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REVIEW ARTICLE

Favorable outcome of early treatment of new onset child and adolescent migraine-implications for disease modification

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Abstract There is evidence that the prevalence of migraine in children and adolescents may be increasing. Current theories of migraine pathophysiology in adults suggest activation of central cortical and brainstem pathways in conjunction with the peripheral trigeminovascular system, which ultimately results in release of neuropeptides, facilitation of central pain pathways, neurogenic inflammation surrounding peripheral vessels, and vasodilatation. Although several risk factors for frequent episodic, chronic, and refractory migraine have been identified, the causes of migraine progression are not known. Migraine pathophysiology has not been fully evaluated in children. In this review, we will first discuss the evidence that early therapeutic interventions in the child or adolescent new onset migraineur, may halt or limit progression and disability. We will then review the evidence suggesting that many adults with chronic or refractory migraine developed their migraine as children or adolescents and may not have been treated adequately with migraine-specific therapy. Finally, we will show that early, appropriate and optimal treatment of migraine during childhood and adolescence may result in disease modification and prevent progression of this disease.

Keywords Disease modification · Child · Adolescent · Migraine

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Introduction

The current prevalence of childhood migraine is 10.2% and as high as 28% in older teenagers [1, 2]. Although studies show that migraine headaches remit in 17–34% of adolescent subjects, headaches persist in 20–48% of subjects, and transform into other types of headaches in 11–37%. In a recent study of 55 subjects aged 11–14 with migraine at baseline, 38.2% had experienced remission, but 41.8% had persistent migraine and 20% transformed to tension-type headache. Familial predisposition predicted a poorer outcome. A sevenfold increased risk of migraine persistence occurs over 10 years among subjects with migraine headaches who have first-degree relatives with migraine [3]. Chronic daily headache in children and adolescents appears to be increasing in the past few decades [4]. In one study from a large headache center, 34.6% of children had chronic daily headache [5].

Among adults with migraine, 20% report that symptoms started before age 10 and 46% say they started before age 20 [6]. More than 80% of patients who develop migraines will have a first attack by age 30 [7]. Episodic migraine, especially when frequent, is a risk factor for developing chronic daily headache. In one study, 78% of adults with chronic daily headache including those not due to

medication overuse had a prior history of episodic migraine. In addition to the epidemiological data, radiological evidence also shows that increasing frequency of migraine impacts on disease outcome. Specifically, they image brain alterations in migraineurs, which correlate with the frequency and duration of clinical disease [8, 9]. Thus, in susceptible individuals, repeated migraine attacks may result in increasing headache frequency and eventually refractory chronic migraines [10].

There is compelling evidence that early comprehensive treatment of the child or adolescent recent onset migraineur will decrease disability and result in a favorable course [11–13]. There is also evidence that many adults with chronic migraine or refractory migraine began their disease with episodic migraine in childhood or adolescence that was often not treated with targeted, specific antimigraine therapy. It appears likely that a window of interventional opportunity for susceptible migraine generators in children and teenagers may exist before refractory central sensitization occurs with progression to high frequency episodic and chronic migraine. Based upon this data, we speculate that targeted, comprehensive, aggressive early treatment of the new onset child and adolescent migraineur may result in disease modification.

Repetitive migraine attacks are associated with brain lesions

Current theories of migraine pathophysiology suggest that the initiating event is either cortical spreading depression or involvement of the trigeminal nucleus caudalis and other brainstem centers. Further research in this area is warranted to dissect out early electrical and biochemical processes. Welch et al. [8] found that iron deposition occurs in the periaqueductal gray (PAG) and red nucleus of the midbrain in both patients with frequent migraines of many years and those who evolved into chronic migraine. The PAG is part of an anti-nociceptive network that modulates pain in descending central pathways. Stimulation [14] and lesions [15] in the PAG can produce migraine-like headaches in non-migraineurs. Iron levels in the PAG were higher in chronic migraine sufferers than in control subjects. It is postulated that free radical cell damage may lead to iron deposition, which is related to duration of illness in episodic and chronic migraine groups. Positive correlations were found for duration of illness in the episodic and chronic daily headache cohorts and no changes were found in the normal controls. The authors concluded that iron homeostasis within the PAG was persistently and progressively impaired in migraine patients. They suggested that the elevation in iron deposition levels in the PAG may reflect progressive neuronal damage related to long standing recurrent migraine attacks [8].

Kruit et al. [9] compared 435 adult migraineurs with and without aura to healthy controls utilizing MRI imaging. Patients who experienced migraine with aura were at much higher risk of subclinical infarcts in the cerebellum than those without aura, even though overall there were no more lesions suggestive of infarct in migraineurs versus non-migraineurs. Among women, the risk for a high frequency of white matter lesions was higher in women with migraine than in those without migraine. And, this risk of higher white matter lesion burden on MRI increased with increasing attack frequency [9].

Both of these imaging studies are comparisons of migraine populations to controls as longitudinal studies following these changes are not available. Although there have been no similar studies performed in the child/adolescent population, the results of these adult imaging studies suggest a correlation between long duration of migraine and white matter lesion load and brainstem iron deposition, possibly reflecting injury to the brain either directly or indirectly in some migraine patients. These data have implications for current concepts of migraine as a disease as migraine should be conceptualized not just as an episodic disorder but as a chronic–episodic and sometimes chronic progressive disorder [16].

Repetitive migraine attacks cause central sensitization and migraine progression

Sciatic nerve ligatures in rats result in long lasting behavioral changes, local and remote allodynia, hyperalgesia, and avoidance behaviors. Autopsy of these rodents revealed significant anatomic and physiological changes within the dorsal horn, thalamic nuclei, and cerebral cortex, areas which are implicated in the central migraine generators of humans. This injury to the rodent sciatic nerve results in increased neural sensitivity, excitation, and receptive field size. The lowered pain threshold results in hyperalgesia and allodynia, which is the clinical marker of central sensitization of the trigeminal nucleus caudalis in migraine. Moreover, increased receptor field size leads to spread of the allodynia to areas not originally affected. Sensitized pathways are more excitable and less inhibited than normal pathways, resulting in increased neuronal firing [17].

In adult migraineurs (and implied in children and adolescents albeit not proven), allodynia is the clinical manifestation of central sensitization, which has been shown to develop in up to 75% of migraineurs. Triptans administered early prevented allodynia, while late triptan intervention did not when allodynia is well established [18–20]. Their action is attributed to their binding to 5-HT_{1B} and 5-HT_{1D}

Table 1 Headache characteristics at initial visit and at follow-up after comprehensive treatment

	Initial visit	1 Year	2 Years	5 Years
Frequency	13.4 ± 10.8	4.9 ± 7 ($P < 0.001$)	4.7 ± 7.6 ($P < 0.001$)	4.6 ± 7.6 ($P < 0.001$)
Severity	6.8 ± 1.8	5.2 ± 2.3 ($P < 0.001$)	5.0 ± 2.4 ($P < 0.001$)	4.6 ± 2.5 ($P < 0.001$)
Duration	17.3 ± 9.5	12.2 ± 18.6 ($P < 0.01$)	9.4 ± 15.1 ($P < 0.001$)	11.5 ± 16.5 ($P = 0.02$)
School days missed	4.5 ± 9.5	5 ± 12.2 ($P = 0.35$)	2.7 ± 6 ($P = 0.01$)	1.5 ± 2.8 ($P < 0.001$)

From Kabbouche et al. [11]

receptors in cranial blood vessels and nerve endings and subsequent inhibition of pro-inflammatory release of neuropeptides including CGRP and substance P. Halting the initial phase of the migraine process with triptans, which have agonist activity at 5HT1B/D receptors will help win the race against the development of cutaneous allodynia caused by central sensitization [21, 22].

Central sensitization explains the progression of the migraine attacks. It may also play a role in the progression of the disease itself. Repeated episodes of central sensitization are associated with permanent neuronal damage, treatment refractoriness, and disease progression [20, 21]. Trigeminovascular fibers projecting to the meninges are activated during a migraine attack, neuropeptide (substance P and CGRP) release and a sterile inflammation characterized by plasma protein leakage, mast cell activation, and vasodilatation. These changes lead to sensitization of the first order trigeminal neurons, explaining pulsating pain, pain aggravated by movements of the head, bending down, and physical exercise [20]. Sensitization of the second order neurons in the brainstem, particularly the trigeminal nucleus caudalis, accounts for cephalic allodynia [20]. Extracephalic allodynia (limb and trunk) can be explained by sensitization of the third order trigeminal neurons, which project from thalamus to the cerebral cortex [20]. Thus, allodynia is the clinical manifestation of central sensitization of the second and third order trigeminal neurons. According to Mathew et al. [23], there is a correlation between the duration of migraine disorder and the development of allodynia. Patients who had migraine for longer duration tended to exhibit more allodynic symptoms. A total of 32.2% of patients who had migraine duration of 0–5 years exhibited allodynia, whereas 75% of patients whose illness duration was 31–35 years had allodynia. Their observation confirms previously reported correlation between duration of illness and occurrence of allodynia. Also, they found a correlation between frequency of migraine and allodynia. Taken together, it appears that there is a higher chance for migraine patients with long history of the disorder and frequent attacks to develop central sensitization. These observations may have important clinical implications with regard to chronic or transformed migraine, which is known to be more refractory to treatment [23].

Treat early and comprehensively

Bille [24] followed a cohort of 73 children with migraine for over 40 years. Interval follow-ups were made at 6, 16, 22, 30, and 40 years. Thirty-five to 50% of children became completely headache free. At 6-year follow-up, 66% of the patients still had headaches. Migraine was still present in 51% of the patients at 40 years. No long-term therapeutic assessment was made. However, the results at 6 and 40 years reveal a disabling problem for a significant number of children.

Kabbouche et al. [11] performed an observational study and assessed the long-term effectiveness and outcome of multidisciplinary treatment of childhood headaches at 1, 2, and 5 years after initial treatment. Headache characteristics were assessed at the initial visit and were re-evaluated 1, 2, and 5 years later in independent sub-groups of consecutive patients. These characteristics included headache frequency, severity, average duration, school absences, and overall perceived response to treatment (Table 1). Ninety-six patients were evaluated (mean age = 11.0 ± 3.4, 59% females) at 1 year, 69 patients at 2 years (mean age = 10.6 ± 3.4, 48% females), and 32 at 5 years (mean age = 10.5 ± 3.9, 66% females). The headaches were reported as better in 94% at 1 year, 85% at 2 years, and 94% at 5 years. The initial frequency was at 13.4 ± 10.8 headaches per month, 4.9 ± 7.0 at 1 year ($P < 0.001$), 4.7 ± 7.6 at 2 years ($P < 0.001$), and 4.5 ± 7.5 at 5 years ($P < 0.001$). The severity decreased from 6.8 ± 1.8 to 5.1 ± 2.3 at 1 year ($P < 0.001$), to 5.0 ± 2.4 at 2 years ($P < 0.001$), and to 4.6 ± 2.5 at 5 years ($P < 0.01$). The school days missed per month showed a marked decrease from 4.5 ± 9.5 at initial visit to 1.55 ± 2.8 at 5 years ($P < 0.001$). Patients who were seen only at their initial visit and did not choose to return for follow-up had less frequent and shorter duration headaches on initial visit when compared with the rest of the sample and continued to be doing well at the 1-, 2-, and 5-year assessments. It was concluded

that multidisciplinary treatment was found to be effective for children and adolescents with improvement of multiple outcome measures of pediatric migraine care, including frequency, severity, and school days missed.

In a large combined preadolescent–adult headache practice, repetitive parenteral treatment with dihydroergotamine(DHE)/dexamethasone/hydroxyzine without daily oral preventive therapy was administered in a small open label observational study of patients with transformed migraine [12]. Seven adolescents and three adults presented in status migrainosus or chronic migraine and either declined daily oral preventative therapy or had previous intolerance to most of the accepted daily preventive agents, but accepted parenteral therapy for escalating severe disabling headache. Patients were treated with intramuscular DHE 1 mg, dexamethasone 12 mg, and hydroxyzine 50 mg for up to three treatments separated by a 1-week interval. No oral preventive treatment was given as per patient and parental choice. After a follow-up period ranging from 6 months to 4 years, all of the adolescents in this small pilot study converted into a sustained, benign episodic migraine course without need for a daily preventive treatment; none of the adults could be converted.

Hering-Hanit et al. [13] studied 26 adolescents with chronic daily headache secondary to medication overuse. Upon withdrawing the offending analgesics and instituting appropriate preventative and abortive therapy, complete cessation of all headaches occurred in 20 patients, and the rest converted to a more benign intermittent episodic migraine. In contrast, the adults in the study by Ferrari et al. [25] evaluating 150 chronic daily headache sufferers from medication overuse did not fare as well as the adolescents, with preventive and abortive treatments. Although 75% experienced a 50% reduction in headache frequency, only 15% converted to infrequent episodic migraine.

Wober et al. [26] followed 64 migraine patients after successful interval prophylaxis with flunarizine and propranolol or metoprolol, to investigate how long the therapeutic success would last, if further prophylaxis would be successful again, and what factors would influence the prognosis. Patients were treated for 3–6 months with flunarizine 10 mg qhs and propranolol (40 mg b.i.d. or t.i.d.) or metoprolol 25–50 mg b.i.d. over a period of 3–6 months, and were followed after discontinuation of prophylaxis for 18–78 months. The long-term responders with a sustained migraine frequency response by at least 50% during the entire follow-up period after treatment were younger (mean age 42.2) with a younger age of onset measured as mean migraine duration years (18.9), than the worst responders who experienced a reduction of migraine frequency even during treatment lasting only a few weeks with further prophylaxis unsuccessful, mean age 50.1; mean migraine duration years (19.9).

Adults with chronic or refractory migraine usually developed it as children or adolescents

Two studies have shown that adults suffering from chronic and/or refractory migraine often have a history of episodic migraine that began in childhood, adolescence or in their 20s. In the first study, clinical features of 100 patients with chronic daily headache were evaluated to determine their headache characteristics and other associated features [27]. Their ages ranged from 11 to 82 years with a peak between 21 and 30. Conspicuously, the reported onset of headache peaked in the second decade between the ages of 11 and 20, 58% began migraine before the age of 20, and 68% began migraine before the age of 30. In many cases, chronic headache evolved from episodic headache. The date of transition to daily headache was difficult to estimate. There was no documentation of migraine-specific treatment at onset.

In the second study, of 630 patients with chronic daily headache evaluated in a headache clinic, 78% were reported to have a prior history of episodic migraine prior to transformation to chronic daily headache [28]. The majority of patients who presented with chronic daily or near daily headache had a previous history of episodic migraine, which transformed into a chronic daily headache over the years. Notably, the mean age of episodic headache onset of the chronic migraine group was 22 ± 9.2 years and there is no evidence this group was treated early on with migraine-specific drugs [28].

Does early treatment of new onset migraine in a child or adolescent result in disease modification?

Disease modifying pharmacological treatment suppresses the underlying progression of a disease by intervening in the biological processes that underlie the pathophysiology of the disease that leads to cell death and/or dysfunction. Disease modifying agents already exist for the disease modification of disorders such as rheumatoid arthritis [29] and multiple sclerosis [30].

Headache experts have conceptualized migraine not just as an episodic disorder, but as a chronic–episodic and sometimes chronic progressive disorder for which there exist treatments known to effectively treat the disease [16]. As proven, effective and safe preventive and abortive therapies for migraine are available in adults, it would be inappropriate and possibly unethical to conduct the double-blind, placebo-controlled studies necessary in

young migraineurs to prove that disease modification is possible in migraine when optimally treated early in its course. Even the elegant study design proposed by Fox [31] to prove drug-induced migraine modification in a sophisticated clinical trial design, would have to include a placebo arm of children and adolescents. This study would utilize complex mathematical methods in a three-dimensional construct and might be capable of detecting disease modifying effects of antimigraine medication [31].

Central sensitization of the trigeminal nucleus caudalis and the initiation of the migraine attack, whether it is cortical spreading depression at cortical levels or in the brainstem, are biochemical processes that cannot be effectively and efficiently quantified in humans. Further research in this area of surrogate markers of migraine attacks and progression is warranted.

Taken together, the information presented thus far suggests that treating migraine early in its course, aggressively and comprehensively in the course of the disease will result in less headache and a decrease in headache related disability. In turn, this may lead to improvement in school attendance and academic progress, social interaction, employment, and ultimately may prevent the transformation of episodic to chronic migraine [32]. Given the findings of this review, there may be merit to the hypothesis that early comprehensive treatment of the child and adolescent migraineur may result in disease modification. In multiple sclerosis, it is important to start early treatment with disease modifying agents in the young adult population to slow progression and diminish disability [30]. This review suggests that the same disease modifying effect may occur with existing migraine therapeutics, provided that they are started early in the young migraineur before chronic central sensitization and other irreversible biochemical effects occur.

If early treatment of the child or adolescent protects against disease progression, what evidence based strategies can be utilized?

If treating the young migraineur comprehensively early in the course of the disease has been shown to result in many levels of improvement and may prevent progression to chronic migraine, it would seem that the following steps should be undertaken to improve long-term outcomes:

- Public awareness programs should be undertaken and aggressively promoted to educate parents, teachers, and non-neurologist physicians such as pediatricians, family physicians, and internists about the existence and the need for urgent treatment of frequent episodic and chronic migraine. Patients and their physicians find these programs effective in decreasing morbidity in other disorders such as hypertension [33]. The myths of the so rarely encountered "sinus, eyestrain, and dental headaches" need to be rectified so that candidates for migraine prevention are not misdiagnosed and thereby prevented from receiving early targeted migraine therapy.
- Appropriate interventions should be made about modifiable risk factors for migraine progression. Some risk factors that seem to be operative are caffeine, analgesic, and other acute care medication overuse, hypothyroidism, sleep disorders, depression, anxiety, oral contraceptives, obesity, and two or more headaches per month [10, 34–37]. We know that the risk of new onset chronic daily headache will increase in a linear manner with baseline headache frequency, especially for those who experience more than one headache per week [38].
- Patients should be considered as possible candidates for preventive treatment, and if so, should be kept on effective medication for a minimum of 6 months and re-evaluated. Given the unpredictability of the efficacy from and the decrease in migraine burden after preventive treatment, and assuming significant reduction in headache disability during treatment with insignificant adverse effects, preventive therapy for as long as a year may be appropriate in some patients [34, 39]. Prevention should be considered if: (1) the patient experiences three or more headache days per month with poor response to acute care medication, (2) the patient has three to four headache attacks per month that are incapacitating with much disability in spite of abortive therapy, (3) the patient has a history and headache diary that reveals a clear trend toward increasing headache frequency or use of acute care medication, (4) the patient has infrequent headache attacks with a profound aura and poor acute response to therapy [34, 39, 40].
- The traditional stratified care approach as well as more current multimechanistic strategy of treating the migraine attack should be first-line treatment in the young headache population and in adults with new onset migraine [41]. Multimechanism use of acute agents has not been studied in adolescents and children. In children under the age 18, it may be appropriate to first try the non-migraine-specific medications but to quickly change to off label use of triptans if that approach fails. Unfortunately, there are no FDA approved triptans for use under the age of 18, when, in fact, this may be the most appropriate age group that should be prescribed triptans for migraine attacks given the effectiveness of early triptan administration. Neurologists should feel confident using triptans based on numerous studies in the literature, which have

demonstrated efficacy and safety in children and adolescents [42–46]. Caution should be exercised as excessive use of triptans can cause medication overuse headache syndrome.

- In light of the known efficacy delay of preventive therapy which can be as long as 2 months while commencing long-term preventive therapy, it is reasonable to consider short- or long-term rational combination therapy in escalating episodic migraine, chronic migraine, refractory migraine, and especially status migrainosus [39]. Guidelines do not currently exist for such combination therapy in migraine [39]. Migraine preventives are predominantly from one of three drug classes: antiepileptic, antidepressant, and antihypertensive agents. However, other classes have data supporting efficacy in migraine prevention, including antihistamines, hormonal agents, dopamine antagonists, nonsteroidal anti-inflammatory agents, DHE, and corticosteroids [12, 39, 47]. Choice of preventives may be based on the presence or absence of comorbidities or risk factors. However, in the absence of prospective longitudinal data, migraine-specific combination therapy is largely anecdotal and based on clinical experience. And though unproven, factors including a strong family history and an earlier age of onset may warrant consideration for migraine-specific combination therapy [39].

Conclusion

Comprehensive acute care and preventive therapy for children, adolescents and the recent onset young adult migraineurs may be appropriate to curtail progression and improve long-term outcome. Rational combination therapy for the chronic migraineur and the patient in status migrainosus may be essential. Aborting and controlling central sensitization, accumulation of white matter lesions, and iron deposition in the PAG, may lead to disease modification based on our current understanding of migraine pathophysiology, epidemiological data, and imaging studies. This is the first time the hypothesis of disease modification focused on treating children and adolescents that first develop migraine as the target population This review has demonstrated several trends in chronic headache: (1) The child and adolescent who is treated early in the disease with targeted, appropriate, therapy, responds more readily to treatment and will have a better prognosis with less disability. (2) Most adults with chronic or refractory migraine began their disease as children or adolescents and many were not treated by a headache expert with appropriate drugs. (3) A window of opportunity seems to exist in the new onset child and adolescent migraineur to significantly suppress the migraine generators to prevent progression possibly through disease modification. The hypothesis that early, prolonged, comprehensive treatment of the new or young migraineur will result in disease modification into adulthood needs to be proven with further appropriate studies. Frequently recurring migraine attacks require targeted abortive and/or preventive therapy putatively to lessen disability and prevent the evolution to chronic or secondary progressive migraine. There should be little debate that early, comprehensive, targeted therapy under existing guidelines will at the very least prevent disability; and in a subset of patients, disease modification may occur.

Conflict of interest None.

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