DE GRUYTER OPEN

http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **22**(4):367-373
doi: 10.1515/rjdnmd-2015-0043

LOW BIRTHWEIGHT, RAPID WEIGHT GAIN AND METABOLIC SYNDROME IN ADOLESCENCE: AN ILLUSTRATIVE CASE REPORT

Alphonsus N. Onyiriuka [1, ✉], ***Chinwe A. Oguejiofor*** [1] , ***Wilson E. Sadoh*** [2]

[1] Endocrine and Metabolic Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria
[2] Paediatric Cardiology Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria

received: September 09, 2015 *accepted*: November 27, 2015
available online: December 15, 2015

Abstract

A 16-year-old boy whose diabetes mellitus was diagnosed 3 months previously in a private hospital but was not placed on medication. The presenting complaints were fast breathing for 24 hours, weakness for 2 hours, and unresponsiveness to calls for 0.5 hours. His father was obese with type 2 diabetes mellitus and died 8 months earlier from cardiac arrest. His birthweight was low, 2.2kg. At first presentation, his weight, BMI and blood pressure were 60kg (25^{th}-50^{th} percentile), 19.4kg/m^2 (25^{th}percentile) and 110/70mmHg (systolic BP 50^{th} percentile, diastolic BP 50^{th}-90^{th} percentile), respectively. He was managed for diabetic ketoacidosis and was discharged on subcutaneous premixed insulin, 1 Unit/kg/day. At point of discharge, weight and BP were 60.5 kg and 120/70 mmHg, respectively. The patient defaulted but presented again 6 months later at the age of 17 years. At second presentation, his weight, BMI and BP were 89 kg (95^{th} percentile), 27.5 kg/m^2 (90^{th}-95^{th} percentile) and 180/80 mmHg (systolic 99^{th} percentile; diastolic 90^{th} percentile), respectively. His waist circumference was 98.7cm (> 90^{th} percentile). We had no record of previous waist circumference. His lipid profile showed low HDL-cholesterol 0.7252 mmol/L [(28mg/dl); <5^{th}percentile]. His fasting blood glucose and HbA1C were 6.5 mmol/L (117mg/dl) and 34 mol/mol (5.3%), respectively. A diagnosis of metabolic syndrome in a patient with ketosis-prone type 2 diabetes was made. He was referred to the pediatric cardiologist for management of his hypertension. He defaulted again and was lost to follow up. ***Conclusion:*** *This report illustrates the association of low birth weight and rapid weight gain with metabolic syndrome in adolescence.*

key words: *adolescence, diabetes mellitus, low birthweight, metabolic syndrome, weight gain.*

Introduction

The metabolic syndrome (also called insulin resistance syndrome) is a constellation of interrelated risk factors of metabolic origin that are associated with the development of atherosclerotic cardiovascular disease [1]. There is no consensus definition of metabolic syndrome (MetS) in childhood and adolescence. This variability in definition is partly due to the growth and developmental changes that occur during childhood and adolescence, thereby

✉ PMB 1111, Benin City, Nigeria. Phone number: 08032529437;
corresponding author e-mail: alpndiony@yahoo.com

complicating the choice of cut-off points for risk factors [2]. The new International Diabetes Federation (IDF) definition is divided into three age groups because of developmental challenges presented by age-related differences in children and adolescents: age 6 to < 10 years; 10 to < 16 years; and 16 years and above. In all three age groups, abdominal obesity is the sine qua non [3]. IDF defines metabolic syndrome in individuals aged 16 years and above by central obesity plus any two of the following four factors: (1) raised triglyceride level > 1.7mmol/L, (2) reduced HDL-cholesterol level < 1.03mmol/L (< 40mg/dl) in males and < 1.29mmol/L (50mg/dl) in females, (3) raised blood pressure (BP) [systolic BP ≥130 or diastolic BP ≥ 85mmHG or on treatment for a previously diagnosed hypertension], and (4) impaired fasting glycaemia, FPG ≥ 5.6mmol/L (≥100mg/dl) or a previously diagnosed type 2 diabetes [3]. With regard to central obesity, IDF applies the existing criteria for adults i.e., waist circumference ≥ 90th percentile (≥ 94cm and ≥ 80cm for European men and women, respectively) [3]. The aim of the IDF definition is to provide a simple, universally accepted tool, which is easy to apply in clinical settings for the early detection and treatment of metabolic syndrome. Early detection followed by appropriate treatment is vital to halt the progression of the metabolic syndrome and safeguard the future health of children and adolescents [4].

The reports of some studies indicate that MetS may originate prenatally from fetal programming [5,6]. Population studies have confirmed the association of low birth-weight with the development of insulin resistance and ultimately, type 2 diabetes (T2D) [7,8]. There are compelling lines of evidence indicating that pediatric metabolic syndrome is strongly associated with adult metabolic syndrome, subclinical atherosclerosis and T2D, independent of other known predictors [2,9]. In this way, they increase the medical and economic burdens on society with their increased early morbidity and mortality [10].

The MetS in the pediatric age group is a growing clinical problem, tracking obesity [11]. Chen et al [12], have observed that data regarding MetS in children is limited, especially in developing countries (Nigeria inclusive). Mehairi et al [13], in a school-based study on MetS in the United Arab Emirate, found a prevalence of 13%. In that study, the most prevalent of the components of the MetS were low HDL-cholesterol followed by increased waist circumference. In a cohort of adolescents in the United States the prevalence metabolic syndrome was 6.8% and 28.7% among overweight and obese adolescents, respectively [14]. In China, a study involving 19,593 subjects aged 6-18 years revealed that the prevalence of metabolic syndrome was 10% and 27.6% among overweight and obese children and adolescents, respectively [12]. The prevalence of metabolic syndrome in adolescents varies by gender and ethnicity [13,15,16]. In addition, the result of a study in US and western Europe showed that the prevalence of metabolic syndrome in children and adolescents is increasing; 2% in mid-1990s to 10% in 2009 [2]. In Africa, a rising trend in prevalence of metabolic syndrome in adults has been observed [17,18] but epidemiologic data for children and adolescents is lacking. The report of a study among Mexican children indicated that MetS is preventable, if interventions in lifestyle are instituted early [19]. The purpose of this report is to illustrate the association of low birth-weight with rapid weight gain and occurrence of metabolic syndrome later in adolescence. Thus, encouraging physicians to look out for metabolic syndrome in the pediatric age group would

promote early diagnosis and appropriate intervention that will halt its progression.

Case report

A 16-year-old boy whose diabetes mellitus was first diagnosed 3 months previously in a private hospital but was not placed on medication and subsequently presented at the Children's Emergency Unit, University of Benin Teaching Hospital (UBTH). The presenting complaints were fast breathing for 24 hours, weakness for 2 hours, and unresponsiveness to calls for 0.5 hours. At the onset of the fast breathing, he was given some herbal concoctions and paracetamol. He also had fever and catarrh, a day before. Our patient is the youngest of 6 children (3 boys and 3 girls) in a monogamous family setting. His father was obese with T2D and died 8 months earlier from cardiac arrest. Perinatal history revealed that his birth weight was 2.2kg (low birth-weight) and this was confirmed from the hospital birth card.

Physical examination revealed an acutely ill-looking adolescent boy with moderate dehydration. His weight was 60kg (25^{th}-50^{th} percentile), height 176cm (50^{th}-75^{th} percentile) and BMI 19.4kg/m^2 (25^{th} percentile). He had altered consciousness with a Glasgow Coma Scale of 11/15. He was tachypnoeic with a respiratory rate 46 cycles/minute. He was noted to have an acidotic breathing pattern. He had tachycardia (pulse rate was 120 minute) and a normal blood pressure reading of 110/70mmHg (systolic BP 50^{th} percentile, diastolic BP 50^{th}-90^{th} percentile). Other body systems were essentially normal. A diagnosis of diabetic ketoacidosis (DKA) was made. The laboratory findings at the point of admission are summarized in Table 1.

Dehydration was corrected with normal saline (0.9% sodium chloride). He was treated with insulin infusion at a rate of 0.1unit/kg/hr and standard protocol for management of diabetic ketoacidosis was followed [20]. As a policy, he was commenced on I.V clavulanate-potentiated amoxicillin (Augmentin) 50 mg/kg/day for presumed bacterial infection. The DKA resolved 24 hours after initiation of treatment and he was switched to subcutaneous insulin. While on admission, the blood glucose concentration ranged between 8.5-17.5 mmol/L. He was subsequently discharged home after 9 days from admission on subcutaneous premixed combination of human insulin, 70% intermediate-acting insulin plus 30% short-acting (regular) insulin, given twice daily (40 units in the morning and 20 units in the evening) at 1 Unit/kg/day, to be followed up in the clinic. At the time of discharge, the diagnosis was modified to ketosis-prone T2D.

Table 1. Summary of laboratory findings at admission.

Laboratory parameters	**Results**	**Comments**
At first presentation:		
Random blood glucose	19.7mmol/L	Hyperglycaemia
Urine ketone	2+	Ketonuria
Urine glucose	3+	Glycosuria
Serum urea concentration	12mg/dl	Within normal limits
Serum sodium concentration	134mmol/L	Slightly low
Serum potassium concentration	3.3mmol/L	Slightly low
Serum chloride concentration	110mmol/L	Within normal limits
Serum bicarbonate concentration	8mmol/L	Severe acidosis
Serum creatinine concentration	0.8mg/dl	Within normal limits
Blood culture	Yielded no growth	Sterile

The patient defaulted but presented again 6 months later at the age of 17 years. At this time, his weight was 89 kg (95^{th} percentile) and height 180 cm (75^{th} percentile) with a BMI of 27.5 kg/m^2 (90^{th}-95^{th} percentile). His waist circumference was 98.7 cm (> 90^{th} percentile). We had no record of previous waist

circumference. His blood pressure was 180/80 mmHg (systolic 99th percentile; diastolic 90th percentile for height, age and sex).

Table 2. Summary of laboratory finding at second visit in the clinic.

Parameters	Results	Comments
Total cholesterol	2.5382 mmol/L (98mg/dl)	< 5th percentile; desirable
Serum HDL-cholesterol	0.7252 mmol/L (28mg/dl)	< 5th percentile; high risk of CVD
Serum LDL-cholesterol	1.5045 mmol/L (51mg/dl)	50th-75th percentile; optimal
Serum triglyceride	1.105 mmol/L (97mg/dl)	75th -90th percentile; borderline
Fasting blood glucose	6.5 mmol/L (117mg/dl)	Impaired fasting blood glucose
Glycosylated haemoglobin	34 mol/mol (5.3%)	Excellent control in past 2-3 months
Total cholesterol:HDL-C	3.5	Good (but ideally < 3.5)
HDL-C:LDL-C	0.549	Optimal
Triglyceride:HDL-C	3.464	Within normal limits (but ideally < 2)

HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; CVD = Cardiovascular disease

A diagnosis of metabolic syndrome was made. He was referred to the paediatric cardiologist for management of his hypertension. His blood pressure was normalized to 110-130/80-90 mmHg, using antihypertensive medications. However, the patient stopped taking the medication after 2 weeks. He said he has been taking the insulin at the prescribed dose during the 6-month period of default. He expressed sadness concerning frequent visits to the hospital. The patient was lost to follow up and efforts to reach him through his mother's phone number were unsuccessful.

Discussion

The diagnosis of metabolic syndrome in our patient was based on the IDF definition for individuals aged 16 years and above [3]. In this regard, the diagnostic features present in our patient were abdominal obesity (defined by his waist circumference of 98.7cm; > 90th percentile) plus an impaired fasting blood glucose, a low HDL-cholesterol level and a high BP. In the index patient, we chose to use the IDF criteria because it is simple and easy to apply in clinical setting [3], as it does not use multiple tables to assess several anthropometric and metabolic criteria [21]. Furthermore, Mancini in his review of the various definitions of metabolic syndrome in children and adolescents, concluded that from convenience point of view, the IDF guideline is the most appropriate as it has cut-offs fixed for blood pressure, lipids, glycaemia and waist circumference points, assessed by percentile [21]. In addition, two very recent studies on metabolic syndrome in children and adolescents also used the IDF definition for identifying their subjects [14,22]. On the other hand, the main drawback of IDF guidelines is that it does not have a well defined proposal for children below six years of age, due to lack of epidemiological data. The other two definitions of metabolic syndrome commonly used by researchers are those of Cook et al [13] and Viner et al [23]. The cut-offs chosen by Cook et al [13] and Viner et al [23] for glucose/insulin levels are so high that only a small number of children exceed the threshold [21]. The resultant effect is that the prevalence of metabolic syndrome is mainly driven by the other three components in these two definitions, thus making them less applicable in clinical setting than the IDF criteria.

Some of the clinical and laboratory profile features of our patient need consideration. The patient was a low birth weight infant and has a parental history of T2D and obesity. These clinical features are known risk factors for the development of metabolic syndrome [5-7,24].

Thus, these risk factors may have contributed to the development of metabolic syndrome in our patient. In addition, the rapid gain in weight and by extension, BMI (each crossing three percentiles curves in 6 months) may also have contributed. Among a cohort of children and adolescents followed-up for two years, multiple linear regression analysis revealed that blood pressure increased by 0.77 mmHg for every kilogram of weight gain [25]. Thus, rapid weight gain may have accounted for the observed increase in blood pressure from 110/70 mmHg to 180/80 mmHg over a period of six months in our patient. Following a diagnosis of diabetes mellitus in the private hospital, the patient was not commenced on any medication until he presented 3 months later with ketoacidosis. An acute emergency which would have been prevented, if therapy was commenced at the time of first diagnosis of diabetes mellitus. The implication of this scenario in our setting is that a significant number of physicians still need some education concerning diabetes mellitus in the paediatric age group. The low HDL-cholesterol level in our patient represents a risk factor for the development of cardiovascular disease [26]. The deleterious changes in lipid profile in obese individuals are known to be more closely correlated with the amount of visceral fat (evidenced by waist circumference > 90^{th} percentile) than to total body fat [26]. In a community-based study (The Bogalusa Heart Study) which assessed risk factors for cardiovascular disease among 9,167 subjects aged 5 to 17 years, it was found that children with BMI above 85^{th} percentile for age and gender were more likely to have abnormal levels of cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and elevated blood pressure respectively, than their normal weight counterparts [27]. Indeed, our patient had a low HDL-cholesterol level and a significant hypertension. The BMI is known to correlate with blood pressure and abnormalities in serum lipid profile [26], a feature depicted in our patient. In a postmortem study (The Pathobiological Determinants of Atherosclerosis in Youth), it was found that 12% of adolescents aged 15 to 19 years had moderate or advanced lesions of atherosclerosis in their right coronary arteries with extent and severity of lesions correlating with BMI and lipoprotein levels [28].

Missing from clinic appointments is a common phenomenon in our setting. This is worrisome and needs to be addressed by encouraging the patients and their parents to keep clinic appointments. The patient expressed sadness with regard to frequent visits to the hospital, suggesting the need for psychological support, particularly as the patient is an adolescent. The death of his father may have contributed to the difficulty in controlling the patient and ensuring adherence to planned therapy.

Conclusion

In conclusion, this case report illustrates the association of low birthweight with rapid weight gain and metabolic syndrome later in adolescence. It is our hope that this report will encourage physicians to look out for metabolic syndrome in the paediatric age group, thereby promoting early diagnosis and appropriate intervention that will halt its progression.

Duality of interest: We have no competing interest with regard to the scope of this case report.

REFERENCES

1. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for critical appraisal: joint statement from American Association and European Association for the study of diabetes. *Diabetes Care* 28: 2289-2304, 2005.

2. Steinberger J, Daniels SR, Eckel RH et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association, Atherosclerosis, Hypertension and Obesity in the Young Committee of the Council on Cardiovascular Disease of the Young: Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity and Metabolism. *Circulation* 119: 628-647, 2009.

3. Zimmet P, Alberti K, Kaufman F et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes* 8: 299-306, 2007.

4. Alberti K, Eckel PRH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Athersclerosis Society and International Association for the Study of Obesity. *Circulation* 120: 1640-1648, 2009.

5. Ozanne SE, Hales CN. Early programming of glucose-insulin metabolism. *Trends Endocrinol Metab* 13: 368-373, 2002.

6. Levitt NS, Lambert EV. The foetal origins of metabolic syndrome – a South African perspective. *Cardiovasc J S Afr* 13: 179-180, 2002.

7. Phipps K, Barker DJ, Hales CN, Fall CN, Osmond C, Clark PM. Fetal growth and impaired glucose tolerance in men and women. *Diabetologia* 36: 225-228, 1993.

8. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 45: 342-348, 2002.

9. Frontini MG, Srinvasan SR, Berenson GS. Longitudinal changes in risk variables underlying metabolic syndrome X from childhood to young adulthood in female subjects with a history of early menarche: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord* 27: 1398-1404, 2003.

10. Gunnel DJ, Frankel SJ, Nanchahal K, Peters TJ, Davey-Smith G. Childhood obesity and adult cardiovascular mortality: a 57-year follow-up study based on the Boyd Orr Cohort. *Am J Clin Nutr* 67: 1111-1118, 1998.

11. Lee L, Sanders RA. Metabolic syndrome. *Pediatr Rev* 33: 459-468, 2012.

12. Chen F, Wang Y, Shan X et al. Association between childhood obesity and metabolic syndrome: evidence from a large sample of Chinese children and adolescents. *PLoSOne* 7(10): e47380, 2012.

13. Mehairi AE, Khouri AA, Naqbi MM et al. Metabolic syndrome among Emirati adolescents: A school-based study. *PLoSOne*8(2): e56159, 2013.

14. Cook S, Weitzman M, Auinger P, Nguyen M, Aietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1998-1994. *Arch Pediatr Adolesc Med* 157: 821-827, 2003.

15. De Ferranti SD, Osganian SK. Epidemiology of paediatric metabolic syndrome and type2 diabetes mellitus. *Diabetes Vasc Dis Res* 4: 285-296, 2007.

16. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *New Engl J Med* 350: 2362-2374, 2004.

17. Okafor CI. The metabolic syndrome in Africa: Current trends. *Indian J Endocrinol Metab* 16: 56-66, 2012.

18. Fezeu L, Balkau B, Kengne A, Sobngwi E, Mbanya JC. Metabolic syndrome in sub-Saharan African setting: central obesity may be the key determinant. *Atherosclerosis* 193: 70-76, 2007.

19. Elizondo-Montemayor L, Gutierrez NG, Moreno DM, et al. School-based individualized lifestyle intervention decreases obesity and metabolic syndrome in Mexican children. *J Hum Nutr Diet* 26(Suppl 1): 82-89, 2013.

20. Wolfsdorf JI, Allgrove J, Craig ME et al. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Diabetes ketoacidosis *Pediatr Diabetes* 15(Suppl 20): 154-179, 2014.

21. Mancini MC. Metabolic syndrome in children and adolescents – criteria for diagnosis. *Diabetol Metab Synd* 1: 20-23, 2009.

22. Ahrens W, Moreno LA, Marild C et al. Metabolic syndrome in young children: definitions and results of the IDEFICS Study. *Int J Obes* 38: S4-S14, 2014.

23. Viner RM, Segal TY, Lichtarowicz-Krynska E, Hindmarsh P. Prevalence of the insulin resistance syndrome in obesity. *Arch Dis Child* 90: 10-14, 2005.

24. Efstathiou SP, Skeva II, Zorbala E, Georgiou E, Mountokalakis TD. The metabolic syndrome in adolescence: can it be predicted from natal and parental profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study. *Circulation* 125:902-910, 2012.

25. Archana D. Metabolic syndrome in children and adolescents. In: *Advances in Pediatrics.* Dutta AK, Sachdeva A (eds). Jaypee Brothers Medical Publishers Ltd, New Delhi, pp 748-754, 2007.

26. McGavock JM, Torrance B, McCuire KA, Wonzy P, Lewanczuk RZ. The relationship between weight gain and blood pressure in children and adolescents. *Am J Hypertens* 20(10):1038-1044, 2007.

27. Freedman DS, Dietz W, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: The Bogalusa Heart Study. *Pediatrics* 103: 1175-1182, 1999.

28. McGill Jr HC, MeMahan CA, Herdeick EE et al. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation* 105:2712-2718, 2002.