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ORIGINAL CONTRIBUTION

Treatment of ADHD with French maritime pine bark extract, Pycnogenol®

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Abstract Attention Deficit/Hyperactivity Disorder (ADHD) is the most common psychiatric disorder in children. Pycnogenol®, an extract from the bark of the French maritime pine, consisting of phenolic acids, catechin, taxifolin and procyanidins, has shown improvement of ADHD in case reports and in an open study. *Aim of the present study* was to evaluate the effect of Pycnogenol® on ADHD symptoms. Sixty-one children were supplemented with 1 mg/kg/day Pycnogenol® or placebo over a period of 4 weeks in a randomised, placebo-controlled, doubleblind study. Patients were examined at start of trial, 1 month after treatment and 1 month after end of treatment period by standard questionnaires: CAP (Child Attention Problems) teacher rating scale, Conner's Teacher Rating Scale (CTRS), the Conner's Parent Rating Scale (CPRS) and a modified Wechsler Intelligence Scale for children. *Results* show that 1-month Pycnogenol® administration caused a significant reduction of hyperactivity, improves attention and visual–motoric coordination and concentration of children with ADHD. In the placebo group no positive effects were found. One month after termination of Pycnogenol® administration a relapse of symptoms was noted. Our results point to an option to use Pycnogenol as a natural supplement to relieve ADHD symptoms of children.

Key words inattention – hyperactivity – ADHD – Pycnogenol®

Abbreviations: BMI: body mass index; CAP: Child Attention Problems; CPRS: The Conner's Parent Rating Scale; CTRS: The Conner's Teacher rating Scale; ICD-10: International Statistical Classification of Diseases and Related Health Problems; PDW: Prague Wechsler Intelligence Scale for children; WISC: Wechsler Intelligence Scale for children

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder among school-age children [8]. Children with ADHD display as early onset of symptoms a developmentally inappropriate overactivity, inattention, academic underachievement and impulsive behaviour [2, 16]. According to a variety of epidemiological data the incidence of ADHD in children and adolescents ranges from 3 to 5 percent. Boys are 2.5 to 9.0 times more likely to be diagnosed with ADHD compared to girls [1]. According to International Statistical Classification of Diseases (ICD-10), ADHD is called Hyperkinetic Dis-

order. In this categorization nosological unit hyperkinetic conduct disorder is also included.

In the pathophysiology of ADHD the dopaminergic and noradrenergic systems are believed to play an important role.

The primary psychopharmacotherapy for ADHD is the prescription of stimulant medication, such as methylphenidate or amphetamine. These drugs modify uptake of catecholamines (dopamine, norepinephrine) and thus enhance the activity of these neurotransmitter systems, reducing symptomatology in ADHD [13]. Recently, the nonstimulant highly selective norepinephrine re-uptake inhibitor atomoxetin has become available for the treatment of ADHD, which effectively reduces symptomatology [3, 18].

Several reports suggest a beneficial effect of Pycnogenol® (Horphag Research Ltd, UK), on patients suffering from ADHD. Pycnogenol® is a special standardized extract from the bark of the French maritime pine (*Pinus pinaster*), corresponding to the monograph "Maritime Pine Extract of the US Pharmacopoeia" [23]. This extract represents a concentrate of polyphenols, composed of diverse phenolic acids, catechin, taxifolin and procyanidins with diverse biological and clinical effects [23].

Phenolic acids and taxifolin are rapidly absorbed and excreted as glucuromides or sulphates, the procyanidins, biopolymers formed from catechin or epicatechin in subunits, are transformed inside the intestinal tract to active metabolites (valerolactones) [9].

First case reports about positive effects following supplementation of ADHD children with Pycnogenol® were collected by Passwater [21]. Heimann [11] reported that Pycnogenol® added to treatment with dextroamphetamine clearly improved symptoms of ADHD of a 10-years-old boy. Withdrawal of Pycnogenol® while continuing dextroamphetamine treatment caused a relapse, reinstated Pycnogenol® caused again significant improvement. Positive experience with Pycnogenol® was also reported by Hanley in her book "Attention Deficit Disorder" [10]. Masao published in Japan a success rate of 70% when treating 40 children with 1 mg/kg Pycnogenol® [17]. An attempt to demonstrate reduction of ADHD symptoms in adults failed in a double-blind, placebo-controlled, comparative study with 24 adults [27]. No significant differences were found between placebo, methylphenidate and Pycnogenol®. As the study could not show a difference between the active drug, methylphenidate, and placebo, the relevance of these results is questionable.

In our pilot study we found a significant improvement of ADHD symptoms after Pycnogenol® administration—1 mg/kg/day [28]. Based on these results, our aim was to determine the effect of Pycnogenol® on ADHD symptoms in children in a double–blind, placebo-controlled study.

Materials and methods

Patients

- Sixty one out-patients with ADHD, 50 boys and 11 girls, treated at the Dept. of Child Psychiatry of the Child University Hospital, average age 9.5 (6–14 years) were enrolled in a randomized, double-blind and placebo controlled study. Patients were randomized to receive either Pycnogenol® or placebo.
- Selection into the groups (Pycnogenol® or placebo) was carefully randomized. Teachers, parents and physicians were not aware of results of randomization. Randomization was done by the principal investigator responsible for the biochemical, but, not for clinical part. The ratio for Pycnogenol® group to placebo group was 2.5:1. The sample size was estimated assuming the power of 80% (beta of 20%), the type one error (alpha) of 5% and the number of controls per subject of 0.4. The recommended number of patients was pre-calculated as 41 for drug investigation and 16 subjects for placebo. We included in the study 44 and 17 patients, respectively. StatDirect® 2.3.7 was used for the randomization an unpaired random allocation to intervention or control group and for the sample size estimation.
- Children were included into study after evaluation of diagnostic criteria of ADHD according to ICD-10 with following diagnoses: Hyperkinetic Disorder (n=44), Hyperkinetic Conduct Disorder (n=11), Attention Deficit without Hyperactivity (n=6). Eighteen patients showed specific learning disabilities additionally to these symptoms. Patients characteristics are given in Table 1.

Inclusion criteria

Early onset of ADHD—by 6 to 7 years, chronicity—at least 6 months of symptoms, general disposition as restless, inattentive, distractible and disorganized.

Disorders of cognitive function: inattention, distractibility, difficulty to persist with any task, difficulty in selective process to information, disturbance of the executive functions (production, sequention and realization of plans), disturbance of motivation, effort and fortitude, visuospacial and memory disturbance.

Disorders in control of activity: child's inability to suppress activity, abnormality in control of activity,

Table 1 Basic parameters of ADHD patients (M, male; F, female; BMI, Body mass index: body mass (kg)/height^2 (m^2)

Parameters	Pycnogenol group	Placebo group
Included patients	44	17
Patients finishing the study	41	16
Patients who did not finished the study	3	1
Age (average)	9.5 (6–14)	8,8 (6–12)
Body mass (average) (kg)	35.28±10.13	34.80±10.05
BMI	17.41±3.13	16.77±2.61
M/F number, (M/F ratio)	37/7 (5,3:1)	13/4 (3,3:1)
Dividing of patients according medication		
Patients medicated before trial, number	13 (noothropics, neuroleptics)	6 (noothropics, neuroleptics)
Patients first time investigated for ADHD	25	8
Patients non-medicated, but under psychiatric observation	6	3
Dividing of patients according diagnosis		
Hyperkinetic disorder	34	10
Hyperkinetic conduct disorder	5	6
Attention deficit without hyperactivity	5	1
Comorbid diagnosis		
Specific learning disabilities	13	5

disorganisation and discontinuation of motoric activity.

Impulsiveness: acting without due reflection, engaging in rash and sometimes dangerous behaviours, disturbances of emotions and affectivity.

Exclusion criteria

Situational hyperactivity, pervasive developmental disorders, schizophrenia, other psychotic disorders as mood, anxiety, personality disorder as unsocial behaviour, personality change due to a general medical condition, mental retardation, understimulating environments, conduct disorder, tics, chorea and other dyskinesias. Patients with acute inflammatory diseases, renal and cardiovascular disorders and diabetics were excluded from this study, too. Only somatically healthy children were included in our study.

The study was approved by the Ethical Committee of the Children University Hospital. Parents gave a written consent for participation of their children in the study.

Medication

At breakfast children received 1 mg/kg body weight/day Pycnogenol® during 1 month or placebo with identical shape and appearance and the same number of tablets/day as in the case of Pycnogenol®. Placebo contained lactose (58 mg) and cellulose (65 mg) in tablet. Both tablets, Pycnogenol® and placebo were produced by the same manufacturer, Drug Research Institute, Modra, Slovakia.

During 1-month period Pycnogenol®, or placebo tablets (equal number of pills as for Pycnogenol®) were administered to patients. Patients were not supplemented with any other drugs including psychotropic drugs or with vitamins E and C during the study.

Methods

Patients were investigated at the beginning of the trial before study drug administration (start 0), after 1 month of treatment (investigation period 1) and 1 month after termination of treatment (wash-out period) (investigation period 2).

In each stage of the study patients were investigated as follows:

1. Basic psychiatric examination.
2. Children were evaluated by teachers and by parents using following scales:
   CAP (Child Attention Problems) teacher rating scale [5]
   Conner's Teacher rating Scale (CTRS) [4, 20]
   Conner's Parent Rating Scale (CPRS) [4, 20]
3. Psychological investigation according to pedopsychiatric standard scheme of psychopathologic phenomenon received from psychiatric interview with Prague Wechsler Intelligence Scale for children (PDW), a modified Wechsler Intelligence Scale for children (WISC) standardized to our population [14].

We applied five subtests of Performance Scale. A Weight score was used for each subject. Weight score is the sum of values of five subtests of the Performance Scale, standardized for adequate age. Higher score represents a better psychological state.

Determination of biochemical parameters

Blood samples for biochemical analyses were taken from venous blood at start, after treatment and after wash-out period into commercial tubes with citrate for determination of individual biochemical parameters.

Basic biochemical parameters (bilirubin, glucose, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotrasferase, alanine aminotransferase, uric acid and lipide profile) were analysed in plasma by standard biochemical procedures using the Hitachi 911 automatic analyser (Roche, Switzerland).

Statistical evaluation

The copies of all data obtained from questionnaires and outputs from computerized analysers were checked twice before their evaluation and statistical analysis.

The effect of Pycnogenol® or placebo was evaluated with one-way ANOVA for repeated measurements (paired comparisons). For multiple comparisons of treatment periods, Wilcoxon's signed rank test was used. The threshold P value was 0.05/3=0.016666 (due to Bonferroni correction for triple comparisons).

For the statistical evaluation of the differences between boys and girls and between Pycnogenol® and placebo groups as well, Mann–Whitney test was used as a non-parametric analysis.

For statistical analysis we employed statistical programmes StatsDirect® 2.3.7 (StatsDirect Sales, Sale, CHeshire M33 3UY, UK) and Statistica® 6.0 (StatSoft, Inc. 2000). Graphical representation of data was made using programmes StatsDirect and Excel 2000 (Microsoft Co.).

Results

The number of investigated patients, age, gender, BMI, pre-study medications of patients and number of patients who failed to complete the study are indicated in Table 1.

From 61 patients included in the study, 57 patients completed the study and four patients dropped out the study, three patients from Pycnogenol group and one patient from placebo group. Two of them decided to discontinue their participation in our study after the first examination, even though they received medication. Two patients had to discontinue their participation after the second examination, during the wash-out period. Their questionnaires were not returned. Data of all patients were evaluated according "intention-to-treat" analysis.

All patients were checked for any side effects. No serious side effects were reported. We just observed a rise of slowness in one patient and a moderate gastritic discomfort in another one. Both patients belonged to Pycnogenol® group and completed the investigation. No side effects were observed in the placebo group.

Basic biochemical parameters (bilirubin, glucose, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotrasferase, alanine aminotransferase, uric acid and lipide profile) were investigated in fasting venous blood. All values of biochemical parameters were in the physiological range before the trial in both groups. None of analysed biochemical parameters raised or decreased beyond the range of physiological values after 1 month of Pycnogenol® or placebo administration.

Based on CAP and CTRS test results, teachers evaluated inattention and hyperactivity. Parents rated hyperactivity and inattention by CPRS tests. Psychologists evaluated the Weight Score, which sums up five subtests (see chapter "Methods"). In the double-blind, placebo-controlled study were evaluated all available data of 44 patients treated with Pycnogenol and of 17 patients receiving placebo:

CAP scores, rated by teachers, revealed no significant differences between groups at start of treatment for hyperactivity as well as for inattention (Fig. 1). Following 1-month of treatment with Pycnogenol®, scores for hyperactivity (P=0.008) as well as for inattention (P=0.00014) dropped significantly com-

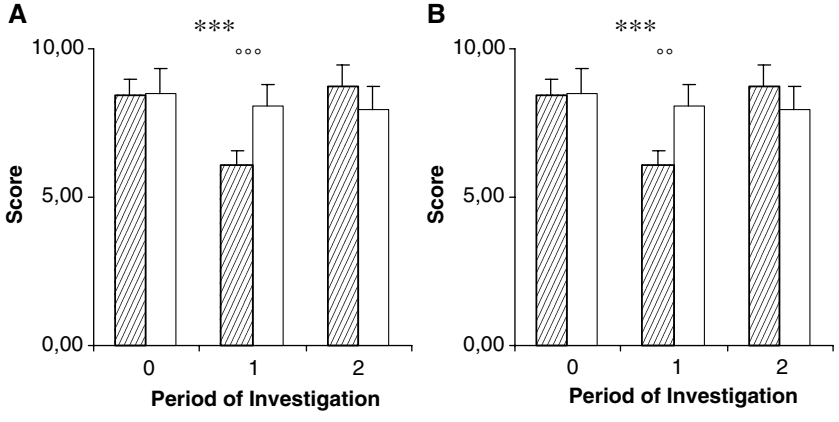

Fig. 1 Influence of 1 month Pycnogenol administration on ADHD symptoms evaluated by teachers (CAP):
– inattention (**A**) and
– hyperactivity (**B**).
empty bar—placebo group;
hatched bar—Pycnogenol group.
Significance between periods 0 and 1:
***P<0.01.
Significance for Pycnogenol versus placebo in period 1: °°°P<0.01, °°P<0.05

pared to start and also compared to placebo (P=0.044 and 0.0067). One month after stop of treatment, ADHD symptoms were scored at the same level as at start of treatment (Fig. 1).

CTRS scores for inattention, obtained from teachers, differed at start considerably between groups, in contrast to CTRS score for hyperactivity and to CAP scores, evaluated by the same teachers. To obtain the effect of treatment independently from starting values, CTRS scores at start for each patient were set as the 100 percent value and changes during treatment were calculated as percentage relative to start. With that CTRS scoring system, teachers noted following 1 month of treatment with Pycnogenol® a marginally significant reduction (P=0.07) of inattention compared to start (Fig. 2) and compared to placebo (P=0.049). Hyperactivity was also lower compared to start as well as to placebo following Pycnogenol® treatment, however, the decrease failed to reach significance level (P=0.45 and P=0.28).

ADHD symptoms evaluated by parents (CPRS) did not significantly differ at start of treatment between both groups. Following 1 month of Pycnogenol® administration, scores for inattention nonsignificantly decreased relative to start, also scores for hyperactivity decreased (Fig. 3), whereas in the placebo group no change of hyperactivity or inattention was registered. Following 1 month of treatment with Pycnogenol®, the lower score for hyperactivity compared to placebo was marginally significant (P=0.065).

The tests for visual–motoric coordination and concentration—Weight scores—were also different for placebo and verum group at start. Therefore, changes under medication were evaluated as percentual changes relative to start. Pycnogenol® treatment enhanced the Weight scores significantly compared to start (P=0.019) as well as to placebo (P=0.05), Fig. 4. The high values 1 month after stop of treatment for both groups point to a learning effect, giving higher Weight scores at the 3rd session.

Discussion

The results of our double-blind, placebo-controled study confirm the earlier reports of successful treatment of ADHD of children with Pycnogenol® [17, 21].

The results reported by Tenenbaum et al. [27], showing no treatment effect of Pycnogenol® in com-

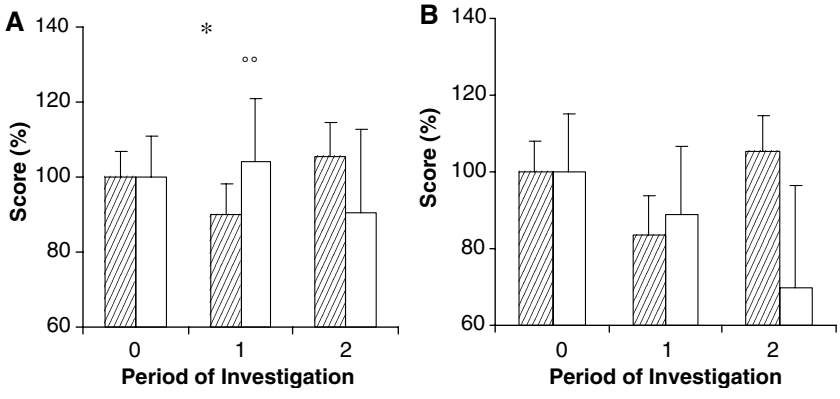

Fig. 2 Influence of 1 month Pycnogenol administration on ADHD symptoms evaluated by teachers (CTRS):
– inattention (%) (**A**) and
– hyperactivity (%) (**B**)
Score at period 0=100%
empty bar—placebo group;
hatched bar—Pycnogenol group.
Significance between periods 0 and 1:
*0.1>P>0.05.
Significance for Pycnogenol versus placebo in period 1: °°P<0.05

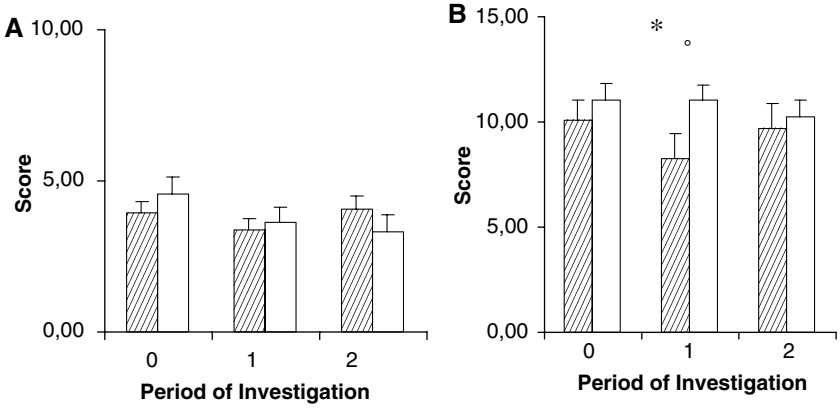

Fig. 3 Influence of 1 month Pycnogenol administration on ADHD symptoms evaluated by parents (CPRS):
– inattention (**A**) and
– hyperactivity (**B**)
hatched bar—Pycnogenol group;
empty bar—placebo group.
Significance between periods 0 and 1:
*0.1>P>0.05
Significance for Pycnogenol versus placebo in period 1: °0.1>P>0.05

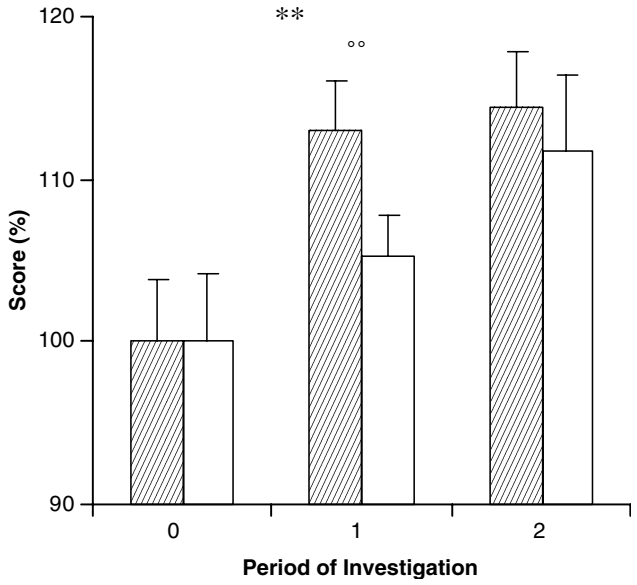

Fig. 4 Influence of 1 month Pycnogenol administration on visual–motoric coordination and concentration evaluated as Weight score (%) Score at period 0=100% empty bar—placebo group; hatched bar—Pycnogenol group. Significance between periods 0 and 1: $^{**}P<0.05$. Significance for Pycnogenol versus placebo in period 1: $^{\circ\circ}P<0.05$

parison to placebo, are not contradictory to our findings, because this study could not demonstrate an effect of methylphenidate. There was no difference between the three treatments: methylphenidate, placebo and Pycnogenol®. Whether the failure to detect the effect of the established drug, methylphenidate, was caused by the fact that adults had been treated or by methodological factors, cannot be judged. However, the lack of a difference between an active drug and placebo found by Tenenbaum et al. suggests that the study also had not the power to detect a possible difference between placebo and Pycnogenol® treatment success.

Our findings seem to present an alternative to treatment with existing drugs for parents fearing the adverse effects of established drugs, however, results of our study have to be further confirmed by studies involving a greater number of patients.

The mechanism of the treatment success remains to be elucidated. Analysis of urine of the patients in our study revealed a lower excretion of catecholamines compared to placebo [6], pointing to an influence of Pycnogenol® on catecholamine formation or on metabolism.

Another hint that Pycnogenol® influences cognitive functions can be deduced from experiments with senescence-accelerated strains of mice. These mice loose memory and learning capabilities early in comparison to normal mice. Feeding the senescence-accelerated mice with Pycnogenol® restored memory and learning dose-dependently, so that they reached nearly the level of the control mice [15]. In a double-blind, placebo-controlled study with elderly intake of Pycnogeol® enhanced spatial memory [26].

It remains speculative whether these findings are connected with an increased production of nitric oxide, which works beside its manifold actions also as a neurotransmitter. Pycnogenol® stimulates the endothelial nitric oxide synthase *in vitro* [7] and *in vivo* [25]. However, whether it also stimulates synthesis of neuronal nitric oxide synthase, is not known.

Nitric oxide (NO) is involved in the regulation of norepinephrine and dopamine release and intake [22]. NO participates in the regulation of normal brain functions, such as memory, learning, modulation of wakefulness [29]. NO has also been proposed to act as a neurotransmitter in the long-term potentiation of synapses by traveling backward across the synapse and enhancing the release of neurotransmitter in the presynaptic neuron [24]. In fact, various reports have indicated that NO may have a role in the mechanism of storage and retrieval of information [19]. The effect of NO on various types of learning has also been examined with conflicting results [12].

In our study, teachers were able to register the decrease of hyperactivity and a better attention, for parents, treatment success for inattention was not that obvious. As reported by Heimann [11], the effect of Pycnogenol® did not persist for a longer period of time. Control after 1 month wash-out period demonstrated a relapse of symptoms, demonstrating that Pycnogenol® has an effect on ADHD symptoms but seems not to change the underlying fundamental processes.

During our experiments we noted that treatment was not significantly effective for girls, in contrast to boys. Because only six girls were in the Pycnogenol® group, we cannot judge whether we observed a true gender-specific effect. Investigation with greater numbers of girls is needed to see whether there is a gender-specific effect of Pycnogenol®. The relative small number of 44 patients treated with Pycnogenol® and the short duration of the study limits the generalization of our findings. However, the small, but significant success of treatment together with the small incidence of mild side effects suggest that Pycnogenol® could find a place as an alternative treatment of ADHD of children.

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