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Acupuncture and the Opioid System: Implications in Management of Migraine

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We investigated the effectiveness of acupuncture in childhood migraine in 22 children with migraine, randomly divided into two groups: a true acupuncture group (12 children) and a placebo acupuncture group (10 children). Ten healthy children served as a control group. Opioid activity in blood plasma was assayed by two methods: (1) determination of total (panopioid) activity with an opiate radioreceptor assay, and (2) determination of β-endorphinlike immunoreactivity by radioimmunoassay. The true acupuncture treatment led to significant clinical reduction in both migraine frequency and intensity. At the beginning of the study, significantly greater panopioid activity was evident in plasma of the control group than in plasma of the migraine group. The true acupuncture group showed a gradual increase in the panopioid activity in plasma, which correlated with the clinical improvement. After the tenth treatment, the values of opioid activity of the true acupuncture group were similar to those of the control group, whereas the plasma of the placebo acupuncture group exhibited insignificant changes in plasma panopioid activity. In addition, a significant increase in β-endorphin levels was observed in the migraine patients who were treated in the true acupuncture group as compared with the values before treatment or with the values of the placebo acupuncture group. The results suggest that acupuncture may be an effective treatment in children with migraine headaches and that it leads to an increase in activity of the opioidergic system.

Pintov S, Lahat E, Alstein M, Vogel Z, Barg J. Acupuncture and the opioid system: Implications in management of migraine. Pediatr Neurol 1997;17:129-133.

Introduction

Migraine is the most common cause of headaches in both children and adults. It affects 2.7% of children by age 7 and 10.6% by age 14 [1,2]. In a group of 9,000 Swedish children, Bille [1] observed that the prevalence of migraine headaches increased during childhood from 1% at age 6 years to 5% at age 11 years. Of the migrainous children, 42% were subject to one or more episodes each month that were sufficiently severe to prevent the child from carrying on with his or her usual daily activities. Another study of Danish children reported an even higher prevalence [3]. The diagnosis of migraine headaches in children is based on clinical manifestations, as suggested by Prensky and Sommer in 1979 [4] or according to specific diagnostic criteria and characteristics as recommended by the International Headache Society (IHS) in 1988 [5]. Episodes of migraine are often precipitated by trigger factors, which include anxiety, fatigue, mild head trauma, stress, exercise, excitement, illness, and certain medications [6]. The therapeutic approaches to patients with migraine must be individualized based on the patient's age, frequency and severity of episodes, reliability of the patient, as well as the family's attitude toward pharmacologic and nonpharmacologic methods of treatment. Nonpharmacologic treatments of migraine headaches include elimination of trigger factors and modification of stress through relaxation therapy and biofeedback [7].

Electroacupuncture has been reported to be of benefit in migraine treatment. In this technique, an acupuncture needle is attached to a low-voltage electricity source [8]. Central pain mechanisms are probably related to a dysfunction in the endogenous opioid antinociceptive system.

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Received December 9, 1996; accepted January 8, 1997.

PII S0887-8994(97)00086-6 • 0887-8994/97/$17.00

This theory was supported by several studies demonstrating a decreased level of activity in patients with variable pain syndromes [9,10]. We wished to determine the effect of conventional acupuncture treatment on migraine headaches in children and any changes in the plasma panopioid activity and levels of β-endorphin, one of its byproducts related to the central pain mechanisms.

Subjects and Methods

The 22 children (7 to 15 years of age) included in the study were observed, for at least 6 months from first assessment until study entry, in the Pediatric Neurology Clinic of Assaf Harofeh Medical Center. All children were diagnosed with migraine headaches, according to Prensky criteria, including recurrent headaches (at least three attacks in a period of 3 months) and symptom-free intervals and three of the following manifestations: (1) abdominal pain, nausea, or vomiting with headaches; (2) hemicrania; (3) throbbing pulsatile pain; (4) complete relief after a brief period of rest; (5) an aura, either visual, sensory, or motor; (6) a history of migraine headaches in 1 or more members of the immediate family, as suggested by Prensky and Sommer [4]. The children underwent a complete physical and neurologic examination, laboratory tests, including blood cell count (hemogram), glucose, and kidney and liver function. Children with chronic illness or allergies or those receiving daily medication were excluded from the study. None of the children included in the study received either specific antimigraine treatment or opiate-containing preparations. The option of participating in the study was offered to all children with migraine in this age group followed in our pediatric neurology clinic. The study was designed to include 10 to 12 children in each group. The children were alternatingly randomized to the true acupuncture (TA) and placebo acupuncture (PA) group. The TA group included 12 children (7 girls, 5 boys) with a mean age of 9.8 ± 1.2 years. Family history of migraine was positive in 5 children. The PA group included 10 children (6 girls and 4 boys) with mean age of 10.4 ± 1.6 years. Family history of migraine was positive in 5 children. Parents and children received a detailed explanation about the study's design and provided their written and informed consent.

The children included in the study were randomly divided into two groups: TA (12 patients) and PA (10 patients). The TA group was treated according to the principles of traditional Chinese medicine with the acupuncture needle inserted subdermally; in the PA group, a needle of the same size was inserted in stratum corneum (Fig 1A and B). Each child attended 10 weekly sessions of acupuncture treatment (either TA or PA). None of the children included in the study received chronic prophylactic treatment for migraine. The treatment included insertion of three acupuncture needles in the upper and lower extremities for 15 min.

Neither children nor parents knew which study group they belonged to. Three blood samples for panopioid activity were taken: the first before treatment, the second after the fifth treatment, and the third after the tenth treatment. As a control, we used blood samples from 10 children (6 girls and 4 boys, mean age 9.4 ± 1.5 years) with no migraine headaches who were followed in the outpatient clinic after an episode of urinary tract infection. All children were asymptomatic at the time of blood sampling. All blood samples were obtained after the time of the acupuncture sessions, between 8:00 and 9:00 AM, to prevent possible diurnal variation differences.

After entering the study, patients of the two experimental groups (TA and PA) completed the same weekly frequency-intensity questionnaire for the 10-week prestudy period, for the 10-week study period, and for the next 10 weeks. This migraine diary included details about the number of migraine headaches and their duration, intensity, and treatment. Patients, with the assistance of their parents, were requested to determine pain intensity on a visual analogue scale (scale of 0° to 10°) and to assess the frequency of migraine headaches. The questionnaires were given to the patients by the clinic nurses who were blinded as to whether the patients was in the TA or PA group.

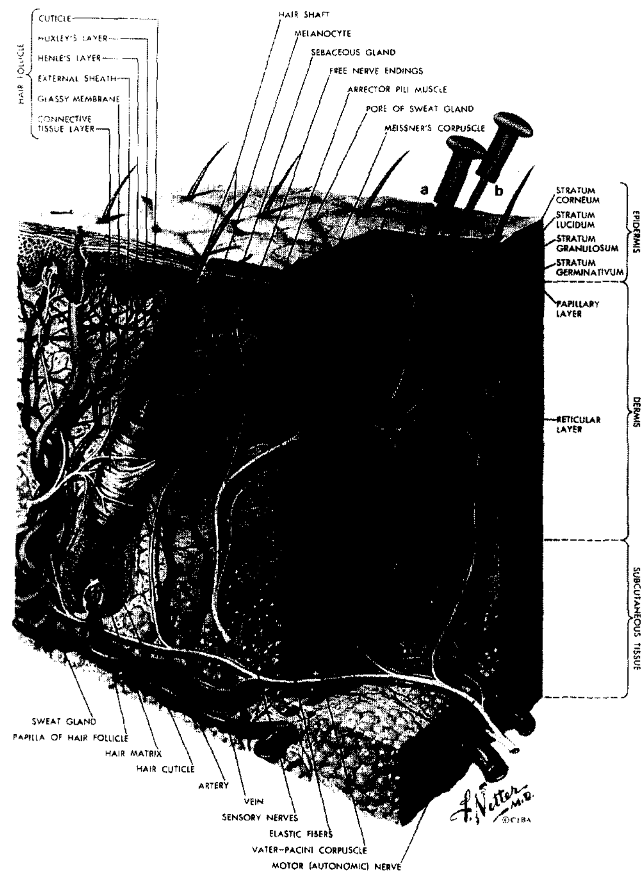

Figure 1. Needle insertion into the skin of patients during placebo acupuncture (PA) and true acupuncture (TA) treatments. (A) TA: Needle is inserted in the dermis. (B) PA: Needle is inserted in stratum corneum.

Plasma Preparation. A mixture of protease inhibitors consisting of bestatin, captopril, and phosphoramidon (Sigma, St. Louis, MO) at a final concentration of 1 μM each was immediately added to the collected blood samples to avoid enzymatic degradation of opioid peptides. Blood samples were fractionated, and the plasma was separated from the blood cells by 10-min centrifugation at 3000 *g*.

Quantitative Determination of β-Endorphin Levels in Plasma. β-Endorphin levels in plasma were determined by solid-phase two-site immunoradiometric assay kit (Allegro β-endorphin kit, Wijchen, Holland), which contains samples of standard β-endorphin, ^{125}I-labeled antibodies to β-endorphin, and antibodies to β-endorphin immobilized on plastic beads. Plasma samples were incubated with a mixture of both antibodies for 24 hr; the beads were then washed to remove all unbound materials. Radioactivity of the complex immobilized on the plastic beads (solid-phase antibodies/β-endorphin/labeled antibody) was monitored with a γ-counter, and the amount of the peptide in the plasma samples was determined from a standard curve using 0 to 50 pg human β-endorphin.

Membrane Preparation. Adult male Wistar rat brains (age 60 days) were homogenized at 4°C in 10 vol 50 mM Tris-HCl buffer (pH 7.4) with a Polytron homogenizer. The homogenate was centrifuged at 1000 *g* for 10 min, and the pellet was discarded. The supernatant was centrifuged at 20,000 *g* for 20 min, and the pellet was resuspended in Tris buffer with a Dounce homogenizer to yield a final concentration of 0.6 to 0.8 mg protein/mL. Protein concentration was determined by Bradford's method [11].

Opioid Binding Assay. Binding of diprenorphine to opioid receptors in brain membranes was performed with 1 nM [^{3}H]diprenorphine (32 Ci/mmol; MNEN, Du Pont, Boston, MA) in the presence or absence of three dilutions of plasma samples. Membranes (0.3 to 0.4 mg/tube) were incubated at 25°C for 40 min in Tris buffer, and the mixtures were

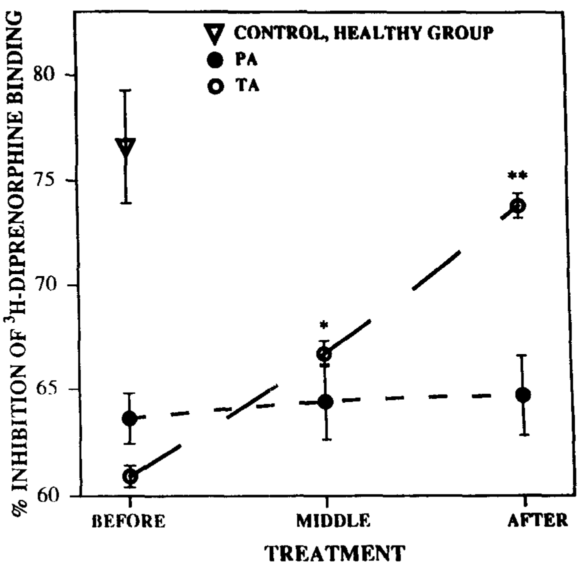

Figure 2. Effect of acupuncture treatment on panopioid activity. Data are mean ± SEM of panopioid activity. Midtreatment (P <.05) and posttreatment (P <.01) activity were significantly different from pretreatment and placebo group panopioid activity.

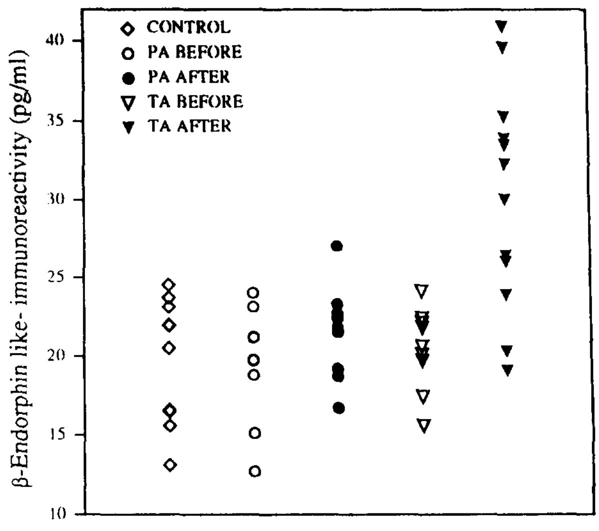

Figure 3. β-Endorphin-like immunoreactivity in plasma from control, placebo acupuncture, and true acupuncture groups before and after acupuncture treatment.

filtered through Whatman GF/B filters presoaked in Tris buffer for 1 hr. Nonspecific binding was determined in the presence of 5 μM etorphine. Because binding of diprenorphine is affected by the plasma concentration itself, it was important to correct the values obtained according to a standard curve of plasma devoid of opioid peptides (to which no protease inhibitors were added). The panopioid activity was calculated as % of inhibition = 100 × (inhibition of binding by plasma) ÷ (inhibition at the same dilution by plasma without protease inhibitors).

Statistical Analysis. Data were analyzed by Student's *t* test. The IC_{50} value of [^{3}H]diprenorphine binding was determined by the Inplot4 computer program (Graph Pad Software, San Diego, CA). The binding curve was generated with the Sigma Plot 4.11 computer program (Jandel Scientific, Corta Madera, CA) using an equation from the ALLFIT program [12].

Results

Results of physical, neurologic, and blood examinations of all children were in the normal range. All children included in the study group completed the 10-week acupuncture treatment (either TA or PA) and the subsequent follow-up period of 10 weeks.

There were no significant differences in migraine headache intensity or frequency between the TA and PA groups before initiation of the acupuncture treatment. TA treatment led to a statistically significant clinical reduction in both frequency and intensity of migraine headaches. The migraine frequency (9.3 ± 1.6 per month) and intensity (8.7 ± 0.4) (mean ± S.D.) were decreased significantly after the treatment to 1.4 ± 0.6 and 3.3 ± 1.0, respectively. By contrast, no significant changes were apparent in the frequency (9.4 ± 1.5) and intensity (7.8 ± 0.6) of the PA group before treatment or after treatment (9.3 ± 1.4 and 6.2 ± 0.4).

Panopioid activity of plasma from both TA and PA groups (expressed as % of inhibition of [^{3}H]diprenorphine binding) was determined before and after treatment and compared with the values in the control group. The panopioid activity of the TA and PA groups before treatment was significantly less than that of the control group. After the treatment, no significant change in the panopioid activity of the plasma from the PA group was evident as compared with the values before treatment. By contrast, a significant potentiation of panopioid activity in the TA group was evident. The plasma obtained from the TA group was more potent in inhibition of [^{3}H]diprenorphine binding (Fig 2) by 13% as compared with the values before treatment. This finding is in agreement with the clinical improvement observed in the TA group. There were no linear correlations between the decrease in the frequency of headaches and associated changes in panopioid activity.

The panopioid activity reflects all plasma components that compete with the binding of [^{3}H]diprenorphine to the receptor. The β-endorphinlike immunoreactivity in the TA group (Fig 3) was significantly ($P < .001$ by Student's *t* test) increased by 50% as compared with both control and PA groups (30.1 ± 2.0, 19.8 ± 1.3, and 21.5 ± 0.7 pg/mL, respectively).

Discussion

Migraine headaches are common in children and adolescents [1,5]. The diagnosis of migraine is a clinical one, based on the history obtained from the child and the family. We preferred to use the criteria of Prensky and Sommer [4] for the diagnosis of migraine rather than the IHS criteria because we found them more clinically applicable in children in terms of the ability of the child or guardian to describe the exact duration, frequency, and clinical features of the migraine episode.

Frequent and severe headaches that cannot be adequately controlled by using analgesic agents or specific migraine medications have become a difficult management problem and prevent normal activities. Therefore, a variety of nonpharmacologic treatment methods have been suggested in an attempt to prevent or at least to decrease the frequency and severity of migraine episodes. These modalities focus on the elimination of trigger factors, regular diet, normal sleep patterns, discontinuation of inappropriate and overused analgesics, relief of stress, and use of counseling, relaxation therapy, and biofeedback [6,13-16].

Acupuncture treatment has been shown to be of clinical value as an analgesic therapy [17]. Although the exact mechanism of this treatment remains unclear, it is apparent that reproducible neurologic and chemical changes occur in response to acupuncture and that these changes almost certainly modify the response to, and the perception of, pain.

The biochemistry of migraine is complex. Many contradictory or never-replicated findings in often small patient groups have been published. The following observations in the platelet-free plasma and urine appear to have some solid relationship to the pathophysiology of migraine [19]:

- Systemic derangement of 5-hydroxytryptophan metabolism relevant to the peripheral vascular component of migraine pathophysiology
- Changes in neuroexcitatory amino acids and magnesium
- Alterations in methionine-enkephalin levels
- Hormonal fluctuations which appear to be important in establishing the threshold for a migrainous episode
- Changes in vasoactive peptides in the craniovascular circulation
- Catecholaminergic changes suggesting sympathetic overactivity

Because pain mechanisms may be related to a dysfunction in the endogenous opioid antinociceptive system, investigators have examined the changes in panopioid activity and β-endorphin levels in blood and cerebrospinal fluid (CSF) of patients with migraine. Two studies [9,10] demonstrated decreased level of β-endorphins in plasma of adults during the episodes, but not in migraine-free periods. Two other studies [20,21] demonstrated a decrease in β-endorphin in CSF of adult patients. However, one study [22] failed to demonstrate significant differences in plasma β-endorphins during migraine episodes in adults. Of interest is a study [23] in which the daily variations in β-endorphins, ACTH, and corticosteroids in plasma of prepubertal untreated children with migraine demonstrated higher levels of β-endorphins in the migraine group as compared with the control group.

In other studies, β-endorphins were used as a marker for assessing the influence of nonpharmacologic treatment methods in patients with migraine. An increase in the level of β-endorphins in plasma, as compared with pretreatment levels and those of a control group, was observed in patients with migraine who were treated with electroacupuncture [17] and behavior therapy [24]. Therefore, we preferred to correlate the clinical efficacy of acupuncture treatment (change in frequency and severity of episodes) performed in a blind fashion from the patient point of view with biochemical changes, i.e., alterations in β-endorphin level and panopioid activity after treatment sessions.

Several previous reports have suggested a role of the opioidergic system in the pathogenesis of migraine headaches. However, the results are slightly conflicting; e.g., Baldi et al. [9] measured the level of β-endorphin in plasma of adult migraine patients in migraine-free periods and during the episodes. Decreased levels of β-endorphin were evident in plasma samples during the episodes, but not in the migraine-free periods. Another study demonstrated a decrease in β-endorphin in CSF of patients with migraine [20]. Leone et al. [10] reported that levels of β-endorphin in peripheral blood mononuclear cells of adult patients with migraine were significantly reduced as compared with those in cells of adult patients with tension-type headaches.

We conclude that acupuncture may be an efficient alternative treatment for children with migraine headaches. This nonpharmacologic treatment is safe and cost-effective, with no side effects, and can be repeated according to clinical need. It is limited to children who are sufficiently mature to cooperate during the treatment sessions. Larger series and more experience is required to assess the efficacy of this promising treatment.

This work was supported in part by the National Institute of Drug Abuse, NIH, Bethesda, MD, the US-Israel Binational Science Foundation, and the Israel Cancer Research Fund. Z.V. is the incumbent of the Ruth and Leonard Simon Professional Chair in Cancer Research.

References

[1] **Bille** B. Migraine in school children. Acta Pediatr Scand 1962; 51[Suppl]:11-5.

[2] **Sillanpaa** M. Changes in the prevalence of migraine and other headaches during the first seven school years. Headache 1983;23:15-9.

[3] **Dalsgaard-Nielsen** T, Engberg-Pederson H, Holm HE. Clinical and statistical investigations of the epidemiology of migraine. Dan Med Bull 1970;17:138-48.

[4] **Prensky** AL, Sommer O. Diagnosis and treatment of migraine in children. Neurology 1979;29:506-10.

[5] **Headache** Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalgia 1988;8(suppl 7):1-96.

[6] **Rothner** AD. The migraine syndrome in children and adolescents. Pediatr Neurol 1986;2:121-5.

[7] **Rothner** AD. Migraine headaches. In: Swaiman KS, ed. Pediatric Neurology: Principles and Practice. St. Louis: C.V. Mosby, 1989: 185-91.

[8] **Veshina** VA, Dubovskaia LA. Treatment of migraine with electropuncture. Zh Neuropathol Psikiatr 1983;83:1499-503.

[9] **Baldi** E, Salmon S, Anselmi B, Soillantini MG, Capelli G, Brosch A, Sicuter F. Intermittent hypoendorphinemia in migraine attack. Cephalgia 1982;2:77-81.

[10] **Leone** M, Sacerdote P, D'Amico D, Panerai AE, Bussone G. β-Endorphin concentration in the peripheral blood mononuclear cells of migraine and tension-type headache pains. Cephalgia 1992;12:154-7.

[11] **Bradford** MM. A rapid and sensitive method for the quantita-

tion of microgram quantities of protein utilizing the principle of protein-dye binding. Ann Biochem 1976;72:248-54.

[12] **DeLean** A, Munson PF, Rodbard D. Simultaneous analysis of families of sigmoidal curves: Application to bioassay, radioligand assay, and physiological dose-response curves. In: A User's Guide to ALLFIT. Bethesda, MD, National Institutes of Health, 1988:97-102.

[13] **Fentress** DW, Masek BJ, Mekegan JE, Benson H. Biofeedback and relaxation response training in the treatment of pediatric migraine. Dev Med Child Neurol 1986;28:139-46.

[14] **McGrath** PJ, Humphreys P, Goodman JT, Izeene D, Firestone P, Jacob P, Cunnigham SJ. Relaxation prophylaxis for childhood migraine: A randomized placebo-controlled trial. Dev Med Child Neurol 1988;30:626-31.

[15] **Labbe** E, Williamson DA. Temperature biofeedback in the treatment of children with migraine headaches. J Pediatr Psychol 1983; 8:317-26.

[16] **Andrasik** F, Burke EF, Attanasio V, Rosenblum EL. Child, parent and physician reports of a child's headache pain: Relationship prior and following treatment. Headache 1985;25:421-5.

[17] **Han** J-S. Acupuncture and stimulation produced analgesia. In: Herz A, ed. Opioids II. Berlin: Springer-Verlag, 1993:105-25.

[18] **Lewith** GT, Kendon JN. Physiological and psychological explanations for the mechanism of acupuncture as a treatment for chronic pain. Soc Sci Med 1984;19:1367-78.

[19] **Ferrani** MD. Biochemistry of migraine. Pathol Biol Paris 1992;40:287-92.

[20] **Vesci** L, Widerlov E, Ekman R, Kovacs K, Jelenscik I, Bozsik G, Kapocs G. Suboccipital cerebrospinal fluid and plasma concentration of somatostatin neuropeptide Y and β-endorphin in patients with common migraine. Neuropeptides 1992;22:111-6.

[21] **Genazzani** AR, Nappi G, Facchinetti F, Micieli G, Petraglia F, Bono G, Monittola C, Savoldi F. Progressive impairment of CSF β-EP levels in migraine sufferers. Pain 1984;18:127-33.

[22] **Bach** FW, Jensen K, Blegvad N. β-endorphin and ACTH in plasma during attacks of common and classic migraine. Cephalgia 1985;5:177-82.

[23] **Facchinetti** F, D'Attoma G, Petraglia F, Pin LA, Sternier E, Genazzani AR. Circadian variations of propiocortin-related peptides in children with migraine. Cephalgia 1983;1(suppl):94-7.

[24] **Helm-Hylkema** H, Orlebeke JF, Enting LA, Thijssen JA, Van-Ree J. Effects of behavior therapy on migraine and plasma endorphin in young migraine patients. Psychoneuroendocrinology 1990;15:39-45.