NEUROCOGNITIVE FINDINGS IN PRADER-WILLI SYNDROME AND EARLY-ONSET MORBID OBESITY

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Objectives To examine whether early-onset morbid obesity is associated with cognitive impairment, neuropathologic changes, and behavioral problems.

Study design This case-control study compared head MRI scans and cognitive, achievement, and behavioral evaluations of subjects with Prader-Willi syndrome (PWS), early-onset morbid obesity (EMO), and normal-weight sibling control subjects from both groups. Head MRI was done on 17 PWS, 18 EMO, and 21 siblings, and cognitive, achievement, and behavioral evaluations were done on 19 PWS, 17 EMO, and 24 siblings.

Results The mean General Intellectual Ability score of the EMO group was 77.4 ± 17.8; PWS, 63.3 ± 14.2; and control subjects, 106.4 ± 13.0. Achievement scores for the three groups were EMO, 78.7 ± 18.8; PWS, 71.2 ± 17.0; and control subjects, 104.8 ± 17.0. Significant negative behaviors and poor adaptive skills were found in the EMO group. White matter lesions were noted on brain MRI in 6 subjects with PWS and 5 with EMO. None of the normal-weight control subjects had these findings.

Conclusions Individuals with EMO have significantly lower cognitive function and more behavioral problems than control subjects with no history of childhood obesity. Both EMO and PWS subjects have white matter lesions on brain MRI that have not previously been described. *(J Pediatr 2006;149:192-8)*

Childhood obesity is a major health problem throughout the world, with increasing prevalence, severity, and appearance at younger ages.[1] The rise in obesity among most age groups in the population is primarily due to the changed environment. In contrast, because infants and very young children have limited access to these environmental factors, the development of obesity in those children under 4 years of age may be due to genetic influences. Determination of the underlying cause and consequences of childhood obesity is crucial to the understanding and ultimate treatment of this condition. Little is known about the effects of early childhood obesity on the developing brain.

Prader-Willi syndrome (PWS) is the most commonly recognized genetic cause of childhood obesity, characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, early-onset obesity, and hyperphagia.[2] Approximately 70% of PWS cases are due to a genetic deletion on chromosome 15 (15q11-13), 25% of PWS cases are from a maternal uniparental disomy (UPD) of chromosome 15, and the remaining cases result from imprinting defects.[3,4] The early-onset morbid obesity is the most significant health problem and the primary cause of morbidity and mortality in individuals with PWS.

Adipose tissue produces various secretory proteins, including leptin, tumor necrosis factor-alpha (TNF-α), and adiponectin. Obesity-induced abnormal levels of these "adipokines" cause increased insulin resistance, with resultant hyperinsulinemia, dyslipidemia, inflammation, and endothelial dysfunction.[5] Childhood obesity results in longer exposure to the adipokines produced by the adipose tissue, putting obese children at risk for developing the metabolic and cardiovascular complications of obesity at relatively younger

ANOVA	Analysis of variance	PKU	Phenylketonuria
BASC	Behavioral Assessment System for Children	PWS	Prader-Willi syndrome
CGH	Comparative genomic hybridization	SES	Socioeconomic status
EMO	Early-onset morbid obesity of unknown cause	UPD	Uniparental disomy
GIA	General Intellectual Ability	WJ-III	Woodcock-Johnson Test of Cognitive Ability and Academic Achievement-Third Edition
IBW	Ideal body weight		

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ages. By 6-12 years of age, one in four overweight children has hyperinsulinemia with impaired glucose tolerance, and 60% of these children have evidence of hypertension, dyslipidemia, subclinical inflammation, and disturbed endothelial function.[1,6]

Prader-Willi syndrome is an excellent model to help assess the causes and effects of early childhood morbid obesity because it has a characteristic age of onset of obesity in addition to well-described learning difficulties and behavioral problems.[7-10] In our study, patients with PWS served as an obesity comparison group for individuals with early-onset morbid obesity (EMO) of unknown cause.

METHODS

Participants

We evaluated subjects with PWS, a well-defined cause of childhood-onset obesity, mental retardation, and behavioral problems, as well as subjects with EMO of unknown cause to compare such factors as age of onset of obesity, nutritional assessment, cognitive function, MRI findings, and behavior. To reduce the effects of socioeconomic and genetic background, the siblings of both of these obese groups served as the control group. This study was approved by the University of Florida Institutional Review Board, and all participants and/or their guardians provided written informed consent.

Molecular testing was done on all PWS subjects.[3] Ten PWS subjects with a deletion of the chromosomal 15q11-13 region and 7 with maternal UPD of chromosome 15 (ages 4 to 39 years) had a 3-D MRI of the head (Table I; available at www.jpeds.com), whereas 11 subjects with deletion and 8 with UPD (ages 4 to 39 years) underwent cognitive and behavioral evaluations (Table II; available at www.jpeds.com).

Subjects with EMO were recruited from the General Pediatric, Pediatric Endocrinology, and Pediatric Genetics clinics at the University of Florida, solely on the basis of a history of weight >150% of ideal body weight (IBW) for height before the age of 4 years and no recognized syndromal cause of obesity. Growth charts documenting the weight, height, and head circumference from birth were required for entry into the study to ascertain that the onset of obesity occurred before the age of 4 years. All participants in the EMO group had a normal chromosomal analysis as well as a normal fluorescence *in situ* hybridization and DNA methylation analysis, using the small nuclear ribonucleoprotein N (*SNRPN*) probe located in the Prader-Willi region of chromosome 15.[3] No EMO patients had diagnostic clinical characteristics of any known genetic obesity syndrome. Sequence analysis of the coding region of the melanocortin 4 receptor (*MC4R*) gene did not reveal any mutations.[11] Fragile X DNA testing done by polymerase chain reaction and Southern blot analysis[12] was normal. No EMO subjects were found to have a leptin deficiency by commercial testing with radioimmunoassay. The EMO subjects who underwent MRI and cognitive/achievement/behavioral evaluation were 4 to 22 years of age (Table I and Table II).

In addition to the extensive genetic testing described above, we also performed array-based comparative genomic hybridization (CGH) on all the EMO subjects, searching for a chromosomal deletion or duplication that would explain their neurocognitive impairment or obesity. The array used for CGH analysis was a chromosome 15–specific targeted array that included 174 genomic bacterial artificial chromosome clones distributed across the length of the long arm of chromosome 15. The highest density of clones was across the approximately 10 Mb chromosomal 15q11-q14 interval encompassing the Angelman/Prader-Willi critical region, including the common deletion/duplication breakpoints. This particular microarray achieved a resolution of greater than one clone per megabase for the entire chromosome 15. Additionally, more than 130 clones (bacterial artificial chromosomes and P1-derived artificial chromosomes) specific for the subtelomeric regions of all other chromosomes were included. Also included were clones specific for the genomic regions for the *SIM1* gene (chromosome 6q16.3) and a number of genomic regions (17p11, 22q11, and 10q23.3) implicated in autism spectrum disorders. The validation of genomic clones and production and analysis of array CGH experiments were carried out as described previously.[13,14] Despite this extensive analysis, no segmental losses or gains were identified in any of the subjects in the EMO cohort.

It should be noted that only one EMO subject who underwent cognitive and behavioral testing did not have fragile X, *MC4R*, or array CGH testing due to insufficient DNA. However, his similarly affected maternal half-brother did have this testing and was normal. Furthermore, fragile X testing on the mother was normal.

Normal sibling control subjects who were generally closest in age to the proband and who did not have a history of childhood obesity or a known genetic abnormality (eg, Down syndrome) were recruited from both the PWS and the EMO families. The sibling control subjects were ages 3.5 to 43 years (Table I and Table II).

Weight of Participants

Age of onset of obesity for subjects with PWS was between 18 and 36 months, although the majority of the PWS subjects became obese after 24 months. All PWS subjects were obese before age 4 years. However, the range of weight at their time of testing varied from IBW to 325% of IBW for height. The EMO group had more variation in age of onset of obesity (2 months to 3 years) and was more consistently and severely obese (150% to 325% of IBW) at the time of evaluation (Figure 4; available at www.jpeds.com). However, it should be noted that percent IBW underestimates the degree of obesity in PWS as the result of their decreased muscle mass.[2] None of the sibling control subjects were obese before age 10 years. Body mass index standard deviation score was calculated from the standardized growth charts distributed by the Centers for Disease Control.