Letter to the editor

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A case of type A insulin resistance syndrome in a 14-year-old adolescent girl without common clinical features

Na Won Lee[1],
Ji Eun Jeong[1],
Young Hwan Kim[1],
Chang Seok Ki[2],
Jin Kyung Kim[1]

[1]Department of Pediatrics, Daegu Catholic University School of Medicine, Daegu, Korea
[2]GC Genome, Yongin, Korea

Highlights

- Type A insulin resistance syndrome presents variably among patients despite the same mutation in the *INSR* gene. For early detection and adequate treatment approaches, clinicians should consider genetic testing either in patients who lack both the characteristics of type 1 (islet auto-antibodies, low C-peptide levels) and type 2 (obese, dyslipidemia, fatty liver) diabetes or in nonobese patients with insulin resistance and ovarian hyperandrogenism.

To the editor,

Type A insulin resistance syndrome (IRS) is a rare congenital disorder caused by insulin receptor dysfunction arising from heterozygous mutations in the insulin receptor (*INSR*) gene. It is characterized by the triad of insulin resistance, acanthosis nigricans (AN), and ovarian hyperandrogenism. The disorder is most commonly discovered around puberty due to the symptoms arising from ovarian dysfunction, which drives the synergistic effect of gonadotropin and insulin action on the ovaries.[1,2] At presentation, hyperglycemia is often not observed. When the β-cell compensatory response to insulin resistance is insufficient to regulate glucose metabolism, impaired glucose tolerance and diabetes mellitus develop, but patients rarely present with hypoglycemia.[1,2]

We present the case of a 14-year-old girl with diabetes. Glucosuria was detected by a school urinary screening test 2 months prior. At presentation, she was not obese, with a height of 153.0 cm (standard deviation score [SDS], -1.02), weight of 46.5 kg (SDS, -0.6), and body mass index (BMI) of 19.9 kg/m^2 (SDS, -0.2). She did not have a dysmorphic face, except for dental abnormalities, including crowding of the upper and lower teeth. She had no facial acne or AN. Coarse hair was observed on the patient's upper lip, chin, midline of the lower abdominal wall, and arms. We calculated a modified Ferriman-Gallwey score of 7 points (hirsutism is defined by a value ≥8 points). She was born at a gestational age of 40 weeks with a birth weight of 3,100 g. According to her mother, she had had darkened skin and hypertrichosis on her extremities since birth. At the age of 8 years, spontaneous thelarche occurred. She had received gonadotropin-releasing hormone (GnRH) agonist treatment for central precocious puberty for 2.5 years at our hospital. At the age of 13 years, she experienced menarche, which was 1 year after the GnRH agonist treatment had ended. Her menstrual cycle was regular.

At presentation, her laboratory results were as follows: fasting plasma glucose, 179 mg/dL; C-peptide level, 1.8 ng/mL; insulin level, 34.8 lU/mL; homeostatic model assessment for insulin resistance score, 15.4 points (cutoff value, ≥3.6 points); and hemoglobin A1c (HbA1c), 10.6% (Table 1). The results for islet cell auto-antibodies, insulin auto-antibodies, and glutamic acid decarboxylase antibodies were negative. Her serum liver function; lipid profile results; and levels of luteinizing hormone, follicle-stimulating hormone, estradiol, dehydroepiandrosterone-sulfate, sex hormone-binding globulin, and testosterone were within normal ranges. A next-generation sequencing–based targeted gene panel for known maturity-

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Address for correspondence:
Jin Kyung Kim
Department of Pediatrics, Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17 gil, Nam-gu, Daegu 42472, Korea
Email: kimjk@cu.ac.kr
https://orcid.org/0000-0003-0018-851X

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Table 1. Levels of HbA1c, insulin, and sex hormones during follow-up

Age (yr)	HbA1c (%)	F-glc (mg/dL)	C-peptide (ng/mL)	F-ins (μIU/mL)	T-chol (mg/dL)	TG (mg/dL)	LH (mIU/mL)	FSH (mIU/mL)	T (ng/mL)
14*	10.6	179	1.8	34.8	160	-	2.8	7.8	0.2
14.5	6.8	-	-	-	-	-	-	-	-
15.3	8.1	137	1.9	26.5			5.9	3.6	0.26
15.8	8.1	150	1.5	35.8	129	44	8.3	2.4	0.3
16	7.1	132	1.7	32.7	114	37	-	-	-
16.5	7	120	1.4	23.9	128	51	2.7	2.3	0.38

F-glc, fasting glucose; F-ins, fasting insulin; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; LH, luteinizing hormone; T-chol, total cholesterol; TG, triglycerides; T, testosterone.
*Initial visit

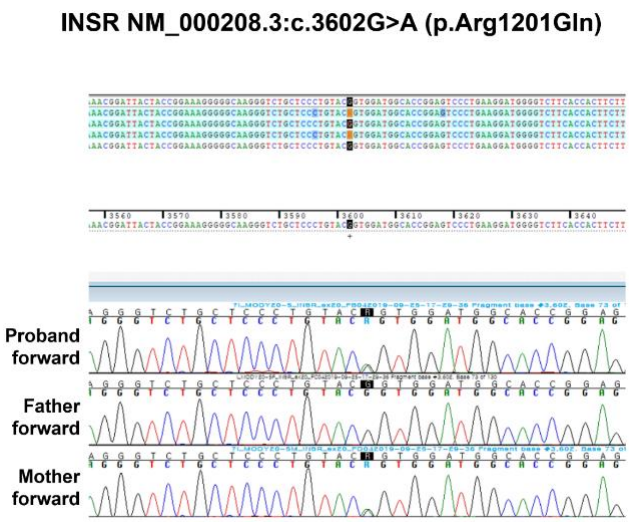

Fig. 1. Sequencing results for a mutation in the *INSR* gene of the patient and her parents. A heterozygous G to A transition at nucleotide 3602 of the *INSR* gene (c.3602G>A) resulting in a missense replacement of arginine with glutamine at amino acid 1201 (p.Arg1201Gln) was identified in the proband and mother but not in her father.

onset diabetes of the young revealed a heterozygous mutation in the *INSR* gene, c.3602G>A (p.Arg1201Gln) (Fig. 1). This has been previously reported as p.Arg1174Gln according to the classical numbering system.[3,4] Metformin with insulin was initiated, but insulin therapy was discontinued because of frequent hypoglycemia. Continued metformin treatment with adequate diet and exercise improved her HbA1c level to 6.8%.

The patient's mother carried the same mutation and also did not present with AN or menstruation abnormalities. She was similarly nonobese (BMI, 16.38 kg/m^2) and had a history of gestational diabetes that required insulin treatment during her pregnancies. Her diabetes improved after delivery. She had no diabetes-related symptoms; however, her fasting blood glucose was 100–150 mg/dL, and her postprandial blood glucose was ≥200 mg/dL, for which she started taking diabetes medications.

There is a diversity of clinical phenotypes, even with the same type of mutation at the same site in the *INSR* gene.[5-7] It is presumed that many such patients are overlooked. Type A IRS is diagnosed more often in women than in men because women have more frequent symptoms associated with hyperandrogenism. In the prediabetic phase, males exhibit only AN and sometimes hypoglycemia, and they often remain undiagnosed even after the development of symptomatic diabetes. Instead, this form of diabetes is probably diagnosed as type 2 diabetes in midlife.[1,2] In women, the features of type A IRS often do not become apparent until puberty or later. Type A IRS is not usually diagnosed during childhood.[1,2] Only a few cases of childhood diagnoses without common clinical features have been reported.[8,9]

In those with severe insulin resistance, puberty is often accelerated, most likely due to the action of hyperinsulinemia, which exerts synergistic effects with gonadotropins on the ovaries.[1,2] However, no cases of type A IRS with precocious puberty have been reported. Although the patient in this study was treated for central precocious puberty, her mother, who had the same mutation, did not experience precocious puberty or menstrual abnormalities. Therefore, we could not conclude that the insulin resistance of this patient was related to CPP.

In our study, the patient did not exhibit dyslipidemia. The absence of dyslipidemia and fatty liver disease as well as inappropriately normal or elevated plasma adiponectin level are characteristic clinical features in patients with severe insulin resistance due to mutation in *INSR*.[1,2]

Although metformin has limited efficacy, it should be introduced early if severe hyperinsulinemia persists, and it can be beneficial at high doses. As diabetes progresses, patients whose condition is not controlled by oral hypoglycemic agents may require high doses of exogenous insulin and may show limited effect. Long-term metabolic control has been reported to be poor, and diabetes complications are frequent in patients with type A IRS.[10]

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Ethics statement: This report was approved by the Institutional Review Board (IRB) of the Daegu Catholic University Medical Center, Daegu, Korea (IRB No. CR-21-061-L). Informed consent was obtained from the patient and her

parents for the preparation and publication.

ORCID
Na Won Lee: 0000-0003-0603-1791
Ji Eun Jeong: 0000-0002-3036-6818
Young Hwan Kim: 0009-0009-5551-677X
Chang Seok Ki: 0000-0001-7679-8731
Jin Kyung Kim: 0000-0003-0018-851X

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