Neuroanatomic Studies in Prader-Willi Syndrome and Early-onset Obesity

Jennifer Miller, MD, Daniel Driscoll PhD, Ilona Schmalfuss MD (University of Florida)

Introduction

Childhood obesity is a worldwide epidemic which is affecting children at increasingly younger ages. In this project we will compare children with a well-defined genetic origin of obesity with those with obesity of unknown origin to test the hypothesis that obesity itself, independent of genetic mechanism, compromises neural development. Prader-Willi syndrome (PWS) is a contiguous gene defect that results in a well-defined pattern of early-onset childhood obesity. Environmental manipulations (i.e. parental vigilance) can markedly reduce the extent of the obesity in PWS, and potentially protect cognitive function. Therefore, PWS is an excellent model for elucidating the relative contributions of genetics and obesity to brain development. A group of children with early-onset morbid obesity of unknown origin (EMO) will serve as a comparison group to further evaluate our hypothesis that obesity, regardless of the etiology, compromises brain development. Excess adipose tissue results in abnormal levels of a variety of hormones and cytokines. We have recently found that individuals in both these groups (EMO and PWS) had premature development of white matter lesions in the brain, in contrast to their normal weight control siblings (1). In this project we are performing qualitative and quantitative measurements of brain MRIs to compare **(1)** individuals with PWS who become obese early in childhood with **(2)** individuals with PWS who remain normal weight during early childhood, and **(3)** children with EMO, and **(4)** normal weight sibling controls from both groups to test our hypothesis that the abnormal hormonal and metabolic milieu present with early-onset obesity compromises neural development. In this grant we are seeking evidence of a connection between early-onset obesity and brain damage in groups with a different etiology and degree of obesity.

Experimental

Participants over 5 years of age undergo a brain MRI examination using the 3T whole body system The MRI protocol can be completed in approximately 10-15 minutes which reduces scanner time for our young patients who have difficulty lying still.

Results and Discussion

We have found that individuals with PWS and early-onset morbid obesity have white matter lesions which can begin as early as age 7. We have scanned 58 individuals at baseline and 2 years, and have completed 118 total baseline scans. We are measuring insulin resistance, glucose tolerance, thyroid function, uric acid, and fasting lipid panel to help identify risk factors associated with the presence of white matter lesions. The 58 individuals with repeat scans have also all undergone repeat measurements of appetite and satiety-related hormones and body composition to try to correlate changes in these measures with the progression of white matter lesions. These individuals have also all undergone cognitive and behavioral evaluation to determine if the white matter lesions correlate with any specific cognitive delays or behavioral problems.

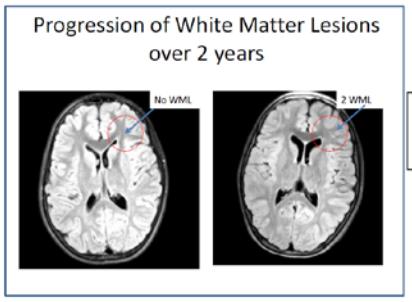

Figure 1. Progression of white matter lesions in lean individual with PWS from age 8 to 10 years who had no significant increase in body fat, but worsening insulin resistance.

Conclusions

There were three lean individuals with PWS who had development of white matter lesions (**Figure 1**), and all had had an increase in insulin resistance, but not a significant change in body composition or BMI. Interestingly, two of the individuals with early-onset obesity who initially had multiple white matter lesions who were clinically treated with metformin and had had a significant reduction in their BMI and %body fat no longer had these lesions on their follow-up scan, further suggesting that insulin resistance may play a role in the progression of the white matter lesions.

Acknowledgements

Funding Support provided by: Lawson Wilkins Pediatric Endocrine Society; National Institutes of Health NIH 1K23 DK081203; 1U54 RR019478; and General Clinical Research Center M01 RR00082 from the National Center for Research Resources, University of Florida.

References

1. Miller JL, *et al.* J Hum Nutr Diet. 2012 Oct 18.
2. Cassidy SB, *et al.* Genet Med. 2012 Jan;14(1):10-26.
3. Kim SJ, *et al.* Eur J Hum Genet. 2012 Mar;20(3):283-90.