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FULL COMMUNICATION

The Effect of Experimental Supplementation with the Klamath Algae Extract Klamin on Attention-Deficit/Hyperactivity Disorder

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ABSTRACT Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurobiological condition with onset in childhood. The disorder is characterized by inattention, impulsivity, and/or motor hyperactivity, which often affect the development and social integration of affected subjects. Phenylethylamine (PEA), naturally contained in the Klamath Lake microalgae and concentrated in the Klamin® extract, is an endogenous molecule with a general neuromodulatory activity. It functions as an activator for the neurotransmission of dopamine and other catecholamines, and very low concentrations of PEA may be associated with specific psychological disorders such as ADHD. The aim of our study was to evaluate the efficacy of the Klamin extract in treating a group of subjects diagnosed with ADHD. Thirty subjects, aged 6–15, who had been diagnosed with ADHD according to the DSM-IV TR criteria, were enrolled. The supplement was administered to all the subjects, who reported to an ADHD clinic for routine follow-up visits. Observations were made and data collected over a 6-month period. After 6 months of therapy the subjects appeared to show significant improvements based on assessments of their overall functioning, behavioral aspects related to inattention and hyperactivity–impulsivity, attention functions in both the selective and sustained component and executive functions. The study appears to confirm the initial hypothesis that the Klamin extract may positively affect the expression of ADHD symptoms. Additional larger studies on the effects of Klamin on ADHD are needed to further investigate the potential of this extract in ADHD treatment.

KEYWORDS: • ***algae extract*** • ***aphanizomenon*** • ***attention-deficit hyperactivity disorder (ADHD)*** • ***phenylethylamine*** • ***supplementations***

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is defined as a psychiatric disorder characterized by a developmentally inappropriate, pervasive, and persistent pattern of severe inattention, hyperactivity, and/or impulsivity with onset in childhood. The disorder is associated with substantial impairment in social, academic, and/or occupational functioning. It has the highest prevalence in school age children, but in 60–86% of cases, it tends to persist during adolescence, and in 15% of cases, into adulthood.[1] A 2007 epidemiological study on the prevalence of the disorder in childhood and adolescence, based on a review of 102 international studies, showed a global prevalence of about 5.3%: 6.5% in childhood and 2.7% in adolescence. ADHD is more common in boys than girls with a ratio of 2.45: 1,[2] and the prevalence of the disorder has remained stable over the last 30 years.[3] Diagnosis, exclusively clinical to date, is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (APA, 2000–2013[4]) or the ICD-10 (WHO, 1992).[5] A complete diagnosis requires observation of the child and the collection of information from his or her parents, teachers and other role models (using questionnaires and semi-structured interviews) to gather information on the child's behavior and functional impairment in multiple contexts. There are currently no diagnostic instrumental and/or laboratory examinations for the diagnosis of ADHD.

The core symptoms of the disorder are inattention, impulsivity, and hyperactivity. These symptoms appear during childhood, are persistent and pervasive in at least two life contexts, and cause significant interference with the child's functioning or development. In 70–80% of cases there is comorbidity with one or more disorders,[6,7] including oppositional-defiant disorder, conduct disorder, anxiety and depression disorders, specific learning disabilities, obsessive compulsive disorder, tics and Tourette's syndrome, and bipolar disorder. The presence of comorbidity significantly worsens ADHD symptoms and complicates the diagnosis and treatment of the disorder.

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The interaction between genetic and environmental factors during pre- and postnatal life (particularly in the early years) determines a neurobiological predisposition to develop ADHD.[8] The clinical expression of the disorder is influenced by socioenvironmental factors. The evidence of its genetic origin is supported by studies on identical twins and families with multiple affected subjects in whom several candidate genes have been identified.[6,9–12] The genes encoding beta hydroxylase dopamine are considered candidates, and monoamine oxidase (MAO) A, the receptors for dopamine D2, D4, and D5,[13] genes involved in the serotonin circuit,[14–17] and noradrenergic system.[18–20] The disorder involves the dysregulation of catecholamine metabolism in the brain, as shown by structural and functional neuroimaging, animal studies, and clinical response to drugs with noradrenergic activity.[21,22] However, current research suggests that ADHD cannot be attributed to alterations of a single neurotransmitter system and that the disorder is rather the consequence of the interaction between many dysfunctional neurotransmitter systems.[23]

Psychostimulants, the most commonly used drugs in the treatment of ADHD, act on the monoamine transporters: methylphenidate acts mainly on the modulation of the amount of dopamine and noradrenaline present in the intersynaptic space, resulting in the enhancement of deficient dopaminergic transmission,[24] or limitation of a dopaminergic state of hyperactivity.[25,26] Psychostimulants appear particularly effective in enhancing certain neuropsychological functions such as the inhibition of responses, the working memory and the processes of discrimination of stimuli, resulting in an improvement in the subject's performance on tests designed to assess attention, vigilance, verbal and visual learning, and short-term memory.[27] Atomoxetine, which is a selective inhibitor of norepinephrine reuptake at the presynaptic level with minimal activity on the other monoamine transporters, in addition to improving the cardinal ADHD symptoms, is also recommended in cases of comorbidity of oppositional-defiant and anxiety disorders. Clonidine and guanfacine are other nonstimulant medications that are used for the treatment of the disorder,[28] but they are not registered in Italy for ADHD treatment.

Phenylethylamine (PEA) is an endogenous neurotransmitter synthesized by decarboxylation of phenylalanine amino acid in the dopamine neurons of the nigrostriatal pathway.[29] It is normally stored and metabolized in the brain and in peripheral tissues and functions as an activator for the neurotransmission of dopamine and the other catecholamines through two complementary mechanisms: stimulus of the release of dopamine and catecholamines from the brain intraneuronal reserves and inhibition of the reuptake of dopamine and norepinephrine (noradrenaline) in neurons, thus extending their life and action.[29,30]

PEA can be found in some algae,[31] fungi, and bacteria,[32] a variety of plants,[33] some foods (chocolate), the human brain and that of other mammals.[34] Unlike amphetamines, its alpha-methylated derivative, PEA is easily degraded to phenylacetic acid by MAO.[35] PEA belongs to the so-called trace amines,[36] a group of amines present in the intra- and extracellular space at much lower concentrations compared to the biogenic amines and the neurotransmitters related to them such as epinephrine, norepinephrine, serotonin, dopamine, and histamine.[37] Trace amines bind to a receptor associated with the G-protein, called TAAR (trace amine associated receptor).[38,39] It is believed that the binding of PEA to TAAR 1 results in an alteration of the functioning of the monoamine carrier, which leads to inhibition of the reuptake of dopamine, serotonin, and norepinephrine,[40] and an increase in the concentration of these neurotransmitters in the synaptic cleft. Some authors have observed that the urinary excretion of PEA in ADHD subjects is lower than in controls.[41,42] Moreover, patients who benefit from the use of methylphenidate have shown a significant increase in the level of PEA compared to nonresponders.[42] The phycocyanins, present in the Klamath algae extract, are powerful natural inhibitors of MAO-B, thus enabling PEA to reach the brain and perform its action.[43]

Study objective: To evaluate, through a pilot study, the effectiveness of PEA (beta-PEA) and phycocyanins (which have reversible anti MAO-B activity) contained in the Klamin® extract on a group of subjects diagnosed with ADHD.

MATERIALS AND METHODS

The study enrolled a total of thirty patients who had been reporting for at least 3 months to the ADHD outpatient clinic of the Neurological and Psychiatric Child Unit, Pediatric Department, Alessandria Hospital, Italy. The subjects, 2 girls and 28 boys, aged 6–15 (average of 9 years and 6 months), had been diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. All the families and patients with a mental age of over 12 were fully informed of the clinically validated pharmacological and nonpharmacological treatments currently available. All the participants agreed to begin the therapeutic trial by signing an informed consent form. Enrollment took place between April 2013 and April 2014 (Table 1).

Inclusion criteria were as follows: aged 6–17, absence of comorbidity with autism spectrum disorder or major psychotic or depressive disorders, no therapy with anticonvulsant or MAO inhibitor drugs.

Out of the 30 subjects, 23 had been diagnosed with ADHD ''combined'' subtype, while 7 belonged to the ''inattentive'' subtype. Eighteen subjects had no associated comorbidity, six subjects had an oppositional defiant disorder, four subjects had a specific learning disorder, and two subjects had simple motor tics. Six subjects were mentally retarded (5 mild, 1 medium severity) and the remaining 24 showed an IQ in the normal range.

At enrollment, 13 subjects had already tried various nonpharmacological treatments (psychoeducational therapy, psychomotor treatment and/or speech therapy, parent training interventions). After diagnosis, the remaining subjects had been referred to local services to start treatment. All subjects were given Klamin for 6 months (in liquid form or in tablets) according to the following dosage (Table 2): Klamin, as indicated in its patent contains[44] concentrations of beta-PEA ranging from 11 to 15 mg/g (average of 13 mg/g);

Table 1. Clinical Characteristics of the Sample

No. of subjects	30
Age T0 mean ± SD	9.8 ± 2.86
	N *(%)*
Sex	
Male	28 (93.3)
Female	2 (6.7)
Subtype	
I	7 (23.3)
C	23 (76.7)
Comorbidity	
No	18 (60.0)
Tics	2 (6.7)
SLD	4 (13.3)
ODD	6 (20.0)
Global IQ	
Normal	24 (80.0)
MD light	5 (16.7)
MD mean	1 (3.3)
Change to MTF	
No	26 (86.7)
Yes	4 (13.3)

C, combined; I, inattentive; MD, mental delay; MTF, methylphenidate; ODD, oppositional defiant disorder; SD, standard deviation; SLD, specific learning disorder.

AFA-phycocyanins (selective inhibitors of MAO-B) from 5% to 7% of the dried extract; and mycosporine-like amino-acids from 0.8% to 1% of the dried extract.

Twenty-five subjects completed the trial. Before therapy (T0), the clinical condition (weight, height, general and neurological objectivity), vital signs (pulse, PA, baseline temperature), biochemical parameters (complete blood count with formula, liver and kidney function tests, thyroid hormones), and routine urinalysis were evaluated. Urinary excretions of phenylacetic acid and plasma levels of beta-phenylethylamine (PEA) were not evaluated; however, urine levels of the PEA metabolite had been measured in previous investigations.[41,42]

Each patient was also evaluated using international standardized tests that assess the overall functioning of the subject (Child Global Assessment Scale [C-GAS]), behavioral aspects related to inattention and hyperactivity–impulsivity (SNAP IV, Conners' parent rating scale-R), oppositional-defiant disorders (subscale ODD, SNAP IV), attention functions in both the selective and in sustained component (Bell's Test), executive functions (Tower of London test), freedom of distractibility parameter (LD, Wechsler Intelligence Scale for Children III [WISC III scale]), short-term verbal memory (numbers memory, WISC III scale) and arithmetic reasoning, and mental math skills (arithmetic reasoning, WISC III scale).

Table 2. Klamin Dosage Used During Study

Body weight (kg)	*Dosage of Klamin® in first month of therapy (mg/day)*	*Dosage of Klamin in second to sixth month of therapy (mg/day)*
<25	125	250
>25	300	600
>40	600	1200

In the first, third, and sixth month of treatment, the clinical condition and vital signs were reassessed and the C-GAS scale was completed. Furthermore, in the sixth month (T1, final visit), patients underwent a second hematological control and all the evaluation scales were administered again.

Statistical analysis

Clinical evaluations and logical reasoning tests repeated at the final visit (T1) were compared with pretreatment baseline values (T0), and psychometric test scores after the Klamin treatment were compared with test results at time T0 (before treatment). As part of an ''intention to treat'' design, the scores of all subjects were included regardless of whether they had finished the Klamin treatment cycle. Statistical analyses were performed using multivariate techniques to show whether the subjects' scores at T1, taken as a whole, were significantly different from their scores at T0. Hence, the multiple analysis of variance for repeated measures was used to highlight the significance of each single questionnaires; the suitable *post hoc* tests were performed after Bonferroni adjustments. Scatter plots were also used; the abscissa shows the initial value, the ordinate shows the difference between the final and initial value. The effects of Klamin were visualized with linear regression; R Pearson coefficients were also calculated to quantify the strength of the correlation between variables. Linear regression slopes were used to assess whether Klamin's effect is dependent on the initial value or if it has a similar effect on all patients, regardless of initial values. The two-tailed significance level was fixed at 0.05. All calculations were performed with SPSS software version 19.0.

RESULTS

All the biochemical parameters (complete blood count with formula, liver and kidney function tests, thyroid hormones) and urinalysis evaluated at T0 e T1 showed values in the normal range. The values, derived from the questionnaires and from the rating scales, were compared for each of the 25 subjects who completed the study at the beginning (T0) and at the end (T1) of the study period. In particular, the overall functioning of the subjects was assessed using questionnaires of clinical detection, both directly (C-Gas) and through the perception of the severity of symptoms by parents (Conners' parent scale); the clinical aspects of inattention and hyperactivity-impulsivity using SNAP IV; the executive functions through the Tower of London Test; the attention functions using the Bell's Test; short-term verbal memory, arithmetic reasoning, and the parameter of freedom from distractibility using WISC III.

Considering the set of all the measured scores, the predictor variable, that is, differences between T0 and T1, was significant ($P = .011$). Reported below are the average ratings and standard deviations (T0 and T1) of each of the variables considered (Table 3). Considering the single independent variables (the specific scores of the tests used), the results of the following assessments were found to be statistically significant: the test that evaluated the overall functioning of the child (C-Gas), assessments of the behavioral aspects

Table 3. Results of Multivariate Analysis: Initial Mean Values in T0 Column, Final Mean Values in T1

Repeated measures analysis	*Tests of within-subjects contrasts*		
Tests	*T0*	*T1*	P
C-GAS	65.28	70.68	<.001*
SNAP IV inattention	12.64	16.28	.002*
SNAP IV hyperactivity	11.32	14.36	.005*
SNAP IV tot	24.32	30.64	.002*
SNAP IV Subscale ODD	4.72	4.44	.743
Conners'	1.50	1.64	.188
London Tower	−1.42	−0.4	.002*
Arithmetic (WISC III)	6.96	6.84	.513
Memory (WISC III)	7.36	7.4	.885
Score LD (WISC III)	81.83	80.42	.682
Bell's test Quickness	−1.36	−0.8	<.001*
Bell's test Carefulness	−1.85	−0.9	<.001*

*Statistically significant. Values of significativity in *P* column.

C-GAS, Child Global Assessment Scale; WISC III scale, Wechsler Intelligence Scale for Children III.

related to inattention and hyperactivity–impulsivity (SNAP IV scale for both individual aspects and in the totality of symptoms), assessments of the attention functions, both in the selective and in sustained component (Bell's Test), and assessment of the executive functions (Tower of London).

On the other hand, the following tests did not yield results showing statistically significant differences between T0 and T1: short-term verbal memory tests (numbers memory, WISC-III), arithmetic reasoning and mental math skill tests (arithmetic reasoning, WISC-III), freedom from distractibility factor tests (WISC-III), assessment of the perception of the severity of symptoms by parents (Conners' Parents scale), and assessment of oppositional-defiant aspects (ODD subscale of SNAP IV).

In all the graphs, T0 values (in the abscissa) were plotted versus T1-T0 values for the following variables: C-Gas (Fig. 1A); SNAP IV (Fig. 1B–D); Tower of London test (Fig. 1E); and Bell's test (Fig. 1F, G). C-Gas value T1–T0 variations were dependent on the Klamin treatment; variation was slight (about 8%) and did not significantly (slope of linear regression = 0.071) depend on the initial values (Fig. 1A); R Pearson (0.224; $P = .282$) showed nonsignificant values. Interestingly, Klamin systematically modified C-Gas scores, improving all initial values for a mean value of 5.4, irrespective of initial values. Bell's carefulness test showed a similar trend to C-GAS; R Pearson did not have a significant value (R = 0.134; $P = .53$), while they showed a systematic higher final values, with a mean differences of 0.56. R Pearson values were all significant ($P < .05$ for Bell carefulness and $P < .01$ for the other variables) for the following variables: inattention, hyperactivity, Total SNAP IV, London tower, and Bell's Quickness and Carefulness; Moreover, the linear regression slopes were always <0, indicating a linear inverse correlation between initial values and T1–T0 values. In other words, the higher the initial value, the higher (in absolute value) the variation, which means that the greatest improvements were obtained with higher initial scores.

Vital signs and blood chemistry parameters remained in the normal range throughout the study.

DISCUSSION

Klamin is a specific extract obtained from the *Aphanizomenon flos aquae* microalgae found in Klamath Lake (Oregon). The extract contains high concentrations of beta-PEA,[44] in addition to AFA Phycocyanins (potent selective inhibitors of MAO-B) and other molecules (AFA-phytochrome and algalMycosporin) that feature a selective MAO-B inhibition activity.[44] PEA acts as a general neuromodulator performing different complementary actions according to the needs of the body, and it is rapidly eliminated in the form of phenylacetic acid when no longer needed. PEA, which acts through the inhibition of the reuptake of the neurotransmitters or by supporting the production and release of the catecholamines, can be replenished orally on an ongoing basis. It is present in small amounts in many foods, but in quantities that are too small to be effective. Moreover, if ingested alone, it is rapidly destroyed by specific enzymes, namely the MAO-B, which are active in the liver and intestine. Phycocyanins have the ability to selectively inhibit the MAOs MAO-B, thus protecting the PEA and allowing it to perform its neurological functions.[43]

Some studies have shown a deficiency of PEA in autistic girls with Rett syndrome,[45] in children with Autism Spectrum Disorders and in subjects with learning disabilities.[42,46] Reduced levels of beta-PEA have also been reported in subjects with ADHD (42). It has also been found that methylphenidate only works if and when it manages to stimulate increased production of endogenous PEA.[42] Therefore, for disorders that are characterized by low PEA levels (*e.g.*, ADHD), the synergy of PEA and MAO-B enzyme inhibitors provided by the Klamin extract appear to be a safe alternative to drugs such as amphetamines or methylphenidate, which have undesirable side effects.[37]

ADHD is a complex disorder, and its treatment is multimodal: treatment approaches that combine psychosocial and drug therapies appear to be the most effective.[47] There are currently two drug therapies (methylphenidate and atomoxetine) available in Italy. However, many families and healthcare professionals are reluctant to turn to drug therapy to treat ADHD. In particular, parents may be concerned about possible side effects associated with ADHD drugs or they may reject this option for cultural reasons. Therefore, the study of therapies that could replace or minimize the use of drugs is of growing interest.

In the present investigation we observed significant improvements in the treatment group after 6 months of continuous treatment with Klamin. Specifically, our results show improvement in overall functioning (C-GAS scale), in behavioral aspects related to inattention and hyperactivity impulsivity (SNAP IV scale), in attention functions both in the selective and in the sustained component (Bell's test), and in executive functions (Tower of London test). On the other hand, there were no significant changes in verbal short-term memory (memory of numbers, WISC-III), in

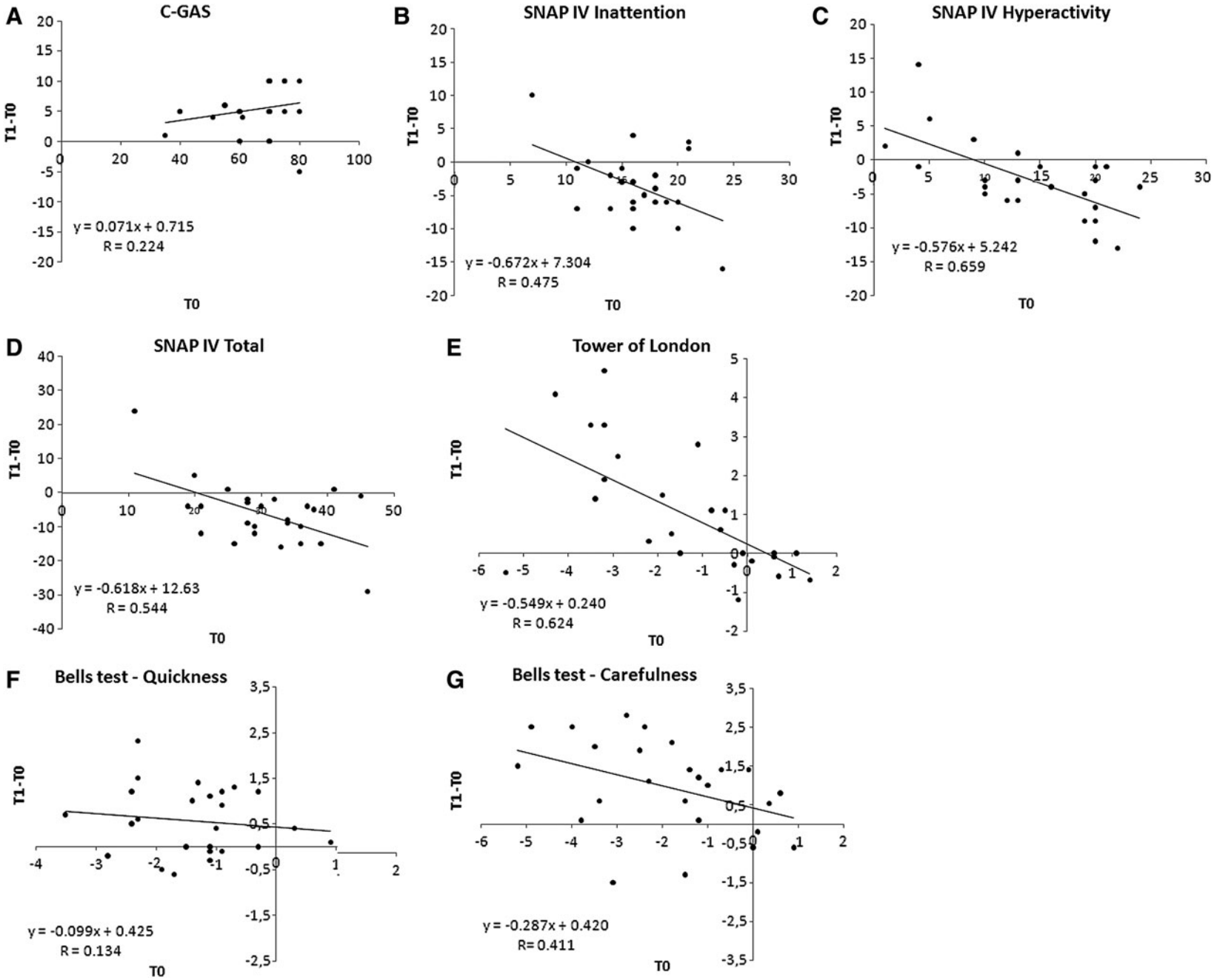

FIG. 1. Score change between baseline evaluations (T0) and end of treatment (T1). In all graphs, T0 values (abscissa) are *plotted* versus T1–T0 values. The following test scores are reported: **(A)** C-GAS; **(B)** SNAP IV Inattention; **(C)** SNAP IV Hyperactivity; **(D)** SNAP IV Total; **(E)** Tower of London; **(F)** Bell's Quickness Test; **(G)** Bell's Carefulness Test. C-GAS, Child Global Assessment Scale; SNAP IV, Rating Scale, revision of the Swanson, Nolan and Pelham Questionnaire.

arithmetic reasoning ability (arithmetic reasoning, WISC-III), in the freedom from distractibility factor of the WISC-III. Moreover, there was no significant change in the perception of the severity of symptoms by parents (Conners parent scale) nor in oppositional-defiant aspects (ODD subscale of SNAP IV).

In conclusion, the study seems to confirm the initial hypothesis that the algal extract Klamin may have a positive impact on the symptoms of ADHD. In particular, our investigation showed statistically significant improvements across all ages in the treatment group in executive and attention functions. Moreover, the severity of symptoms, assessed through a semi-structured interview with the parents, appears to have been reduced.

On the other hand, we found no significant improvements in verbal memory or arithmetic reasoning. Likewise, there were no significant changes in the perception of parents regarding their children's behavior assessed through the Conners' questionnaire, although the severity of symptoms, assessed through a semi-structured interview with parents (inattention-hyperactivity-impulsivity), appeared to be generally reduced for all age groups. Moreover, the C-GAS scale of the child's overall functioning showed significant improvement, especially in patients who continued treatment after the end of study. This difference could be attributed to the parents' high expectations regarding the resolution of their children's behavioral problems. None of the subjects were found to have abnormalities in their vital signs or blood chemistry parameters. Since the subjects are in a developmental phase, it was decided to use BMI instead of body weight to assess possible effects on height-weight growth, and the treatment was found to have no significant impact on the growth of the subjects.

At the end of the study more than 50% of the subjects (13 families) chose to continue the treatment with Klamin, although the product was no longer being provided free of charge and had to be purchased, further confirmation of the apparent tangible and lasting benefits of the treatment. The relatively small sample size did not allow us to analyze possible correlations between age, sex, cognitive level, subtype, and comorbidities. However, these positive preliminary results, especially in light of the fact that the dosages of the Klamin extract used in the study were lower than normal indications, justify further investigations with larger sample sizes (possibly a randomized, controlled, double-blind, multicenter trial).

This is the first study to investigate the overall effects of Klamin on patients formally diagnosed with ADHD, and further investigations are necessary to gain a better understanding of this extract and how its beneficial effects might be heightened.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Alessandria Hospital, Italy—No ASO.Npi.12.01 CE 12/12/2012; authorization and executive determination n. 13 on February 22, 2013 adopted by S.C. G.A.A.S. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (DM on July 15, 1997).

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AUTHOR DISCLOSURE STATEMENT

S.S. is the R&D Director of the company that owns Klamin's patent, and he is the main inventor of the patent. E.C. is an employee at the same company.

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