CHILDHOOD OBESITY: BETWEEN NATURE AND NURTURE

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Abstract

Introduction: In the last decades, the incidence of overweight and obesity has reached epidemic proportions. Both genetic and environmental factors are involved. When a disease clusters in a family our first instinct is to search for a genetic cause, but where obesity is concerned, careful evaluation is required. Purpose: to discuss the possible factors related the early and severe weight gain of three morbidly obese siblings. Methods: Mădălina, Denisa and Cătălin were referred to our Medical Genetic department for evaluation. We performed a complete assessment. Results: The siblings were born to obese parents. The family had chaotic eating habits and lived a profoundly sedentary life and did not attend kindergarten or school. Mădălina, the oldest, had multiple admissions to the hospital for obstructive sleep apnea (OSA). Anthropometric measurements confirmed the severe obesity. Their facial features resembled each other's' and their mother's. Only Mădălina presented with acanthosis nigricans, while all 3 children had skeletal complications of obesity. Metabolic markers were in normal range, Mădălina's leptin and Denisa's adiponectin levels were low. In all 3 children the abdominal ultrasound was suggestive for nonalcoholic fatty liver disease. All children proved to be under stimulated and below average intellects were found. Lifestyle modifications recommendations were made and after 2 months all children lost weight. They also underwent psychological counseling. Mădălina's OSA improved. Conclusions: Nurture is the major determinant of the siblings' severe obesity. While on the short term prognosis is fair, on the long run, the multiple comorbidities associated with obesity make it reserved.

Key words: childhood obesity, genetics, environmental factors

Introduction

In the last decades, the incidence of overweight and obesity has reached epidemic proportions, affecting all ages, races, and sexes, and becoming a major health problem worldwide (1,2). Most worrisome is that increasing numbers in childhood obesity will have huge implications on adult morbidity and mortality (3).

In Romania, childhood overweight and obesity is estimated at 18.2% and 7.2%, respectively (4).

Both genetic and environmental factors are involved in the etiology of obesity. Although, there has not been such a dramatic change in mankind's genetic profile to explain the ascending trend of obesity we are facing, it is clear that not all individuals exposed to obesogenic environments become obese. A genotype predisposition for weight gain must exist for the environment factors to result in an overweight/obese phenotype. Twin, family, and adoption studies estimate a heritability for obesity/overweight ranging from 50% to over 90% (1,2).

An easy access to cheap, high caloric foods and beverages combined with a sedentary lifestyle defines an obesogenic environment and represents the main culprit of the obesity epidemic (2,5). Parents play a crucial role in shaping a healthy lifestyle in their children (5,6).

Usually, when a disease clusters in a family our first instinct as physicians is to search for a genetic cause. Where obesity is concerned, due to the multiple and intricate factors involved, matters tend to be more complicated and careful evaluation is required.

Purpose

Our aim was to discuss the possible factors related the early and severe weight gain of three morbidly obese siblings.

Materials and Methods

Mădălina Nicoleta- 7 years and 6 months old, Denisa- 6 years and 1 month old and Cătălin Andrei- 3 years and 7 months old were referred to our Medical Genetic department for evaluation regarding the morbid obesity of all siblings. We performed a complete assessment that ranged from obtaining a detailed medical history to karyotyping and multidisciplinary consults.

Results

Mădălina Nicoleta was born to non-sanguineous, obese parents that came from an urban setting. She was the first born, from a physiological pregnancy, at full term, weighing 3.2 kg- appropriate for gestational age (AGA). She was exclusively breastfed for 2 months, than was started on cow's milk; solid food was introduced at 1 year old. Currently, her eating habits were chaotic, she was not involved in any form of physical activity and does not attend kindergarten or school. Her medical history was positive for multiple admissions to the hospital for obstructive sleep apnea (OSA).

Physical assessment: the anthropometric measurements are represented in Figure 1.

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The facial phenotype was similar to the mother's: epicantus, hypertelorism, convergent strabismus of the right eye. No stretch marks were present, but she had acanthosis nigricans in the cervical area. The distribution of adipose tissue was generalized (Figure 2). The girl had thoracal kyphosis, thoracolumbar scoliosis and inwards rotation of both thighs.

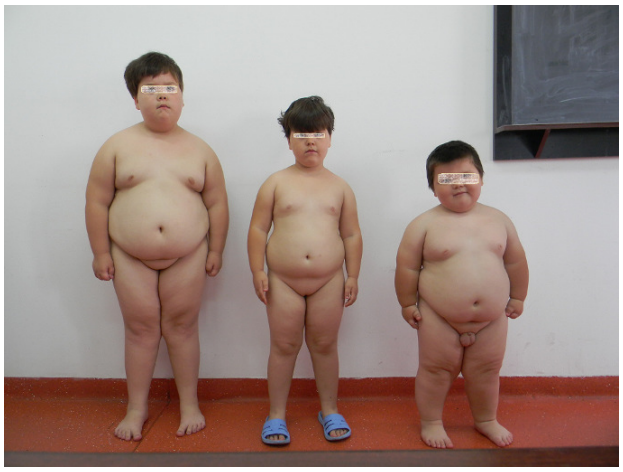

Figure 1 From left to righ: Mădălina Nicoleta, Denisa, Cătălin Andrei

The blood work-up revealed polycythemia, secondary to chronic and severe sleep apnea. Basal glycaemia, oral glucose tolerance test (OGTT), glycated hemoglobin (A1c), lipids' profile and transaminase were in normal range. Basal insulinemia and the calculated Homeostasis Model Assessment (HOMA= insulin x glucose/22.5), C peptide and adiponectin were in normal range. Leptin was very low.

The karyotype was 46 XX. We performed a fluorescence in situ hybridization (FISH) test to detect a possible deletion on the 15th chromosome (Prader-Willi syndrome). It was negative.

Imaging studies: X-rays revealed a cardiothoracic index of 0.66 (normal range for age 0.5-0.4), thoracal kyphosis, thoracolumbar scoliosis, bilateral coxa valga, genu valgum and pattelar subluxation.

The ECG showed an extreme deviation to the right of the heart axis (QRS +150°), while the heart ultrasound was normal.

The abdominal ultrasound revealed an enlarged liver (right hepatic lobe 15 cm, left hepatic lobe 12-13 cm, caudate lobe 3 cm) with high echogenicity, an uneven structure and posterior attenuation.

Consults: The pneumologist reconfirmed the diagnosis of OSA and recommended Continuous Positive Airway Pressure (CPAP) therapy during sleep. The otolaryngology consult found a sub-acute adenoiditis. The pediatric orthoped confirmed the skeletal complications associated with morbid obesity. The pediatric endocrinology consult reviewed the anthropometric measurements, recommended additional hormonal investigations and made lifestyle modifications recommendations: nutritional and physical activity plan.

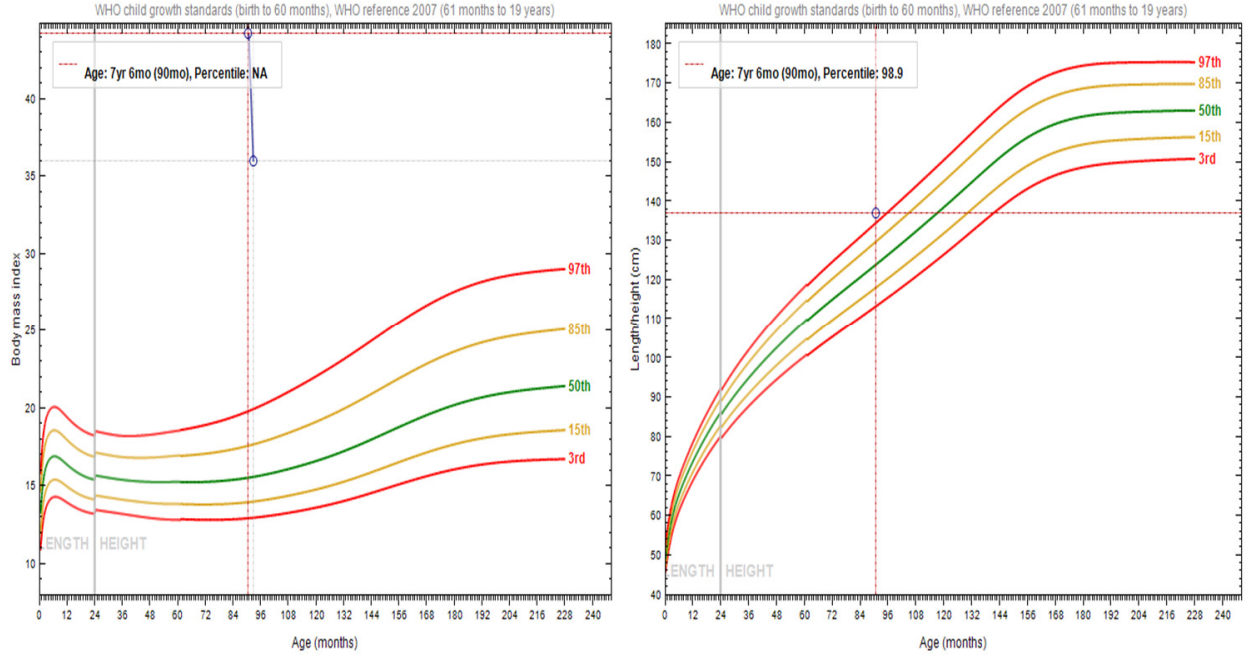

Figure 2 Mădălina Nicoleta: Left: BMI > 97th WHO percentile; weight loss after 2 months. Right: height > 97th WHO percentile

A psychology consult found an IQ (Raven) of 80 (below average) due to inappropriate cognitive stimulation, polymorphic dyslalia, low prosexia capacity, irritability, limited social skills and low self-esteem.

Auxologic measurements confirmed the diagnosis of severe obesity; comorbidities are shown in Table 1.

Denisa was the second born, from a physiological pregnancy, at full term, weighing 3.1 kg, AGA. She was exclusively breastfed for 2 months, than was started on formula; solid food was introduced at 6-7 months. Identical to her sister, the eating habits were chaotic; she was not involved in any form of physical activity and does not attend kindergarten.

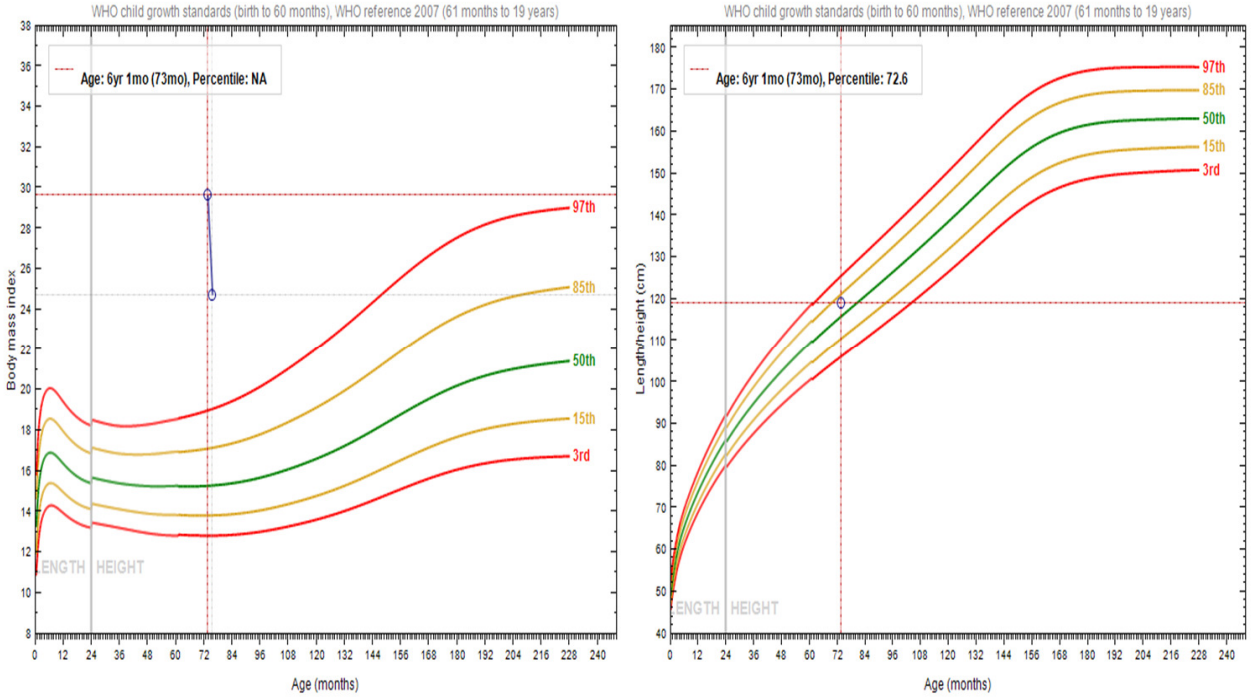

Figure 3 Denisa: Left: BMI > 97th WHO percentile; weight loss after 2 months. Right: height > 50th WHO percentile

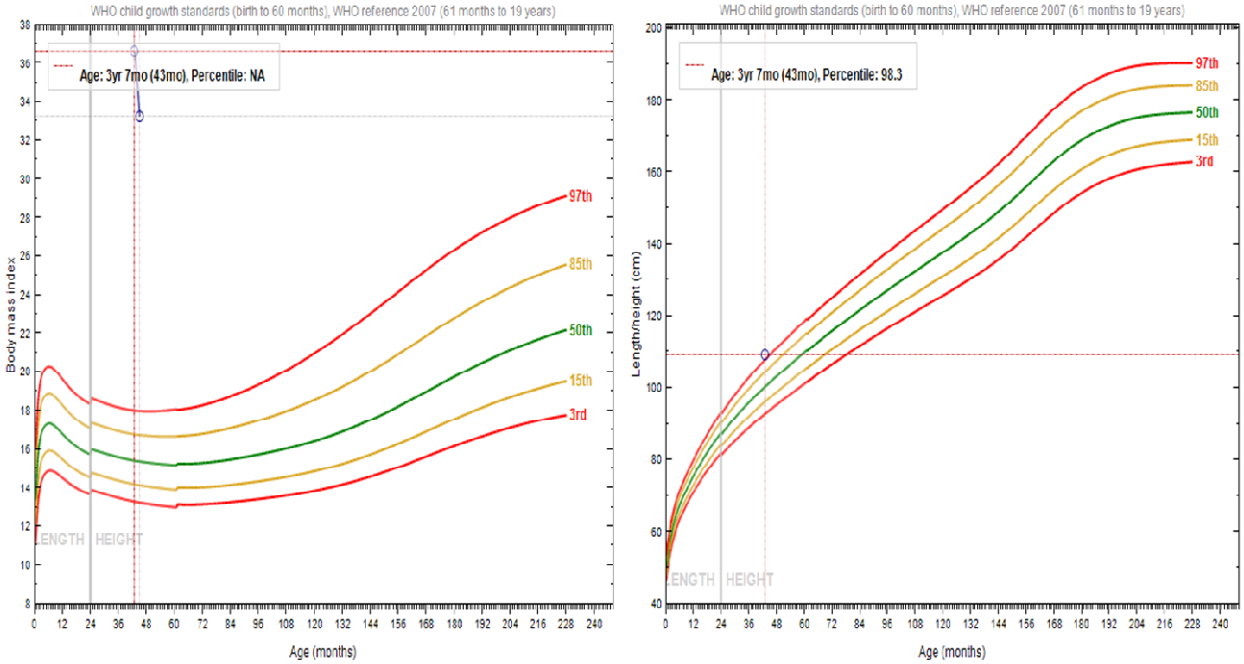

Figure 4 Cătălin Andrei: Left: BMI > 97th WHO percentile; weight loss after 2 months. Right: height > 97th WHO percentile

Physical assessment: the anthropometric measurements are represented in Figure 3.

The facial phenotype was similar to her mother and sister. No stretch marks or acanthosis nigricans were present. The distribution of adipose tissue was generalized.

The girl had mild thoracal kyphosis, thoracolumbar scoliosis and inwards rotation of both thighs.

The blood work-up revealed normal basal glycaemia, OGTT, A1c, lipids' profile and transaminase. Basal insulinemia and HOMA, C peptide and leptin were in normal range. Adiponectin was low.

Table I Obesity asociated comorbidities, complete diagnosis; *NAFLD= nonalcoholic fatty liver disease; ** only ultrasound criteria

Morbidity/Child	Mădălina Nicoleta	Denisa	Cătălin Andrei
Skeletal (lumbar spine deformities, femur/tibia/foot deformities)	Thoracal kyphosis Thoracolumbar scoliosis Bilateral coxa valga Bilateral genu valgum Bilateral pattelar subluxation	Mild thoracal kyphosis Thoracolumbar scoliosis Bilateral genu valgum	Thoracolumbar scoliosis Bilateral inwards rotation of thighs Plat feet
Pulmonary (bronchiolitis, asthma, sleep apnea)	Obstructive sleep apnea	-	-
Cardiologic (high blood pressure, ischemic heart disease, heart failure)	-	-	-
Metabolic (diabetes, hyperlipidemia, NAFLD*)	NAFLD**	NAFLD**	NAFLD**
Hormonal (insulin resistance, hypoadiponectinemia, high leptin levels)	Acanthosis nigricans	-	-
Psychological (limited social skills, introversion, isolation, depresion)	Limited social skills Low self-esteem	Introversion Isolation	Psycho-motor delay (mainly due to inappropriate stimulation)

The karyotype was 46 XX. We performed FISH test to rule out Prader-Willi syndrome, which came out negative.

Imaging studies: X-rays revealed a mild thoracal kyphosis, thoracolumbar scoliosis, bilateral genu valgum. A spina bifida occulta was found.

The ECG and heart ultrasound were unremarkable.

The abdominal ultrasound revealed an enlarged liver (right hepatic lobe 12 cm, left hepatic lobe 8 cm) with high echogenicity, an uneven structure and posterior attenuation.

Consults: The pediatric orthopedic and endocrinology consults were similar to the older sister.

The psychology consult showed an IQ (Raven) of 80 (below average) due to inappropriate cognitive stimulation, limited social skills; introversion and isolation.

Aside severe obesity, the complete diagnosis is shown in Table 1.

Cătălin Andrei was the youngest of the 3 sibling, from a physiological pregnancy, at full term, weighing 3.2 kg, AGA. He was started on formula from birth; solid food was introduced at 6-7 months. Identical to his sisters, the eating habits were chaotic and he was not involved in any form of physical activity and does not attend kindergarten.

Physical assessment: the anthropometric measurements are represented in Figure 4.

The facial phenotype was similar to his mother and sisters. No stretch marks or acanthosis nigricans were present. The distribution of adipose tissue was generalized. He had mild thoracolumbar scoliosis, inwards rotation of both thighs and plat feet.

The blood work-up revealed normal basal glycaemia, OGTT, A1c, lipids' profile and transaminase. Basal insulinemia and HOMA, C peptide, adiponectin and leptin were in normal range.

The karyotype was 46 XY. The FISH test for Prader-Willi syndrome was negative.

Imaging studies: X-rays revealed a thoracolumbar scoliosis.

The heart ultrasound was unremarkable, while the abdominal ultrasound revealed an enlarged liver (right hepatic lobe 12 cm, left hepatic lobe 10 cm) with an uneven structure.

Consults: The pediatric orthopedic and endocrinology consults were similar to the older sisters.

The psychologist found a psycho-motor delay (QD=79) due to inappropriate cognitive stimulation and polymorphic dyslalia.

Based on the anthropometric measurements, the diagnosis of severe obesity is sustained. The complete diagnosis is shown in Table 1.

Discussions

Anthropometric considerations

The growth of a child is of high importance for us pediatricians. Genetic, hormonal and nutritional factors are responsible for normal growth. When evaluating a child

with obesity, height is the anthropometric measurement that differentiates between primary (due to unhealthy lifestyle) and secondary (syndromic) obesity. Overweight and obese children and adolescent are generally taller than their peers during childhood and early puberty (7). Genetic and endocrine diseases that have obesity as a symptom (Cushing's syndrome/disease, hypothyroidism, Laron syndrome etc) are all associated with height deficit.

It is obvious that the siblings do not present with impaired height, on the contrary their respective heights tend to be above average. This makes a diagnosis of secondary obesity unlikely.

Metabolic considerations

While all of the metabolic markers were in normal range, it is clear to us that the metabolic risk of these children is significant. Furthermore, in spite of a normal insulin level, as well as HOMA index, Mădălina had acanthosis nigricans, a well-known marker of insulin resistance.

The human body may be capable of maintaining for a variable period a metabolic homeostasis, but signs of metabolic disturbance are already present. The US appearance of the liver in all 3 siblings is suggestive for nonalcoholic fatty liver disease (NAFLD). This entity is characterized by the accumulation of large droplets of triglycerides within hepatocytes in the absence of chronic alcohol consumption. In adults, it is believed that fat accumulation within organs such as the liver is a major step in the development of insulin resistance and the metabolic syndrome (8). In children, NAFLD has been consistently associated with obesity and insulin resistance, biopsies revealing specific liver abnormalities in children as small as 4 years of age (9), in the absence of altered transaminase profiles. A recent study, Shannon et al. demonstrate the utility of hepatic ultrasonography for non-invasive diagnosis and estimation of hepatic steatosis in children, showing a tight correlation between ultrasonographic steatosis score and severity of steatosis on liver biopsy (10).

Leptin and adiponectin profile

We strongly believe that the leptin and adiponectin disturbances are a consequence of primary obesity, rather than its cause.

Leptin is almost exclusively excreted by the adipocyte, dependent of the fat cell volume, invoking satiety and ceasing nutritional intake. Increased levels have been found in obese. The release of leptin is partly dependent on sleep timing, duration and quality. The human leptin profile is mainly dependent on meal intake, with a morning minimum and increasing levels throughout the daytime, followed by a nocturnal maximum (maybe to inhibit hunger during the overnight fast). Leptin levels were lowest in a state of sleep debt, signaling the brain an unnecessary need for extra caloric intake (11).

The low levels of leptin found in Mădălina may reflect her prolonged OSA, but this is debatable because several studies found high levels of leptin in adult patients with OSA (12,13).

Adiponectin is a hormone secreted exclusively by the adipose tissue. It correlates inversely with obesity and insulin resistance and has been linked with features of the metabolic syndrome in obese children and adolescents (14). It has been suggested that adiponectin may be a useful biomarker to identify children at risk of cardiometabolic adverse effects of adiposity (15), but its role as an early marker of the metabolic syndrome in overweight and obese children is unknown. Furthermore, there are only a few studies of adiponectin in preschool children (16).

Denisa's low adiponectin may reflect a more precarious metabolic homeostasis in comparison with her siblings.

Nature versus nurture

While genetic factors may be suspected, it is clear to us that nurture played a significant role in the development of the siblings' severe obesity. Their meals are unorganized, uncontrolled, lacking nutrients and including high amounts of bread, refined sugars and unsaturated fats. In addition, the family lives a profoundly sedentary life. All children proved to be under stimulated with psychological age appropriate deficits. The socioeconomic status significantly affects families like this one all over the world: unhealthy lifestyles are more common among those with lower education and poor financial conditions (17,18).

Outcome

On the short term prognosis is fair: the family was given dietary and activity recommendations and after 2 months all children lost weight (Figures 2-4). They also underwent psychological counseling and will be closely followed-up. Mădălina's OSA improved and she does not require CPAP therapy.

On the other hand, the long term prognosis may be reserved due to the frequent drawbacks and inability to maintain the weight loss. An emphasis must be made: in an obese child, most excess weight before puberty is gained before 5 years of age (19). Furthermore, early weight gain is associated with inflammation, endothelial activation and major metabolic risks (20, 21).

It is encouraging that early prevention and intervention on risk aimed at managing obesity in preschoolers seems to be the most effective (22, 23). Needles to say a supportive parent is mandatory.

Conclusions

Nurture is the major determinant of the siblings' severe obesity. Signs of metabolic disturbance are already present and hormonal disturbances are a consequence of primary obesity, rather than its cause. While on the short term prognosis is fair, all children having already lost weight, on the long run, the multiple comorbidities associated with obesity make it reserved..

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