NDPH, the type of pain must not have specific characteristics [14]. From a qualitative point of view, headache pain can in fact resemble migraine or tension headache [2••, 4•, 17]. Cases of thunderclap headache have also been reported but only in adults [16].

Although most of the time patients report bilateral pain with varying intensity, in many cases there are accompanying symptoms reminiscent of migraine and for example the association with photophobia or phonophobia or nausea or vomiting [2••, 4•]. Robbins et al. describe qualitative features of pain in 3 pediatric subjects with headache and he found that 12% reported photophobia, 9% phonophobia and 19% nausea [4•]. In a recent retrospective study, we identified 46 children and adolescents with NDPH and migraine features were reported in 73% of cases (Table 1) [2••].

Compared with children with chronic migraine, the NDPH patients experienced nausea and vomiting less often [2••].

Approximately 20–30% of individuals with NDPH have a family history of primary headache [4•, 17].

NDPH can be comorbid with other conditions such as sleep disturbances, visual disturbances such as blurred vision, muscle aches, fatigue and other general symptoms [4•, 7••, 12].

However, it is very important to consider comorbidity with neuropsychological or psychiatric symptoms. Depression and anxiety are often present in patients with NDPH and can begin long before the headache [7••, 12, 18]. Furthermore, the ongoing pain of NDPH can itself be a cause of interference with the child's daily activities and for example cause a number of absences from school and reduce play activities. All this can therefore cause a deflection of mood in the child with NDPH and also have repercussions on the life of parents and relatives [2••].

Onset and Trigger Factors

The onset of NDPH is so abrupt that most patients remember exactly the first day of headache. The ICHD 3 classification emphasizes the importance of onset by including the precise and distinct memory of the onset of symptoms as the main diagnostic criterion [14].

Several studies in both adults and children have pointed out that a trigger factor could be identified in many cases of NDPH [1•, 2••, 11, 16–20].

In adult series, these included emotionally stressful events, infections or surgical treatment, while in children the most frequent trigger factors are infectious episodes or school stress. [1•, 20].

Some pediatric studies have also reported an onset of NDPH after a head injury and here care must be taken to distinguish headache from head injury from NDPH [11, 17].

In a study of 40 pediatric headache patients with NDPH, precipitating events were noted in 88% of cases: febrile illness in 43%, preceding minor head injury in 23% and cranial or extra cranial surgery in 10% [11]. In addition, some authors have described a relationship between the onset of NDPH and school stress. In fact, in many case series the higher incidence of NDPH coincided with the end of the summer holidays and the return to school [7••, 21].

Table 1 Resume of results from pediatric studies on NDPH; SD: standard deviation; sbj: subjects; NR: not reported

Study	Grengs et al. 2016 [7••]	Puledda et al. 2018 [8]	Gelfand et al. 2014 [9]	Robbins et al. 2010 [4•]	Scalas et al. 2005 [10]	Mack et al. 2004 [11]	Gladstein et al. 1996 [12]	Papetti et al. 2021 [2••]
Criteria	ICHD 3 beta	ICHD 3 beta	ICHD 3 beta	ICHD 2	ICHD 2	NR	Silberstein [13]	ICHD 3
Number of patients	92	22	9	31 (adult and children) 3 sbj < 18 years	8	40	13	46
Mean age (years)	14.4 ± 2.6 SD	15 ± 2 SD (range 8–18)	14.7 ± 2.5 SD (range 7–17)	NR range for pediatric patients (10–18 years)	11.5 (range 3–18)	NR (< 18 years)	13.0 ± 2.7 SD (range 7–17)	13.4 ± 3.2 SD (range 5–18)
Trigger factor	39% starting school	NR	NR	(total sbj) Upper respiratory illness 14.1% stressful life event 9.9% menarche 4.2%	NR	Febrile Illness 43% Minor head trauma 23% IIH 10% Surgery 10%	NR	46% school stress 22% upper respiratory infections
Comorbidities	- Anxious 17% - Sad 15% - Sleep difficulty 59.8% - Concentration difficulty 56.1% - School Problems 21%	NR	NR	(total sbj) Depression 19.4% anxiety 22.6%	NR	NR	psychological factors 62%	NR
Past history of headache	NR	NR	NR	(total sbj) 25.4%	NR	NR	NR	None
Qualitative features	NR	NR	NR	(NDPH sbj) Throbbing pain 43.7% Bilateral pain 93.5% Nausea 19.4% Vomiting 0% Photophobia 12.9% Phonophobia 9.7%	NR	NR	Migraine features 38%	Migraine features 73% TTH features 27% Throbbing pain 41% Gravative pain 15% Pressing pain 28% Monolateral pain 61% Bilateral pain 39% photophobia79.2% phonophobia 63%
Therapy	NR	Greater occipital nerve (GON) Injections (methylprednisolone 40 mg and lidocaine 1% 30 mg) 100%	Greater occipital nerve (GON) injections (methylprednisolone acetate, adjusted for weight, and lidocaine 2%) 100%	(total sbj) Triptans 38% GON with bupivacaine 29%	NR	NR	NR	33 subjects (67%) flunarizine 5 mg/die 3.7% topiramate 1–2 mg/kg/die 14.8% amitriptyline 1 mg/kg/die 92.3%

Table 1 (continued)

Study	Grengs et al. 2016 [7••]	Puledda et al. 2018 [8]	Gelfand et al. 2014 [9]	Robbins et al. 2010 [4•]	Scalas et al. 2005 [10]	Mack et al. 2004 [11]	Gladstein et al. 1996 [12]	Papetti et al. 2021 [2••]
Efficacy of therapy	NR	59% decrease in headache frequency or intensity > 1/3	33% One of: - Decrease in headache frequency > 1/3 - Decrease in headache intensity > 1/3 - Decrease in headache duration > 1/3	Triptans 16.7% GON 88.9%	NR	NR	NR	80% decrease in headache frequency > 50%
Outcome	NR	NR	NR	Remitting 17% Relapsing remitting 5% Persisting 76%	NR	NR	NR	Remitting within 6 months 43% Remitting within 12 months 39% Persisting 18%

In our previous study on 46 pediatric NDPH patients, stressful school activity was a frequently recognized trigger event (46% of patients) and a significant increase in NDPH onset was found in the months when students started school after summer break (September) or returned to school after winter break (January). The second most frequent trigger identified in our patients was represented by flu-like infectious episodes (22% of patients) [2••]. In previous case series, an episode of flu or a "cold" preceded NDPH onset in 30–40% of patients [4•, 11].

It is necessary to be careful if the diagnosis of NDPH can be maintained in the presence of a factor that precedes the onset of the headache. If head trauma or infection precipitates, it would be more appropriate to have the diagnosis of "headache attributed to injury to the head" or "headache attributed to infection" [2••].

According to ICHD-III (part 2, paragraph 9) when a *new headache* occurs for the first time in close temporal relation to an infection, it is coded as a secondary headache attributed to that infection and the evidence of causation should be demonstrated. *Headache attributed to infection* is usually the consequence of active infection, resolving (acute) or not (chronic) within 3 months of eradication of the infection [14]. Otherwise, NDPH triggered by an infection instead refers to a headache that persists beyond 3 months without evidence of another cause including an infection [2••].

The presence of an infection as a trigger event has suggested to some authors to look for a pathogenetic relationship between virus and NDPH [6, 18, 19].

A study of 40 children with NDPH reported that 23% of cases were positive for Epstein Barr Virus (EBV). An other case series of 18 NDPH patients did not identify any EBV infection, but they found evidence of herpes simplex virus infection in 42% and of cytomegalovirus in 11% [6]. Other associations have been made with Herpes zoster, Adenovirus, Toxoplasmosis, Salmonella, Streptococcal infection and Escherichia coli urinary tract infections [18].

Given the variety of infectious associations, it has been suggested that the nonspecific inflammatory response initiated by the infection, rather than the infectious agent itself, may be the trigger [19].

However, the pathogenetic role of infections as well as other triggers as inducers of NDPH remains speculative. The origin of NDPH therefore remains a mystery and controlled studies are needed to better clarify these aspects.

Diagnosis

The diagnosis of NDPH is based on the characteristics of the headache, the normality of the general and neurological physical examination and the normality of the instrumental examinations (Table 2).

The clinical history can reveal a precise moment of the onset of the headache that the patient can remember well. The normality of the neurological examination including the fundus oculi can help to exclude intracranial causes of headache. However, it is almost always necessary to resort to a computed tomography (CT) scan or brain magnetic resonance imaging (MRI) to definitively exclude secondary causes of continuous headache [2••].

Several morbid conditions can mimic NDPH. Clinical evaluation and neuroimaging should exclude post-traumatic headache (i.e., subarachnoid hemorrhage, subdural hematoma), central nervous system (CNS) infections (i.e., meningitis, sphenoid sinusitis), intracranial tumors or vascular events such as cerebral venous thrombosis or arteritis of the intracranial vessels [1•, 2••] Among the causes of headache that can resemble a NDPH, we must then consider changes in the pressure of the cerebrospinal fluid like (CSF) spontaneous CSF leak and idiopathic intracranial hypertension (IIH) [1•, 2••, 14].

The third version of ICHD includes in the notes the need to exclude in all cases of possible NDPH other headaches attributed to alteration of fluid pressure [14]. In pediatric age, however, performing lumbar puncture is not always an easy procedure as for adults and often also requires sedation [2••].

We discussed that in pediatric age the execution of lumbar puncture for the measurement of CSF pressure can be reserved for selected patients in whom the clinical and neuroradiological characteristics suggested an origin of this type. In particular, IIH should be suspected in obese patients or with endocrinological disorders or with comorbidities (i.e., peritoneal ventricle derivation, systemic diseases) or finding of papilledema at ocular fundus or typical neuroradiological signs (i.e., prominent subarachnoid space around the optic nerves, empty sella turcica and vertical tortuosity of the optic nerves) On the other hand, CSF hypotension should be thought of in patients with orthostatic headache or if the MRI shows pachymeningeal enhancement or venous distension sign [2••].

Previously, we found that secondary forms of headache have been identified in 23% of 60 patients with headache onset, suggestive for possible NDPH. All patients with secondary forms had neuroimaging or fundus oculi alterations that suggested the presence of a brain tumor, Chiari malformation type 1, or IIH [2••].

We also remember that all subjects with a suspected NDPH should carry out a trial with indomethacin to rule out a paroxysmal migraine. The indomethacin dosage necessary for successful treatment ranges from 25 to 300 mg per day, with an average of 100 mg per day. The beneficial effects appear within 2 days (range 1 to 5 days). On discontinuation, headache reappears in about 3 days (range 1 to 14 days) [2••, 14].

Treatment

The NDPH is one of the most difficult headaches to treat. Unfortunately, there is a lack of targeted pharmacological studies on this type of headache and most of the drugs used are those that derive from experiences on other types of headache such as chronic migraine or chronic tension-type headache [10, 22, 23, 24, 25]. There is also a lack of mainly controlled studies and especially dedicated to

Table 2 Differential diagnosis of NDPH. MOH: Medication overuse headache; CSN: Central nervous system; TACs: Trigeminal autonomic cephalalgias; CSF: Cerebrospinal fluid [2••]

	Presence of:	Consider other conditions:
Headache history	Previous history of primary headache Absence of trigger factor Excessive use of drugs for the attacks Head or neck trauma Worsening with Valsalva or changes in posture Pain lasting 15–180 min Pain lasting 2–30 min	Worsening of primary headache Considering MOH Headache secondary to trauma Altered CSF pressure Cluster headache Paroxysmal hemicrania
Neurological exam	Focal sign Altered consciousness	Secondary cause of headache (i.e., vascular disorders, altered CSF pressure, neoplasia, CNS infections)
General examination	Fever Prominent cranial parasympathetic autonomic features	Secondary cause of headache (i.e., CSN infections) TACs
Fundus oculi	Papilledema	Idiopathic intracranial hypertension Other secondary causes of headache
Drug response	Indomethacin	Hemicrania continua

the pediatric age. In addition, the risk of excessive use of analgesics in patients with NDPH must be considered.

The most commonly used medications in pediatric NDPH include the tricyclic antidepressants (amitriptyline) and antiepileptics like topiramate and valproic acid [1•, 2••, 22, 25]. Other treatments with benefit, but with insufficient data in pediatric age, include propranolol, selective serotonin reuptake inhibitors and onabotulinumtoxinA [1•, 25, 26]. Few evidence available only on adult cases concerns treatment with intravenous methylprednisolone [27], mexiletine [28], intravenous dihydroergotamine [29], ketamine [30] and nimodipine [31].

In our retrospective study, we observed that 35% of 46 patients with NDPH did not have a response to the symptomatic drugs (NSAIDs or triptans). Around 80% of patients had beneficial response (reduction in monthly headache day by at least 50%) using preventative drugs as flunarizine (5 mg/die)(3.7%), topiramate (1–2 mg/kg/die) (14.8%) and amitriptyline (1 mg/kg/die) (92.3%) [2••]. The most chosen drugs were amitriptyline and topiramate for its real-world evidence of efficacy in chronic pediatric headaches [2••].

Intravenous lidocaine and nerve blockade are possible treatment options for patients who do not respond to common prophylactic drugs [8, 9].

Akbar reported a 16-year-old boy diagnosed as NDPH who was refractory to several aggressive inpatient therapies. He was treated with intravenous (IV) lidocaine infusion and reported that the headache fully resolved for 2 weeks and severity and frequency decreased for almost 3 months [32].

In a survey for Pediatric & Adolescent Section of the American Headache Society in June 2015, pediatric headache clinicians were queried about the use of peripheral nerve block in adolescent and children with primary headache. The 67% of NDPH and 70% of chronic migraine demonstrate that these conditions were the most frequent indications for the use of the nerve block [23].

Puledda et al. reported that improvement was seen in 13 of 22 (59%) children and adolescents with NDPH who received greater occipital nerve block using 1% lidocaine and methylprednisolone [8].

Anecdotal cases of efficacy concern non-pharmacological treatments. Alexander et al. reported a 15-year-old girl with NDPH who had pain relief after osteopathic manipulation treatment. He proposed that osteopathic manipulation treatment might be helpful in treatment-resistant NDPH cases [33].

Most patients will not respond to medications so it is desirable to consider alternative approaches, including the use of biobehavioral strategies like physiotherapy, biofeedback and cognitive behavior approaches [25]. Non-pharmacological treatments are integral to optimize the possibility of a good outcome [17].

Alternative therapies included also nutraceutics like riboflavin, butterbur, coenzyme Q10, magnesium, massage, acupuncture, exercise, physical therapy, weight loss and yoga [17].

A few reports have suggested a better response when adequate treatment of NDPH administered early in the course of the disease (within 3–12 months of NDPH onset) [1•, 34].

Although the difficulty in finding effective therapies could lead to the development of MOH, there is no evidence of a correlation between MOH and NDPH in pediatric-age patients. In pediatrics patients with NDPH and concomitant history of MOH, the withdrawal of the overused drugs did not improve headache [2••]. In light of these data, and considering that even the self-limiting forms of NDPH can be disabling, we suggest trying a pharmacological approach.

Prognosis

NDPH has two subtypes: a self-limiting subtype that typically resolves within several months without therapy and a refractory subtype that is resistant to aggressive treatment regimens [14].

In refractory cases, pain may persist continuously for over a year from onset. Furthermore, even after a period of remission, cases of relapse have been described. Generally, the longest duration has been found in NDPH cases with pain that resembles migraine [2••, 4•]. In our study, we found some risk factors associated with a long duration of NDPH. In our study, the average duration of continuous daily pain was about 8.4 ± 2 months. While 43% of patients had continuous pain resolution within 6 months, 39% within 12 months and 18% kept suffering from continuous pain beyond 12 months. Patients who did not receive prophylaxis therapy were at greater risk of having a worse prognosis, in particular the persistence of NDPH after 12 months. Another negative prognostic indicator was the absence of a well-recognized trigger factor [2••]. Robbins et al. conducted a study on 31 patients with NDPH including 3 children and he found that 17% of subjects presented a remitting course, 5% relapsing remitting and 76% persisting [4•].

Studies in pediatric [2••, 4•, 17, 35] and adult [18, 20, 36] NDPH patients often reached conflicting results concerning the outcome. While according to some studies NDPH does not interfere with the subject's activities and its resolution is spontaneous within 24 months [5, 37], others emphasize its disabling trend, drug resistance and poor prognosis [2••, 35, 38, 39].

Conclusions

NDPH is a very complex form of primary headache to diagnose and treat. It is always necessary to exclude other conditions that can mimic NDPH through a thorough clinical

history, physical examination and instrumental examinations. The ICHD 3 criteria represent a valid support for the diagnostic path. Treatment of NDPH also in pediatric age should be considered in order to reduce the risk of disability associated with the disease. This should include both a pharmacological and a non-pharmacological approach. More studies on NDPH in pediatric age could help to better understand the mechanisms that trigger this condition and what might be the best therapeutic strategies. The diagnosis and management remain somewhat enigmatic and challenging for pediatrics and neurologists.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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