CONSIDERATIONS UPON METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

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Abstract

The presence of cardiovasculary risk factors in childhood and adolescence is beginning to attract a growing interest in the medical world and in research.

Obesity plays an important role in the increased prevalence of its comorbid conditions. One of these, the metabolic syndrome (MS), includes a cluster of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), including insulin resistance, obesity, hypertension, and dyslipidemia.

MS appeared at an early age will surely have repercusions in adulthood. The early detection of MS and its major complications – early atherosclerosis – would allow prophylactic interventions that aim to decrease the precocious morbidity and mortality due to atherosclerotic cardiovascular diseases, to be as efficient as possible and targeted on the issue of interest.

Key words: child, adolescent, obesity, metabolic syndrome

Background

The metabolic complications associated with childhood obesity have been extensively studied over the last 10 years. Childhood obesity is a major risk factor for the development of chronic diseases and mortality in adult life.[1, 2, 3]

MS includes a cluster of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), including abdominal obesity, insulin resistance, hypertension, and dyslipidemia.[4] Obesity in children and adolescents has reached epidemic proportions, with the prevalence tripling in the past 3 decades. MS and type 2 diabetes have paralleled this obesity epidemic in children.[5]

MS continues to challenge the experts but both insulin resistance and central obesity are considered significant factors. Genetics, physical inactivity, ageing, a proinflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.

There is now evidence to suggest that features of the MS commonly found in abdominally obese patients with an excess of visceral adipose tissue increase coronary heart diseases risk. Childhood obesity, with concomitant hypertension, impaired carbohydrate metabolism, hyperlipidemia – included or not included in MS, are linked to CVD in adulthood. The atherosclerotic process develops silently for decades during childhood and adolescence before cardiovascular complications such as myocardial infarction and stroke occur in adulthood.[4]

With the MS driving the twin global epidemics of T2DM and CVD there is an overwhelming moral, medical and economic imperative to identify those individuals with MS early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or CVD disease. [6]

Aim of study

The authors target the evaluation of MS frequency in children and adolescents obesity, as well as the study of clinical manifestations and biological aspects.

Material and Methods

We have incorporated in the study a number of 247 obese between the ages of 5 months and 18 years, 135 girls and 112 boys who were in the care of the 2nd Clinic of Pediatrics Timişoara. 85 of these showed mild obesity, 106 had moderate obesity and 56 severe obesity.

According to the new definition of pediatric MS, for a child or adolescent to be defined as having the MS they must have: obesity plus any two of the following factors: fasting hyperglicemia / impaired glucose tollerance (IGT) / T2DM, low HDL cholesterol serum levels, hygh triglicerides serum levels and hypertension (table 1).

- The diagnosis of obesity was established:
  * for the infant and the child up to the age of two with a PI bigger than 1,1.
  * for the toddler over 2 years of age:
  - with a weight excess larger than 20%, or over 2 standard deviations, or greater than the 95th percentile, according to the normal weight for age, heigh and sex.
  - with a BMI greater than the 95th percentile.

The degree of severity of obesity has been interpreted taking into account the size of the weight excess in the following way:

- *Mild* obesity when the excess weight is between 20 and 30%;
- *Moderate (medium)* obesity, at a weight excess of 30-50%;
- *Severe* obesity, when the excess weight is greater then 50% of the normal weight.

In all cases a full clinical examination has been performed (including the repeated measurement of the blood pressure).

◆ In order to identify MS, the glucidic and lipidic metabolism have been studied.

Evaluation of the glucidic metabolism

* *Fasting glycaemia* has been determined after a minimum of 8 hours of fasting. The glycaemia was determined from venous blood throught the glucose-oxidase method. The value of fasting glycemia was interpreted as follows:

- *Normal values* - for a glycaemia over 60mg% and under 100mg%;
- *Abnormal values* - when glycaemia is < 50mg% (low) or > 100mg% (high).

* *OGTT*

According to WHO recomandations, this means (in conformity with the fasting rules and physical activity stated before) the administration of a 1,75g dose of glucose pulvis/kg of the body, without exceeding 75g - regardless of the bodyweight of the child. The glucose dissolved in 250-300 ml water, maybe flavoured, is drank in a short time interval (under 5 minutes), after a sample of blood has been taken to determine the fasting glycemia. The test has been done for obese pacients with a glycaemia à jeun under 126mg%.

Evaluation of the lipidic metabolism:

* the dosage of triglycerides – throught the enzime method using GPO-PAP peroxidase;
* the dosage of HDLc – throught the precipitation method.

The determinations have been made with the help of a *Hitachi 717*.

Table 1 Elements of new definition of pediatric MS.

MS factor	Age (years)	Boys	Girls
1. Fasting glycaemia (mg%)	-	≥ 100	≥ 100
2. 2^{hrs} glycaemia (mg%) at oral glucose tollerance test (OGTT)	-	≥ 140	≥ 140
3. Sistolic blood pressure (SBT) (mmHg)	8 12 15 17	112 119 125 135	111 119 124 125
Diastolic blood pressure DBT (mmHg)	8 12 15 17	73 77 79 83	71 76 80 81
4. Triglicerides TG (mg%)	12-16 16-19	135 ≥ 150	140 ≥ 150
5. HDLc (mg%)	6-8 9-11 12-15 16-19	37 39 35 ≤ 35	37 38 36 ≤ 35
6. Ponderal Index (PI)	< 2	> 1,1	> 1,1
Body mass Index (BMI) (G kg/T^2 cm)	> 2	According to CDC tables	According to CDC tables

Results and Discussion

We have identified 32 cases of MS (12,92% of the total) with ages between 7 months – 18 years, 17 girls (53%) and 15 boys (47%) (figure1).

All the cases of MS had a duration of obesity of over 5 years and/or collaterals to obesity, T2DM, CVD, dyslipidemias.

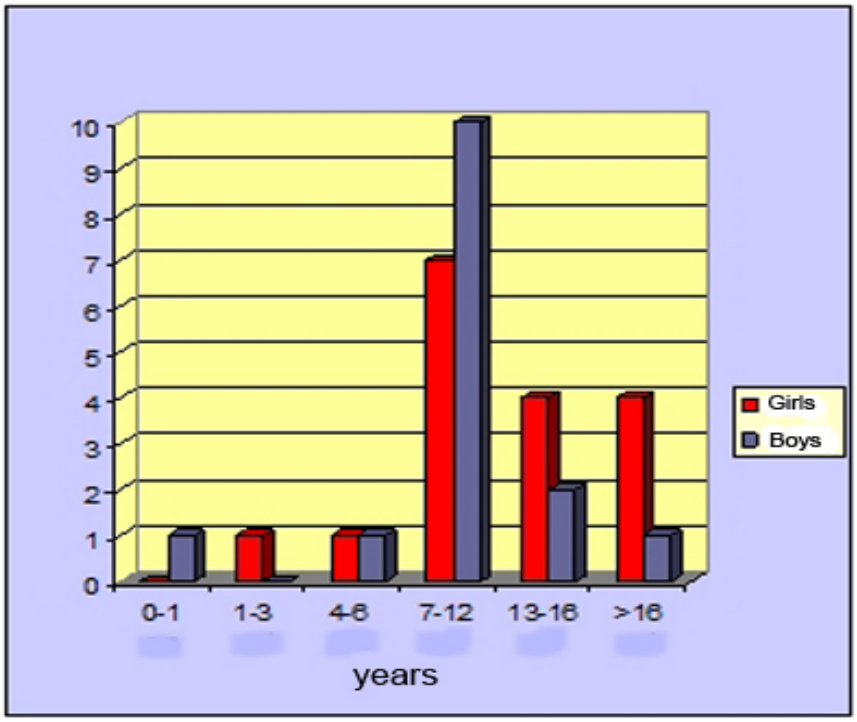

Fig.1. The distribution of cases of MS according to age and sex.

In our study, up to puberty the distribution according to sex is similar. At the age of puberty the percentage is higher for boys, and in adolescence the figures show higher percentage for girls.

As the degree of obesity increases, the prevalence of MS increases, with obesity occurring in 2,35% of mildely obese, 16% of moderately obese and 23,2% of severely obese children and adolescents. So the prevalence of MS in our cases has increased with the degree of obesity, therefore parallel with the BMI, as is emphasized in the recent medical literature.[7]

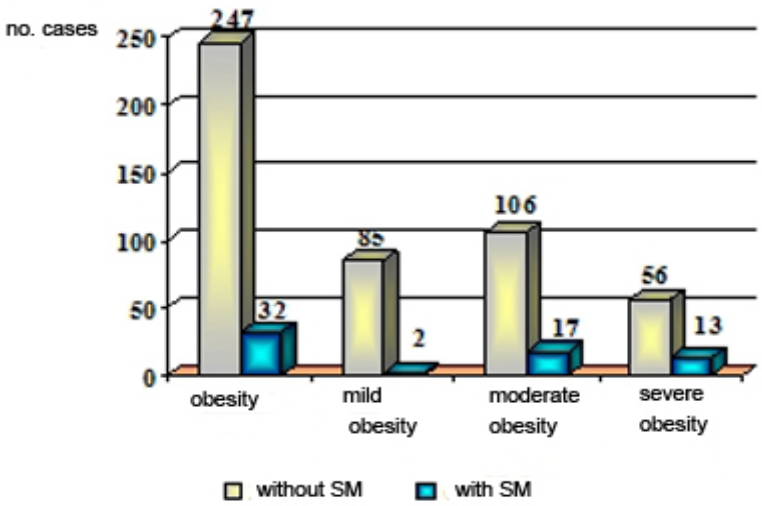

Fig.2. Distribution of cases according to the degree of obesity.

Obesity is strongly associated with insulin resistance, T2DM, and atherosclerotic CVD.[8] Data from the Framingham Study have established an increased incidence of cardiovascular events in both men and women with increasing weight; Obesity tracks from childhood to adulthood, and childhood adiposity is a strong predictor insulin resistance, and abnormal lipids in adulthood. Moreover, the rate of increase in adiposity during childhood was significantly related to the development of cardiovascular risk in young adults.[4]

17 of the cases with MS (53%) had a clinical symptomatology, and 15 have been asymptomatic, which proves once again that MS can become a "silent killer" in a significant number of cases (fig.3).

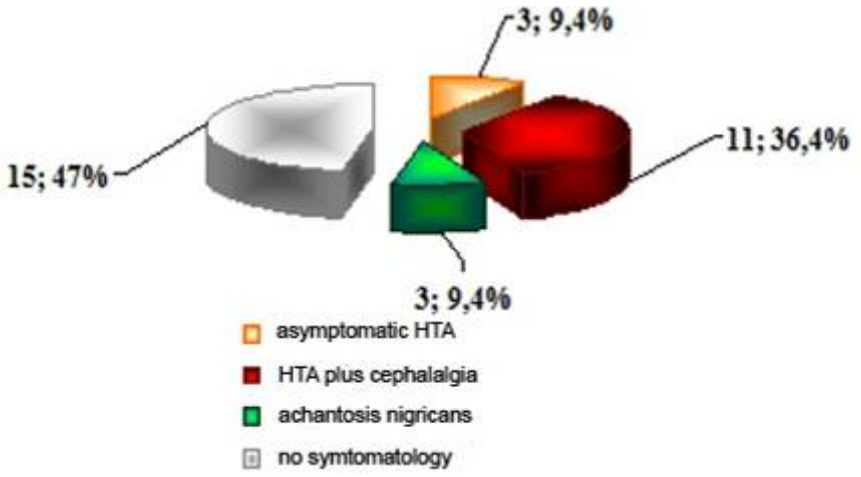

Fig.3. Clinical overview of MS.

The obese child's cephalalgia represented frequently the reason for coming to the hospital, this being the sympomatic manifestation of high blood pressure.

Hypertension is an integral component of the MS.[9] Increased sympathetic tone has been associated with obesity in adolescents, and both insulin and leptin appear to have a direct effect on sympathetic nervous system activity.[4] Insulin infusions stimulate sodium retention by the kidney, and insulin stimulates vascular smooth muscle growth. Fasting insulin, used as an estimate of insulin resistance, has been significantly correlated with blood pressure in children and adolescents.[10] The Cardiovascular Risk in Young Finns study showed a significant correlation between fasting insulin and blood pressure in children and adolescents and also showed that the level of fasting insulin predicted the level of blood pressure 6 years later.[11] Similarly, leptin has direct central effects that increase sympathetic outflow to the kidney. It has been hypothesized that selective leptin resistance maintains leptin-induced sympathetic activation in obesity, which permits leptin to play an important role in the pathogenesis of obesity-related hypertension and MS.[12] Studies in 11- to 15-year-olds[13] showed a lack of significant correlations for blood pressure with fasting insulin (adjusted for BMI), insulin resistance, triglycerides, HDL-C, and low-density lipoprotein (LDL) cholesterol. However, when the MS factors (triglycerides, HDL-C, fasting insulin, and BMI) were considered together as a cluster and comparisons made between children with high and low blood pressure, the cluster score was significantly higher in the high blood pressure group. Thus, despite the lack of a significant relation between blood pressure and the individual risk factors, its relation with the cluster of risk factors is consistent with a clinical association of blood pressure and the MS before adulthood. Most recently, the Fels Longitudinal Study showed a strong association between childhood hypertension and adult MS.[14]

With the current obesity epidemic and its metabolic consequences, the identification of children with impaired fasting glucose, that is, fasting glucose 100 to 126 mg/dL is very important, because appropriate management may decrease the progression to T2DM. Diabetes mellitus is associated with accelerated development of vascular disease. Nevertheless, not all children with impaired carbohydrate metabolism develop T2DM. In a study of children with impaired glucose tolerance followed up over a period of 1 year, one third became euglycemic, one third developed T2DM, and one third maintained impaired glucose tolerance.[15]

We have observed metabolic disturbances in 24 of the MS cases (75%) (fig.4).

One or more defining modifications of the lipidic metabolism have been present in 30 of the MS cases (94%) (fig.5).

Lipid abnormalities, particularly high triglycerides and low HDLc serum levels, are strongly associated with insulin resistance[16] and are criteria for the MS. Studies in rats have shown that hyperinsulinemia stimulates the synthesis of fatty acids by increasing the transcription of genes for lipogenic enzymes in the liver.[17] Fatty acids in turn stimulate increased production of very-low-density lipoprotein. It is currently unknown whether insulin resistance induces dyslipidemia or whether insulin resistance and dyslipidemia are associated via an underlying cause.

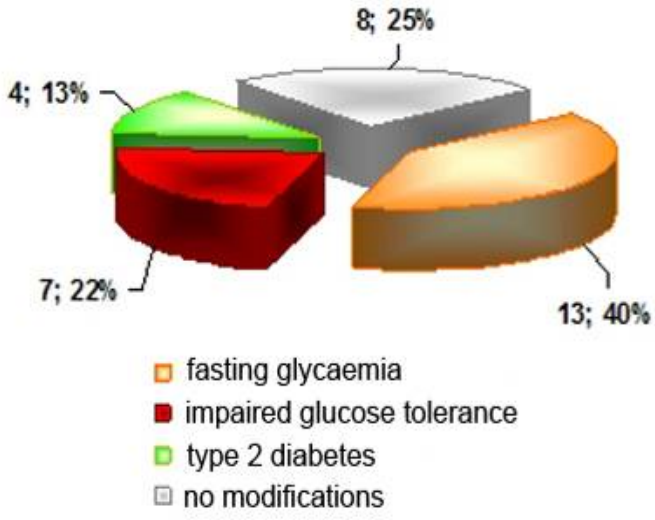

Fig.4. Glucidic metabolic disturbances in the MS cases.

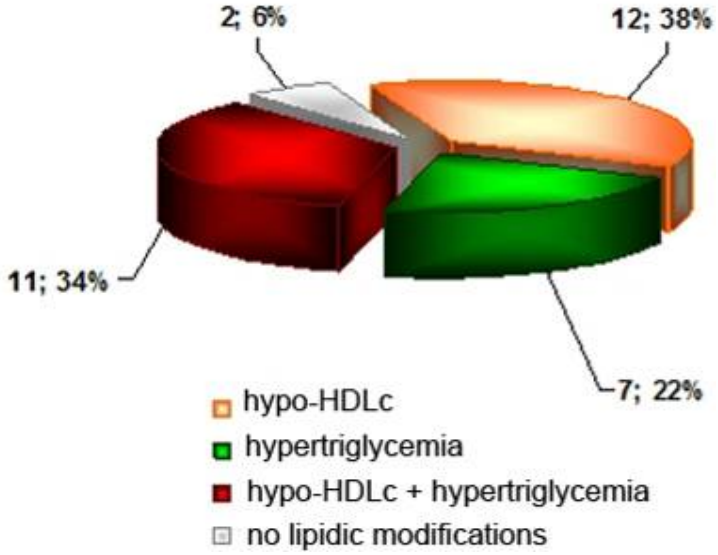

Fig.5. Lipidical metabolical disorders for the MS cases.

Abnormal lipid profiles also are found in children with obesity and insulin resistance.[18,19] Data from the Bogalusa Heart Study have shown that overweight children have significantly higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower HDL-C levels than normal-weight children.[20] The hypertriglyceridemic waist phenotype has been proposed in adults as a predictor of the MS.[21] A recent study in more than 3000 adolescents that used the modified ATP III cut points for serum triglycerides (≥110 mg/dL) and waist circumference (≥90th percentile for age and sex) has shown that the concomitant presence of these criteria was significantly associated with a clustering of metabolic abnormalities, which is characteristic of the MS.[22]

A third of the cases analyzed associated more than three defining factors for MS (table2), which means that the risk for developing cardovascular diseases in adulthood is very high: 7 pacients presented an association of 4 factors (21,8%) and 4 cases presented 5 factors (12, 5%).

Obese individuals develop different degrees of insulin resistance, but not all those with obesity develop glucose intolerance. The factors that make some individuals more likely to progress to T2DM are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment. Patients with T2DM often have other risk factors for cardiovascular disease; hypertriglyceridemia has been reported in 4% to 32% of children with T2DM.[23] Essential hypertension is known to be associated with diabetes in adults,[24] and it is estimated that cardiovascular risk doubles when hypertension and diabetes mellitus coexist; however, population-based prevalence data on hypertension in children with diabetes are not available.

Indeed, although the majority of children with MS tend to be overweight or obese, not all overweight or obese children develop MS, T2DM, or cardiovascular disease. In view of the increasing prevalence of and adverse trends in obesity and its comorbidities in children, the question is whether tools can be developed to identify children who are most at risk metabolically.

Conclusions

1. Pediatrical MS is a complex pathological problem.
2. Althought scarce, the clinical sympthomatology can be very valuable for the monitoring of complications/comorbidities present in the obese pacients.
3. The metabolical modifications represent the most frequent morbid states for the child affected by MS, observed even at very early ages.
4. Detecting and treating obesity and the present complications/comorbidities from childhood must be included in the heath programmes - as rational means of decreasing the morbidity and mortality of the adult due to atherogenic cardiovascular diseases.

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