CLINICAL VIGNETTE

Cohen Syndrome as Cause of Childhood Central Obesity Leading to Increased Risk of Metabolic Complications

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A 19-year-old, Hispanic-Asian female with clinical diagnosis of Cohen syndrome was referred for hyperinsulinemia and dyslipidemia management. Patient was clinically diagnosed with Cohen Syndrome during childhood after presenting with typical features including failure to thrive, developmental delay, microcephaly, myopia, neutropenia, joint hypermobility, truncal obesity, and hypotonia. Hypertriglyceridemia was diagnosed at age 11 on routine labs when fasting triglycerides were found to be at >700 mg/dl. Patient's mother reported that around that time patient had significant unintentional weight gain. Her physical activity had been limited due to hypotonia since childhood. She was also found to have vitamin D deficiency. She had menarche at age 16 and history of regular menstrual periods. Patient had a strong family history of diabetes and obesity in the maternal side of the family.

Initial treatment was lifestyle modifications with medical nutrition therapy and regular physical activity. She had strong family support and she was started on strict carb controlled diet with close monitoring of carb and caloric intake, plus an exercise daily routine using a treadmill and going to swimming classes. She managed to lose 15 pounds after initial diagnosis of hyperlipidemia with lifestyle changes.

Physical exam revealed normal blood pressure, BMI of 21, waist circumference of 92 cm, hip circumference of 83 cm, and waist-to-hip ratio 0.9 (central obesity). No evidence of acanthosis nigricans or abnormal fat accumulation. She had low hairline, high-arched and wave-shaped eyelids, long and thick eyelashes and thick eyebrows, slender extremities, small feet and hands, markedly reduced visual acuity. Heart and lungs were normal and extremities had hypotonic muscles.

Labs revealed elevated insulin levels and persistent abnormal lipids, and she was started on dual medical therapy with omega 3 and gemfibrozil. She also required consistent daily vitamin D supplementation to keep optimal levels.

Repeat labs after initiation of medical therapy showed a total cholesterol of 171 mg/dl, LDL 102 mg/dl, HDL 35 mg/dl, triglycerides 170 mg/dl, non HDL cholesterol was 132 mg/dl. Fasting blood glucose was 90 mg/dl and 2 h oral glucose tolerance test revealed a 2-h glucose of 108 mg/dl, fasting insulin level 215 uU/ml, hemoglobin A1c 4.9%.

After lifestyle and medical therapy her lipid panel showed improvements and she has been able to maintain stable weight and normal blood glucose with improvement on insulin level

Discussion

Cohen syndrome was first described in 1973[1] and more than 200 affected individuals have been reported to date in all continents.[2] The diagnosis of Cohen syndrome is based on clinical findings or identification of allelic pathogenic variants in VPS13B (also known as COH1) on molecular genetic testing if clinical features are inconclusive.[2] It is an autosomal recessive genetic disorder caused by an abnormal gene located on chromosome 8 at 8 q 22-q23 (2, National Organization of Rare Diseases website). Cohen syndrome is characterized by failure to thrive during childhood, followed by development of truncal obesity during teenage years in more than 80% of affected individuals.[3] The average age of the onset of obesity is 11.3 years. Reports have described a rapid change over the period of 4-6 months, despite no significant changes in appetite, food intake or physical activity.[2]

Other characteristics include early-onset hypotonia and developmental delays, microcephaly, psychomotor retardation, progressive retinochoroidal dystrophy, high myopia, neutropenia with recurrent infections, a cheerful disposition, joint hypermobility and characteristic facial features with thick hair and eyebrows, long eyelashes, broad nasal tip, short philtrum.[2,4,5-7] From the NCSD statistics, the prevalence of short stature is approximately 65% and delayed puberty 74% without specific endocrinology cause found. Previous studies in Finish population revealed no significant abnormalities in the pituitary, adrenal, and thyroid function.[8]

Growth hormone deficiency has been reported, but the prevalence is unknown.[2,9] In individuals with Cohen Syndrome, the association of truncal obesity and hypotonia that limit physical activity le0ad to increased risk for metabolic complications at early age. Clinical definitions of metabolic syndrome have been variable, most of the definitions includes several of the following five conditions: elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), increased blood pressure, elevated fasting plasma glucose, and increased waist circumference.[10] Obesity is an important risk

factor for cardiovascular disease (CVD) and often associated with above comorbidities

Our patient fulfilled criteria for metabolic syndrome per the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) 2005 criteria with central obesity, elevated triglyceride and low HDL. She also presented with early stages of abnormal glucose metabolism and insulin resistance with fasting hyperinsulinemia.

Individuals with insulin resistance have abnormal adipose tissue storage, release of fatty acids, and control by insulin before the development of type 2 diabetes. The basal lipolysis is elevated since suppression by insulin is diminished and the increased free fatty acids are diverted from adipose tissue toward nonadipose tissues. Triglyceride accumulation in nonadipose tissues such as muscle and liver is linked to the development of insulin resistance as these tissues attempt to protect themselves from energy overload. Insulin resistance imposes a chronic stress on pancreatic β-cells and ultimately result in β-cell dysfunction and damage. Ultimately complications such as hepatic steatosis, dyslipidemia and diabetes develop.[11]

Treatment of Cohen Syndrome is centered on management of all complications. Raising awareness about the metabolic risk and early intervention with medical nutrition therapy, physical therapy and regular exercise is important to prevent further health complications including T2DM and CVD. Medical therapy should be considered when lifestyle changes fail to control metabolic abnormalities as was the case in our patient

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