C-reactive Protein, Obstructive Sleep Apnea, and Cognitive Dysfunction in School-aged Children

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***Rationale*: Obstructive sleep apnea (OSA) in children is associated with substantial neurobehavioral and cognitive dysfunction. However, not all children with OSA exhibit altered cognitive performance.**

***Objectives*: To assess the magnitude of the systemic inflammatory response, as measured by high-sensitivity C-reactive protein (hsCRP) serum levels which may identify children with OSA at higher susceptibility for cognitive morbidity.**

***Methods*: Habitually snoring children and nonsnoring children (total, 278; age range, 5–7 yr) were recruited from the community, and underwent overnight polysomnography and neurocognitive testing and a blood draw the next morning. Snoring children were divided into OSA and no-OSA groups, and children with OSA were further subdivided into those with two or more abnormal cognitive subtests and into those with normal cognitive scores. Serum levels of hsCRP were also measured.**

***Measurements and Main Results*: Among snoring children without OSA, mean hsCRP was 0.19 ± 0.07 mg/dl compared with 0.36 ± 0.11 mg/dl in those with OSA ($p < 0.01$). Furthermore, hsCRP was 0.48 ± 0.12 mg/dl in children with OSA and cognitive deficits, compared with 0.21 ± 0.08 mg/dl in children with OSA and normal cognitive scores ($p < 0.002$).**

***Conclusions*: hsCRP levels are higher in children with OSA, and particularly in those who develop neurocognitive deficits, suggesting that the magnitude of the inflammatory responses elicited by OSA is a major determinant of increased risk for neurocognitive dysfunction.**

Keywords: sleep-disordered breathing; systemic inflammation; hypoxia; sleep fragmentation

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obstructive sleep apnea in children induces cognitive deficits, but not all children with this condition exhibit altered cognitive performance, suggesting individual, unknown susceptibility determinants may play a role.

What This Study Adds to the Field

The level of systemic inflammation as evidenced by morning C-reactive protein levels in relation to pediatric obstructive sleep apnea is associated with the cognitive morbidity that accompanies this condition.

Pediatric sleep-disordered breathing (SDB), which encompasses the spectrum of habitual snoring, upper airway resistance syndrome, obstructive alveolar hypoventilation, and frank obstructive sleep apnea (OSA), is a frequent condition affecting up to 3% of all prepubertal children (1). The mechanisms underlying SDB in children are multiple, and involve anatomic, craniofacial, and neuromuscular components (2). The major implications of SDB reside in its morbid consequences, which primarily implicate the occurrence of neurobehavioral deficits and cardiovascular sequelae (3, 4). However, it has become evident that the emergence of cognitive deficits cannot be accounted for solely by the severity of OSA, because not all children with OSA present neurobehavioral deficits (5). Therefore, other factors, such as individual genetic susceptibility and environmental lifestyle and nutritional factors, may also play major contributing roles (5, 6).

High-sensitivity C-reactive protein (hsCRP), an important circulating marker of inflammation, is currently considered an extremely robust and reliable marker for cardiovascular morbidity (7–9). Serum levels of this protein, which is synthesized in the liver in response to interleukin-6 signaling pathways, are increased in children with SDB, and correlate with disease severity measures, such as hypoxemia and sleep fragmentation, even after adjusting for the degree of obesity (10). Similar findings have been reported by Larkin and coworkers (11), but not by others (12). We reported that circulating levels of CRP in children with SDB will decrease in the vast majority of patients after treatment (13), thereby confirming the causative link between systemic inflammation and OSA.

In this study, we hypothesized that elevated hsCRP would more likely occur in children with SDB and neurocognitive morbidity compared with age-, sex-, and body mass index (BMI)–matched children with SDB of similar severity and normal neurocognitive function.

METHODS

Survey Questionnaire

The study was approved by the University of Louisville (Louisville, KY) Human Research Committee and the Jefferson County Public Schools (Louisville, KY) Board of Education. A previously validated questionnaire was used (14, 15) for the initial approach to identify potential participants, and a scannable version was prepared with Teleform software (Cardiff Software, San Marcos, CA). Parents of all children 5–7 years of age enrolling into the Jefferson County Public Schools system were invited to complete the detailed questionnaire on their child's sleeping habits. In addition to demographic information and significant medical history of the child, questions were included on whether the child had difficulty initiating sleep, restless sleep, enuresis,

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apnea, cyanosis during sleep, and/or snoring and, if so, the severity of the snoring. The responses were graded as "never," "rarely" (once per week), "occasionally" (twice per week), "frequently" (three or four times per week), and "almost always" (more than four times per week). Returned questionnaires were scanned into a computerized database, using Microsoft Access, and both nonsnoring children (responses of "never" or "rarely" on snoring frequency and "not applicable" on loudness of snore in the questionnaire) as well as habitually snoring children (responses of "almost always" [more than four nights per week] or "always" on snoring frequency and "medium loud" to "loud" on loudness of snoring) were randomly selected and invited to the Sleep Medicine Research Center at Kosair Children's Hospital (Louisville, KY) for an overnight polysomnographic assessment. The next morning they underwent a fasting blood draw followed by a battery of neurobehavioral tests. Children were excluded if they had any chronic medical conditions, genetic syndromes, craniofacial syndromes, or if they were obese.

Polysomnographic Assessment

Children were studied for up to 12 hours in a quiet, darkened room with an ambient temperature of 24°C in the company of one of their parents. No drugs were used to induce sleep. The following parameters were measured during the overnight sleep recordings: chest and abdominal wall movement by respiratory impedance or inductance plethysmography; heart rate by ECG; and air flow, which was triply monitored with a sidestream end-tidal capnograph also providing breath-by-breath assessment of end-tidal carbon dioxide levels (BCI SC-300; Pryon, Menomonee Falls, WI; now Welch Allyn OEM Technologies, Beaverton, OR), a nasal pressure cannula, and an oronasal thermistor. Arterial oxygen saturation was assessed by pulse oximetry (Sp_{O_2}) (Nellcor N-100; Nellcor Inc., Pleasanton, CA), with simultaneous recording of the pulse waveform. The bilateral electrooculogram, eight channels of electroencephalogram, chin and anterior tibial electromyograms, and analog output from a body position sensor (Braebon Medical Corporation, Ogdensburg, NY) were also monitored. All measures were digitized with a commercially available polysomnography system (Rembrandt; MedCare Diagnostics/Embla Systems, Amsterdam, The Netherlands). Tracheal sound was monitored with a microphone sensor (Sleepmate Technologies, Midlothian, VA) and a digital time-synchronized video recording was performed.

Sleep architecture was assessed by standard techniques (16). The proportion of time spent in each sleep stage was expressed as a percentage of total sleep time (%TST). Central, obstructive, and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths (17, 18). Hypopneas were defined as a decrease in oronasal flow of at least 50% with a corresponding decrease in Sp_{O_2} of at least 4% and/or arousal (17). The obstructive apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST. The obstructive apnea index (AI) was defined as the number of apneas per hour of TST. The diagnostic criteria for OSA included an obstructive AI greater than 1/hour TST, and/or an obstructive AHI greater than 2/hour TST with a nadir oxygen saturation value less than 92%. Control children were defined as nonsnoring children with an obstructive AHI not exceeding 1/hour TST.

Height and weight were obtained for each child. BMI was calculated and also expressed as relative BMI, using the following formula: (BMI/BMI of the 50th percentile for age and sex) × 100, based on standardized percentile curves (19). Obesity was defined as BMI greater than the 95th percentile for sex and age, and all children fulfilling obesity criteria were excluded from this study.

Neurocognitive Assessments

The cognitive tests administered the morning after polysomnographic assessment consisted of the Differential Ability Scales (DAS) (20) and the NeuroPsychological Assessment Battery (NEPSY [21]). The DAS (20) is a battery of cognitive tests designed to measure reasoning and conceptual ability in children ages 2 through 17 years. This measure was designed to provide specific information about an individual's strengths and weaknesses across a wide range of intellectual activities. Children were administered either the preschool form or the school-age form of the DAS. The preschool form is divided into a Verbal Cluster (including two subtests) and a Nonverbal Cluster (including two spatial subtests and one nonverbal reasoning subtest) and yields a global composite score that is commensurate with an intelligence quotient (IQ). The school-age form yields a Spatial Cluster score in addition to the Verbal, Nonverbal, and global composite scores. The test was designed so that the global composite scores could be examined across forms and throughout the age range. Individual DAS subtests are designed to measure separate and distinct areas of cognitive functioning, and thus have high specificity. The ability score for a subtest is expressed as a T score with a mean of 50 and a standard deviation of 10. The sum of the core subtest T scores is converted to a total standard score, the General Conceptual Ability (GCA) score, with a mean of 100 and a standard deviation of 15. The NEPSY (21) is a relatively new neurobehavioral test battery, and was designed to assess neurobiological development in five functional domains. These include attention/executive functions, language, sensorimotor functions, visuospatial processing, and memory and learning with a mean score of 100 and SD of 15. All these subtests have good to excellent reliability (r = 0.77–0.91). As is customary in clinical practice, subjects were considered as being affected if they scored 1 standard deviation below the mean for at least two subtests on either DAS or NEPSY batteries.

Plasma hsCRP Assay

Plasma hsCRP was measured within 2 to 3 hours of collection, using the Flex reagent cartridge (Dade Behring, Newark, DE), which is based on a particle-enhanced turbidimetric immunoassay technique. This method has a detection level of 0.05 mg/dl and exhibits linear behavior up to 255 mg/dl, with intraassay and interassay coefficients of variability of 9 and 18%, respectively.

Data Analysis

Data are presented as means ± SE unless otherwise indicated. For questionnaire-derived responses, comparisons of the distribution of demographic and risk factors according to group membership were made with independent t tests (continuous variables) with p values adjusted for unequal variances when appropriate (Levene's test for equality of variances), or chi square (χ^2) analyses with Fisher's exact test (dichotomous outcomes). Analyses of variance and independent t tests were used for comparisons of polysomnographic, hsCRP, and neurobehavioral variables, and were followed by post hoc tests as appropriate. For comparisons across groups with and without decreases in cognitive function, an estimate of effect size was conducted using Cohen's d values (22). All p values reported are two tailed, with statistical significance set at $p < 0.05$.

RESULTS

A total of 278 children were randomly recruited from among 8,856 questionnaire respondents and completed all phases of the experimental protocol. There were 73 children who did not snore and who also exhibited normal polysomnographic studies. All control children had normal cognitive scores and their mean hsCRP levels were 0.18 ± 0.05 mg/dl. Of the 205 habitually snoring children, 103 children did not fulfill the criteria for OSA, whereas 102 children had polysomnographic evidence of OSA. As shown in Table 1, these children were similar with respect to age, sex, ethnicity, and BMI. Table 2 shows the polysomnographic characteristics for the three groups.

Among the 103 snoring children without OSA, hsCRP levels were 0.19 ± 0.07 mg/dl (p value not significant vs. control children). However, 12 of the habitually snoring children without OSA had evidence of cognitive deficits and their hsCRP levels were 0.33 ± 0.10 ($p < 0.04$ vs. habitual snorers with normal cognitive scores). Among the 102 children with OSA, 57 had GCA scores less than 85%. Thus, the presence of OSA increased the risk of children displaying reduced global cognitive function when compared not only with control subjects ($p < 0.0001$) but also when compared with children with habitual snoring but no OSA ($p < 0.0001$; Table 1). Platelet counts, a sensitive acute-phase reactant marker, revealed small, albeit significant differences between subjects with OSA compared with habitual snorers

TABLE 1. DEMOGRAPHIC, COGNITIVE, AND HIGH-SENSITIVITY C-REACTIVE PROTEIN CHARACTERISTICS OF 103 CHILDREN WITH HABITUAL SNORING, 102 CHILDREN WITH OBSTRUCTIVE SLEEP APNEA, AND 73 CONTROL CHILDREN

		Snoring Children (*n = 205*)		p Value		
	Group 1: Nonsnoring (*n = 73*)	Group 2: No OSA (*n = 103*)	Group 3: OSA (*n = 102*)	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Age, yr	6.3 ± 0.3	6.6 ± 0.3	6.4 ± 0.4	NS	NS	NS
Sex, F:M	33:40	46:57	43:59	NS	NS	NS
African American, n (%)	21 (29)	35 (30)	31 (30)	NS	NS	NS
BMI, kg/m^2	16.8 ± 0.5	17.1 ± 0.6	17.0 ± 0.5	NS	NS	NS
GCA < 85%, n (%)	0	12 (11.7)	57 (55.9)	< 0.003	< 0.000001	< 0.0001; OR, 9.61 (CI, 4.46–21.07)
hsCRP, mg/dl	0.18 ± 0.05	0.19 ± 0.07	0.36 ± 0.11	NS	< 0.01	< 0.01
WBC count, cells/mm^3	6,261 ± 873	6,161 ± 667	6,242 ± 673	NS	NS	NS
Platelet count, × 10^3/mm^3	297.6 ± 55.9	315.2 ± 75.3	355.7 ± 85.5	NS	< 0.03	< 0.04

Definition of abbreviations: BMI = body mass index; CI = confidence interval; F:M = female:male; GCA = general conceptual ability score; hsCRP = high-sensitivity C-reactive protein; NS = not significant; OR = odds ratio; OSA = obstructive sleep apnea; WBC, white blood cell.

or control subjects. However, no differences emerged in platelet counts among those with and without cognitive deficits. However, mean hsCRP levels among children with OSA and abnormal cognitive scores were 0.48 ± 0.12 mg/dl compared with 0.21 ± 0.08 mg/dl in children with OSA and normal cognitive scores ($p < 0.002$; Cohen's d value for effect size, 2.035). Of note, measures of sleep and respiratory disturbance differed significantly when the OSA cohort was subdivided according to the presence or absence of abnormal cognitive scores, with the children presenting with decreased performance in two or more cognitive subtests being more severely affected in their respiratory disturbance. Therefore, we conducted a subanalysis of the data in which sex, ethnicity, obstructive AHI (± 2/h TST), nadir Sp_{O_2} (± 2%), and respiratory arousal index (± 1/h TST) were all closely matched among the cognitive performance subgroups. Among 21 children with OSA and lower cognitive tests, mean hsCRP was 0.51 ± 0.13 mg/dl, as compared with 0.20 ± 0.06 mg/dl in the 21 matched children who had normal cognitive performance ($p < 0.001$; Cohen's d value for effect size, 2.267).

DISCUSSION

This study shows that hsCRP levels are not usually affected in habitually snoring children without OSA compared with matched

TABLE 2. POLYSOMNOGRAPHIC CHARACTERISTICS OF 103 CHILDREN WITH HABITUAL SNORING, 102 CHILDREN WITH OBSTRUCTIVE SLEEP APNEA, AND 73 CONTROL CHILDREN

		Snoring Children (*n = 205*)		p Value		
	Group 1: Nonsnoring (*n = 73*)	Group 2: No OSA (*n = 103*)	Group 3: OSA (*n = 102*)	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Sleep latency, min	22.8 ± 15.4	19.0 ± 13.6	13.5 ± 7.2	NS	< 0.01	< 0.04
REM latency, min	121.8 ± 32.5	122.6 ± 33.3	116.5 ± 38.1	NS	NS	NS
Total sleep time, h	8.4 ± 0.3	8.3 ± 0.3	8.4 ± 0.2	NS	NS	NS
Sleep efficiency, %	92.0 ± 6.2	90.6 ± 6.4	87.7 ± 6.5	NS	NS	NS
Stage 1, %	7.2 ± 4.1	8.1 ± 5.2	8.7 ± 5.3	NS	NS	NS
Stage 2, %	42.2 ± 6.7	46.1 ± 6.9	49.9 ± 5.6	NS	< 0.01	NS
Stage 3, %	6.4 ± 1.6	5.2 ± 2.1	4.1 ± 1.8	NS	< 0.01	< 0.05
Stage 4, %	20.2 ± 5.5	17.3 ± 6.2	14.9 ± 5.9	< 0.05	< 0.01	< 0.05
Slow wave sleep, %	24.1 ± 5.9	22.0 ± 6.4	19.6 ± 6.2	NS	< 0.01	< 0.05
REM sleep, %	23.6 ± 4.4	19.6 ± 5.8	17.7 ± 5.7	< 0.05	< 0.01	NS
Spontaneous arousal index, /h TST	7.6 ± 3.1	7.1 ± 4.2	4.4 ± 3.8	NS	< 0.01	< 0.05
Respiratory arousal index, /h TST	0.0 ± 0.0	1.9 ± 0.6	4.8 ± 1.0	< 0.001	< 0.0001	< 0.001
Total arousal index, /h TST	7.6 ± 3.1	8.9 ± 3.7	9.2 ± 3.9	< 0.05	< 0.01	NS
PLM index with arousal, /h TST	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	NS	NS	NS
PLM index in sleep, /h TST	1.1 ± 1.1	1.8 ± 1.2	2.0 ± 1.3	NS	NS	NS
PLM index total, /h TST	1.3 ± 1.4	2.1 ± 1.6	2.3 ± 1.5	NS	NS	NS
AHI, /h TST	0.0 ± 0.0	0.8 ± 0.2	8.9 ± 2.1	< 0.0001	< 0.00001	< 0.0001
AI, /h TST	0.0 ± 0.0	0.2 ± 0.1	2.9 ± 0.4	< 0.001	< 0.00001	< 0.0001
Mean Sp_{O_2}	97.8 ± 0.8	97.1 ± 1.1	96.5 ± 1.2	NS	NS	NS
Sp_{O_2} nadir	94.1 ± 0.2	90.4 ± 0.8	80.9 ± 2.1	< 0.01	< 0.00001	< 0.0001
% TST Sp_{O_2} < 90%	0.0 ± 0.0	0.0 ± 0.0	2.5 ± 0.2	NS	< 0.00001	< 0.0001
Mean $P_{ET_{CO_2}}$	41.9 ± 0.7	45.4 ± 1.2	48.1 ± 1.3	< 0.01	< 0.001	< 0.01
%TST $P_{ET_{CO_2}}$ > 50 mm Hg	3.4 ± 0.1	14.2 ± 2.7	25.7 ± 3.9	< 0.0001	< 0.00001	< 0.0001

Definition of abbreviations: AHI = apnea–hypopnea index; AI = apnea index; $P_{ET_{CO_2}}$ = end-tidal carbon dioxide level; PLM = periodic limb movement; Sp_{O_2} = oxygen saturation as measured by pulse oximetry; TST = total sleep time.

nonsnoring children, and that hsCRP levels will be increased overall when OSA is present. However, not all children with OSA will exhibit elevations in circulating hsCRP, and the latter will be particularly increased among those children with SDB who present with cognitive deficits.

There is now substantial evidence to support the existence of adverse neurocognitive consequences in children with habitual snoring and SDB. Indeed, both habitual snoring and OSA have been shown to increase the probability for the presence of cognitive and behavioral deficits that span over several functional domains such as attention, executive function, problem solving, intelligence, and short- and long-term memory-based recall (3, 23–27). The present study further confirms these previous studies as illustrated by the different frequencies at which evidence of reduced cognitive functioning was present among children with OSA and those with habitual snoring without OSA when compared with healthy control subjects. Of note, decreases in neuronal metabolite ratio (*N*-acetylaspartate:choline) have been reported to occur in the left hippocampus and right frontal cortex of children with OSA in concordance with the magnitude of their corresponding cognitive deficits, thereby confirming that the intermittent hypoxemia and hypercapnia and sleep fragmentation that characterize OSA will interact to induce neuronal cell loss within specific brain regions and lead to the observed functional alterations (28).

The present study also highlights the fact that not all children with SDB will manifest deceased cognitive performance, even when SDB is relatively severe. Thus, these observations further reinforce the putative concept that posits that both genetic and environmental factors may be operating in addition to disease severity to elicit end-organ morbidity in patients with SDB (5). For example, patients with SDB and a history of preterm birth (29), those of African-American ethnicity (30), patients who are obese (31), and patients with low socioeconomic status (32) have thus far been identified as having increased risk for SDB and related symptoms. Furthermore, we have shown that dietary habits (5), physical activity (33), and intellectual endeavors (34) are potent modifiers of cognitive outcome in a rodent model of SDB (35). On the basis of the conceptual framework of genetic and environmental contributions to the morbidity of SDB, variances in the magnitude of the systemic inflammatory response to SDB, as evidenced from circulating hsCRP levels, seemed a viable candidate for exploration of individual susceptibility, particularly when considering the previously published associations between OSA and this protein (10, 11). Our current findings not only reinforce the concept that systemic inflammation is a constitutive component and consequence of OSA, but also support the hypothesis that if SDB develops, then the presence of increased systemic inflammation, as dictated by hsCRP levels and potentially the levels of other inflammatory markers, will increase the probability for decreased neurocognitive function. Indeed, we have found that circulating tumor necrosis factor-α morning levels are correlated primarily with the degree of sleepiness and sleep fragmentation induced by SDB in children (36). An important issue pertaining to this and other studies on CRP in SDB deserves a comment. Overall, plasma CRP levels were within the normal range, that is, the range considered as not indicative of an acute infection or inflammatory process (normative range for our laboratory, 0.05–0.49 mg/dl). However, in contrast to customary clinical practice reference values, plasma CRP levels greater than 0.30 mg/dl should be viewed as bearing an increased risk for cardiovascular morbidity (37).

One of the possible mechanisms associated with the vulnerability of children with increased hsCRP levels and OSA may involve the role of inflammation in neuronal injury. Indeed, the proinflammatory and oxidative stress effects of both intermittent hypoxia (38, 39) and sleep disruption (11, 40) are likely to elicit a more robust proinjury response and amplify the global deficits induced by OSA. Of note, neurons can generate CRP and other pentraxins, which will promote induction of neuronal proapoptotic pathways and play a role in neurodegenerative disorders (41–43). Furthermore, corroborative evidence on the association between systemic inflammatory markers such as hsCRP and cognitive decline has accumulated in a large series of epidemiologic studies, further supporting the assumption that higher hsCRP levels either directly or indirectly promote cognitive attrition (44–48). We should point out, however, that the present study is unable to test the mechanistic role of OSA in causing elevated CRP release and that, in turn, CRP is the cause of cognitive deficits. Furthermore, we are unaware of any such studies in pediatric populations. Thus, the current mechanistic considerations remain speculative.

Some methodologic considerations deserve comment. First, we sought to recruit children from the community rather than target symptomatic children referred to our pediatric sleep center for clinical evaluation of SDB. Such an approach lends further value to our findings. Second, we excluded obese children. Obesity is now viewed as a low-grade systemic inflammatory disorder (49, 50), and is associated with increased risk for cognitive deficits (32) and with more prominent symptoms such as excessive daytime sleepiness in the presence of SDB (51). Third, because dose-dependent relationships emerged between the severity of SDB and hsCRP (10), and between the severity of SDB and cognitive function, we conducted a subanalysis of hsCRP levels in children with OSA in whom the severity of SDB was matched in addition to age, sex, and race matching, and who differed only in their global cognitive functioning. This approach revealed clear differences in hsCRP, with hsCRP levels being markedly higher in those children with demonstrable cognitive declines. Nevertheless, although hsCRP levels will usually be reduced in a large proportion of children with OSA after treatment (13), we were unable to ascertain whether the anticipated reduction in hsCRP with treatment correlates with the anticipated improvements in cognitive performance. Finally, because acute infection could be theoretically present in some of the children studied (even though none of such children was symptomatic), we analyzed their white blood cell and platelet counts. None of the subjects participating in our study had elevated white blood cell counts, although platelet counts were slightly, albeit significantly elevated in the OSA group, suggesting and confirming the presence of subclinical inflammation.

In summary, we show in a community-based study of snoring and nonsnoring school-aged children, that children with OSA have increased levels of hsCRP and also exhibit decreased cognitive performances compared with control children. Furthermore, hsCRP levels are significantly increased among patients with OSA and cognitive dysfunction, and this phenomenon persists even when after the severity of OSA is matched for the two cognitive function groups. Thus, hsCRP variation emerges as a predictive measure of risk for OSA-induced cognitive deficits in children.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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