

Metabolic Syndrome in a Teenager as a Clinical Picture of R482W LMNA Mutation

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Abstract

Metabolic Syndrome (MS) can be diagnosed from the age of 10 years, when the coexistence of abdominal obesity, glucose metabolism disorders, dyslipidemia, and hypertension is observed. A binding part of MS is insulin resistance. Severe insulin resistance may be caused by a mutation in lamin (LMNA) gene. A teenager with MS due to mutation in LMNA gene is presented.

A 17.5-yr-old Caucasian girl was admitted to the hospital with the suspicion of diabetes mellitus due to causal blood glucose 393 mg/dl (21.8 mmol/l), without typical diabetic symptoms. Since the age of 13 years she had been presented with excessive weight gain, hirsutism, and oligomenorrhoea. Her family history was positive for diabetes and partial lipodystrophy in three generations. Physical examination revealed abdominal obesity (waist-circumference 86 cm, BMI 27 kg/m²), android/cushingoidal habitus, acanthosis nigricans in axillae and neck, hirsutism, enlarged liver, and pseudohypertrophy of muscles of limbs with partial lipodystrophy. Based on oral glucose tolerance test diabetes was diagnosed (HOMA-IR 14). HbA1c was 9.2% (78 mmol/mol). Diabetes autoantibodies were negative. Lab tests revealed also dyslipidemia (total cholesterol 6.42 mmol/l, triglycerides 7.42 mmol/l, HDL cholesterol 0.73 mmol/l) and elevated liver enzymes. Ultrasonography revealed steatosis

hepatitis and polycystic ovaries. Genetic tests confirmed that she is a carrier of heterozygous missense mutation (c.1444C>T; R482W) in the LMNA gene. Lifestyle changes, metformin dosage 500 mg three times a day and ursodeoxycholic acid were introduced as her therapy. After 4 months of this treatment HbA1c levels dropped 5.8% (40 mmol/mol). Moreover an improvement of lipid profile, liver tests and 2 kg body weight loss were observed.

Diabetes mellitus as a component of MS in a young obese patient should be diagnosed individually. When other non-typical for diabetes mellitus clinical signs and symptoms exist with positive, multigenerational family history, genetic causes of MS should be taken into consideration.

Keywords: Insulin resistance; Metabolic syndrome; Familiar partial lipodystrophy; FLPS

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Introduction

Metabolic Syndrome (MS) is a cluster of conditions - increased blood pressure, a high blood sugar level, excess body fat around the waist and abnormal cholesterol levels - that occur together, increasing the risk of the heart disease, stroke and diabetes with all its complications [1]. Moreover metabolic syndrome is also associated with an increased risk of some common cancers [2, 3].

The underlying pathophysiology of metabolic syndrome seems to be related to insulin resistance [4]. The exact causes of insulin resistance are not completely understood. Insulin resistance is caused by a persistently high level of insulin over a prolonged period of time that eventually causes the body's sensitivity to insulin to decrease. The major contributors to insulin resistance seem to be excess weight and physical inactivity, so risk factors associated with lifestyle, which could be modified. However some cases of insulin resistance are associated with not modifiable genetic risk factors. MS is common in adults but it is also observed in obese children. Metabolic syndrome can also occur in lean individuals, suggesting that obesity is a marker for the syndrome, not a cause [5].

The definition of MS is a matter of debate since 1998 [6]. In 2009 the International Diabetes Federation (IDF) and American Heart Association (AHA) defined MS as three (or more) of the following factors: increased waist circumference, raised triglycerides, reduced HDL-cholesterol, raised blood pressure, and raised fasting plasma glucose. In 2007 IDF proposed a definition of MS for children 10-y-old or older [7]. For teenagers older than 16 yrs existing IDF criteria of MS for adults should be used. Some clinical observations suggest that in very young person the genetic cause of MS should be searched and identified.

There is an ongoing discussion on the diagnosis clinical usefulness of MS.

Although the metabolic syndrome appears to have limited utility for the identification of individuals at increased risk of type 2 diabetes mellitus or cardio-vascular diseases, the diagnosis of the metabolic syndrome presents an opportunity to rationalize

health services to deliver coordinated care to those with MS [8, 9].

The aim of the study is to present a teenager with metabolic syndrome due to LMNA mutation existing also in other members of the patient's family.

Case Report

A 17.6-yr-old, Caucasian overweight girl (BMI 27 kg/m²) of non-consanguineous couple of Central-European descent, with hirsutism/androgenisation and oligomenorrhea was admitted to our department with a suspicion of diabetes mellitus due to incidental, causal blood glucose 393 mg/dl (21.8 mmol/l). She did not present with typical Diabetes Mellitus (DM) signs and symptoms. Her family history was positive for DM (grand-mother, father's brother), disorders of carbohydrate metabolism (impaired fasting glucose – father, glucose intolerance - older sister) and PolyCystic Ovaries, PCOS (older sister). Her medical revealed increased appetite, excessive weight gain, appearance of acanthosis nigricans, hirsutism, androgenoidal habitus, irregular menses observed since 13 yrs of life. Puberty appeared normal, menarche occurred at the age 12.3 yrs. At the age of 15 yrs she was diagnosed with depression and pharmacological treatment had been administrated over one year with good result.

Being admitted to the hospital she presented with a good clinical condition. The overweight (50% excess of body weight for her height) with abdominal obesity (WHR 0.9) [Figure 1], android habitus with cushingoidal face, severe acanthosis nigricans in neck and axillae regions, acnae on face and upper trunk, and hirsutism (10 pts in Ferriman-Galleway score) were observed. In addition pseudohypertrophy of muscles of limbs with partial lipodystrophy (extremitas and gluteal region) [Figure 2] and enlargement of liver were notice. Blood pressure was normal. Some of her family members, whose with carbohydrate metabolism disorders presented with similar phenotype [Figure 3].

DM was diagnosed on the basis of an oral glucose tolerance test. Fasting plasma glucose was 162 mg/dl (9 mmol/l) and 2-hour plasma glucose 252 mg/dl (14 mmol/l). Insulin levels were 35.8 IU/ml and 88.5 IU/ml, respectively. High fasting level of

Figure 1

Growth, Body mass and BMI charts of the patient with LMNA mutation.

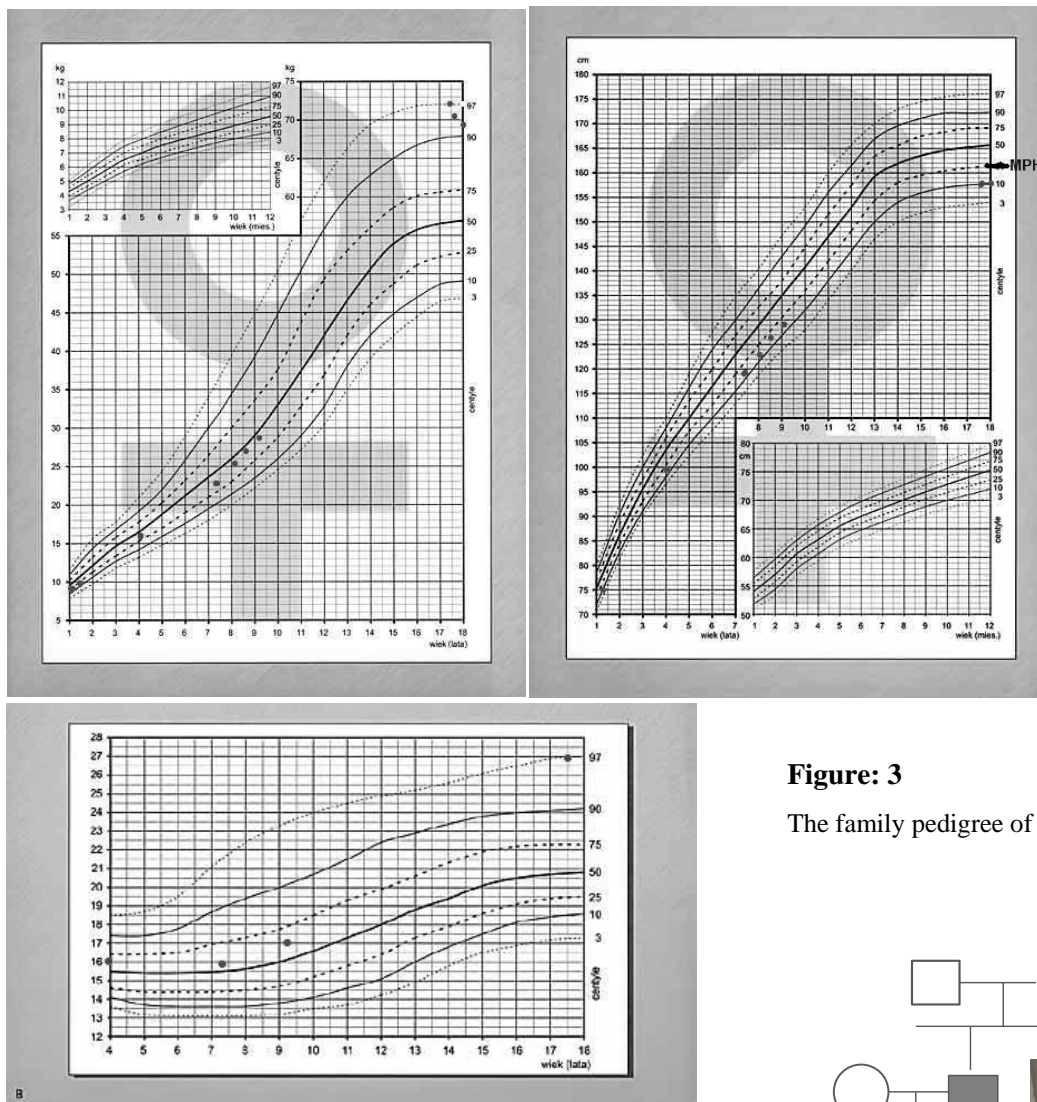


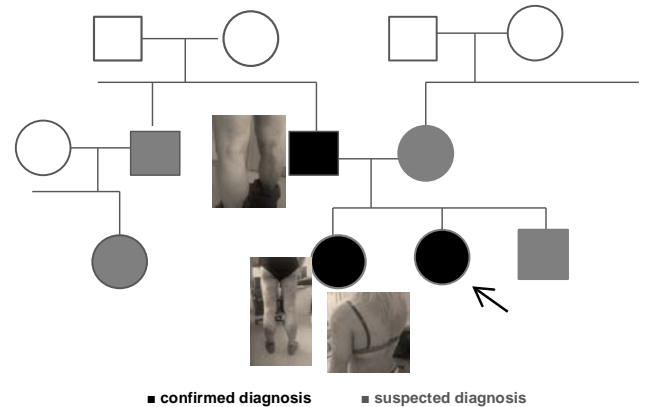
Figure: 2

Lipoatrophy of legs and muscular hypertrophy in calves of the patients with LMNA mutation.



Figure: 3

The family pedigree of the patient with LMNA mutation.



insulin and high HOMA index - 14 indicated severe insulin resistance. High HbA1c 9.2% (78 mmol/mol) confirmed the diagnosis of DM. Further diagnostics revealed also dyslipidemia with elevated total cholesterol (6.42 mmol/l), triglycerides (7.42 mmol/l), and LDL cholesterol (3.34 mmol/l) and decreased HDL cholesterol (0.73 mmol/l). Moreover elevated liver

enzymes such as AST 161.5 U/L (N 15-45), ALT 166.6 U/L (N 10-40), and GGT 39 U/L (N 10-29) were observed. Diabetes autoantibodies were negative: Islet cell antibodies - ICA 0 (N<0), Glutamic Acid Decarboxylase antibodies - anti-GAD 1 IU/ml (N<10).

In the differential diagnosis of elevated liver enzymes hepatic viral infections (HBs antigen – negative, anti-HCV antibodies – negative) were excluded. Detailed assessment of the liver function showed normal results of albumin level - 45.5 g/l (N 37-56), protrombin (prothrombin index – 99.8 %, INR (Quick index) - 1.0) ammonia - 24.5 μ mol/l (N 20-70), total bilirubin 20.9 - μ mol/l (N 3-22) and alkaline phosphatase - 51 U/l (N 58-237). Ultrasonography of liver revealed hyperechoic liver and blurring of vascular margins characteristic for steatosis hepatis, so Non-Alcoholic Fat Liver Disease, NAFLD was diagnosed.

In the diagnostic process of oligomenorrhea, LH - 2.93 mIU/ml (N 1-21.55), FSH - 4.16 mIU/ml (N 1.5-8.77), estrogen - 116.2 pg/ml (N 14 – 238) and testosterone 0.48 ng/ml (N 0.1-1.12) levels were assessed and were within normal ranges for a second phase of menstrual cycle. Thyroid function: TSH 5.39 uIU/ml, FT4 17.1 pmol/l (N 10-25), aTPO <5.5 IU/ml (N 0-60) was assessed and revealed subclinical hypothyroidism. In the assessment of adrenal function an ACTH level - 30.6 pg/ml (N 10-60) and a cortisol profile: 8.00 AM 219.6 ng/ml (N 50-230) and 8.00 PM 55.5 ng/ml were checked and were normal so test with dexametason was not made. Moreover the level of 17-OHP was measured and was normal - 1.43 ng/ml (N 1-5.2). The only abnormalities were slightly elevated level of DHEA-S - 288 ug/dl (N 20-260) and notably decreased the level of SHBG 5.9 nmol/ml (N 21-139). Ultrasonography of pelvis revealed presence of an ovarian cyst/cysts (size 40x40x38 mm) at left. Tumor markers were checked: AFP 2.7 ng/ml (N 0-10), β -HCG 4.9 mIU/ml (N 0-5), and Ca 125 25.71 U/ml (N 0-35) and were negative.

On the base of above-mentioned data, she was diagnosed with MS and polycystic ovarian syndrome, PCOS. Despite the introduction of the initial treatment such as diet and physical activity, her 24 hour blood glucose profile was still abnormal. Therefore, metformin was introduced. After three days of

treatment with metformin ALT level increased - 183.4 U/L (N 10-40), therefore metformin was replaced with insulin therapy - Insulin analog (glulisin) for main meals. After three weeks of this treatment a decrease of the ALT level - 83 U/l was observed, so again metformin was replaced with insulin therapy. Follow-up after four months of treatment with metformin dosage 500 mg three times a day, the reduction of body weight - 2.4 kg (body weight 70 kg), normalization of menstrual cycles and the level of HbA1c - 5.8% (40 mmol/mol). Moreover improvement of lipids profile: total cholesterol 4.68 mmol/l, triglycerides 3.51 mmol/l, HDL cholesterol 0.86 mmol/l, LDL cholesterol 3.11 mmol/l was observed. Also improvement of liver tests: ALT 66 U/L and AST 40.6 U/L was visible.

Due to observed abnormalities and similar phenotypes in the family of our patient genetic cause of insulin resistance in the patient such as: MS, NAFLD, severe acanthosis nigricans, PCOS was suspected. According WHO classification, diabetes mellitus type 3b consisting of different types of diabetes due to genetic causes of insulin resistance. Among them the most probable for the patient had been seemed to be type 2 of familiar partial lipodystrophy, FDLP2 caused by the mutation in lamin gene, LMNA. Therefore DNA of the patient was extracted and sent to the reference genetic laboratory in Lodz, Poland. Genetic analysis using Sanger DNA sequencing revealed that the patient was a carrier of heterozygous missense mutation (c.1444C>T; R482W) in the LMNA gene (OMIM 151660). LMNA mutation was also found in some members of her family [Figure 3]. The diagnosis of the Familial Partial Lipodystrophy type 2, named the Dunnigan type FPLD was made.

Discussion

Familial Partial Lipodystrophy type 2, named the Dunnigan type FPLD is a rare, about 1: 10 mln, form of monogenic form of insulin resistance [10-12]. It is caused by the mutation of LMNA gene [13, 14]. Lamin is a filamentous structure located between the inner membrane of the nuclear envelope and the chromatin in the nucleus. Nuclear lamins are responsible for: shape and architecture of the nucleus, nuclear envelope assembly, organization and anchoring of chromatin,

and the nuclear channel system. Therefore lamins are essential for DNA replication and mRNA transcription [15]. Because of such multiple roles of the lamina in cells, mutations in the LMNA gene result in the diverse group of disorders (muscular dystrophies, lipodystrophies, neuropathies, systemic laminopathies) [16, 17]. Because lamin participates in the insulin transduction pathway, LMNA mutation could cause insulin resistance, the clinical picture of FPLD2.

The essential hallmark of the FPLD2 is abnormal distribution of subcutaneous fat [10]. Partial lipodystrophy with lipodystrophy of limbs, gluteal region and trunk coexist with cervico-facial accumulation. The presence of excess adipose tissue in the face and neck giving the pseudo-Cushingoid appearance. Patients with FDLP are born with normal fat distribution. Alteration in body fat distribution starts gradually at the time of puberty. Furthermore FDLP patients have normal stores of intermuscular, intra-abdominal, intrathoracic and bone marrow fat. In spite of abnormal fat distribution muscular hypertrophy is observed, predominant in calves [14]. Other clinical features of the syndrome are associated with insulin resistance, such as: acanthosis nigricans, obesity, pre-diabetes or diabetes; hyperandrogenism, hirsutism, irregular menses and polycystic ovaries, hepatic steatosis, hepatomegaly; lipid abnormalities: high levels of serum total cholesterol and TG and low levels of HDL cholesterol hypertriglyceridemia. All of the above mentioned abnormalities were present in the proband. Women are more severely affected with metabolic complications. This fact was confirmed in the described patients family. Genetic confirmation of FDLP explain the lack of an effect of life style management initially indicated in patients with MS without genetic abnormalities [18]. Moreover the result of genetic tests allows to take into consideration replacement of metformin treatment with thiazolidinediones, eventually leptin [19, 20, 21]. In FDLP patients glitazones may be initially effective however their side effects should be taken into consideration. Glitazones can cause further accumulation of fat in the face and neck [22]. In partial lipodystrophy, leptin replacement has limited value with improvement of hypertriglyceridemia but not hyperglycemia [23].

The patients with FDLP should be monitored due to different metabolic complications of the disease throughout all her life. Because of known clinical risk of cardiovascular complications in patients with MS appropriate prophylaxis and treatment should be used. The younger patient with MS the longer time of exposition on metabolic risk factors. There is still limited number of reports of the syndrome and it is regarded as underrecognized [24]. The LMNA R482 mutation has an extremely strong statistical association with FDLP [14]. Carriers of the LMNA R482W mutation were recognized under the circumstances of diabetes treatment [25] Particularly this LMNA R482W mutation FPLD induces clinical early atherosclerosis and in vitro endothelial dysfunction [26]. Carriers of the LMNA R482W mutation present with dyslipidemia as an early and prominent feature [27]. Particularly dyslipidemia but also other components of MS increase blood viscosity. Chronic blood viscosity seems to play an important role in the pathogenesis of vascular diseases [28].

In FDLP also psychologic/psychiatric management is often necessary as it is impossible to change the abnormal appearance with pharmacological treatment. Due to variety of clinical picture of LMNA mutation genetic counseling should continued in FDLP families.

In conclusion, FPLD should be taken into consideration in young people with MS coexisting with other disorders associated with insulin resistance, abnormal distribution of subcutaneous fat and with family history of similar abnormalities.

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