Acute treatment of migraine in children and adolescents

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Summary

The management of headaches with juvenile onset presents several problems, related not only to appropriate drug selection but also to the specific features distinguishing headache disorders in children and adolescents: a child is not a "little adult". Many age-related factors influence the clinical expression of headache and these should be taken into account not only in the treatment, but also in the diagnosis, of juvenile headache.
Few randomised placebo-controlled clinical trials of acute or preventive drugs have been conducted in paediatric headache patients, and those that have show a high placebo response rate in children (e.g. up to 55% for prophylactic drugs and up to 69% for symptomatic ones).
The available data on symptomatic drugs are presented and discussed, focusing, in particular, on mechanisms of action, evidence of efficacy, and tolerability.

KEY WORDS: acute treatment, adolescence, childhood, migraine, review.

Introduction

Migraine can be regarded as an episodic-chronic disorder (1). The therapeutic approach to migraine should cover not only treatment of attacks but also, in many cases, preventive treatment.
Even when prophylactic treatment of migraine is successful the patient will, in most cases, still suffer some migraine attacks and need treatment for these (2).
A recent study has found that children obtaining adequate relief from pain and associated symptoms by resting in a darkened, quiet room and sleeping for a few hours may not require pharmacotherapy (3). However, the benefits of sleeping for a few hours have to be set against the activity that is lost as a result of it; moreover, in view of the complex and bidirectional association between migraine and cerebrovascular disease (4), a specific therapy might be beneficial in preventing complications of migraine.
In view of these considerations, the use of a mild analgesic could be recommended to try to speed up relief.
The aim of symptomatic treatment of migraine is to relieve moderate or severe migraine pain (5), and to alleviate other symptoms, such as nausea and vomiting. Acute treatment should be used on a maximum of three to four days a month.
The management of headaches with juvenile onset presents several problems, related not only to appropriate drug selection but also to the specific features distinguishing headache disorders in children and adolescents: a child is not a "little adult". Many age-related factors influence the clinical expression of headache and these should be taken into account not only in the treatment, but also in the diagnosis, of juvenile headache.
Children seem to find it difficult to describe their headache, and questions regarding the onset of the headache history, as well as the duration and frequency of headaches, are answered more reliably by parents (6). This also applies to the history of migraine precursors (i.e. cyclical vomiting, abdominal migraine, and benign paroxysmal vertigo of childhood) (7). There are strategies that can be usefully adopted to help improve migraine diagnosis in children:
i) take as long as you need to take the history, remembering to exercise patience and to use age-appropriate terminology;
ii) instruct the patient or the patient's parents to keep an appropriate headache diary (e.g. recording the main headache characteristics and associated symptoms) over a period of some weeks to document the headache frequency and duration, the degree of disability induced, and the occurrence of associated symptoms, as well as the use of medications;
iii) ask the child to draw a picture of what his or her headache feels like, in accordance with the suggestion of Stafstrom et al. (8), who showed that children's headache drawings are useful in the diagnosis of headache type and provide valuable insights into their experience of pain. An adolescent, on the other hand, is usually able to give a detailed description of his or her headache and answers all questions adequately (6).
Moreover, headache occurring in childhood and adolescence rarely presents the characteristics typically found in adult headache (6,9-12).

This observation led to several proposals – e.g. Lanzi (13) – for modification of the diagnostic criteria set out in the 1988 International Headache Society (IHS) classification of headache (14). Indeed, the recently revised version of this classification (the International Classification of Headache Disorders-II, ICHD-II) includes criteria that better reflect the peculiarities of migraine with and without aura (MA and MwA, respectively) in childhood and adolescence (Table I), such as the minimum attack duration of 1 hour and the bilateral location of the pain (15). Nevertheless, it has been demonstrated that, in spite of the introduction of notes to take into account the situation of children and adolescents, the ICHD-II criteria are poorly applicable to children under six years of age (16). Therefore, the development of alternative criteria, better able to take into account the peculiarities of early-onset headache forms (such as duration of < 1 h for MwA), would seem to be useful and opportune (17).

Table I - International Classification of Headache Disorders (ICHD)-II. Diagnostic criteria for paediatric migraine without aura.

- At least five attacks fulfilling criteria B-D
- Attacks lasting 1-72 h
- Headache has at least two of the following characteristics:
  i) either bilateral or unilateral location
  ii) pulsating quality
  iii) moderate or severe pain intensity
  iv) aggravated by routine physical activities
- At least one of the following accompanies headache:
  i) nausea and/or vomiting
  ii) phonophobia and photophobia (may be inferred from children's behaviour)

Once a diagnosis has been definitely established, headache should be treated as early as possible, both to prevent its escalation and to increase the effectiveness of medication.
The presence of aura or of prodrome symptoms can help patients to optimise the timing of drug intake. Important considerations, particularly in childhood and adolescence, are the risks of medication overuse and of self-treatment without parental control (18).
It is important, before selecting an appropriate treatment for childhood and adolescent migraine, to be aware of medications that have shown efficacy in adults, but whose safety and efficacy have not been assessed in younger patients (children and adolescents) (19). In fact, few randomised placebo-controlled clinical trials, either of acute or of preventive drugs, have been conducted in paediatric headache patients.
Moreover, the few studies that have been published have shown high placebo response rates in children (e.g. up to 55% for prophylactic drugs and up to 69% for symptomatic ones; Table II), and because these high placebo response rates drastically reduce the possibility of finding effective agents, drug companies and independent researchers have little interest in performing new pharmacological clinical trials in this field.
On the other hand, the placebo effect is a psychobiological phenomenon that can be attributed to different mechanisms (20), and it has to be taken into account; the physician should bear in mind that all medical treatment is set in a psychosocial context that affects the therapeutic outcome.
The available efficacy data on symptomatic drugs are summarised in Table II and these drugs will be discussed in detail, focusing in particular on their different mechanisms of action, and on evidence of their efficacy and tolerability.
Medication for an acute attack can be specific or non-specific (21). Non-specific medications are used to control the pain and associated symptoms of migraine but they are also used in other pain disorders; specific medications, on the other hand, control the migraine attack but are not useful for non-headache pain disorders. Non-specific acute headache medications include analgesics (non-steroidal anti-inflammatory drugs, NSAIDs, and combination analgesics) and antiemetics. Specific acute headache medications include dihydroergotamine and selective 5-HT1 agonists (triptans).

Non-specific medications

Acetaminophen and NSAIDs

The analgesic effects of acetaminophen are likely to be mediated centrally, but the mechanism is unclear (22). An indirect involvement of spinal serotonin receptors has been suggested (23,24).
As with all the NSAIDs, ibuprofen inhibits prostaglandin synthesis via inhibition of cyclooxygenase, thus reducing the hypothesised neurogenically-mediated inflammatory process in migraine (25).
Hämäläinen (26) compared acetaminophen (15 mg/kg) with ibuprofen (10 mg/kg) in a double-blind, placebo-controlled, single-dose, three-way crossover study and showed that both drugs were well tolerated and effective in relieving migraine attacks. At 1 hour, acetaminophen tended to be slightly more effective (39% of children relieved) than ibuprofen (37% of children relieved), but at 2 hours after administration, ibuprofen was more effective than acetaminophen (68% and 54% of children obtaining relief on ibuprofen and acetaminophen, respectively vs 37% for placebo).
A more recent study also showed that a lower ibuprofen dosage (7.5 mg/kg) is more effective than placebo in reducing headache severity at 2 hours (76% versus 53%; p=0.006) (27).
Evers et al. (28) conducted a trial to investigate the efficacy of oral zolmitriptan and ibuprofen in the treatment of migraine in children and adolescents. The authors found that ibuprofen (200 to 400 mg) was more effective than placebo in providing pain relief after 2 hours (28% for placebo versus 69% for ibuprofen; p<0.05).
The efficacy and safety of other NSAIDs (e.g. acetylsalicylic acid, diclofenac, naproxen, mefenaminic acid) in the treatment of migraine in children and adolescents have still not been assessed.

Antiemetics

The associated symptoms of migraine, such as nausea and vomiting, can be as disabling as the headache pain itself. The gastric stasis and delayed gastric emptying that are associated with migraine can decrease the effectiveness of oral medications (29).
Early administration of analgesics in the course of a migraine attack seems to alleviate nausea as well as pain.

Dopamine antagonists such as metoclopramide and prochlorperazine may, exploiting their antiemetic, antiserotonergic, antiadrenergic, and anticholinergic properties, relieve migraine symptoms.
Metoclopramide or prochlorperazine may be used to alleviate nausea and vomiting in migraine, but there is a lack of controlled trials on their use in children.
The use of such medications can be complicated by extrapyramidal and dystonic reactions, which usually disappear after withdrawal of the drug.

Table II - Symptomatic drugs evaluated in placebo-controlled and open clinical trials.

Drug	Dose	Age range	n.	% of responders*		p	Ref.	Notes
Non-specific drugs								
Ibuprofen	10 mg/kg	4-16 y	88	68%	37%	<0.05	26	
	7.5 mg/kg	6-12 y	84	76%	53%	0.006	27	
	200-400 mg	6-18 y	32	69%	28%	<0.05	28	
Acetaminophen	15 mg/kg	4-16 y	88	54%	37%	<0.05	26	
Specific drugs								
Dihydroergotamine	20 µg/kg and 40 µg/kg	5-15 y	12	58%	16%	NS	32	
Sumatriptan nasal	20 mg	6-10 y	14	86%	43%	0.03	35	
	5/10/20 mg	12-17 y	510	66%§	53%	<0.05	36	
	10-20 mg	8-17 y	83	64%	39%	0.003	37	
	20 mg	12-17 y	738	61%	52%	NS	38	1 hour post-dose: primary end point.
				42%	33%	0.046		30 min post-dose: secondary end point
				68%	58%	0.025		2 hours post-dose: secondary end point
Sumatriptan oral	50-100 mg	8-16 y	23	30%	22%	NS	31	
Sumatriptan subcutaneous	3-6 mg	6-16 y	17	64%		OT	33	
	0.06 mg/kg	6-18 y	50	78%		OT	34	
Rizatriptan oral	5 mg	12-17 y	296	66%	56%	NS	39	
	5 mg	12-17 y	234	68%	69%	NS	39	Therapy on school-days
				74%	58%	0.002		Therapy also at week ends
Zolmitriptan oral	5 mg	12-17 y	686	77%		OT	40	
	2.5/5 mg	12-17 y	38	88/70%		OT	41	
	2.5 mg	6-18 y	32	62%	28%	<0.05	28	
Almotriptan oral	6.25-12.5 mg	11-17 y	15	86%		OT	42	
Eletriptan	40 mg	12-17 y	267	57%	57%	NS	44	Significant differences in secondary endpoints (see text)

Abbreviations: NS=non-significant difference (active drug vs placebo); RCT=randomised controlled trial; OT=open trial.
* the % is expressed as overall % of responders (OT) or active-drug vs placebo % of responders (RCT); § 5 mg.

Specific medications

Dihydroergotamine

Dihydroergotamine (DHE) is an agonist of arterial serotonin receptors and blocks α-adrenergic receptors. DHE is hypothesised to exert an antimigraine effect by producing a powerful vasoconstriction of the external carotid artery and its branches, but also by a receptor-mediated neural pathway and a serotonergic mechanism (30).
Hämäläinen et al. conducted a stepwise series of studies: following the first acetaminophen and ibuprofen comparison study (26), the children who had not responded to paracetamol and ibuprofen were entered into two subsequent studies that assessed the effects of sumatriptan (31) and DHE (32). In the children with acetaminophen/ibuprofen-resistant migraine, DHE was more effective than placebo, but the difference between the treatments was not statistically significant (32).

Triptans

Triptan agents selectively stimulate vascular serotonin 5-HT1 receptors; they thus relieve pain by constricting the affected vessels and blocking nociceptive impulses, and the subsequent inflammatory response.
The triptans are thought to act predominantly as 5-HT1B/D receptor agonists, although their therapeutic effect may also be mediated through binding to other receptor subtypes. During a migraine attack, triptans, by stimulating the 5-HT1B receptors on cranial blood vessels, are thought to induce vasoconstriction that is relatively selective for these vessels, given that vasoconstriction in the peripheral circulation is mediated mainly by 5-HT2 receptors.
In addition, triptans activate inhibitory presynaptic 5-HT1D receptors located on the terminal endings of trigeminal nociceptive afferents, effectively decreasing the release of the neuropeptides responsible for vasodilatation of meningeal and cerebral blood vessels, and for activation of second-order neurons in the trigeminal nucleus caudalis. Recently, 5-HT1D receptors have been shown to be present on postsynaptic second-order neurons in the caudal trigeminal nucleus. Whether triptans bind to and modulate the activity of these neurons is not yet clear.

Sumatriptan. Sumatriptan has been investigated in several clinical trials. The first studies (33,34) were non-controlled trials of subcutaneously administered sumatriptan, and they showed partial relief from migraine in 64 and 78% of patients, respectively. The first randomised placebo-controlled trial (31) was conducted with the aim of studying the effectiveness of oral sumatriptan (50 to 100 mg) in children and adolescents with acetaminophen-/ibuprofen-resistant migraine. In that study, the response rates were lower than those demonstrated in adult studies, and oral sumatriptan was not more effective than placebo (31).
More recently, four prospective, randomised, placebo-controlled trials assessed both the efficacy and the safety of sumatriptan nasal spray in adolescent migraineurs (35-38).
Ueberall (35) found significant headache relief at 2 hours in 85.7% of treated patients (20 mg sumatriptan nasal spray) compared with 42.9% in the placebo group (p=0.03).
Winner et al. (36) compared the effectiveness of 5-, 10- and 20-mg sumatriptan nasal spray with placebo in 510 adolescents. The 2-hour response rate (reduction in headache severity) was 66% for the 5-mg dose (p<0.05), 63% for the 20-mg dose (p=0.059) and 53% for placebo. Both photophobia and phonophobia were reduced with the 20-mg dose (p<0.05). The only adverse effect was taste disturbance (26%).
Ahonen et al. (37) evaluated the effectiveness of sumatriptan nasal spray in children aged 8-17 years (10 mg for children weighing < 40 kg and 20 mg for children weighing > 40 kg). The primary end point (reduction in headache severity at 2 h) was met in 64% of the treated patients and in 39% of the placebo group (p<0.003). In addition, at 1 hour sumatriptan was more effective than placebo in providing headache relief (51% versus 29%; p<0.014). The most common adverse effect was, again, taste disturbance (29%).
The fourth trial was conducted by Winner et al. (38) to compare the efficacy and tolerability of sumatriptan nasal spray (5 and 20 mg) versus placebo in the acute treatment of migraine in adolescent subjects. The study was conducted because the previous randomised, placebo-controlled study of 510 adolescent subjects (36), had shown sumatriptan (5, 10 and 20 mg) to be well tolerated. However, the primary efficacy analysis for headache relief with 20 mg at 2 hours did not demonstrate statistical significance (p=0.059).
This more recent trial (38) was a randomised (1:1:1), placebo-controlled, double-blind, parallel-group study. In total, 738 adolescent subjects (mean age: 14 years) with ≥ 6-month histories of migraine (with or without aura) self-treated a single attack of moderate or severe migraine. The primary end points were headache relief at 1 hour and sustained relief from 1 to 24 hours. The authors found that sumatriptan 20 mg provided greater headache relief than placebo at 30 minutes (42% versus 33%, respectively; p=0.046) and at 2 hours post-dose (68% versus 58%; p=0.025), but did not reach statistical significance at 1 hour (61% versus 52%; p=0.087), or for sustained headache relief from 1 to 24 hours (p=0.061). Significant differences (p<0.05) in favour of sumatriptan 20 mg over placebo were observed for several secondary efficacy end points including sustained relief from 2 to 24 hours. In general, response rates to sumatriptan nasal spray 5 mg were slightly higher than to placebo, but the differences did not reach statistical significance. Sumatriptan was well tolerated and no serious adverse events occurred, taste disturbance being the most common adverse effect.

Rizatriptan. Rizatriptan was studied by in a randomised, placebo-controlled trial that included 296 adolescents aged 12-17 years (39). No difference in pain relief was found compared to placebo at the 2-h primary end point (66% versus 56%; p=0.79). Tolerability and adverse event rates were comparable with placebo.
More recently, two studies were conducted in migraine patients aged 12-17 years to examine the short- and long-term efficacy and tolerability of rizatriptan 5 mg (40). The first study was a randomised, double-blind, placebo-controlled, single-attack study followed by a

randomised, one-year, open-label extension. The second was a randomised, one-year, open-label study.
In the single-attack study, patients used rizatriptan 5-mg tablets (n=234) or placebo (n=242) to treat a moderate or severe migraine headache and up to two recurrences. The study medication had to be used only on non-school days.
In the one-year studies, patients were treated for up to six migraine attacks per month with rizatriptan 5-mg tablets (n=273), rizatriptan 5-mg wafers (n=281) or standard-care therapy (n=132). Headache severity was assessed by the patient 2 hours after the initial dose. In all the studies, the primary efficacy measure was pain relief at 2 hours post-dose. In the single-attack study, the proportion of patients reporting pain relief at 2 hours was not significantly different between the rizatriptan 5 mg (68.2%) and placebo (68.8%) arms. Fewer patients than expected (~ 30%) treated their migraine attacks at the weekend. Among these patients, the proportion with pain relief at 2 hours was significantly higher in the rizatriptan group than in the placebo group (74% versus 58%; p=0.022).
In the multiple-attack studies, pain relief at 2 hours was achieved in significantly more attacks treated with the rizatriptan 5-mg tablet (77%) or with a rizatriptan 5-mg wafer (77%) than with standard care (64%). Rizatriptan 5 mg was well tolerated.

Zolmitriptan. Zolmitriptan was assessed in adolescents (12-17 years of age) in an open-label multicentre trial (41). Doses of 2.5 or 5.0 mg were used to treat 276 migraine attacks reaching an overall response at 2 hours of 88% and 70%, respectively. The treatment was well tolerated.
More recently, Evers et al. conducted a double-blind, placebo-controlled, crossover study to investigate the efficacy of oral zolmitriptan in the treatment of migraine in children and adolescents (28). Patients (n=32) received placebo, zolmitriptan 2.5 mg and ibuprofen 200 to 400 mg to treat three consecutive migraine attacks. Pain relief rates at 2 hours were 28% for placebo, 62% for zolmitriptan, and 69% for ibuprofen (placebo versus zolmitriptan $p<0.05$; placebo versus ibuprofen $p<0.05$). Both drugs were well tolerated with only mild side effects.

Almotriptan. Almotriptan was studied in a small open-label pilot study in 15 patients with a history of migraine with or without aura, aged 11-17 years (42). Almotriptan in doses ranging from 6.25 to 12.5 mg was well tolerated (no adverse effects except for one case of transient mild stiffness). Of the 15 patients, only two demonstrated no efficacy without adverse effects. In the other 13 patients almotriptan was effective.

Naratriptan. Naratriptan has not been assessed for efficacy in a clinical trial involving children and adolescents. The only study of this drug conducted to date set out to characterise its pharmacokinetics for 2.5-mg tablets in adolescents (43). No serious adverse events were apparent.

Eletriptan. Eletriptan, a potent 5-HT1B/1D agonist, has proven efficacy in the acute treatment of migraine in adults.
Winner et al. (44) evaluated the efficacy and tolerability of eletriptan 40 mg versus placebo in adolescent patients (aged 12-17) in a multicentre, double-blind, parallel-group, placebo-controlled trial.
The primary efficacy endpoint was 2-hour headache response. Of 274 patients who treated a migraine attack, 267 were evaluated (n=138 eletriptan; n=129 placebo). The authors found no significant difference in 2-hour headache response for eletriptan 40 mg versus placebo (57% vs 57%), and, moreover, no significant improvements were observed for any of the outcomes at 1 or 2 hours post-dose. The authors found a significant advantage for eletriptan 40 mg in reducing headache recurrence within 24 hours post-dose (11% vs 25%, p=0.028), and post hoc analyses showed statistically significant differences for sustained headache response rates (52% vs 39%; p=0.04) and sustained pain-free response rates (22% vs 10%; p=0.013). The strongest clinical predictor of placebo response was triptan-naive status (i.e. no previous use of any triptan).
Eletriptan 40 mg was well tolerated in this population, and the profile of adverse events was similar to that observed in phase III trials in adult patients.

Adverse events

Acetaminophen is considered a safe drug and, if used in therapeutic doses, adverse events are extremely rare, although their exact incidence is unknown. Overdoses can occur and are associated with hepatotoxicity and renotoxicity. The potential adverse effects of ibuprofen are similar to those of other NSAIDs. However, gastrointestinal bleeding, renal failure or anaphylaxis are rare with short-term use in children (26). Sumatriptan is well tolerated; no serious adverse events occurred in clinical trials, taste disturbance emerging as the most common adverse effect (35-38).

Discussion

The available published data on the efficacy and safety of symptomatic drug treatment for migraine in children and adolescents (summarised in Table II) suggest that ibuprofen (7.5 to 10.0 mg/kg) and acetaminophen (15 mg/kg) are effective treatments and should be considered. Sumatriptan nasal spray (5 and 20 mg) is also probably effective, but should be considered for the treatment of adolescents only.
There are not yet sufficient data to allow the use of other NSAIDs and triptans to be recommended for the treatment of migraine in children and adolescents.
As also shown by the high impact of the placebo effect on migraine-treatment efficacy, headache, which results from an interaction between biological, psychological and environmental factors, is a complex condition, both pathogenetically and clinically; this is particularly true in childhood and adolescence.
The role of psychological factors, life events and excessively stressful lifestyles in influencing recurrent headache has been outlined repeatedly (3,36,45,47). In a population study, Anttila et al. (48) showed that 28.8% of migraine patients had internalising symptom scores above the cut-off point of normal functioning. Other research, using not only behavioural check-lists compiled

by parents, but also more in-depth psychodiagnostic evaluations, found higher rates of psychiatric comorbidities in children with persistent headache compared with headache-free patients (78% versus 31%) after a long follow-up period (16). Thus, alongside the right choice of drug therapy, it is also mandatory to look for possible psychiatric comorbidities linked to the headache, and factors generating stress or psychological distress. A good review on this issue draws attention to the high number of person-specific and situational variables that influence headache (49). Indeed, it has been demonstrated that headache is the most frequent somatic symptom in children and adolescents referred for emotional and behavioural disorders, as well as in patients with depression and/or anxiety (50).

Moreover, as a consequence of the headache, psychosocial functioning may be impaired in various areas, including family life, relations with the peer group and friends, leisure activities and working capacity, and productivity at school or at work (45).

In conclusion, the clinical approach to the child or adolescent with acute migraine, and to his/her parents, should be holistic. Migraine in childhood and adolescence, as in adulthood, is a disorder highly influenced by biological variables: genetic predisposition, electrochemical and neurobiochemical events, vascular or blood flow modifications. Future advances in the field of migraine genetics could provide new insight into the pathophysiology of migraine and thus new treatment options (51).

In our experience the migraine attack in childhood, unlike adulthood, can also be closely linked to psychological variables: specific life events and/or constitutional predisposition, can play a significant role in the genesis and evolution of the pain. As a result, the patient-clinician relationship is often a central factor in the therapy, even influencing the course of the disease (18).

References

1. Lipton RB, Bigal ME, Stewart WF. Clinical trials of acute treatments for migraine including multiple attack studies of pain, disability, and health-related quality of life. Neurology 2005;65(Suppl 4):S50-S58
2. Tfelt-Hansen P. Acute pharmacotherapy of migraine, tension-type headache, and cluster headache. J Headache Pain 2007;8:127-133
3. Wöber C, Wöber-Bingöl C. Clinical management of young patients presenting with headache. Funct Neurol 2000;15 (Suppl 3):89-105
4. Agostoni E, Rigamonti A. Migraine and cerebrovascular disease. Neurol Sci 2007;28(Suppl 2):S156-S160
5. Mortimer MJ, Kay J, Jaron A. Childhood migraine in general practice: clinical features and characteristics. Cephalalgia 1992;12:238-243
6. Wöber-Bingöl C, Wöber C, Karwautz A et al. Diagnosis of headache in childhood and adolescence: a study in 437 patients. Cephalalgia 1995;15:13-21
7. Lanzi G, Balottin U, Fazzi E, Tagliasacchi M, Manfrin M, Mira E. Benign paroxysmal vertigo of childhood: a long-term follow-up. Cephalalgia 1994;14:458-460
8. Stafstrom CE, Goldenholz SR, Dulli DA. Serial headache drawings by children with migraine: correlation with clinical headache status. J Child Neurol 2005;20:809-813
9. Prensky AL, Sommer D. Diagnosis and treatment of migraine in children. Neurology 1979;29:506-510
10. Lanzi G, Balottin U. The semeiology of migraine attacks in childhood. In: Occipital Seizures and Epilepsies in Children. Mariani Foundation Pediatric Neurology Series - 1. London; John Libbey 1993:87-91
11. Winner P, Martinez W, Mate L, Bello L. Classification of pediatric migraine: proposed revisions to the IHS criteria. Headache 1995;35:407-410
12. Balottin U, Borgatti R, Zambrino CA, Lanzi G. Clinical characteristics and long-term outcome of migraine with aura in children and adolescents. Dev Med Child Neurol 1997;39:26-30
13. Lanzi G, Balottin U, Zambrino CA et al. Guidelines and recommendations for the treatment of migraine in paediatric and adolescent patients. Italian Society for the Study of Headache. Funct Neurol 1996;11: 269-275
14. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(Suppl 7):1-96
15. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 (Suppl 1):9-160
16. Balottin U, Termine C, Nicoli F, Quadrelli M, Ferrari-Ginevra O, Lanzi G. Idiopathic headache in children under six years of age: a follow-up study. Headache 2005;45: 705-715
17. Arruda MA, Bordini CA, Ciciarelli JC et al. Decreasing the minimal duration of the attack to 1 hour: is this sufficient to increase the sensitivity of the ICHD-II for migraine in childhood? J Headache Pain 2004;5:131-136
18. Balottin U, Termine C. Recommendations for the management of migraine in paediatric patients. Expert Opin Pharmacother 2007;8:731-744
19. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754-762
20. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390-10402
21. Silberstein SD, Saper JR, Freitag FG. Migraine: diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ eds Wolff's Headache and Other Head Pain, 7th edition. New York; Oxford University Press 2001: 98-115
22. Piletta P, Porchet HC, Dayer P. Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 1991;49:350-354
23. Pelissier T, Alloui A, Caussade F et al. Paracetamol exerts a spinal antinociceptive effect involving an indirect interaction with 5-hydroxytryptamine3 receptors: in vivo and in vitro evidence. J Pharmacol Exp Ther 1996;278:8-14
24. Raffa RB, Codd EE. Lack of binding of acetaminophen to 5-HT receptor or uptake sites (or eleven other binding/uptake assays). Life Sci 1996;59:PL37-40
25. Buzzi MG, Sakas DE, Moskowitz MA. Indomethacin and acetylsalicyclic acid block neurogenic plasma protein extravasation in rat dura mater. Eur J Pharmacol 1989;165: 251-258
26. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 1997;48:103-107
27. Lewis DW, Kellstein D, Dahl G et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. Headache 2002;42:780-786
28. Evers S, Rahmann A, Kraemer C et al. Treatment of child-

hood migraine attacks with oral zolmitriptan and ibuprofen. Neurology 2006;67:497-499.
29. Boyle R, Behan PO, Sutton JA. A correlation between severity of migraine and delayed gastric emptying measured by an epigastric impedance method. Br J Clin Pharmacol 1990;30:405-409.
30. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. Working Panel of the Headache and Facial Pain Section of the American Academy of Neurology. Neurology 1995;45:577-584
31. Hämäläinen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently from adults? Neurology 1997;48: 1100-1103
32. Hämäläinen ML, Hoppu K, Santavuori PR. Oral dihydroergotamine for therapy-resistant migraine attacks in children. Pediatr Neurol 1997;16:114-117
33. MacDonald JT. Treatment of juvenile migraine with subcutaneous sumatriptan. Headache 1994;34:581-582
34. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first 50 consecutive patients with acute migraine in a pediatric neurology office practice. Headache 1996; 36:419-422
35. Ueberall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 1999; 52:1507-1510
36. Winner P, Rothner AD, Saper J et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics 2000;106:989-997
37. Ahonen K, Hämäläinen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. Neurology 2004;62:883-887
38. Winner P, Rothner AD, Wooten JD, Webster C, Ames M. Sumatriptan nasal spray in adolescent migraineurs: a randomized, double-blind, placebo-controlled, acute study. Headache 2006;46:212-222
39. Winner P, Lewis D, Visser WH et al. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind placebo-controlled study. Headache 2002; 42:49-55
40. Visser WH, Winner P, Strohmaier K et al. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies. Headache 2004;44:891-899
41. Linder SL, Dowson AJ. Zolmitriptan provides effective migraine relief in adolescents. Int J Clin Pract 2000;54:466-469
42. Charles JA. Almotriptan in the acute treatment of migraine in patients 11-17 years old: an open-label pilot study of efficacy and safety. J Headache Pain 2006;7:95-97
43. Christensen ML, Eades SK, Fuseau E, Kempsford RD, Phelps SJ, Hak LJ. Pharmacokinetics of naratriptan in adolescent subjects with a history of migraine. J Clin Pharmacol 2001;41:170-175
44. Winner P, Linder SL, Lipton RB, Almas M, Parsons B, Pitman V. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. Headache 2007;47:511-518
45. Karwautz A, Wöber C, Lang T et al. Psychosocial factors in children and adolescents with migraine and tension-type headache: a controlled study and review of the literature. Cephalalgia 1999;19:32-43.
46. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM. Headache and major depression: is the association specific to migraine? Neurology 2000;54:308-313
47. Lanzi G, Zambrino CA, Ferrari-Ginevra O et al. Personality traits in childhood and adolescent headache. Cephalalgia 2001;21:53-60.
48. Anttila P, Sourander A, Metsähonkala L, Aromaa M, Helenius H, Sillanpää M. Psychiatric symptoms in children with primary headache. J Am Acad Child Adolesc Psychiatry 2004;43:412-419
49. Bandell-Hoekstra I, Abu-Saad HH, Passchier J, Knipschild P. Recurrent headache, coping, and quality of life in children: a review. Headache 2000;40:357-370
50. Masi G, Favilla L, Millepiedi S, Mucci M. Somatic symptoms in children and adolescents referred for emotional and behavioral disorders. Psychiatry 2000;63:140-149
51. Sacco S, Carolei A. Migraine attributed to genetic disorder. Funct Neurol 2007;22:117-118