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Case Report Open Access

Effectiveness of Metformin Treatment in the Teenager with Maturity-Onset Diabetes of the Young Type 3 and Oligomenorrhoea: A Case Presentation

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Abstract

Sulphonyloureas are a treatment of choice for Maturity-Onset Diabetes of the Young type 3 (MODY3) young patients with excellent results, although they should be used with a great caution. In adult MODY3 patients hypersensitive response to sulphonyloureas and a decreased response to metformin in compare to sulphonyloureas were reported.

A case of teenager with MODY 3 and oligomenorhoea, successfully treated with metformin is presented.

A fifteen and a half year-old girl was diagnosed with oligomenorrhoea. Due to detected glucosuria and blood glucose (BG) at 267 mg/dl she was referred to a pediatric endocrinologist. She did not present with typical diabetes mellitus (DM) symptoms, however she had a three generations family history positive for insulin-dependent DM. She presented with a good clinical condition. The underweight (Body mass index 18.7 kg/m^2) and discrete hirsutism were observed. Glucosuria, ketonuria, BG above 200 mg/dl in 24-h BG profile, and HbA1c 7.1% confirmed the diagnosis of DM, and insulinotherapy was initiated. Further diagnostics revealed high C-peptide levels and negative diabetes autoantibodies. Due to a low requirement of insulin and a presence of oligomenhorea, insulinotherapy was replaced with metformin. Three months after metformin introduction, HbA1c level normalized and menstruation cycles became regular. Genetic tests confirmed the diagnosis of MODY3 in the patient and her family. No pathology in the morphology and function of the kidneys was found. Due to the positive effect of metformin on regulation of menstrual cycles, and the continued high C-peptide level, the treatment with metformin has been continued. During the last three years follow-up, HbA1c levels fluctuated between 5.6-5.8% and menstrual cycles have been regular.

Our case presents that metformin could be an adequate treatment for teenagers with MODY 3 and oligomenorhea/PCOS with good results of diabetes control and benefits for ovarian function.

Keywords: Maturity-Onset Diabetes of the young type 3; MODY3; HNF 1 alpha mutation; Oligomenorrhoea; Teenager

Background

MODY represents a genetically and clinically heterogenous group of diabetes subtypes. It is characterized by an autosomal dominant mode of inheritance as well as early onset of hyperglycemia due to defects in β-cell function and disturbed insulin secretion, whereas insulin action is usually not impaired [1,2]. In most populations, mutations in the hepatocyte nuclear factor (HNF)-1 alpha gene - resulting in MODY3, are the most common cause of MODY [3-7]. In the pediatric population however, MODY2 is the most common [8]. In general, the mutations have a high penetration, with most cases having diabetes by the age of 25 [3]. In adolescence and early childhood MODY3 patients may show only minimal elevation of their fasting blood glucose but be diabetic on the 2 h value in an oral glucose tolerance test [9]. Most cases under the age of 10 have normal fasting blood glucose and a normal glucose tolerance. There appears to be progressive deterioration in beta cell function throughout the life span. As the result, the clinical diagnosis of diabetes is being made at the average age of 22 and at that time most patients present with polyuria and polydipsia [10]. These symptoms are associated with the low renal threshold for glucose, typical for MODY3 patients, and they are confirmed by the measurement of 1,5-anhydroglucitol plasma concentration [11]. Patients with HNF1 alpha mutations are not only more insulin sensitive than type 2 diabetic subjects, but they also have greater insulin secretory response to sulfonylureas [12,13]. The replacement of sulfonylureas with metformin had caused a dramatic deterioration in glycemic control [14]. Patients with HNF 1 alpha mutation presented with a 5-fold increase response to a gliclazide than metformin [12]. Sulphonyloureas are still a treatment of choice for young MODY3 patients showing excellent results for decades. It is important to remember that sulphonyloureas should be used with a great caution, by starting with a minimal dose. However the slow loss of insulin secretory capacity is progressive and as a result that majority of older patients eventually will need insulin.

Women with oligomenorrhea and polycystic ovaries show a high incidence of ovulation failure that is linked to insulin resistance and related metabolic features. It was shown in a large randomized placebo-controlled trial that metformin treatment improves ovulation frequency in women with abnormal ovarian function, oligomenorrhea and polycystic ovaries [15]. A recent survey indicated that 30% of pediatric endocrinologists are considering metformin treatment as appropriate for adolescents with PCOS, and 68% of those specialists

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consider it for obese adolescents with PCOS [16]. There is some data supporting a beneficial effect of metformin in improving ovarian function in adolescents [17,18].

The aim of the study is a case presentation of teenager with MODY3 and oligomenorhoea treated successfully with metformin.

Case Presentation

A fifteen and a half year-old patient visited the office of the general physician because of oligomenorrhoea. In basic biochemical tests glucosuria was detected (glucose in urine 226 mmol/l), BG level was 267 mg/dl. The patient was referred to the Department of Pediatric and Adolescent Endocrinology. She did not present with any typical diabetes symptoms. She was born from a 3rd uncomplicated pregnancy, in 37 week of gestation and with 2680 g body weight. She had no chronic diseases. Her psychosomatic development appeared to be normal. Her menarche occurred when she was 11 years old. Menstrual cycles were regular until last year. An amenorrhea has been observed for last four months. Her family history was positive for DM, which had been diagnosed in her grandmother – father's mother, her father and older brother. Her father has been receiving insulin since adolescence. Currently, he is blind due to diabetic retinopathy. He also presents with diabetic neuropathy. Other complications are not observed. Patient's older brother was diagnosed with type 1 diabetes mellitus at the age of 17. He presented with typical diabetes symptoms, and an intensive insulin therapy was administered for the management of his DM.

When the patient was tested in the Outpatient Clinic, 2.5 h after meal her BG level was 276 mg%. Glycosuria and ketonuria were also detected. Therefore she was admitted to the hospital. During the time of admission she was in a good clinical state. However, low body weight (Body Mass Index (BMI) 18.7 kg/m^2) and discrete hirsutism were observed in physical examination. Her height reached level of 50 percentile in accordance with mid-parental height, body mass was (-) 8.3% of body weight appropriate for height, pubertal status was stage V according to Tanner scale. Presence of glucosuria, ketonuria, BG above 200 mg/dl in 24-h BG profile (premeal and 2-h postprandial), and HbA1c 7.1% confirmed the diagnosis of DM. Other basic biochemical tests including acid-base balance were within normal ranges. As an initial treatment, diabetic diet and short acting insulin analog for each meal were introduced. Normoglycemia was achieved with the daily insulin dose of 0.4 IU/kg b.w. In order to establish the type of DM, diabetic autoantibodies such as Islet Cell Antibodies (ICA), Glutamic Acid Decarboxylase (GAD) antibodies, and Islet Antigen 2 (IA2) were measured. They were negative. Moreover C-peptide levels were quite high: fasting they presented at 3.5 ng/ml, 2 hours after meal its value reached 6.8 ng/ml. Thyroid function presented normal (TSH- 2.36 uIU/ml, fT4-13.8 pmol/l; N 10-25 pmol/l). Other autoantibodies such as anti-thyroid peroxidase (18.5 U/ml; N to 60 U/ml) and anti endomysium were negative. The patient was referred to the gynecologist but she misunderstood this recommendation.

Due to low daily requirement of insulin and oligomenhorea, a decision for the replacement of insulinotherapy with metformin was made. This happened one month after the patient was diagnosed with DM, when the results of autoantibodies and C-peptide were known. Within three months of the treatment with metformin dosage 500 mg twice a day, HbA1c level normalized and menstruation cycles became regular. At that time, the control level of fasting C-peptide was still high and reached 3.39 ng/ml. At the same time we received the results of genetic tests that had been performed due to family history positive for DM. As the result, heterozygotic mutation in HNF 1 alfa was detected.

It was discovered that the patient and other living diabetic members of her family have P291fsinsC frameshift mutation. Further detailed diagnostics of morphology and function of kidneys and other organs were performed and no pathology was found. Due to positive effect of metformin treatment on the regulation of menstrual cycles and still high level of C-peptide we decided to continue with the treatment. For the last three years, when checked during the follow-up visits, HbA1c has been varied between 5.2-5.8%, menstrual cycles have been regular, and patient's body weight presents stable (Table 1 and Figure 1). Lactic acid levels have been checked regularly and stayed within normal ranges. Levels of patient's blood pressure and serum lipids were within normal ranges during the observation time. The patient was screened for diabetic complications as neuropathy, retinopathy, and nephropathy (albuminuria level) and none of them have been detected. The last result of patient's C-peptide after 3 years of treatment with metformin has been still high 2.89 ng/ml.

Date	HbA1c [%]	Height [cm]	Body weight [kg]
Oct 2010	7.1	164	50.3
Jan 2011	6.6	165	48
Metformin administration			
April 2011	5.7	165	48
June 2011	5.8	165	48
Aug 2011	5.8	165.5	49.5
Nov 2011	5.6	165.5	50
Jan 2012	5.7	165.5	50
April 2012	5.7	165.5	49.5
July 2012	5.6	165.5	49
Sept 2012	5.7	165.5	49
Jan 2013	5.7	165.5	49
March 2013	5.6	165.5	49
June 2013	5.2	165.5	48.8
Sept 2013	5.6	165.5	49

Table 1: The changes of HbA1c and height and body weight values in the patient with MODY3 during treatment with metformin.

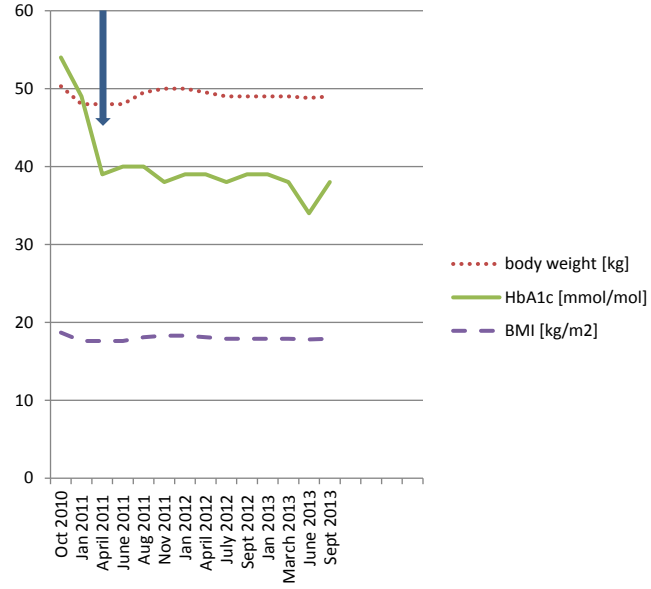

Figure 1: The clinical outcome of HbA1c and Body Mass Index (BMI) in the patient with MODY3 during treatment with metformin.

Discussion

The type of mutation that has been detected in the presented case patient had been previously reported in numerous patients with MODY3 [19]. The diagnosis of diabetes in most of the carries of this mutation had followed typical diabetes symptoms. Most of them were treated with sulfonylureas, the minor part required insulin or only diabetic diet.

In the case presented, DM was diagnosed in adolescence without typical diabetes symptoms. It was a chance discovery during the diagnostic of oligomenorhhea. At least 20% of MODY3 patients remain free of diabetes until their 30s [19-21]. These non-penetrant patients have a low BMI and are likely to be sensitive to insulin [9]. Our patient was indeed slim and her initial insulin requirement was not high. Moreover the mutation came from her father. If the mutation came from the mother, diabetes would be diagnosed at a younger age, and the treatment would more likely be insulin [20].

Early observation showed that HNF1 alfa mutation patients were extremely sensitive to the hypoglycemic effects of sulfonylureas [14,22,23]. When sulfonylureas were replaced with metformin a dramatic deterioration in glycemic control was noticed [14]. Initial reports were case reports or small series. Currently there is evidence from a randomized cross-over trial in which glycemic responses to metformin were compared between MODY3 patients and type 2 DM matched for fasting glucose and body mass index [12]. In patients with HNF 1 alpha mutation, however there was a 5-fold greater response to gliclazide than to metformin, and the response to the sulfonylurea was 4-fold greater than that in type 2 patients [12]. Some other environmental factors such as obesity and physical activity may affect insulin sensitivity and cause an imbalance between insulin secretion and insulin demand in MODY3 patients [20]. The patient presented, was slim, moreover C-peptide level at the time of the diagnosis was high. This fact however did not reflect the progressive deterioration of beta cell function but the opposite, and might rather indicate insulin resistance. As a matter of fact, MODY3 patients do not exhibit the insulin resistance characteristic for type 2 DM and probably due to that reason, hypertension and macrovascular disease appears less frequently in MODY3 than in type 2 DM [24]. On the other hand, microangiopathic complications occur with the same frequency in MODY3 and type 2 DM and hyperglycemia is the main predictor of these complications. As to confirm the above-cited study we present the patient's father who suffers from progressive diabetic retinopathy without clinical signs of macrovascular complications.

High C-peptide levels and a very good clinical response to metformin suggest the insulin resistance as an explanation for oligomenorrhea observed in the presented case. Metformin, primarily works by inhibiting hepatic glucose output. In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation, and decreases absorption of glucose from the gastroinstestinal tract [25]. Therefore the effect of metformin action is the reduction of glucose and insulin levels. One of the hypothesis of metformin action in PCOS is androgens reduction follows from insulin reduction as an effect of metformin treatment. On the other hand the effect of metformin upon insulin secrtion could not be clearly separated from that of weight loss [26]. There are studies presenting that metformin treatment improves ovulation frequency in as well women as adolescents with abnormal ovarian function, oligomenorrhea and polycystic ovaries [15-18]. It is impossible to diagnose PCOS in our patient due to lack of ultrasonography assessment of ovaries. The coexistence of hiperinsulinism, oligomenorrhoea and moreover the normalization of menstruation cycles after metformin administration could indicate that the patient could have had a sub-phenotype of PCOS.

The opportunity to treat our patient with metformin may have resulted in early diagnosis of diabetes due to the accidental coexistence of oligomenorhhea. At the moment of diagnosis of MODY3, administration of sulfonyloureas, which are a treatment of choice, was not possible, because of detected high C-peptide levels and therefore highly probable hyperexcitability to that treatment [12,23]. Currently there is difficult to predict the future of the therapy for the patient, because progressive deterioration of beta cell function has been reported several times throughout the life of MODY3 patients [19,20].

As it is confirmed by the results of metabolic control of diabetes during last three years of follow-up treatment, nowadays metformin has a real beneficial effect for the teenager with MODY3 and oligomenorhhea who has been presented during the case study.

Conclusion

Metformin could be an adequate treatment for teenagers with MODY3 and oligomenorhea/PCOS.

This observation has an important clinical value. In MODY3 teenagers standard treatment with sulfonyureas, which is the treatment of choice, should be used with a great caution. The patients with HNF 1 alpha mutation tend to have an exacerbated response to sulphonylureas. Our case presents that sulfonyureas could be replaced with metformin with good results of diabetes control and other benefits for ovarian function.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' Contributions

AW has made a conception of the work, and has collected and interpreted the data. AW also drafted the manuscript. MC, MS, and JS have revised the manuscript critically for important intellectual content. AW and JS have given final approval of the version to be published. AW agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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