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Caloric and nutrient intake in children with attention deficit hyperactivity disorder treated with extended-release methylphenidate: analysis of a cross-sectional nutrition survey

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Abstract

Objectives: To study calorie and nutrients intake in a group of patients diagnosed with attention deficit hyperactivity disorder (ADHD) under treatment with extended-release methylphenidate (MPH-ER), and to analyse the need to design nutrition intervention strategies.
Design: Observational (case-control).
Setting: Navarra Hospital Complex, Pamplona, Spain.
Participants: A total of 100 patients diagnosed with ADHD under treatment with MPH-ER and 100 healthy children (control group).
Main outcome measures: A nutrition survey was carried out (food intake registration of 3 consecutive school days). Calorie and nutrient intake, as well as nutrition status, were evaluated and compared in both groups.
Results: Nutritional status in ADHD group was significantly lower ($p < 0.05$) than in control group. Calorie intake in mid-morning snack, lunch and afternoon snack was significantly higher ($p < 0.05$) in the control group. Calorie intake in supper was significantly higher ($p < 0.05$) in the ADHD group. There were no significant differences in breakfast. Total calorie intake, as well as protein, carbohydrates, fat, fibre, calcium, iron, magnesium, zinc, selenium and phosphorous, thiamine, niacin, vitamin B6 and folate intake, in control group was significantly higher than in ADHD group.
Conclusions: The daily calorie and nutrients intake in patients under treatment with MPH-ER is, generally, lower than in healthy population of similar age. The need to impart programmes of nutrition education simultaneously with multimodal treatment in order to avoid the nutrition consequences of treatment with MPH should be considered.

Keywords

attention deficit hyperactivity disorder, nutrients intake, nutritional status, methylphenidate

Introduction

Multimodal treatment in attention deficit hyperactivity disorder (ADHD) combines psychosocial intervention with drug therapy, which usually implies prolonged therapy with a long-acting stimulant medication.[1–4] Stimulant drugs, and specifically methylphenidate (MPH), are first-line treatment in patients diagnosed with ADHD. Many clinical trials confirm the maintained efficacy of MPH in attentional and behavioural symptoms, which allows, in most cases, the optimization of the child's academic, familiar and social situations.[2,3,5–9]

In Spain, there are two preparations of extended-release MPH (MPH-ER): one is an osmotic-controlled release oral delivery system (OROS-MPH) and the other one is made up of double action microspheres or modified release MPH (MR-MPH).[10] The pharmacokinetic properties of these prolonged release forms guarantee relatively constant plasma levels throughout the day in contrast to immediate release forms.[11] Nevertheless, this fact could hypothetically affect appetite in different meals during the day owing to the hyporexia associated with administration of MPH.

In fact, the nutritional status in patients with ADHD tends to aggravate in prolonged treatment with MPH-ER,[12,13] and justifies the interest to know the dietary intake of these patients during the treatment. The purpose of this study is to evaluate the caloric and nutrients intake dietary patterns in a group of patients diagnosed with ADHD under treatment with MPH-ER, and to analyse the need to design nutrition intervention strategies in these patients.

Material and methods

Patients

A nutrition survey has been conducted in the first 100 patients diagnosed with ADHD in the neuropaediatric unit of the 'Complejo Hospitalario de Navarra' who attended follow-up consultation within the year 2012 (the nutrition survey was carried out between January and April).

Every patient should be under exclusive and maintained treatment with OROS-MPH or MR-MPH for at least 12 months. The criteria from the last edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-R) were applied for diagnosis and classification.[14] Patients were grouped into two clinical subtypes: those who showed mainly attention deficit of *inattentive subtype* and those who presented attention deficit, hyperactivity and impulsivity or *combined subtype*. Another nutrition survey was carried out simultaneously in 100 healthy patients (50 men and 50 women) of similar ages.

Patients and/or controls who suffered from any known chronic disease which could condition the nutrition status and those who took any energy, mineral or vitamin supplements were also excluded.

Nutrition survey

The nutrition survey was carried out in the form of personal interview at the time of consultation using a food intake registration of 3 consecutive school days. Every patient was asked about food intake in every meal during the previous 3 consecutive days (breakfast, mid-morning snack, lunch, afternoon snack and supper). A photograph album with portions and measures from the *Institut Scientifique et Technique de la Nutrition et de l'Alimentation* (París, 2002)[15] was used to calculate the size of the corresponding portions of the different foods that the participants referred to have eaten.

Energy and nutrient consumption (proteins, carbohydrates, total fat, saturated fatty acid, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), total fibre and cholesterol), minerals (calcium, iron, iodine, magnesium, zinc, selenium and phosphorus) and vitamins (thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin C, vitamin A, vitamin D and vitamin E) was calculated using the CESNID 1.0® nutrition calculation programme (Centro de Enseñanza Superior de Nutrición y Dietética, Universidad de Barcelona).[16]

Nutrition study

Sex, age, clinical subtype and MPH dose (mg/kg/day), weight, height, triceps skinfold and mid-upper arm circumference from every patient and control were recorded. Weight and height assessment were done in underclothes and shoes off. Weight was measured using an Año-Sayol® scale (read range 0–120 kg and precision 100 g) and height was measured using a wall-mounted rigid stadiometer (ranking 60–210 cm and with 0.1 cm precision). A constant pressure Holtain-type skinfold calliper was used to measure triceps skinfold. Weight, height and mid-upper arm circumference *Z*-scores as well as body mass index (BMI) were calculated using the SEINAPTRACKER program (Medicalsoft Intercath, S.L. Universidad de Barcelona, 2007–2008). Reference growth curves and charts were the Centro Andrea Prader (Zaragoza, 2002) charts.

This research protocol was approved by the Ethics Committee of the Navarra Hospital Complex.

Results are displayed as means (M) with standard deviation (SD). Statistical analysis was done using the *IMB SPSS Statistics program 20 version* (Chicago, Illinois, EE.UU.). Statistical significance was considered when $p < 0.05$.

Results

The sample of patients was made up of 68 boys and 32 girls, being the male/female ratio 2.1. Combined subtype represented 61% of cases, whereas inattentive subtype was 39%. The proportion of combined subtype was significantly higher ($P < 0.001$) in boys (67.6%) than in girls (46.8%). Mean age of patients was 11.4 years (CI 95%: 11.13–11.67) and there were no statistically significant differences compared with the control group (mean age: 11.2 years, CI 95%: 10.91–11.49).

All patients surveyed were under treatment with MPH-ER for a mean time of 27.9 months (CI 95%: 24.8–31.1) and a mean dose of 1.01 mg/kg/day (CI 95%: 0.96–1.06). Sixty-three patients were treated with OROS-MPH at a mean dose of 1.07 mg/kg/day (CI 95%: 0.99–1.15) and 37 were treated with MR-MPH at a mean dose of 0.90 mg/kg/day (CI 95%: 0.81–0.99), this difference not being significant.

Table 1 displays and compares the results of the nutrition study in both groups. The mean values of weight (*Z*-score), height (*Z*-score), BMI (*Z*-score), mid-upper arm circumference (*Z*-score) and triceps skinfold (cm) in the ADHD group were significantly lower than values in the control group.

Table 2 shows and compares the total daily calorie intake and each meal (breakfast, mid-morning snack, lunch, afternoon snack and supper) intake in both groups. Total daily calorie intake, as well as mid-morning snack, lunch and afternoon snack energy intake were significantly higher ($P < 0.05$) in the control group than in the ADHD group. In contrast, supper calorie intake was significantly higher ($P < 0.05$) in the ADHD group than in the control group. There were no statistically significant differences in breakfast energy intake between the groups. In addition, there were no differences in total daily calorie intake and each daily meal (breakfast, mid-morning snack, lunch, afternoon snack and

Table 1. Results of the nutrition study in both groups.

Item	ADHD group M (DS)	Control group M (DS)	*p*
Weight (Z-score)	−0.729 (0.88)	−0.196 (1.10)	<0.001
Height (Z-score)	−0.219 (0.99)	+0.095 (1.10)	<0.040
BMI (Z score)	−0.805 (0.77)	−0.360 (0.97)	<0.001
MUAC (Z-score)	−0.578 (0.89)	−0.084 (1.07)	<0.001
TS (cm)	12.7 (5.2)	16.3 (6.8)	<0.001

ADHD: attention deficit hyperactivity disorder; BMI: body mass index; MUAC: mid-upper arm circumference; TS: triceps skinfold.

Table 2. Total daily calorie intake and intake from different meals in both groups.

Intake	ADHD group M (DS)	Control group M (DS)	*p*
Breakfast	322.4 (137.4)	313.8 (94.7)	<0.616
Mid-morning snack	148.2 (128.2)	263.2 (105.4)	<0.001
Lunch	401.5 (176.1)	735.3 (175.7)	<0.001
Mid-afternoon snack	267.6 (136.6)	312.4 (102.3)	<0.011
Supper	577.0 (205.3)	477.6 (169.0)	<0.001
Total	1786.5 (335.9)	2061.1 (242.4)	<0.001

ADHD: attention deficit hyperactivity disorder.

supper) in patients treated with OROS-MPH or MR-MPH.

Table 3 shows and compares macronutrients, minerals and vitamins daily intake for both groups. In the control group, the daily intake of some macronutrients (proteins, carbohydrates, total fat, MUFA, PUFA and total fibre), minerals (calcium, iron, magnesium, zinc, selenium and phosphorus) and vitamins (thiamine, niacin, vitamin B6 and folate) was significantly higher ($p < 0.05$) than in the ADHD group. In the control group, the recommended daily intakes for individuals (RDIs) for minerals and vitamins were sufficiently fulfilled except for calcium, iodine, vitamin A, vitamin D and vitamin E. In contrast, in the ADHD group, the RDIs corresponding to calcium, iodine, magnesium, folate, vitamin A, vitamin D and vitamin E were not adequately covered.

Discussion

Among the epidemiological aspects of this series, its remarkable the presence of a slight male predominance (male/female ratio: 2.1) and the higher prevalence of the combined subtype. These aspects match with other research.[17,18] These peculiarities let us consider this sample as representative of a standard population of patients diagnosed with ADHD and, therefore, no statistical bias in results or conclusions in this sense was suspected.

The condition to be included in this study was a long-time and exclusive therapy with MPH-ER: OROS-MPH or MR-MPH, since pharmacokinetics facilitates a better compliance and makes them preferable to other immediate release formulations.[9,11,19,20] Nevertheless, the schedule of administration should be personalized, given the interindividual variability in plasma concentrations and/or the duration of therapeutic effect. It should be adapted to schedule, academic and behavioural needs, which requires an adjustment of dosage in relation to the clinical response. In this series, dosage of MPH was within safety and tolerability margins, since in any case where the prescribed dose was manifestly high (maximum dose as 1.68 mg/kg/day) it would lead to the possibility of suspending treatment in order to avoid secondary effects.[2,7,21–23]

Pharmaceutical preparations of immediate release MPH initiate clinical action 20 min after

Table 3. Daily intake of macronutrients, minerals and vitamins in both groups.

Nutrients	ADHD group M (DS)	Control group M (DS)	*p*
Proteins (g)	82.2 (19.3)	98.6 (20.0)	<0.001
Carbohydrates (g)	207.0 (54.2)	250.9 (45.0)	<0.001
Total fat(g)	63.4 (19.2)	69.4 (18.6)	<0.028
SFA (g)	26.72 (8.5)	28.6 (8.2)	<0.122
MUFA (g)	22.5 (7.8)	24.8 (7.9)	<0.047
PUFA(g)	7.2 (2.5)	8.7 (2.6)	<0.001
Total fibre (g)	15.1 (6.3)	23.8 (12.2)	<0.001
Cholesterol (mg)	313.7 (127.7)	302.9 (103.2)	<0.522
Calcium (mg)	787.8 (201.5)	877.0 (204.7)	<0.003
Iron (mg)	13.5 (5.0)	17.1 (5.8)	<0.001
Iodine (μg)	76.6 (22.6)	80.0 (20.3)	<0.266
Magnesium (mg)	223.1 (51.5)	295.2 (88.9)	<0.001
Zinc (mg)	8.7 (2.5)	10.2 (2.7)	<0.001
Selenium (μg)	111.8 (54.3)	133.3 (42.8)	<0.001
Phosphorous (mg)	1344.3 (305.0)	1550.1 (305.7)	<0.001
Thiamine (mg)	1.5 (0.5)	1.7 (0.5)	<0.019
Riboflavin (mg)	1.8 (0.5)	19 (0.5)	<0.528
Niacin (mg)	33.7 (9.1)	38.2 (8.7)	<0.001
Vitamin B6(mg)	1.7 (0.6)	2.0 (0.7)	<0.001
Folate (μg)	220.8 (109.2)	301.6 (151.5)	<0.001
Vitamin B12(mg)	5.9 (3.9)	5.5 (3.3)	<0.451
Vitamin C (mg)	48.0 (34.7)	58.4 (36.6)	<0.460
Vitamin A (μg)	486.0 (312.2)	438.9 (204.0)	<0.223
Vitamin D (μg)	4.3 (2.8)	4.1 (2.8)	<0.744
Vitamin E (mg)	5.4 (1.6)	5.8 (1.6)	<0.120

ADHD: attention deficit hyperactivity disorder; SFA: saturated fatty acid; MUFA: monounsaturated fatty acids; PUFA; polyunsaturated fatty acids.

administration and reach maximum plasma concentrations 1 hour after administration; the therapeutic effects have duration of approximately 4–5 hours. However, each OROS-MPH tablet has 22% MPH in its cover which releases immediately, and the remaining 78% releases slowly through an osmotic-controlled release mechanism. In this way, a high plasma concentration is rapidly obtained (in 1–2 hours), followed by an ascending prolonged release with a maximum plasma concentration in 6–7 hours and a duration of action of 10–12 hours. The MR-MPH tablets contain microspheres, 50% of which are covered by an antacid substance that prevents dilution in the stomach and therefore present

extended release and/or action. The remaining 50% are non-covered microspheres and have immediate absorption and/or release. Therefore, the pharmacokinetic profile means a more intense immediate action and a lesser extended action with respect to OROS-MPH, approximately 7-8 hours being its duration of action.[10]

However, it should be considered that searching and finding a sustained therapeutic effect during the day with the different MPH-ER preparations might also lead to an increase and/or lengthening of the secondary effects such as appetite loss in those meals whose period of time coincide with ascending plasma concentrations of MPH. In normal conditions, the administration of MPH-ER usually coincides with breakfast between 8:00 and 9:00 a.m. in order to adjust its predictable therapeutic effect to the academic and/or social schedule of the patient. However, this circumstance inevitably entails the coincidence of ascending or maximum concentration and the time for mid-morning snack and lunch, and so this chronological overlap could interfere in the nutritional optimization of these patients.

The results obtained in this survey highlight how treatment with MPH-ER modifies substantially the per cent distribution of calorie intake of the different meals, most likely in relation to the pharmacokinetic curves. In fact, those patients diagnosed with ADHD under continued therapy with OROS-MPH or MR-MPH manifest a significant reduction of calorie intake in mid-morning snack as well as in lunch, which even extended until afternoon snack. This fact can be explained by the overlap of the time of the different meals and the maximum plasma concentrations of the components of immediate and extended release of these formulations, respectively. Subsequently, and after the therapeutic effect is supposed to have ended, a rebound effect was manifested as a relatively exaggerated increase in appetite at the time of supper, which, consequently, would explain the higher calorie intake of these patients compared with the control group. However, this 'bulimia-like' effect was not intense enough to make calorie and nutrients intake (macronutrients, minerals and vitamins) similar to the healthy population of the same age. This means, patients under treatment with OROS-MPH or MR-MPH eat breakfast as children of the same age do, but simultaneously with the beginning of the pretended therapeutic effects, a loss of appetite manifests especially during breakfast and lunch time and, to a lesser extent, mid-afternoon snack. A rebound effect appears in supper time, but this is not enough to compensate for the lower calorie and nutrients intake consequence of the lower consumption of food throughout the day. This eventuality can be counterproductive in these patients since a continuous lower calorie and nutrients intake can affect the cognitive functions and, therefore, worsen school abilities.[24–26]

Even though daily mean intake of macronutrients (proteins, carbohydrates, fat, total fibre), some minerals (calcium, iron, magnesium, zinc, selenium, phosphate) and vitamins (thiamine, niacin, vitamin B6, folate) were significantly higher in the control group than in the ADHD group, the recommended dietary intake for minerals and vitamins were virtually covered in both groups. This fact explains that these patients do not develop specific nutrient deficiencies every so often despite a lower nutrition status.[12,27–30]

This study has methodological limitations. A group of ADHD but without MPH treatment has not been included because of ethical implications. Therefore, the results of caloric and nutrient intake and nutritional status of the patients have been compared with a group of healthy children of the same age. Setting up a control group of patients with mild to moderate ADHD who were receiving no pharmacological treatment proved to be impracticable. The total number of patients in these circumstances who were followed was rather limited. Many of them finally required methylphenidate due to progressive psychosocial and/or educational deterioration, and the rest faced diagnostic uncertainty.

Conclusion

In conclusion, daily calorie and nutrient intake in patients under continuous treatment with MPH-ER are, in general, slightly lower than healthy people of the same age. This would explain why the nutritional parameters registered in these patients were also significantly lower. Therefore, the need to dispense programmes of nutritional education programmes to the patients and/or their families simultaneously with multimodal treatment should be considered. In addition, the application of nutrition strategies, such as increasing calorie intake by offering 'favourite' foods and/or adding energy supplements, especially in mid-morning snack and lunch, can avoid the nutritional consequences of the treatment with MPH-ER.

Declarations

Competing interests: None declared

Funding: None declared

Ethical approval: This study has been approved by the Ethics Committee of the Navarra Hospital Complex, which had no objections to the study.

Guarantor: TDT

Contributorship: TDT participated in study design and data analysis, and wrote the first draft of the manuscript. FGV participated in data collection and analysis. Both the authors participated in manuscript preparation and approved its final version.

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