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ORIGINAL ARTICLE

Lack of correlation between asprosin serum levels and hyperphagic behavior in subjects with prader-Willi Syndrome

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Abstract

Purpose Individuals with Prader-Willi syndrome (PWS) exhibit hyperphagic behavior, the severity of which varies throughout life. The mechanisms underlying this behavior are still unknown. Asprosin is a new discovered adipokine involved in the regulation of food intake, glucose homeostasis and energy balance. In this study we assessed asprosin serum levels in a cohort of children, adolescents and adults with PWS with the aim to correlate them with hyperphagic behavior, body mass index (BMI) and metabolic parameters, and to evaluate age-related changes.

Methods This cross-sectional study included 87 children and adolescents and 31 adults with PWS. Auxological data, fasting levels of glucose, insulin, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and asprosin were collected, and the homeostasis model assessment for insulin resistance (HOMA-IR) was determined. The 11-item Italian version of the Hyperphagia Questionnaire (HQ) was administered to the parents/caregivers of the patients to assess hyperphagia.

Results Patients were analysed according to age (children < 10 years, adolescents between 10 and 17.9 years, adults ≥ 18 years) or BMI categories [normal weight (NW), overweight (OW), and obesity (OB)]. No significant correlations were found between asprosin levels and cardiometabolic risk factors in the whole cohort. Higher values of asprosin were found in adults compared with adolescents, as well as in the OB group compared to the NW group ($p = 0.014$). Hyperphagia total score and hyperphagic subdimensions were significantly lower in children compared to adults ($p < 0.05$). Similarly, hyperphagia total score and hyperphagic subdimensions were significantly lower in the NW group compared to the OB group. Asprosin levels were significantly higher in patients with deletion *versus* patients with uniparental disomy ($p = 0.037$). By logistic regression analysis, HQ total score and hyperphagic subdimensions were significantly associated with BMI-SDS independently of age, sex, and asprosin levels.

Conclusion In conclusion, our data demonstrated higher asprosin levels in PWS individuals with OB compared to NW, while differences by age and sex were inconsistent. The lower levels of hyperphagia, BMI-SDS, and metabolic variables in children with PWS compared to adults underline that prevention of obesity should start very early in life and should be maintained over time.

Keywords Asprosin · Prader-Willi Syndrome · Obesity · Hyperphagia

Introduction

Prader-Willi Syndrome (PWS) is a complex genetic disease caused by the lack of paternally-expressed, imprinted genes on chromosome 15q11–13, with an estimated incidence ranging from 1/10,000 to 1/30,000 [1]. Three major mechanisms are responsible for PWS: (i) microdeletion (DEL) of the paternally inherited chromosome (60–70% of cases); (ii) maternal uniparental disomy (mUPD) (30–40% of cases); (iii) imprinting center defect (IC) or translocation (3–5% of cases) [2, 3].

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Hypotonia, poor feeding, and stunted growth are dominant features during the first years of life [4].

Subjects with PWS exhibit hyperphagic behavior, which consists of a strong desire for food, and they develop progressively severe obesity along with various related cardiovascular and metabolic complications [5, 6]. The severity of hyperphagia varies across the lifespan, with seven phases that characterize the clinical course of PWS [7]. The hyperphagic behavior generally begins in early childhood in PWS individuals, and worsens through adolescence and adulthood, when appetite is impossible to satisfy for some individuals with PWS. However, the age of transition from one phase to the following one as well as the severity of hyperphagia, can vary among subjects. The mechanisms underlying hyperphagia in PWS subjects are not fully understood. Data supporting the role of specific genes involved in neural circuits controlling food intake are inconclusive [8].

The condition of overweight/obesity would appear associated with a more severe hyperphagic behavior, regardless of the age group [3], although individual variability has been observed [9].

In addition, PWS subjects have hypoinsulinemia, and elevated fasting ghrelin levels compared to non-syndromic obese subjects, which may contribute to hyperphagia and food-related thoughts and cravings [10, 11].

Recently, a new cytokine called asprosin that is involved in the regulation of appetite, glucose metabolism, insulin resistance (IR) and energy expenditure, has been discovered [12]. It is encoded by Fibrillin 1 (*FBN1*) gene located on chromosome 15q21.1, and it is released by white adipose tissue and by other tissues such as skin, salivary glands, and pancreatic ß-cells [12]. In the liver, asprosin induces hepatic glucose release by binding the olfactory G protein–coupled receptor (OR4M1) [12].

The central role of asprosin in appetite regulation has been demonstrated in a transgenic mouse model with loss-of-function mutation in one of the alleles of *FBN1* which showed hypophagia, leanness, and insulin sensitivity [13]. Asprosin serum levels increase during fasting and rapidly decrease after food intake; this cytokine can cross the blood-brain barrier and directly activate orexigenic agouti-related peptide-releasing (AgRP) neurons via cAMP-dependent pathway [14]. This signalling results in the inhibition of downstream anorexigenic proopiomelanocortin (POMC) neurons in a GABA-dependent manner, causing appetite stimulation and fat accumulation. Furthermore, this cytokine acts through a pathway independent of the leptin, an anorexigenic hormone, as demonstrated in $Lepr^{db/db}$ obese mice [13]. In addition to the direct effect on AgRP and POMC neurons, asprosin-mediated modulation of food intake appears to involve other cells and neuronal circuits such as olfaction, motor control of ingestion, locomotion, etc [15]. However, results regarding the actual mechanism of action of aprosin are very conflicting.

Elevated levels of asprosin have been found in subjects with obesity [16], type 2 diabetes mellitus (T2DM) [17], polycystic ovary syndrome (PCOS) [18], and non-alcoholic fatty liver disease (NAFLD) [19, 20]. Furthermore, recent studies demonstrated an important role of this adipokine in cardiovascular diseases [21]. Only one previous study has evaluated the association between serum asprosin levels and metabolic parameters in children with PWS, and no significant correlations were found [22].

In this study we evaluated serum levels of asprosin and correlated them with hyperphagic behavior, body mass index (BMI), and metabolic parameters in a cohort of children, adolescents, and adults with PWS. Our aim was to evaluate age-related changes in asprosin levels to gain insight into the variations in hyperphagic behavior that characterizes this syndrome from childhood to adulthood.

Methods

Study population

One hundred and eighteen subjects, 43 children (18 males, mean age 6.8 ± 1.9 years, range 2.9–9.9 years, 44 adolescents (24 males, mean age 14.1 ± 2.2 years, range 10.3–17.9) and 31 adults (13 males, mean age 34.3 ± 10.2 years, range 19.8–52.8 years) were enrolled in this multicentric and cross-sectional study. Genetic investigation was performed in all PWS patients: 62 of them had DEL15, 49 subjects had mUPD, and 7 subjects showed imprinting defects.

Written informed consent was obtained from all the legal guardians, and from the patients when applicable, prior to inclusion. All procedures were approved by local institutional review boards.

Anthropometric data collection

All patients underwent anthropometric measurements (height in cm, weight in kg). BMI was defined as weight in kilograms divided by the square of height in meters, and for the pediatric age transformed into BMI standard deviation score (BMI-SDS) according to the Italian growth reference standards [23].

Individuals were stratified according to BMI categories (normal-weight, overweight, and obesity). Definition of normal weight, overweight, and obesity was based on BMI percentiles in individuals < 18 years; absolute values of BMI were employed in adults (> 18 years) to define normal-weight (NW: BMI 18–24.9), overweight (OW: BMI 25–29.9), obesity (OB: ≥30). Normal weight was defined as

BMI-SDS between −1 and +1, OW as BMI-SDS between 1.01 and 1.99, OB as BMI-SDS ≥ 2.

Hyperphagia questionnaire

The 11-item Italian version of the Hyperphagia Questionnaire (HQ) [24] was administered to the parents/caregivers of the patients [25]. Questionnaire was filled in a written form, but an assistant researcher was present during administration to parents/caregivers/patients, if required.

Items refer to parental reports of food-related preoccupations (Hyperphagic Drive, 5 items); atypical food-related behaviors (Hyperphagic Behaviors, 4 items), and severity of these concerns (Hyperphagic Severity, 2 items). The response format was on a 5-point scale (score 1 = 1 not a problem to 5 = severe and/or frequent problem). A total Hyperphagic score was obtained by summing up the scores obtained in the three subdimensions.

Biochemical measurements

Blood samples were drawn under fasting conditions, centrifuged, and stored at −80 °C until required. Blood glucose, insulin, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured in the central laboratory of each participating centre on a venous sample taken in the morning, after at least 10 h of fasting.

Insulin resistance was evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR), calculated by the formula fasting glucose (mg/dL) X insulin (U/mL)/405 [26].

Fasting asprosin serum levels were measured, after overnight fasting, using an enzyme-linked immunosorbent assay (ELISA) kit accordingly to the manufacturer's instructions (MyBioSource, USA; catalog number: MBS2707373). The intra- and inter-assay coefficients of variation (CV) of asprosin were < 10% and < 12%, respectively, as indicated by the vendor claims.

Asprosin concentrations were expressed as ng/mL. The detection threshold was 1 ng/mL, and no significant cross-reactivity between human asprosin and analogues was reported.

Statistical analyses

Data were expressed as means and standard deviations or medians and interquartile ranges. All variables had skewed distribution apart BMI-SDS. Between-groups differences were evaluated by using the Mann Whitney test. Chi-square or Fisher's exact test, as appropriate, was used to compare proportions. The Spearman's rho test was used to assess relationships between asprosin and cardiometabolic risk factors. Quartiles of HF total score and its subdimensions were calculated; a value ≥ top quartile was used to categorize high HF total score or HF subdimensions. Adjusted binary logistic regression analyses were used and OR with corresponding 95% Confidence Intervals were calculated to evaluate the association of high HF total score or HF subdimensions and the variables of interest (age, sex, BMI-SDS and asprosin levels). A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using the IBM SPSS Statistics, Version 28.0 (Armonk, NY: IBM Corp.).

Results

In Table 1 are reported the characteristics of the study population according to age classes.

BMI and BMI-SDS significantly increased from children to adults. Regarding metabolic parameters, children had lower triglycerides and higher HDL-cholesterol levels than adolescents and adults, while they had lower glucose levels only compared to adults. Adolescents had higher insulin and HOMA-IR than children and adults. No differences were found in the asprosin levels between children and adults, while slightly higher values of asprosin were observed in adults compared to adolescents (Table 1). No sex-related differences were found in the asprosin levels (expressed as median and interquartile range) within the three groups (children: males 1.62 ng/ml (1.34–1.80) versus females 1.49 ng/ml (1.28–1.80), $p = 0.571$; adolescents: males 1.47 ng/ml (1.16–1.69) versus females 1.53 ng/ml (1.29–1.71), $p = 0.389$; adults: males 1.85 ng/ml (1.32–2.01) versus females 1.68 ng/ml (1.37–1.98), $p = 0.900$).

No significant correlations were found between asprosin levels and cardiometabolic risk factors (glucose: r 0.054, $p = 0.568$; insulin: r −0.112, $p = 0.269$; HOMA-IR: r −0.118, $p = 0.245$; total cholesterol: r 0.121, $p = 0.192$; HDL-cholesterol: r 0.024, $p = 0.798$; triglycerides: r 0.166, $p = 0.073$) in the whole sample.

Regarding hyperphagia, HQ total score and hyperphagic subdimensions were significantly lower in children compared to adults ($p < 0.05$). Compared to adolescents, children had lower scores only in the hyperphagic behavior and hyperphagic severity scores (Table 1).

In Table 2 are reported the characteristics of the study population according to BMI categories. As expected, individuals with OB showed a worse metabolic profile (glucose, HOMA-IR, triglycerides) than NW or OW patients. They also had higher levels of insulin and lower levels of HDL-Cholesterol than the NW and the OW counterparts, respectively.

Table 1 Characteristics of the study population according to age

	Age classes			*P*		
	Children $N=43$	Adolescents $N=44$	Adults $N=31$	Children vs. Adolescents	Children vs. Adults	Adolescents vs. Adults
Males, n (%)	18 (41.9)	24 (54.5)	13 (41.9)			
Age, years	7.2 (4.8–8.5)	13.9 (12.2–15.9)	31.0 (24.3–44.3)	**<0.001**	**<0.001**	**<0.001**
BMI, kg/m^2	19.8 (16.1–22.3)	27.4 (22.4–33.0)	35.3 (30.6–42.0)	**<0.001**	**<0.001**	**<0.001**
BMI-SDS	1.29 (−0.13–1.63)	1.6 (0.70–2.54)	2.8 (2.1–3.3)	**0.033**	**<0.001**	**0.001**
Glucose, mg/dL	78 (70–84)	80 (76–89)	89 (80–97)	0.066	**<0.001**	**0.012**
Insulin, U/mL	7.9 (3.6–12.9)	14.8 (9.6–19.2)	9.6 (6.9–11.8)	**<0.001**	0.238	**0.002**
HOMA-IR	1.4 (0.6–3.0)	3.2 (1.7–4.2)	2.0 (1.5–3.1)	**<0.001**	0.059	**0.037**
Total Cholesterol, mg/dL	171 (157–184)	162 (141–189)	190 (153–209)	0.206	0.244	0.078
HDL-Cholesterol, mg/dL	57 (49–66)	51 (43.59)	47 (42–57)	**0.012**	**0.006**	0.566
Triglycerides, mg/dL	56 (51–78)	75 (59–122)	94 (70–125)	**0.001**	**<0.001**	0.264
Asprosin, ng/ml	1.52 (1.29–1.80)	1.48 (1.24–1.69)	1.76 (1.35–2.0)	0.447	0.08	**0.017**
HQ total score	19 (16–24)	24 (15–35.2)	25 (17–32)	0.063	**0.006**	0.714
Hyperphagic Drive	1.6 (1.0–2.2)	2.0 (1.2–2.8)	2.0 (1.6–2.8)	0.080	**0.028**	0.634
HyperphagicBehavior	2.0 (1.75–2.5)	2.4 (1.75–3.5)	2.5 (1.75–3.25)	**0.034**	**0.036**	0.978
Hyperphagic Severity	1.5 (1.0–2.5)	2.2 (1.1–3.0)	2.0 (1.5–3.5)	**0.032**	**0.021**	0.671

Table 2 Comparison of demographic and anthropometric variables, asprosin levels, Hyperphagia Questionnaire and hyperphagic subdimensions by BMI categories

	BMI categories			*P*		
	Normal-weight $N=28$	Overweight $N=29$	Obesity $N=61$	NW vs. OW	NW vs. OB	OWvs. OB
Males, n (%)	10 (35.7)	15 (51.7)	30 (49.2)			
Age, years	9.6 (6.2–14.0)	9.9 (7.1–14.5)	17.1 (10.3–31.0)	0.737	**<0.001**	**<0.001**
BMI, kg/m^2	17.0 (15.0–19.9)	22.4 (20.1–25.3)	34.1 (28.7–39.2)	**<0.001**	**<0.001**	**<0.001**
BMI-SDS	−0.2 (−1.1-0.1)	1.3 (0.9–1.5)	2.6 (2.1–3.2)	**<0.001**	**<0.001**	**<0.001**
Glucose, mg/dL	76 (71–82)	80 (74–88)	84 (78–93)	0.093	**<0.001**	**0.043**
Insulin, U/mL	6.5 (4.8–9.8)	9.6 (7.0–14.9)	12.3 (8.5–18.2)	0.069	**<0.001**	0.115
HOMA-IR	1.3 (0.7–1.9)	1.8 (1.1–3.1)	3.0 (1.6–3.9)	0.084	**<0.001**	**0.032**
Total Cholesterol, mg/dL	167 (142–187)	163 (152–198)	173 (153–204)	0.513	0.253	0.546
HDL-Cholesterol, mg/dL	56 (47–62)	59 (47–66)	48 (42–57)	0.329	0.107	**0.018**
Triglycerides, mg/dL	62 (55–79)	64 (51–80)	92 (66–127)	0.539	**0.001**	**0.001**
Asprosin, ng/ml	1.4 (1.2–1.6)	1.6 (1.3–1.8)	1.7 (1.4–1.9)	0.052	**<0.001**	0.258
HQ total score	18.0 (14.3–20.8)	22.0 (15.0–28.0)	25.0 (18.5–34.5)	**0.048**	**<0.001**	0.072
Hyperphagic Drive	1.2 (1.0–1.8)	1.8 (1.4–2.6)	2.2 (1.4–2.8)	**0.005**	**<0.001**	0.195
Hyperphagic Behaviour	1.9 (1.5–2.3)	2.3 (1.6–3.0)	2.5 (1.9–3.6)	0.117	**0.002**	0.100
Hyperphagic Severity	1.5 (1–2.5)	1.5 (1–2.5)	2.5 (1.5–3.5)	0.961	**0.034**	**0.026**

No differences were found in the asprosin levels between NW vs. OW patients. On the contrary, significantly higher asprosin levels were found in the OB group compared to the NW group ($p=0.014$). Similarly, HQ total score and hyperphagic subdimensions were significantly higher in the OB group compared to the NW group (p between 0.034 and <0.001), while only HQ total score and Hyperphagic Drive scores significantly differed between OW and NW patients ($p=0.048$ and 0.005, respectively).

Eighty-two individuals (42 children, 32 adolescents, and 3 adults) were on growth hormone treatment when the study was performed: no difference was found in the levels of asprosin between patients who were on growth hormone treatment [1.53 ng/ml (1.29–1.81)] compared to those who were not [1.58 ng/ml (1.34–1.89), $p=0.540$].

Eight individuals (2 adolescents and 6 adults) were on metformin when the study was performed. Slightly lower asprosin levels were found in patients who were on metformin treatment [1.27 (1.11–1.54)] compared to those patients who were not [(1.57 (135 − 1.89), $p=0.070$)].

Lastly, comparisons by genetic defect showed that asprosin levels were significantly higher in patients with DEL15 (1.660 ng/ml, interquartile range 1.387–1.947) vs. patients with mUPD (1.530ng/ml, interquartile range 1.185–1.775, $p=0.037$), while no difference was found concerning age,

BMI-SDS, HQ and hyperphagic subdimensions between these two groups.

By logistic regression analysis, HQ total score and hyperphagic subdimensions were significantly associated with BMI-SDS independently of age, sex and asprosin levels (Table 3).

Discussion

In this study we evaluated asprosin serum levels in a cohort of children, adolescents and adults with PWS with the aim to establish a possible association with hyperphagic behavior associated with this syndrome. As secondary aim, we correlated asprosin levels with anthropometric and metabolic data. The strength of our study is the size of the sample and the wide range of ages considered.

Our results demonstrated that asprosin levels did not differ between children and adolescents with PWS, while higher asprosin levels were observed in adults compared to adolescents. This finding is novel, since to our knowledge there are no studies about age-related changes of asprosin from childhood to adulthood in PWS subjects. Furthermore, we found that asprosin levels were higher in PWS individuals with OB compared to NW. Again, as far as we know, only one study that analysed the levels of asprosin in PWS children according to weight status, found no difference probably due to the limited sample size [22].

Previous studies evaluated serum asprosin levels in pediatric non-syndromic obesity reporting conflicting data [16, 27–29]. A recent systematic review and meta-analysis concluded that there is no statistical difference in circulating asprosin levels in children with or without obesity, while a positive association between asprosin levels and total cholesterol was observed in childhood obesity [30].

Table 3 Odds ratio (95% confidence intervals) for high Hyperphagia Questionnaire total score, high Hyperphagic Drive, Hyperphagic Behavior and Hyperphagic Severity

	HQ Total score	Hyperphagic Drive	Hyperphagic Behavior	Hyperphagic Severity
Sex (reference male)	0.707 (0.292–1.714)	1.041 (0.444–2.439)	0.718 (0.301–1.709)	0.978 (0.418–2.291)
Age, years	0.992 (0.955–1.032)	0.998 (0.961–1.036)	0.978 (0.941–1.018)	1.018 (0.980–1.057)
BMI-SDS	1.949 (1.251–3.036)***	1.887 (1.245–2.861)***	2.013 (1.301–3.115)**	1.550 (1.054–2.278)*
Asprosin, ng/ml	1.046 (0.495–2.213)	0.949 (0.449–2.004)	1.129 (0.568–2.246)	0.483 (0.174–1.342)

***$P = 0.003$; ** $p = 0.002$; * $p = 0.026$

In adults, Wang et al., reported significantly higher concentrations of fasting asprosin in obese subjects compared to controls [31]. Consistent with this data some recent studied have found in patients with T2DM a positive correlation between asprosin and BMI [32–34]; in particular Hu et al. found a positive correlation between asprosin and both waist and hip circumference suggesting a possible role of asprosin in fat distribution [32].

Regarding eating behavior, in agreement with a previous study performed by our group [24], hyperphagic scores were higher in PWS adults than children, confirming a worsening of hyperphagia at the transition to adulthood. This is in agreement with phase 3 of the nutritional phases described in PWS subjects [7].

In parallel with the increase in hyperphagia and BMI-SDS scores with age, we also found higher HQ total scores and hyperphagia subdimensions in OB subjects than NW. Our results are in agreement with the data of Matesevac et al., who explored hyperphagia in a large cohort of children and young adults with PWS using the Hyperphagia Questionnaire for Clinical Trials, finding higher scores in individuals with increased BMI [35].

Logistic regression analysis was not able to demonstrate an independent association between high HQ total score and hyperphagic subdimensions and asprosin, but only a significant association of these variables with BMI-SDS, independent of other confounders such as age and sex.

In our cohort, the metabolic profile slightly worsened in PWS with aging and weight status, although it generally remained within the normal values. In fact, only three individuals showed impaired fasting glucose and two individuals had fasting glucose in the diabetic range. Insulin and insulin resistance were higher in adolescents, reflecting the hormonal induced pubertal changes, occurring spontaneously or induced by therapy. In line with a previous study performed in PWS children [20], we found no correlation among fasting asprosin serum levels, glucose levels, insulin levels and HOMA-IR.

Therefore, our data cannot support the role of asprosin in the regulation of glucose metabolism in PWS subjects, contrarily to the accumulating evidence in other metabolic diseases, such as T2DM [36].

According to genotype we found significant higher asprosin serum levels in subjects with deletion than in those with mUPD. This is an interesting difference, indeed correlation between phenotype and genotype in PWS subjects has always been debated [37]. In a previous study Faienza et al. found higher serum levels of irisin, a myokine able of mimicking the effects of physical exercise, in DEL15 subjects than UPD ones [38]. Recently it has been found that adipocytes are larger in PWS than obese controls, with anthropometric and metabolic variations observed in different genotypic subclasses: patients

with a deletion genotype tend to have higher BMI and glycosylated hemoglobin levels, despite similar values of glycemia, insulinemia, HOMA-IR, body composition, metabolic profile, adipocyte size, resting energy expenditure, and hyperphagia score compared to those with UPD [39].

In this context, a possible association between UPD genotype and a more adverse metabolic and cardiovascular profiles following GH therapy in paediatric age has been suggested [39–41].

The main limitation of our study relies on the cross sectional design that does not allow to draw any causal inference. In addition, most children and adolescents received growth hormone treatment, while adults with PWS were treated predominantly for several metabolic complications, such as diabetes. Therefore, it is difficult to dissect the interactions between concomitant therapies on asprosin levels. In particular, the trend found towards lower concentrations of asprosin in PWS patients treated with metformin, an oral antidiabetic that decreases hepatic glucose output, which aligns with a previous research [42] needs to be further detailed by studies specifically designed for this purpose.

In conclusion, studying the age-related variations of hyperphagia, BMI and metabolic parameters in individuals with PWS is useful for understanding the syndrome and managing the related consequences on morbidity, mortality and reduced life expectancy.

Our findings provide the first evidence that asprosin concentrations are higher in PWS individuals with OB compared to NW, with negligible influence of age and sex.

The lower levels of hyperphagia, BMI-SDS and metabolic variables in children with PWS compared to adults confirm the need to implement prevention strategies for obesity since the very early ages of life. We cannot support the role of asprosin in the progressively disrupted pathway that sustains hyperphagia in PWS. Much remains to be learned about this hormone and more research is needed to further explain the age-related associations between asprosin, food intake, metabolism and obesity in PWS.

BMI-SDS: Body Mass Index-Standard Deviation Score; HQ: Hyperphagia Questionnaire.

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Data availability The data presented in this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare no conflict of interest.

Informed Consent Written consent was obtained from all participants and their parents, after having informed them of the purpose of the study.

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