Int J Clin Exp Med 2015;8(5):8243-8248
www.ijcem.com /ISSN:1940-5901/IJCEM0006665

Case Report

Recombinant human growth hormone in treatment of diabetes: report of three cases and review of relative literature

Dandan Wang[1*], Naicheng Zhao[2*], Ziyang Zhu[1]

[1]Department of Endocrinology, Nanjing Children's Hospital Affiliated to Nanjing Medical University, China; [2]Department of Cardiac Medicine, Nanjing Children's Hospital Affiliated to Nanjing Medical University, China. [*]Equal contributors.

Received February 3, 2015; Accepted April 3, 2015; Epub May 15, 2015; Published May 30, 2015

Abstract: To explore the clinical profile and laboratory changes in three patients with diabetes mellitus treated with recombinant human growth hormone (rhGH). Results showed that the patient in the first case was diagnosed as T1DM according to the classical course of disease, weight loss, polyuria, polydispsia, polyphagia, and positive GAD-Ab. The second patient's plasma glucose and urine glucose were at a high level, then stored immediately with the negative OGTT. But, the level of insulin increased significantly suggesting there is insulin resistance. In the last case, fasting plasma glucose level was higher than 7.0 mmol/l several times. The level of HbA1c increased. In an oral glucose tolerance test (OGTT), fasting glucose > 7.0 mmol/l, plasma glucose < 7.8 mmol/l two hours after a 75 g oral glucose load. We postulate that the higher than expected incidence of type 2 diabetes mellitus with GH treatment may be an acceleration of the disorder in predisposed individuals. The rhGH therapy may eventually induce transitory glucose metabolic disorder in a very small proportion of patients, which was restored gradually after the discontinuance of rhGH.

Keywords: Growth hormone, growth hormone deficiency, diabetes mellitus, children

Introduction

Growth hormone deficiency (GHD) is the common cause of short statures in children of which the incidence is about 1/5000-1/4000. In 1954 [1], human pituitary growth hormone (phGH) was first reported to be effective in promoting the linear growth of GHD children, and soon put into use, but some time later it was stopped for Creutzfeldt-Jakob disease caused by the pollution in pituitary preparation. In 1985, recombinant human growth hormone (rhGH) came onto the scene, which was generally believed to have satisfactory effect and less adverse reactions, now it has become the first choice in the treatment of GHD, and is widely used in clinic. But during the treatment observation, glucose tolerance abnormalities and diabetes were detected in a few patients who were treated with rhGH, now there're few reports in this respect at home, since growth hormone has insulin resistance effect, the effects of rhGH on diabetes and glycometabolism are getting attention by experts at home and abroad. Since the application of growth hormone began in our hospital at 1998, we have treated and followed almost 2000 patients, and 3 of which were diagnosed with diabetes during the period, now it is reported as follows.

Clinical data

Case 1, male, visiting age of 8 years and 7 months, was injected with gene recombinant human growth hormone every night in the locality because of slow growth, height then was 124.5 cm (height according to age range -2SD-1SD, body weight was 25 kg, BMI 15.63 kg/cm^2), IV dose was 3 IU/d (0.12 IU/kg.d). Symptoms of polyphagia, polydispia, polyuria were relieved after 1 month's treatment, came to our hospital, trace blood glucose appeared HI, blood gas analysis: PH 7.21, HCO_3^-: 11.6

mmol/l, SBE: -9 mmol/l; urinalysis: urine sugar 3+, urine ketone 2+; HbA1C 13.2%; INS-AB 2.7% (normal value < 5%), GAD-AB weak positive (negative); insulin and C peptide release test: insulin 0' 4.29 mU/L, 120' 5.42 mU/L ((2.6-24.9) mU/L); C peptide 0' 0.107 mU/L, 120' 0.172 mU/L, significantly lower than normal value ((0.366-1.47) mU/L), diagnosed with type 1 diabetes, type 1 diabetic ketoacidosis. Admission weight was 22.5 kg. Discharged from the hospital after treating with insulin injection for 17 days, total amount of insulin was 11 U then. Review result was HbA1C 6.2%, insulin amount 2U (R1N1 before breakfast, no injecton before diner), blood glucose was controlled to a stable level. C peptide amount was at the lower limit on an empty stomach when reviewed after 6 months, hypoglycemia appeared frequently, so we decided to let him take meibine 0.25 g tid orally instead of injecting insulin, blood glucose level went up again after a few day's steady, insulin injection restarted then. After discharged from the hospital for 1 year, HbA1C 6.5%, blood glucose level is stable, insulin amount: Novolin R2N4 before breakfast, R1 before diner. Now follow-up visiting is continuing. No family history of diabetes was told.

Case 2, male, visiting age of 12.5, was admitted to hospital for slow growth. Body weight was 33 kg, height was 143.6 cm (height according to age range -2SD-SD), BMI 15.71 kg/cm^2, bone age was 11.5 years old. Growth Hormone stimulate test (arginine + levodopa) GH peak value was 6.946 ng/ml; LHRHa stimulate test LH peak value was 23.3 mIU/ml, LH peak value/FSH peak value was 1.93, IGF1 227 ng/ml, diagnosed with growth hormone deficiency (partial), adolescent development.

Review was suggested after observing for 3 months. But his parents let the patient see a doctor in other hospital, after treating with recombinant human growth hormone 5I U/d for 1 month, the patient came to our hospital to take a review, told no special discomfort. Urinalysis result: urine sugar 4+, urine ketone was weak positive, OGTT blood glucose level was 5.10 mmol/L, 2 h blood glucose level was 12.70 mmol/L, HbA1C 6.5%, insulin level was 65.36 uIU/ml, C peptide was 748.4 pmol/L, diagnosed with type 2 diabetes (T2DM). Insulin was stopped and came to our department for reviewing after 3 months: ACTH, cortisol was normal, blood RT was normal, urinalysis was normal, urine sugar was negative; HbA1C 5.8%; OGTT test: blood glucose level at 0'30'60'90'120'150'180' was 4.36, 7.45, 6.54, 5.58, 3.99, 6.53, 5.64 mmol/L respectively, insulin was 25.72, 106.3, 206.9, 163.3, 135, 244.72, 207.8 mU/L (2.6-24.9 mU/L) respectively, C peptide was 0.722, 2.51, 2.4, 2.19, 2.22, 1.26, 1.9 nmol/L (0.366-1.47) nmol/L respectively; GAD-Ab negative (negative), INS-Ab 0.18% (< 5%); blood biochemistry was normal, chromosome 46XY. No family history of diabetes was told.

Case 3, female, visiting age of 11 years, came to our department because of "menstruation" half a year ago, diagnosed with "puberty development", and treated with "triptorelin hydrochloride" for half a year, 2 months ago, treated with "growth hormone" additionally because of height growth was not ideal (the specific condition is not clear), detected to have a raise in blood glucose on an empty stomach 1 month later, 7.04 mmol/L, stopped using "growth hormone", blood glucose level was 6.3 mmol/L when reviewed 3 days later, blood glucose level was 7.76 mmol/L on an empty stomach 1 month later, diagnosed with T2DM, no special discomfort were told during the course of disease, height was 147.5 cm when hospitalized, body weight was 47 kg, BMI was 21.36 kg/cm^2, urinalysis: normal. OGTT test: blood glucose at 0'30'60'90'120 was 7.42, 10.58, 9.50, 8.90, 7.50 mmol/l respectively, insulin was 11.46, 68.01, 72.89, 41.46, 14.91 mU/L (2.6-24.9 mU/L) respectively; C peptide was 0' 0.622, 1.97, 2.45, 1.91, 1.55 nmol/l (0.366-1.47 nmol/L) respectively. Cortisol, ACTH and thyroid function were normal. HbA1c: 6.7%. Grandfather has a history of "diabetes", grandmother has a history of "high blood glucose".

Discussion

Since Food and Drug Administration (FDA) approved the use of rhGH on children, in the past 20 years, there have been hundreds of thousands of children who are suffered from growth disorder accept the treatment of rhGH, now it's widely used in the treatment of growth hormone deficiency (GHD), idiopathic short stature (ISS), Turner syndrome (TS), Prader-Willi syndrome (PWS), small for gestational age (SGA), chronic renal function failure (CRF) etc., but the increase in drug regimen and dose that

come with age, weight and excepted value of parents, are causing the fear of parents about the safety of drug.

In 2006, NCGS reported 4084 cases of AE in total, and there are 1559 cases of SAEs, including death of 174 cases, most of the deaths have no relationship with rhGH, or there is no causal relationship, so generally speaking, the safety of rhGH is good. NCGS data displays that after using rhGH, there is no significant increase in morbidity of T1DM, morbidity of T2DM exceeds the early reported one (higher than American children for 10 times, increasing from 0.7/10 million to 7/10 million), and are much close to the morbidity of ethnic minorities during the age of 15-19 (see research report of diabetes epidemiology in American teenager who are under 20 years old in SEARCH), morbidity of T2DM is increasing gradually, but there is no significant increase when compared with T2DM in common children, rhGH related increase in morbidity of T2DM can be explained by the increase in morbidity of T2DM in common children. But there are fewer reports at home.

The relationship between growth hormone and diabetes may due to the resistance to insulin, abnormal glucose tolerance, and finally lead to T2DM. The study state of glucose in children rely on the balance between output and use of glycogen, the output of glycogen comes from glycogenolysis and gluconeogenesis, they accounts for 25% and 75% of glycogen output respectively when on an empty stomach.

Blood glucose regulation is similar with that in adults, insulin can inhibit the production of glycogen, accelerate the use of glucose in peripheral tissue, while the function of growth hormone is opposite which can show insulin resistance effect, the appearance of hypoglycemia in GHD infants may due to the decrease of gluconeogenesis or abnormality of glycogenolysis. Blood glucose level in acromegalic patients often appears to be abnormal, and then spread to the whole body gradually, glucose resistance decrease generally, 20% of them are detected with T2DM [3, 4], so GH plays a very important role in the process of blood glucose regulation. Insulin resistance effect of rhGH [5, 6] include acute effect and chronic effect, acute effect [7] often appears after 1-2 hours of administration, include stimulating lipolysis, activating glucose-fatty acids circulation, and further lead to the increase of free fatty acids, then reach the peak after 5-6 hours, and vanish gradually after 6-7 hours. K. C. J. Yuen etc. [8] discovered that chronic effect appears after the treatment of growth hormone, decrease the sensitivity of liver tissue to insulin, increase glycogenolysis, gluconeogenesis, and decrease the use of blood glucose in peripheral tissue, this is due to the flow of backward receptor. In addition, rhGH can act on islet B cells directly to stimulate the secretion of insulin. However, islet B cells collapse gradually because of insulin resistance, insulin secretion decrease, the same with glucose tolarence. But insulin resistance that led by the treatment of rhGH are usually transient, reversible, and can be compensated by the increase of insulin level which can hardly lead to overt diabetes.

In the case 1, the age of patient was 8 years and 7 months, young, polydipsia, polyuria, and more food and weight loss of “a little more than three disease” appeared after using rhGH for 1 month, random blood glucoseHi can not be detected when hospitalized, but was larger than 11.1 mmol/L, so diagnosed with diabetes, GAD-Ab was weak positive, insulin and C peptide release test indicated that the storage and release of insulin were not enough, HbA1c 13.2%, failed to control blood glucose by taking melbine orally, subcutaneous injection of insulin was needed, conformed to the appearance of typical type 1 diabetes, blood gas analysis indicated that there were acidosis, urinalysis showed that urine ketone 2+, so type 1 diabetic ketoacidosis was clearly diagnosed. The appearance time of symptom overlapped with GH using time, so the action of GH can not be excluded. But HbA1c of patients was 13.2% which were significantly higher than normal value, indicated that average blood glucose level was high during the last 3 months, course of disease was at least as long as 3 months; GAD-Ab was weak positive, indicated that it was autoimmune type 1 diabetes, there were reports on the ability of growth hormone to enhance immune response in organism, but there is still no evidence to approve that it can change the state of immune response in organism [9]. Blood glucose can not be controlled by taking meibine orally, subcutaneous injection of insulin was needed to control it, insulin was absolutely deficient, type 1 diabetes was sustained. In addition, according to that GH treat-

ment related insulin resistance, glucose tolerance decrease can not lead to type 1 diabetes, so for this patient, there might be coupling phenomena between T1DM and use of rhGH [10].

In the case 2, the patient accepted OGTT test after treated with rhGH for 1 month, blood glucose at 120' was 12.7 mmol/L, larger than 11.1 mmol/L, HbA1c 6.5%, urine glucose was positive, urine ketone was weak positive, insulin level was higher than normal value, considered to diagnose as type 2 diabetes, stopped using growth hormone for 3 months and then had a review: blood glucose recovered to normal value, but insulin level was higher than before, indicated the existence of insulin resistance, this may be related to the increased compensatory secretion of insulin during the course of disease to maintain the normal blood value.

In the case 3, the patient accepted treatment of rhGH for 1 month, blood glucose value was detected as 7.04 mmol/L, and then decreased to 6.03 mmol//L after stopped for 3 days, continued to stop medication for 1 month, blood glucose increased to 7.76 mmol/L, OGTT test in our hospital showed that blood glucose at 0' was 7.42 mmol/l, higher than 7.0 mmol/l, while the value at 120' was normal; random test for 2 times showed that blood glucose was higher than 7.0 mmol/l; glycated hemoglobin was 6.7%, higher than 6.5%; according to the newest diabetes diagnostic guide [12], the patient can be diagnosed as diabetes, among the direct blood relatives within two generations for this patient, her grandfather has "diabetes", her grandmother has "high blood glucose", there are high risk of family history, the relationship between rhGH and diabetes need a further assessment. What is sorry about is that the three patients above all did not measure blood glucose before using rhGH, so the relationship between diabetes and rhGH using is much more difficult to define.

Up to now, there have been relatively more documents talking about whether rhGH would lead to diabetes abroad, van Dijk et al. [13] studied 62 cases of SGA, 25 of which did not receive treatment, 37 of which accepted treatment of rhGH, average treating time is 7.3 years, after stopped medication, level of SI, DI, BG, INS, BMI, waistline, IGF1, IGFBP3 were monitored, the results were same between treatment group and control group, so think that long-term treatment of rhGH wouldn't increase the risk of having T2DM and MS. Cutfield et al. [14] did retrospective study on 23333 cases of children who were treated with rhGH, 11 cases of T1DM, 18 cases of T2DM, 14 cases had decrease in glucose tolerance, morbidity of T1DM did not increase significantly, but the morbidity of T2DM was 34/100000 treatment year, which increased by 6 times compared to healthy people, so consider that rhGH cannot increase the morbidity of T1DM, 2/3 of the 18 cases of T2DM patients in this study were teenagers, there were at least one high risk of diabetes in 7 cases, T2DM did not get right until rhGH treatment was stopped, speculate that increase in morbidity of T2DM may be related to body susceptibility [15], which lead to T2DM occur prematurely in childhood or adolescence.

Case 3 was an 11-year-old patient, reaching puberty, has a family history of diabetes, now the correlation between diabetes and rhGH using is unknown, it may due to the early happening in adolescence, continued follow-up, regular review of HbA1c and OGTT etc. are needed, so as to see how the recovery is going on.

There are also some reports on the effect of glycometabolism at home, Liang et al. [16] discovered that rhGH alternative treatment has INS antagonistic effect, can induce INS antagonism, but blood glucose level on an empty stomach is normal, there is no indication of abnormal glucose tolerance or diabetes. Liang et al. [17] discovered that blood glucose level on an empty stomach and IGF-1 had significant increase after treating for 3 months, blood glucose level recovered to an normal value after stopping using growth hormone by monitoring BMI, OGTT, IGF-1, HOMA-IR for 44 cases of GHD patients before and after treatment. In the research on the discussion of therapeutic effect and safety of rhGH on 30 cases of children who are suffered from idiopathic short stature in post pubescence (ISS), Luo et al. [18] discovered that there were two cases of patients suffered from high blood glucose after treatment, and then recovered after stopping medication for 2 weeks, no indication of high blood glucose when administrated again

Nowadays, the morbidity of T2DM is increasing year by year all over the world, patients who

choose to receive rhGH treatment are increasing as also, so the coincidence between attack of DM and GH treatment may happen frequently. Now there are no clear-cut data indicates the relationship between rhGH treatment and morbidity of IGT and T2DM, so more random double-blind clinical research are needed to exclude the interference of some risk factors on result such as race, age and body mass index for each individual.

But generally speaking, the rhGH dose (0.1-0.15 IU/kg·d) for children is safe and effective, during the treatment of growth hormone, there are very little probably of abnormal blood glucose adverse reaction, if diabetes of patient that has already existed before administration was not detected or did not receive a formal treatment, the therapeutic effect of growth hormone would also be influenced, so before using rhGH, HbA1c, blood glucose on an empty stomach, insulin level should be tested, so as to exclude the probability of abnormal blood glucose regulation that has already existed. In addition, some individuals that have glucose intolerance factors such as Turner syndrome [19], PWS [20], fetal growth restriction [11], family history of diabetes, obesity etc. are high risk factors of type 2 diabetes themselves, so close monitoring is greater needed during the treatment of rhGH, in order to deal with in a timely manner.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ziyang Zhu, Department of Cardiac Medicine, Nanjing Children's Hospital Affiliated to Nanjing Medical University, 72 Guangzhou Road, Nanjing 210008, Jiangsu Province, China. Tel: 86-25-83117399; E-mail: zhuziyang_2015@163.com

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