Complementary and alternative medicine (CAM) in headache of children and adolescents: open-label Italian study

A. Onofri1, S. Necozione2, E. Tozzi1

1Neuropsychiatric Clinic, Department of Life, Health and Environmental Sciences, University of L’Aquila; 2Epidemiology Unit, Department of Life, Health and Environmental Sciences, University of L’Aquila, Italy

Abstract

Objective. The aim of the present research is to evaluate and to compare various nutraceuticals and food supplements in the headaches prophylaxis.

Background. Recently the use of complementary and alternative medicine, nutraceuticals and food supplements, in prophylaxis and attack therapy of headaches is spreading both in adulthood and in childhood age.

Methods. 99 children, 6-17 years, females 44 and males 55, suffering from primary headaches and admitted to Headache Center in the years 2016-2017 are the sample. 7 patients were excluded because they did not adhere to the study due to lack of therapeutic compliance and because they did not return to clinical controls. The patients referred to the Headache Center are selected consecutively. The open-label study evaluating clinical trial concerns the evaluation of the following parameters: headache diagnosis according to International Headache Society criteria (ICHD-III, 2013 beta version), migraine index; the prophylaxis and attack therapies at time zero and after 12 months. The compounds used to prophylaxis therapy are: Mg citrate, Mg oxide and Mg aspartate (compound n°1), Bisglycinate Mg + L-Tryptophan + Niacin + B2 Vitamin + D Vitamin (compound n°2), Oxide Mg + Partenium + Andrographis paniculata + coenzyme Q10, B2 Vitamin (compound n°3). Each compound was compared with the other to evaluate clinical efficacy. Attack therapy: Paracetamol, Ibuprofen, ketoprofen, Indomethacin. Informed consent was obtained for participation in the study by the parents of the children. Statistical analysis is made by Kruskal-Wallis test and analysis post hoc Conover.

Results. 22 females and 24 males suffer from Migraine without aura, 9 females and 12 males from Migraine with Aura, 11 females and 14 males from Tension Type Frequent Headache. The therapy as with compounds n°1, 2 and 3 is effective in reducing migraine index and reduces the use of attack therapy in all the cases very significantly (p=0.000001). In MwA the compound n° 1 is less effective than compounds n°2 and 3 (p=0.00089). In MA compound n° 3 is less effective than compounds n°2 and 1 (p=0.0044). In FETTH, compound n°3 is less effective compared to compound n°2 (p=0.052).

Conclusion. The use of nutraceuticals and food supplements appears to be effective and also encouraging as it is well accepted by parents and children themselves.

Key words: Headache, children, nutraceuticals, food supplements, migraine disability

Introduction

The primary headaches and migraine represent a significant cause of social disability, are ranked in the top 5 health issues in childhood. It’s known that 1% of school absences are due to headaches in Italy (1).

Up to nearly 60% of children and adolescents will experience a period of headaches lasting at least 3 months, and approximately 8% of youth will experience migraine for a period of at least 3 months at some point in their lifetime (2).

The attack therapy and preventive treatment of headaches in development age represents an important problem because many drugs used in adults are off label in children. In this regard, guidelines on therapeutic approaches to migraine have been introduced in Italy as well as in other European countries and in the United States (3-7).

In the absence of consistent, high-quality efficacy data for the use of pharmacologic preventive migraine interventions target at children and adolescents, another treatment modality that can be explored is the use of non-pharmacologic pill based interventions, namely nutraceuticals. Nutraceuticals are a form of complementary and alternative medicine (CAM) and have been defined as health or medical interventions that are also foods or parts of a food (8). The use of CAM is very common in children and adolescents with headaches, and nutraceuticals are consistently listed among the most commonly used forms of CAM in this population (9-12).

The National Institutes of Health defines complementary and alternative medicine (CAM) as “a group of diverse medical and health care systems, practices, and products that are not generally considered conventional medicine”. In the general population, chronic pain is among the main reasons for CAM use (13-17). A survey of CAM providers in the UK revealed headaches as the second most frequently quoted condition believed to benefit from CAM (18).

In recent years, CAM use has increased considerably also in pediatric populations, especially for chronic conditions such as pain, headache, attention deficit hyperactivity disorder, asthma, colic and emotional distress. The use of CAM is increasing as shown by epidemiological, meta-analysis studies and reviews: 76% of Italian centers use CAM, 60-70% in Norway and 80% in Germany and Austria (2,19,20). The main reasons for seeking CAM were: the wish of avoiding chronic use of drugs with...
their related side effects, the desire of an integrated approach, the reported inefficacy of conventional medicine, and a more suitable children disposition to CAM than to pharmacological compound. Female gender, younger age, migraine without aura, parents’ higher educational status, maternal use of CAM and other associated chronic conditions, correlated with CAM use (p<0.05). 73 % patients chose CAM also to treat other diseases (allergies, colitis, asthma, insomnia, muscle-skeletal disorders and dysmenorrhoea). The most assumed CAM were: herbal remedies (64 %) such as Valeriana, Ginkgo biloba, Boswellia serrata, Vitexagnus-castus, passion flower, Linden tree; vitamins/minerals supplements (40%) with magnesium, 5-Hydroxytryptophan, vitamin B6 or B12, Multivitamin compounds (nutraceuticals). Many young headache patients suffer significant functional disability, with a worse school, physical and psychosocial and emotional quality of life, especially if their headache is associated to other chronic conditions, and they are seeking for alternative options to pharmacological treatment (21-23). A variety of herbs and other supplements (such as Ginkgo biloba, magnesium, Tanacetum parthenium, Petasites hybridus root, Boswellia serrata) have already been largely studied for headache treatment (24-27). The presence of comorbidity is an additional factor in the use of CAM as the side effects

<table>
<thead>
<tr>
<th>CAM</th>
<th>REFERENCES</th>
<th>DESIGN</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETADOLEX (Petasites Hybridus/Butterbur)</td>
<td>Pochmann R, Danesch U, 2005(32)</td>
<td>Open-label trial</td>
<td>77.2% of the sample were responders</td>
</tr>
<tr>
<td>Nutraceutical</td>
<td>Oelkers Ax R et al, 2007(34)</td>
<td>Partly double-blind RCT</td>
<td>Butterbur was not different from placebo, except in the 6 month follow-up (p=0.044)</td>
</tr>
<tr>
<td>RIBOFLAVIN (Vitamin B2) Nutraceutical</td>
<td>Condó M et al, 2009(35)</td>
<td>Retrospective open-label trial</td>
<td>Reduction after treatment for 3 or 4 month switch was not sustained at 6 months of treatment</td>
</tr>
<tr>
<td>Mac Lennon SC et al, 2008(36)</td>
<td>Double-blind RCT</td>
<td>No difference between the groups (44.4% of the riboflavin Vs 66.6% of the placebo group (p=0.125)</td>
<td></td>
</tr>
<tr>
<td>Bruini J et al, 2010(37)</td>
<td>Double-blind crossover RCT</td>
<td>Reduction in the frequency of tension-type headaches compared with placebo (p=0.44)</td>
<td></td>
</tr>
<tr>
<td>Tozzi E, Onofri A, 2018(38)</td>
<td>Open-label trial</td>
<td>Reduction in migraine attack frequency (p&lt;0.0001), severity of pain (p&lt;0.0003) and use of acute treatment (p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>GINKGOLIDE B Nutraceutical</td>
<td>Usai S et al, 2010(39)</td>
<td>Open-label trial</td>
<td>Decreased from 7.4 ±5 to 2.2 ±2.8 (p=0.0015)</td>
</tr>
<tr>
<td>Esposito M, Carotenuto M, 2011(40)</td>
<td>Open-label trial</td>
<td>Decreased from 9.71 ± 4.33 to 4.53 ± 3.96 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Esposito M, 2012(41)</td>
<td>Open-label trial</td>
<td>Greater reduction in the ginkgolide group compared with the other group</td>
<td></td>
</tr>
<tr>
<td>MAGNESIUM Nutraceutical</td>
<td>Castelli S et al, 1993(42)</td>
<td>Open-label trial</td>
<td>Response in 72.5% of patients after 1 month of treatment</td>
</tr>
<tr>
<td>Wang F et al, 2003(43)</td>
<td>Double-blind RCT</td>
<td>Both groups had a down ward trend in number of headache days, with only the magnesium group sustaining the trend past 6 weeks</td>
<td></td>
</tr>
<tr>
<td>Aloisi P, Tozzi E, 1997(44)</td>
<td>Open-label study</td>
<td>A 20 day treatment seemed to normalize the magnesium balance in 90% of patients</td>
<td></td>
</tr>
<tr>
<td>COENZYME Q10 Nutraceutical</td>
<td>Hershey AD et al, 2007(45)</td>
<td>Open-label trial</td>
<td>Significantly reduced after the treatment period</td>
</tr>
<tr>
<td>Slater SK et al, 2011(46)</td>
<td>A double-blind, crossover RCT</td>
<td>Significant reduction in headache frequency after 4 months of treatment in both groups</td>
<td></td>
</tr>
<tr>
<td>POLYUNSATURATED FATTY ACIDS Nutraceutical</td>
<td>Harel Z et al, 2002(47)</td>
<td>Double-blind crossover RCT</td>
<td>Reduction migraine attack frequency for both groups but no significant difference between the groups (mean number of migraine during treatment 4± 1 for both groups)</td>
</tr>
<tr>
<td>MELATONIN Food Supplement</td>
<td>Fallah R et al, 2018(48)</td>
<td>Single-blinded randomized clinical trial</td>
<td>Effective in reduction of onthly frequency, severity, duration and disability of headache</td>
</tr>
<tr>
<td>Fallah R et al, 2015(49)</td>
<td>quasi-experimental study</td>
<td>Reduction monthly frequency, severity and duration of headache.</td>
<td></td>
</tr>
<tr>
<td>5-HYDROXYTRYPTAMINE Food Supplement</td>
<td>Nagata E. et al, 2006(50)</td>
<td>Research study</td>
<td>Plasma tryptophan and 5-HTP levels were not significantly different between the controls and migraine patients</td>
</tr>
<tr>
<td>Santucci M et al, 1986(51)</td>
<td>Double-blind crossover study</td>
<td>Reduction of the migraine index and frequency of migraine attacks during the 3rd month of treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Complementary and alternative medicine (CAM) are lower than in traditional drugs. It is difficult to evaluate the efficacy of nutraceuticals because in Italy but also in the rest of Europe there are no controlled studies regarding the use of pure nutraceuticals, but only those regarding the nutraceuticals associated with other components (28). Therefore, more than talking about nutraceuticals it would be more correct to talk about food supplements.

Materials and methods

This study is conducted at the Department of Neuropsychiatric Clinic afferring to Regional Headache Center of Region Abruzzo, University of L’Aquila (Italy) and the patients, were selected and observed sequentially during the years 2016 and 2017. The sample of study consists of 99 patients, aged 6-17 years, 44 females and 55 males; 7 patients were excluded because they did not adhere to the study due to lack of therapeutic compliance and because they did not made the follow-up.

The open-label study evaluating clinical trial concerns the evaluation of the following parameters: primary headache diagnosis according to ICHD-III.2013 beta version(29), migraine index calculated by following formulæ: \( MI = \frac{\text{n° crisis} \times \text{pain intensity/month 30 days}}{30} \), the type of prophylaxis therapy and the attack therapy at time zero and after 12 months. For better clarity the nutraceuticals and food supplements used in the field of CAM as compounds 1,2,3 have been indicated and precisely the following preparations have been used: Mg citrate, Mg oxide and Mg aspartate(compound n°1) vs Bisglycinate Mg + L-Tryptophan + Niacin + B2 Vit + D Vit (compound n°2) and vs Oxide Mg + Partenium + Andrographis paniculata + coenzyme Q10, B2 Vit (compound n°3). The pharmacological attack therapy is: Paracetamol, Ibuprofen, Ketoprofen, Indomethacin. Of course, informed consent was obtained for participation in the study by the parents of the children. Statistical analysis is made by Kruskal –Wallis test and analysis post hoc Conover and a probability value<0.05 was considered significant.

Results

22 females and 24 males are suffering from Migraine without aura (MwoA), 9 females and 12 males from Migraine with Aura (MA), 11 females and 14 males from Frequent Episodic Tension Type Headache (FETTH). All the sample divided by diagnosis and sex is shown in Fig 1.

Therapy is effective in reducing migraine disability, in fact the migraine index decreases in all the sample (\( M and SD = -0.153 \pm 0.710 \), but not significantly. The number of subjects using attack therapy is greatly reduced but the difference is not significant. Regarding prophylactic therapy, the compound n°1 and the compounds n°2 and 3 are efficacious in reducing MI and the use of attack therapy in all the sample. The comparison is very significant (\( p=0.000001 \)), as shown in the Fig 2.

If the comparison is made on the basis of headache diagnosis, in MwoA (\( p=0.00089 \) (Fig 3), the compound n°1 is less effective than compounds n°2 and 3. In MA (\( p=0.0044 \))
A. Onofri et al.

(Fig 4) compound n° 3 is less effective than compounds n° 2 and 1. This difference is less evident in MA than MwoA. In FETTH, compound n° 3 is less effective only compared to compound n° 1 e 2 (p=0.052) (Fig 5).

Discussion

Despite the availability of several drugs for the treatment of primary headaches in adulthood, in the childhood and adolescence there has been a growing demand for “natural” and alternative therapies whose use was the subject of recent studies and literature review. There is confusion in terms of nutraceutical and food supplement and often their terms are misunderstood.(30) Our study therefore does not want to evaluate the efficacy of a single type of compound, but to compare the use of 2 compounds vs the most known nutraceutical, the most used in all ages: Magnesium. All the compounds were been effective and in particular the compound 3 (Oxide Mg + Partenium + Andrographis paniculata + coenzyme Q10, B2 Vitamin) exhibits a specificity of action, being useful in migraines and not in tension headaches. There were no significant side effects wich they led to treatment interruption. The tolerability was excellent for all compounds. The combined products are better results than the products with only Magnesium. The placebo effect can be neglected as the study was open study and therefore the placebo effect common for all the compounds used. From the comparison with the literature data it can be stated that food supplements and nutraceuticals have a specificity of action, that the choice of a product must be conditioned by diagnosed headache and that the doctor’s prescription is also important in the use of this form of therapy. Infact’s known that CAM, often integrated with conventional care, was auto-prescribed in 30% of the cases, suggested by non-physician in 22%, by the General Practitioner in 24% and by paediatrician in 24 %. Both general practitioners and neurologists were mostly unaware of the use of CAM by their patients with headaches or other neurological pain. (9,31,32,52,53) In conclusion, neurologists should inquire for CAM use and be prepared to learn about CAM therapies or to directly interact with CAM trained experts, in order to coordinate an integrative approach to health, as especially required in paediatric headache patients and their parents. (9) It is known to neurologists and psychologists dealing with the treatment of headaches, that good management in pediatric age must include, in addition to pharmacological treatment or alternative therapy, recommendations on lifestyle, diet, sleep habits and management strategies of the stress.(4) Further studies are required to investigate safety and efficacy of CAM in pediatric headache, as a possible side-medicine to conventional pharmacological approach. It’s also desirable to insert the CAM correctly in the guidelines of primary headaches of the developmental age.

References


26. Taylor FR. When West meets East: is it time for headache medicine to complement “convention” with alternative practices? Headache 2011; 51(7):1051–1054


