

MEDICATION-OVERUSE HEADACHE IN CHILDREN AND ADOLESCENTS: THE PRESENT

Cefalea da uso eccessivo di farmaci nel bambino e nell'adolescente: stato attuale

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SUMMARY

Primary chronic daily headache (CDH) can evolve from either episodic tension-type headache or episodic migraine, or can appear with no previous headache history. CDH occurs in 1-2% of children and adolescents. CDH frequently results in school absence. Children and adolescents with CDH are at risk for medication overuse. Medication overuse headache (MOH) is a secondary headache, whose diagnostic criteria were settled by the Second Edition of the International Classification of Headache Disorders and its subsequent revisions. Children and adolescents with CDH frequently have sleep disturbance, pain at other sites, dizziness, medication-overuse headache, and a psychiatric comorbidity (anxiety and mood disorders). Successful approaches to treatment include education, use of preventative medication and avoidance of analgesics.

RIASSUNTO

La cefalea cronica quotidiana primaria (CDH) rappresenta l'evoluzione nel tempo sia della cefalea di tipo tensivo episodica sia dell'emicrania episodica, oppure può manifestarsi in assenza di precedente storia di cefalea. La CDH si presenta nel 1-2% dei bambini e degli adolescenti. Essa comporta frequenti assenze scolastiche. I bambini e gli adolescenti con CDH sono esposti al rischio di abuso di farmaci. La cefalea da uso eccessivo di farmaci (MOH) è una cefalea secondaria i cui criteri diagnostici sono adottati dalla Seconda Edizione della Classificazione Internazionale delle Cefalee e successive revisioni. Bambini ed adolescenti con CDH frequentemente presentano disturbi del sonno, dolore in altre sedi, vertigini, cefalea da uso eccessivo di farmaci, e comorbidità psichiatrica (ansia e disturbo dell'umore). L'approccio al trattamento della MOH prevede educazione, utilizzo di farmaci preventivi ed evitamento gli analgesici.

INTRODUCTION

Headaches in children are common. Many varieties of headache exist, each with different causes and symptoms. Almost all varieties of headache increase in frequency as patients grow from early childhood to preadolescence (prepuberty) to adolescents and then adults. Recurrent headache is a common complaint in paediatric practice and may have a significant impact on the child's and parents' lives¹. The criteria broadly divide headache into primary and secondary headache disorders. The primary headache disorders are those in which the headache condition itself is the problem, and no underlying or dangerous cause for it can be identified. The secondary headaches are classified according to their causes. Primary headache disorders are divided into four major groups: migraine headaches, tension-type headaches, trigeminal autonomic cephalalgias including cluster headaches, and other primary headache disorders. Several studies indicate that Medication Overuse Headache (MOH) can occur in children and adolescents migraine may change its pattern into one of chronic daily headache (CDH) due to rebound or medication withdrawal.

KEY WORDS

Pediatric headache - Medication overuse - Medication-overuse headache - Children - Adolescent - Psychiatric disorders

PAROLE CHIAVE

Cefalea pediatrica - Abuso di farmaci - Cefalea da eccessivi uso di farmaci - Bambino - Adolescente - Disturbi psichiatrici

This phenomenon may also occur with tension-type headache. Tension-type headache (TTH) may be as common a headache disorder as migraine in children and adolescents. Medication overuse commonly, but not invariably, is responsible for the transformation of the episodic form into the chronic form. In recent years there has been an explosion of interest for daily or near-daily headache in a patient who uses analgesic medications daily. Chronic overuse of all symptomatic headache drugs alone or in combination, in patients with primary headache disorders, is frequently associated with the development of a secondary headache, called MOH. However, little is known about the prevalence of headache associated with analgesic overuse in children. Whereas a cause and effect has not been firmly established, overuse of symptomatic migraine drugs, is implicated in the development of CDH with either a migraine-like or a mixed migraine-like and tension-type-like presentation. Conceptually, MOH is a chronic headache pattern that etiologically is related to the frequent use of medication used to treat acute episodes of migraine (Tab. I). In this Review, we evaluate recent data on the classification, epidemiology, pathophysiology, characterization, Psychiatric comorbidity, and Therapeutic Approach of this disorder.

CLASSIFICATION BY THE INTERNATIONAL HEADACHE SOCIETY

Chronic daily headaches can evolve from an episodic primary headache disorder, such as migraine or tension-type headaches, or they can start de novo^{2,3}. Each of these types of CDH is further divided into those with or without superimposed medication overuse. Analgesic misuse headache occurs when drugs given for the treatment of headache aggravate symptoms. In the first two groups, there can a rebound effect from daily or near-daily use of analgesics⁴. Several expressions have been used to describe what is now called MOH: "drug-induced headache", "chronic daily headache", "transformed migraine". MOH is a chronic disorder that results from the overuse of analgesics, triptans, or other acute headache compounds. Analgesic medication overuse is a major clinical issue which is directly implicated in the development of chronic pain, probably because of complex sensitization mechanisms⁵.

Classifications are dynamic and they normally expand as knowledge increases. In 2006, the Headache Classification Committee published an invitation to use in a "much more liberal" way the diagnosis of chronic migraine (CM) and MOH. The International Classification of Headache Disorders (ICHD-II) defines MOH with the following criteria: (a) headache present on ≥ 15 days/month; (b) regular overuse for ≥ 3 months of 1 or more acute/ symptomatic treatment drugs; (c) headache has developed or markedly worsened during medication overuse⁶. Current classification allows to diagnose both a chronic headache disorder and a secondary disorder MOH that might be concurrently present. In particular, it suggested eliminating the diagnosis of probable MOH. The attack frequency prognosis of the headaches depends on the cause/effect relationship of the headache and the medication overuse. Before definite diagnoses can be ascertained, patients with medication overuse are temporarily given a diagnosis of probable chronic migraine or probable chronic tension-type headache with probable MOH. The headache occurs daily or almost daily but disappears within a few weeks of withdrawal of medication^{7,8}. MOH should be suspected in any child with a history of headache on 4 or more days per week⁹. A high percentage of those with medication overuse headache have significant psychiatric comorbidities and overuse medications for their psychoactive features.

TAB. I. Appendix criteria for medication-overuse.

headache (for research and clinical trial purposes only)(6)
Medication-overuse headache (appendix 8.2)
Diagnostic criteria: A Headache present on ≥ 15 days per month B Regular overuse for > 3 months of one or more acute/symptomatic treatment drugs as defined under
subforms of 8.2: 1 Ergotamine, triptans, opioids, or combination analgesic medications on ≥ 10 days per month on a regular basis for > 3 months 2 Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥ 15 days per month on a regular basis for > 3 months without overuse of any single class alone C Headache has developed or markedly worsened during medication overuse

EPIDEMIOLOGICAL IMPACT

Definition of CDH is based on the presence of headache for ≥ 15 headache days in 1 month, over a period of 3 consecutive months, and with no underlying organic pathology¹⁰. In children, epidemiologic data are limited and case definitions are variable, but the prevalence of very frequent headache in late childhood and adolescence may approach levels seen in adults. CDH occurs in 2% of middle school girls and 0.8% of middle school boys aged 12-14 years¹¹. CDH has been shown to represent up to 60% of cases seen in paediatric headache specialty clinics^{12,13}. CDH affects 2 to 4% of adolescent females and 0,8 to 2% of adolescent males^{14,15}. Many teenage patients with CDH have a history of episodic migraine¹⁶. Persuasive study of the importance of excessive medication intake as a risk factor for CDH and medication frequency as a cause of transformation of episodic migraine into CDH is described¹⁷. Patients experiencing MOH have primary headache disorders (migraine, tension-type headache or the combination of migraine and tension-type headache) that change to a pattern of daily or near-daily headaches over a period of years or decades following the overuse of symptomatic headache medications. Medication overuse may be one of the precipitants of CDH, so care must be taken not to contribute to the overuse of analgesic agents. MOH is an interaction between a therapeutic agent used excessively and a susceptible patient. Discussing the epidemiology of MOH in detail is beyond the scope of this review. In the literature, prevalence of MOH varies greatly. For example, no child in the series of Chakravarty and of Seshia suffered MOH^{18,19}. In the series of Esposito and Gherpelli, 82.5% of children had MOH²⁰. A population based epidemiological study in Taiwan detected a 1-year prevalence of 0-3% in adolescents who overused analgesics available over the counter¹¹. In a consecutive series of 34 French children and adolescents with chronic daily headache, MOH was present in 52.9% of the 34 cases²¹. In the series of Moore and Shevell, the figure was 52%²². Prevalence of 0-5% with a preponderance in females of 4:1 was found in Norwegian adolescents²³.

PATHOPHYSIOLOGY

The precise mechanisms underlying the development of chronic migraine with medication overuse are not understood. It is only possible to describe some of the endocrine and neurotransmitter function that are associated with MOH or that predispose patients to this disorder. Various abnormalities have been reported: increased pain after electrical forearm stimulation suggesting central sensitization, low serotonin levels with receptor up-regulation, N-methyl-D-aspartic acid receptor dysfunction, low beta-endorphin and opioid levels, increased norepinephrine turnover, and increased inositol phosphate production in platelets²⁴⁻²⁶. Although some of these findings may help us understand the source of the chronic pain itself, they offer no explanation for clinical observations suggesting that dependence and predisposition might play a role in chronic migraine with medication overuse.

CHARACTERIZATION OF MEDICATION OVERUSE IN PEDIATRIC PATIENTS

By definition, overuse of simple analgesics for headache is defined as more than 15 headache treatment days per month of analgesic use¹⁰. MOH mainly occurs in patients with primary headache disorders and this has been clearly shown for migraine and tension-type headache. Adolescents with weekly and daily headaches using analgesics sometimes or almost daily are, however, at risk of developing MOH. These may start to self-administer medication as early as 11 to 12 years of age²⁷. Drug-induced headache has been recognized as the major cause of chronic daily or almost daily headache in adult²⁸, and only following, this phenomenon reported in children^{29,30}. There is now substantial evidence that all drugs used for the treatment of headache can cause MOH in patients with primary headache disorders³¹. Many adolescents do not consult their parents nor their physician when taking over-the counter medication³². Nearly all abortive medications can induce medication-overuse headache, including acetaminophen, aspirin, ibuprofen, naproxen, ergotamine, triptans, and caffeine^{33,34}. Children and adolescents with high daily caffeine consumption in the form of cola drinks may suffer from

caffeine-induced daily headache³⁵. A study of 26 children between the ages of 9 to 11 years showed that children with high caffeine intake had headaches after a brief period of abstinence, which was rapidly reversed by caffeine administration³⁶. Studies reporting that the use of analgesics is common among adolescents, and a higher prevalence of analgesic use among girls with headache comparable to boys³⁷. Medication overuse even less recognized in children^{2,38}. The type of abused medication is changing as new drug become available³⁹.

PSYCHIATRIC COMORBIDITY

The role of psychological factors in the development of CDH needs to be elucidated, and more attention is being focused on this topic. CDH include the following diagnostic subtypes. CM, CTTH, hemicrania continua (HC), and new daily persistent headache (NDPH). Many adolescents also have MOH^{37,40}. Many children with CDH have comorbid psychiatric diagnoses, and this may contribute to disability. Conversely, children with psychiatric disorders have a higher incidence of primary headache disorders. Studying the relationship between subtypes of migraine headaches and affective disorders may be a way to explore further a possible common pathomechanism in both disorders⁴¹. The serotonergic systems are involved in the pathophysiology of both migraine and affective disorders^{42,43}. Guidetti and Galli found sleep disorder, anxiety, and mood disorder elevated in a sample of 54 children with mixed episodic migraine and tension-type headache⁴⁴. Psychiatric comorbidity plays a role in the chronicization of headache⁴⁴ and in the evolution of migraine to MOH⁴⁵. Several clinic-based studies showed that adolescents with CDH were not uncommon and frequently had psychiatric disorders^{46,47}. Migraine and female gender increased the frequencies of comorbid psychiatric disorders and suicidal risk in adolescent⁴⁸. In a population-based study of adolescents, the higher risk for anxiety, depression, and suicide was linked to chronic daily headache in general and not to MOH specifically, and presence of migraine attacks, especially migraine with aura, was the predictor for these associations⁴⁸. Female children and adolescents with MOH report

anxiety and depression significantly more often than do age-matched healthy control individuals⁴⁹.

THERAPEUTIC APPROACH

The treatment of choice for MOH requires the abrupt withdrawal of drug(s) overuse. While giving up those drugs, it is possible that the patient faces, from 2 to 10 days, withdrawal symptoms, which include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety and nervousness. Withdrawal therapy should be offered to patients with MOH, although the evidence base for this approach is limited. Children benefit from withdrawal therapy⁵⁰. The procedures for withdrawal vary substantially, and no study has compared abrupt withdrawal treatment with tapered withdrawal in prospective randomised trials. The goal of withdrawal treatment is not only to detoxify the patients and stop the chronic headache but also to improve responsiveness to acute or prophylactic drugs; although withdrawal of the offending analgesic is a well established treatment, many paediatric neurologist also often concurrently begin a prophylactic medication. In a retrospective study the outcomes of 43 children aged 6 to 17 with MOH, 1 month after withdrawal analgesic, 20 children received daily doses of preventive medication, and 23 received no preventive medication, headache reduction was assessed 1 month later. There was no difference in the percentage, with 90% or greater headache reduction at a month between children treated by withdrawal of analgesic drugs only and those receiving preventive medications⁵¹. Predictor for a poor outcome after withdrawal therapy was a duration of MOH of longer than years⁵¹. Since all preventive medications have potential side effects this decision is not trivial. But in a recent study, Hagen et al pointed out that prophylactic medication given during the management of MOH is more effective than abrupt withdrawal with standard outpatient detoxification⁵². One aspect of acute treatment that needs to be included in any treatment plan is the avoidance of medication overuse. Clinical experience suggests that non-specific analgesics should be used fewer than 2-3 times per week, and migraine-specific drugs should be used fewer than 6 times per month⁵³.

CONCLUSION

MOH should be familiar to every paediatric neurologist and parents. This disorders needs to be clearly definite as a separate subtype within the concept of the CDH and with specific treatment requirements. MOH in children and adolescents is a difficult problem but once recognized the prognosis is generally

favourable. MOH genesis is due to at least 3 factors:

1. the individual, with his/her genetic characteristics, headache, and medical and psychiatric comorbidity;
2. the drugs, with their different dynamic and kinetic properties;
3. the environment where the individual lives⁵⁴.

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