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Butterbur extract: Prophylactic treatment for childhood migraines

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A B S T R A C T

The incidence of migraine headaches in childhood is increasing. Migraines are often difficult to diagnose in pediatrics and even more difficult to treat and prevent. In order to decrease the impact of the condition on the child and the family, prophylactic treatment is recommended if the child is experiencing disabling migraines. The medications currently prescribed for the prevention of pediatric migraines often have significant side effects and are of questionable therapeutic value. For those patients and parents who are interested in alternative therapies and natural remedies for preventive treatment of pediatric migraines, butterbur extract derived from the butterbur plant, *Petasites hybridus*, has emerged as a promising treatment. This paper discusses the impact of migraines among pediatric patients, the rationale for the preventative treatment of pediatric migraines, the current therapies and the relevance of butterbur extract as a prophylactic treatment for migraines in this patient population.

1. Introduction

Migraine headache is the most common recurrent headache condition occurring in children [1]. Migraines affect the quality of life of children and their families and have a negative impact on school attendance and performance, home and family interaction, and peer socialization [2]. The rate of occurrence of migraines is increasing in young and school age children [3]. It is estimated that migraines occur in approximately 3%–5% of young children; the incidence gradually increases to 17%–18% among adolescents [1,4]. More boys are affected than girls up until puberty when the ratio shifts to 2–3 times more girls affected than boys [1,4]. The average medical cost of migraines is $100 per migraine [5].

The exact cause of migraine is unknown; however, there are three proposed theories. The vascular theory suggests that either vasodilatation and/or vasoconstriction may play a role in the pain associated with migraine [6,7]. The second, the neurological theory, proposes that migraine attacks occur due to hyper-excitability of neurons in different brain areas that are mediated by alterations in the neurotransmission system [6]. A third theory proposes that migraine occurs as a result of inflammatory neuropeptide release from the trigeminal system, representing a culmination of neuro-vascular events [6,7]. Environmental and genetic factors may play a role in migraine [8]. However, the genetic risk factors for migraine have not been fully identified [9].

There are a number of factors that trigger migraine attacks in children. These include stress, climate changes, sensory stimuli, and changes in sleep-wake patterns [8]. Chocolate, cheese, nuts, shell-fish, caffeine, as well as foods with a high monosodium glutamate content, have been identified as triggers in some patients [10]. In addition, hormonal changes occurring in adolescence may play a role in the pathophysiology of pediatric migraine, explaining the higher prevalence rate of migraine in adolescent girls [9].

2. Diagnosis

Migraines are more problematic to diagnose in children than in adults for several reasons. It is difficult to obtain an accurate diary of headaches or headache history in children under the age of 12 [11]. Additionally, young children are often not able to describe the pain experience or identify triggers to migraines [11,12]. The symptoms of migraines in children also differ from those experienced by adults [11,12]. Migraines in children tend to be of shorter duration than those in adults, sometimes lasting an hour or less; they tend to be bilateral in young children versus unilateral in late adolescence and in adults [11,12]; and children tend to have fewer migraine attacks per month than adults [11]. Further compounding the diagnosis of migraine in children is that the child may present with a variety of symptoms that eclipse the complaint of headache, such as disturbed sleep, dizziness, nausea, vomiting, depression, anxiety, and eating disorders [1,4,12,13].

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The International Headache Society's (IHS) criteria for the diagnosis of migraine, the International Classification of Headache Disorders (ICHDII), is not specific to childhood migraines [12]. The ICHDII criteria may be overly restrictive when applied to childhood migraines [12,13]. Thus, many clinicians base the diagnosis of pediatric migraine on more inclusive clinical criteria that takes into account the variety of symptoms with which pediatric migraineurs present [12–14].

3. Treatment

Once the diagnosis of migraine has been made, treatment revolves around the avoidance of triggers, dietary adjustments, regular exercise, stress reduction, improving sleep hygiene, and to treat acute attacks, oral analgesics such as NSAIDS and acetaminophen as well as anti-emetics [1,14,15]. There is a consensus of opinion among many experts in the management of pediatric migraines that attempts should be made to prophylactically treat and prevent migraines in children who are experiencing disabling headaches that interfere with the child's life [4,14–16]. Preventive therapy should be initiated if any of the following conditions exist: the child's migraines occur more frequently than once a week; the symptoms of the migraines are intolerable and/or disabling; the migraines do not respond to acute treatment; or the side effects of acute treatment are intolerable [4,15,16]. In addition to preventing the pain of migraine, the rationale for prophylactically treating migraines in children includes lessening the impact of the condition on the child's school attendance, decreasing the impact on the family, and decreasing the risk of progression of the disease into adulthood [16].

Currently there are no Federal Drug Administration (FDA) approved medications in the United States for the prophylactic treatment of migraine in children [15–17]. Further, there have been very few controlled trials investigating prophylactic treatment of childhood migraine [15,16]. Therefore, the medications for pediatric migraine prevention are prescribed empirically based on the theories of migraine pathophysiology. Medications currently prescribed off-label for the prevention of childhood migraines include the following: the anti-convulsants, topiramate and disodium valproate; the anti-depressants, amitriptyline and nortriptyline; the calcium channel blockers, verapamil and flunarizine; the beta-blocker, propranolol; and the antihistamine, cyproheptadine [14,16,18]. Yet many of these medications demonstrate conflicting evidence as to their effectiveness, lack sufficient evidence to support their use, or are not available in all countries [19].

Despite pharmacological migraine prophylactic treatment options, many patients do not report a reduction in migraine frequency. Only about half of all migraineurs who receive prophylactic treatment will obtain up to a 50% reduction in recurrence [18]. In addition, prophylactic migraine medications carry risk for adverse effects including, but not limited to, weight loss or gain, hypotension, and fatigue [18,20]. These adverse effects may decrease patient compliance. There remains a lack of prophylactic migraine treatment options that are both safe and highly effective, especially in the pediatric population.

Primary healthcare providers often hear requests from patients and parents for alternative therapies or natural remedies. Nutraceuticals, food or plant derivatives that have health benefits, provide alternative migraine prophylaxis and may have fewer side effects than the current pharmacological treatments [19,21]. While some supplements have been used for migraine prophylaxis with varying degrees of success including coEnzyme Q10, riboflavin, magnesium, alpha lipoic acid, and feverfew [13,15,16,21], butterbur has emerged as a nutraceutical with promising results in migraine prophylaxis [15,22,23]. Butterbur extract is derived from the butterbur plant, *Petasites hybridus* [23]. This perennial grows natively in moist areas and along rivers in North America, Europe, Asia, and Africa [24–26]. Butterbur extract use dates back to ancient times [23,25] and has been used as an anti-inflammatory, anti-spasmodic, and analgesic [7,20,24,25]. Butterbur has many other common names including bladderdock, bog rhubarb, butterdock, exwort, flapperdock, langwort, Petasites, and umbrella plant and by the brand names Petadolex, Petaforce, Petadolor H, Tesalin, and Tussilago [25].

Petasins are some of the active components of butterbur [15,20,24]. The calcium channel blocking effects of petasins have been demonstrated clinically [15,20,24]. Thus the calcium channel blocking effects of butterbur may counteract vasoconstriction and play a role in preventing hyper-excitation of the neurons via blockage of calcium specific ion gates in the cerebral arteries [5,6,15,20]. In addition to calcium channel blocking, butterbur has other proposed mechanisms of action in the prevention of migraines; however, the exact pathways are not fully understood at this time. In laboratory studies, butterbur was found to have anti-inflammatory and vasodilatory effects on the cerebral arteries by lipoxygenase and leukotriene inhibition [15,20,22,23,25,27]. Given that migraines are suspected to be the result of vascular, neurological, or inflammatory or hyper-excitable neurovascular reactions, butterbur has the potential to have significant impact on migraine prevention.

Butterbur's effectiveness as an anti-migraine prophylactic has been established in several studies, the majority of which were adult-based. An adult study on Petadolex butterbur by Grossman and Schmidramsl [7] included 60 migraine sufferers who were blinded and randomized to treatment with 100 mg of butterbur divided two times daily or placebo for 12 weeks [7]. Migraine frequency was decreased by up to 60% with the use of butterbur as compared to baseline [7]. Diener et al. [28] re-analyzed Grossman and Schmidramsl's study and found that 45% of the butterbur group reported a decrease in migraine frequency of 50% or more compared to 15% of the placebo group [28]. An adult randomized control trial of 245 patients conducted by Lipton et al. [23] found that migraine attack frequency was decreased by 48% after receiving 75 mg Petadolex two times daily for four months, which was significant. However, the second treatment group who received lower dose Petadolex at 50 mg two times daily did not reach statistical significance, which may indicate that 75 mg two times daily Petadolex is of greater therapeutic value in the adult population [23].

While there are several studies that substantiate the benefits of butterbur in adults, few pediatric studies have been done and even fewer have been of high quality or based on a large sample. In one open-label pediatric study conducted in Germany, 77% of patients reported at least a 50% reduction in migraine frequency with use of Petadolex butterbur [15]. This study included 108 children who were between the ages of 6 and 17 years [15]. According to the IHS, a reduction in migraine frequency rate of 50% or more per month is clinically relevant [15]. The findings of this study demonstrated a 63.2% reduction in migraine attack frequency [15]. A second pediatric study compared the effects of Petadolex butterbur to music therapy and placebo [3]. In this randomized, controlled, and partially blinded study of 58 children ages 8–12 years, the results were mixed [3]. Immediately post-study, only music therapy was superior to placebo in reducing migraine attack frequency [3]. However, 6 months following conclusion of the study, both Petadolex butterbur and music therapy were superior to placebo [3].

Butterbur is available as a prescribed medication in Germany and Switzerland, thereby subject to regulation and standards of preparation [23,24]. However, butterbur is considered a food in the United States and as such is not subject to FDA approval or